Drug Class Review

Second Generation Antipsychotic Drugs†

Final Update 4 Evidence Tables

November 2013

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TABLE OF CONTENTS

Shading indicates new information for Update 4.

Abbreviations used in evidence tables

Abbreviation	Meaning
AAP	Atypical Antipsychotic
ABC	Aberrant Behavior Checklist
ACT	Active-control trial
AD	Alzheimer's Disease
ADHD	Attention deficit hyperactive disorder
ADI-R	Autism Diagnostic Interview-Revised
AE	Adverse event
AIMS	Abnormal Involuntary Movement Scale
ALT	Alanine aminotransferase
AMDP-5	Association for Methodology and Documentation in Psychiatry adverse event questionnaire
ANCOVA	Analysis of covariance
ANOVA	Analysis of variance
ASD	Autism spectrum disorders
ASEX	Arizona Sexual Experience Scale
AST	Aspartate aminotransferase
BARS	Barnes Akathisia Rating Scale
BAS	Behavioral Approach System scale
BEHAVE-AD	Behavioral Pathology in Alzheimer's Disease
bid	Twice daily
BIS	Behavioral Inhibition System scale
BMI	Body mass index
BNT	Boston Naming Test
BPAD	Empirical Behavioral Pathology in Alzheimer's Disease scale
BPRS	Brief Psychiatric Rating Scale
BRMS	Bech Rafaelsen Melancholia Scale
BWISE	Body weight, image and self-esteem evaluation questionnaire
CBCL	Child Behavior Checklist
CCT	Controlled clinical trial
CDI	Children's Depression Inventory scale
CDSS	Calgary Depression Scale for Schizophrenia
CERAD	Consortium to Establish a Registry for Alzheimer's Disease
CGI	Clinical global impressions (S, C and I versions)
CGI-I	Clinical global impression scale - Improvement
CGI-S	Clinical global impression scale - Severity
CI	Confidence interval
CMAI	Cohen-Mansfield Agitation Inventory
CMMSE	Cantonese version of Mini-Mental State Examination
CNS	Central nervous system
COGLAB	COGnitive LABoratory (computer-assisted cognitive test battery)
COPD	Chronic obstructive pulminary disease
COSTART	US FDA Coding Symbols for a Thesaurus of Adverse Reaction Terms
CPM	Concomitant psychotropic medication
CPRS	Conners Parent Rating Scale
CPT	Continuous Performance Test
CR	Controlled release

Abbreviation	Meaning
CSFQ	Changes in Sexual Functioning Questionnaire
CSQ-8	Client Satisfaction Questionnaire-8
CTD	Cognitive Test for Delirium
CUAD	Chemical Use, Abuse, and Dependence Scale
CV	Cardiovascular
CVA	Cerebrovascular accident
CVLT	California Verbal Learning Test
CVS	Cardiovascular system
d	Day
DAI	Drug Attitude Inventory
DAS	Disability Assessment Schedule
DB	Double-blind
DIEPSS	Drug-induced Extrapyramidal Symptom Scale
DIS III	Diagnostic Interview Schedule III
DISCUS	Dyskinesia Identification System Condensed User Scale
dL	Deciliter
DOTES	Dosage Record and Treatment Emergent Symptom Scale
DSDT	digit span distraction test
DSM-III	Diagnostic and Statistical Manual of Mental Disorders-Third Edition
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders-Fourth Edition
DVP	Digital volume pulse
E-BEHAVE-ED	Empirical Behavioral Pathology in Alzheimer's Disease Rating Scale
ECG	Electrocardiogram
ECT	Electroconvulsive therapy
EEG	Electroencephalogram
EF	Ejection fraction
EPS	Extrapyramidal symptoms
ER	Extended release
ESRS	Extrapyramidal Symptom Rating Score
FAST	Functional Assessment Staging Rating Scale
FDA	US Food and Drug Administration
FGIR	Final Global Improvement Rating
FU	Follow-up
g	Gram
GAF	Global Assessment of Functioning Scale
GAS score	Global Assessment Scale Score
GBAS	General Behavior Assessment Scale
GI	Gastrointestinal
GP	General practitioner
GPS	General Psychopathology Subscale
h	Hour
HAM-D	Hamilton Depression Scale
HAS	Hamilton Anxiety Scale
HDI	Hamilton Depression Inventory
HDL-C	High density lipoprotein cholesterol
HMO	Health maintenance organization
HOMA	Homoeostasis model assessment index

Abbreviation	Meaning
HPL	Hyperprolactinemia
HR	Hazard ratio
HRQOL	Health related quality-of-life
ICD-10	International Classification of Diseases, Tenth Revision
ICD-9	International Classification of Diseases, Ninth Revision
IDS-C	Inventory of Depressive Symptomatology-Clinician Rated
INS	Insulin
IR	Immediate release
IRI	Insulin resistance index
ISST	Information-Seeking Skills Test
ITT	Intention-to-treat
L	Liter
LA	Long acting
LDL-C	Low-density lipoprotein cholesterol
LFT	Liver function test
Li	Lithium
LOCF	Last Observation Carried Forward
LQL	Lehman Quality of Life
LS means	Least squares means
MADRS	Montgomery-Asberg Depression Rating Scale
MANCOVA	Multivariate analysis of covariance
MASC	Multidimensional Anxiety Scale for Children
mcg	Microgram
MDB	Movement Disorder Burden
MDD	Major depressive disorder
MDE	Major depressive episode
mg	Milligram
min	Minute
MINI	Mini International Neuropsychiatric Interview
MITT	Mother-Infant Treatment Team
mL	Milliliter
MLDL	Munich List of Quality-of-Life Dimensions
MMSE	Mini-Mental State Examination
mo	Month
MOSES	Multidimensional Observational Scale for Elderly Subjects
MSQ	Medication Satisfaction Questionnaire
N	Sample size (entire sample)
n	Subgroup sample size
NA	Not applicable
NAART-R	North American Adult Reading Test-Revised
NINCDS-ADRDA	National Institute of Neurological and Communicative Diseases and Stroke/Alzheimer's Disease and Related Disorders Association
NINDS-AIREN	National Institute of Neurological Disorders and Stroke and the Association Internationale pour la Recherche et l'Enseignement en Neurosciences
NIP	National Institute of Psychiatry
NMS	Neuroleptic malignant syndrome
NOSGER	Nurses' Observation Scale for Geriatric Patients
NOSIE	Nurses' Observation Scale for Inpatient Evaluation

Abbreviation	Meaning
NPI	Neuropsychiatric Inventory
NPI-NH	Neuropsychiatric Inventory-Nursing Home
NR	Not reported
NRS	Neurologic Rating Scale
NS	Not significant
NSA	Negative Symptom Assessment
NSD	No significant difference
OAS	Overt Aggression Scale
OAS-M	Modified Overt Aggression Scale
OR	Odds ratio
P	*P* value
P	Placebo
PANSS	Positive and Negative Syndrome Scale
PANSS-D	PANSS Depression Cluster
PANSS-EC	Positive and Negative Syndrome Scale-Excited Component
PCT	Placebo-controlled trial
PDD	Pervasive developmental disorder
PDD-NOS	Pervasive developmental disorder - not otherwise specified
PDS	Progressive Deterioration Scale
PEAT	Penn Emotional Acuity Test
PETiT	Personal Evaluation of Transitions in Treatment
PGDRS	Psychogeriatric Dependency Rating Scale
PGWB	Psychological General Well-Being
PPR	Positive Psychopathology Rating
PPY	Per person year
PRAEQ	Prolactin Related Adverse Event Questionnaire
PSP scale	Personal and Social Performance scale
PSQI	Pittsburgh Sleep Quality Index
Q-LES-Q	Quality of Life Enjoyment and Satisfaction Questionnaire
qd	Once daily
QLDS	Quality-of-Life in Depression Scale
QLI	Lehman Brief Quality-of-Life Interview
QOL	Quality-of-life
QUALID	Quality-of-Life in Late-Stage Dementia scale
RAAP	Rating of Aggression Against People and/or Property Scale
RAVLT	Rey Auditory Verbal Learning Task
RBANS	Repeatable Battery for the Assessment of Neuropsychological Status
RCT	Randomized controlled trial
RDQ	Reflux Disease Questionnaire
RFS	Role Functioning Scale
RODOS-UK	UK Risperidone Olanzapine Drug Outcomes Studies in Schizophrenia Program
RR	Relative risk
SADS-CB	Schedule for Affective Disorders and Schizophrenia-Change Bipolar Scale
SAFE	Social Adaptive Functioning Evaluation
SAGE	Systematic Assessment of Geriatric drug use via Epidemiology
SANS	Scale for Assessment of Negative Symptoms
SAPS	Scale for the Assessment of Positive Symptoms

Abbreviation	Meaning
SAR-S	Simpson Angus Rating Scale for Extrapyramidal Side Effects
SAS	Social Adjustment Scale
SB	Single-blind
SCID	Structural Clinical Interview for DSM-IV
SD	Standard deviation
SE	Standard error
SFS	Social Functioning Scale
SIP	Sickness Impact Profile
SMB	Suicide Monitoring Board
SOFA	Social and Occupational Functioning Assessment
SOT	Standard olanzapine tablets
SR	Sustained release
SSPA	Social Skills Performance Assessment
SSRI	Selective serotonin reuptake inhibitor
SSTICS	Subjective Scale to Investigate Cognition in Schizophrenia
SUD	Substance use disorder
SVLT	Serial Verbal Learning Test
SWMT	Spatial Working Memory Test
SWN	Subjective Well-being under Neuroleptic Treatment Scale
SWS	Slow-wave sleep
TA	Typical Antipsychotic drugs (e.g. haloperidol, perphenazine)
TAS	Total Aggression Severity
TC	Total cholesterol
TD	Tardive dyskinesia
TEAEs	Treatment emergent adverse events
TESS	Treatment Emergent Symptom Scale
tid	Three times daily
TMT	Trail Making Test
TNR	Treatment nonresponsive
ToL test	Tower of London test
UKU-SERS	Udvalg for Kliniske Undersogelser Side Effect Rating Scale
VAS	Visual analog scale
vs.	Compared with (versus)
WAIS-R	Wechsler Adult Intelligence Scale - Revised
WCST	Wisconsin Card Sorting Test
WD	Withdrawal
WHO	World Health Organization
WHO-QL	World Health Organization - Quality-of-Life
WHR	Waist-hip circumference ratio
WISC-R	Wechsler Intelligence Scales for Children - Revised
WMS-R	Wechsler Memory Scale - Revised
XR	Extended release
y	Year
Y-BOCS	Yale-Brown Obsessive-Compulsive Scale
YMRS	Young Mania Rating Scale

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Eligibility criteria	Interventions (drug, dose, duration)	Allowed other medications	Age Gender Ethnicity	Other population characteristics
Trials on Adolescents					
AstraZeneca D1441C00112 DB RCT International (43 sites)	Inclusion: Male and female inpatient and outpatient adolescents (aged 13 to 17 ys), with a DSM-IV diagnosis of schizophrenia as confirmed by the Schedule for Affective Disorders and Schizophrenia for School-Aged Children Present and Lifetime Version were recruited for the study; PANSS total score of ≥60 and a score of 4 or greater on delusions (P1), conceptual disorganization, (P2), or hallucinations (P3) at both screening and randomization.	Quetiapine 400 mg/d vs Quetiapine 800 mg/d or P given in divided doses either bid or tid 6 wks	NR	Mean age (SD): 15.41 (1.32) ys 58.6% male 61.4% Caucasian 12.3% black 18.2% oriental 8.2% other	Quetiapine 400 mg/d vs Quetiapine 800 mg/d vs P DSM-IV diagnosis: Schizophrenia, disorganized: 8.2% vs 6.8% vs 6.8% Schizophrenia, paranoid: 72.6% vs 67.6% vs 71.2% Schizophrenia, residual: 0 vs 1.4% vs 0 Schizophrenia, undifferentiated: 19.2% vs 24.3% vs 21.9% v Mean PANSS score (SD): 98.1 (15.41) vs 97.7 (15.32) vs 97.2 (16.83) Mean PANSS Positive Symptom Subscale score (SD): 23.3 (5.80) vs 23.8 (4.84) vs 24.5 (5.57) Mean PANSS Negative Symptom Subscale score (SD) 25.4 (5.65) vs 25.8 (5.43) vs 24.8 (5.85) Mean Sum of PANSS Items S1, S2,and S3 scores (SD): 8.7 (3.86) vs 8.3 (3.74) vs 8.3 (3.98) Mean Children GAS score (SD): 43.4 (9.16) vs 42.6 (11.12) vs 41.8 (11.39)

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Number screened/ eligible/ enrolled	Withdrawn/ Lost to follow-up/ Analyzed	Results
Trials on Adolescents			
AstraZeneca D1441C00112 DB RCT International (43 sites)	NR/NR/268 enrolled and 222 randomized	NR/NR/222	Quetiapine 400 mg/d vs Quetiapine 800 mg/d vs P; P values are vs P Mean change PANSS total score: -27.31 (P=0.043) vs -28.44 (P=0.009) vs -19.15 Mean change PANSS positive symptom subscale score: -8.56 (P0.075) vs -9.34 (P=0.008) vs -6.51 Mean change PANSS negative symptom subscale score: -6.35 (P=0.239) vs -6.21 (P=0.245) vs -5.09 Mean change Sum of PANSS items S1, S2, and S3 scores: -2.58 (P=0.059) vs -2.39 (P=0.091) vs -1.51

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Adverse effects reported
Trials on Adolescents	
AstraZeneca D1441C00112 DB RCT International (43 sites)	Quetiapine 400 mg/d vs Quetiapine 800 mg/d vs P Any AEs: 79.5% vs 74.3 vs 60.0% vs 71.2% Serious AEs: 5.5% vs 6.8% vs 5.3% vs 5.9% n (%) Somnolence: 20 (27.4) vs 22 (29.7) vs 5 (6.7) Headache: 6 (8.2) vs 16 (21.6) vs 14 (18.7) Dizziness: 6 (8.2) vs 11 (14.9) vs 4 (5.3) Dry mouth: 3 (4.1) vs 7 (9.5) vs 1 (1.3) Insomnia: 9 (12.3) vs 7 (9.5) vs 17 (22.7) Agitation: 6 (8.2) vs 6 (8.1) vs 10 (13.3) Tachycardia: 4 (5.5) vs 6 (8.1) vs 0 Increased appetite: 3 (4.1) vs 5 (6.8) vs 3 (4.0) Fatigue: 4 (5.5) vs 4 (5.4) vs 3 (4.0) Irritability: 2 (2.7) vs 4 (5.4) vs 0 Nausea: 3 (4.1) vs 4 (5.4) vs 13 (17.3) Sedation: 4 (5.5) vs 4 (5.4) vs 3 (4.0) Vomiting: 3 (4.1) vs 4 (5.4) vs 6 (8.0) Anxiety: 4 (5.5) vs 3 (4.1) vs 5 (6.7) Diarrhea: 4 (5.5) vs 1 (1.4) vs 4 (5.3) No AEs related to prolactin. No deaths. Changes in mean weight: +2.2 vs +1.8 vs -0.4 kg Changes in mean pulse rate: +6 vs +3.9 vs -1.4 BPM

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Extrapyramidal symptoms
Trials on Adolescents	
AstraZeneca D1441C00112 DB RCT International (43 sites)	Quetiapine 400 mg/d vs Quetiapine 800 mg/d vs P n(%) AEs associated with EPS: 9 (12.3%) vs 10 (13.5%) vs 4 (5.3%) Majority of patients showed no change in EPS as assessed by SAR-S, AIMS and BARS Incidence of anticholinergic medication use for treatment of emergent EPS: 5.48% vs 1.35% vs 0%

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Total withdrawals; withdrawals due to adverse events	Comments
Trials on Adolescents		
AstraZeneca D1441C00112 DB RCT International (43 sites)	Total WD: NR WD due to AEs: 14	

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Eligibility criteria	Interventions (drug, dose, duration)	Allowed other medications	Age Gender Ethnicity	Other population characteristics
Arango, 2009 Spain	Inclusion - with a diagnosis of psychosis (i.e., schizophrenia or any other psychotic disorder according to DSM-IV criteria; first episode of psychosis before the age of 18, lasting less than 1 year after onset of the first positive symptom; 12–18 years of age. Exclusion - if the psychotic symptoms appeared to result from acute intoxication or withdrawal; DSM-IV criteria for any substance abuse, mental retardation, or pervasive developmental disorder, suffered from any organic central nervous system disorder, history of traumatic brain injury with loss of consciousness, were pregnant or breast-feeding, or were taking olanzapine or quetiapine before enrolment.	Quetiapine vs. olanzapine 532.8 (459.6) vs. 9.7 (6.5) mg/day 180 days	Yes except for other anti-psychotics	Mean age 16 yrs 78% male 82% Caucasian 4% Caribbean Black 12% Hispanic 2% Gipsy	Schizophrenia 34% Bipolar disorder 26% Other psychoses 40%

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Number screened/ eligible/ enrolled	Withdrawn/ Lost to follow-up/ Analyzed	Results
Arango, 2009 Spain	NR/NR/50	17/7/50	Quetiapine baseline/6 months vs. olanzapine baseline/6 months CGI 5.04 ± 1.30 / 2.96 ± 1.40 vs 5.46 ± 0.86 / 3.54 ± 1.30 P = 0.605 YOUNG 15.70 ± 12.85 / 5.50 ± 6.39 vs. 18.73 ± 12.69 / 6.34 ± 9.62 P = 0.464 HAMILTON 17.27 ± 9.69 / 8.00 ± 6.70 vs. 17.83 ± 10.03 / 9.12 ± 7.91 P = 0.660 GAF 41.17 ± 15.56 / 67.79 ± 16.79 vs. 37.58 ± 17.33 / 61.88 ± 16.01 P = 0.118 PANSS Positive 23.25 ± 7.25 / 15.08 ± 4.07 26 vs. 12 ± 4.10 / 14.04 ± 4.75 P = 0.118 PANSS Negative 21.88 ± 6.835 / 16.29 ± 5.15 vs. 26.58 ± 8.34 / 22.15 ± 7.24 P = 0.340 PANSS General 46.05 ± 11.26 /34.45 ± 9.89 vs. 52.96 ± 10.84 / 35.42 ± 8.88 P = 0.093 PANSS Total 91.05 ± 21.42 / 67.29 ± 17.86 vs. 105.65 ± 19.97 / 71.62 ± 17.33 P = 0.41

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Adverse effects reported
Arango, 2009 Spain	Quetiapine vs. olanzapine n (%) Concentration difficulties 16 (67) vs. 18 (72) Asthenia/lassitude/increased fatigability 19 (79) vs. 19 (73) Sleepiness/sedation 19 (79) vs. 21 (84) Failing memory 14 (58)vs. 12 (52) Depression 9 (37) vs. 11 (44) Tension/inner unrest 15 (62) vs. 13 (54) Increased duration of sleep 11 (46) vs. 12 (48) Reduced duration of sleep 4 (17) vs. 6 (25) Increased dream activity 9 (39) vs. 6 (26) Emotional indifference 7 (29) vs. 14 (56) Rigidity 4 (17) vs. 7 (29) P < 0.05 Hypokinesia/akinesia 11 (46) vs. 14 (54) Tremor 7 (37 vs. 13 (50) Akathisia 6 (26) vs. 8 (32) Accommodation disturbances 6 (26) vs. 7 (32) Increased salivation 10 (42) vs. 13 (52) Reduced salivation 9 (39) vs. 2 (8) Constipation 10 (42) vs. 7 (27) Polyuria/polydipsia 7 (30) vs. 8 (31) Orthostatic dizziness 3 (13) vs. 5 (21) Palpitations/tachycardia 11 (46) vs. 8 (35) Increased tendency to sweat 8 (33) vs. 7 (28) Weight gain 13 (72) vs. 20 (91) Amenorrhea 1 (20) vs. 4 (50) Increased sexual desire 1 (6) vs. 5 (28) Dry vagina 0 (0) vs. 2 (22) Tension headache 6 (25) vs. 6 (24) Weight gain 15.5 kg, vs. 5.4 kg,

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Extrapyramidal symptoms
Arango, 2009 Spain	Quetiapine vs. olanzapine n (%) Rigidity 4 (17) vs. 7 (29) P < 0.05 Hypokinesia/akinesia 11 (46) vs. 14 (54) Tremor 7 (37 vs. 13 (50) Akathisia 6 (26) vs. 8 (32) Accommodation disturbances 6 (26) vs. 7 (32)

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Total withdrawals; withdrawals due to adverse events	Comments
Arango, 2009 Spain	17 withdrawals 0 due to Aes	

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Eligibility criteria	Interventions (drug, dose, duration)	Allowed other medications	Age Gender Ethnicity	Other population characteristics
Gothelf 2003 Israel	Adolescents with a diagnosis of schizophrenia was established according to DSM-IV criteria	Risperidone 3.3 (1.1) mg/day (range 1–5), for olanzapine 12.9 (3.1) mg/day (range 10–20), and for haloperidol 8.3 (3.8) mg/day (range 5–15). Duration 8 weeks	Lorazepam and anticholinergic agents	Mean age 17 yrs 63% male Ethnicity NR	Paranoid 49% Undifferentiated 30% Disorganized 21%

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Number screened/ eligible/ enrolled	Withdrawn/ Lost to follow-up/ Analyzed	Results
Gothelf 2003 Israel	NR/NR/43	4/0/39	Baseline / 8 weeks Positive symptoms Risperidone 17.4 (6.9) / 13.2 (3.8) Olanzapine 15.0 (4.9) / 13.3 (8.0) Haloperidol 21.3 (8.9) / 13.0 (5.8) Negative symptoms Risperidone 24.2 (9.3) / 20.8 (8.4) Olanzapine 18.1 (11.0) / 14.9 (8.0) Haloperidol 20.3 (8.0) / 16.4 (8.5) Total Scores Risperidone 90.2 (26.4) / 73.9 (19.1) Olanzapine 71.6 (23.8) / 61.6 (28.4) Haloperidol 86.1 (24.4) / 66.3 (21.8) Effect of Week F(2,72) 12.7, p 0.001

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Adverse effects reported
Gothelf 2003 Israel	Risperidone vs. Olanzapine vs. Haloperidol n (%) Concentration difficulties 2 (11.8) vs. 7 (36.8) vs. 3 (42.9) Increased fatigability 2 (11.8) vs. 8 (42.1) vs. 5 (71.4) Sleepiness/sedation 3 (17.6) vs. 9 (47.4) vs. 3 (42.9) Failing memory 2 (11.8) vs. 7 (36.8) vs. 2 (28.6) Depression 2 (11.8) vs. 5 (26.3) vs. 5 (71.4) Tension/inner rest 3 (17.6) vs. 7 (36.8) vs. 2 (28.6) Increased duration of sleep 4 (23.5) vs. 9 (47.4) vs. 3 (42.9) Reduced duration of sleep 1 (5.9) vs. 4 (21.1) vs. 0 Increased dream activity 1 (5.9) vs. 4 (21.4) vs. 0 Accommodation disturbances 1 (5.9) vs. 2 (10.5) vs. 0 Increased salivation 5 (29.4) vs. 4 (21.1) vs. 1 (14.3) Reduced salivation 0 vs. 1 (5.3) vs. 1 (14.3) Nausea/vomiting 1 (5.9) vs. 2 (10.5) vs. 1 (14.3) Constipation 1 (5.9) vs. 3 (15.8) vs. 2 (28.6) Micturition disturbances 3 (17.6) vs. 1 (5.3) vs. 1 (14.3) Polyuria/polydipsia 3 (17.6) vs. 2 (10.5) vs. 2 (28.6) Orthostatic dizziness 4 (23.5) vs. 3 (15.8) vs. 1 (14.3) Palpitations/tachycardia 2 (11.8) vs. 4 (21.1) vs. 0 Pruritus 0 vs. 3 (15.8) vs. 0 Diminished sexual desire 1 (5.9) vs. 4 (21.1) vs. 1 (14.3)

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Extrapyramidal symptoms
Gothelf 2003 Israel	

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Total withdrawals; withdrawals due to adverse events	Comments
Gothelf 2003 Israel	4 withdrawals 0 due to Aes	

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Eligibility criteria	Interventions (drug, dose, duration)	Allowed other medications	Age Gender Ethnicity	Other population characteristics
Trials on Adults					
Addington, 2004 DB, RCT, parallel Addington 2009	Schizophrenia, schizoaffective disorder, 18-65 ys of age, PANSS total score >60, a score of >4 on 2 of the PANSS core items.	ziprasidone 40-80 mg BID. (N=149) or risperidone 3-5mg BID. (N=147) 8 wks duration	NR	Mean age: 35 ys 72.5% Male Ethnicity NR	NR

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Number screened/ eligible/ enrolled	Withdrawn/ Lost to follow-up/ Analyzed	Results
Trials on Adults			
Addington, 2004 DB, RCT, parallel Addington 2009	NR/NR/296	NR/NR/198	Efficacy evaluations: LS mean change from baseline to last visit: PANSS total: Z: -25.8 vs R: -27.3 CGI-S: Z: -1.1 vs R: -1.2 PANSS negative subscale: Z: -6.4 vs R: -6.4 BPRSd total: Z: -15.2 vs R: -15.9 BPRSd core: Z: -5.5 vs R: -6.0 GAF: Z: 16.5 vs R: 15.6 Body weight increase (>7% change): Z: 10(8.2%) vs R: 20(16.0%) Body weight decrease (>7% change): Z: 9(7.4%) vs R: 3(2.4%) Long term data from 44 wks extension study (Addington 2009) Z vs R Mean change from baseline in PANSS total Change(SE) -28.0 (3.8) vs -33.2 (3.3), p=0.29 Mean change from baseline in CGI-S (SE) -1.2 (0.2) vs -1.6 (0.2), p=0.22 Mean change from baseline in GAF (SE) 14.4 (3.0) vs -19.1 (3.6),p=0.22 Mean change from baseline in MADRS total score -5.2 (1.3) vs -4.3 (1.2), p=0.63

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Adverse effects reported
Trials on Adults	
Addington, 2004 DB, RCT, parallel Addington 2009	Treatment-emergent AEs reported: Z: 113 (75.8%) vs R: 122(83.0%) Events reported by patients: Insomnia: Z: 37(24.8%) vs R: 18(12.2%) Somnolence: Z: 31(20.8%) vs R: 26(17.7%) Agitation: Z: 24(16.1%) vs R: 20(13.6%) Headache: Z: 23(15.4%) vs R: 27(18.4%) Akathisia: Z: 19(12.8%) vs R: 30(20.4%) Tremor: Z: 15(10.1%) vs R: 14(9.5%) Sexual Dysfunction Questionnaire: Symptom absent at baseline and present at last visit: Erectile dysfunction: Z: 8% vs R: 10% Ejaculatory dysfunction: Z: 3% vs R: 11% Increased libido: Males: Z: 1% vs R: 5% Females: Z: 10% vs R: 0% Decreased libido: Males: Z: 9% vs R: 15% Females: Z: 5% vs R: 3% Orgastic dysfunction: Males: Z: 5% vs R: 13% Females: Z: 0% vs R: 0% AEs reported in the 44 wks continuation study (Addigton 2009) occurring in >10% of patients Z vs R Agitation:16.1% vs 16.9%, Akathisia: 27.4% vs 28.6%, Anxiety: 16.1% vs 11.7%, Constipation: 6.5% vs 11.7%, Dizziness: 11.3% vs 7.8%, Headache: 21.0% vs 23.4%, Hypertonia: 3.2% vs 11.7%, Insomnia: 32.3% vs 18.2%, Nausea: 14.5% vs 9.1%, Respiratory tract infection: 8.1 vs 15.6%, Somnolence: 24.2 vs 28.6%, Tremor: 11.3% vs 13.0%, vomiting: 12.9 vs 3.9%

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Extrapyramidal symptoms
Trials on Adults	
Addington, 2004 DB, RCT, parallel Addington 2009	Simpson-Angus scores: Z: -0.57 (0.33) vs R: -0.23 (0.33); P=.04 Barnes Akathisia scores: Z: -0.28 vs R: +0.28 (0.21); P=.04 AIMS scores: Z: -0.04 (0.17) vs R: -0.25 (0.17); P=.3 MDB scores: Z: 0.20 vs R: 0.35; P=.015 Number of patients who experienced a movement disorder AE: R: 54(36.7%) vs Z: 44(29.5%) % of patients with Extrapyramidal reaction in 44 week continuation study (Addington 2009) Z vs O: 12.9% vs 9.1%

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Total withdrawals; withdrawals due to adverse events	Comments
Trials on Adults		
Addington, 2004 DB, RCT, parallel Addington 2009	98 WD; 18 WD due to AE	

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Eligibility criteria	Interventions (drug, dose, duration)	Allowed other medications	Age Gender Ethnicity	Other population characteristics
Akerele, 2007 RCT	Met DSM-IV criteria for schizophrenia or schizoaffective disorder; met DSM-IV criteria for current cocaine and/or marijuana abuse or dependence; and were using marijuana at least twice/week, or cocaine at least once/week on average during 3 mos prior to study enrollment Exclusion criteria: pregnant; currently psychologically dependent on alcohol or other drugs such that they had significant WD symptoms in the past (except nicotine and caffeine); unstable psychiatric symptomatology; unstable medical condition; enzyme function tests > 3 times upper limit of normal; history of seizures or neuroleptic malignant syndrome; commission of violent crime in past 2 ys; not responded to olanzapine or risperidone in past; or score > 30 on positive and negative sub-scales of Positive and Negative Symptom Scale	olanzapine: 5-20 mg/d risperidone: 3-9 mg/d duration: 14 wks	NR	Mean age: 35.5 yrs Male: 89% African American: 54% Hispanic: 32% Caucasian: 14%	Current marijuana use: 93% Current cocaine use: 78.6%
Alvarez, 2006 RCT, open-label Outpatients	DSM-IV schizophrenia diagnosis; baseline summary SANS score ≥10; age 18-65 yrs; if previously treated with antipsychotics, only those patients treated with first generation drugs accepted; no psychiatric hospitalizations within 3 mos of study entry	olanzapine 10 mg/d* risperidone 3 mg/d* *recommended starting doses; titration allowed at investigator's discretion mean doses during time on trial: olanzapine 12.2 mg/d (SD 5.8) risperidone 4.9 mg/d (SD 2) end point mean doses: olanzapine 13.1 mg/d (SD 6.9; median 10 mg/d) risperidone 5.1 mg/d (SD 2.3; median 6 mg/d)	biperiden; benzodiazepines up to 40 mg/d diazepam equivalent	Mean age: 36.3 yrs 72% male Ethnicity NR	Schizophrenia type: paranoid 64%; residual 19%; undifferentiated 13%; disorganized 3%; catatonic <1% Mean SANS summary score: 14.3 Mean CGI: 4.4 Mean Calgary Depression Score: 4.2 Statistically significant difference between intervention groups for mean baseline weight (O 73.8 kg v R 80.5 kg; P=0.0005) and mean baseline BMI (O 25.9 v R 27.5; P=0.0072)

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Number screened/ eligible/ enrolled	Withdrawn/ Lost to follow-up/ Analyzed	Results
Akerele, 2007 RCT	76/29/28	12 dropped out/16 completed	Marijuana use: Urine toxicology showed significant decrease in both groups (Z= -2.52, P=0.01) Self-reported marijuana craving showed significant x time interaction (Z=2.06, P=0.04) for risperidone group; virtually no change in craving severity for olanzapine group Cocaine use: No significant differences in terms of cocaine craving over time Self-reported drug use: Olanzapine group reported on avg. significantly fewer ds of use than risperidone group (3 ds vs. 4.3 ds; Z= -2.27, P=0.02) PANSS positive and negative subscales: Severity decreased over time on positive subscale for both groups (Z= -2.53, P=0.01) but no significant between-group differences (Z= 0.49, P=0.62) Severity did not decrease significantly over time for negative subscale (Z=0.34, P=0.73) HAM-D Mean scores at study end were approximately 7 points for both groups; no significant difference between groups in mean change from baseline (olanzapine 0.14 [0.91], risperidone 0.03 [0.70]; t=.031, df=20, P=0.76) AIMS Worsening of abnormal movements: olanzapine=0, risperidone=1 Improvement of abnormal movements: olanzapine=3, risperidone=4
Alvarez, 2006 RCT, open-label Outpatients	NR/NR/250	87/12/235 efficacy; 247 safety	SANS summary score, mean change from baseline: O -6.0 v R -4.7; P=0.0151; effect size 0.34 Affective flattening, mean change from baseline: O -9.1 v R -6.5; P=0.0065; effect size 0.39 Speech difficulty, mean change from baseline: O -5.2 v R -4.2; P=0.0747; effect size 0.22 Avolition/apathy, mean change from baseline: O -4.7 v R -3.5; P=0.0283; effect size 0.03 Anhedonia/unsociability, mean change from baseline: O -4.8 v R -3.5; P=0.1216; effect size 0.26 Attention, mean change from baseline: O -3.6 v R -2.6; P=0.1106; effect size 0.34 SANS composite, mean change from baseline: O -27.4 v R -20.4; P=0.0183; effect size 0.35 SAPS summary score and SAPS composite score changes favored olanzapine (P=0.0207 and P=0.0115 respectively) CGI score significantly favored olanzapine (P=0.0082) No SS difference in Calgary Depression Score (P=0.9745)

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Adverse effects reported
Akerele, 2007 RCT	Sedation: olanzapine 54%, risperidone 77% No WDs in either group due to AEs
Alvarez, 2006 RCT, open-label Outpatients	Percentage of pts experiencing any AE: O 62.9% (n=78) v R 72.4% (n=89); P=NS Mean weight gain: O 3.8 kg (SD 6.1) v R 2.1 kg (SD 6.0) Proportion of pts with weight increase >7%: O 40.7% (n=35) v R 17.3% (n=13); P=0.0012 Specific AEs: O v R Anxiety: 12.1% (n=15) v 13.8% (n=17); P=0.6866 Insomnia: 6.5% (n=8) v 13.8% (n=17); P=0.0549 Tremor: 5.6% (n=7) v 13.8% (n=17); P=0.0301 Libido decrease: 5.6% (n=7) v 6.5% (n=8); P=0.7775 Akathisia: 1.6% (n=2) v 8.9% (n=11); P=0.0099 Somnolence: 4.0% (n=5) v 6.5% (n=8); P=0.3844 Headache: 5.6% (n=7) v 4.1% (n=5); P=0.5636 Weight increase: 6.5% (n=8) v 2.4% (n=3); P=0.1264 Hypertension: 5.6% (n=7) v 3.3% (n=4); P=0.3620 Appetite increased: 6.5% (n=8) v 1.6% (n=2); P=0.1023 Muscle rigidity: 1.6% (n=2) v 6.5% (n=8); P=0.596 Sexual dysfunction: 0.8% (n=1) v 5.7% (n=7); P=0.0357

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Extrapyramidal symptoms
Akerele, 2007 RCT	NR
Alvarez, 2006 RCT, open-label Outpatients	Treatment emergent and worsening of pre-existing EPS based on UKU questionnaire affected 28.9% (n=35) of olanzapine and 50.4% (n=61) of risperidone patients (P=0.0006) Specific symptoms: Rigidity: O 5% (n=6) v R 25.6% (n=31); p<0.001 Hypokinesia/akinesia: O 10.7% (n=13) v R 24.0% (n=29); P=0.0103 Akathisia: O 7.4% (n=9) v R 18.2% (n=22); P=0.0198

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Total withdrawals; withdrawals due to adverse events	Comments
Akerele, 2007 RCT	12 total WD 0 due to AE	
Alvarez, 2006 RCT, open-label Outpatients	72 total WD 10 due to AEs	

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Eligibility criteria	Interventions (drug, dose, duration)	Allowed other medications	Age Gender Ethnicity	Other population characteristics
Apiquian, 2003 Mexico Mexican First-Episode Psychotic Study	Between 18 and 45 yr old and met DSM-IV criteria for schizophrenia, schizoaffective or provisional schizophreniform disorders; if they were on their first psychiatric admission due to psychosis (with a maximum duration of illness of 5 yr) and had a baseline Positive and Negative Syndrome Scale (PANSS) positive syndrome score greater than 17 points with two items scoring at least 4 Exclusion- had received treatment for a period longer than 1 month with an equivalent dose of 5 mg/d haloperidol, if they had concomitant medical or neurological illness, current substance abuse or a history of substance dependence, history of bipolar disorder; high risk for suicide or were agitated.	Risperidone (1 mg/d), olanzapine (5 mg/d) or haloperidol (1 mg/d). 6 mos	Biperiden and benzodiazepines	Mean age 25.5 yrs 73.8% male Ethnicity: NR	Schizophrenia (61.9% n=26), schizoaffective disorder (16.7%, n=7) and schizophreniform disorder, provisional (21.4%)
AstraZeneca D1444C00133, 2006 DB RCT Multicenter (40 sites) in U.S.	Inclusion: acutely ill male and females aged 18-65 diagnosed with DSM-IV schizophrenia; with PANSS total score >=70 and CGI-S >=4.	5 treatment groups (double-dummy): Quetiapine SR: 400 mg/d, 600 mg/d, 800 mg/d Quetiapine IR: 800 mg/d P 6 wks duration	NR	Mean age 41 28.5% female 32.5% Caucasian 58.4% Black 1.3% Asian	82.7% paranoid subtype 14.5% undifferentiated subtype

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Number screened/ eligible/ enrolled	Withdrawn/ Lost to follow-up/ Analyzed	Results
Apiquian, 2003 Mexico Mexican First-Episode Psychotic Study	NR/NR/36	12/NR/30	Mean scores at endpoint Haloperidol vs. Risperidone vs. Olanzapine Total 38 vs. 65.7 vs. 38.5 Positive 7.4 vs. 13.3 vs. 8.4 Negative 11.5 vs. 17.3 vs. 10.8 CDSS 1.6 vs. 4.3 vs. 0.4
AstraZeneca D1444C00133, 2006 DB RCT Multicenter (40 sites) in U.S.	Screened NR Eligible NR 565 enrolled	232 (42.6%) withdrew Lost to followup NR 544 (96.2%) analyzed	P vs Quetiapine SR 400 mg vs SR 600 mg vs SR 800 mg vs IR 800 mg/d: PANSS total score, LS mean change from baseline: -12.1 vs -13.8 vs -16.8 vs -14.8 vs -15.0 Quetiapine SR at each of the 3 doses and quetiapine IR 800 mg/d were not statistically superior to P. PANSS response, % of patients responding (>=30% improvement in PANSS total score): 20.7 vs 19.5 vs 26.7 vs 23.6 vs 22.9 CGI-S, LS mean change from baseline: -0.5 vs -0.6 vs -0.6 vs -0.6 vs -0.6 CGI-I, % of patients showing improvement (defined as much improved, improved, and minimally improved): 56.8 vs 65.5 vs 67.3 vs 62.7 vs 61.5. On improvement there was no superiority to P for any of the quetiapine dose groups. No differences between quetiapine IR 800 mg/d and P on any outcome.

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Adverse effects reported
Apiquian, 2003 Mexico Mexican First-Episode Psychotic Study	NR
AstraZeneca D1444C00133, 2006 DB RCT Multicenter (40 sites) in U.S.	P vs Quetiapine SR 400 mg vs SR 600 mg vs SR 800 mg vs IR 800 mg/d, % of group: Dry mouth: 2.6 vs 21.1 vs 17.1 vs 17.7 vs 16.5 Sedation: 9.4 vs 21.1 vs 17.1 vs 13.3 vs 21.7 Somnolence: 2.6 vs 16.7 vs 10.5 vs 13.3 vs 14.8 Dizziness: 6.8 vs 12.3 vs 9.5 vs 7.1 vs 9.6 Headache: 15.4 vs 10.5 vs 6.7 vs 10.6 vs 8.7 Constipation: 7.7 vs 7.9 vs 4.8 vs 8.0 vs 7.8 Dyspepsia: 10.3 vs 7.9 vs 3.8 vs 1.8 vs 0.9 Arthralgia: 1.7 vs 6.1 vs 0 vs 1.8 vs 1.7 Psychotic disorder: 4.3 vs 6.1 vs 3.8 vs 1.8 vs 1.7 Agitation: 6.0 vs 5.3 vs 5.7 vs 2.7 vs 3.5 Fatigue: 0 vs 3.5 vs 4.8 vs 2.7 vs 5.2 Nausea: 8.5 vs 3.5 vs 6.7 vs 6.2 vs 4.3 Schizophrenia: 1.7 vs 3.5 vs 5.7 vs 5.3 vs 4.3 Diarrhea: 1.7 vs 1.8 vs 1.9 vs 5.3 vs 6.1 Stomach discomfort: 2.6 vs 1.8 vs 1.0 vs 2.7 vs 5.2 Vomiting 5.1 vs 1.8 vs 3.8 vs 7.1 vs 2.6

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Extrapyramidal symptoms
Apiquian, 2003 Mexico Mexican First-Episode Psychotic Study	Haloperidol vs. Risperidone vs. Olanzapine mean BAS 0 vs. 0.6 vs. 0.4 mean AIMS 0.3 vs. 0 vs. 0.1
AstraZeneca D1444C00133, 2006 DB RCT Multicenter (40 sites) in U.S.	A slight increase in EPS-related AEs occurred in quetiapine SR 800 mg/d and IR 800 mg/d compared with P. No other details specified.

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Total withdrawals; withdrawals due to adverse events	Comments
Apiquian, 2003 Mexico Mexican First-Episode Psychotic Study		
AstraZeneca D1444C00133, 2006 DB RCT Multicenter (40 sites) in U.S.	232 WDs; 60 withdrew due to AE	

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Eligibility criteria	Interventions (drug, dose, duration)	Allowed other medications	Age Gender Ethnicity	Other population characteristics
AstraZeneca, 2010 5077IL/0089 RCT, Open-label multi-center USA	18-65 years, DSM IV schizophrenia or schizoaffective disorder, qualifying Lens Opacities Classification System II lens opacity score assessment	Quetiapine titrated over 8 days to a flexible dosing range of 200-800 mg/d, in 2 or 3 doses/d Risperidone titrated over 8 days to a flexible dosing range of 2-8 mg/d, in 1 or doses/d	NR	Age: approximately 40 y Gender: approximately 40% female Ethnicity: approximately 50% caucasian, 40% black	"Representative of general schizophrenia or schizoaffective disorder population"
AstraZeneca, Data on File, Study D1444C00132 DB RCT	Acutely ill male and female patients, 18 to 65 ys of age, diagnosed with schizophrenia as stated in DSM-IV; PANSS total score of at least 70 and a CGI Severity of Illness score of at least 4 at randomization	Quetiapine SR 400 mg/d, 600 mg/d and 800 mg/d, quetiapine IR 400 mg/d and P 6 wks	NR	P vs Quetiapine SR 400 vs 600 vs 800 vs Quetiapine IR 400 Mean age (SD): 34.1 (12.1) vs 34.1 (9.6) vs 34.2 (9.9) vs 34.4 (10.3) vs 34.4 (10.2) Male: 58.3% vs 70.3% vs 55.0% vs 59.8% vs 58.0% Caucasian: 59.1% vs 56.8% vs 59.5% vs 60.7% vs 59.7% Black: 4.3% vs 4.5% vs 3.6% vs 4.3% vs 5.9% Oriental: 36.5% vs 38.7% vs 36.0% vs 35.0% vs 34.5% Other: 0 vs 0 vs 0.9% vs 0	P vs Quetiapine SR 400 vs 600 vs 800 vs Quetiapine IR 400 DSM-IV diagnosis, schizophrenic subtype n (%) --Disorganized: 5 (4.3) vs 8 (7.2) vs 5 (4.5) vs 5 (4.3) vs 2 (1.7) --Catatonic: 1 (0.9) vs 2 (1.8) vs 0 vs 1 (0.8) --Paranoid: 79 (68.7) vs 71 (64.0) vs 72 (64.9) vs 75 (64.1) vs 88 (73.9) --Undifferentiated: 30 (26.1) vs 30 (27.0) vs 34 (30.6) vs 37 (31.6) vs 28 (23.5) Mean PANSS (SD): 96.2 (13.3) vs 95.8 (13.9) vs 96.8 (14.1) vs 97.3 (14.7) vs 96.5 (16.0) Mean CGI severity of illness (SD): 4.9 (0.7) vs 4.9 (0.7) vs 4.9 (0.7) vs 5.0 (0.7) vs 4.9 (0.6)

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Number screened/ eligible/ enrolled	Withdrawn/ Lost to follow-up/ Analyzed	Results
AstraZeneca, 2010 5077IL/0089 RCT, Open-label multi-center USA	NR/1837/1098	732/NR/329 primary analysis; 1082 safety	Efficacy: Quetiapine vs. Risperidone: First relapse (%) by 24 months: 30.5% vs. 26.0% mean PANSS, CGI, Quality of Life Enjoyment and Satisfaction Questionnaire, and Personal Evaluation of Transitions in Treatment; All NSD between treatment groups Risk differences for increase in lens opacity, difference vs. risperidone (95%CI): Cortical opacification: -0.035 (-0.072 to 0.001), p=0.063 Nuclear opalescence: -0.012 (-0.028 to 0.004), p=0.165 Posterior subscapsular opacification: -0.017 (-0.055 to 0.022), p=0.396 Any: -0.058 (-0.111 to -0.005), p=0.035
AstraZeneca, Data on File, Study D1444C00132 DB RCT	NR/NR/588	142/NR/573	P vs Quetiapine SR 400 vs 600 vs 800 vs Quetiapine IR 400 (P value is vs P) LS mean from baseline in PANSS total score: -18.8 vs -24.8 (P<0.05) vs -30.9 (P<0.001) vs -31.3 (P<0.001) vs -26.6 (P<0.01) PANSS response: 30.4% vs 44.1% (P<0.05) vs 60.4% (P<0.001) vs 56.4% (P<0.001) vs 52.9% (P<0.01) LS mean from baseline in CGI Severity of Illness score: -1.0 vs 1.3 vs -1.5 (P<0.001) vs -1.6 (P<0.001) vs -1.3 (P<0.05) CGI Global Improvement score, % of patients showing improvement: 60.0% vs 73.9% (P<0.05) vs 79.3% (P<0.01) vs 76.9% (P<0.01) vs 75.6% (P<0.05) Quetiapine SR 600 mg/d and SR 800 mg/d groups demonstrated significant improvement compared to P for the PANSS Negative symptom subscale score and PANSS depression cluster score at d 42

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Adverse effects reported
AstraZeneca, 2010 5077IL/0089 RCT, Open-label multi-center USA	Quetiapine vs. Risperidone: Any AE (%): 93.0 vs. 88.7 AE with outcome death (%): 1.2 vs. 0.4 SAE (%): 25.8 vs. 23.0 Suicide, n: 1 vs. 1 QT prolongation (%): 0.7 vs. 0 Diabetes (%): 3.1 vs. 5.2 Neutropenia or Agranulocytosis (%): 1.0 vs. 1.8 Suicidality (%): 4.8 vs. 4.6 Somnolence (%): 50.0 vs. 23.8 >7% weight gain (%): 21.9 vs. 20.7
AstraZeneca, Data on File, Study D1444C00132 DB RCT	P vs Quetiapine SR 400 vs 600 vs 800 vs Quetiapine IR 400 AEs n (%): 50 (42.4) vs 51 (45.1) vs 62 (54.9) vs 56 (46.3) vs 66 (53.7) Serious AEs n (%): 2 (1.7) vs 2 (1.8) vs 3 (2.7) vs 1 (0.8) vs 6 (4.9) Death: 0 vs 0 vs 0 vs 0 vs 1 Insomnia n (%): 23 (19.5) vs 13 (11.5) vs 7 (6.2) vs 9 (7.4) vs 13 (10.6) Somnolence n (%): 2 (1.7) vs 8 (7.1) vs 10 (8.8) vs 14 (11.6) vs 9 (7.3) Dizziness n (%): 1 (0.8) vs 6 (5.3) vs 10 (8.8) vs 8 (6.6) vs 7 (5.7) Headache n (%): 8 (6.8) vs 6 (5.3) vs 4 (3.5) vs 4 (3.3) vs 2 (1.6) Sleep disorder n (%): 11 (9.3) vs 4 (3.5) vs 6 (5.3) vs 4 (3.3) vs 6 (4.9) Constipation n (%):5 (4.2) vs 2 (1.8) vs 6 (5.3) vs 5 (4.1) vs 1 (0.8)

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Extrapyramidal symptoms
AstraZeneca, 2010 5077IL/0089 RCT, Open-label multi-center USA	Quetiapine vs. Risperidone: EPS (%): 12.5 vs. 21.4 Tardive dyskinesia (%): 0.9 vs. 1.0
AstraZeneca, Data on File, Study D1444C00132 DB RCT	"Incidence of EPS-related AEs was consistent across the quetiapine SR and IR groups and similar to P" Few patients using anticholinergic medication for symptoms of EPS in all groups Overall the assessment of parkinsonian and akathisia symptomatology as assessed by mean SAS and BARS scores indicated that quetiapine treatments were similar to P, and an improvement or no worsening in symptomatology in all active treatment groups

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Total withdrawals; withdrawals due to adverse events	Comments
AstraZeneca, 2010 5077IL/0089 RCT, Open-label multi-center USA	Total: 732 Due to AE: 195	
AstraZeneca, Data on File, Study D1444C00132 DB RCT	P vs Quetiapine SR 400 vs 600 vs 800 vs Quetiapine IR 400 Total WD: 33 vs 30 vs 21 vs 31 vs 27 WD due to AEs: 3 (2.5%) vs 6 (5.3%) vs 3 (2.7%) vs 3 (2.5%) vs 6 (4.9%)	

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Eligibility criteria	Interventions (drug, dose, duration)	Allowed other medications	Age Gender Ethnicity	Other population characteristics
Atmaca, 2003 Inpatients	Schizophrenia Exclusion: Co-morbid Axis I disorders, severe physical illness, history of alcohol/substance abuse, history of lipid-lowering treatment, presence of endocrinologic disorder, autoimmune, pulmonary, infectious diseases, neoplasms.	6 week study quetiapine(N=14): olanzapine(N=14): risperidone(N=14): clozapine(N=14): control group w/no treatment(N=11):	Biperiden hydrochloride, benzodiazepines	Mean age: 30.2 ys 54.6% Female Ethnicity NR	29% psychotropic drug naïve
Azorin, 2001 DB, multicenter (France and Canada)	Diagnosis: schizophrenia (DSM-IV), Treatment-resistant: severe, chronic disease and poor response to previous neuroleptic drugs (no period of good functioning for ≥ 24 mos despite use of two antipsychotic drugs; current episode without significant improvement for ≥ 6 mos despite use of antipsychotic equivalent to haloperidol, 20 mg, for ≥ 6 wks; total BPRS ≥ 45; CGI ≥ 4)	clozapine 200–900 mg/d Mean dose 597.5 mg/d; risperidone 2–15mg/d Mean dose 8.3 mg/d individual dose titration Duration: 12 wks	NR	Mean age 37.8 ys 71% male Ethnicity NR	Mean PANSS score: 111 Mean BPRS score: 62 Mean CGI-S score: 5.5
Bai, 2006 Single-blind, RCT, single center (Taiwan)	Symptomatic stable hospitalized patients 18-65 w/ DSM IV diagnosis of schizophrenia treated for 3 mos with oral risperidone, good health Exclusion due to neuroleptic malignant syndrome, organic disease of the CNS and seizure disorder; violent behavior; suicide risk.	Oral risperidone: 2-6 mg/d Long-acting risperidone: 20-50 mg every 2 wks Duration: 12 wks active treatment	Anticholinergics and benzodiazepines	Mean age: 46.4 Male: 50% Ethnicity: NR	Risperidone long-acting injection vs oral risperidone PANSS Total 65.2 $\pm$ 17.6 vs 70.2 $\pm$ 19.6 CGI-S 3.96 $\pm$ 0.20 vs 3.92 $\pm$ 0.28 GAF 64.4 $\pm$ 10.4 vs 59.6 $\pm$ 11.4

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Number screened/ eligible/ enrolled	Withdrawn/ Lost to follow-up/ Analyzed	Results
Atmaca, 2003 Inpatients	NR/NR/71	NR/NR/64	Mean scores changes at Endpoint: Quetiapine: Body weight: 4.41; (p<.05), PANSS score: (p<.01), BMI: (P=.26) Olanzapine: Body weight: 8.92; (p<.01), PANSS score: (p<.001), BMI: (p<.05) Risperidone: Body weight: 0.54; (P=.91), PANSS score: (p<.01), BMI: (P=.71) Clozapine: Body weight: 6.52; (p<.01), PANSS score: (p<.01), BMI: (p<.05) No treatment/control group: Body weight: -1.32; (P=.82), PANSS score: (p<.01), BMI: (P=.62)
Azorin, 2001 DB, multicenter (France and Canada)	NR/NR/273 olanzapine = 138 risperidone = 135	72/3/256	Mean change from Baseline to 12 wks (ITT) clozapine/risperidone: BPRS: -23.3/-17.7 (ANCOVA p = 0.006) CGI-S: -1.8/-1.4 (p = 0.008) PANSS total:-37.5/-29.9 (p = 0.02) PANSS positive: -10.4/-8.3 (p = 0.02) PANSS negative: -8.8/-7.1 (p = 0.06) PANSS general psychopathology: -18.3/-14.1 (p = 0.008) Calgary Depression Scale: -3.2/-2.3 (p = 0.10) Psychotic Anxiety Scale: --18.5/-13.5 (p = 0.02) Psychotic Depression Scale: -24.8/-20.2 (p = 0.15) Responders (Kane criteria): 48.4%/43.1% (p<0.38) Improvement in BPRS of 20%, 30%, 40%: SS C>R, 50% NS
Bai, 2006 Single-blind, RCT, single center (Taiwan)	NR/NR/50	1/NR/49	Change from baseline - LA risperidone vs. regular risperidone Total PANSS -0.16 vs. -2.4 P=NS Negative -0.64 vs. 0.08 P=NS Positive 0.72 vs. -1.24 P=0.022 CGI-S -0.08 vs. -0.04 P=NS Side effects UKU -2.12 vs. -0.13 P=0.037

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Adverse effects reported
Atmaca, 2003 Inpatients	NR
Azorin, 2001 DB, multicenter (France and Canada)	Adverse Effects Reported: clozapine 78.7% risperidone 82.8% (P=0.44) AEs SS more frequent: clozapine: convulsions, dizziness, sialorrhea, tachycardia, somnolence risperidone: EPS, insomnia, dry mouth
Bai, 2006 Single-blind, RCT, single center (Taiwan)	See results

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Extrapyramidal symptoms
Atmaca, 2003 Inpatients	NR
Azorin, 2001 DB, multicenter (France and Canada)	AEs SS more frequent: clozapine: convulsions, dizziness, sialorrhea, tachycardia, somnolence risperidone: EPS, insomnia, dry mouth
Bai, 2006 Single-blind, RCT, single center (Taiwan)	Risperidone long-acting injection vs Oral risperidone change from BL AIMS: -3.20 ± 4.7 vs -4.36 ± 3.9 BARN:-0.04 ± 1.74 vs -0.2 ± 1.11 SAS: -3.50 ± 5.57vs -2.95 ± 5.82

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Total withdrawals; withdrawals due to adverse events	Comments
Atmaca, 2003 Inpatients	NR; NR	
Azorin, 2001 DB, multicenter (France and Canada)	Overall 72 (26%) Due to AE: 28 (10%) clozapine: 11.6%, risperidone 10.3%	BPRS score extracted from PANSS score
Bai, 2006 Single-blind, RCT, single center (Taiwan)	1 and 1	

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Eligibility criteria	Interventions (drug, dose, duration)	Allowed other medications	Age Gender Ethnicity	Other population characteristics
Bellack, 2004 DB, substudy within larger trial	Patients with schizophrenia or schizoaffective disorder, including those with adjunctive medications or history of poor compliance and substance abuse; at least two previous trials of a conventional antipsychotic at doses equivalent to 600 (1st trial) and 250-500 (2nd trial) mg/d chlorpromazine; and a rating of at least moderate on BPRS or SANS subscales	clozapine: 500mg/d; max 800 mg/d after 5 wks risperidone: 6 mg/d, max 16 mg/d after 5 wks Duration: 29 wks	Not specified	Not specified for full study population. Of 72 subjects assessed for social competence at baseline: mean age 41.4 ys 73% male 58% Caucasian	Illness
Bender, 2006 (Companion to Naber 2005) DB, RCT - sub sample	Inclusion- considered for clozapine therapy, i.e. they had a documented history that they had either failed to respond to at least one antipsychotic other than clozapine and olanzapine or had experienced intolerable side-effects during these prior antipsychotic treatments, 18 to 65 ys and a normalized BPRS score of at least 24 at baseline. Exclusion- pregnant or lactating and a history of substance abuse or dependence within the past 3 mos and serious, unstable somatic illnesses, previous use of olanzapine and/or clozapine	subsample of 54 patients from 114 [olanzapine (n = 30) vs. clozapine (n = 24) for 24 wks	benzodiazepines for agitation (lorazepam up to 8 mg/d, diazepam up to 60 mg/d, oxazepam up to 100 mg/d, temazepam up to 30 mg/d) or chloral hydrate up to 1500 mg/d for insomnia, and biperiden up to 6 mg/d for treatment-emergent EPS.	Mean age 33 ys 67% male Ethnicity: NR	Age of onset 25.2 ys

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Number screened/ eligible/ enrolled	Withdrawn/ Lost to follow-up/ Analyzed	Results
Bellack, 2004 DB, substudy within larger trial	NR/NR/107 enrolled Number per group NR	Total loss to f/u: 47% (MASC), 66% (WCST) Loss of efficacy: 36% Subject WD 32% Adverse reactions 17% Number of WDs varied and crossover by test administered.	Symptoms: Change in CGI: risperidone: -1.42 (95%CI -1.93 to -0.99); clozapine: -1.48 (95%CI -2.11 to -0.99) WD due to lack of efficacy: 38% of risperidone 15% of clozapine (SS different, p-value NR) Social Skill and Problem Solving: At week 29: risperidone: SS decrease in perseverative errors clozapine: SS decrease in verbal score Change in Effect Size for verbal behavior: risperidone: 0.33 (95%CI: 0.01to 0.79); clozapine: -0.037 (95%CI -0.47 to 0.30).
Bender, 2006 (Companion to Naber 2005) DB, RCT - sub sample	NR/NR/54	23/NR/31	Schizophrenia symptoms, extrapyramidal side-effects and cognitive performance improved significantly in the course of either drug treatment. Stroop test performance and Tower of London planning time improved significantly over 26 wk compared to baseline and 4-wk follow-up assessment while Wisconsin Card Sorting and Tower of London execution time improved significantly after 4 wk with no further improvement after 26 wk. Improved executive function was not related to improving positive symptoms and easing extrapyramidal side-effects, thus indicative of a primary treatment effect of either antipsychotic. However, Stroop reaction time improved with olanzapine while clozapine had a stronger effect on improving negative symptoms, thus suggestive of a differential drug effect.

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Adverse effects reported
Bellack, 2004 DB, substudy within larger trial	NR
Bender, 2006 (Companion to Naber 2005) DB, RCT - sub sample	NR

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Extrapyramidal symptoms
Bellack, 2004 DB, substudy within larger trial	NR
Bender, 2006 (Companion to Naber 2005) DB, RCT - sub sample	SAS Olanzapine vs. clozapine n=31 Baseline 0.5(0,5) vs.0.6(0.4) 26 wks 0.2(0.2) vs 0.1 (0.1)

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Total withdrawals; withdrawals due to adverse events	Comments
Bellack, 2004 DB, substudy within larger trial	17% of WD due to AE's but numbers per drug not clear	While some differences are apparent between drugs on results for verbal score and problem solving, changes were not considered clinically important by authors. Lack of ITT, low power, and poor reporting make result difficult to interpret or generalize.
Bender, 2006 (Companion to Naber 2005) DB, RCT - sub sample	23 WD	Completers analysis.

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Eligibility criteria	Interventions (drug, dose, duration)	Allowed other medications	Age Gender Ethnicity	Other population characteristics
Bitter, 2004 RCT, Multicenter (Hungary & South Africa)	Hospitalized patients 18-65 yrs, with schizophrenia; minimum BPRS score (items 1-7) of 42, and have failed to respond to standard treatment with typical antipsychotics (at least 1 trial of 4-6 wks, 400-600mg chlorpromazine or equivalents) due to insufficient effectiveness or intolerable side effects	180 18 wks	Episodic use of benzodiazepines not allowed, stable doses of chronically used benzodiazepines allowed with max doses, anticholinergic meds to treat new or worsening EPS allowed but all other uses not allowed	Mean age 38 48% white 60% male	NR, stated to have NS differences
Bondolfi, 1998 DB, RCT, single-center Inpatients	Chronic schizophrenia (DSM-II-R); Treatment-resistant: failed to respond or intolerant of ≥ 2 different classes of antipsychotic drugs in appropriate doses for ≥ 4 wks each; total PANSS 60–120	clozapine: 150–400 mg/d mean 291 mg/d; risperidone: 3–12 mg/d mean 6.4 mg/d Duration: 8 wks	lorazepam and oxazepam (sleep induction), biperiden and procyclidine (EPS), clothiapine (emergency treatment) as required	Mean age: 37.2 ys 70.9% Male Ethnicity NR	Mean age at onset: 23 ys Mean age at first hospitalization: 26 ys Mean # hospitalizations 6.1 Mean # mos in hospital: 36.6 100% inpatient Schizophrenia type: paranoid: 58% disorganized: 27.9% undifferentiated: 8.1% residual: 5.8%

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Number screened/ eligible/ enrolled	Withdrawn/ Lost to follow-up/ Analyzed	Results
Bitter, 2004 RCT, Multicenter (Hungary & South Africa)	189/150/147	7/NR/140 for efficacy assessments 62/NR/147 for safety assessments	Change in PANSS total: clozapine -37.9 olanzapine -37.7 (NS) Change in PANSS positive clozapine -11.8 olanzapine -11.7 (NS) Change in PANSS negative clozapine -7.7 olanzapine -7.6 (NS) Change in CGI-S clozapine -1.5 olanzapine -1.4 (NS) Kane criteria: clozapine 60.8% olanzapine 57.9% (NS) PANSS criteria for Response: NS differences between groups Discontinue study due to lack of efficacy: clozapine 4.2% olanzapine 5.3%
Bondolfi, 1998 DB, RCT, single-center Inpatients	NR/NR/86 clozapine: 43 risperidone: 43	18/0/86	Clozapine vs risperidone (p value) Proportion with 20% improvement: 67% vs 65% (p = 0.30) Mean Change at 8 wks (ITT) All NS PANSS total: -23.2 vs -27.4 PANSS positive: -6.7 vs -8.3 PANSS negative: -6.1 vs -6.0 PANSS general psychopathology: -10.4 vs 12.2 Survival Analysis indicated risperidone patients responded faster than clozapine patients

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Adverse effects reported
Bitter, 2004 RCT, Multicenter (Hungary & South Africa)	clozapine, olanzapine, p-value Weight gain: 9.5%, 9.2%, P=0.958 Mean change in weight: NS Somnolence: 14.9%, 2.6%, P=0.008 Dizziness: 8.1%, 1.3%, P=0.049 Hypersalivation: 6.8%, 1.3%, P=0.089 Postural hypotension: 5.4%, 1.3%, P=0.163 Back Pain 0.0%, 5.3%, P=0.045 NS difference on CBC parameters EPS: Baseline to Endpoint on SAS, AIMS, or HAS: NS difference Treatment emergent akathisia (HAS >/= 3) or dyskinesia: NS Difference Treatment emergent parkinsonism: NR in either group
Bondolfi, 1998 DB, RCT, single-center Inpatients	Adverse effects reported, risperidone vs clozapine: Asthenia/lassitude/increased fatigability: 28% vs 51% (p<0.05) Weight gain: 23% vs 37% (P=0.24) Sleepiness/sedation: R: 30% vs C: 47% (NS) Failing memory: R: 21% vs C: 35% (NS) Concentration difficulties: R: 16% vs C: 26% (NS) Increased duration of sleep: R: 19% vs C: 21% (NS) Nausea/vomiting: R: 16% vs C: 21% (NS) Orthostatic dizziness: R: 12% vs C: 21% (NS) Reduced duration of sleep: R: 14% vs C: 7% (NS) Diminished sexual drive: R: 9% vs 5% (NS)

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Extrapyramidal symptoms
Bitter, 2004 RCT, Multicenter (Hungary & South Africa)	EPS: Baseline to Endpoint on SAS, AIMS, or HAS: NS difference Treatment emergent akathisia (HAS >/= 3) or dyskinesia: NS Difference Treatment emergent parkinsonism: NR in either group
Bondolfi, 1998 DB, RCT, single-center Inpatients	EPS: "No significant difference between the groups at endpoint in the mean total ESRS scores, the different cluster scores, or the different cluster scores on the parkinsonism scales" - data NR Proportion scoring 0 (clozapine vs risperidone) at week 8 on ESRS: Total with 0 on ESRS total score: 37% vs 54% (NS) % with 0 on ESRS parkinsonism score: 37% vs 61% (p = 0.03) % with 0 on ESRS dystonia: 98% vs 95% (NS) % with 0 on ESRS dyskinesia: 84% vs 84% (NS)

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Total withdrawals; withdrawals due to adverse events	Comments
Bitter, 2004 RCT, Multicenter (Hungary & South Africa)	Overall: 85 (58%) Due to AE: clozapine 7 olanzapine 7	Refractoriness includes intolerance, does not use Kane criteria.
Bondolfi, 1998 DB, RCT, single-center Inpatients	Overall 18 (21%) Due to AE: 2.3% (2.3% in each group)	Differences at baseline: # mos in hospital, PANSS positive; analyses presented focus on within group differences more than between group comparisons. Dose of clozapine low.

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Eligibility criteria	Interventions (drug, dose, duration)	Allowed other medications	Age Gender Ethnicity	Other population characteristics
Breier, 1999 DB, RCT, single-center (NIH Clinical Center) Unclear if inpatient	Diagnosis: schizophrenia (DSM-IV); Partial response to neuroleptic drugs: (i) history of residual positive and/or negative symptoms after ≥ 6 week trial of therapeutic dose of neuroleptic agent; (ii) at least minimum level of positive (4 positive BPRS items > 8) and/or negative (SANS score > 20) symptoms at time of evaluation for study; (iii) at least minimum level of positive and negative symptoms after prospective trial of ≥ 2 wks of fluphenazine, 20 mg/d (range 10–30 mg/d)	clozapine: 200–600 mg/d; fixed dose mean 403.6 mg/d; risperidone: 2–9 mg/d; fixed dose mean 5.9 mg/d Duration: 6 wks fluphenazine treatment for ≥ 2 wks; then, 66% patients underwent drug-free period	benztropine mesylate (EPS) as required	Mean, age: 35.0 ys, range 18–55 ys 66% male Ethnicity NR	History: duration of illness, about 12.5 ys; chronic schizophrenia; partial response to neuroleptic drugs*

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Number screened/ eligible/ enrolled	Withdrawn/ Lost to follow-up/ Analyzed	Results
Breier, 1999 DB, RCT, single-center (NIH Clinical Center) Unclear if inpatient	NR/NR/29	NR/NR/29	Mean Change in score (clozapine/risperidone, *P* value) BPRS total:-6.36/-4.73 (P= 0.19) BPRS Positive symptoms: -2.5/-1.0 (P= 0.04) BPRS Responders (20% improvement): 35.7%/20% (P= 0.34) SANS: -2.14/4.4 (P= 0/54) HAM-D: -4.5/-1.92 (P= 0.25)

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Adverse effects reported
Breier, 1999 DB, RCT, single-center (NIH Clinical Center) Unclear if inpatient	Mean change in SAR-S clozapine: -0.93 risperidone: +0.26 (P=0.05) Mean Change in serum Prolactin: clozapine: -41.1ng/ml risperidone: +11.8 (P=0.001) Growth Hormone, cortisol: changes NS

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Extrapyramidal symptoms
Breier, 1999 DB, RCT, single-center (NIH Clinical Center) Unclear if inpatient	Clozapine vs risperidone: Simpson-Angus Rating Scale Mean Change: -8 vs 2, P=0.05

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Total withdrawals; withdrawals due to adverse events	Comments
Breier, 1999 DB, RCT, single-center (NIH Clinical Center) Unclear if inpatient	NR/NR	

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Eligibility criteria	Interventions (drug, dose, duration)	Allowed other medications	Age Gender Ethnicity	Other population characteristics
Breier, 2005 DB, parallel-group 28 week RCT, multicenter (Europe, North and South America) Inpatients and outpatients	Schizophrenia (DSM-IV); baseline score of 42 or higher on BPRS; score of 4 or higher on at least one positive symptom item of the Positive and Negative Syndrome Scale; score of 4 or higher on CGI	olanzapine: 5-20 mg/daily (mean: 15.27) ziprasidone 40-160 mg/d (mean: 115.96)	lorazepam (≤4 mg/d); benzodiazepine or hypnotic monotherapy during study period 2 (≤10 mg/d of diazepam equivalents recommended). Benztropine mesylate or biperiden up to 6 mg/d if EPS occurred or existed at visit 1.	mean age: O: 40.1 ± 11.6; Z: 38.2 ± 12.1; P=0.04 Gender (%) male: O: 180 (65%); Z: 172 (63.5%) Caucasian: 43.6% African descent 26.3% Hispanic: 22.6% Other: 7.5%	Mean Age at onset of disease ys: O: 23.9; Z: 22.8 Number of previous episodes, n O: 7; Z: 7.2 Baseline Positive and Negative Syndrome Scale total score: O: 99.8; Z: 102

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Number screened/ eligible/ enrolled	Withdrawn/ Lost to follow-up/ Analyzed	Results
Breier, 2005 DB, parallel-group 28 week RCT, multicenter (Europe, North and South America) Inpatients and outpatients	NR/NR/548	268 (discontinued) / 24/280 Lack of efficacy (O: 20 vs. Z 37 , P=0.02) and aggravation of psychosis (O: 4 vs. Z: 12, P=0.05)	SANS summary score, mean change from baseline: O -6.0 v R -4.7; P=0.0151; effect size 0.34 Affective flattening, mean change from baseline: O -9.1 v R -6.5; P=0.0065; effect size 0.39 Speech difficulty, mean change from baseline: O -5.2 v R -4.2; P=0.0747;

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Adverse effects reported
Breier, 2005 DB, parallel-group 28 week RCT, multicenter (Europe, North and South America) Inpatients and outpatients	Montgomery Asberg Depression Rating Scale: LOCF: Mean Chg in Score at 28 wk: O: (n=270) vs. Z: (n=260) (difference btw groups) -7.1 vs. -5.5 (p =0.05) 7.5 vs. 8.1 (p= NS) ---using Mixed-Effects Model Hamilton Anxiety Rating Scale: LOCF Mean Chg in Score at 28 wk O (n=270) vs. Z (n=261) -5.8 vs. -4.3 (p=0.002) 4.5 vs. 5.2, (p=NS)-using Mixed-Effects Model AE: Treatment-Emergent AE in 28 week: O: (n=277) ; Z: (n=271) AE: statistically different rates or occurred in at least 10%): O: % vs. Z: %; p Any: 75.1% vs. 80.4%; NS Headache, Anxiety, Anorexia, all NS Weight increase: 12.6% vs. 1.8%; <0.001 Appetite increase: 7.2% vs. 1.8%; 0.02 Insomnia: 6.9% vs. 22.1%; <0.001 Vomiting: 4% vs. 9.2%; 0.02 Dystonia: 0 vs. 2.2%; 0.02 Hypotension: 0 vs. 1.8%; 0.03 Weight (kg): LOCF: Mean Change in Value at 28 wk: O:(n=269) vs. Z:(n=260) (diff btw groups) 3.06 vs. -1.12 (p<0.001) Mean Fasting gluc. (mmol/L): LOCF: Mean Chg at 28 wk: O: (n=228) vs. Z: (n=219) 0.28 vs. -0.01 (NS) TC (mmol/L): LOCF: Mean Chg at 28 wk: O: (n=215) vs. Z: (n=203) 0.08 vs. -0.33 (p<0.002) HDL (mmol/L): LOCF Mean Chg at 28 wk: O: (n=212) vs. Z: (n=201) -0.06 vs. 0.02 (p<0.001) LDL (mmol/L): LOCF Mean Chg at 28 wk O: (n=204) vs. Z: (n=196) 0.02 vs. -0.27 (p=0.02) TG (mmol/L): LOCF Mean Chg at 28 wk O: (n=215) vs. Z: (n=203) 0.39 vs. -0.24 (p<0.001) Prolactin level (pmol): LOCF Mean Chg at 28 wk: O: (n=250) vs. Z: (n=241) 0.20 vs. 0.38 (NS) QTc interval (msec): LOCF Mean Chg at 28 wk: O: (n=270) vs. Z: (n=259) 4.81 vs. 5.58 (NS)

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Extrapyramidal symptoms
Breier, 2005 DB, parallel-group 28 week RCT, multicenter (Europe, North and South America) Inpatients and outpatients	Simpson-Angus Rating Scale: Mean Change in Score BL to Endpoint: O: (n=268) vs. Z: (n=260) Difference btw. groups: -1.16 vs. -0.82 (p=NS) Baseline to maximum: -0.05 vs. 0.62 (p<0.001) Barnes Rating Scale for Drug-Induced Akathisia, Mean Change in Score BL to Endpoint: O (n=270) vs Z (n=260) Difference btw. groups: -0.21 vs. -0.10 (p=0.04) Baseline to maximum: 0.19 vs. 0.30 (p=0.03) Abnormal Involuntary Movement Scale: Mean Change in Score BL to Endpoint: O (n=268) vs. Z (n=261) Difference btw. groups: -0.53 vs. -0.45 (p=NS) Baseline to maximum: 1.47 vs. 1.83 (p=0.01) Use of BZD: Z 53.5% vs. O: 40.4 %, p=0.003. More Z pts took BZD for 1-14 ds than O (22.9% vs. 14.8%, p=0.02) but not for durations >14 ds (30.6% vs. 25.6%, p=0.22). More Z pts than O pts received at least one dose of an anticholinergic (15.5% vs. 7.2%, p=0.003). More Z pts took an anticholinergic than O pts for 1-14 ds (8.9% vs. 1.4%, p<0.001 but not for duration > 14 ds (6.6% vs. 5.8%, p=0.73).

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Total withdrawals; withdrawals due to adverse events	Comments
Breier, 2005 DB, parallel-group 28 week RCT, multicenter (Europe, North and South America) Inpatients and outpatients	268 (discontinued) / 73 (O: 32, Z: 41)	Compliant with study drug regimen: O: 97.8% vs. Z 94.9%; p<0.001 Because there was a higher percentage of dropouts in the Z group, the analysis with the LOCF may have had a greater likelihood of detecting a SS difference in the case of smaller effect sizes that favor O.

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Eligibility criteria	Interventions (drug, dose, duration)	Allowed other medications	Age Gender Ethnicity	Other population characteristics
Buchanan 2012 DB RCT	Schizophrenia, Men and women 18 ys or older (primarily outpatients), PANSS score of 20 or greater, had to be clinically stable for 5 mos before screening.	Asenapine = 10 mg. Max dose. Olanzapine = 20 mg. Max dose. Duration: 26 wks	Anti-parkinsons medications	Mean Age: 43 Male = 26% Female = 74% Ethnicity: NR	Three deaths were reported in the EH study. (1) Committed suicide during initial cross-titration period. (1) Hospitalized with suspected tuberculosis and died of metastatic lung cancer. (1) Committed suicide during the 30-d follow-up period.
Byerly, 2008 DB RCT 5 Dallas County public mental health outpatient clinics	Outpatients (n=42, age ≥18 ys) with schizophrenia or schizoaffective disorder who experienced risperidone-associated sexual dysfunction.	Risperidone mean dose=4.1 mg (1.2) n=22 Quetiapine mean dose=290.0 mg(55.2) n=20 6 wks	Yes- antidepressants	Mean age 42.3 yrs 52.4% male Ethnicity NR	Risperidone vs. quetiapine ASEX total at baseline, M (S.D.) 22.4 (4.6) vs. 22.8 (5.1) PANSS total at baseline, M (S.D.) 78.2 (12.2) vs. 74.1 (12.2) PANSS total at week 6, M (S.D.) 72.1 (6.2) vs. 71.5 (6.2)

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Number screened/ eligible/ enrolled	Withdrawn/ Lost to follow-up/ Analyzed	Results
Buchanan 2012 DB RCT	"XX/XX*/949 *Need to find and download Figure A supplemental material to determine-- not provided with the pdf."	"XX/XX*/Asenapine: EH, N =216;WH, N = 234. Olanzapine: EH, N = 217, WH, N = 218). *Need to find and download Figure A supplemental material to determine -- not provided with the pdf."	Effectiveness:EH and WH core studies (LS Mean + SE), change from baseline, 26 weeks The 16-item Negative Symptom Assessment Scale (NSA-16) Total score: EH - Asenapine: -12.2 + 0.81, Olanzapine: -12.5 + 0.76 WH - Asenapine: -9.7 + 0.95, Olanzapine: -9.2 + 0.89 Quality of life scale: EH - Asenapine: 11.7 + 1.14, Olanzapine: 11.8 + 1.05 WH - Asenapine: 11.1 + 1.54, Olanzapine: 7.1 + 1.41 PANSS negative subscale: EH - Asenapine: 27 -7.1 + 0.38, Olanzapine: 26 -6.6 + 0.35 WH - Asenapine: -6.3 + 0.48, Olanzapine: -6.5 + 0.44 PANSS Marder factor for negative symptoms: EH - Asenapine: -8.0 + 0.40, Olanzapine: -7.4 + 0.37 WH - Asenapine: -7.0 + 0.48, Olanzapine: -6.7 + 0.45 PANSS Total score: EH - Asenapine: -13.6 + 0.93, Olanzapine: -14.2 + 0.87 WH - Asenapine: -11.6 + 1.14, Olanzapine: -13.8 + 1.07 PANSS positive subscale: EH - Asenapine: -0.1 + 0.23, Olanzapine: -1.0 + 0.23 WH - Asenapine: 0.1 + 0.28, Olanzapine: -0.9 + 0.28 PANSS Marder factor scores: 52-week completion rates: EH 84.3% , WH 66.3%, asenapine EH 89.0% , WH 80.9%, olanzapine
Byerly, 2008 DB RCT 5 Dallas County public mental health outpatient clinics	NR/NR/42	6/6/1936	ASEX at week 6 (SD) Risperidone 20.53 (5.78) vs. quetiapine 18.51 (5.69) P = 0.30

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Adverse effects reported
Buchanan 2012 DB RCT	EH and WH core studies, n (%) Treatment-emergent AEs: 180 (74.7) 165 (68.8) and 190 (77.9) 184 (82.1) Treatment-emergent SAEs: 26 (10.8) 14 (5.8) and 28 (11.5) 15 (6.7) Treatment-related AEs: 133 (55.2) 131 (54.6) and 158 (64.8) 137 (61.2) Treatment-related SAEs: 11 (4.6) 8 (3.3) and 9 (3.7) 7 (3.1) Treatment-emergent AEs reported by >5% of subjects: Insomnia: 38 (15.8) 26 (10.8) and 43 (17.6) 26 (11.6) Headache: 31 (12.9) 23 (9.6) and 33 (13.5) 23 (10.3) Somnolence: 30 (12.4) 27 (11.3) and 36 (14.8) 43 (19.2) Anxiety: 23 (9.5) 20 (8.3) and 26 (10.7) 16 (7.1) Dizziness: 9 (3.7) 5 (2.1) and 18 (7.4) 21 (9.4) Sedation: 7 (2.9) 9 (3.8) and 16 (6.6) 17 (7.6) Worsening of schizophrenia: 17 (7.1) 9 (3.8) and 15 (6.1) 12 (5.4) Agitation: 15 (6.2) 3 (1.3) and 10 (4.1) 6 (2.7) Nausea: 13 (5.4) 9 (3.8) and 20 (8.2) 11 (4.9) Fatigue: 11 (4.6) 16 (6.7) and 12 (4.9) 8 (3.6) Increased weight: 11 (4.6) 51 (21.3) and 23 (9.4) 48 (21.4) Dry mouth: 4 (1.7) 3 (1.3) and 9 (3.7) 18 (8.0) Increased appetite: 3 (1.2) 6 (2.5) and 8 (3.3) 12 (5.4)
Byerly, 2008 DB RCT 5 Dallas County public mental health outpatient clinics	NR

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Extrapyramidal symptoms
Buchanan 2012 DB RCT	extrapyramidal effects: EH and WH core studies, n (%) Any 20: (8.3) 8 (3.3) and 40 (16.4) 27 (12.1) Akathisia: 7 (2.9) 3 (1.3) and 22 (9.0) 13 (5.8) Parkinsonism: 5 (2.1) 4 (1.7) and 12 (4.9) 10 (4.5) Dyskinesia: 2 (0.8) 1 (0.4) and 5 (2.0) 2 (0.9) Dystonia: 4 (1.7) 3 (1.3) and 4 (1.6) 1 (0.4) Oculogyric crisis: 1 (0.4) 0 (0.0) and 0 (0.0) 0 (0.0) Bradykinesia: 2 (0.8) 0 (0.0) and 1 (0.4) 0 (0.0) Gait disturbance: 1 (0.4) 0 (0.0) and 1 (0.4) 1 (0.4) Tardive dyskinesia: 0 (0.0) 0 (0.0) and 1 (0.4) 2 (0.9) Cogwheel rigidity: 0 (0.0) 0 (0.0) and 0 (0.0) 1 (0.4) Head titubation: 0 (0.0) 0 (0.0) and 0 (0.0) 1 (0.4)
Byerly, 2008 DB RCT 5 Dallas County public mental health outpatient clinics	NR

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Total withdrawals; withdrawals due to adverse events	Comments
Buchanan 2012 DB RCT	Withdrawals due to adverse events: EH and WH core studies, n (%) Discontinuation due to treatment-emergent AEs: 36 (14.9) 17 (7.1) and 40 (16.4) 30 (13.4) Discontinuation treatment-related AEs: 30 (12.4) 15 (6.3) and 30 (12.3) 20 (8.9)	
Byerly, 2008 DB RCT 5 Dallas County public mental health outpatient clinics	6 WD due to AEs NR	Completers analysis.

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Eligibility criteria	Interventions (drug, dose, duration)	Allowed other medications	Age Gender Ethnicity	Other population characteristics
Canive, 2006 DB, RCT, crossover	Inpatients 18-65 yrs.; met DSM-IV criteria for schizophrenia determined by SCID-I; rating at screening of moderate or greater on at least 1 of 4 PANSS psychoticism screening items; decrease in PANSS total score between screen and baseline of no more than 20 points; PANSS total score at baseline with a minimum level of severity of 60; rating at screening of moderate or greater on CGI Severity of Illness item; good health; negative urine drug screen and no history of alcoholism or drug abuse in 3 mos prior to enrollment; no other psychotropic medications	olanzapine: avg. dose 15 mg/d risperidone: avg. dose 6 mg/d Duration: Two 8 week treatment phases	NR	Mean age: 42 yrs Gender: NR Ethnicity: NR	NR

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Number screened/ eligible/ enrolled	Withdrawn/ Lost to follow-up/ Analyzed	Results
Canive, 2006 DB, RCT, crossover	NR/NR/15	6 withdrawn/9 analyzed	Improvement occurred on most negative and positive symptom scales regardless of assigned medication. Main effects and/or linear trends found for PANSS positive, PANSS negative, PANSS general, PANSS total, CGI severity, SANS alogia, SANS anhedonia, SANS attention, SANS avolition, and SANS total scores. For PANSS positive and CGI, all improvements occurred between week 1 (unmedicated) and week 8 (end of 1st drug treatment phase) and remained constant between week 10 and week 18. Both medications led to significant improvements on al PANSS subscales; olanzapine led to greater improvements on PANSS General and PANSS Total; means for all scales followed pattern of olanzapine being more efficacious than risperidone; CGI scores improved during first treatment period and held steady during second. Both medications led to significant improvements in SANS Anhedonia, SANS Avolition, SANS Attention, SANS Alogia, and SANS total scores; olanzapine led to greater improvements on SANS Attention; means for all scales followed pattern of olanzapine being more efficacious; olanzapine also more effective for treating negative symptoms as shown by analysis performed using all SANS subscales and the PANSS negative subscale. No improvements found on movement rating scales, with no main effects or interactions for AIMS, Barnes, and Simpson-Angus scales (all Fs <1.4, Ps >0.27). Both medications showed consistent improvement across assessments at wks 1, 8, and 18 in scores for memory storage, attention, and verbal fluency; no significant improvements in test scores for working memory; no difference between medications seen for any of the neuropsychologic test scores.

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Adverse effects reported
Canive, 2006 DB, RCT, crossover	NR

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Extrapyramidal symptoms
Canive, 2006 DB, RCT, crossover	NR

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Total withdrawals; withdrawals due to adverse events	Comments
Canive, 2006 DB, RCT, crossover	WD: 6 WD due to AE: NR	

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Eligibility criteria	Interventions (drug, dose, duration)	Allowed other medications	Age Gender Ethnicity	Other population characteristics
Canuso 2009 DB RCT India, Russia, the Ukraine, and the United States Inpatient	Inclusion: 18 to 65 ys; schizophrenia (paranoid, disorganized, or undifferentiated types); acute exacerbation < 4 wks but > 4 ds; symptom scores ≥4 (at least moderate) on at least two of the PANSS items of hostility, excitement, tension, uncooperativeness, and poor impulse control, and a total combined score ≥17 for these items; a score ≥5 (at least markedly ill) on CGI-S and were hospitalized or required hospitalization. Exclusion: DSM-IV axis I diagnosis (except for schizophrenia and substance abuse); an axis II diagnosis of MR or borderline personality disorder; acute psychotic symptoms explained by substance use or medical illness; evidence for imminent risk of self-harm; a history of treatment resistance; treatment with quetiapine, paliperidone extended-release, or risperidone for 7 or more ds prior; sensitivity to paliperidone extended-release, risperidone, or quetiapine; depot antipsychotic treatment within one cycle before baseline; and ECT within 3 mos	Paliperidone extended-release (mean 9.8 mg), quetiapine (599.1 mg), or P for 6 wks	After 1st 14 ds, the additive-therapy phase, any psychotropic medication, including antipsychotics, was permitted	36 yrs old 66% male 45% Caucasian 37% Asian 16% Black 1% Hispanic 1% other	Paranoid 91% Undifferentiated 6% Disorganized 3%
Chan 2010 Rater-blinded	Schizophrenia, 18-65, women, DSM-IV score (>4).	Risperidone= 6 mg. Max dose. Olanzapine = 20 mg. Max dose. Duration: 8 wks	Anticholinergic drugs	Mean Age: 41 Male = 46% Female = 54% Ethnicity = NR	Duration of illness (ys) = 12 Duration of Antipsychotics (ys) = 8

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Number screened/ eligible/ enrolled	Withdrawn/ Lost to follow-up/ Analyzed	Results
Canuso 2009 DB RCT India, Russia, the Ukraine, and the United States Inpatient	NR/NR/399	116/21/394 it and 397 safety WDs by group Paliperidone 34 (21.3%) Quetiapine 53 (33.3%) P 29 (36.3%)	Between-Group Least-Squares Mean Differences in Change Scores on Efficacy Measures (SE) at 42 ds Paliperidone vs. Quetiapine / Paliperidone vs. P / Quetiapine vs. P PANNS total –4.7* (2.0) / –7.8* (2.5) / –3.1 (2.5) Positive subscore –1.1 (0.6) / –1.9*(0.8) / –0.8 (0.8) Negative subscore –1.2* (0.5) / –2.1* (0.6) / –1.0 (0.6) CGI-S –0.3*(0.1) / –0.5* (0.1) / –0.2 (0.1) CGI-C –0.1 (0.1) / –0.4* (0.2) / –0.3 (0.2) * P < 0.05
Chan 2010 Rater-blinded	94/70/70	NR/NR*/35 *4 with irregular f/u.	Effectiveness: (Risperidone vs. Olanzapine) Mean (+SD) CGI-S: −0.5 (1.0) vs. −0.9 (1.1) BPRS total scores: −4.9 (8.3) vs. −4.7 (6.6)

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Adverse effects reported
Canuso 2009 DB RCT India, Russia, the Ukraine, and the United States Inpatient	Paliperidone vs. quetiapine vs. P Participants with at least one AE 119 (75.3) vs. 123 (77.4) vs. 54 (67.5) GI disorders Constipation 7 (4.4) vs. 12 (7.5) vs. 2 (2.5) Diarrhea 2 (1.3) vs. 8 (5.0) vs. 2 (2.5) Dry mouth 5 (3.2) vs. 10 (6.3) vs. 1 (1.3) Dyspepsia 4 (2.5) vs. 8 (5.0) vs. 4 (5.0) Vomiting 12 (7.6) vs. 10 (6.3) vs. 2 (2.5) General disorders Asthenia 10 (6.3) vs. 8 (5.0) vs. 6 (7.5) Weight increase 5 (3.2) vs. 9 (5.7) vs. 2 (2.5) Nervous system disorders Akathisia 15 (9.5) vs. 10 (6.3) vs. 5 (6.3) Dizziness 6 (3.8) vs. 24 (15.1) vs. 1 (1.3) Drooling 13 (8.2) vs. 4 (2.5) vs. 1 (1.3) Headache 23 (14.6) vs. 19 (11.9) vs. 13 (16.3) Hypertonia 19 (12.0) vs. 6 (3.8) vs. 3 (3.8) Sedation 7 (4.4) vs. 17 (10.7) vs. 3 (3.8) Somnolence 18 (11.4) vs. 24 (15.1) vs. 2 (2.5) Tremor 31 (19.6) vs. 12 (7.5) vs. 12 (15.0) Psychiatric disorders Agitation 7 (4.4) vs. 5 (3.1) vs. 4 (5.0) Depressed mood 4 (2.5) vs. 0 (0) vs. 4 (5.0) Insomnia 19 (12.0) vs. 16 (10.1) vs. 12 (15.0) Schizophrenia 9 (5.7) vs. 14 (8.8) vs. 10 (12.5)
Chan 2010 Rater-blinded	Overall adverse events: (Risperidone vs. Olanzapine) N (%) Headache: 4 (11.4) vs.1 (2.9) Blurred vision: 2 (5.7) vs.0 (0) Nausea: 2 (5.7) vs.0 (0) Dizziness: 2 (5.7) vs.3 (8.6) Thirst: 0 (0) vs.2 (5.7) Drowsiness: 5 (14.3) vs.4 (11.4) Weakness: 4 (11.4) vs.6 (17.1) Palpitation: 3 (8.6) vs. 2 (5.7) Postural hypotension: 1 (2.9) vs. 1 (2.9) Constipation: 2 (5.7) vs.3 (8.6) Body weight change >7%: 6 (17.1) vs. 9 (25.7) Psychotic symptoms worsening: 2 (5.7) vs.3 (8.6)

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Extrapyramidal symptoms
Canuso 2009 DB RCT India, Russia, the Ukraine, and the United States Inpatient	Paliperidone vs. quetiapine vs. p Change in LSM (SE) Simpson-Angus Scale total score –0.1 (0.2) vs. –0.4 (0.2) vs. 0.2 (0.3) AIMS total score –0.1 (0.2) vs. –0.2 (0.2) vs. –0.2(0.2) BAS, rating for global severity of akathisia, shifts from baseline n(%) Worsened 11 (7.1) vs. 6 (4.0) vs. 5 (6.5) Unchanged 130 (84.4) vs. 125 (83.3) vs. 62 (80.5) Improved 13 (8.4) vs. 19 (12.7) vs. 10 (13.0)
Chan 2010 Rater-blinded	Extrapyramidal effects: Parkinsonism total scores of ESRS: −0.6 (1.4) vs. −0.4 (2.0) Dystonia total scores of ESRS: −2.5 (5.7) vs. −1.1 (4.7) Parkinsonism global impression of ESRS: 0.1 (0.2) vs. −0.3 (0.2) Dystonia global impression of ESRS: −0.2 (0.1) vs. −0.1 (0.2) Akathisia global impression of ESRS: −0.3 (1.8) vs. −0.7 (0.8)

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Total withdrawals; withdrawals due to adverse events	Comments
Canuso 2009 DB RCT India, Russia, the Ukraine, and the United States Inpatient	116 WD 31 due to AEs	
Chan 2010 Rater-blinded		

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Eligibility criteria	Interventions (drug, dose, duration)	Allowed other medications	Age Gender Ethnicity	Other population characteristics
Chan 2010 RCT	Schizophrenia, schizoaffective, schizophreniform disorder, 18-70, female, DSM-IV (>4).	Risperidone= 6 mg. Max dose. Olanzapine = 20 mg. Max dose. Duration: 24 wks	Benzodiazepines Propranolol	Mean Age: 45 Male = 35% Female = 65% Ethnicity = NR	• Psychotic symptoms worsening = 5%

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Number screened/ eligible/ enrolled	Withdrawn/ Lost to follow-up/ Analyzed	Results
Chan 2010 RCT	81/60/60	16/NR*/30 *7 with irregular f/u.	(Risperidone vs. Olanzapine) Mean (+SD) CGI -S: 60.6 (1.3) vs. -0.5 (1.5) BPRS total score: -4.4 (16.8) vs. -2.7 (8.1)

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Adverse effects reported
Chan 2010 RCT	Overall adverse events: (Risperidone vs. Olanzapine) N (%) Drowsiness: 6 (20) vs. 4(13) Weakness: 5 (17) vs. 4(13) Dizziness: 5 (17) vs. 5 (17) Headache: 4 (13) vs. 3 (10) Palpitation: 4 (13) vs. 1 (3) Nausea: 4 (13) vs. 0 (0) Constipation: 3 (10) vs. 1 (3) Muscle ache: 2 (7) vs. 3 (10) Thirst: 2 (7) vs. 3 (10) Blurred vision: 2 (7) vs. 2 (7) Psychotic symptoms worsening: 1 (3) vs. 2 (7) Dyspnea: 1 (3) vs. 2 (7) Postural hypotension: 0 (0) vs. 1 (3)

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Extrapyramidal symptoms
Chan 2010 RCT	Extrapyramidal effects: (Risperidone vs. Olanzapine) Mean +SD AIMs total score: -7.4 (6.9) vs. -6.2 (8) Dyskenisia: -1.7 (2.8) vs. -1.4 (1.9) Parkinsonism: 0.1 (1.2) vs. -0.6 (1.3) Akathisia: -0.1 (1.4) vs. -0.9 (2.3)

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Total withdrawals; withdrawals due to adverse events	Comments
Chan 2010 RCT	Withdrawals due to adverse events: NR Time to withdrawal: NR (no severe Aes were reported)	

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Eligibility criteria	Interventions (drug, dose, duration)	Allowed other medications	Age Gender Ethnicity	Other population characteristics
Chan, 2007 DB, RCT, parallel, multicenter Inpatients	Nonpregnant, non-lactating; 18-65 yrs.; primary diagnosis of DSM-IV schizophrenia or schizoaffective disorder; hospitalized due to acute relapse; evidence of response to antipsychotic medication; PANSS total score of at least 60 and a minimum score of 4 on at least 2 of the 4 items of the PANSS positive subscale; patients taking long-acting neuroleptic could be included if time period of at least 1 treatment cycle plus 1 week had elapsed since last injection. Exclusion criteria: psychiatric disorder other than schizophrenia or schizoaffective disorder requiring pharmacotherapy; serious suicidal ideations; first episode of schizophrenia or schizoaffective disorder; clinically significant neurologic abnormality other than tardive dyskinesia or EPS; current diagnosis of psychoactive substance dependence or history of drug or alcohol abuse within 1 mo of study start; any acute or unstable medical condition; treatment with an investigational drug within 4 wks of start of P washout.	aripiprazole: 15 mg/d risperidone: 6 mg/d Duration: 4 wks	Benzodiazepines for anxiety or insomnia; intramuscular benzodiazepines for emerging agitation if deemed necessary by investigatory; anticholinergic drugs for EOS not permitted during washout but allowed for treatment of EPS during double-blind period if deemed necessary (dose of anticholinergic drug could not exceed an equivalent of 6 mg/d of benztropine)	Mean age: 35 yrs Male: 54% Ethnicity: NR	Schizophrenia: 96% Schizoaffective: 4%

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Number screened/ eligible/ enrolled	Withdrawn/ Lost to follow-up/ Analyzed	Results
Chan, 2007 DB, RCT, parallel, multicenter Inpatients	95/12/83	83 analyzed	Both groups showed significant improvement in primary and secondary efficacy parameters (all P values < 0.001) Both treatments demonstrated rapid onset of efficacy with statistically significant effects from week 1 (P<0.001 for primary efficacy parameter; P<0.007 for all secondary efficacy parameters) Responders (defined as CGI-I score </= 2 or >/= 30% decrease from baseline in PANSS total score): aripiprazole 51% risperidone 68% No significant difference; P=0.126

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Adverse effects reported
Chan, 2007 DB, RCT, parallel, multicenter Inpatients	Experienced at least 1 treatment emergent AE: aripiprazole: 84%, risperidone: 79% (no statistical difference between groups) AEs (aripiprazole vs. risperidone), all P values >0.05 between groups: Abdominal pain: 6% vs. 0% Abdominal pain, upper: 8% vs. 3% Constipation: 10% vs. 12% Diarrhea: 8% vs. 3% Nausea: 4% vs. 6% Toothache: 6% vs. 9% Vomiting: 10% vs. 3% Nasopharyngitis: 6% vs. 0% Akathisia: 2% vs. 12% Dizziness: 4% vs. 12% Extrapyramidal disorder: 12% vs. 24% Headache: 8% vs. 3% Agitation: 8% vs. 0% Anxiety: 2% vs. 6% Insomnia: 27% vs. 21% Psychotic disorders: 16% vs. 6% Both groups showed mild body weight gain with no statistical difference [mean (SD)] aripiprazole vs. risperidone: 0.9 (2.2) kg vs. 1.5 (2.5) kg >7% weight increase: 4% vs. 12%; P=0.221 Serum prolactin levels, change from baseline aripiprazole vs. risperidone: -9.0 (96.4) vs. 55.4 (42.3) mg/dL; P<0.001)

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Extrapyramidal symptoms
Chan, 2007 DB, RCT, parallel, multicenter Inpatients	Overall EPS -related AEs lower in aripiprazole than risperidone group EPS: aripiprazole 12%, risperidone 24% Akathisia: aripiprazole 2%, risperidone 12% For relief of EPS, 25% of aripiprazole patients and 12% of 41% of risperidone patients used anticholinergics as concomitant medications

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Total withdrawals; withdrawals due to adverse events	Comments
Chan, 2007 DB, RCT, parallel, multicenter Inpatients	Total: 22 (26.5%) Due to AE: 7 (8.4%)	

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Eligibility criteria	Interventions (drug, dose, duration)	Allowed other medications	Age Gender Ethnicity	Other population characteristics
Chiu, 2006 Prospective, RCT, open-label study to evaluate pancreatic beta-cell function	18-60 yrs; BMI 20-30 kg/m2; fasting glucose level of 110 mg/dL or less; no personal or family history of diabetes; DSM-IV diagnosis of schizophrenia Exclusion criteria: Axis I disorder except schizophrenia; current substance abuse; medical conditions that could confound glycoregulatory assessment, including diabetes mellitus and other endocrine diseases; severe CV, hepatic, or renal disease; malignancy; epilepsy; pregnancy	olanzapine: 10 mg/d risperidone: 2 mg/d Duration: 2 wks	Not allowed: medications (e.g., lithium, carbamazepine, valproic acid, propranolol, tricyclic antidepressant, SSRI) that may influence body weight, glucose/lipid metabolism, or drug disposition. Others: NR	Mean age (SD): 37.3 (8.3) yrs Male: 69% Taiwanese: 100%	No significant differences between treatment groups in weight, BMI, glucose, insulin, total cholesterol, triglyceride, HDL, LDL, and leptin
Chowdhury, 1999	Schizophrenia by ICD10, aged 15–60 ys; duration of illness > 6 mos and received at least one full course of treatment with conventional antipsychotic drugs (either chlorpromazine, 600–800 mg daily, haloperidol or trifluoperazine in equivalent doses) without adequate response; patients intolerant to traditional neuroleptic drugs because of intractable neurological and non-neurological side-effects, necessitating WD of drug or inadequate dosing	Clozapine initial dose 50 mg/d, increased by 50 mg to 150 mg/d by week 2. By week 3, dose range 250–300 mg/d. Risperidone 1mg bid starting dose, then 2 mg bid from d 2 onwards. After week 1, 6 mg daily up to maximum 8 mg/d Duration:16 wks Mean maximum daily dose, clozapine, 343 mg daily; risperidone, 5.8 mg	NR	Mean age (SD): clozapine 30.3 (8.78) ys risperidone 32.43 (9.79) ys clozapine 73.3% male risperidone 76.7% male Ethnicity NR	Paranoid subtype, clozapine 56.67%; risperidone 60%; Other subtypes included hebephrenia, residual and undifferentiated

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Number screened/ eligible/ enrolled	Withdrawn/ Lost to follow-up/ Analyzed	Results
Chiu, 2006 Prospective, RCT, open-label study to evaluate pancreatic beta-cell function	NR/NR/26	0/0/26	Risperidone group: weight, BMI, fasting glucose, fasting insulin, triglyceride, total cholesterol, HDL, LDL, and leptin did not change significantly Olanzapine group: weight, BMI, fasting glucose, fasting insulin, triglyceride, total cholesterol, HDL, LDL, and leptin did not change significantly No significant difference between groups for glucose disappearance rate or insulin sensitivity Insulin secretion decreased significantly in olanzapine group (P=0.004)
Chowdhury, 1999	NR/72/60 clozapine: 30 risperidone: 30	14/3/NR	PANSS scores total (positive, negative, general subscales): Clozapine: (n= 30) 93.16 (SD 9.57) (22.0,SD 6.74;23.67,SD 6.46;47.53,SD 7.18)(n= 30) 92.97,SD 14.80 (21.67,SD 5.92;23.73,SD 8.66;47.57,SD 8.72) Risperidone: (n= 24) 50.0,SD 17.80 (10.08,SD 3.06;14.08,SD 6.66;25.83,SD 8.74)(n= 22) 50.45,SD 20.74 (10.04,SD 3.26;14.55,SD 8.33;25.86,SD 9.98) Treatment success rate (> 20% reduction from baseline on PANSS) total; positive; negative; general subscales: Clozapine: 80%;80%;73.33%;80%66.7%;66.7%;63.33%;66.7%

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Adverse effects reported
Chiu, 2006 Prospective, RCT, open-label study to evaluate pancreatic beta-cell function	NR
Chowdhury, 1999	Clozapine: tachycardia 76.66%; hypersalivation 60%; sedation 60%; weight gain 43.33%; constipation 30%; leucocytosis 26.66%. (1 patient suffered an episode of seizure) Risperidone: constipation 50%; dry mouth 46.66%; weight gain 43.33%; akathisia 36.67%; insomnia 33.33%; tachycardia 30%; impotence 26.66%

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Extrapyramidal symptoms
Chiu, 2006 Prospective, RCT, open-label study to evaluate pancreatic beta-cell function	NR
Chowdhury, 1999	NR

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Total withdrawals; withdrawals due to adverse events	Comments
Chiu, 2006 Prospective, RCT, open-label study to evaluate pancreatic beta-cell function	0 WD 0 due to AEs	
Chowdhury, 1999	clozapine: 6/30 (20%) Due to AE: 4/30 (13.3%) risperidone: 8/30 (26.7%) Due to AE: 3/30 (10%)	

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Eligibility criteria	Interventions (drug, dose, duration)	Allowed other medications	Age Gender Ethnicity	Other population characteristics
Chrzanowski et al., 2006 (Extension of Pigott 2003) RCT, open-label extension	(1) stable patients who had completed the acute phase, and (2) patients who met the protocol criteria for relapse and had completed at least 2 wks of double-blind therapy.	aripiprazole (15–30 mg/d) or olanzapine (10–20 mg/d) 52 wks	Other antipsychotics, investigational agents, or participation in another study were not allowed.	Mean age: 41.5 54% male 96% white 1% African American 2% Hispanic	Weight- mean 73.0 kg Age at time of 1st diagnosis 30.4 ys
Chue, 2005 DB, RCT, double-dummy, multicenter, parallel, noninferiority study	Inpatients or outpatients aged 18-65; DSM-IV diagnosis of schizophrenia; total PANSS score > 50; no clinically relevant abnormal biochemistry, hematology or urinalysis lab values; remained symptomatically stable as indicated by stable oral dose and stable CGI scores for last 4 wks of oral risperidone run-in period Exclusion criteria: Moderate or severe symptoms of tardive dyskinesia at study entry; history of neuroleptic malignant syndrome, known to be risperidone unresponsive; required mood stabilizers; had been treated with clozapine in 2 mos prior to screening or depot antipsychotic within one treatment cycle of screening or antidepressant within 30 ds of run-in period	Oral risperidone: 2-6 mg/d Long-acting risperidone: 25-75 mg every 2 wks Duration: 12 wks active treatment	Anticholinergic medication could be initiated for emergent or worsening movement disorders and propranolol could be initiated for emergent or worsening akathisia; medication prescribed for sleep could be continued if used before study entry, or temazepam, zopiclone, zolpidem or chloral hydrate could be initiated during the study; lorazepam or oxazepam could be given intermittently for agitation Concomitant psychotropic meds received during double-blind treatment included antiparkinsonians and sedatives (lorazepam, oxazepam, clonazepam and zopiclone)	Mean age: 40.0 yrs Male: 64.7% White: 87.8% Black: 5.5% Asian: 2.5% Hispanic: 0.15% Other: 4.1%	Oral vs long-acting risperidone Schizophrenia type: paranoid: 60.7% vs 62.7% undifferentiated: 17.4% vs 17.9% residual: 15% vs 13.5% disorganized: 6.5% vs 5.0% catatonic: 0.6% vs 0.9%

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Number screened/ eligible/ enrolled	Withdrawn/ Lost to follow-up/ Analyzed	Results
Chrzanowski et al., 2006 (Extension of Pigott 2003) RCT, open-label extension	NR/NR/214	67/8/214	PANSS Total scores of aripiprazole −21.8 and olanzapine −23.8 (p=0.606) Aripiprazole vs. Olanzapine Chronic, stable mean changes at 52 wks PANSS Positive −0.41 vs. −0.86 PANSS Negative −1.89 vs. −2.01 CGI-S −1.89 vs. −2.01 At 52 wks CGI-I 3.17 vs. 3.08 Acute psychosis mean changes at 52 wks PANSS Positive -6.30 vs. -7.47 PANSS Negative -4.54 vs. -3.84 CGI-S -0.75 vs. -0.87 At 52 wks CGI-I 2.98 vs. 2.89
Chue, 2005 DB, RCT, double-dummy, multicenter, parallel, noninferiority study	NR/779 (run-in period)/642	2 withdrawn before beginning DB treatment 541 analyzed for efficacy 640 analyzed for safety	Changes ± (SE) in PANSS at endpoint, oral risperidone vs. long-acting risperidone, 95%CI PANSS total: -6.3 ± (0.7) vs. -5.4 ± (0.7); -0.90, 2.78 Positive symptoms: -2.0 ± (0.3) vs. -1.7 ± (0.3); -0.34, 0.99 Negative symptoms: -1.6 ± (0.3) vs. -1.5 ± (0.3); -0.59, 0.82 Disorganized thoughts: -1.2 ± (0.2) vs. -1.1 ± (0.2); -0.34, 0.71 Uncontrolled hostility/excitement: -0.4 ± (0.1) vs. -0.3 ± (0.1); -0.22, 0.43 Anxiety/depression: -1.0 ± (0.2) vs. -0.9 ± (0.2); -0.25, 0.57 CGI scores improved in both treatment groups; percentage of patients rated as not ill or with mild illness increased from 46.9% to 57.8% in oral risperidone group and from 49.2% to 57.9% in long-lasting risperidone group

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Adverse effects reported
Chrzanowski et al., 2006 (Extension of Pigott 2003) RCT, open-label extension	Aripiprazole vs. Olanzapine n(%) Insomnia 24 (24) vs. 29 (26) Anxiety 10 (10) vs. 12 (11) Headache 9 (9) vs. 13 (12) Somnolence 9 (9) vs. 8 (7) Infection 7 (7) vs. 5 (5) Nervousness 6 (6) vs. 5 (5) Akathisia 5 (5) vs. 6 (5) Reaction schizophrenic 5 (5) vs.6 (5) Flu syndrome 4 (4) vs. 9 (8) CNS stimulation 4 (4) vs. 6 (5) Lightheadedness 3 (3) vs. 7 (6) Tremor 3 (3) vs. 7 (6) Extrapyramidal syndrome 3 (3) vs. 6 (5) Weight gain 0 vs. 6 (5)
Chue, 2005 DB, RCT, double-dummy, multicenter, parallel, noninferiority study	Oral risperidone vs. long-acting risperidone: Overall AEs: 59.9% vs. 61.1% Insomnia: 9.0% vs. 9.7% Anxiety: 7.2% vs.10.0% Headache: 7.2% vs. 8.2% Psychosis: 4.7% vs. 5.3% No significant changes in vital signs, ECG including QTc interval and lab values other than prolactin from baseline to endpoint; adverse effects potentially attributable to prolactin elevation reported in 2.5% of oral risperidone group and 1.3% of long0acting risperidone group No between-group differences or changes from baseline in ESRS total or cluster scores Pain at injection site was low (mean scores 18-20 on 100 point VAS scale) and comparable between P and risperidone

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Extrapyramidal symptoms
Chrzanowski et al., 2006 (Extension of Pigott 2003) RCT, open-label extension	SAS (aripiprazole, −0.08; olanzapine-pine, −0.24; p=0.442), AIMS (aripiprazole, −0.42; olanzapine,−0.26; p=0.198), BARS (aripiprazole, −0.06;olanzapine, −0.13; p=0.176) EPS-related AEs Olanzapine 18 vs aripiprazole 10% Concomitant anticholinergic use for EPS aripiprazole, 22% vs. olanzapine,26%
Chue, 2005 DB, RCT, double-dummy, multicenter, parallel, noninferiority study	No statistically significant difference between treatment groups at any timepoint on CGI dyskinesia, parkinsonism, or dystonia scales or in stage of parkinsonism

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Total withdrawals; withdrawals due to adverse events	Comments
Chrzanowski et al., 2006 (Extension of Pigott 2003) RCT, open-label extension	66 WD 8 due to AEs	
Chue, 2005 DB, RCT, double-dummy, multicenter, parallel, noninferiority study	113 total WDs WD due to AEs: Oral vs LA risperidone 4.7% vs 5.6%	

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Eligibility criteria	Interventions (drug, dose, duration)	Allowed other medications	Age Gender Ethnicity	Other population characteristics
Citrome 2012 DB RCT	DSM - Schizophrenia, schizo-affective disorder, 18-75, male or female, duration of illness for at least a y, clinically stable for 8 wks, CGI-S score of >4, and PANSS of <4.	Lurasidone = 120 mg. Max dose. Risperidone = 6 mg. Max dose Duration = 12 mos	Medications used for movement disorders. • Benztropine • Biperiden • Trihexyphenidyl • Propranolol • Diphenhydramine • Amantadine	Mean Age: 42 Male = 69% Female = 31% Ethnicity: Hispanic or Latino = 21% Not Hispanic or Latino = 79% American Indian or Alaska Native = 1% Asian = 3% Black or African American = 52% Native Hawaiian or other Pacific Islander = 1% White = 39% Other = 6%	Previous hospitalizations for schizophrenia or schizoaffective disorder. 0 = 20% 1 = 18% 2 = 15% 3 = 13% 4 or more = 34%
Ciudad, 2006 (Companion to Alvarez 2006) RCT, multicenter, open-label, parallel, flexible-dose study	Outpatient; 18-65 yrs; DSM-IV diagnosis of schizophrenia; baseline SANS global score >/= 10. Exclusion criteria: hospitalization in psychiatry department within 3 mos prior to enrollment; treatment with either injectable depot antipsychotic within 2 wks of enrollment, or clozapine, olanzapine, risperidone, or sertindole within previous mo; severe risk of suicide or allergy; severe diseases other than schizophrenia requiring hospitalization within previous 3 mos; glaucoma; history or presence of unclassified seizures, leucopenia or jaundice; pregnancy.	olanzapine: mean dose 12.2 mg/d risperidone: mean dose 4.9 mg/d Duration: 48 wks randomized assessment	Biperiden (up to 6 mg/d) to treat EPS symptoms but not as preventive measure; benzodiazepines/hypnotics up to 40 mg/d diazepam equivalent	Age: 36.5 yrs. Male: 72.3% Spanish: 100%	Body weight: Olanzapine: 73.6 kg Risperidone: 80.8 kg

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Citrome 2012 DB RCT	109/629/629	103/65/621	Relapse overall:114/608 (19%) (Lurasidone vs. Risperidone) Relapse: 82/410 (20%) vs 32/198 (16%) Positive and Negative Syndrome Scale: Clinical Global Impression-Severity: decreased from baseline to month 12 (MMRM): – 0.4; (95% CI – 0.5 to – 0.3) vs. (– 0.4;95% CI – 0.5 to – 0.2) MADRS total score: decreased from baseline to month 12 (MMRM): – 0.8; 95% CI – 1.6 to – 0.0) vs. – 2.4;95% CI – 3.4 to – 1.4)
Ciudad, 2006 (Companion to Alvarez 2006) RCT, multicenter, open-label, parallel, flexible-dose study	NR/NR/250	250 randomized; 3 terminated before receiving study meds; 12 had no post-baseline efficacy data Safety analysis: 247 Efficacy analysis: 235	Significant within-group SFS total score improvements seen in both treatment groups (P=0.0006) In olanzapine group, significant improvements also seen in social engagement/WD (P<0.0001), interpersonal communication (P<0.0001), independence (performance, P=0.0014), and independence (competence, P<0.0001) scores In risperidone group, significant improvements observed for social engagement/WD (P=0.0284) and interpersonal communication (P<0.0001); significant worsening seen in occupation/employment category (P=0.0092) Olanzapine patients showed greater improvement over baseline in SFS total score and all SFS domains compared to risperidone patients, with significant between-group differences on the SFS total score and all SFS domains except interpersonal communication and prosocial activities; greatest intergroup divergence in SFS-related endpoints was occupation/employment domain (P=0.0024) Visit-wise comparisons showed significant differences of olanzapine over risperidone in SFS total score at all visits. Reduction in effectiveness measures from baseline, mean change (SD) olanzapine vs. risperidone: SANS global: 5.93 (0.4) vs. 4.53 (0.4), P=0.0151 SANS total: 32.9 (2.3) vs. 24.97 (2.4), P=0.0168 SANS composite: 26.65 (2.0) vs. 20.45, P=0.0183 SAPS global: 3.31 (0.3) vs. 2.41 (0.3), P=0.0207 SAPS total: 18.98 (1.5) vs. 13.65 (1.6), P=0.0116 SAPS composite: 15.66 (1.2) vs. 11.25 (1.3), P=0.0115 CGI-S: 1.0 (1.0) vs. 0.6 (1.1), P=0.0082 Higher proportion of olanzapine subjects showed clinical response : 69.2% vs. 48.7%, P=0.0014

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Author, year Study design	Adverse effects reported
Citrome 2012 DB RCT	Incidence of treatment-emergent adverse events reported in > 5% of patients in either treatment group: (Lurasidone vs. Risperidone) Nausea: (16.7 vs. 10.9%), Insomnia (15.8 vs. 13.4%) Sedation (14.6 vs. 13.9%) (Risperidone vs. Lurasidone) Increased weight (19.8 vs. 9.3%) Somnolence (17.8 vs. 13.6%) Headache (14.9 vs.10.0%)
Ciudad, 2006 (Companion to Alvarez 2006) RCT, multicenter, open-label, parallel, flexible- dose study	Most Frequent AEs (drug groups combined) : anxiety: 13% insomnia: 10.1% tremor: 9.7% AEs (olanzapine vs. risperidone): tremor: 5.6% vs. 13.8%; P=0.0301 akathisia: 1.6% vs. 8.9%; P=0.0099 sexual dysfunction: 0.8% vs. 5.7%; P=0.0357 weight gain: 3.8kg [SD=6.1] vs. 2.1 kg [SD=6.0]; P=0.5467 >7% weight increase: 40.7% vs. 17.3%; P=0.0012

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Extrapyramidal symptoms
Citrome 2012 DB RCT	Extrapyramidal effects: in >5% of patients in either treatment group: (Lurasidone vs. Risperidone)
Ciudad, 2006 (Companion to Alvarez 2006) RCT, multicenter, open-label, parallel, flexible-dose study	NR for olanzapine vs. risperidone

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Total withdrawals; withdrawals due to adverse events	Comments
Citrome 2012 DB RCT	Withdrawals due to adverse events: All-cause discontinuation rates higher for lurasidone versus risperidone: lurasidone group, 90/419 (21.5%), vs risperidone group, 29/202 (14.4%), Number needed to harm (NNH): 14 (95% CI 8–113) Median survival time to discontinuation for any cause: 181 days (95% CI 143–217 days) vs. 293 days (95% CI 179 days)	
Ciudad, 2006 (Companion to Alvarez 2006) RCT, multicenter, open-label, parallel, flexible-dose study	Total WD: 72 (30.6%) WD due to AEs: 10 (4.3%)	

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Author, year Study design	Eligibility criteria	Interventions (drug, dose, duration)	Allowed other medications	Age Gender Ethnicity	Other population characteristics
Conley, 2001	Schizophrenia or Schizoaffective disorder by DSM-IV diagnosis, baseline PANSS score, 60–120, aged 18–64 ys; out- or inpatients hospitalized ≤4 wks	risperidone 2–6 mg/d (flexible dose); oral olanzapine 5–20 mg/d; oral Duration: 8 wks Both drugs given qd according to following regimens: ds 1–2, 2 mg risperidone or 10 mg olanzapine; ds 3–7, 2–4 mg risperidone or 5–10 mg olanzapine; ds 8–14, 2–6 mg risperidone or 5–15 mg olanzapine; ds 15–56, 2–6mg risperidone or 5–20 mg olanzapine	NR	Mean age: risperidone 41.0 (11.0) ys olanzapine 38.9 (10.5) ys 72.7% male Ethnicity NR	79% were outpatients Schizophrenia (n= 325) or schizoaffective disorder (n= 52) Duration of illness: mean risperidone 16.5 (10.5) ys, olanzapine 15.4 (10.6) ys
Conley, 2003 Kelly, 2003 DB, crossover Inpatients Funding: NIHM grant	Schizophrenia	olanzapine: 50 mg/d, and clozapine: 450 mg/d, each for 8 wks	NR	Mean age: 38 ys	100% inpatients

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Number screened/ eligible/ enrolled	Withdrawn/ Lost to follow-up/ Analyzed	Results
Conley, 2001	NR/NR/377 risperidone 188 olanzapine 189	Risperidone 53/NR/188 olanzapine 43/NR/189	Change scores: PANSS total; PANSS positive; PANSS negative; PANSS disorganized thoughts; PANSS uncontrolled hostility; PANSS anxiety/depression: Risperidone: (n= 134) –16.0 (16.6);–5.6 (6.4);–3.5 (6.0);–2.9 (4.6);–1.4 (2.8);–2.5 (3.6) Olanzapine: (n= 144) –15.4 (16.8);–4.8 (6.4);–3.3 (5.7);–3.5 (4.7);–1.7 (2.7);–2.2 (3.4) Response: ≥20% reduction in PANSS; 40% reduction in PANSS; CGI-I much or very much improved: Risperidone: 69/188;34/188;60/188(data not available for all participants) Olanzapine: 68/189;23/189;58/189 (data not available for all participants) CGI-S: Risperidone: (n= 133) not ill/very mild/mild n= 67, moderate/marked n= 62, severe/extremely severe n= 4 Olanzapine: (n= 145) not ill/very mild/mild n= 69, moderate/marked n= 75, severe/extremely severe n= 1 Change scores: ESRS total, questionnaire, parkinsonism, akathisia, and dyskinesia: Risperidone: (n= 133) –1.3 (4.6);–0.6 (2.4);–0.8 (3.4);–0.2 (1.0);–0.4 (2.4) Olanzapine: (n= 145) –1.6 (4.1);–0.5(2.4);–1.0 (3.3);–0.2 (0.8);–0.5 (2.2)
Conley, 2003 Kelly, 2003 DB, crossover Inpatients Funding: NIHM grant	NR/NR/13	NR/NR/13	Change scores from baseline: clozapine vs olanzapine: Total BPRS: C: -6.5 vs O: -1.0 Positive: C: -1.7 vs O: -0.5 Negative: C: +0.5 vs O: +1.3 Activation: C: -1.7 vs O: -0.6 Anxiety/depression: C: -2.5 vs O: -1.6 Hostility: C: -1.1 vs O: -0.1 CGI-S: C: -0.3 vs O: +0.1 Laboratory Values: Baseline fasting blood glucose (mg/dL): O: 94.6 + 14.4; C: 92.8 +10.2 Change in fasting blood glucose (mg/dL): O: 3.4 + 27.8; C: 10.8 + 2.9 Baseline total cholesterol (mg/dL): O: 198.0 + 44.0; C: 209.6 + 28.6 Change in total cholesterol (mg/dL): O: 4.3 + 35.6; C: 37.6 + 41.2 Baseline serum triglycerides (mg/dL): O: 141.4 + 40.4; C: 181.0 + 146.2 Change in serum triglycerides (mg/dL): O: 6.6 + 33.1; C: 162.8 + 258.1 Baseline alanine aminotransferase (ALT) (IU/L): O: 42.4 + 49.8; C: 22.0 + 13.5 Change in alanine aminotransferase (ALT) (IU/L): O: -12.3 + 28.2; C: 14.6 + 20.0 Baseline aspartate aminotransferase (AST) (IU/L): O: 23.7 + 15.9; C: 18.0 + 5.1 Change in aspartate aminotransferase (AST) (IU/L): O: -3.6 + 7.0; C: 10.4 + 11.5 Baseline lactate dehydrogenase (LDH) (IU/L): O: 153.4 + 45.5; C: 128.6 + 6.7 Change in lactate dehydrogenase (LDH) (IU/L): O: -1.6 + 41.3; C: 88.2 + 125.5

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Author, year Study design	Adverse effects reported
Conley, 2001	All risperidone vs olanzapine Serious AEs: 15/188 vs 22/189; psychosis: 8/188 vs 8/189; suicide attempt: 2/188 vs 5/189; agitation: 3/188 vs 3/189; depression: 3/188 vs 3/189; insomnia: 3/188 vs 2/189; hallucinations: 2 vs 3; drug abuse: 0 vs 3; CV symptoms: 0 vs 3; GI disorders: 0 vs 3; other: 14 vs 21 Weight gain: 3.4 lb (SD 7.8) vs 7.2 lb (SD 11.2); increase in body weight of 7%: 18/155 vs 44/161 Less serious AEs: somnolence: 69/188 vs 73/189; insomnia: 45 vs 35; headache: 41 vs 32; agitation: 29 vs 40; dry mouth: 21 vs 42; rhinitis: 30 vs 31; dizziness: 26 vs 27; anxiety: 20 vs 23; vision abnormalities: 12 vs 19
Conley, 2003 Kelly, 2003 DB, crossover Inpatients Funding: NIHM grant	Dry mouth: O: 8(80%), C: 2(20%) Blurry vision: O: 4(40%), C: 0 Urinary hesitancy: O: 0, C: 1(10%) Constipation: O: 6(60%), C:1(10%)0 Tachycardia: O: 2(20%), C: 0 Diarrhea: O: 3(30%), C: 0 Nausea: O: 9(90%), C: 6(60%) Dyspepsia: O: 3(30%), C: 7(70%) Headache: O: 6(60%), C: 4(40%) Somnolence: O: 10(100%), C:10(10%) Lethargy: O: 6(60%), C: 9(90%) Myoclonus: O: 1(10%), C: 3(30%) Stuttering: O: 0, C: 2(20%) Sialorrhea: O: 1(10%), C: 8(80%) Sweating: O: 1(10%), C: 5(50%) Urinary frequency: O: 1(10%), C: 4(40%) Dysphagia: O: 0, C: 2(20%) Orthostasis: O: 3(30%), C: 1(10%) Dizziness: O: 6(60%), C: 6(60%) Increased appetite: O: 4(40%), C: 5(50%)

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Extrapyramidal symptoms
Conley, 2001	Extrapyramidal symptoms: 45/188 vs 38/189. Patients using antiparkinsonian medication: 61/188 vs 53/189 Outcome: change scores: ESRS total, questionnaire, parkinsonism, akathisia, and dyskinesia Risperidone: (n = 133) –1.3 (4.6); –0.6 (2.4); –0.8 (3.4); –0.2 (1.0); –0.4 (2.4) Olanzapine: (n = 145) –1.6 (4.1); –0.5 (2.4); –1.0 (3.3); –0.2 (0.8); –0.5 (2.2)
Conley, 2003 Kelly, 2003 DB, crossover Inpatients Funding: NIHM grant	SAS scores decreased by 1.3 clozapine increased 0.3 olanzapine Akathisia 20% clozapine 20% olanzapine 1 subject received benztropine while on olanzapine

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Total withdrawals; withdrawals due to adverse events	Comments
Conley, 2001	Risperidone 53/188 (28.2%) Due to AE 22/188 (11.7%) Olanzapine 43/189 (22.8%) Due to AE 17/189 (8.99%)	
Conley, 2003 Kelly, 2003 DB, crossover Inpatients Funding: NIHM grant	6 WD 1 WD due to AE	

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Eligibility criteria	Interventions (drug, dose, duration)	Allowed other medications	Age Gender Ethnicity	Other population characteristics
Conley, 2005 RCT, parallel, DB X 12 wks Inpatients - treatment resistant	Between 18 - 65 ys who met DSM-IV criteria for schizophrenia, and were treatment resistance: (definition: persistent positive psychotic symptoms at study entry "moderate" severity (≥ 4 points on a 1-7 point scale) on 2 of 4 psychosis items on the BPRS; persistent global illness severity (BPRS ≥45 points on the 18-item scale and a CGI score of ≥4 points; 2 prior failed treatment trials with 2 different antipsychotic at doses of at least 600mg/d chlorpromazine equivalents, each of at least 6 wks duration; and no stable period of good social/occupational functioning within the previous 5 ys).	Risperidone 3-5mg/d (Mean 4.31± 0.63 mg/d), Quetiapine 300 mg to 500 mg/d (Mean 463.6 ± 50.5 mg/d); Fluphenazine 10-15 mg/d (Mean 13.2 ±1.17 mg/d (flexible dosing to target doses during the initial week of therapy)	up to 10mg/d of lorazepam prn; benztropine (up to 4mg/d) and propranolol 30-120mg/d if experiencing EPS	Mean age: 44.3±7.6 Male: 85% African-American: 58% Ethnicity: NR	During lead-in phase, 12 (23%) were treated with olanzapine and 40 (77%) with conventional antipsychotics. Mean chlorpromazine dosing equivalents were 724.3 ± 564.6 mg/d for those treated with conventional antipsychotics (n=40) and 18.2 ± 6.0 mg/d for those treated with olanzapine (n=12). Positive Psychopathology Rating: Significant time effect for all groups: p=0.05; no drug-by time effect

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Number screened/ eligible/ enrolled	Withdrawn/ Lost to follow-up/ Analyzed	Results
Conley, 2005 RCT, parallel, DB X 12 wks Inpatients - treatment resistant	NR/52/40	NR/2/38	Discontinuation Rate: NS Psychopathology Ratings: BL to Endpoint Total BPRS score: ≥ 20% decrease noted in 23% of R subjects, 25% quetiapine subjects, and 15% fluphenazine-treated subjects; p=0.89 CGI severity score: No change Positive: (final change score: R: 1.77 ±1.31; Q: 0.67 ± 1.02, F: 0.92 ± 0.93 ;combined, p=0.05) Negative: (final change score: R: -0.15 points; Q: 0.42 points, F: -0.23 points, p=0.01). Significant time-by-drug interactions was noted driven primarily by fluphenazine during wks 1-11 Anxiety/depression-(final change score: R: -1.15 ±5.91, Q: -1.33 ± 3.70, F:-1.08 ± 5.20; p=NS Hostility: p=NS Activation: p=NS

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Adverse effects reported
Conley, 2005 RCT, parallel, DB X 12 wks Inpatients - treatment resistant	"No significant differences in side effects noted among the groups" R (n=13) vs. Q (n=12); F (n=12) Dry mouth: 15%, 33%, 17% Blurry vision: 15%, 17%, 17% Urinary hesitancy: 0, 17%, 17% Constipation: 0, 17%, 17% Diarrhea: 15%, 17%, 0 Nausea: 23%, 8%, 17% Dyspepsia: 7%, 8%, 23% Headache: 54%, 42%, 42% Somnolence: 38%, 25%), 33% Lethargy: 31%, 17%, 25% Insomnia: 23%, 25%, 42% Anxiety: 15%, 8%, 8% Urinary frequency: 8%, 8%, 0 Increased appetite: 23%, 35%, 17% Dizziness: 23%, 8%, 8% Orthostasis:38%, 8%, 17% Weight reduction at endpoint:: R: -0.65 ±2.43 kg; Q: -1.2 ± 11.22 kg; F: -2.6 ± 5.7 kg; p=NS QOL Interview at Endpoint: How do you feel about your life in general (endpoint compared to BL): R (+0.9), Q: (+0.1), F-(-0.9) Endpoint: Mean rating for all questions: R: 4.73 (mostly satisfied), Q: 4.65 (mostly satisfied), and F: 4.07 (mixed); p=NS

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Extrapyramidal symptoms
Conley, 2005 RCT, parallel, DB X 12 wks Inpatients - treatment resistant	"No significant differences among the group with all 3 groups showing improvements" Benztropine was given to 36%, 17%, 30% of F, R and Q -treated pts; p=NS Propranolol was given to 1 pts in each of the drug groups lorazepam was given to 82%, 75%, 70% of F, R, and Q pts; p=NS SAS: Q: all improved -1.64 points, R: -1.3 points; F: -0.69 points; p=NS

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Total withdrawals; withdrawals due to adverse events	Comments
Conley, 2005 RCT, parallel, DB X 12 wks Inpatients - treatment resistant	18 total WD 2 due to AEs (both on quetiapine-1-abnormal EKG, 1-tremor)	Doses were increased in 39%, 58%, and 31% for R, Q, F respectively. Doses were lowered in 1 subject each on F and R. QoL Interview: The risperidone group had the lowest ratings at baseline, and no significant differences were noted after controlling for it.

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Eligibility criteria	Interventions (drug, dose, duration)	Allowed other medications	Age Gender Ethnicity	Other population characteristics
Crespo-Facorro, 2006 Crespo-Facorro, 2009 Crespo-Facorro, 2011b Spain	15-60 yrs; met DSM-IV criteria for principal diagnosis of schizophreniform disorder, schizophrenia, schizoaffective disorder, brief reactive psychosis, schizotypal personality disorder or psychosis not otherwise specified; habitually living in the catchment area; no prior treatment with antipsychotic medication or, if previously treated, a total lifetime of adequate antipsychotic treatment < 6 wkss; current psychotic symptoms of moderate severity or greater assessed by 1 of the 5 items on the SAPS; referred to PAFIP Exclusion criteria: DSM-IV diagnosis of mental retardation; met DSM-IV criteria for drug dependence	Haloperidol: 3-9 mg/d Risperidone: 3-6 mg/d olanzapine: 5-20 mg/d 6 weeks	Lormetazepam and clonazepam permitted for management of agitation, general behavior disturbances, and/or insomnia; if clinically significant EPS occurred, anticholinergic medication (biperiden at dose of up to 8 mg/d) was allowed; antidepressants (sertraline) and mood stabilizers (lithium) permitted if clinically needed	Mean age: 27.3 yrs Male: 62.2% 100% Spanish	No previous antipsychotic treatment: 98.3% Inpatient: 63.4%

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Number screened/ eligible/ enrolled	Withdrawn/ Lost to follow-up/ Analyzed	Results
Crespo-Facorro, 2006 Crespo-Facorro, 2009 Crespo-Facorro, 2011b Spain	202/182/182	10 withdrawn after randomization 172 analyzed	**Mean change (SD) from baseline to endpoint (haloperidol vs. olanzapine vs. risperidone)** CGI-S: -2.5 (1.0) vs. -2.2 (1.1) vs. -2.2 (1.0); P=0.266 BPRS: -25.3 (14.1) vs. -24.5 (14.9) vs. -21.6 (12.0); P=0.308 SANS: -1.1 (6.5) vs. -3.5 (6.0) vs. -2.1 (5.3); P=0.137 SAPS: -9.7 (4.9) vs. -9.0 (4.8) vs. -9.6 (4.3); P=0.679 HAM-D: -5.5 (8.4) vs. -8.3 (6.8) vs. -5.8 (7.5); P=0.132 CDS: -0.1 (3.6) vs. -1.2 (3.3) vs. -0.7 (3.0); P=.256 YMRS: -6.4 (4.5) vs. -6.6 (4.9) vs. -5.9 (4.8); P=0.720 **Clinical response rate (>/= 40% BPRS total improvement from baseline:** haloperidol: 57.1% risperidone: 52.5% olanzapine: 63.6% **Mean time to response (SD):** haloperidol: 4.32 wkss (0.24) risperidone: 4.85 wkss (0.21) olanzapine: 4.36 wkss (0.23) **Cognitive changes at one y follow-up for 69 patients** olanzapine vs risperidone mean (SD)change in SAPS score: -10.70(5.36) vs -11.33(5.01) mean (SD) change in SANS score: -3.50(8.22) vs -2.41 (7.94) mean (SD) change in CDSS:-0.70(3.55) vs -0.70(3.55) vs -0.59 (2.88) **Mean change (SD) from baseline to 1 year (Haloperidol (n=24), Olanzapine (n=37), Risperidone (n=41), P):** CGI: -3.0 (1.1), -2.9 (1.2), -2.5 (1.4), 0.242 BPRS Total: -28.8 (11.1), -29.5 (14.1), -22.3 (14.9), 0.050 SANS: -1.3 (6.9), -3.9 (7.1), -0.8 (7.5), 0.140 SAPS: -11.5 (4.4), -10.6 (5.0), -10.9 (5.6), 0.797 H-DRS: -8.6 (8.3), -9.6 (8.5), -6.0 (7.2), 0.133 CDSS: -1.4 (3.6), -1.5 (3.3), -0.3 (2.5), 0.205 YMRS: -5.5 (4.5), -6.8 (5.9), -6.5 (5.1), 0.626 **Per protocol sample: mean (SD) severity of extrapyramidal sx from baseline to 1 year (Haloperidol, Olanzapine, Risperidone, P)** BAS: 0.54 (0.98), 0.00 (0.00), 0.32 (0.72), 0.007 Simpson-Angus Scale: 0.46 (1.77), -0.48 (1.74), 0.27 (1.57), 0.057

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Author, year Study design	Adverse effects reported
Crespo-Facorro, 2006 Crespo-Facorro, 2009 Crespo-Facorro, 2011b Spain	Mean change (SD) from baseline to endpoint in EPS severity (haloperidol vs. olanzapine vs. risperidone) BAS: 0.66 (1.16) vs. 0.13 (0.64) vs. 0.36 (0.91); P=0.012 Simpson Angus Scale: 2.27 (2.62) vs. 0.25 (1.61) vs. 1.31 (2.55); P=0.000 AEs reported (risperidone vs. olanzapine vs. haloperidol): Concentration difficulties: 14.3% vs. 3.6% vs. 3.3%; P=0.044 Asthenia: 42.9% vs. 29.1% vs. 27.9%; P=0.169 Sleepiness/sedation: 46.4% vs. 45.5% vs. 23.0%; P=0.012 Increased duration of sleep: 23.2% vs. 12.7% vs. 6.6%' P=0.033 Increased salivation: 17.9% vs. 3.6% vs. 14.8%; P=0.055 Reduced salivation: 12.5% vs. 12.7% vs. 4.9%; P=0.270 Weight gain (increase >/=4kg): 8.9% vs. 47.3% vs. 23.0%; P<0.001 Erectile dysfunction: 13.9% vs. 3.0% vs. 7.9%; P=0.244 Ejaculatory dysfunction: 5.6% vs. 0.0% vs. 13.2%; P=0.072 Amenorrhea: 10.0% vs. 0.0% vs. 8.7%' P=0.549

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Extrapyramidal symptoms
Crespo-Facorro, 2006 Crespo-Facorro, 2009 Crespo-Facorro, 2011b Spain	Prescribed anticholinergics for EPS during treatment (haloperidol vs. risperidone vs. olanzapine): 74.5% vs. 32.8% vs. 3.8%; P<0.0001 Rigidity: 14.3% vs. 0.0% vs. 4.9%; P=0.005 Hypokinesia: 19.6% vs. 1.8% vs. 8.2%; P=0.006 Tremor: 7.1% vs. 3.6% vs. 8.2%; P=0.633 Akathisia: 23.2% vs. 5.5% vs. 14.8%; P=0.029 Per protocol sample: severity of extrapyramidal sx. change from baseline after 1 yr follow-up period Haloperidol mean (SD) vs. Olanzapine mean (SD) vs. Risperidone (SD), P BAS: 0.54 (0.98) vs. 0.00 (0.00) vs. 0.32 (0.72), 0.007 Simpson-Angus Scale: 0.46 (1.77) vs. -0.48 (1.74) vs. 0.27 (1.57), 0.057

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Total withdrawals; withdrawals due to adverse events	Comments
Crespo-Facorro, 2006 Crespo-Facorro, 2009 Crespo-Facorro, 2011b Spain		

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Eligibility criteria	Interventions (drug, dose, duration)	Allowed other medications	Age Gender Ethnicity	Other population characteristics
Crespo-Facorro, 2011 Crespo-Facorro, 2012 Spain	Age 15-60 years, experiencing first psychotic episode, <6 weeks lifetime antipsychotic treatment, meet DSM-IV criteria for brief psychotic disorder, schizophreniform disorder, schizophrenia, schizoaffective disorder. Excluded DSM-IV criteria for drug dependence or mental retardation, history of neurological disease or head injury.	Haloperidol: n, 56; mean dose, 2.9 (1.4) mg/d Olanzapine: n, 55; mean dose, 10.1 (3.9) mg/d Risperidone: n, 63; mean dose, 3.4 (1.8) mg/d 3 yrs	As clinically indicated, Lormetazepam; Clonazepam; Biperiden, up to 8 mg/d; Setraline; Lithium	Age, mean: 27.4 Gender: 38% female Ethnicity: NR	Age, psychosis onset: 26y Duration of illness: 25 months Duration of psychosis: 11 months Diagnosis: Schizophrenia, 60.8%; Schizophreniform, 24.1%; Schizoaffective, 2.4%, Brief psychotic disorder, 5.4%; Unspecified psychotic disorder, 7.2%

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Number screened/ eligible/ enrolled	Withdrawn/ Lost to follow-up/ Analyzed	Results
Crespo-Facorro, 2011 Crespo-Facorro, 2012 Spain	243/184/174	21/NR/174 analyzed for remission, 164 analyzed for relapse	Haloperidol vs. Olanzapine vs. Risperidone: Relapse Rate: 11.1% vs. 18.5% vs. 13.8%; p=0.541 Time to relapse, mean (95% CI): 10.9 (10.89-11.72) vs. 10.78 (9.99-11.56) vs. 10.98 (10.25-11.71); p=0.857 Relapse, adherent vs. non-adherent: 11.2% vs. 26.9%, p=0.040 Remission at 1 year: 25% vs. 32.7% vs. 34.9%; x^2=1.471, p=0.479 Remission at 1 year, patients continuing on drug: 25% vs. 43.2% vs. 41.5%, p=0.308 Remission, adherent vs. non-adherent: 36.9% vs. 27.6%, p=0.347 Treatment discontinuation rate and time to discontinuation: (Haloperidol %, Olanzapine %, Risperidone %, P) Discontinuation for any cause: 80.4, 50.9, 66.7, 0.005 Discontinuation, insufficient efficacy: 17.9, 12.7, 6.3, 0.155 Discontinuation, side effect: 32.1, 12.7, 25.4, 0.050 Discontinuation, noncompliance: 16.1, 5.5, 6.3, 0.095 Discontinuation, dropout: 14.3, 20.0, 28.6, 0.158 Adherence and global functioning @ 3 yr follow-up: Adherence NSD between tx (83.3% haloperidol, 68.2% olanzapine, 78.9% risperidone, p=0.605) Global functional outcome NSD between tx (81.8% haloperidol-tx, 63% olanzapine-tx, 71.4% risperidone-tx w/ good functionality @ 3 yr follow-up, p=0.505) Clinical efficacy: No advantages to any of the 3 txs in reduction of symptomology @ 3 yr Safety: NSD in increment of extrapyramidal signs @ 3 yrs between txs (p=0.132) NSD in treatment-emergent parkinsonism between treatment arms (p=0.114) Greater increase in akathisia severity w/ haloperidol tx @ 3 yr assessment (p=0.013) Sig. increase in akathisia severity in risperidone-tx patients compared to olanapine-tx patients (p=0.042) Sig. higher number in haloperidol-tx group experienced tx-emergent akathisia compared to risperidone-tx and olanzapine-tx patients (p=0.013)

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Adverse effects reported
Crespo-Facorro, 2011 Crespo-Facorro, 2012 Spain	Haloperidol % vs. Olanzapine % vs. Risperidone %, P Concentration difficult: 9.1 vs. 7.7 vs. 0.0, 0.419 Asthenia: 9.1 vs. 23.1 vs. 0.0, 0.057 Daytime drowsiness: 0.0 vs. 34.6 vs. 10.0, 0.022 Increased sleep hours: 9.1 vs. 11.5 vs. 5.0, 0.739 Akathisia: 27.3 vs. 0.0 vs. 5.0, 0.011 Sialorrhea: 0.0 vs. 0.0 vs. 15.0, 0.053 Dry mouth: 0.0 vs. 7.7 vs. 10.0, 0.571 Weight gain: 9.1 vs. 26.9 s. 20.0, 0.473 Amenorrhea (only females, n=23): 0.0 vs. 0.0 vs. 40.0, 0.043 Sexual dysfunctions (only males, n=34): 14.3 vs. 5.9 vs. 40.0, 0.078

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Extrapyramidal symptoms
Crespo-Facorro, 2011 Crespo-Facorro, 2012 Spain	NR

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Total withdrawals; withdrawals due to adverse events	Comments
Crespo-Facorro, 2011 Crespo-Facorro, 2012 Spain		

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Eligibility criteria	Interventions (drug, dose, duration)	Allowed other medications	Age Gender Ethnicity	Other population characteristics
Crespo-Facorro, 2013 Spain	(1) 15–60 years; (2) living in the catchment area; (3) experiencing their first episode of psychosis; (4) no prior treatment with antipsychotic medication or, if previously treated, a total lifetime of adequate antipsychotic treatment of less than 6 weeks; (5) DSM-IV criteria for brief psychotic disorder, schizophreniform disorder, schizophrenia, or schizoaffective disorder. Patients were excluded for any of the following reasons: (1) meeting DSM-IV criteria for drug dependence, (2) meeting DSM-IV criteria for mental retardation, (3) having a history of neurological disease or head injury.	Aripiprazole 5–30 mg/day Ziprasidone 40–160 mg/day Quetiapine 100– 600 mg/day Rapid titration schedule (5 days), until optimal dose	Antimuscarinic medication, lormetazepam and clonazepam, were permitted for clinical reasons. No antimuscarinic agents were administered prophylactically. Antidepressants and mood stabilizers were permitted if clinically needed	Mean age 32.0 53% male 95% White	Age at psychosis onset: mean 30.8 Duration of illness: mean 23.8 months Diagnosis = schizophrenia: 54% Inpatient: 66% Family history: 24%
Cutler, 2008 DB RCT 35 centers United States and 9 in India.	Men and women aged 18 to 65 ys, a BMI between 18 and 35 kg/m2, schizophrenia, CGI-S or 4 or more , PANSS > 70 and rating of 4 (moderate) or greater on at least 2 of PANSS Positive symptoms: delusions, conceptual disorganization, hallucinations, and suspiciousness/ persecution .	3 wks - Iloperidone 24 mg n=295 Ziprasidone 160 mg n=149 P n=149.	Zolpidem (or similar medication) and Benztropine	Age 39.9 yrs 79.6% male 35.1% white 50.4% black 8.8% Asian 0.5% American Indian 0.3% Pacific Islander 4.9% other	Diagnosis Schizophrenia, disorganized 3.9% Schizophrenia, paranoid 84.5% Schizophrenia, undifferentiated 11.6%

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Number screened/ eligible/ enrolled	Withdrawn/ Lost to follow-up/ Analyzed	Results
Crespo-Facorro, 2013 Spain	249/224/224	Quetiapine: 54, 11 LFTU/51 Ziprasidone: 42; 6 LTFU/56 Aripiprazole: 28/ 10 LTFU/68	Response (≥40 % BPRS and ≤4 CGI) aripiprazole, 84.8 %; ziprasidone, 88.9 %; quetiapine, 76.0 %; p =0.195. Response = at least 50 % decrease in total BPRS: aripiprazole, 84.8 %; ziprasidone, 87.0 %; quetiapine, 76.0 %; p =0.285 Treatment discontinuation for any cause:. Quetiapine 82.3 %, aripiprazole 43.6 %, ziprasidone 66.1 %. p <0.001 Time to discontinuation: aripiprazole 106.71 (95 % CI, 75.19–138.22), ziprasidone 129.88 (95 % CI, 95.50–164.25) and quetiapine 77.24 (95 % CI, 52.88–101.59); p <0.001
Cutler, 2008 DB RCT 35 centers United States and 9 in India.	913/ NR / 593	212 / 0 / 593	Iloperidone vs. Ziprasidone vs. P Adjusted mean changes BPRS 7.39 (0.63)* vs.7.21 (0.89)* vs. 4.62 (0.91) PANSS-P 4.21 (0.34)*** vs. 4.23 (0.48)*** vs. 2.22 (0.49) PANSS-N 2.96 (0.27)* vs. 3.06 (0.38)* vs. 1.91 (0.39) PANSS-GP 4.94 (0.54) vs. 5.24 (0.76)vs. 3.18 (0.77) CGI-S 0.65 (0.05)** vs. 0.67 (0.08)* vs. 0.39 (0.08) *P < 0.05 (2-tailed) vs P **P < 0.01 (2-tailed) vs P ***P < 0.001 (2-tailed) vs P

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Adverse effects reported
Crespo-Facorro, 2013 Spain	Discontinuation due to adverse effects: quetiapine 11.3%, ziprasidone 29 % and aripiprazole 10.3 %; p =0.005.
Cutler, 2008 DB RCT 35 centers United States and 9 in India.	Iloperidone vs. Ziprasidone vs. P n(%) At least 1 AE 255 (85) vs. 130 (87) vs. 108 (74) Dizziness 51 (17) vs. 20 (13) vs. 11 (8) Sedation 38 (13) vs. 41 (27) vs. 12 (8) Weight increased 34 (11) vs. 7 (5) vs. 3 (2) Dry mouth 26 (9) vs. 11 (7) vs. 1 (0.7) HR increased 24 (8) vs. 9 (6) vs. 1 (0.7) Nasal congestion 25 (8) vs. 5 (3) vs. 4 (3) Tachycardia 28 (9) vs. 3 (2) vs. 1 (0.7) EPS 10 (3) vs. 14 (9) vs. 3 (2) Agitation 10 (3) vs. 10 (7) vs. 4 (3) Orthostatic hypotension 21 (7) vs. 0 vs. 3 (2) Somnolence 12 (4) vs. 9 (6) vs. 2 (1) Restlessness 11 (4) vs. 8 (5) vs. 3 (2) Anxiety 9 (3) vs. 8 (5) vs. 1 (0.7) Akathisia 4 (1) vs. 11 (7) vs. 0

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Extrapyramidal symptoms
Crespo-Facorro, 2013 Spain	No significant differences in the increment of extrapyramidal signs at 1 year (SARS total score) between treatments (p =0.510). The percentage of patients with treatment– emergent parkinsonism (SARS total score > 3 at 6-week, 3-month or/and 1-year assessments, with total score of < 3 at baseline): aripiprazole=17.7 %; ziprasidone= 19.6 % and quetiapine 14.3 %; p =0.794 Severity of akathisia (BAS total score) at 12-months:p =0.185 across groups Treatment–emergent akathisia (BAS global score of >2 at 6-week, 3-month or/and 1-year, given a score < 2 at baseline): aripiprazole- 30.6 %, ziprasidone 26.0 % quetiapine14.0 %; p =0.142
Cutler, 2008 DB RCT 35 centers United States and 9 in India.	Iloperidone vs. Ziprasidone vs. p n(%) EPS 10 (3) vs. 14 (9) vs. 3 (2) Additional results presented graphically

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Total withdrawals; withdrawals due to adverse events	Comments
Crespo-Facorro, 2013 Spain	Quetiapine: 54, 7 due to AE Ziprasidone: 42; 18 due to AE Aripiprazole: 28; 8 due to AE	
Cutler, 2008 DB RCT 35 centers United States and 9 in India.	212 total 40 due to AEs	

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Eligibility criteria	Interventions (drug, dose, duration)	Allowed other medications	Age Gender Ethnicity	Other population characteristics
Daniel, 1996 Crossover	Patients with chronic schizophrenia or schizoaffective disorder, with treatment failures or intolerant to conventional antipsychotic side effects	clozapine or risperidone; dose titrated by clinician x 6 wks. Dose was held stable during wks 5 & 6. mean clozapine dose: 375mg/d (range 75-800mg) mean risperidone dose: 6.1mg/d (range 1-10mg)	estazolam, lorazepam for insomnia, lorazepam for agitation, benztropine for EPS. Other psychoactive drugs continued, but no dose changes allowed. Drugs used: valproic acid, fluoxetine, paroxetine, sertraline, clonazepam, and clorazepate	Mean age 33.8 ys (22-51) 35% male ethnicity NR	Mean age at onset: 22.7 (15-32) mean # prior hospitalizations: 3.9 (1-10) mean # prior antipsychotic trials: 4.3 (2-8) 95% outpatients
Davidson, 2007 RCT, DB, PCT, parallel, multicenter (international sites)	Male & female ≥ 18 ys of age and experiencing an acute episode of schizophrenia, as represented by a PANSS total score between 70 and 120. Must have been diagnosed with schizophrenia according to DSM-IV criteria for at least 1 y prior to screening and have agreed to voluntary hospitalization for a minimum of 14 ds.	Paliperidone ER (3mg, 9mg, and 15mg) as qd dosing compared with P or Olanzapine 10mg/d in a 6-week study.	Benzodiazepines were permitted with a stable dose for at least 3 mos. Benztropine 1 or 2mg bid or biperiden 2mg 3 times daily were permitted for movement disorder treatment.	Mean age: 36.8 ys 68.0% male 32.0% female 49.0% white 21.0% black/ African American 24% Asian 6% Other	Previous antipsychotic therapy atypical 59 conventional 55 PANSS total score 93.0 age at diagnosis 25.1 weight 75.2 Kg

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Number screened/ eligible/ enrolled	Withdrawn/ Lost to follow-up/ Analyzed	Results
Daniel, 1996 Crossover	NR/NR/20 enrolled	3 withdrawn (during risperidone treatment): 1 due to AEs, 1 due to AEs and lack of effect, 1 withdrew after achieving satisfactory response, in order to obtain non-study drug 17 analyzed	No significant difference on PANSS total, positive or negative subscales, or CGI (data NR). No significant differences on cognitive tests (after application of Bonferroni adjustment for multiple comparisons)
Davidson, 2007 RCT, DB, PCT, parallel, multicenter (international sites)	732/NR/618	253/6/605	Paliperidone ER = significant improvements in PANSS total and PANSS factor scores ($p<0.05$) and in personal and social functioning ($p<0.001$) compared with P. 59% completed 6-week study. PANSS total score in P vs. Paliperidone ER = -2.8±20.9, -15.0±19.6,-16.3±21.8 and -19.9±18.4, respectively. PANSS Marder factor shows paliperidone ER improvement over P ($P\leq0.005$)

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Adverse effects reported
Daniel, 1996 Crossover	7/17 (41%) required Anti-EPS meds while on risperidone 0 required Anti-EPS meds while on clozapine Prior to Bonferroni adjustment: Sleepiness/lack of alertness: SS more with clozapine Restlessness/insomnia: SS more with risperidone Inability to think clearly/inability to concentrate: SS related to clozapine dose After correction: restlessness NSly different no dose correlation apparent
Davidson, 2007 RCT, DB, PCT, parallel, multicenter (international sites)	Study discontinuation similar in all groups (2-5%). TEAEs in all groups were insomnia, headache and tachycardia. Serious TEAEs were low in all treatment groups (P = 7%, paliperidone ER 3mg = 6%, paliperidone ER 9mg = 10%, paliperidone ER 15mg = 5%, and olanzapine = 6%) Most commonly reported TEAE as serious was psychosis (6% in P, 5% in paliperidone ER 3mg, 6% in paliperidone ER 9mg, 3% in paliperidone ER 15 and olanzapine groups). Glucose related AE's across all groups = n = 6 SAS = no statistically significant increase in paliperidone ER 3 mg and 15 mg groups compared to P. Increase in SAS global score for paliperidone ER 9 mg compared to P (p=0.004)

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Extrapyramidal symptoms
Daniel, 1996 Crossover	7/17 (41%) required Anti-EPS meds while on risperidone 0 required Anti-EPS meds while on clozapine
Davidson, 2007 RCT, DB, PCT, parallel, multicenter (international sites)	BARS = absent in 76-79% of patients in p, paliperidone ER 9mg and 15mg groups and 85% in paliperidone ER 3mg group. AIMS score reported as 0.0. Most movement disorder-related TEAEs = mild or moderate

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Total withdrawals; withdrawals due to adverse events	Comments
Daniel, 1996 Crossover	3/20 (15%) total WD 2/20 (10%) due to AEs	Results NR by first intervention/second intervention. Not possible to evaluate effect of order of assignment, although authors use Bonferroni adjustment to correct for this.
Davidson, 2007 RCT, DB, PCT, parallel, multicenter (international sites)	253 total WD 23 due to AEs	

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Eligibility criteria	Interventions (drug, dose, duration)	Allowed other medications	Age Gender Ethnicity	Other population characteristics
Deberdt, 2008 DB RCT	Males and females between 18 and 75 ys of age and diagnosed with schizophrenia or schizoaffective disorder according DSM-IV: a confirmed psychotic episode within the last 5 ys prior to enrollment; clinically stable for at least 15 ds on a fixed dose of olanzapine (10–20 mg/d) prior to enrollment; obese (BMI [BMI] 30 kg/m2) or overweight (BMI 25 kg/m2 and 30 kg/m2) with at least one CV risk factor (diabetes mellitus or impaired fasting glucose, dyslipidemia, elevated blood pressure, or waist circumference 102 cm for men or 88 cm for women); free of any other signifi cant medical illness at enrollment.	Olanzapine group: continue with original olanzapine treatment, then 7.5-20 mg/d; Mean modal dose of 16.9 mg/d; 24 wks Quetiapine griyo: olanzapine dose gradually decreased and completely discontinued by d 7, with quetiapine dose gradually increased to 300-800 mg/d; mean modal dose of 439.7 mg/d; 24 wks	concomitant medications with primary central nervous system activity were not allowed in this protocol.	Olanzapine vs Quetiapine Age (SD): 45.4 (9.4) vs 42.5 (11.5) ys Gender: NR Ethnicity: NR	Olanzapine vs Quetiapine Mean time on olanzapine (SD) 67.5 (98.5) vs 69.4 (107.8) wks; P=0.554 Mean total PANSS (SD): 61.1 (17.9) vs 65.9 (20.4); P= 0.033 Mean BMI (SD): 34.6 kg/m2 (7.1) vs 37.5 kg/m2 (8.6); P=0.042
Dollfus, 2005 DB, RCT	Age 18-65 pts with post-psychotic depression according to DSM-IV criteria with maximum PANSS score of 28 and minimum total MADRS score of 16 at screening and baseline	Olanzapine 5-15 mg/d Risperidone 4-8 mg/d	benzodiazepines; biperidine	Mean age: 39.3 yrs 69.7% male Ethnicity NR	Use of biperiden during study: 9% (7/76 enrolled pts)
Emsley, 1999 Australia, Belgium, Canada, France, Germany, Great Britain, Korea, The Netherlands, South Africa, and Sweden	15 to 45 ys; had a diagnosis of provisional schizophreniform disorder (295.40) or schizophrenia without prior treatment according to DSM-III-R; psychotic symptoms requiring an oral antipsychotic agent; had received a maximum of 3 ds of emergency treatment for this disorder; Exclusion- had clinically relevant neurological, electrocardiographic, or laboratory test abnormalities; pregnant or lactating; women of reproductive age not using adequate contraception; mental illness other than schizophreniform disorder or schizophrenia (according to Axis I of DSM-IH-R); psychoactive substance abuse (DSM-III—R criteria)	Risperidone or haloperidol 2- 8 mg/d for 6 wkss	Antiparkinsonian drugs or benzodiazepines	Median age 24-26 ys Male 67% 62% white 17% oriental 15% black 6% other	Age at onset of first symptoms of psychosis (median)=23.5 ys Primary diagnosis (% patients): Provisional schizophreniform disorder=93.5 Paranoid schizophrenia=4.5 Undifferentiated schizophrenia=1.5 Disorganized schizophrenia=0.5 Level of functioning (% patients): 1-20=11.4 21-50=74.6 51-80=13.9

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Number screened/ eligible/ enrolled	Withdrawn/ Lost to follow-up/ Analyzed	Results
Deberdt, 2008 DB RCT	NR/NR/133	57/NR/133	Olanzapine vs Quetiapine Hospitalization for psychiatric reasons after Visit 2: 1 (1.47%) vs 5 (7.69%); P=NS 20% worsening in PANSS Total score and increase in Level of Care for psychiatric reason after Visit 2: 0 vs 2 (3.08%); P=NS 20% worsening on the PANSS Total score 7 and worsening of CGI-S by at least one level compared to baseline and CGI-S score: 4(10.29%) vs 7 (10.77%); P=NS Patients meeting at least one of the above criteria: 8 (11.76%) vs 10 (15.38%); P=NS Discontinuations due to psychiatic AEs higher in quetiapine group (P=0.031) Improvements in PANSS total socres throughout study for both groups (shown in figure 3). At wks 13 and 19, improvement from baseline was no longer significant for quetiapine group, and significantly worse than olanzapine group.
Dollfus, 2005 DB, RCT	NR/NR/76	NR/NR/76	Mean change from baseline in MADRS score at 8 wks: O -14.1 (SD 8.4) v R -14 (SD 8.8); p reported as not SS (no figure provided) Mean change from baseline in positive PANSS score at 8 wks (or at point of WD) in pts with MADRS decrease of ≥30%: O -2 (SD 4.4) v R -2.9 (SD 3.4) Mean change from baseline in negative PANSS score at 8 wks (or at point of WD) in pts with MADRS decrease of ≥30%: O -6.2 (SD 6.1) v R -6.2 (SD 5.4)
Emsley, 1999 Australia, Belgium, Canada, France, Germany, Great Britain, Korea, The Netherlands, South Africa, and Sweden	NR/NR/NR	46/NR/182	Clinically improved according to total PANSS scores Risperidone 63% vs. haloperidol 56% (p = 0.19), and Improved according to total BPRS scores Risperidone 65% and haloperidol 55% (p = 0.08) CGI change scale - much or very much improved; Risperidone 71% vs. haloperidol 70%

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Adverse effects reported
Deberdt, 2008 DB RCT	Weight gain higher in olanzapine group from wks 2 to week 13 (P<0.05). No difference in weight gain at last visit. LOCF analysis showed no significant between group differences in weight (P=0.088), BMI (P=0.15), fasting glucose (P=0.228), HbA1c (P=0.318), cholesterol (P=0.471), LDL (P=0.981), HDL (P=0.872), Insulin (P=0.262) and triglycerides (P=0.167). No statistically significant differences in treatment-emergent AEs between treatment groups. Most common (≥5%) in the olanzapine treatment group were sedation, vomiting, anxiety, hypertension, insomnia, pharyngolaryngeal pain, somnolence, weight decrease, and weight increase. In the quetiapine treatment group,most common(≥5%) were sedation, anxiety, insomnia, weight increase, headache, constipation, dry mouth, auditory hallucination, paranoia, and agitation.
Dollfus, 2005 DB, RCT	NR
Emsley, 1999 Australia, Belgium, Canada, France, Germany, Great Britain, Korea, The Netherlands, South Africa, and Sweden	Haloperidol vs. risperidone Total AEs 90% vs. 78% p < 0.05 Insomnia 16% vs. 10% Headache 10% in each group Agitation 11% vs. 8% Anxiety 8% in each group

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Extrapyramidal symptoms
Deberdt, 2008 DB RCT	NR
Dollfus, 2005 DB, RCT	NR
Emsley, 1999 Australia, Belgium, Canada, France, Germany, Great Britain, Korea, The Netherlands, South Africa, and Sweden	Antiparkinsonian medications required - haloperidol 75% vs. risperidone 50%; p < 0.001 Shift from baseline Haloperidol vs. risperidone Questionnaire 5.1 vs. 3.9 p = 0.101 Hypokinesia factor 5.4 vs.4.5 p = 0.273 Hyperkinesia factor 2.4 vs. 1.4 p = 0.007 Parkinsonism total 8.1 vs. 6.1 p = 0.060 Parkinsonism + dystonia 8.6 vs. 6.3 p = 0.060 Parkinsonism + dystonia + dyskinesia 9.0 vs. 6.5 p = 0.046 CGI Parkinsonism severity 2.2 vs. 1.9 p = 0.150

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Total withdrawals; withdrawals due to adverse events	Comments
Deberdt, 2008 DB RCT	Olanzapine vs Quetiapine Total WD: 20 vs 37 WD due to AEs: NR (total given in figure; 20-25%)	
Dollfus, 2005 DB, RCT	NR / NR	Study did not enroll an adequate number of patients to achieve statistical significance (76 pts enrolled vs 160 intended N)
Emsley, 1999 Australia, Belgium, Canada, France, Germany, Great Britain, Korea, The Netherlands, South Africa, and Sweden		

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Eligibility criteria	Interventions (drug, dose, duration)	Allowed other medications	Age Gender Ethnicity	Other population characteristics
Feldman, 2003 Sutton, 2001 (Tran, 1997 sub-analysis) RCT, multicenter, multinational (6 European, South Africa and US) Post-hoc Analysis of Negative symptoms in older patients	Subset of Tran - patients aged 50 to 65 ys.	olanzapine 10-20mg/d risperidone 4-8mg/d Duration: 28 wks mean dose for subset NR	NR	Mean age: 57 92.3% white 56.4% male	82% schizophrenia diagnosis 64% had prominent negative symptoms mean # prior episodes: 10

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Number screened/ eligible/ enrolled	Withdrawn/ Lost to follow-up/ Analyzed	Results
Feldman, 2003 Sutton, 2001 (Tran, 1997 sub-analysis) RCT, multicenter, multinational (6 European, South Africa and US) Post-hoc Analysis of Negative symptoms in older patients	NR/NR/39 19 olanzapine 20 risperidone	20/NR/39	At 8 wks: Mean change in total PANSS: olanzapine 27.2, risperidone 21.0 (NS) Mean change in PANSS positive: olanzapine -6.8, risperidone -6.5 (NS) Mean change in PANSS General Psychopathology olanzapine: -10.8, risperidone: -10.0 (NS) Mean change PANSS negative: olanzapine: -8.8, risperidone: -4.9 (p = 0.032) Mean change SANS summary: olanzapine: -3.6, risperidone: -2.1 Mean change SANS composite olanzapine: -13.0, risperidone: -6.5 Mean change CGI-S olanzapine -0.8, risperidone: -0.7 At 28 wks: Overall, change in scores decreased slightly Differences remained NS for all but PANSS negative (p=0.032) Differences on SANS remained NS for summary and composite scores Analysis of 5 components revealed SS on 2 items: Affective flattening: olanzapine: -5.2, risperidone -0.6 (p=0.033) Alogia olanzapine: -3.8, risperidone: -0.3 (p=0.007)

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Adverse effects reported
Feldman, 2003 Sutton, 2001 (Tran, 1997 sub-analysis) RCT, multicenter, multinational (6 European, South Africa and US) Post-hoc Analysis of Negative symptoms in older patients	% Olanzapine, % Risperidone, (p-value) Weight gain 25%, 0%, (p=0.047) Mean weight gain: 4.7kg, 0.6kg (p=0.052) With >20% incidence, but NS difference: somnolence 25%, 32% agitation 10%, 21% anxiety 30%, 5% (p=0.091) EPS: For measures of EPS, data for only 12 olanzapine and 9 risperidone available AIMS, BAS, and SAS NS difference, small changes

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Extrapyramidal symptoms
Feldman, 2003 Sutton, 2001 (Tran, 1997 sub-analysis) RCT, multicenter, multinational (6 European, South Africa and US) Post-hoc Analysis of Negative symptoms in older patients	For measures of EPS, data for only 12 olanzapine and 9 risperidone available AIMS, BAS, and SAS NS difference, small changes

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Total withdrawals; withdrawals due to adverse events	Comments
Feldman, 2003 Sutton, 2001 (Tran, 1997 sub-analysis) RCT, multicenter, multinational (6 European, South Africa and US) Post-hoc Analysis of Negative symptoms in older patients	20 total WD 6 due to AE	Small N; power for statistical differences lacking. Length of current episode: 120 ds for risperidone patients, 61 ds for olanzapine patients, but NS difference olanzapine: 70% male; risperidone: 42% male.

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Eligibility criteria	Interventions (drug, dose, duration)	Allowed other medications	Age Gender Ethnicity	Other population characteristics
Fleischhacker, 2009 DB RCT Multinational - Australia, Europe, and South Africa Multicenter (119)	18 and 65 ys of age, who were diagnosed with schizophrenia (according to the DSM-IV criteria) and were in acute relapse and who had demonstrated a previous response to antipsychotic drugs.	Olanzapine mean 15.4 mg/d n=348 Aripiprazole mean 23.0 mg/d n=355 6 week duration	Benzodiazepines and 4 mg/d lorazepam (or 20 mg/d diazepam) for anxiety plus 1–2 mg lorazepam (5–10 mg diazepam) if needed for sleep and anticholinergic drugs for extrapyramidal symptoms (EPS)	Mean age olanzapine 37.3 aripiprazole 35.9 yrs % male olanzapine 56 aripiprazole 57 % white olanzapine 90 aripiprazole 92 % black olanzapine 5 aripiprazole 4 % other olanzapine 5 aripiprazole 5	Diagnosis olanzapine vs. aripiprazole Schizophrenia Type, n (%) Disorganized 28 (8) vs. 28 (8) Catatonic 1 (1) vs. 1 (1) Paranoid 272 (78) vs. 276 (78) Residual 4 (1) vs. 9 (3) Undifferentiated 43 (12) vs. 41 (12)
Fleischhacker, 2012 DB RCT Multi-Center	Schizophrenia for at least a y, men and women (>18 yr), PANSS score between 60-120, BMI >15.0kg/m2.	• PP (intramuscular gluteal injection) = 100 mg. Max dose. • P • RIS-LAI (gluteal injection) = 50 mg. Max dose. Duration: 53 wks.	• Risperidone • Oral lorazepam = 6 mg. Max dose. • Other benzodiazepines • Oral propranolol • Antidepressants were allowed if used at a stable dose 30 ds before screening.	Mean Age = 41 Men = 59% White = 92% Black = 4% Asian = 2.5% American Indian or Alaskan Native = .5% Other = 1.5%	Prior Hospitalization • None = 11% • Once = 18% • Twice = 16% • Three= 13% • Four or More = 42%
Gaebel 2010 Multi-Center	Symptomatically stable adults, >18 ys, DSM-IV criteria for schizophrenia or shizoaffective disorder. Considered symptomatically stable when using stable dose >4 wks (including monotherapy with oral risperidone <6mg daily, olanzapine <20 mg daily, or a conventional neuroleptic <10 mg haloperidol or its equivalent) and were living in the same residence for >30 ds.	RLAI = 50 mg. Max dose. Quetiapine = 750 mg. Max dose. Duration: 2 ys	NR	Mean Age = 42 Male = 58% Female = 42% Ethnicity: NR	Schizophrenia = 82% Schizoaffective disorder = 18%

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Number screened/ eligible/ enrolled	Withdrawn/ Lost to follow-up/ Analyzed	Results
Fleischhacker, 2009 DB RCT Multinational - Australia, Europe, and South Africa Multicenter (119)	NR/NR/750	181 / 0 / 703	Mean change in PANSS Total score olanzapine: -29.5 vs. aripiprazole: -24.6 Mean change in CGI-S olanzapine, 1.42; vs. aripiprazole, 1.25 Mean CGI-I score olanzapine, 2.23; vs. aripiprazole, 2.50 Responders olanzapine, 78%; vs. Aripiprazole 73%
Fleischhacker, 2012 DB RCT Multi-Center	807/749/749	410/23/ ITT analysis set :674 patients, per-protocol analysis: 570	Effectiveness: Symptom response: Improved PSP scores compared to baseline: ITT analysis set, 43% (n=138/322) of PP groupvs. 46% (n=148/323) RIS-LAI group Responders, 30% improvement in PANSS total score compared to baseline: ITT, 44% (n=152/343) vs PP group vs 54% (n=179/329) for the RIS-LAI group. Positive and Negative Syndrome Scale: Mean (S.D.) change from baseline to endpoint in PANSS total score: -11.6 (21.22) PP; -14.4 (19.76) RIS-LAI (per-protocol analysis set, primary measure) ; least-squares means difference: -2.6 (95% CI -5.84 to 0.61)
Gaebel 2010 Multi-Center	808/808/710	395/19/666	RLAI vs Quetiapine Relapse: 16.5% vs, 31.3% Symptom response: PANSS Total Scores at endpoint: mean (N): 63.4 (326) vs. 72.1 (325)

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Adverse effects reported
Fleischhacker, 2009 DB RCT Multinational - Australia, Europe, and South Africa Multicenter (119)	Significant weight gain at Week 26 - olanzapine 40%vs. aripiprazole 21%; p < .05 Mean weight gain at Week 26 - olanzapine 4.30 kg vs. aripiprazole 0.13 kg Olanzapine vs. aripiprazole - n (%) Weight Gain 73 (21) vs. 21 (6) Insomnia 71 (21) vs. 95 (27) Anxiety 45 (13) vs. 56 (16) Somnolence 37 (11) vs. 15 (4) Asthenia 32 (9) vs. 27 (8) Headache 28 (8) vs. 54 (15) Reaction Schizophrenic 24 (7) vs. 32 (9) Akathisia 21 (6) vs. 33 (9) Dry mouth 20 (6) vs. 10 (3) Agitation 18 (5) vs. 23 (7) Nausea 12 (3) vs. 30 (9) Tremor 11 (3) vs. 21 (6) Vomiting 10 (3) vs. 23 (7) Psychosocial Support 8 (2) vs. 21 (6) Extrapyramidal Syndrome 4 (1) vs. 20 (6)
Fleischhacker, 2012 DB RCT Multi-Center	Overall, the rates of TEAEs: PP 76% vs. RIS-LAI 9% Insomnia: 15% vs. 15% Psychotic disorder:14% PP vs12% RIS-LAI Worsening or relapse of schizophrenia: 12% PP vs. 9% RIS-LAI Anxiety:10% PP vs. 15% RIS-LAI Headache: 9% PP vs.11% RIS-LAI Treatment-emergent glucose-related AEs: N=14 RIS-LAI N=8 vs. PP N=14 Study related death: 3
Gaebel 2010 Multi-Center	Overall adverse events: Treatment-emergent potentially prolactin-related AEs: 5% vs. 2% Hyperprolactinemia: 13.1% vs. 1.5% Somnolence: 2% vs. 11% Weigth gain: 7% vs. 6%, mean end point increases 1.25±6.61 vs. 0±6.55 kg

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Extrapyramidal symptoms
Fleischhacker, 2009 DB RCT Multinational - Australia, Europe, and South Africa Multicenter (119)	Mean change at Week 52 Simpson-Angus Scale Total score olanzapine 1.2 vs. aripiprazole .7 (p < .001; LOCF analysis). Barnes Akathisia Global Clinical Assessment score olanzapine .10 vs. aripiprazole no change (p = .043; LOCF analysis). EPS related AEs olanzapine 44 (13%) vs. aripiprazole 73 (21%)
Fleischhacker, 2012 DB RCT Multi-Center	Extrapyramidal effects: Treatment-emergent EPS-related adverse events: 6% PP vs. 10% RIS-LAI Akathisia: N=2 PP only Neuroleptic malignant syndrome: N=1 PP, only aNo Tardive dyskinesia: N=0
Gaebel 2010 Multi-Center	Extrapyramidal AEs: 10% vs. 6%

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Total withdrawals; withdrawals due to adverse events	Comments
Fleischhacker, 2009 DB RCT Multinational - Australia, Europe, and South Africa Multicenter (119)	181 WD 55 due to AEs	
Fleischhacker, 2012 DB RCT Multi-Center	Withdrawals due to adverse events: Neuroleptic malignant syndrome: N=1 PP (Reports withdrawl due to any event) AEs occurred in 10% of patients with RLAI and 6% with quetiapine.	
Gaebel 2010 Multi-Center	Withdrawals due to adverse events: 4.6%	

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Eligibility criteria	Interventions (drug, dose, duration)	Allowed other medications	Age Gender Ethnicity	Other population characteristics
Garyfallos, 2003	50 acute ward patients fulfilling DSM IV criteria for schizophrenia, schizophreniform or schizoaffective disorder; at time of admission, they had not been on antipsychotic treatment	During stable period, mean doses: olanzapine: 18 mg/d (range: 10-20 mg/d) risperidone: 7.7 mg/d (range: 6-12 mg/d) 8-week study	Anticholinergic and lorazepam allowed if clinically indicated	Mean age: NR 68% male Ethnicity: NR	NR
Glick, 2004 Subanalysis of InterSePT showing patterns of concomitant psychotropic medication (CPM) use	see above	see above	Any required to treat patient and reduce risk of suicide. See results section for numbers of patients taking CPMs	see above	see above
Green, 2004 Sub-analysis of Lieberman 2003: Effects of comorbid substance abuse	Same as Lieberman 2003	Same as Lieberman 2003	Same as Lieberman 2003	Same as Lieberman 2003	Same as Lieberman 2003

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Number screened/ eligible/ enrolled	Withdrawn/ Lost to follow-up/ Analyzed	Results
Garyfallos, 2003	NR/NR/50	0/0/50	Mean change in PANSS totals score at endpoint: olanzapine: -26 vs risperidone: -32.7
Glick, 2004 Subanalysis of InterSePT showing patterns of concomitant psychotropic medication (CPM) use	see above	NR/NR/NR	Patients who received at least 1 Concomitant Psychotropic Medication (CPM) / study duration: Clozapine: 92.4% vs olanzapine: 91.8% Mean number of CPM/patient: 3.8 (SD: 2.9) for clozapine vs 4.22 (SD: 3.16) for olanzapine Patients receiving CPM and least squares mean (LSM) daily dose, clozapine vs olanzapine: Antipsychotics: clozapine 85.6% vs olanzapine 81.7%, p = NR LSM daily dose:2.1mg (SD: 0.33 mg) vs 3.8mg (SD: 0.34mg), p<0.001 Antidepressants: clozapine 50.3% vs olanzapine 56.6%, p= NR LSM daily dose:16.7mg (SD: 1.05mg) vs 20.7mg (0.97mg), p<0.01 Sedative/anxiolytics: clozapine 59.3% vs olanzapine 66.0%, p = NR LSM daily dose:6.3mg (SD: 0.64mg) vs 10.1mg (0.61mg), p<0.001 Mood stabilizers: clozapine 25.0% vs olanzapine 30.2%, p = NR LSM daily dose: 487.3mg (SD: 43.2mg) vs 620.6mg (SD: 39.9mg), p<0.05 Daily dose of CPM in suicide attempters (ATs) and non-attempters (NATs): (Numbers of patients per group: ATs C=102, O=141; NATs: C=388, O=349 patients) Antipsychotics: for ATs: C: 2.7 vs O: 4.8, p=0.15; and for NATs: C: 2.1 vs O:3.8, p=0.001 Antidepressants: for ATs: C:20.7 vs O: 23.8, p=0.20; and for NATs: C: 15.6 vs O:19.3, p<0.01 Sedatives/anxiolytics: for ATs: C:8.9 vs O: 12.1, p<0.05; and for NATs: C: 5.7 vs O:9.6 p<0.001 Mood stabilizers: for ATs: C: 535.7 vs O; 656.2, p=0.26; and for NATs: C: 503.9 vs 624.9, p<0.05
Green, 2004 Sub-analysis of Lieberman 2003: Effects of comorbid substance abuse	Same as Lieberman 2003	Same as Lieberman 2003	Within-group (olanzapine or haloperidol) RR (95% CI) of response for non-substance abusers compared to substance abusers: Substance abuse disorder: olanzapine=1.24 (0.98, 1.57), haloperidol=1.01 (0.80, 1.29) Alcohol use disorder: olanzapine=1.47 (1.21, 1.79), haloperidol=1.10 (0.85, 1.42) Cannabis use disorder: olanzapine=1.18 (0.92, 1.50), haloperidol=0.99 (0.76, 1.28) Mean change in PANSS Total Score for substance use vs non-substance use within olanzapine or haloperidol groups (all p-values NS): Substance abuse vs non-substance abuse: olanzapine=17.37 vs 19.77, haloperidol=15.20 vs 18.43 Alcohol abuse vs non-alcohol abuse: olanzapine=15.27 vs 19.73, haloperidol=14.13 vs 18.09 Cannabis use vs non-cannabis use: olanzapine=15.94 vs 20.16, haloperidol=13.44 vs 18.64

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Adverse effects reported
Garyfallos, 2003	Mean change (SD) at endpoint, olanzapine vs risperidone: Weight Change: +4.2 (2.6) vs +2.0 (0.7), p<0.001 BMI Change: +1.4 (0.8) vs +0.7(0.3), p<0.001 Triglycerides: +43.5 (26.9) vs +7.5 (20.1), p<0.001 Cholesterol: +10.2 (23.1) vs + 0.7 (16.4) , p=NS
Glick, 2004 Subanalysis of InterSePT showing patterns of concomitant psychotropic medication (CPM) use	NR in this paper, for general InterSePT, see above
Green, 2004 Sub-analysis of Lieberman 2003: Effects of comorbid substance abuse	NR

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Extrapyramidal symptoms
Garyfallos, 2003	NR
Glick, 2004 Subanalysis of InterSePT showing patterns of concomitant psychotropic medication (CPM) use	NR in this paper, for general InterSePT, see above
Green, 2004 Sub-analysis of Lieberman 2003: Effects of comorbid substance abuse	NR

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Total withdrawals; withdrawals due to adverse events	Comments
Garyfallos, 2003	NR / NR	
Glick, 2004 Subanalysis of InterSePT showing patterns of concomitant psychotropic medication (CPM) use	NR in this paper, for general InterSePT, see above	
Green, 2004 Sub-analysis of Lieberman 2003: Effects of comorbid substance abuse		

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Eligibility criteria	Interventions (drug, dose, duration)	Allowed other medications	Age Gender Ethnicity	Other population characteristics
Green, 2006 Companion to Lieberman, 2003: Two-y data	Same as Lieberman 2003	Same as Lieberman 2003	Same as Lieberman 2003	Same as Lieberman 2003	Same as Lieberman 2003
Grootens, 2011 The Netherlands & Belgium	18-40 years; DSM-IV diagnosis of schizophrenia, schizoaffective disorder, or schizophreniform disorder; maximum lifetime exposure to antipsychotics <16 weeks; duration of ilness <5 years; CGI-S ≥5. Excluded DSM-IV diagnosis of substance dependency or positive drug screen for amphetamines, cocaine or opiods, epilepsy, mental disease, history of psychosurgery	Ziprasidone, n=39; dose: 40, 60 or 80mg twice daily; mean dose, 104mg/d; duration: 8 weeks Olanzapine, n=35; dose: 10, 15 or 20mg/d; mean dose, 14mg/d; duration: 8 weeks	Prescribed if needed: Biperiden, Propanolol, Temapzepam or Oxazepam up to 20mg/d, Benzodiazepines, Lithium, Antidepressants	Age, mean: 24 Gender: 17.6% female Ethnicity: NR	Diagnosis: 36.5% Schiophreniform disorder; 39.2% Schizophrenia, paranoid; 9.5% Schizophrenia, disorganied; 1.4% Schizophrenia, residual; 5.4% Schizophrenia, undifferentiated; 8.1% Schizoaffective disorder
Guerje, 1998 Thomas, 1998	Diagnosis: schizophrenia, schizophreniform or schizoaffective disorders; Min score of 36 on BPRS as extracted from PANSS (items scored 1-7)	olanzapine 10-20mg/d risperidone 4-8mg/d Duration: 30 wks	NR	Mean age 35 - 36 58% male 89% Caucasian	Duration of Hospitalization prior 12 mos: means 12 to 19 ds Baseline PANSS means 89 to 95 Baseline BPRS: means 32 to 35

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Number screened/ eligible/ enrolled	Withdrawn/ Lost to follow-up/ Analyzed	Results
Green, 2006 Companion to Lieberman, 2003: Two-y data	Same as Lieberman 2003	216 (82%) withdrawn/14 (5%) lost to fu (olanzapine=11% vs haloperidol=3%, p=0.0138)/N analyzed unclear (see comment)	**PANSS Total Score: no differences between olanzapine and haloperidol groups at wkss 12, 24, 52 and 104 (data NR, Figure 1 reflects symptom changes over time based on results of a mixed repeated measure model analysis)** **MADRS: Lower values for olanzapine vs haloperidol at wkss 12 (p<0.008) and 24 (p<0.045), but not at wkss 52 and 104 (data NR)** **% patients remaining on treatment at 2 ys: olanzapine=23.4% vs haloperidol=12.1%, p<0.0161** **Mean survival time in treatment (ds): olanzapine=322.09 vs haloperidol=230.38, p<0.0085** **Response rates (% patients): olanzapine=67.18% vs haloperidol=59.85%, p=NS** **Remission rates (% patients): olanzapine=57.25% vs haloperidol=43.94%, p<0.036** **Time to remission: trend toward shorter time for olanzapine (p=0.12)**
Grootens, 2011 The Netherlands & Belgium	81/74/74	NR/NR/61	Olanzapine vs. Ziprasidone Clinical response: 61% vs. 60%, P=1.00 Remission: 35% vs. 40%, P=0.80 Olanzapine vs. Ziprasidone, difference score at endpoint PANSS positive: -6.70 vs. -5.62, P=0.91 PANSS negative: -2.76 vs. -2.38, P=0.88 PANSS general psychopathology: -7.82 vs. -6.41, P=0.45 PANSS total: -17.15 vs. -14.86, P=0.68 CGI Severity: -0.97 vs. -0.85, P=0.66 Heinrich QOL: -1.20 vs. -2.42, P=0.63 Calgary Depression Scale for Schizophrenia: -1.27 vs. -0.21, P=0.19
Guerje, 1998 Thomas, 1998	NR/NR/65 olanzapine = 21 risperidone = 21 haloperidol = 23	36/0/62	Compared with risperidone-treated patients, olanzapine-treated patients showed greater reduction in PANSS total (and PANSS psychopathology, and BPRS total score. Greater proportion also achieved reduction of 20% or more on PANSS total score at week 30. At week 30, olanzapine-treated patients had better profile of QOL (SF-36 and disease-specific QOL in Schizophrenia scale)

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Adverse effects reported
Green, 2006 Companion to Lieberman, 2003: Two-y data	WDs due to AE's: olanzapine=7/131 (5%) vs haloperidol=19/132 (14.4%); p=0.0147 (StatsDirect) Weight gain (mean kg): olanzapine=10.2 vs haloperidol=4.0, p-value NR Greater than 7% weight gain (% patients): olanzapine=72% vs haloperidol=42%, p<0.0001 Cholesterol level (mg/dl): olanzapine=140 vs haloperidol=133, p=0.005 Non-fasting glucose level: greater with olanzapine at wkss 12 and 24, but not later (data NR) Fasting blood glucose: similar in both groups (data NR) At least 1 abnormal SGOT: olanzapine=54.2% vs haloperidol=22%, p<0.0001 At least 1 abnormal SGPT: olanzapine=63.4% vs haloperidol=28.8%, p<0.0001 At least 1 abnormal prolactin level: olanzapine=49.6% vs haloperidol=67.4%, p<0.0040 Serum prolactin level at endpoint: no between-group differences (data NR)
Grootens, 2011 The Netherlands & Belgium	Olanzapine vs. Ziprasidone Weight gain: 57.1% vs. 12.8%, p<0.001; Increased appetite: 14.3% vs. 0, p=0.02; GI, Fatigue/sedation, sexual side effects, hypersalivation, headach, extrapyramidal symptoms and tremors, sychiatric symptoms, sucicide attempts/suicidality all NSD between groups Metabolic parameters, difference scores at endpoint (olanzapine vs. ziprasidone): SGOT/ASAT: 8.0 vs. -10.7, p=0.02 SGPT/ALAT: 21.8 vs. -7.3, p<0.001 Cholesterol: 0.48 vs. -0.24, p=0.001 Triglycerides: 0.41 vs. -0.21, p=0.008 QTc, systolic blood pressure, diastolic blood pressure, heart rate, fasting glucose, Hb1Ac, Prolactin all NSD between groups
Guerje, 1998 Thomas, 1998	Trend for olanzapine-treated patients to evidence fewer treatment-emergent adverse effects

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Extrapyramidal symptoms
Green, 2006 Companion to Lieberman, 2003: Two-y data	Simpson-Angus Scale (max value): olanzapine=4.57 vs haloperidol=2.28, p<0.001 Barnes Scale (max value): olanzapine=2.83 vs haloperidol=0.98, p<0.0001 AIMS: no between-groups difference, data NR Anticholinergic use (% patients): olanzapine=20% vs haloperidol=47%, p<0.0001
Grootens, 2011 The Netherlands & Belgium	Barnes Akathisia Rating Scale, overall; Abnormal Involuntary Movement Scale, total score; St. Hans Rating Scale, total score; All NSD
Guerje, 1998 Thomas, 1998	No differences found by rating scales or spontaneously reported AE.

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Total withdrawals; withdrawals due to adverse events	Comments
Green, 2006 Companion to Lieberman, 2003: Two-y data		It was noted that not all subjects finished all measurements at their final visit before dropping out, so on any given measure there were fewer than 263 with follow-up visits, but no N's were provided for any outcomes.
Grootens, 2011 The Netherlands & Belgium		
Guerje, 1998 Thomas, 1998	36/NR	3 risperidone patients withdrawn due to "sponsor decision."

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Eligibility criteria	Interventions (drug, dose, duration)	Allowed other medications	Age Gender Ethnicity	Other population characteristics
Hardy, 2011 randomized, double-blind	Age 18-65; stable psychiatric illness [no hospitalizations for ≥3 months, total score on Brief Psychiatric Rating Scale (BPRS) ≤42 and scores ≤4 on each BPRS positive symptom item] Exclusion criteria: treatment with olanzapine, risperidone or depot antipsychotics within 4 weeks of study entry, or with clozapine within 2 years of entry; BMI 40 kg/m^2; diabetics; patients with severe fasting hypertriglyceridaemia; use of medications konwn to affect insulin secretion or sensitivity	Olanzapine mean dose 12.9mg/d Risperidone mean dose 4.3mg/d Duration: 12 wks	During the 'washout phase (pts discontinued previous antipsychotic treatment for at least five plasma half-lives (3-10 days)), patients were allowed limited use of haloperidol, benzodiazepines and anticholinergice medications as needed. During the 12 week treatment period, except for selective serotonin reuptake inhibitors, use of other antipsychotics and mood stabilizers was prohibited.	Mean age : 43 Gender: 34% female Caucasian 68% African decent 71% Hispanic 11% Others 3.5%	Diagnosis Schizophrenia, paranoid 65.4% Schizoaffective disorder 33.1% Schizophrenia, undifferentiated 1.5% Mean BPRS total 15
Harvey 2006 (Companion to Zhong 2006) DB, RCT Inpatients for 1st week then outpatients	Male and female; 18–65 ys of age; a diagnosis of DSM-IV schizophrenia, a baseline PANSS score of ≥60, a CGI severity rating ≥4, and a score of ≥4 on one of the following PANSS positive symptom subscale items: delusions, conceptual disorganization, hallucinatory behavior, or suspiciousness/persecution; stable laboratory and ECG (ECG) results and to have a negative urine drug screen at study entry.	Quetiapine 400 mg Risperidone 4 mg 8 wks	Sleep medication and benzodiazepines were allowed as needed but were not allowed within 24 hs of clinical or neuropsychological assessments	Mean age- 40 yrs 77% male 50% Caucasian 41% African-American 8% Hispanic 2% Asian	

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Number screened/ eligible/ enrolled	Withdrawn/ Lost to follow-up/ Analyzed	Results
Hardy, 2011 randomized, double-blind	NR/NR/130	NR/NR/74 33 from risp group and 41 from olan group completed baseline and endpoint clamp measurements.	Change from baseline to last observation LS mean, Olanzapine vs Risperidone: LDL: 2.32 vs -3.09 HDL: 2.7 vs 1.54 Weight: 3.90 vs 2.16 BMI: 1.29 vs .69
Harvey 2006 (Companion to Zhong 2006) DB, RCT Inpatients for 1st week then outpatients	NR/ NR/673 of which 289 had valid assessments	NR/NR.NR	There were no overall differences between the treatments in their impact on social competence and neuropsychological performance. Change from baseline (SD) risperidone vs. quetiapine PANSS Total 21.53 (19.22) vs.22.52 (22.10) P = 0.68 Negative subscore 4.76 (5.69) vs. 5.37 (5.69) P = 0.41 Positive subscore 6.83 (5.82) vs. 6.69 (5.80) P = 0.85

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Adverse effects reported
Hardy, 2011 randomized, double-blind	Frequency of discontinuation due to AEs was higher in risperidone pts than olanzapine pts (p=.023) Data NR
Harvey 2006 (Companion to Zhong 2006) DB, RCT Inpatients for 1st week then outpatients	NR

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Extrapyramidal symptoms
Hardy, 2011 randomized, double-blind	Baseline mean EPS scores, no follow up EPS scores reported. Simpson-gangus .9 Barnes Akathisia .3 Abnormal involuntary movement scale 34
Harvey 2006 (Companion to Zhong 2006) DB, RCT Inpatients for 1st week then outpatients	NR

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Total withdrawals; withdrawals due to adverse events	Comments
Hardy, 2011 randomized, double-blind	NR	
Harvey 2006 (Companion to Zhong 2006) DB, RCT Inpatients for 1st week then outpatients	NR/NR	Sub- analysis of Zhong K, Harvey P, Brecher M, Sweitzer D: A randomized, DB study of quetiapine and risperidone in the treatment of schizophrenia. Neuropsychopharmacology 2004; 29(suppl 1):S232.

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Eligibility criteria	Interventions (drug, dose, duration)	Allowed other medications	Age Gender Ethnicity	Other population characteristics
Harvey, 2003a (Harvey, 2002a; Harvey, 2002b; Harvey, 2002c all = Sub-analysis of Jeste, 2003) RCT, multicenter (US, Austria, Israel, Norway, Poland and The Netherlands)	Patients > 60 yrs with schizophrenia or schizoaffective disorder. PANSS scores 50-120 at baseline. Inpatient, outpatient, nursing home, board and care patients.	olanzapine: flexible dose 5-20mg/d mean modal dose: 11.46mg risperidone 1-3mg/d mean modal dose: 1..95mg Duration: 8-wks	unclear	Mean age 71 36% male 60% white	N Prior Admits: 5.65 mean total PANSS score: 77 mean MMSE: 25 mean BQoL: 4.66 mean HAM-D: 7.66 mean ESRS: 11.4
Harvey, 2003b (Harvey, 2002a,b,c & Harvey, 2003a all = Sub-group analysis of Conley, 2001) RCT, multicenter (US)	Schizophrenia or schizoaffective disorder; baseline PANSS score 60-120; age 18-64 yrs; inpatient or outpatient (hospitalized </= 4wks at screening); not refractory to treatment with olanzapine or risperidone).	olanzapine 5-20mg/d risperidone 2-6mg/d qd dosing titration unclear Duration: 8 wks	not specified	Mean age 40 73% male Ethnicity NR	Mean # prior hospitalizations: 6.3 Mean Total PANSS score: 81

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Number screened/ eligible/ enrolled	Withdrawn/ Lost to follow-up/ Analyzed	Results
Harvey, 2003a (Harvey, 2002a; Harvey, 2002b; Harvey, 2002c all = Sub-analysis of Jeste, 2003) RCT, multicenter (US, Austria, Israel, Norway, Poland and The Netherlands)	NR/NR/176 79 olanzapine 74 risperidone	67/NR/153 55 olanzapine 54 risperidone	Attention: SS change from baseline in both groups on TMT-A, not CPT NS difference between groups Memory: SS change from baseline in both groups on both tests NS difference between groups Executive domain: olanzapine: NS change from baseline on any test risperidone: SS change from baseline on TMT-B, WCST total errors, and verbal fluency NS difference between groups Analysis of categories of improvement (markedly, substantially, slightly or not improved) NS difference between drugs on any test except TMT-A: olanzapine SS > substantial or markedly improved, AND SS> not improved MANCOVA analysis of change in scores from baseline as function of medication: NS differences between groups MANCOVA analysis of completer/non-completer status and endpoint scores: NS differences between groups
Harvey, 2003b (Harvey, 2002a,b,c & Harvey, 2003a all = Sub-group analysis of Conley, 2001) RCT, multicenter (US)	NR/NR/377* 189 olanzapine 188 risperidone *an unknown number of patients were enrolled at 2 additional sites, whose data were removed after it was deemed low quality."	96/11/n varied by test and time-point (range 258-363)	Overall: SS changes from baseline for each drug on all measures except category fluency and SWMT (5-s delay). After Bonferroni adjustment, CVLT delayed recognition showed NS difference to baseline. Olanzapine vs Risperidone: NS difference on any variable Treatment x time effects: WCST total errors: risperidone > olanzapine (p = 0.042), BUT NS after Bonferroni adjustment. Stratification by improvements of 0.5 or 1.0 SD : NS difference between drug 40% improved by 0.5 SD 15% improved by 1.0 SD Anticholinergic med effects: NS Analyses of effect of smoking status and dose: NS

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Adverse effects reported
Harvey, 2003a (Harvey, 2002a; Harvey, 2002b; Harvey, 2002c all = Sub-analysis of Jeste, 2003) RCT, multicenter (US, Austria, Israel, Norway, Poland and The Netherlands)	NR
Harvey, 2003b (Harvey, 2002a,b,c & Harvey, 2003a all = Sub-group analysis of Conley, 2001) RCT, multicenter (US)	NR

	Placebo	Paliperi-done6	Paliperi-done9	Paliperi-done12	Total paliperi-done	Olanzapine
Total # s/AEs	79 (63)	74 (60)	77 (63)	95 (73)	346 (66)	81(63)
Psychiatric disorders						
Insomnia	22(17)	14 (11)	20 (16)	16 (12)	50 (13)	18 (14)
Somnolence	7 (6)	5 (4)	8 (7)	10 (8)	23 (6)	18 (14)
Agitation	7 (6)	8 (7)	5 (4)	3 (2)	16 (4)	3 (2)
Anxiety	7 (6)	5 (4)	5 (4)	6 (5)	16 (4)	7 (5)
Psychosis	8 (6)	4 (3)	0	4 (3)	8 (2)	4 (3)
Central and peripheral nervous system disorders						
Extrapyramidal disorder	1 (1)	4 (3)	9 (7)	13 (10)	26 (7)	2 (2)
Hyperkinesia	4 (3)	4 (3)	7 (6)	14 (11)	25 (7)	5 (4)
Headache	10 (8)	1 (1)	8 (7)	10 (8)	19 (5)	8 (6)
Hypertonia	0	1 (1)	7 (6)	5 (4)	13 (3)	0
Heart rate and rhythm disorders						
Tachycardia	13 (10)	22 (18)	17 (14)	29 (22)	68 (18)	18 (14)
Gastro-intestinal system disorders						
Saliva increased	1 (1)	1 (1)	2 (2)	10 (8)	13 (3)	0
Vomiting	2 (2)	2 (2)	2 (2)	6 (5)	10 (3)	1 (1)
Cardiovascular disorders, general						
ECG abnormal specific	3 (2)	4 (3)	5 (4)	9 (7)	18 (5)	2 (2)
Hypotension postural	1 (1)	4 (3)	3 (2)	7 (5)	14 (4)	6 (5)

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Extrapyramidal symptoms
Harvey, 2003a (Harvey, 2002a; Harvey, 2002b; Harvey, 2002c all = Sub-analysis of Jeste, 2003) RCT, multicenter (US, Austria, Israel, Norway, Poland and The Netherlands)	NR
Harvey, 2003b (Harvey, 2002a,b,c & Harvey, 2003a all = Sub-group analysis of Conley, 2001) RCT, multicenter (US)	NR - check anticholinergic med use?

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Total withdrawals; withdrawals due to adverse events	Comments
Harvey, 2003a (Harvey, 2002a; Harvey, 2002b; Harvey, 2002c all = Sub-analysis of Jeste, 2003) RCT, multicenter (US, Austria, Israel, Norway, Poland and The Netherlands)	67/NR	Analysis of correlations of baseline scores on individual tests to significant change in test showed some significant findings. Dose comparisons: higher relative doses of olanzapine used than risperidone.
Harvey, 2003b (Harvey, 2002a,b,c & Harvey, 2003a all = Sub-group analysis of Conley, 2001) RCT, multicenter (US)	96 ((25%) 39 (10.3% of total N) due to AE	Analysis of correlations of baseline scores on individual tests to significant change in test showed some significant findings. Mean doses NR.

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Eligibility criteria	Interventions (drug, dose, duration)	Allowed other medications	Age Gender Ethnicity	Other population characteristics
Hatta 2008 Open-label CT pseudorandomized Multicenter (7) Japan	Inclusion: Patients in psychiatric emergency departments with acute agitation (PANSS-EC score >=15). Exclusion: Patients who refused oral medication	Patients seen during 1st mo of study were assigned to olanzapine 10 mg oral disintegrating tablet. Patients seen in June were assigned to risperidone oral solution 3 mg. Same dose could be given at anytime if patient remained agitated. Patients with previously effective treatment on olanzapine or risperidone were treated with the same drug. Follow-up: 60 mins after initial dose; 12 hs for EPS.	Anticholinergic meds not permitted unless acute EPS appeared. Adjunctive drugs not allowed during 1st h of treatment.	Mean age 38 512% male (Note: 41% in olanzapine vs. 62% in risperidone; P=0.08) Study in Japan, ethnicity NR;	Olanzapine (N=34) vs. risperidone (N=53): N (% of group) kept on drug used previously: 3 (8.8) vs. 10 (18.9) Schizophrenia, schizotypal, and delusional disorders (%): 79.4 vs. 62.3 Mood disorders (%): 11.8 vs. 15.1
Hatta 2009 RCT- rater blinded Psychiatric emergency centers (15) Japan	Inclusion: 18–64 ys old, newly admitted as emergency cases, and met criteria of the ICD-10 for schizophrenia, acute schizophrenia-like psychotic disorder, or schizoaffective disorder. Exclusion: obvious complications such as liver dysfunction, renal dysfunction, heart failure, respiratory failure, or diabetes mellitus; were pregnant or who wanted to become pregnant	Risperidone (3–12 mg/d; n=20), Olanzapine (10–20 mg/d; n=17), Quetiapine (300–750 mg/d; n=20), or Aripiprazole (12–30mg/d; n=21),for 8 wks	Benzodiazepines and anticholigenerics	Mean age 41 yrs 42% male 100% Asian	Antipsychotic-naïve 38% Schizophrenia 96% Acute schizophrenia-like psychotic disorder 1% Schizoaffective disorder 3%

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Number screened/ eligible/ enrolled	Withdrawn/ Lost to follow-up/ Analyzed	Results
Hatta 2008 Open-label CT pseudorandomized Multicenter (7) Japan	853/90/87	0/0/87	Olanzapine oral disintegrating tablet (N=34) vs. risperidone oral solution (N=53) CGI-C mean (SD): 2.8 (1.3) vs. 3.2 (1.4); P=0.22 Additional injection due to worsening of symptoms, N (%): 4 (11.8) vs. 5 (9.4); P=0.73 Repeated-measures ANOVA: PANSS-EC scores decreased progressively in both groups, with no significant difference between groups (F=2.94; P=0.09).
Hatta 2009 RCT- rater blinded Psychiatric emergency centers (15) Japan	813/334/80	29/0/78	Risperidone vs. olanzapine vs. quetiapine vs. aripiprazole CGI-C 3.4 (1.7) vs. 2.8 (1.1) vs. 4.1 (2.1) vs. 4.4 (2.1) PANSS (mean change from baseline) Total −24.7 (27.9) vs. −33.4 (20.8) vs. −28.9 (28.6) vs.−18.4 (26.0) Positive scale −10.8 (10.9) vs. −12.6 (9.3) vs. −9.4 (8.6) vs.−6.5 (9.1) Negative scale −3.3 (5.6) vs.−5.6 (5.7) vs. −6.3 (9.5) vs. −3.8 (5.2)

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Adverse effects reported
Hatta 2008 Open-label CT pseudorandomized Multicenter (7) Japan	Olanzapine vs. risperidone, N (%): 0 (0) vs. 3 (5.7); P=0.91 Change in heart rate (beats/min), mean: -9.2 vs. 1.1; P=0.03 1 patient with bradycardia (47 beats/min) at 60 min, a decline from 76 beats/min at time 0.
Hatta 2009 RCT- rater blinded Psychiatric emergency centers (15) Japan	Poorly reported AEs ; Comparisons between groups - mean change from baseline for weight (p=0.098), fasting glucose (p=0.17), cholesterol (p=0.88), or triglycerides (p=0.62). Sexual side effects and sedation were not observed.

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Extrapyramidal symptoms
Hatta 2008 Open-label CT pseudorandomized Multicenter (7) Japan	Olanzapine vs. risperidone, N (%): 0 (0) vs. 3 (5.7); P=0.91
Hatta 2009 RCT- rater blinded Psychiatric emergency centers (15) Japan	Risperidone vs. olanzapine vs. quetiapine vs. aripiprazole Extrapyramidal symptoms (DIEPSS) Any symptoms 13/20 (65%) vs. 8/17 (47%) vs. 5/20 (25%) vs. 8/21 (38%) Parkinsonism 12/20 (60%) vs. 5/17 (29%) vs. 5/20 (25%) vs. 7/21 (33%) Akathisia 5/20 (25%) vs. 2/17 (12%) vs. 2/20 (10%) vs. 4/21 (19%) Dystonia 3/20 (15%) vs. 1/17 (6%) vs. 0/20 (0%) vs. 0/21 (0%) Dyskinesia 1/20 (5%) vs. 0/17 (0%) vs. 1/20 (5%) vs. 0/21 (0%)

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Total withdrawals; withdrawals due to adverse events	Comments
Hatta 2008 Open-label CT pseudorandomized Multicenter (7) Japan	0 WD 0 due to AEs	
Hatta 2009 RCT- rater blinded Psychiatric emergency centers (15) Japan	29 WD 1 due to AEs	

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Eligibility criteria	Interventions (drug, dose, duration)	Allowed other medications	Age Gender Ethnicity	Other population characteristics

Huang, 2005
RCT, blinding - NR, Taiwan
Inpatients
	Inclusion: Inpatients with schizophrenia according to DSM-IV.
	Exclusion: Systemic diseases.
		conventional antipsychotic drugs (haloperidol 10–15 mg/d, sulpiride 800–1200 mg/d, and loxapine 100–150 mg/d) and atypical antipsychotic drugs (risperidone 3–5 mg/d, olanzapine 10–20 mg/d, and clozapine 100–300 mg/d)
		3 wks
			NR	Mean age 32.4 yrs
				51% male
				Ethnicity NR
					mean BMI= 23.8
					mean TC=175.0 mg/dl;
					mean TG=110.5 mg/dl;
					mean HDL=43.3 mg/dl;
					mean VLDL=21.2 mg/dl
					mean LDL=110.4 mg/dl;
					mean TC/HDL=4.3
					mean LDL/HDL=2.8

Ingole, 2009 Open-label RCT Single site, India	Inclusion: Newly diagnosed DSM-IV patients with schizophrenia; male or females aged 18-60. Exclusion: Patients with history of taking antipsychotics before study; patients with history of diabetes mellitus; patients taking antidiabetic treatment; patients with documented CV diseases.	Oral olanzapine 5 mg two times a d Oral risperidone 3 mg two times a d 12 wks duration	Rescue medications available for managing emergency and side effects: lorazepam, trihexyphenidyl, clonazepam	Mean age 26 41.7% male 100% nationals of India	NR

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Number screened/ eligible/ enrolled	Withdrawn/ Lost to follow-up/ Analyzed	Results
Huang, 2005 RCT, blinding - NR, Taiwan Inpatients	NR/126/97	NR/NR/97	Haloperidol - no significant changes in any of the lipid profile levels. sulpiride had significantly decreased ratio of LDL/HDL (t = 2.576, P=0.024). Loxapine decreased ratios of TC/HDL (t = 3.127, P=0.009) and LDL/HDL (t = 5.027, P=0.000). risperidone - significantly increased TC (t =2.292, P=0.032) and HDL levels (t =4.735, P=0.000) and significantly decreased ratios of TC/HDL (t = 3.065, P=0.006) and LDL/HDL (t = 3.043, P=0.006). Olanzapine - significantly increased TG level (t =2.480, P=0.026). clozapine had significantly increased TG (t =2.179, P=0.049) and VLDL levels (t =2.213, P=0.044) Changes from baseline Haloperidol vs. sulpiride vs. loxapine vs. risperidone vs. olanzapine vs. clozapine TC (mg/dl) 4.3 vs. -5.3 vs. -3.7 vs. 12.7 vs. 12.9 vs. -3.8 TG (mg/dl) 25.9 vs. 9.5 vs -26.8 vs. 8.9 vs. 50.3 vs. 28.7 HDL (mg/dl) 3.7 vs. 3.2 vs. 3.6 vs. 8.1 vs. 2.2 vs. -2.3 VLDL (mg/dl) 5.2 vs. 1.8 vs.1.0 vs. 1.7 vs. 10.1 vs. 5.9 LDL (mg/dl) 5.1 vs. -17.6 vs. -8.3 vs. 2.9 vs. 0.5 vs. -7.4 TC/HDL 0.2 vs.-0.3 vs. -0.6 vs. -0.6 vs. -0.1 vs. 0.2 LDL/HDL 0.1 vs. -0.3 vs. -0.5 vs. -0.5 vs. -0.3 vs. 0.0
Ingole, 2009 Open-label RCT Single site, India	Screened NR Eligible NR 60 enrolled	0 withdrawn 0 lost to followup 60 analyzed	Olanzapine and risperidone were both associated with significantly (p<0.001) elevated body weight and BMI at 6 and 12 wks. Significant increase (p<0.001) in fasting blood sugar level occurred in olanzapine, but not in risperidone. Mean change ±SEM from baseline at 6wks, olanzapine vs risperidone: Body weight (kg): 1.77 ±0.157 vs 1.17 ±0.240; p<0.05 BMI (kg/m2): 0.68 ±0.059 vs 0.48 ±0.097; p<0.05 Blood sugar level (mg/dL): 7.33 ±0.569 vs 0.30 ±0.699; p<0.001 Mean change ±SEM from baseline at 6wks, olanzapine vs risperidone: Body weight (kg): 4.67 ±0.193 vs 2.20 ±0.246; p<0.001 BMI (kg/m2): 1.80 ±0.090 vs 0.9 ±0.101; p<0.001 Blood sugar level (mg/dL): 17.43 ±1.316 vs 1.03 ±0.652; p<0.001

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Adverse effects reported
Huang, 2005 RCT, blinding - NR, Taiwan Inpatients	NA
Ingole, 2009 Open-label RCT Single site, India	Abstracted in Results

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Extrapyramidal symptoms
Huang, 2005 RCT, blinding - NR, Taiwan Inpatients	NR
Ingole, 2009 Open-label RCT Single site, India	NR

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Total withdrawals; withdrawals due to adverse events	Comments
Huang, 2005 RCT, blinding - NR, Taiwan Inpatients	NR / NR	
Ingole, 2009 Open-label RCT Single site, India	0 WD 0 due to AEs	

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Eligibility criteria	Interventions (drug, dose, duration)	Allowed other medications	Age Gender Ethnicity	Other population characteristics
InterSePT; Meltzer, 2003 Potkin, 2003a Meltzer, 1996 RCT, open-label, masked ratings, multicenter (67 sites, 11 countries; US, Europe, South Africa, South America)	Patients with schizophrenia, or schizoaffective disorder considered to be at high risk for committing suicide by meeting at least one of the following criteria: 1) a history of previous attempts or hospitalizations to prevent a suicide attempt in the 3 ys before enrollment, 2) moderate to severe current suicidal ideations with depressive symptoms, or 3) command hallucinations for self-harm within 1 week of enrollment.	Clozapine or olanzapine Dose determined by treating clinician Duration: 2 ys	Any required to treat patient and reduce risk of suicide Both groups seen weekly/biweekly - clozapine group for blood monitoring, olanzapine for vital sign monitoring	Mean age 37.1 yrs % male: 61.4% Ethnicity: 71% White 15% Black 1.3% Oriental 13% Other	62% Schizophrenic 38% Schizoaffective Mean # suicide attempts: 3.4 83% had attempted suicide at least once 63% had attempted suicide in last 36 mos 84% had been hospitalized to prevent suicide attempt 27% Treatment resistant NS difference at baseline on PANSS, CGI-SS, ISST, CDS, and Covi-Anxiety scales

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Number screened/ eligible/ enrolled	Withdrawn/ Lost to follow-up/ Analyzed	Results
InterSePT; Meltzer, 2003 Potkin, 2003a Meltzer, 1996 RCT, open-label, masked ratings, multicenter (67 sites, 11 countries; US, Europe, South Africa, South America)	1065 screened 980 eligible and enrolled (490 per group)	24 (2.4%) never received drug 380 (39%) withdrew early: 10% withdrew consent 8% due to AE's 7% lost to follow-up 980 analyzed ITT analysis includes any data obtainable on patients who left the study, method of analyzing data for those whose data were not obtainable was NR	Type 1 events (C vs O) HR 0.76 (95% CI 0.58 to 0.97) Cox-proportional hazard model (including treatment, # prior suicide attempts, active substance or alcohol abuse, country, sex and age group as variables): HR 0.74 (95% CI 0.57 to 0.96) Clozapine also superior on individual measures (significant suicide attempts, hospitalizations to prevent suicide) Kaplan-Meier estimates indicate SS reduction in 2-y event rate in clozapine group (p=0.02, NNT = 12) Type 2 events: (C vs O) HR 0.78 (95% CI 0.61 to 0.99) Other outcomes: Drop-outs due to unsatisfactory anti-suicidal effect: 1% vs 0% (p - 0.03) (as determined by treating physician) olanzapine: SS higher rates of antidepressants and anxiolytics used olanzapine: SS higher rates of rescue interventions to prevent suicide Suicide deaths: NS (5 clozapine, 3 olanzapine) Predictive Factors: Risk of suicide: clozapine SS < olanzapine in: Schizophrenic patients, No hospitalizations to prevent suicide w/in 36 mos, 2-3 lifetime suicide attempts, no Hx alcohol abuse, smokers, high ISST, Covi-Anxiety Scale and CDI scale scores

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Adverse effects reported
InterSePT; Meltzer, 2003 Potkin, 2003a Meltzer, 1996 RCT, open-label, masked ratings, multicenter (67 sites, 11 countries; US, Europe, South Africa, South America)	Overall number NR, but stated NS difference Rate of serious AE NR, but stated NS difference Most frequent AEs: clozapine: hypersalivation, somnolence, weight gain, and dizziness olanzapine: weight gain, somnolence, dry mouth, and dizziness clozapine vs olanzapine: Somnolence 45.9% vs 24.7% (p<0.001) Weight Gain: 31.3% vs 55.6% (p<0.001) Dizziness: 26.9% vs 12.4% (p<0.001) Other AEs with SS difference: clozapine causes SS lower rate: insomnia, akathisia, muscle rigidity, dry mouth olanzapine causes SS lower rate: convulsions, postural hypotension, syncope, dysarthria, constipation, hypersalivation, dyspepsia, nausea, vomiting, urinary incontinence, weakness, WBC count decreased (5.8% vs 0.8%) Other outcomes clozapine SS lower rate than olanzapine: Suicidal ideation, suicide attempts, laceration, depression, mood alteration, mood disorder, drug abuse, alcoholism. All of these were also considered under efficacy analysis. The comparisons here are based only on patients who received drug.

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Extrapyramidal symptoms
InterSePT; Meltzer, 2003 Potkin, 2003a Meltzer, 1996 RCT, open-label, masked ratings, multicenter (67 sites, 11 countries; US, Europe, South Africa, South America)	NR

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Total withdrawals; withdrawals due to adverse events	Comments
InterSePT; Meltzer, 2003 Potkin, 2003a Meltzer, 1996 RCT, open-label, masked ratings, multicenter (67 sites, 11 countries; US, Europe, South Africa, South America)	379 total Due to AE: 8.4% clozapine, 6.7% olanzapine When add in w/d due to abnormal labs or lab test procedure result: 9% clozapine, 6.7% olanzapine (NS)	Study powered to assess all significant suicide attempts (successful/non-successful). Drug and alcohol abuse found to be a significant predictor of suicide attempt, and SS > drug abuse in the olanzapine group reported as AE. Baseline prevalence of use NR. Mean doses seem non-comparable; mean dose clozapine = 274mg (+/- 155 SD), mean dose olanzapine = 16.6mg (+/- 6.4mg SD).

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Eligibility criteria	Interventions (drug, dose, duration)	Allowed other medications	Age Gender Ethnicity	Other population characteristics
Jerrel, 2002 RCT, open-label with economic analysis	Medicaid patients age 18-54, with schizophrenia or schizoaffective disorder and >/= 2 acute psychiatric hospitalizations within 12 mos, and noncompliant with outpatient treatment and not taking atypical antipsychotics for 6-8 wks or more during the prior 3 mos. Patients screened during acute inpatient stay.	olanzapine, risperidone or continue on typical antipsychotic as prescribed. Doses determined by treating physician. Average doses: olanzapine: 12-15mg/d risperidone: 4-6mg/d haloperidol: 14-17mg/d Duration: 12 mos	Discretion of treating physician	Mean age 36.91 68% male 29% white	72% schizophrenic Mean prior inpatient admits: 9.75 Acute hospitalization ds in past 6 mos: 12.56 Atypical antipsychotic use: 29% Supplemental antipsychotic use: 17% Anti-EPS med use: 72% Taking mood stabilizer: 49%
Jeste, 2003 Jeste, 2002 Jeste, 2001 RCT, multinational (US, Israel, Poland, Norway, The Netherlands, Austria) 1 full paper, 2 conf proc	Patients aged 60+ with chronic schizophrenia or schizoaffective disorder; without dementia; with baseline PANSS score range 50-120, inpatient (hospitalized </= 4wks at screening) or outpatient (including nursing home, boarding care and hospitalized patients receiving only board and care).	olanzapine: flexible dose 5-20mg/d mean modal dose: 11.1 mg risperidone 1-3mg/d mean modal dose: 1..9 mg Duration: 8-wks	lorazepam	Mean age: 71.1 35% male 77% white 17% black 3% Hispanic 2% Asian	85% schizophrenia 15% schizoaffective disorder mean baseline PANSS score: 77.1

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Number screened/ eligible/ enrolled	Withdrawn/ Lost to follow-up/ Analyzed	Results
Jerrel, 2002 RCT, open-label with economic analysis	NR/343/343 Final group of 108: olanzapine 30 risperidone 36 Typicals 42	235/ NR /108 Patients or physician could withdraw patient after randomization but prior to receiving medication. 74 patients refused 146 physicians refused to have patients enrolled	Treatments Received: Logistic regression analysis: Prescribed assigned med significantly decreased over time (OR 0.19 (95% CI 0.09 to 0.43), but NS between groups Compliance with assigned med, odds of being prescribed a supplemental antipsychotic, odds of being prescribed a mood stabilizer were higher with risperidone vs typicals, and olanzapine vs typicals, but no difference between atypicals. PANSS positive: NS group x time interaction, but scores SS decreased over time PANSS negative: NS group x time interaction, but scores SS decreased over time BPRS: NS group x time interaction, but scores SS decreased over time DIS-II-R Mania and Depression scores: NS group x time interaction, but scores SS increased over time CUAD: NS group x time interaction, but scores SS decreased over time RFS: NS group x time interaction, but role functioning SS decreased over time Self-report Psych Function: NS group interaction effect Time to Discharge: Kaplan-Meier Survival Analysis and Cox proportional hazard analysis: NS difference between groups Time to Rehospitalization: Kaplan-Meier Survival Analysis and Cox proportional hazard analysis: NS difference between groups: Client satisfaction: NS by group, but increased over 1st 3 mos (p<0.03)
Jeste, 2003 Jeste, 2002 Jeste, 2001 RCT, multinational (US, Israel, Poland, Norway, The Netherlands, Austria) 1 full paper, 2 conf proc	203/176/175	41/1/174	Baseline PANSS score reduced by >=20%: 58% risperidone, 59% olanzapine (within groups P<0.005). Change in mean Ham-D score: -1.8 risperidone (p<0.01, within group) -1.5 olanzapine (p<0.05, within group). CGI improved in 32.5% risperidone, 36% olanzapine. Between-group differences NS for PANSS, Ham-D, and CGI.

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Adverse effects reported
Jerrel, 2002 RCT, open-label with economic analysis	Use of Anti-EPS drugs: SS decrease in use over time (OR 0.51 (95% CI 0.28 to 0.90), but no difference between groups After controlling for time-dependent effects of anticholinergic drug use: DISCUS: SS time effect; decrease from baseline to 12 mos (p =0.0007) S-A EPS SS time effect; lower scores from baseline to 12 mos (p<0.0001) GBAS: SS decrease in ratings baseline to 12 mos (p=0.002)
Jeste, 2003 Jeste, 2002 Jeste, 2001 RCT, multinational (US, Israel, Poland, Norway, The Netherlands, Austria) 1 full paper, 2 conf proc	Risperidone vs olanzapine: Somnolence 13.8% vs 13.6% (ns) Insomnia 16.1% vs 10.2% (ns) Dizziness 10.3% vs 11.4% (ns) EPS 9.8% vs 15.9% (ns) 7% Weight gain 5.1% vs 14.8% (p=0.043)

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Extrapyramidal symptoms
Jerrel, 2002 RCT, open-label with economic analysis	Use of Anti-EPS drugs: SS decrease in use over time (OR 0.51 (95% CI 0.28 to 0.90), but no difference between groups After controlling for time-dependent effects of anticholinergic drug use: DISCUS: SS time effect; decrease from baseline to 12 mos (p =0.0007) S-A EPS SS time effect; lower scores from baseline to 12 mos (p<0.0001) GBAS: SS decrease in ratings baseline to 12 mos (p=0.002)
Jeste, 2003 Jeste, 2002 Jeste, 2001 RCT, multinational (US, Israel, Poland, Norway, The Netherlands, Austria) 1 full paper, 2 conf proc	EPS 9.8% vs 15.9% (ns) 7% Weight gain 5.1% vs 14.8% (p=0.04)

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Total withdrawals; withdrawals due to adverse events	Comments
Jerrel, 2002 RCT, open-label with economic analysis	NR (3 patients not included in rehospitalization analysis due to never being discharged from index hospitalization)	Study focused on patients with recent hospitalizations and who were either non-compliant with treatment or whose treatment was not stabilized.
Jeste, 2003 Jeste, 2002 Jeste, 2001 RCT, multinational (US, Israel, Poland, Norway, The Netherlands, Austria) 1 full paper, 2 conf proc	Total: 41/175 (23%) Due to AE: 5.7% risperidone, 5.7% olanzapine	

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Eligibility criteria	Interventions (drug, dose, duration)	Allowed other medications	Age Gender Ethnicity	Other population characteristics
Josiassen, 2010 United States	Male or female; between 18 and 30 years; DSM-IV diagnosis for first episode of schizophrenia, schizoaffective disorder, schizophreniform disorder or psychosis NOS; active and measurable psychotic symptoms of at least one month duration but not more than 12 months; Exclusion criteria: non-english speaking; mental retardation as assessed using the Wechsler Adult Intelligence Scale or as noted in historical records; pregnant or nursing females; serious, unstable medical illness; a documented history of seizures; known allergy to any prior antipscychotic medications; serious risk of assaultive behaviour; serious risk of suicide; or participation in an investigational drug trial within 30 days.	Aripiprazole (5-20mg/d; n=19) Mean (SD) starting dose (TDD, mg): 5.5 (1.58) Mean (SD) final dose (TDD, mg): 14.5 (4.38) Risperidone (.5-6mg/d; n=16) Mean (SD) starting dose (TDD, mg): .75 (.26) Mean (SD) final dose (TDD, mg): 2.9 (1.42) Olanzapine (2.5-20/d; n=14) Mean (SD) starting dose (TDD, mg): 2.86 (.91) Mean (SD) final dose (TDD, mg): 13.2 (4.21) Quetiapine (50-800mg/d; n=11) Mean (SD) starting dose (TDD, mg): 54.5 (15.1) Mean (SD) final dose (TDD, mg): 513.6 (150.2) Duration: 8 weeks	NR	Mean age: 22.8 Gender: 70% male Ethnicity: NR	Diagnosis: Schizophreniform: 33% Schizophrenia: 52% Schizoaffective: 3.3% Psychosis NOS: 11.7
Kahn, 2009 50 sites in 14 countries data from EUFEST study	first episode schizophrenia patients with minimal prior antipsychotic treatment	haloperidol (1-4 mg/d; n=103), amisulpride (200-800 mg/d; n=104), olanzapine (5-20 mg/d; n=105), quetiapine (200-750 mg/d; n=104), or ziprasidone (40-160 mg/d; n=82) 12 months	NR	NR	NR

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Number screened/ eligible/ enrolled	Withdrawn/ Lost to follow-up/ Analyzed	Results
Josiassen, 2010 United States	NR/NR/60	NR/NR/60	Aripiprazole vs risperidone vs olanzapine vs quetiapine PANSS total: -30.4% vs -24.2% vs -35.7% vs -29.4% PANSS positive: -44.7% vs -31.4% vs -49.6 vs -42.4% PANSS negative: -22.7% vs -20.8% vs -28.9% vs -23.9%
Kahn, 2009 50 sites in 14 countries data from EUFEST study	NR/NR/498	243/NR/not clear	haloperidol vs amisulpride vs olanzapine vs quetiapine vs ziprasidone Treatment discontinuations: 72% vs 40% vs 33% vs 53% vs 45% Comparisons with haloperidol showed lower risks for discontinuation for amisulpride (HR, 0.36; 95% CI, 0.23 to 0.55), olanzapine (HR, 0.27; 95% CI, 0.17 to 0.42), quetiapine (HR, 0.49; 95% CI, 0.33 to 0.73), and ziprasidone (HR, 0.47; 95% CI, 0.29 to 0.76).

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Adverse effects reported
Josiassen, 2010 United States	Mean % weight change: 7% vs 7.3% vs 6.9% vs 7.9% % obese: 0% vs 3.2% vs 14% vs 0%
Kahn, 2009 50 sites in 14 countries data from EUFEST study	NR

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Extrapyramidal symptoms
Josiassen, 2010 United States	NR
Kahn, 2009 50 sites in 14 countries data from EUFEST study	NR

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Total withdrawals; withdrawals due to adverse events	Comments
Josiassen, 2010 United States		
Kahn, 2009 50 sites in 14 countries data from EUFEST study		data from the European First Epidsode Schizophrenia Trial (EUFEST)

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Eligibility criteria	Interventions (drug, dose, duration)	Allowed other medications	Age Gender Ethnicity	Other population characteristics
Kane 2009 DB RCT Multinational, multicenter (60)	Inclusion: Inpatients or outpatients; 18-65 yrs; schizophrenia diagnosis; initial PANSS 75 or more; minimum of 4 on one of PANNS positive; CGI-S of 4 or more at screening and randomization; CGI-I 3 or more at randomization Exclusion: Pregnancy; lactation; significant medical illness	Olanzapine vs. aripiprazole Mean doses 16.7 vs. 19.3 mg/d 28 wks	Benzodiazepines	Mean 38 ys 68% male 30% White 31% African descent 32% Hispanic 7% other	16% inpatients and 84% outpatients
Kane, 2007 DB, RCT, P and active-controlled, multicenter (Europe and India)	Inclusion: Male or female; ≥18 ys; acute episode of schizophrenia; diagnosed with schizophrenia according to DSM-IV criteria for at least 1 y prior to screening and have agreed to voluntary hospitalization for a minimum of 14 ds. Exclusion: Substance dependence within 6 mos, a medical condition that could affect absorption, metabolism or excretion of the study drug; tardive dyskinesia or neuroleptic malignant syndrome; significant risk for suicide or violent behavior,; pregnant or breastfeeding, patients receiving a depot antipsychotic within 120 ds or paliperidone palmitate.	Paliperidone ER 6 mg, 9 mg, 12 mg P Olanzapine 10mg 6 wks	Benzodiazepine and antidepressants assuming a stable dose for at least 3 mos and benztropine 1 or 2 mg bid or biperiden 2 mg tid was also permitted for the treatment of movement disorders	Mean age 37.1 ys 52% male 86% white <1% Asian 14% other	Age at diagnosis 27.0 ys Baseline PANSS total 93.9

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Number screened/ eligible/ enrolled	Withdrawn/ Lost to follow-up/ Analyzed	Results
Kane 2009 DB RCT Multinational, multicenter (60)	726/645/566	263/47/566	Olanzapine vs. aripiprazole CGI-I 2.7 vs. 2.8 P = 0.279 Change in PANSS -30.2 vs. -25.9 P = 0.014 PANSS-P -5.9 vs. -5.0 P = 0.025 PANSS-N -8.8 vs. -7.6 P = 0.053 CGI-S -1.2 vs. -1.1 P = 0.336
Kane, 2007 DB, RCT, P and active-controlled, multicenter (Europe and India)	680/NR/630	215/7/628	P - palperidone6 - paliperidone9 - paliperidone12 Total PANSS score mean (SD) Baseline 94.1 (10.7) 94.3 (10.5) 93.2 (11.9) 94.6 (11.0) Change from baseline −4.1 (23.2) −17.9 (22.2) −17.2 (20.2) −23.3 (20.1) p-value < compared to P 0.001 0.001 0.001 ≥30% decrease in PANSS total paliperidone6 =56%, paliperidone9 =51%, paliperidone12 =61%, P=30%; p< 0.001 for all paliperidone ER groups vs P. classified as ‘marked’ or ‘severely ill’ on the CGI-S scale baseline vs. endpoint paliperidone6 62.6% vs 21.3% paliperidone9 57.3% vs 23.0% paliperidone12 64.4% vs 16.3% P 59.5% vs 50.8% olanzapine 64.1% vs 23.5%

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Adverse effects reported
Kane 2009 DB RCT Multinational, multicenter (60)	Olanzapine vs. aripiprazole Insomnia 16.7 vs. 27.4 P = 0.002 Weight increase 16.4 vs. 7.0 P = 0.001 Somnolence 14.6 vs. 8.4 P = 0.025 Headache 11.7 vs. 17.5 Increased appetite 11.7 vs. 6.7 P = 0.047 Anxiety 7.8 vs. 10.9 Fatigue 7.8 vs. 6.3 Dizziness 6.8 vs. 8.4 Dry mouth 6.8 vs. 5.3 Exacerbation of schizophrenia 6.4 vs. 5.6 Sedation 6.4 vs. 2.8 P = 0.046 Nausea 6.0 vs. 8.1 Akathisia 5.3 vs. 9.1 Depression 3.9 vs. 1.1 P = 0.032 Upper abdominal pain 1.8 vs. 5.3 P = 0.038
Kane, 2007 DB, RCT, P and active-controlled, multicenter (Europe and India)	

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Extrapyramidal symptoms
Kane 2009 DB RCT Multinational, multicenter (60)	Olanzapine vs. aripiprazole Change in BAS -0.1 vs. -0.1 Change in SAS -1.2 vs. -0.9 Change in AIMS -0.5 vs. -0.2
Kane, 2007 DB, RCT, P and active-controlled, multicenter (Europe and India)	Akathisia, as assessed by the BARS, was rated as absent 92%–93% paliperidone6 and P 90% of the paliperidone9 87% of the paliperidone12. 93% olanzapine use of anti-cholinergic medication 6% P 11% paliperidone6 17% of the paliperidone9 22% of the paliperidone12 8% olanzapine

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Total withdrawals; withdrawals due to adverse events	Comments
Kane 2009 DB RCT Multinational, multicenter (60)	263 WG 53 due to AEs	
Kane, 2007 DB, RCT, P and active-controlled, multicenter (Europe and India)	215 W 38 due to AEs	

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Eligibility criteria	Interventions (drug, dose, duration)	Allowed other medications	Age Gender Ethnicity	Other population characteristics
Kane, 2010 McDonnell, 2011 McDonnell, 2011 Erratum DB, RCT active-controlled, multicenter, international	18-75 years, DSM-IV schizophrenia, clinically stable outpatient status for at least 4 weeks before first study visit	A. Low dose olazapine injection, 150 mg every 2 weeks B. Medium dose olanzapine injection, 405 mg every 4 weeks C. High dose olanzapine injection, 300 mg every 2 weeks D. Very low reference dose, 45 mg every 4 weeks E. Stabilized oral dose olanzapine, 10, 15 or 20 mg/d	Benzodiazepines and sedative-hypnotics as sleep aids, anticholinergic medications for treatment emergent EPS (no prophylactic use)	Mean Age: 38.96 Gender: 35% female Ethnicity: 71.2% Caucasian	Age at illness onset: 25.62 years Baseline PANSS total, mean: 55.89

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Number screened/ eligible/ enrolled	Withdrawn/ Lost to follow-up/ Analyzed	Results
Kane, 2010 McDonnell, 2011 McDonnell, 2011 Erratum DB, RCT active-controlled, multicenter, international	1315/1205/1065	312/14/1062	Very low dose injection vs. low dose injection vs. medium dose injection vs. high dose injection vs. stabilized oral dose Mean (SE) Change from baseline PANSS total: 7.2 (1.6) vs. 2.7 (1.3) vs. -0.1 (0.8) vs. -2.2 (1.1) vs. -2.5 (0.7); p<0.001 overall; NSD high dose injection vs. stabilized oral dose (p=0.61) PANSS positive: 3.0 (0.5) vs. 1.3 (0.4) vs. 0.6 (0.2) vs. 0.2 (0.3) vs. -0.2 (0.2); p<0.001 overall; NSD high dose injection vs. stabilized oral dose (p=0.31) PANSS negative: 0.5 (0.4) vs. -0.1 (0.4) vs. -0.7 (0.2) vs. -1.0 (0.4) vs. -1.1 (0.4); p<0.001 overall; NSD high dose injection vs. stabilized oral dose (p=0.77) Brief Psychiatric Rating Scale: 4.6 (1.0) vs. 2.3 (0.8) vs. 0.3 (0.5) vs. -1.0 (0.6) vs. -1.1 (0.4); p<0.001 overall; NSD high dose injection vs. stabilized oral dose (p=0.64) CGI-S: 0.3 (0.1) vs. 0.1 (0.1) vs. -0.0 (0.0) vs. -0.0 (0.1) vs. -0.1 (0.0); p<0.001 overall; NSD vs. stabilized oral dose: low dose injection (p=0.12), medium dose injection (p=0.15), high dose injection (0.79) Patients free of exacerbation (%): 69 vs. 84 vs. 90 vs. 95 vs. 93 Risk of Exacerbation: 2-week vs. 4-week dosing schedules: HR, 1.0; 95% CI, 0.6 to 1.8; p=0.89 2-week injection regimen vs. oral formulation: HR, 1.5; 95%CI, 0.8 to 2.7; p=0.17 4-week injection regimen vs. oral formulation: HR, 1.4; 95%CI, 0.8 to 2.6; p=0.21 Very low dose injection vs. low dose injection: HR, 2.1; 95%CI, 1.2 to 3.7; p=0.007 Very low dose injection vs. medium dose injection: HR, 3.5; 95%CI, 2.2 to 5.8; p<0.001 Very low dose injection vs. high dose injection: HR, 7.4; 95%CI, 3.1-17.5; p<0.001 Low dose injection vs. high dose injection: HR, 3.5; 95% CI, 1.4 to 8.7; p=0.008 Mean changes in metabolic measures from baseline to endpoint: Olz LAI mean (SD) vs. Oral Olz mean (SD), Treatment P-value Weight (kg): +1.0 (4.1) vs. +1.3 (4.0), 0.34 BMI (kg/m2): +0.4 (1.4) vs. +0.5 (1.4), 0.33 Gluc (mg/dL): +3.1 (23.1) vs. +1.3 (16.2), 0.17 TChol (mg/dL): -2.3 (28.0) vs. -6.0 (32.8), 0.17 HDL (mg/dL): -0.5 (9.2) vs. -0.3 (8.1), 0.95 LDL (mg/dL): -1.5 (25.5) vs. -6.4 (27.8), 0.039 Trigly (mg/dL): -4.3 (122.5) vs. +11.3 (97.6), 0.07

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Adverse effects reported
Kane, 2010 McDonnell, 2011 McDonnell, 2011 Erratum DB, RCT active-controlled, multicenter, international	Deaths: 0 SAEs, Total: 57; schizophrenia (11), psychotic disorder (8), acute psychosis (5), suicidal ideation (3) Very low dose injection vs. low dose injection vs. medium dose injection vs. high dose injection vs. stabilized oral dose Insomnia (%): 15 vs. 8 vs. 7 vs. 6 vs. 4; very low dose significantly different than medium and high dose injection and stabilized oral dose ($p<0.05$) Weight increase (%): 4 vs. 9 vs. 5 vs. 11 vs. 8; high dose injection significantly different than medium dose and very low dose injections Headache (%): <1 vs. 5 vs. 3 vs. 2 vs. 4; very low injection significantly different than stabilized oral dose and low dose injections Treatment-emergent adverse events: Olz LAI % vs. Oral Olz %, P Patients with >= 1 TEAE: 52.1 vs. 46.9, 0.15 Weight increased: 7.2 vs. 7.5, 0.90 Insomnia: 7.2 vs. 4.0, 0.06 Nasopharyngitis: 4.3 vs. 4.3, >0.99 Anxiety: 4.8 vs. 2.8, 0.17 Headache: 3.2 vs. 4.3, 0.36 Somnolence: 3.8 vs. 2.8, 0.46 Influenza: 2.0 vs. 2.8, 0.49 Fatigue: 2.0 vs. 2.2, 0.81 Dizziness: 1.3 vs. 2.8, 0.13 Injection site pain: 2.3 va. 0.9, 0.20 Hallucination: 2.3 vs. 0.6, 0.07 Corrected in Erratum: During randomized treatment phase, serious adverse events were reported among 42 patients, one of which was metabolic-related (hyperglycemia). 29 patients discontinued participation due to adverse events (2 due to weight increase, 1 due to hyperglycemia, 1 due to diabetes mellitus). The percentages of patients who experienced treatment-emergent adverse events did not differ significantly between Olz LAI and Oral Olz treatment groups.

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Extrapyramidal symptoms
Kane, 2010 McDonnell, 2011 McDonnell, 2011 Erratum DB, RCT active-controlled, multicenter, international	Very low dose injection vs. low dose injection vs. medium dose injection vs. high dose injection vs. stabilized oral dose Mean (SD) change from baseline, p-value vs. very low dose injection Simpson-Angus Total: -0.35 (2.20) vs. -0.35 (1.53), p=.81 vs. -0.28 (1.67), p=0.66 vs. -0.43 (1.78), p=0.81 vs. -0.14 (1.90), p=0.34 Barnes Global Score:-0.05 (0.56) vs. 0.00 (0.50), p=0.45 vs. 0.01 (0.52), p=0.26 vs. -0.18 (0.73), p=0.02 vs. -0.03 (0.41), p=0.74 Abnormal Involuntary Movement Scale: -0.14 (1.54) vs. -0.06 (0.98), p=0.52 vs. -0.04 (1.37), p=0.41 vs. -0.40 (1.55), p=0.04 vs. -0.18 (1.20), p=0.68

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Total withdrawals; withdrawals due to adverse events	Comments
Kane, 2010 McDonnell, 2011 McDonnell, 2011 Erratum DB, RCT active-controlled, multicenter, international	WD: 312 Due to AE:35	

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Eligibility criteria	Interventions (drug, dose, duration)	Allowed other medications	Age Gender Ethnicity	Other population characteristics
Karagianis 2009 DB RCT Multicenter Canada, the Netherlands, USA and Mexico The PLATYPUS Study	Inclusion: 18–65 ys; a diagnosis of schizophrenia, schizoaffective disorder, schizophreniform, bipolar disorder or other related psychotic disorder and had gained > 5 kg or an increase in BMI > 1 kg/m3 Exclusion: ODO treatment in the preceding six mos, had a medical condition or were taking other medications that could influence weight, or were participating in a weight-loss prog.	Standard olanzapine tablets (SOT) vs. orally disintegrating olanzapine (ODO) tablets; patients continued treatment with 5–20 mg olanzapine in a flexible, single daily dose and were randomly assigned (1:1) to receive ODO plus oral P, or sublingual P plus SOT for 16 wks.	NR	Mean age 39 yrs 54.4 % male 52.3% Caucasian 33.6% Hispanic 10.1% Black 2% Asian 1.3% First-nation 0.7% Other	Schizophrenia 55% Bipolar 27.5% Schizoaffective disorder 10.1% Schizophreniform 6% Other 1.3%
Kaushal 2012 RCT	(ICD) -10 Schizophrenia, schizophreniform, or schizo-affective disorder, 16-40, male or female,	Risperidone = 2 mg/d Olanzapine = 5 mg/d Duration: 8wks	NR	Mean Age: 29 Male 14% Female = 16% Ethnicity = NR	Systolic blood pressure = 119 Diastolic blood pressure = 43 BPRS score = 43

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Number screened/ eligible/ enrolled	Withdrawn/ Lost to follow-up/ Analyzed	Results
Karagianis 2009 DB RCT Multicenter Canada, the Netherlands, USA and Mexico The PLATYPUS Study	186/153/149	27/7/149	ODO vs. SOT BMI, kg/m2 0.52±0. vs. 2 0.72±0.2 P = 0.465 Weight, kg 1.42±0.5 vs. 2.08±0.6 P = 0.385
Kaushal 2012 RCT	NR/NR/60	NR/NR/60	Effectiveness: NR

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Adverse effects reported
Karagianis 2009 DB RCT Multicenter Canada, the Netherlands, USA and Mexico The PLATYPUS Study	ODA vs. SOT Increased appetite 9 (10.7) vs. 10 (15.4) Headache 5 (6.0) vs. 5 (7.7) Somnolence 5 (6.0) vs. 5 (7.7) Anxiety 3 (3.6) vs. 2 (3.1) Constipation 3 (3.6) vs. 1 (1.5) Decreased appetite 3 (3.6) vs. 0 (0.0) Depression 3 (3.6) vs. 2 (3.1) Fatigue 3 (3.6) vs. 5 (7.7) Akathisia 2 (2.4) vs. 2 (3.1) Insomnia 2 (2.4) vs. 3 (4.6) Dizziness 1 (1.2) vs. 4 (6.2) Dry mouth 1 (1.2) vs. 2 (3.1) Dyspepsia 1 (1.2) vs. 2 (3.1) Nasopharyngitis 1 (1.2) vs. 3 (4.6) Tremor 1 (1.2) vs. 2 (3.1) Arthralgia 0 (0.0) vs. 2 (3.1) Influenza 0 (0.0) vs. 2 (3.1)
Kaushal 2012 RCT	Factors associated with metabolic syndrome: (at 8 weeks) Mean increase in the blood sugar level: 4.4 ± 1.97 mg/dL vs 2.2 ±0.69 mg/dL Mean increase in LDL: 8.23 ± 2.09 mg/dL vs 4.66 ± 1.41 mg/dL Mean change in VLDL: 6.06 ± 0.428 mg/dL and 2.56 ± 0.49 mg/dvc Mean increase in total cholesterol:12.53 ± 1.43 mg/dL vs 4.63 ± 0.52 mg/dL

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Extrapyramidal symptoms
Karagianis 2009 DB RCT Multicenter Canada, the Netherlands, USA and Mexico The PLATYPUS Study	NR
Kaushal 2012 RCT	NR

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Total withdrawals; withdrawals due to adverse events	Comments
Karagianis 2009 DB RCT Multicenter Canada, the Netherlands, USA and Mexico The PLATYPUS Study	27 WD 4 due to AEs	
Kaushal 2012 RCT	Withdrawals due to adverse events: NR Time to withdrawal: NR	

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Eligibility criteria	Interventions (drug, dose, duration)	Allowed other medications	Age Gender Ethnicity	Other population characteristics
Keefe, 2006 DB, R, X 1 y Multicenter: North America (US and Canada) conducted July 1999-Nov. 2000.	18-55 ys of age; schizophrenia or schizoaffective disorder, and a minimum score of 4 on at least 2 positive items on PANSS; score of 18 or more on BPRS; English speaker, level of understanding sufficient to agree to all tests and examinations, illness duration of at least 2 ys from first hospitalization and/or diagnosis/treatment.	olanzapine: 5-20 mg/d (mean dose 12.3mg/d) risperidone: 2-10 mg/d (mean dose 5.2mg/d) or haloperidol: 2-19 mg/d or (mean dose 8.2mg/d) Initial 8 wks (flexible dosing); thereafter a fixed dosed based on investigator's judgment	antidepressants, except fluvoxamine and lithium. Acute usage of valproic acid, carbamazepine, antiemetics, and steroids. Benztropine mesylate or biperiden (up to 6mg/d)	Mean age: 39 Male: 295 (71.3%) 59.7% Caucasian 28.3% African 0.5% Western Asian 1.4% East/Southeast Asian 6.8% Hispanic 3.8% Other origin	40.6% -previously admitted to the hospital in past y due to psychiatric problems 40.9% O; 48.1% R; and 61.9% H used anticholinergic medication at any time during the trial; p<0.01. Mean PANSS total score was 82.1 at baseline. Mean PANSS positive score for pts randomized prior to dropping the haloperidol arm was significantly lower when compared to pts randomized after haloperidol arm was dropped, p=0.007
Keks, 2007 RCT	Diagnosis of schizophrenia or schizoaffective disorder ; PANSS total score 50 or over at least 18 ys; BMI not exceeding 40 mg/ kg2; within the previous 2 mos the patient had been hospitalized or required medical intervention for an acute exacerbation of psychosis and had experienced an additional acute exacerbation during the previous 2 ys.	long-acting risperidone (25mg or 50mg every14 ds) or olanzapine (5-20mg/d). 13 wks and one y	Long-acting risperidone vs. olanzapine concomitant medication: 85% vs 80% sedates/hypnotics: 65% vs 53% antidepressants: 43% vs 34% antiparkinsonian drugs: 37% vs 18% anticonvulsants: 21% vs 19% muscle relaxants: 11% vs 10%	Long-acting injection vs olanzapine: Mean age: 35 ys Male: 56% vs 58% Caucasian: 96% vs 97%	Age at diagnosis 26.5

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Number screened/ eligible/ enrolled	Withdrawn/ Lost to follow-up/ Analyzed	Results
Keefe, 2006 DB, R, X 1 y Multicenter: North America (US and Canada) conducted July 1999-Nov. 2000.	NR/NR/414	174 / 90 /339* *=number evaluated at week 52 for neurocognitive composite score based on sample's baseline data	Neurocognitive Efficacy: Primary: Sample composite LOCF: No significant difference between any of the tax groups at wks 8, 24, 52; p=NS 52 week endpoint: z-scores based on sample composite mean ± SD: 0: 17 ± 0.51; p<0.01, R: 0.18 ± 0.46; p<0.01 Sample composite OC: R. vs. O, p=NS 52 week endpoint: Mean change within O group, p<0.01 and R p<0.01 treatment groups. Normative composite LOCF: change in composite scores was NSly different between group; p=NS 52 week endpoint: Within group improvement: O group, p<0.01; R group, p<0.01 Normative composite OC: No significant difference between O and R 52 week endpoint: Within-group improvement: O group, p<0.01; R group, p<0.01 Individual neurocognitive domains: 52 week LOCF mean change from baseline: O vs R, p=NS. O improved on all domains (all p=0.04) except visuospatial ability and verbal fluency; R improved on all domains (all p<0.05) except verbal fluency. Normative neurocognitive domains 52 week LOCF mean change from baseline: "similar profile was found" (data not shown) Secondary: PANSS depression: 52 week LOCF mean change from baseline pairwise group: O vs R for PANSS total, positive score, and negative score: p=NS. LOCF at 52 wks: all treatment groups significantly improved on all three PANSS measurement: p<0.02. MADRS or HAMA-No statistical differences between any tax groups 52 week visit-wise OC: within group: O, p<0.001; R, p<0.001 52 week OC pairwise group: O vs. R; NS
Keks, 2007 RCT	693/NR/629	200/NR/ short-term 378 and long-term 362	Risperidone vs. olanzapine Short-term mean (s.d..) and LSM of the difference (95% CI) PANSS Total change at endpoint -16.9 (15.5) vs. -17.8 (15.4) and 0.2 (-2.7 to 3.0) Long-term mean (s.d..) and LSM of the difference (95% CI) PANSS Total change at endpoint -20.4 (18.8) vs -20.5 (20.3), 0.2(-3.4 to 3.8) Anxiety/depression change at endpoint -3.1 (3.6) vs. -3.4 (3.7) and 0.6 (0.1 to 1.2) P < 0.05 CGI- S at endpoint (not or mildly ill) 66% vs. 67%

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Adverse effects reported
Keefe, 2006 DB, R, X 1 y Multicenter: North America (US and Canada) conducted July 1999-Nov. 2000.	Treatment-emergent AE in > 10% of any group or significantly different between groups: Olanzapine > R: somnolence, depression, headache, insomnia, anxiety, nausea, weight gain, pain, rhinitis, hallucinations, nervousness, dry mouth, diarrhea, dizziness, akathisia, tremor, paranoid reaction, abnormal thinking, vomiting, agitation, (each p= NS) Constipation: O> R; p=0.01 Mean change from baseline to 52 week endpoint: Weight (kg) gain: O > R: p<0.01 Triglyceride mean change: O> R, p=0.01 Cholesterol mean change (mg/dL): O > R; <0.01 Glucose, non-fasting (mg/dL): O vs. R; p=NS Prolactin mean change: (ng/mL): R > O; p <0.01
Keks, 2007 RCT	Risperidone vs. olanzapine (%) Psychosis 29 vs. 25 Insomnia 22 vs. 14 Depression 20 vs. 14 Anxiety 14 vs. 16 Agitation 10 vs. 5 Headache 8 vs. 5 Hyperkinesia 8 vs. 3 Rhinitis 7 vs. 6 Weight increase 6 vs. 9 Somnolence 5 vs. 7 Tremor 5 vs. 2 Injury 5 vs. 2

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Extrapyramidal symptoms
Keefe, 2006 DB, R, X 1 y Multicenter: North America (US and Canada) conducted July 1999-Nov. 2000.	AIMS Total Mean Change Score: O vs. R; p=NS Barnes Global Mean Change Score: O vs. R; p=NS Simpson-Angus Total Mean Change Score: O vs. R; p=NS Akathisia: Olanzapine 8.8%, Risperidone 12.7%
Keks, 2007 RCT	Extrapyramidal symptoms risperidone 25% vs olanzapine 15% (p<0.05)

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Total withdrawals; withdrawals due to adverse events	Comments
Keefe, 2006 DB, R, X 1 y Multicenter: North America (US and Canada) conducted July 1999-Nov. 2000.	269/53 O: 15 (9.4%) R:24 (15.2%) Haloperidol: 14 (14.4%)	After ~52 wks of enrollment, the haloperidol arm was dropped due to recruitment difficulties. After the study was completed, it was discovered that 17.7% O group, 14.1% R , and 18.6% H group were on antipsychotic medications prior to randomization. Approx. 25.8% were randomized to the same antipsychotic medication they were taking prior to enrollment (18% olanzapine, 14% risperidone). 61% of pts were considered to be compliant with prescribed treatment. Relapse Rate: Pts who responded: No difference Pts who stabilized: O: 15/129, 11.6%; R 27/121, 22.3%; p=0.03.
Keks, 2007 RCT	200 total WD 18 due to AEs	

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Eligibility criteria	Interventions (drug, dose, duration)	Allowed other medications	Age Gender Ethnicity	Other population characteristics
Kelly, 2005 DB, RCT Thyroid results from Conley 2003 (different from the Conley 2003 above)	Treatment-resistant schizophrenia and medically healthy.	N=38 400 mg/d quetiapine, or 4 mg/d risperidone, or 12.5 mg/d fluphenazine 6 wks duration	lorazepam, benztropine, oral hypoglycemics, laxatives, diuretics, nonsteroidal anti-inflammatory agents, antibiotics, antihypertensives	Mean age: 43.8 Male: 73% Black: 60% White: 40%	NR
Kelly, 2006 R, DB, parallel-group SC, treatment-resistant schizophrenia	Treatment resistant schizophrenia: 1. Persistent positive psychotic symptoms: item score ≥ (moderate) on at least 2 of 4 positive symptom items on BPRS; 2. Presence of at least moderately severe illness on total BPRS score (score ≥ 45 on the 18-item scale) and a score of ≥4 (moderate) on CGI; 3. Two failed historical trials of antipsychotics of at least 6 wks duration at doses of at least = to 600mg/d chlorpromazine; 4. No stable period of good social and/or occupational functioning within the last 5 ys.	Risperidone: 4mg/d (n=12) Quetiapine: 400mg/d (n=6) OR fluphenazine 12.5mg/d (n=9) x 12 wks	agitation or anxiety: up to 10mg/d of lorazepam prn; Benztropine mesylate (up to 4 mg/d); propranolol (30-120 mg/d) for EPS	Age: R: 46; Q 42; F 45 Gender: (male) R 75%; Q: 67%; F: 88% Race: (Black) R: 50%; Q 67%; F 56%	

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Number screened/ eligible/ enrolled	Withdrawn/ Lost to follow-up/ Analyzed	Results
Kelly, 2005 DB, RCT Thyroid results from Conley 2003 (different from the Conley 2003 above)	NR/NR/38	NR/NR/30	Change in Thyroid Function Test Results: Mean + SD Change Total serum thyroxine: Q: -2.37 + 1.48 vs R: -0.01 + 1.02 vs F: 0.62 + 1.91; p=.01 Free thyroxine index: Q: -0.76 + 0.68 vs R: -.0.07 + 0.48 vs F: 0.22 + 0.62; p=NS Serum T3 resin uptake: Q: -0.00 + 2.76 vs R: 0.38 + 1.92 vs F: 0.30 + 1.36; p=NS Thyroid-stimulating hormone: Q: -0.86 + 1.6 vs R: -0.28 + 1.05 vs F: -0.49 + 1.68; p=NS
Kelly, 2006 R, DB, parallel-group SC, treatment-resistant schizophrenia	NR/NR/38	18*/ NR/ 28 *4-risperidone (31%); 5 on quetiapine (42%) and 9 on fluphenazine (69%)	Sexual Dysfunction: 7/9 F (78%); 5/12 R (42%); 3/6 q (50%); P=NS Sexuality at end of study: subjective improvement: 1/8 F (13%); 6/11 R (55%); 2/5 Q: 40%; p=NS Orgasm: Q: significant improvement ; not seen with R and F; p=0.033 Arousal: Q: improved, not seen with R and F; p=NS Post-hoc analysis: (data not shown) Higher prolactin levels were correlated to lower BPRS scores. Total BPRS scores; p=0.048 positive symptoms, p=0.050 Trend was noted for activating symptoms, p=0.051. Higher prolactin levels were associated with higher negative symptoms, p=0.037. (Significant findings were not evident by drug group)

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Adverse effects reported
Kelly, 2005 DB, RCT Thyroid results from Conley 2003 (different from the Conley 2003 above)	NR
Kelly, 2006 R, DB, parallel-group SC, treatment-resistant schizophrenia	12 week prolactin levels: R: 50.6± 40.4, F: 24.4± 18.5; Q: 8.2 ±4.4, p=0.005, controlling for baseline and sex R: galactorrhea and gynecomastia 1/9 males (11%), amenorrhea: 2 females (100%) F: gynecomastia:1 female: No hormonal effects were noted in males Q: No hormonal side effects occurred; 1 out of 2 women with amenorrhea regained menstruation during Q treatment All cases of gynecomastia resolved during treatment No difference btw groups for the following: Headache: 48.1%; somnolence; 37%; insomnia 29.6%; lethargy, increased appetite and orthostasis 25.9%; dry mouth, nausea, constipation 18.5%; blurry vision, dizziness, dyspepsia, diarrhea, and anxiety 18.5% Mean prolactin levels for: pts experiencing sexual dysfunction (all drugs) were 29.25 ± 27.44 mg/dl pts with no sexual dysfunction the mean levels were 35.56 ± 41.63; p=NS.

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Extrapyramidal symptoms
Kelly, 2005 DB, RCT Thyroid results from Conley 2003 (different from the Conley 2003 above)	NR
Kelly, 2006 R, DB, parallel-group SC, treatment-resistant schizophrenia	NR

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Total withdrawals; withdrawals due to adverse events	Comments
Kelly, 2005 DB, RCT Thyroid results from Conley 2003 (different from the Conley 2003 above)	NR / NR	
Kelly, 2006 R, DB, parallel-group SC, treatment-resistant schizophrenia	7 total WD NR due to ASs	Sexual dysfunction was defined as "any trouble maintaining an erection, painful prolonged erections, trouble ejaculating when wanted, loss of interest once aroused, and/or not able to have an orgasm if wanted. " Sexual dysfunction was not found to be correlated with prolactin levels (p>0.05). Those on quetiapine who noted "improvement" in sexual functioning tended to have a larger decrease in prolactin than for the subjects reporting no improvement (-44.25 vs. -32.57 mg/dl). No trends noted for R or F in relation to prolactin levels and subjective sexual function changes. Limitations: N; few subjects received O during lead-in phase

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Eligibility criteria	Interventions (drug, dose, duration)	Allowed other medications	Age Gender Ethnicity	Other population characteristics
Kelly, 2008 goes with Conley 2001 DB RCT	Schizophrenia or Schizoaffective disorder by DSM-IV diagnosis, baseline PANSS score, 60–120, aged 18–64 ys; out- or inpatients hospitalized ≤4 wks.	Risperidone 2–6 mg/d (flexible dose); oral Olanzapine 5–20 mg/d Duration: 8 wks Both drugs given qd according to following regimens: ds 1–2, 2 mg Risperidone or 10 mg Olanzapine; ds 3–7, 2–4 mg risperidone or 5–10 mg Olanzapine; ds 8–14, 2–6 mg risperidone or 5–15 mg Olanzapine; ds 15–56, 2–6mg Risperidone or 5–20 mg Olanzapine	NR	Mean age: risperidone 41.0 (11.0) ys olanzapine 38.9 (10.5) ys 72.7% male Ethnicity NR	79% were outpatients Schizophrenia (n= 325) or schizoaffective disorder (n= 52) Duration of illness: mean risperidone 16.5 (10.5) ys, olanzapine 15.4 (10.6) ys Weight olanzapine 82.7 kg risperidone 83.7 kg BMI olanzapine 28.15 kg/m, risperidone 28.78
Kern, 2006 RCT, open-label	Inclusion - outpatients, schizophrenia or schizoaffective disorder, between ages of 18 and 65, able to speak and understand English, were on a stable dose of an oral typical antipsychotic, risperidone, or quetiapine for at least 1 mo, and had not been hospitalized for psychiatric treatment for at least 2 mos. Exclusion - current suicidality, neurological disorder (e.g., epilepsy), acute or unstable medical condition, a clinically significant laboratory test value, GI resection or stapling that may interfere with study medication absorption, and alcohol- or substance-dependence within the past 3 mos; received aripiprazole in a prior clinical study, had taken a selective serotonin reuptake inhibitor within 2 wks before screening, or if they had taken an investigational drug within 4 wks	30 mg of oral aripiprazole or 15 mg of oral olanzapine	NR	Mean age: 40 64% male 60% Caucasian	

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Number screened/ eligible/ enrolled	Withdrawn/ Lost to follow-up/ Analyzed	Results
Kelly, 2008 goes with Conley 2001 DB RCT	NR/NR/377 Risperidone 188 Olanzapine 189	Risperidone 53/NR/188 Olanzapine 43/NR/189	Weight gain at week 8 olanzapine 3.8 kg vs. risperidone 2.0 kg P < 0.001 BMI increase at week 8 olanzapine 1.3 kg/m risperidone 0.7 kg/m P < 0.001 Total cholesterol olanzapine 13.5 vs. risperidone -3.9 mg/dl P = 00.058
Kern, 2006 RCT, open-label	NR/NR/255	146 (57%)/21 (8%)/169	General cognitive functioning - aripiprazole and olanzapine showed significant improvement from baseline at week 8 (p=0.023 and 0.015, respectively) that fell to a trend at week 26 (p=0.055 and 0.087, respectively). No significant between-group differences at either week 8 or 26 comparisons Executive functioning - LOCF analyses failed to show significant improvement from baseline to week 8 or 26 for either group (all p>0.20) Verbal learning -, aripiprazole showed a significant improvement from baseline at both week 8 (p<0.0001) and week 26 (p<0.0001); olanzapine did not. Examination of between-group differences revealed a significant difference in favor of the aripiprazole group compared to the olanzapine group at both week 8 (p=0.020) and week 26 (p=0.040)

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Adverse effects reported
Kelly, 2008 goes with Conley 2001 DB RCT	NR
Kern, 2006 RCT, open-label	NR

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Extrapyramidal symptoms
Kelly, 2008 goes with Conley 2001 DB RCT	NR
Kern, 2006 RCT, open-label	NR

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Total withdrawals; withdrawals due to adverse events	Comments
Kelly, 2008 goes with Conley 2001 DB RCT	Risperidone 53/188 (28.2%) Due to AE 22/188 (11.7%) Olanzapine 43/189 (22.8%) Due to AE 17/189 (8.99%)	
Kern, 2006 RCT, open-label	146 total WD 46 due to AEs	WD (53%) from the olanzapine group and (62%) from the aripiprazole group.

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Eligibility criteria	Interventions (drug, dose, duration)	Allowed other medications	Age Gender Ethnicity	Other population characteristics
Kim 2012 RCT	DSM - Schizophrenia, 18-59, male or female, have been recieiving risperidone monotherapy, stable dose of risperidone for a minimum of 2 wks, symptomatically stable,	Risperidone = 6 mg. Max dose. Paliperidone ER = 12 mg. Max dose. Duration = 12 wks	Antidepressants , mood stabilizers used for more than 1 mo. • Anticholinergics • Propranolol • Benzodiazepines	Mean Age: 34 Male 19% Female = 10% Ethnicity = NR	Adjunctive use of anticholinergics = Baseline: 85% Adjunctive use of propranolol = Baseline: 36% Adjunctive use of benzodiazepine = Baseline: 38%
Kim 2010 RCT Korea	Age 20-64 years	Drugs: Risperidone Olanzapine Aripiprazole Dose: NR Duration: 8 weeks	For insomnia, anxiety and irritability, .5-2mg lorazepam and 1-2mg benztropine as needed	Mean age: 39.6 Male: 71% Female: 29% Ethnicity: NR	Antipsychotics dose (mg/day) baseline: 13.2 Smoking years baseline: 20 SAPS total baseline: 76 SANS total baseline: 73.7 AIMS total baseline: 4.6

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Number screened/ eligible/ enrolled	Withdrawn/ Lost to follow-up/ Analyzed	Results
Kim 2012 RCT	NR/NR/58	8/6/1949	Changes in efficacy measures from baseline to endpoint between: Adjusted mean change (SE) (Risperidone vs. Paliperidone ER) PANSS: Positive – 1.0 (1.2) vs. – 1.6 (1.9) Negative – 0.9 (0.5) vs. – 0.5 (0.5) General psychopathology – 2.3 (0.7) vs. – 2.1 (0.6) Total – 4.6 (1.1) vs. – 4.2 (1.0) SOFAS 1.3 (0.9) vs. 3.8 (0.8) CDSS – 1.4 (0.5) vs. – 1.1 (0.4) BDI – 2.0 (1.8) vs. – 4.4 (1.5) SWN-K 3.1 (2.9) vs. 2.4 (2.5) DAI 3.2 – 0.1 (0.8) 2 vs. 1.2 (0.7) VAS – sleep quality (mm) – 5.8 (4.2) vs. 0.9 (3.8) VAS – daytime sleepiness (mm) 5.7 (4.6) vs. 2.2 (4.2) Changes in the neurocognitive function from baseline to endpoint: *Adjusted mean change (SE) (Risperidone vs. Paliperidone ER) Digit Span Test: Forward (n) 0.3 (0.2) vs. 0.2 (0.2) Backward (n) 4.4 (1.3) vs. 0.1 (0.2) Verbal learning test: Trial A6 (n) 0.7 (0.6) vs. 2.3 (0.5) Delayed recall (n) 0.9 (0.6) vs. 1.4 (0.5) Continuous Performance Test: Reaction time (ms) – 19.2 (10.6) vs. – 4.4 (9.1) Correct response (n) 2.0 (2.9) vs. 1.8 (2.5) Finger Tapping Test (n) – 10.2 (9.9) vs. –7.9 (8.8) Trail Making Test Part A (s) – 3.4 (3.3) vs. – 1.6 (2.9) Part B (s) – 0.1 (8.2) vs. – 1.6 (7.0) COWAT (n) – 1.8 (2.4) vs. – 1.1 (2.1) MMSE 0.3 (0.3) vs. 28.0 (2.1) *unless otherwise noted
Kim 2010 RCT Korea	NR/NR/139	NR/NR/139	Risperidone vs Olanzapine vs Aripiprazole SAPS total: -26.3% vs -24% vs -19.5% SANS total: -15.3% vs 26.6 vs 36%

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Adverse effects reported
Kim 2012 RCT	10% Reported no adverse events (both groups) Menstruation disturbance: Amenorrhea: 45.5% vs.44.4% Oligomenorrhea 36.3% vs. 22.2%
Kim 2010 RCT Korea	NR

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Extrapyramidal symptoms
Kim 2012 RCT	Extrapyramidal effects: NR
Kim 2010 RCT Korea	At 8 wks, the AIMS score of the haloperidol group was higher than for those groups taking atypical antipsychotics (F=6.6, p<.01) No other data reported.

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Total withdrawals; withdrawals due to adverse events	Comments
Kim 2012 RCT	Withdrawals due to adverse events: Gastric discomfort, paliperidone N=1 Aggressive behavior, risperidone N=1	
Kim 2010 RCT Korea	NR	

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Eligibility criteria	Interventions (drug, dose, duration)	Allowed other medications	Age Gender Ethnicity	Other population characteristics
Kinon, 2006a DB, RCT, multicenter (40 US centers)	Age 18-65 yrs; met DSM-IV criteria for schizophrenia or schizoaffective disorder; had prominent depressive symptoms defined by score >/= 16 on MADRS and score >/=4 on item 2 of MADRS. Exclusion criteria: history of nonresponse to at least 6 wks of olanzapine or ziprasidone; received a depot neuroleptic within 2 wks of visit 1.	olanzapine (n=202): 10, 15, or 20 mg/d ziprasidone (n=192): 80, 120, or 160 mg/d Doses were fixed by end of week 2 24 week study	Concomitant medications with psychotropic activity were not allowed with the following exceptions: benzodiazepines, hypnotics, medication for treatment of EPS (excluding prophylaxis) and antidepressants if taken in stable doses for at least 30 ds before enrollment and maintained throughout study	Age: NR Gender: NR Ethnicity: NR	Outpatients: 99.0% olanzapine vs. ziprasidone Use of antipsychotics within 30 ds before baseline: 70.8% vs. 82.3% MADRS mean (SD): 27.3 (6.2) vs. 27.3 (6.5) PANSS: 79.6 (17.5) vs. 79.1 (17.3) Concurrent use of antidepressants upon study entry: 51.1% vs. 54.7%
Kinon, 2006b Bushe, 2010 DB, RCT, U.S. (Journal of Clinical Psychopharmacology)	Inclusion: Outpatients; DSM IV schizophrenia or schizoaffective disorder; met criteria for prominent negative symptoms, defined as a Positive and Negative Syndrome Scale (PANSS) score > 4 (moderate) on at least 3, or > 5 (moderately severe) on at least 2 of the 7 negative scale items; and for social and functional impairment, defined as a Global Assessment of Functioning Scale (GAF) score of less than or equal to 60 (moderate difficulties). Exclusion criteria: NR	Olanzapine 10-20 mg/d Quetiapine 300-700 mg/d 6 mos	NR	Mean age 41 yrs 66% male 52% white 37% African descent 3% other	

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Number screened/ eligible/ enrolled	Withdrawn/ Lost to follow-up/ Analyzed	Results
Kinon, 2006a DB, RCT, multicenter (40 US centers)	NR/NR/394	247 withdrew olanzapine: 112 (55.4%) ziprasidone: 135 (70.3%) ITT analysis	CDSS change from baseline at 8 wks (olanzapine vs. ziprasidone): -6.4 vs. -6.1; P=0.493, MMRM; P=0.497, LOCF Changes from baseline at 24 wks (olanzapine vs. ziprasidone): CDSS: -6.0 vs. -4.8; P=0.017, LOCF; P=0.105, MMRM MADRS: -12.1 vs. -9.15; P=0.003, LOCF; P=0.010, MMRM PANSS: -13.5 vs. -8.3; P=0.008, LOCF; P=0.061, MMRM % of patients using benzodiazepines 29.2% vs. 39.0%; P=0.043 GAF improvement over 24 wks: olanzapine: 6.64 (n=168) ziprasidone: 3.15 (n=158) P=0.017 GAF improvement >/= 5 points: olanzapine: 54.2% ziprasidone: 41.1% percentage difference, 13.0, 95% CI: 12.3 to 23.8
Kinon, 2006b Bushe, 2010 DB, RCT, U.S. (Journal of Clinical Psychopharmacology)	NR/NR/346	190/21/195-288(varied)	Change from baseline SANS score olanzapine -12 quetiapine -8.3 P= 0.09 PANSS total olanzapine -11.3 quetiapine -7.2 P= 0.151 CGI-S olanzapine -0.5 quetiapine -0.2 P= 0.02 CGI-I (endpoint) olanzapine 3.2 quetiapine 3.8 P< 0.001 Glucose (pooled), mmol/L: change in mean (SD) from baseline to endpoint OLZ: 0.75 (2.47) [within group p-value = 0.001] vs. QUE 0.13 (2.37) [within group p-value = 0.183] Between group p-value = 0.250 Haemoglobin A1c (%): change in mean (SD) from baseline to endpoint OLZ: 0.09 (0.89) [within group p-value = 0.815] vs. QUE: -0.02 (0.43) [within group p-value = 0.977] Between group p-value = 0.823 Treatment emergent diabetes and impaired glucose: OLZ vs. QUE, P (between groups) Patients with TED, n^e/N^f (%): 4/158 (2.5) vs. 2/151 (1.3), 0.685 Patients with TE IG, n^e/N^f (%): 2/152 (1.3) vs. 1/137 (0.7), >0.999

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Adverse effects reported
Kinon, 2006a DB, RCT, multicenter (40 US centers)	Differences in AEs (olanzapine vs. ziprasidone) Weight gain: 20.3% vs. 5.8%, P<0.001 Increased appetite: 10.4% vs. 4.2%, P=0.021 Peripheral edema: 3.0% vs. 0.0%, P=0.031 Psychosis: 2.5% vs. 7.9%, P=0.020 Decreased appetite: 1.0% vs. 5.3%, P=0.017 Influenza & migraine: 0.0% vs. 2.6%, P=0.026
Kinon, 2006b Bushe, 2010 DB, RCT, U.S. (Journal of Clinical Psychopharmacology)	Olanzapine vs quetiapine (%) Psychosis 2.9 vs.9.7 P = 0.014 Pain 2.3 vs. 7.4 P = 0.044 Anorexia 0 vs. 4.6 P = 0.007 Headache 9.8 vs. 14.3 P = 0.131 Somnolence 24 vs. 22.9 P = 0.899

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Extrapyramidal symptoms
Kinon, 2006a DB, RCT, multicenter (40 US centers)	Olanzapine vs. ziprasidone SAS (mean change from baseline): -0.37 vs. -0.03, P=0.037 AIMS: -0.68 vs. -0.34, P=0.001 Barnes Akathisia Scale: -0.12 vs. -0.12, P=0.431 Adjunctive use of anticholinergic agents: 18.8% vs. 21.6%, P=0.530
Kinon, 2006b Bushe, 2010 DB, RCT, U.S. (Journal of Clinical Psychopharmacology)	The treatment groups did not differ significantly; data=NR

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Total withdrawals; withdrawals due to adverse events	Comments
Kinon, 2006a DB, RCT, multicenter (40 US centers)	Total WD: 247 (62.7%) olanzapine: 112 (55.4%) ziprasidone: 135 (70.3%) WD due to AEs: NR	
Kinon, 2006b Bushe, 2010 DB, RCT, U.S. (Journal of Clinical Psychopharmacology)	190 WD 96 due to AEs	

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Eligibility criteria	Interventions (drug, dose, duration)	Allowed other medications	Age Gender Ethnicity	Other population characteristics
Klieser, 1991 Heinrich, 1994 Klieser, 1995 DB, RCT Inpatients	Patients diagnosed with acute, paranoid schizophrenia.	28 d study risperidone(N=20): 4mg/d risperidone(N=19): 8mg/d clozapine(N=20): 400mg/d	Biperiden, short-acting lorazepam	Median age: 33 ys 52.3% Male Ethnicity NR	100% inpatient with diagnosis of schizophrenia Schizophrenia Diagnosis: Disorganized: 1 Catatonic: 1 Paranoid: 46 Paranoid/residual: 1 Unspecified: 2 Schizoaffective psychosis: 8
Kluge, 2007 Kluge, 2012 DB RCT Single center Germany	18 to 65 ys old, schizophrenia, schizophreniform, or schizoaffective disorder with a Brief Psychiatric Rating Scale (BPRS0–6) score of 24 or more.	Clozapine 266.7 (77.9) mg n=15 Olanzapine 21.2 (2.5) mg. n=15 6 wks	Benzodiazepines	Mean age 29 yrs 60% male Ethnicity NR	Clozapine vs. Olanzapine BMI 25.4 vs. 24.4 Weight, kg 75.7 vs. 73.5 BPRS 36.6 (8.8) vs. 36.7 (9.9) BPRS positive 9.4 (3.7) vs. 10.2 (3.8) BPRS negative 5.9 (2.1) vs. 7.1 (3.4) BPRS anxiety/depression 10.9 (4.5) vs. 8.7 (4.5) CGI S 4.7 (0.6) vs. 4.5 (0.6)

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Number screened/ eligible/ enrolled	Withdrawn/ Lost to follow-up/ Analyzed	Results
Klieser, 1991 Heinrich, 1994 Klieser, 1995 DB, RCT Inpatients	NR/NR/59	31/3/28	Clinical Global Impression at Endpoint (CGI): CGI Rating: very much/much improved: R4: 12 vs R8: 8 vs C: 12 CGI Rating: minimally improved: R4: 3 vs R8: 5 vs C: 4 CGI Rating: minimally worse or deteriorated: R4: 5 vs R8: 6 vs C: 4 BPRS scores : baseline vs week 4 vs endpoint Activity: R4: 10.1 vs 5.1 vs 6.9, R8: 9.5 vs 4.7 vs 7.7, C400: 10.5 vs 5.9 vs 7.7 Anergia: R4: 10.3 vs 6.9 vs 8.7, R8: 10.5 vs 8.7 vs 9.1, C400: 10.5 vs 6.9 vs 8.5 Anxiety/depression: R4: 13.5 vs 7.6 vs 9.7, R8: 12.6 vs 8.3 vs 9.2, C400: 13.9 vs 6.2 vs 8.9 Hostility: R4: 8.2 vs 4.4 vs 4.9, R8: 8.7 vs 3.5 vs 6.1, C400: 9.6 vs 5.7 vs 6.8 Thought disturbances: R4: 13.8 vs 6.3 vs 8.5, R8: 11.3 vs 5.3 vs 9.1, C400: 13 vs 7.1 vs 8.5 Total Score: R4: 55.5 vs 30.3 vs 38.7, R8: 52.6 vs 30.5 vs 41.2, C400: 57.4 vs 31.9 vs 40.3
Kluge, 2007 Kluge, 2012 DB RCT Single center Germany	37/ NR/ NR	4/ 0/ 30	Clozapine vs. Olanzapine Endpoint values BPRS 15.9 (13.7) vs. 19.1 (13.8) BPRS positive 3.5 (3.9) vs. 5.1 (4.3) BPRS negative 3.2 (3.7) vs. 3.9 (2.2) BPRS anxiety/depression 5.5 (4.2) vs. 5.1 (4.1) CGI-S 2.5 (1.5) vs. 2.3 (1.2) Binge eating at 6 wks % 13 vs. 27 Food craving at 6 wks % 27 vs. 53 Sleep latency (min): BL (SD), week 2 (SD), week 4 (SD), week 6 (SD), P in ANOVA Clozapine 17.3 (1.0), 13.9 (1.3), 13.5 (1.7), 13.5 (1.2), P=0.124 Olanzapine 16.6 (0.7), 14.1 (1.5), 13.5 (1.2), 14.1 (1.1), P=0.039 (BL vs. week 4, P=0.008) Number of sleep onsets: BL (SD), week 2 (SD), week 4 (SD), week 6 (SD), P in ANOVA Clozapine 1.4 (0.4), 3.0 (0.4), 3.1 (0.5), 2.9 (0.4), P=0.012 (BL vs. week 2, P=0.006; vs. week 4, P=0.004; vs. week 6, P=0.009) Olanzapine 2.0 (0.4), 2.4 (0.40), 2.9 (0.4), 2.3 (0.4), P=0.176

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Adverse effects reported
Klieser, 1991 Heinrich, 1994 Klieser, 1995 DB, RCT Inpatients	28;7 WDs due to AEs: Sleep and vigilance: R4: 14(70%) vs R8: 11(58%) vs C400: 13(65%) Appetite: R4: 7(35%) vs R8: 3(16%) vs C400: 14(70%) Gastro-intestinal: R4: 10(50%) vs R8: 7(37%) vs C400: 15(75%) Cardio-respiratory: R4: 4(20%) vs R8: 5(26%) vs C400: 9(45%) Other vegetative: R4: 2(10%) vs R8: 7(37%) vs C400: 12(60%) Other disturbances: R4: 8(40%) vs R8: 7(37%) vs C400: 11(55%) Neurologic: R4: 6(30%) vs R8: 7(37%) vs C400: 6(30%) % Patients worsened on the AMDP scale: R4: 89% vs R8: 79% vs C400: 85%
Kluge, 2007 Kluge, 2012 DB RCT Single center Germany	Clozapine vs. Olanzapine n (%) Salivary hypersecretion 7 (47) vs. 3 (20) P = NS Dizziness 6 (40) vs. 1 (6.7) P = NS Fever* 6 (40) vs. 0 (0) P < 0.01 Fatigue 2 (13) vs. 3 (20) P = NS Constipation 3 (20) vs. 1 (7) P = NS Tachycardia 3 (20) vs. 0 (0) P = NS

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Extrapyramidal symptoms
Klieser, 1991 Heinrich, 1994 Klieser, 1995 DB, RCT Inpatients	Simpson and Angus Rating Scale scores (SAS): Mean change from baseline Gait: R4: 0.2 vs R8: 0.4 vs C400: -0.1; p=NS Arm dropping: R4: 0.2 vs R8: 0.2 vs C400: 0.2; p=NS Shoulder shaking: R4: 0.4 vs R8: 0.1 vs C400: 0.1; p=NS Elbow rigidity: R4: 0.1 vs R8: 0.2 vs C400: 0.2; p=NS Wrist rigidity: R4: 0.1 vs R8: 0.2 vs C400: 0.1; p=NS Leg pendulousness: R4: 0.3 vs R8: 0.2 vs C400: 0.1; p=NS Head dropping: R4: 0.1 vs R8: 0.2 vs C400: 0.1; p=NS Glabella tap: R4: 0.1 vs R8: 0.1 vs C400: 0.0; p=NS Tremor: R4: 0.1 vs R8: 0.1 vs C400: 0.2; p=NS Salivation: R4: 0.0 vs R8: 0.2 vs C400: 0.7; p=0.007 Total score: R4: 0.1 vs R8: 0.2 vs C400: 0.1; p=NS Akathisia: R4: 0.1 vs R8: 0.3 vs C400: 0.0; p=NS
Kluge, 2007 Kluge, 2012 DB RCT Single center Germany	SAS olanzapine, baseline 0.09±0.17 to endpoint 0.03 ± 0.06; clozapine, baseline 0.35+ 0.57 to endpoint 0.14 ± 0.16

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Total withdrawals; withdrawals due to adverse events	Comments
Klieser, 1991 Heinrich, 1994 Klieser, 1995 DB, RCT Inpatients	31 total WD 7 due to AEs	
Kluge, 2007 Kluge, 2012 DB RCT Single center Germany	7 WD 1 due to AEs	

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Eligibility criteria	Interventions (drug, dose, duration)	Allowed other medications	Age Gender Ethnicity	Other population characteristics
Knegtering, 2004 Open-label Inpatients and outpatients	Schizophrenia, schizophrenia-related psychotic illness.	N=51 quetiapine(N=25): 200-1200 mg/d risperidone (N=26): 1-6 mg/d	NR	Mean age: 70.5% Male	Clinical Diagnoses: Brief psychotic disorder: 3(5.8%) Schizophreniform disorder: 8(15.6%) Schizophrenia: 29(56.8%) Schizoaffective disorder: 2(3.9%) Delusional disorder: 1(1.9%) Psychosis: 7(13.7%)

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Number screened/ eligible/ enrolled	Withdrawn/ Lost to follow-up/ Analyzed	Results
Knegtering, 2004 Open-label Inpatients and outpatients	NR/51	NR	Patients Reporting Sexual Dysfunction at Endpoint: Q: 4/25(16%) vs R: 12/24(50%); p=0.006 Prolactin levels (Mean + SD) and Sexual Dysfunction: Prolactin: Male: Q: 12.1 + 10.1 vs R: 47.1 + 24.1; P=0.00 Female: Q: 18.0 + 21.5 vs R: 78.1+ 55.4; P=0.001 Decreased libido: Male: Q: 4/19(21%) vs R: 6/15(40%); P=0.12 Female: Q: 0 vs R: 3/10(30%); P=0.07 Decreased erection: Male: Q: 2/15(11%) vs R: 5/15(33%); P=0.05 Decreased vaginal lubrication: Female: Q: 0 vs R: 3/9(38%); P=0.05 Decreased orgasm: Male: Q: 1/16(6%) vs R: 4/15(27%); P=0.05 Female: Q: 4/15(27%) vs R: 3/8(38%); P=0.06 Ejaculation dysfunction: Male: Q: 2/14(14%) vs R: 4/14(29%); P=0.18 Sexual dysfunction: Male: Q: 4/19(21%) vs R: 8/14(57%); P=0.02 Female: Q: 0 vs R: 4/10(40%); P=0.04 PANSS total scores: Q: 5.4+12.3 vs R: 8.4+11.2; P=0.43

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Adverse effects reported
Knegtering, 2004 Open-label Inpatients and outpatients	NR

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Extrapyramidal symptoms
Knegtering, 2004 Open-label Inpatients and outpatients	NR

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Total withdrawals; withdrawals due to adverse events	Comments
Knegtering, 2004 Open-label Inpatients and outpatients	NR / NR	

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Eligibility criteria	Interventions (drug, dose, duration)	Allowed other medications	Age Gender Ethnicity	Other population characteristics
Knegtering, 2006 RCT, open-label naturalistic study Inpatients and outpatients	Schizophrenia who were to be switched to a new antipsychotic for clinical reasons as determined by attending psychiatrists.	olanzapine starting dose 10mg (5-15 mg/d permitted, mean dose: 9.4mg/d) risperidone starting dose 1mg (1-6mg/d permitted; mean dose: 3.4mg/d x 6 wks	Any antipsychotic before entering the study except depot neuroleptics, olanzapine or risperidone	Mean age: O: 27.2± 7.2; R 26.0 ±6.3 (range: 19-40) Male:(%) O: (n=25) 80; R: (n=21) 90.5 Ethnicity: NR	Clinical diagnoses per DSM-4: brief psychotic disorder: 2 schizophreniform disorder: 4 schizophrenia: 31 schizoaffective disorder: 1 delusional disorder: 3 psychosis NOS: 5

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Number screened/ eligible/ enrolled	Withdrawn/ Lost to follow-up/ Analyzed	Results
Knegtering, 2006 RCT, open-label naturalistic study Inpatients and outpatients	NR/NR46	0/0/46	CGI: Both groups were considered effective: (rated as much worse, worse, unchanged, improved, or much improved) . "75% of the pts were rated by MD as being clinically significantly improved (improved and much improved) after 6 wks." (data now shown) Numerically more R pts were rated as improved vs. O, p=NS

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Adverse effects reported
Knegtering, 2006 RCT, open-label naturalistic study Inpatients and outpatients	Sexual severity score: R worse than O; p=0.002 (of the 46 pts who completed the trial, 4 (8.7%) reported sexual dysfunction spontaneously) Semi-structure interview: 14/46 (30.4%) mild or severe sexual dysfunction O: 3/25 (12%) reported sexual dysfunction vs. R: 11/21 (52%) Prolactin: O vs. R; NS Type of sexual dysfunction (%) O (n=25) vs. R (n=21), p Decreased libido: 12 vs. 33.3; NS Decreased orgasm: 0 vs. 19; NS Any sexual dysfunction: 12 vs. 52.4, p =.008 Men only: O (n=20) vs. R (n=19) Prolactin: ng/ml, mean ± SD: 15.9 ±5.3, 41.5 ± 19.5, p=±.001 Type of sexual dysfunction (%) O vs. R , p Decreased erection;) vs. 31.6; p=.04 Decreased libido: 5 vs. 31.6; NS Decreased orgasm: 0 vs. 21.1; NS Ejaculation dysfunction: 0 vs. 16.7, NS Any sexual dysfunction: 6.3 vs. 47.4, p =.01 R experienced more serious problems vs. O pts; p=.003 Women only: 2/7 reported missed period and both had high prolactin levels > 48.6 ng/ml (1 taking olanzapine 10mg/d and other risperidone 6 mg/d)

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Extrapyramidal symptoms
Knegtering, 2006 RCT, open-label naturalistic study Inpatients and outpatients	NR

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Total withdrawals; withdrawals due to adverse events	Comments
Knegtering, 2006 RCT, open-label naturalistic study Inpatients and outpatients	NR / NR	Baseline sexual dysfunction was not recorded because most of the pts were psychotic and considered too ill at study entry to participate in assessment of sexual function. Prolactin level was not measured at baseline. Medication compliance was not formally assessed.

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Eligibility criteria	Interventions (drug, dose, duration)	Allowed other medications	Age Gender Ethnicity	Other population characteristics
Krakowski, 2006 DB, RCT, parallel, multicenter Inpatients with persistent June 1999-November 2004, USA Krakowski 2009	Confirmed episode of physical assault directed at another person during the hospitalization and some persistence of aggression, as evidenced by the presence of some other aggressive event, whether physical or verbal or against property.	6 wks escalation and fixed dose schedule: (mg/d) olanzapine 20 clozapine 500 haloperidol 20 Last 6 wks (variable-dose): antipsychotic dose was allowed to vary within the following ranges: (mg/d) clozapine 200-800 olanzapine 10-25 haloperidol 10-30 X 12 wks	Prestudy antipsychotic meds (adjusted during baseline week to not exceed 750mg/d in chlorpromazine equivalents). Double-blind benztropine or benztropine P or a combination of both. Pts assigned to atypical antipsychotics were initially receiving benztropine P, but if psychiatrist (unaware of assignment) determined clinically that the pts should be treated for EPS, "benztropine supplements" up to 6mg/d (replace the benztropine P) was used. Lorazepam, diphenhydramine, or chloral hydrate open-label prn. Mood stabilizers or antidepressants if taking prestudy.	Age: Clozapine: 35.1 ±12.3 ; Olanzapine: 35.6 ± 9.4 Male, no (%) : C: 31 (83.8) ; O: 29 (78.4%) Ethnicity: (n, %) C vs. O White: 7 (18.9%); 5 (13.5%) Black: 20 (54.1%); 28 (75.7%) Hispanic: 8 (21.6%); 4 (10.8%) Other: 2 (5.4%); 0	No significant difference in the following: median time of survival, length of hospitalization upon entry with a median length of hospitalization of 48 ds; proportion of subjects receiving typical or atypical antipsychotic agents prior to randomization; proportion of subjects receiving other psychotropic medications, including mood stabilizers or antidepressants; total number of physical assaults during the 4-wk period preceding the qualifying physical assault

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Number screened/ eligible/ enrolled	Withdrawn/ Lost to follow-up/ Analyzed	Results
Krakowski, 2006 DB, RCT, parallel, multicenter Inpatients with persistent June 1999-November 2004, USA Krakowski 2009	NR/134/110 (102 pts were enrolled in 1 site; 36 were assigned to haloperidol arm)	40 (discontinued) C: 13; O 11: H 16 /NR/110 (ITT)	MOAS total score: clozapine: mean, 25.1; median 18; interquartile range, 6-34. olanzapine: mean, 32.7; median, 29; interquartile range, 6-51, (Haldol: not abstracted).(all, p<.001) MOAS physical aggression score: clozapine: mean, 10.3 median 4; interquartile range, 0-16. Olanzapine: mean, 14.1; median, 12; interquartile range, 0-20, (Haldol: not abstracted). ; (all, p<.001 Secondary Analysis: Aggression against property: clozapine: mean, 2.6 ;median 0; interquartile range, 0-2. olanzapine: mean, 2.7; median, 0; interquartile range, 0-4, (Haldol: not abstracted). ; (all p<.001) Secondary Analysis: Verbal aggression: clozapine: mean, 12.2 median 0; interquartile range, 2-15. Olanzapine: mean, 16.0; median, 11; interquartile range, 4-23, (Haldol: not abstracted). ; (all. p<.001) Post-hoc analysis: C vs. O, OR (95% CI for less severe violence)- Total score: 1.30 (1.2-1.4), p<.001 Physical aggression: 1.30 (1.2-1.4); p<.001 Aggression against property:1.10 (0.8-1.5); NS Verbal aggression: 1.32 (1.1-1.5); p<.001 PANSS: (Mean ±SD),p (Haldol not abstracted) Total score C: 2.39 ±14.2; O: 4.83± 9.7; (all p=NS) Positive symptoms: C 1.54± 5; 0: 1.41 ± 3.6; (all p=NS) Negative symptoms: C -0.56 ±4.9; O: 0.72 ± 3.0;(all p=NS) General psychopathology: C 1.43 ± 7.0, O: 2.69 ± 5.5; (all p=NS)

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Adverse effects reported
Krakowski, 2006 DB, RCT, parallel, multicenter Inpatients with persistent June 1999-November 2004, USA Krakowski 2009	"No differences in sedation….among the 3 medication groups" Mean change in body weight from baseline (Kg) Clozapine: 2.36 (7.1), p=0.06 Olanzapine: 3.59 (4.2),p<0.001 Mean change in BMI from baseline: Clozapine:0.76 (2.3), p=0.07 Olanzapine:1.31 (1.6), p<0.001 Mean change in cholesterol from baseline Clozapine:11.4 (38.3)p=0.09 Olanzapine: -1.2 (34.5), p=0.84 Main change in Triglyceride from baseline Clozapine: 56.7 (111.1), p=0.006 Olanzapine:10.7 (56.2), p=0.31 Mean change in Glucose from baseline Clozapine:19.8 (59.6)p=0.7 Olanzapine: -0.1(18.8), p=0.97

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Extrapyramidal symptoms
Krakowski, 2006 DB, RCT, parallel, multicenter Inpatients with persistent June 1999-November 2004, USA Krakowski 2009	"No differences in …. and EPS among the 3 medication groups"

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Total withdrawals; withdrawals due to adverse events	Comments
Krakowski, 2006 DB, RCT, parallel, multicenter Inpatients with persistent June 1999-November 2004, USA Krakowski 2009	40 total WD 8 (C 3; O 1; H 4) due to AEs	Study was conducted on research ward. Overall total MOAS score was computed b y assigning a different weight for each type of aggressive event, using a psychometrically validated method developed by the MOAS authors. Verbal aggression assigned the lowest weight and physical aggression the highest.

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Eligibility criteria	Interventions (drug, dose, duration)	Allowed other medications	Age Gender Ethnicity	Other population characteristics
Kusumi, 2011 Kusumi, 2012 RCT	DSM - Schizophrenia, male or female. No age critera given.	Risperidone = 6mg	Benzaodiazepines	Mean Age: 47 Male 24% Female = 10% Ethnicity = NR	NR

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Number screened/ eligible/ enrolled	Withdrawn/ Lost to follow-up/ Analyzed	Results
Kusumi, 2011 Kusumi, 2012 RCT	NR/NR/82	NR/NR/81	Symptom response: mean ±SE Changes in PANSS-EC score at 4 weeks: 8.7±3.0 10.7±4.3 PANSS scores at 24 weeks: 59.2±19.4 63.7±16.6 Change in body weight during 1 yr in OST and ODT groups (overall): OST kg (SD) vs. ODT (SD), P All Patients: 3M: +1.2 (2.8) vs. +1.0 (3.8), 0.69 6M: +1.9 (3.9) vs. +0.8 (4.5), 0.11 12M: +3.0 (4.7) vs. +1.8 (5.5), 0.07 Male Patients: 3M: +1.1 (3.1) vs. -0.2 (4.7), 0.28 6M: +1.4 (4.3) vs. -0.3 (5.6), 0.26 12M: +2.5 (4.9) vs. +1.5 (5.8), 0.54 Female Patients: 3M: +1.6 (2.3) vs. +1.6 (3.1), 0.94 6M: +2.8 (2.9) vs. +1.4 (3.8), 0.23 12M: +3.8 (4.2) vs. +1.9 (5.4), 0.25 Change in body weight during 1 yr in OST and ODT groups (completers): OST kg (SD) vs. ODT (SD), P All Patients: 3M: +1.3 (2.7) vs. +0.9 (3.6), 0.57 6M: +2.0 (2.7) vs. +0.5 (4.3), 0.08 12M: +3.2 (3.8) vs. +1.6 (5.6), 0.14 Male Patients: 3M: +1.2 (2.9) vs. -1.1 (4.3), 0.07 6M: +1.7 (2.7) vs. -1.2 (5.3), 0.03 12M: +2.9 (3.5) vs. +1.2 (6.0), 0.30 Female Patients: 3M: +1.7 (2.3) vs. +1.7 (2.9), 0.99 6M: +2.5 (2.9) vs. +1.1 (3.8), 0.29 12M: +4.0 (4.6) vs. +1.7 (5.5), 0.24

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Adverse effects reported
Kusumi, 2011 Kusumi, 2012 RCT	Serum prolactin: no significant increase between the groups

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Extrapyramidal symptoms
Kusumi, 2011 Kusumi, 2012 RCT	Extrapyramidal effects: (Risperidone oral solution vs Risperidone) Proportion of patents requiring anticholinergic drugs: All patients: Baseline 20.5 vs. 40.5 3 days 22.7 vs. 48.6 1 week 27.9 vs. 51.4 2 weeks 28.6 vs. 55.6 4 weeks 24.4 vs. 54.3 8 weeks 27.5 vs. 51.4 16 weeks 28.2 vs. 57.6 24 weeks 33.3 vs. 54.8 Drug-free patients: Baseline 0 vs. 0 3 days 5.3 vs. 10.0 1 week 11.1 vs. 10.0 2 weeks 11.8 vs. 11.1 4 weeks 12.5 vs. 12.5 8 weeks 12.5 vs. 12.5 16 weeks 13.3 vs. 28.6 24 weeks 18.2 vs. 33.3

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Total withdrawals; withdrawals due to adverse events	Comments
Kusumi, 2011 Kusumi, 2012 RCT		

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Eligibility criteria	Interventions (drug, dose, duration)	Allowed other medications	Age Gender Ethnicity	Other population characteristics
Li 2011 RCT, single-blind	Age ≥18, DSM-IV diagnosis of schizophrenia for ≥1 year, PANSS total score 60-120 at screening and baseline, BMI ≥17.0 kg/m^2. Excluded other Axis I diagnoses, 25% decrease in PANSS between screening and baseline	A. Paliperidone palmitate (INVEGA® SUSTENNA): 50 mg eq, 100mg eq, 150mg eq IM injections; 150mg eq on day 1, 100mg eq on day 8 and 50 or 100mg eq on day 36 and 50, 100 or 150 mg eq on day 64 B. Risperidone long acting injection (Risperdal® CONSTA®): 25mg, 37.5mg and 50mg microspheres; 25mg on day 8, 25 mg on day 22, 25 or 37.5mg on days 36 and 50, 25, 37.5 or 50mg on days 64 and 78 AND Risperidone: 1mg tablets; 2mg/d at baseline, 1-6mg/d for first 28 days and for up to 3 weeks of treatment with each dose increase.	trihexyphenidyl, benztropine, biperidin, antihistamines, benzodiazepines, beta-blockers, zolpidem, zaleplon, zopiclone, or eszopiclone, topical anesthetic creams, pre-study stable dose antidepressants	Age, mean: 31.75 Gender: 59.96% female Ethnicity:99.8% Han	Schizophrenia Types: Disorganized, 3.5%; Catatonic, 0.2%; Paranoid, 66.6%; Residual, 0.7%; Undifferentiated, 29.0%
Li, 2012 China	18-60 years, diagnosis of "psychotic syndrome convincible with first manifestation of schizophrenia," PANSS total ≥60, score of at least 4 on 2 or more psychotic items and >4 on the CGI-S; Excluded DSM-IV axis I psychiatric disorders other than schizophrenia, ever used psychoactive substances; no previous history of significant antipsychotic treamtnet (more than 4 weeks of treatment; and a negative urine drug screen at baseline. Females required to have a negative urine pregnancy test and utilize a medically acceptable form of contraception.	Ziprasidone, n=; dose, 160 mg/d maximum; mean dose, 127.5mg/d; duration, 6 weeks Olanzapine, n=; dose, 20 mg/d maximum; mean dose, 19.1mg/d; duration, 6 weeks	Alprazolam, Propranolol, Trihexyphenidyl hydrochloride	Age, mean: 24.73y Gender: 31.25% female Ethnicity: NR	Duration of disease, mean: 7.6 months PNSS total at baseline, mean: 94.07

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Number screened/ eligible/ enrolled	Withdrawn/ Lost to follow-up/ Analyzed	Results
Li 2011 RCT, single-blind	NR/NR/452	102/23/452 for safety and 413 for efficacy	Change from baseline, difference of LSM (95%CI)- per protocol population. Paliperidone vs. Risperidone PANSS total: -23.6 vs. -26.9, difference: -2.3 (-5.20 to 0.63) CGI-S: -1.5 vs. -1.7, difference: -0.1 (-0.33 to 0.10) Personal and Social Performance Scale: 16.8 vs. 18.6, difference 0.5 (-2.14 to 3.12) Study reports ITT population did not demonstrate noninferiority of paliperidone palmitate.
Li, 2012 China	NR/NR/80	1/NR/80	PANSS total, mean change rate: ziprasidone vs. olanzipine: 66.3 (22.1)% vs. 67.0 (20.4)%, p=0.0000 PANSS positive and negative subscales, and general psychopathology: significant improvement from baseline to end of study (all p=0.0000) NSD between ziprasidone and olanzapine for PANSS and CGI scores. Response rate, >50% change in PANSS total, week 2 vs. week 4 vs. week 6: NSD between groups ziprasidone: 5% vs. 32.5% vs. 80% olanzapine: 7.5% vs. 47.5% vs. 82.5%

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Adverse effects reported
Li 2011 RCT, single-blind	Paliperidone vs. Risperidone Overall AEs:73.4% vs. 74.9% Serious AEs: 3 vs. 8 Discontinuation due to AEs: 3.5% vs. 4% Suicide-related events, n: 0 vs. 3 (1 completed suicide)
Li, 2012 China	QTc intervals: NSD QTc interval ≥500msec: 0 Weight gain and BMI increases: olanzapine, p=0.000 vs. ziprasidone, NS

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Extrapyramidal symptoms
Li 2011 RCT, single-blind	Paliperidone vs. Risperidone: Akathisia: 13.1% vs. 19.7% Tremor: 10.5% vs. 17.9% Prolactin-related events: 8.3% vs. 9.0%
Li, 2012 China	ziprasidone vs. olanzapine: 11 vs. 1, p=0.003

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Total withdrawals; withdrawals due to adverse events	Comments
Li 2011 RCT, single-blind	102/9	
Li, 2012 China		

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Eligibility criteria	Interventions (drug, dose, duration)	Allowed other medications	Age Gender Ethnicity	Other population characteristics
Lieberman, 2003 Zipursky, 2005 (time to weight gain results) US & Europe HGDH Research Group	Age 16-40 ys; onset of psychotic symptoms before age 35 ys; DSM-IV criteria for schizophrenia, schizoaffective disorder or schizophreniform disorder as assessed by using the Structured Clinical Interview for DSM-IV; experienced psychotic symptoms (delusions, hallucinations, thought disorder and grossly bizarre behavior) for 1-60 months; two active psychotic symptoms characterized by at least 2 PANSS psychosis items ≥4 or one psychosis item ≥5; CGI score ≥4; required treatment with antipsychotic drugs on a clinical basis; able to provide informed consent and cooperate with research staff, tests and examinations; use of medically accepted contraception for female patients of childbearing potential	Olanzapine 5-10 mg/d up to wk 6; 5-20 mg/d wk 6-12 Haloperidol 2-6 mg/d up to wk 6; 2-20 mg/d wk 6-12	Medications for insomnia or agitation (lorazepam, diazepam, chloral hydrate) or antipsychotic side effects (benzatropine, biperiden, propanolol, procyclidine)	Mean age 23.8 yrs (SD 4.8) 82% male 53% Caucasian 38% African descent 3% East/Southeast Asian 0.8% West Asian 5% Hispanic 2% Other (% >100 due to rounding)	Duration of previous antipsychotic use: 5.9 wks (SD 10.7) Diagnosis: schizophrenia 59% schizoaffective disorder 10% schizophreniform disorder 31%

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Number screened/ eligible/ enrolled	Withdrawn/ Lost to follow-up/ Analyzed	Results
Lieberman, 2003 Zipursky, 2005 (time to weight gain results) US & Europe HGDH Research Group	NR/NR/263	104/NR/263	PANSS mean change, based on observed cases at 12 wks: Total score: O -20.05 (SD 1.55) v H -14.22 (SD 0.87) Negative scale score: O -2.95 (SD 0.51) v H -1.21 (SD 0.66) Positive scale score: O -7.41 (SD 1.64) v H -7.06 (SD 0.83) General scale score: O -9.85 (SD 1.33) v H -6.24 (SD 0.57) PANSS mean change, based on least squares mean at 12 wks: Total score: O -16.23 (SD 4.51) v H -10.67 (SD 4.52) Negative scale score: O -2.27 (SD 0.45) v H -0.76 (SD 0.43) Positive scale score: O -6.24 (SD 1.22) v H -5.77 (SD 1.22) General scale score: O -7.93 (SD 1.72) v H -4.36 (SD 1.73) PANSS between-group p-values, mixed model analysis v LOCF analysis Total score: p<0.02 v p=0.58 Negative scale score: p<0.04 v p=0.89 Positive scale score: p=0.50 v p=0.76 General scale score: p<0.003 v p=0.25 CGI Severity Score, mean change based on observed cases at 12 wks: O -1.34 (SD 0.22) v H -1.02 (SD 0.23) CGI Severity Score, mean change based on least squares means at 12 wks: O -1.01 (SD 0.57) v -0.73 (SD 0.57) CGI between-group p-values: mixed-model analysis p=0.07; LOCF analysis p=0.46 Montgomery-Asberg Depression Rating Scale Score, mean change based on observed cases at 12 wks: O -2.58 (SD 0.25) v H -1.93 (SD 1.56) Montgomery-Asberg Depression Rating Scale Score, mean change based on least squares means at 12 wks: O -1.63 (SD 2.84) v H 0.92 (SD 2.84) Montgomery-Asberg Depression Rating Scale Score between-group p-values: mixed model analysis p<0.02; LOCF analysis p=0.07

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Adverse effects reported
Lieberman, 2003 Zipursky, 2005 (time to weight gain results) US & Europe HGDH Research Group	Weight change: >7% increase in body weight from baseline: O 76/124 (61.5%) v H 28/124 (22.7%);p<0.001 (percentages taken from text; number of patients calculated based on percentages and n listed in Table 3) Mean increase in BMI: O 2.39 v H 0.88; p<0.001 Time to clinically-significant weight gain of ≥ 7% (wkss): olanzapine=5 vs haloperidol=28; HR5.19, p<0.0001

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Extrapyramidal symptoms
Lieberman, 2003 Zipursky, 2005 (time to weight gain results) US & Europe HGDH Research Group	Parkinsonism: O 29/111 (26.1%) v H 63/115 (54.8%); p<0.001 Akathisia: O 14/118 (11.9%) v H 62/121 (51.2%); p<0.001

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Total withdrawals; withdrawals due to adverse events	Comments
Lieberman, 2003 Zipursky, 2005 (time to weight gain results) US & Europe HGDH Research Group		

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Eligibility criteria	Interventions (drug, dose, duration)	Allowed other medications	Age Gender Ethnicity	Other population characteristics
Lieberman, 2005 (CATIE Study) Row 1 of 4	Patients age 18-65, DSM-IV criteria for schizophrenia, be appropriate candidates for oral therapy (patients assessment in conjunction with clinician), have adequate decisional capacity to decide to participate.	olanzapine 7.5mg quetiapine 200mg risperidone 1.5mg perphenazine 8mg ziprasidone 40mg The dose of medications was flexible, ranging from one to four capsules daily, and was based on the study doctor's judgment	Concomitant medications were permitted throughout the trial, except for additional antipsychotic agents.	Mean age: 40.6 ys 26% Female Ethnicity: white 60%; black 35%; Hispanic 12%; 5% other	depression 28% alcohol dependence or alcohol abuse 25% drug dependence or drug abuse 29% obsessive-compulsive disorder 5% other anxiety disorder 14%

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Number screened/ eligible/ enrolled	Withdrawn/ Lost to follow-up/ Analyzed	Results
Lieberman, 2005 (CATIE Study) Row 1 of 4	NR/NR/1493	NR/NR/1460	The time to the discontinuation of treatment for any cause: HR (95%CI) olanzapine vs quetiapine: 0.63(0.52-0.76) olanzapine vs risperidone: 0.75(0.62-0.90) olanzapine vs perphenazine: 0.78(0.63-0.96), NS after adjustment olanzapine vs ziprasidone: 0.76(0.60-0.97), NS after adjustment quetiapine vs risperidone: 1.19(0.99-1.42) quetiapine vs perphenazine: 1.14(0.93-1.39) quetiapine vs ziprasidone: 1.01(0.81-1.27) risperidone vs perphenazine: 1.00(0.82-1.23) risperidone vs ziprasidone: 0.89(0.71-1.14) perphenazine vs ziprasidone: 0.90(0.70-1.16) The time to the discontinuation of treatment for lack of efficacy: HR (95%CI) olanzapine vs quetiapine: 0.41(0.29-0.57) olanzapine vs risperidone: 0.45(0.32-0.64) olanzapine vs perphenazine: 0.47(0.31-0.70) olanzapine vs ziprasidone: 0.59(0.37-0.93), NS after adjustment quetiapine vs risperidone: 0.49(NR) quetiapine vs perphenazine: 0.47(NR) quetiapine vs ziprasidone: 0.69(NR) risperidone vs perphenazine: 0.59(NR) risperidone vs ziprasidone: 0.93(NR) perphenazine vs ziprasidone: 0.44(NR) The time to the discontinuation of treatment owing to intolerability: HR (95%CI) olanzapine vs quetiapine: 0.84(NR) olanzapine vs risperidone: 0.62(0.41-0.95) olanzapine vs perphenazine: 0.49(NR) olanzapine vs ziprasidone: 0.28(NR) quetiapine vs risperidone: 0.65(0.42-1.00) quetiapine vs perphenazine: 0.97(NR) quetiapine vs ziprasidone: 0.87(NR) risperidone vs perphenazine: 0.60(0.36-0.98) risperidone vs ziprasidone: 0.79(0.46-1.37) perphenazine vs ziprasidone: 0.19(NR)

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Adverse effects reported
Lieberman, 2005 (CATIE Study) Row 1 of 4	olanzapine vs quetiapine vs risperidone vs perphenazine vs ziprasidone, p value Hospitalization for exacerbation of schizophrenia, no(%): 33(11%) vs 68(20%) vs 51(15%) vs 41(16%) vs 33(18%), p<0.001 Hospitalization risk ratio: 0.29 vs 0.66 vs 0.45 vs 0.51 vs 0.57 Any serious AEs, no(%): 32(10%) vs 32(9%) vs 33(10%) vs 29(11%) vs 19(10%), p=0.47 Any moderate or severe spontaneously reported AE, no(%): 122(36%) vs 113(34%) vs 123(36%) vs 79(30%) vs 65(35%), p=0.10 Insomnia: 55(16%) vs 62(18%) vs 83(24%) vs 66(25%) vs 56(30%), p,0.001 Hypersomnia: 104(31%) vs 103(31%) vs 96(28%) vs 74(28%) vs 45(24%), p=0.18 Urinary hesitancy, dry mouth, constipation: 79(24%) vs 105(31%) vs 84(25%) vs 57(22%) vs 37(20%), p,0.001 Decreased sex drive, arousal, ability to reach orgasm: 91(27%) vs 69(20%) vs 91(27%) vs 64(25%) vs 35(19%), p=0.59 Gynecomastia, galactorrhea: 7(2%) vs 6(2%) vs 14(4%) vs 4(2%) vs 6(3%), p=0.15 Menstrual irregularities: 11(12%) vs 5(6%) vs 16(18%) vs 7(11%) vs 8(14%), p=0.17 Incontinence, nocturia: 18(5%) vs 15(4%) vs 25(7%) vs 6(2%) vs 10(5%), p=0.04 Orthostatic faintness: 31(9%) vs 38(11%) vs 37(11%) vs 29(11%) vs 24(13%), p=0.08 Discontinuation of treatment owing to intolerability, no(%) -discontinuation: 62(18%) vs 49(15%) vs 34(10%) vs 40(15%) vs 28(15%), p=0.04 -weight gain or metabolic effects: 31(9%) vs 12(4%) vs 6(2%) vs 3(1%) vs 6(3%), p<0.001 -extrapyramidal effects: 8(2%) vs 10(3%) vs 11(3%) vs 22(8%) vs 7(4%), p=0.002 -sedation: 7(2%) vs 9(3%) vs 3(1%) vs 7(3%) vs 0(0%), p=0.10 -other effects: 16(5%) vs 18(5%) vs 14(4%) vs 8(3%) vs 15(8%), p=0.16

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Author, year Study design	Extrapyramidal symptoms
Lieberman, 2005 (CATIE Study) Row 1 of 4	Olanzapine vs quetiapine vs risperidone vs perphenazine vs ziprasidone, P value Simpson-Angus Extrapyramidal Signs Scale mean score >= 1: 23(8%) vs 12(4%) vs 23(8%) vs 15(6%) vs 6(4%), p=0.47

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Total withdrawals; withdrawals due to adverse events	Comments
Lieberman, 2005 (CATIE Study) Row 1 of 4	Olanzapine vs quetiapine vs risperidone vs perphenazine vs ziprasidone, *P* value Total WD, no(%): 210(64%) vs 269(82%) vs 245(74%) vs 192(75%) vs 145(79%) discontinuation due to intolerability: 62(18%) vs 49(15%) vs 34(10%) vs 40(15%) vs 28(15%), P=0.04	

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Number screened/ eligible/ enrolled	Withdrawn/ Lost to follow-up/ Analyzed	Results
Lieberman, 2005 (CATIE Study) Row 2 of 4 (for results and AEs)			Duration of successful treatment: HR (95%CI) olanzapine vs quetiapine: 0.53(0.43-0.67) olanzapine vs risperidone: 0.69(0.55-0.87) olanzapine vs perphenazine: 0.73(0.57-0.93) olanzapine vs ziprasidone: 0.75(0.58-0.94) quetiapine vs risperidone: 1.30(1.04-4.63) quetiapine vs perphenazine: 1.28(1.00-1.64) quetiapine vs ziprasidone: 1.06(0.85-1.33) risperidone vs perphenazine: 0.72(NR) risperidone vs ziprasidone: 0.74(NR) perphenazine vs ziprasidone: 0.25(NR) Patients' decision to discontinue treatment: HR (95%CI) olanzapine vs quetiapine: 0.56(0.42-0.75) olanzapine vs risperidone: 0.67(0.50-0.90) olanzapine vs perphenazine: 0.70(0.50-0.98) olanzapine vs ziprasidone: 0.63(0.43-0.93) quetiapine vs risperidone: 0.21(NR) quetiapine vs perphenazine: 0.46(NR) quetiapine vs ziprasidone: 0.63(NR) risperidone vs perphenazine: 0.95(NR) risperidone vs ziprasidone: 0.21(NR) perphenazine vs ziprasidone: 0.27(NR) *p=0.004 for the interaction between treatment and time From Meyer 2008 Change in metabolic syndrome: Olanzapine vs Risperidone vs Quetiapine vs Ziprasidone Metabolic Syndrome prevalence at 3 mos 43.9% vs 30.6% vs 37.1% vs 29.9% Olanzapine vs Ziprasidone p=0.001 Olanzapine vs quetiapine vs Risperidone vs Ziprasidone 3 mos changes from baseline in non fasting triglyceride(mg/dl) Adjusted LSM±SE: 23.4±22.8 vs 54.7±23.5 vs -18.4 ±24.0 vs 0.0 ±32.7, p=0.0009 % of patients reporting paid employment at 18 mos: 17% vs 25% vs 23% vs 31%, (Data interpreted from Graph) p=NS Decline in rates of violence at 6 mos: 33.9% vs 14.1% vs 25.0%, 24.3%

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Adverse effects reported
Lieberman, 2005 (CATIE Study) Row 2 of 4 (for results and AEs)	Weight gain >7%: 92(30%) vs 49(16%) vs 42(14%) vs 29(12%) vs 12(7%), p<0.001 Weight change, lb, mean(SE): 9.4(0.9) vs 1.1(0.9) vs 0.8(0.9) vs -2.0(1.1) vs -1.6(1.1), p<0.001 Weight change, lb/mo, mean(SE): 2(0.3)vs 0.5(0.2) vs 0.4(0.3) vs -0.2(0.2) vs -0.3(0.3), p<0.001 AIMS global severity score >= 2: 32(14%) vs 30(13%) vs 38(16%) vs 41(17%) vs 18(14%), p=0.23 Barnes Akathisia Rating Scale global score >= 3: 15(5%) vs 16(5%) vs 20(7%) vs 16(7%) vs 14(9%), p=0.24 Simpson-Angus Extrapyramidal Signs Scale mean score >= 1: 23(8%) vs 12(4%) vs 23(8%) vs 15(6%) vs 6(4%), p=0.47 Laboratory values, change from baseline, mean(SE) after adjustment, p value -blood glucose, mg/dl: 13.7(2.5) vs 7.5(2.5) vs 6.6(2.5) vs 5.4(2.8), p=0.59 -glycosylated hemoglobin, %: 0.40(0.07) vs 0.04(0.08) vs 0.07(0.08) vs 0.09(0.09) vs 0.11(0.09), p=0.01 -cholesterol, mg/dl: 9.4(2.4) vs 6.6(2.4) vs -1.3(2.4) vs 1.5(2.7) vs -8.2(3.2), p<0.001 -triglycerides, mg/dl: 40.5(8.9) vs 21.2(9.2) vs -2.4(9.1) vs 9.2(10.1) vs -16.5(12.2), p<0.001 -prolactin, ng/dl: -8.1(1.4) vs -10.6(1.4) vs 13.8(1.4) vs -1.2(1.6) vs -5.6(1.9), p<0.001 Prolonged corrected QT interval, no(%): 0(0%) vs 6(3%) vs 7(3%) vs 2(1%) vs 2(1%), p=0.03

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Number screened/ eligible/ enrolled	Withdrawn/ Lost to follow-up/ Analyzed	Results
Lieberman, 2005 (CATIE Study) Row 3 of 4 (for results only) Funding: NIHM grant, Foundation of Hope of Raleigh, N.C. Meyer 2008 "change in metabolic.. Meyer 2008 "Impact of antipsychotic treatment Resnick 2008 Swanson 2008 Swartz 2008 Miller 2008 Levine 2011			Difference in incidence or severity of TEAE between Olanzapine vs Quetiapone vs Risperidone vs Ziprasidone=NS based on ratign scales for Parkinsonism, Akathisia, Dystonia or tardive Dyskinesia use of antiparkinsonism medications greater with risperidone and lower with quetiapine (P=0.029), and lower rates of discontinuation due to Parkinsonism symptoms were found with quetiapine and ziprasidone (P< 0.05; rates NR). Remission rates over 18 months irrespective of switching medications: Dropouts (%) vs. Completers (%) vs. Total (%) No symptom remission: 60.0 vs. 40.0 vs. 55.53 Any symptomatic remission: 32.7 vs. 67.3 vs. 44.47 At least 3 months: 19.9 vs. 80.1 vs. 21.03 At least 6 months: 13.0 vs. 87.0 vs. 11.68 Prevalence of attaining and maintaining remission rates for at least 6 months, while taking the first randomized antipsychotic medication (phase 1): Olanzapine: 12.4% Quetiapine: 8.2% Perphenazine: 6.8% Ziprasidone: 6.5% Risperidone: 6.3% Pairwise comparisons from ANCOVA adjusted for multiple comparisons: Olanzapine-tx patients had significantly or nearly significantly higher rates of any period of sx remission than quetiapine (p=0.02; adj. p=0.06), ziprasidone (p<0.01; adj. p<0.01), risperidone (p<0.01; adj. p<0.01), and perphenazine (p=0.01; adj. p=0.05). Rates of any sx remission period were higher for perphenazine (p=0.03; adj. p=0.09) and quetiapine (p=0.02; adj. p=0.06) than ziprasidone. Rates of attaining and maintaining 3 months of remission were higher for the olanzapine group than the perphenazine (p=0.04; adj. p=0.17), quetiapine (p=0.09; adj. p=0.34), risperidone (p=0.01; adj. p=0.04) and ziprasidone groups (p=0.04; adj. p=0.23), but differences were not significant after controlling for multiple comparisons.

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Adverse effects reported
Lieberman, 2005 (CATIE Study) Row 3 of 4 (for results only) Funding: NIHM grant, Foundation of Hope of Raleigh, N.C. Meyer 2008 "change in metabolic.. Meyer 2008 "Impact of antipsychotic treatment Resnick 2008 Swanson 2008 Swartz 2008 Miller 2008 Levine 2011	Rates of discontinuation and time to all-cause discontinuation median time in mos (illicit drug non users) Olanzapine: 56%, 13.02 mo Quetiapine:81%, 5.02 mo Risperidone: 69%, 5.57 mo Discontinuation rate significantly lower and time to all cause discontinuation significantly longer for olanzapine compared to quetiapine and risperidone Ziprasidone: 77%, 4.34 mo Odds of discontinuation olanzapine vs quetiapine (HR=0.52, CI 0.40 to 0.67, p<0.001) olanzapine vs risperidone (HR=0.70 , CI 0.53 to 0.92, p=0.01) olanzapine vs ziprasidone (HR=0.78, CI 0.56 to 1.08, p=0.13) Quetiapine to risperidone: (HR=1.35; CI 1.05 to 1.73, p=0.021) Rates of medication compliance=NSD between groups. Rates of discontinuation and time to all-cause discontinuation median time in mos (illicit drug users) Olanzapine: 74%, 6.75 mo Quetiapine:82%, 4.36 mo Risperidone: 79%, 4.61 mo Ziprasidone: 82%, 3.29 mo, discontinuation rates between olanzapine and other drugs NSly different. olanzapine vs quetiapine: HR=0.90, CI 0.67 to 1.20, p=0.47 olanzapine vs risperidone: HR=0.93, CI 0.70 to 1.24 olanzapine vs ziprasidone :HR=0.75, CI0.53 to 1.07, p=0.11

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Author, year Study design	Number screened/ eligible/ enrolled	Withdrawn/ Lost to follow-up/ Analyzed	Results
Lieberman, 2005 (CATIE Study) Row 4 of 4 (for results only) Funding: NIHM grant, Foundation of Hope of Raleigh, N.C. Meyer 2008 "change in metabolic.. Meyer 2008 "Impact of antipsychotic treatment Resnick 2008 Swanson 2008 Swartz 2008 Miller 2008 Levine 2011			Rates of attaining and maintaining 6 months of remission were hgiher for the olanzapine group than the perphenazine (p=0.03; adj. p=0.12) and risperidone (p=0.02; adj. p=0.01) groups but differences were not significant after controlling for multiple comparisons. Sensitivity analysis 1: The olanzapine group who did not receive off-label doses (n=79) was significantly (adj. and unadj. p<0.05) more likely to attain any period of sx remission gradients than the four other medication groups studied. Any period of remission was more likely for perphenazine than ziprasidone (p=0.03; adj. p=0.09), and quetiapine than both risperidone (p=0.07; adj. p=0.14) and ziprasidone (p=0.01; adj. p=0.03) groups. Significant differences were not observed between medication groups over 3- or 6-month remission periods. Sensitivity analysis 2: The olanzapine group (n=132) was significantly (unadj. and adj. p<0.05) more likely to attain any period of sx remission gradients than the four other antipsychotic medication groups studied. Any period of sx remission was more likely for groups treated with perphenazine than ziprasidone (p=0.03; adj. p=0.09), quetiapine than risperidone (p=0.07; adj. p =0.14) and ziprasidone (p=0.02; adj. p=0.06). The olanzapine group was significantly (unadj. and adj. p<0.05) more liekly to attain 3 months of sx remission than the other four medication groups studied. Olanzapine was associated with a higher 6-month remission rate than quetiapine (p=0.03; adj. p=0.12), risperidone (p=0.01; adj. p=0.06), ziprasidone (p=0.01; adj. p=0.10) and perphenazine (p=0.01; adj. p=0.04). Sensitivity analysis 3: patients randomized after the inclusion of ziprasidone (n=612) Significantly higher rates of any sx remission period for olanzapine than risperidone (p<0.01; adj. p=0.01) and ziprasidone (p<0.01; adj. p=0.01). Sx remission over any period was higher for the quetiapine than ziprasidone group (p=0.03; adj. p=0.13). Remission over 3 months was higher for the olanzapine than risperidone (p<0.01; adj. p=0.02), quetiapine (p=0.08; adj. p=0.33) and ziprasidone (p=0.03; adj. p=0.15) groups.

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Eligibility criteria	Interventions (drug, dose, duration)	Allowed other medications	Age Gender Ethnicity	Other population characteristics
Lindenmayer, 1998 Open-label Inpatients	Treatment-refractory schizophrenia.	12 week study Mean dose: clozapine: 363.02 mg/d risperidone: 8.95 mg/d	Anticholinergics	Mean age: 39.29 ys 74.3% Male White: 25.7% African-American: 37.1% Hispanic: 37.1%	100% inpatient Schizophrenia: Disorganized: 5.7% Paranoid: 40% Undifferentiated: 54.3%
Lindenmayer, 2008 DB RCT Multisite, 45 centers in USA, 4 centers in Canada	Inclusion: Men or women aged 18-65 with DSM-IV diagnosis of schizophrenia catatonic, disorganized, paranoid, or undifferentiated; PANSS total score >=60; score of >=4 for at least one of the PANSS items of delusions, conceptual disorganization, hallucinatory behavior, and suspiciousness/persecution; a CGI-S score >=4; and a worsening of the patient's condition in the previous 3 wks. Exclusions: Axis I DSM-IV diagnosis such as MR, or alcohol or substance abuse; hospitalization for schizophrenia for >1 mo prior to study; any clinically relevant other diseases; previous treatment resistance to quetiapine; known lack of response to clozapine, use of clozapine for symptom control, or treated with clozapine within 1 mo of randomization.	6 treatment groups: Quetiapine XR 300, 600, or 800 mg/d Quetiapine IR at 300 or 600 mg/d P Patients who were screened as outpatients were hospitalized when enrolled and could be discharged on d 10. Dose initiation phase: ds 1-7.	During ds 1-6: lorazepam allowed for agitation. Anticholinergics were discontinued >=48 hs before randomization but allowed for emergent EPS.	Mean age 39.1 74.7 % male 49.7% White 37% Black 1.43% Asian 10.7 % Hispanic	80.5% paranoid subtype 17.1% undifferentiated Mean age at first treatment of schizophrenia 23.5 245 with 11 or more previous hospitalizations 30.4% with full response to previous AP. 60.7% with partial response to previous AP 3.6% with poor response to previous AP. 5.0% with no previous exposure to AP. Mean PANSS total score: 90.5 Mean CGI-S: 4.7

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Number screened/ eligible/ enrolled	Withdrawn/ Lost to follow-up/ Analyzed	Results
Lindenmayer, 1998 Open-label Inpatients	NR/NR/35	3/0/32	Mean PANSS/CGI scores: Clozapine: baseline vs week 6 vs week 12: Positive factor: 17.5 vs 15.7 vs 13.8 Negative factor: 20.6 vs 17.5 vs 15.5 Cognitive factor: 17.2 vs 14.5 vs 13.4 Excitement factor: 9.0 vs 6.7 vs 6.2 Anxiety-depression factor: 8.2 vs 7.1 vs 6.3 CGI Global Severity: 4.8 vs 4.2 vs 3.9 CGI Global Improvement: 3.8 vs 3.3 vs 2.6 Risperidone: baseline vs week 6 vs week 12: Positive factor: 18.5 vs 15.2 vs 15.5 Negative factor: 20.3 vs 18.1 vs 16.1 Cognitive factor: 16.7 vs 14.7 vs 13.4 Excitement factor: 7.5 vs 7.0 vs 6.8 Anxiety-depression factor: 7.4 vs 7.3 vs 5.5 CGI Global Severity: 4.7 vs 4.4 vs 3.9 CGI Global Improvement: 3.6 vs 3.5 vs 3.3
Lindenmayer, 2008 DB RCT Multisite, 45 centers in USA, 4 centers in Canada	Screened NR Eligible NR 532 enrolled	310 withdrew 33 lost to followup 48 analyzed	Improvement from baseline in PANSS total score at d 42, LSM, p-value compared with P: P: -5.19 Quetiapine XR 300 mg/d: -5.01; p=NS Quetiapine XR 600 mg/d: -13.01; p=0.033 Quetiapine XR 800 mg/d: -11.17; p=NS Quetiapine IR 300 mg/d: -9.42; p=NS Quetiapine IR 600 mg/d: -6.97; p=NS No significant differences between active treatment groups and P on improvement in PANSS positive and negative subscale scores, PANSS response rates at d 42, or change from baseline in CGI-S score. CGI-I response rate was significantly greater in Quetiapine XR 800 mg/d (35.3%; p<0.05) and Quetiapine IR 300 mg/d (42.4%; p<0.01) compared with P (19.2%). All other treatment groups were NSly different from P. Adherence: 494/498 (99.2%) of patients in the efficacy analysis were adherent to the study medication.

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Author, year Study design	Adverse effects reported
Lindenmayer, 1998 Open-label Inpatients	Seizure: 1, leukopenia: 2, hypertension: 1, tachycardia: 1
Lindenmayer, 2008 DB RCT Multisite, 45 centers in USA, 4 centers in Canada	AEs in 5 patients led to WD: Orthostatic hypotension: 1 in quetiapine XR 600 mg/d. Grand mal convulsion: 1 in quetiapine IR 600 mg/d, 1 in P Psychotic disorder: 1 in quetiapine IR 600 mg/d EPS (dyskinesia and akathisia): 1 in quetiapine IR 600 mg/d P vs Quetiapine XR 300 vs XR 600 vs XR 800 vs IR 300 vs IR 600, % of group: Sedation: 9.5 vs 13.2 vs 20.7 vs 23.6 vs 15.6 vs 22.1 Somnolence: 7.1 vs 7.7 vs 15.2 vs 9.0 vs 13.3 vs 10.5 Dry mouth: 1.2 vs 12.1 vs 14.1 vs 12.4 vs 8.9 vs 8.1 Hypotension: 1.2 vs 8.8 vs 4.3 vs 3.4 vs 4.4 vs 7.0 Dizziness: 2.4 vs 7.7 vs 13.0 vs 9.0 vs 6.7 vs 8.1 Constipation: 0 vs 7.7 vs 7.6 vs 3.4 vs 0 vs 3.5 Diastolic BP decreased: 2.4 vs 7.7 vs 2.2 vs 3.4 vs 3.3 vs 5.8 Tachycardia: 2.4 vs 5.5 vs 8.7 vs 5.6 vs 8.9 vs 11.6 Heart rate increased: 4.8 vs 3.3 vs 10.9 vs 10.1 vs 4.4 vs 10.5 Weight increased: 2.4 vs 2.2 vs 4.3 vs 5.6 vs 6.7 vs 4.7 Blurred vision: 0 vs 0 vs 5.4 vs 1.1 vs 1.1 vs 0 % of patients with >=7% increased in body weight: 1.3 vs 8.0 vs 7.7 vs 3.5 vs 6.8 vs 14.8 Mean change in total cholesterol at Week 6, mg/dL: 0.13 vs 14.62 vs 8.20 vs 14.19 vs 5.72 vs 12.8 Mean change in prolactin (microg/L) at week 6: -6.62 vs -13.47 vs -7.0 vs -12.23 vs -7.86 vs -10.29

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Extrapyramidal symptoms
Lindenmayer, 1998 Open-label Inpatients	NR
Lindenmayer, 2008 DB RCT Multisite, 45 centers in USA, 4 centers in Canada	Dyskinesia and akathisia in 1 patient on quetiapine IR 600 mg/d led to WD. P vs Quetiapine XR 300 vs XR 600 vs XR 800 vs IR 300 vs IR 600:, Incidence of EPS-related AEs, % of group: 4.8 vs 9.9 vs 10.9 vs 12.4 vs 8.9 vs 10.5

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Total withdrawals; withdrawals due to adverse events	Comments
Lindenmayer, 1998 Open-label Inpatients	NR total WDs 5 due to AEs	
Lindenmayer, 2008 DB RCT Multisite, 45 centers in USA, 4 centers in Canada	310 WD 36 due to AE	Figure 1 states that 36 withdrew due to AE, but narrative describes only 5 of these patients and the AE that led to WD.

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Eligibility criteria	Interventions (drug, dose, duration)	Allowed other medications	Age Gender Ethnicity	Other population characteristics
Lublin 2009 RCT Multicenter	Schizophrenia, schizoaffective, schizophreniform disorder, 18 or older, females, with lack of efficacy or intolerance to their previous antipsychotic treatment.	Ziprasidone = 160 mg. Max dose. Olanzapine = 20 mg. Max dose. Risperidone = 8 mg. Max dose. Quetiapine = 750 mg. Max dose. Duration: 12 wks.	Concomitant Medications: Hypnotic Sedative Anxiolytic Antidepressant antiepileptic	Mean Age: 42 Female = 48% 18-44 = 60% 45-64 = 38% >65 = 2% Ethnicity: NR	Primary Diagnosis: Schizophrenia = 63% Schizoaffective disorder = 20% Schizophreniform disorder = 17%
Macfadden 2010 RCT Multicenter	Schizophrenia, men and women, 18 and older, must have experienced two psychotic relapses two ys prior.	RLAT = 50mg. Max dose. Aripiprazole = 30 mg. Max dose. Duration: 2 ys	Antidepressants Anxiolytics Mood stabilizers	Mean Age: 38 Male = 60% Female = 40% Ethnicity: Caucasian = 21% Black = 11% Hispanic = 14% Asian = 53% Other = 1%	NR
Malla, 2004 Canada	Diagnosis of schizophrenia, schizophreniform psychosis, schizoaffective psychosis or psychosis not otherwise specified; no medial or neurological disorder likely to cause psychotic symptoms; treatment with only one antipsychotic (risperidone or olanzapine) during the first y; no previous exposure to antipsychotics; completion of ratings of positive and negative symptoms, motor side effects and a neurocognitive battery close to the time of initiation of antipsychotic treatment and 1 y later	Risperidone: allowed dose 1-6 mg/d; median dose 2.5 mg/d Olanzapine: allowed dose 5-20 mg/d; median dose 10 mg/d durartion=1 yr	Antidepressants (sertraline, paroxetine, venlafaxine, citalopram and nefazodone) and anti-anxiety medications (lorazepam and clonazepam)	Mean age 23.7 yrs (SD 7.4) 63% male Ethnicity NR (note: these characteristics are based on the 32 pts included in the final analysis)	Mean age at diagnosis: 21.6 yrs

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Number screened/ eligible/ enrolled	Withdrawn/ Lost to follow-up/ Analyzed	Results
Lublin 2009 RCT Multicenter			
Macfadden 2010 RCT Multicenter	409/355/355	/ /349 Withdrawal: 14.1% vs13.0% Lost to FU: 10.1% vs 5.7%	Symptom response: (injectable risperidone [RLAT] vs. oral aripiprazole) Time to relapse: days Subjects relapsed, N (%) 81 (45.8) vs 75 (43.6) 25% quartile (95% CI)a 131.0 (100.0, 197.0) vs 113.0 (99.0, 169.0) Median (95% CI) NE (407.0, NE) vs NE (365.0, NE) P =b 0.684 Time in Remission: days Mean (SD) 373.5 (282.6) vs 356.7 (292.0) Median (range) 380.3 (0-741) vs 347.8 (0-735) P=c 0.646 aBased on Kaplan-Meier product limit estimates bLog-rank test stratified with pooled site cBased on Wilcoxon Rank Sum test
Malla, 2004 Canada	NR/NR/84	52/NR/32	SANS Positive symptom score: O baseline: 33.3 (SD 18.2); 1 yr: 2.2 (SD 2.6) R baseline: 24.7 (SD 6.0); 1 yr: 6.2 (SD 10.3) SANS Negative symptom score: O baseline: 29.3 (SD 17.8); 1 yr: 9.6 (SD 6.9) R baseline: 27.6 (SD 15.8); 1 yr:12.6 (SD 8.3)

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Author, year Study design	Adverse effects reported
Lublin 2009 RCT Multicenter	
Macfadden 2010 RCT Multicenter	Adverse events >10% in either group (safety analysis set) N (%) Any treatment-emergent adverse events: 161 (89.9) vs 152 (86.4) Psychiatric disorders: Insomnia 47 (26.3) vs 51 (29.0) Psychotic disorder 38 (21.2) vs 36 (20.5) Anxiety 32 (17.9) vs 26 (14.8) Schizophrenia 29 (16.2) vs 28 (15.9) Depression 24 (13.4) vs 15 (8.5) Nervous system disorders: Tremor 39 (21.8) vs 40 (22.7) Headache 30 (16.8) vs 27 (15.3) Dizziness 25 (14.0) vs 13 (7.4) Gastrointestinal disorders: Vomiting 18 (10.1) vs 14 (8.0) Diarrhea 12 (6.7) vs 19 (10.8)
Malla, 2004 Canada	NR

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Author, year Study design	Extrapyramidal symptoms
Lublin 2009 RCT Multicenter	
Macfadden 2010 RCT Multicenter	Extrapyramidal effects: Akathisia: 20 (11.2) vs 20 (11.4)
Malla, 2004 Canada	No difference between groups reported in text; no further data provided

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Total withdrawals; withdrawals due to adverse events	Comments
Lublin 2009 RCT Multicenter		
Macfadden 2010 RCT Multicenter	AE (as the primary reason) with RLAT: 0 2.3 percent withdrew because of an AE with aripiprazole; 2.2 percent of RLAT and 1.7 percent of aripiprazole subjects withdrew for lack of efficacy	
Malla, 2004 Canada		Of note: the results are only based on those pts who stayed on the drug they were initially assigned to AND who were completers (32/84 pts) Also, in Table 2 it is not clear if the 1 y results represent the SANS score at 1 y or the mean change from baseline

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Eligibility criteria	Interventions (drug, dose, duration)	Allowed other medications	Age Gender Ethnicity	Other population characteristics
McCue, 2006 RCT, open-label, U.S. Inpatients Funding - NR	Inclusion: 18 ys and older of either gender, who were newly admitted to the hospital's psychiatric inpatient service between January 2004 and February 2005, diagnosed with schizophrenia, schizoaffective disorder or schizophreniform disorder Exclusion: Pregnant or lactating women; a medical condition in which pharmacotherapy would prove a significant clinical risk; a clear history of response or lack of response to a particular antipsychotic drug and who, in the judgment of the treating psychiatrist, would best be treated accordingly; a diagnosis of bipolar disorder, major depressive disorder or substance-induced psychotic disorder. .	aripiprazole, mean 21.8 mg, range 10–45; haloperidol, mean 16.0 mg, range 4–30; olanzapine, mean 19.1 mg, range 5–40; quetiapine, mean 652.5 mg, range 50–1200; risperidone, mean 5.2 mg, range 2–9; ziprasidone, mean 151.2 mg, range 40–240. minimum of 3 wks	haloperidol, lorazepam and diphenhydramine for agitation; diphenhydramine for sleep. Benzatropine could also be prescribed for extrapyramidal side-effects; after 2 wks an antidepressant, mood stabilizer or anxiolytic could be prescribed	Mean age 37.6 62% male Ethnicity- NR	BPRS total score (mean): 42.3 Length of illness (mean ys): 13.2 Diagnosis: Schizophrenia=75.9% Schizoaffective=19.4% Schizophreniform=4.7% Substance misuse (% patients): 35.7
McEvoy, 2006 CATIE Phase 2E	Discontinuation of previous phase 1 treatment because of inefficacy.	Open-label clozapine 332.1mg or blinded capsules of olanzapine 23.4mg, quetiapine 642.9mg, or risperidone 4.8mg (mean modal doses)	Concomitant medications were permitted throughout the trial, except for additional antipsychotic agents.	Mean age=39.7 ys 81% male 64% white 33% black/African American 3% all other racial groups	DSM-IV diagnosis present in the past 5 ys (% pts): Depression=33% Alcohol dependence/abuse=25% Drug dependence/abuse=24%

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Number screened/ eligible/ enrolled	Withdrawn/ Lost to follow-up/ Analyzed	Results
McCue, 2006 RCT, open-label, U.S. Inpatients Funding - NR	584/NR/364	18//NA/319 analyzed	Aripiprazole vs Haloperidol vs Olanzapine vs Quetiapine vs Risperidone vs Ziprasidone Patient outcome, n (%) Effective 34 (64) vs 51 (89) vs 48 (92) vs 32 (64) vs 50 (88) vs 32 (64) Change in BPRS total score: mean (SD.) 12.9 (12.3) vs 16.4 (11.4) vs 14.9 (11.3) vs 14.2 (12.5) vs 15.4 (10.6) vs 14.2 (12.9) Time to 'Effective', ds: mean (SD.) 17.6 (10.5) vs 18.6 (10.6) vs 19.5 (13.1) vs 16.8 (8.0) vs 20.4 (13.5) vs 19.5 (8.5)
McEvoy, 2006 CATIE Phase 2E	1,052/1,052/99 509 (48%) left study from Phase 1 444 (42%) entered Phase 2T	62 (63%) withdrawn/none lost to fu/90 (91%) included in analysis	Median time until treatment discontinuation for any reason (mos) Clozapine=10.5 vs olanzapine=2.7 vs quetiapine=3.3 mos vs risperidone=2.8 mos HRs (95% CI) for pair-wise comparisons: Clozapine vs quetiapine=0.39 (0.19, 0.80) Clozapine vs risperidone=0.42 (0.21, 0.86) Clozapine vs olanzapine=0.57 (0.29, 1.16) Discontinuations due to lack of efficacy (% pts) Clozapine=11% vs olanzapine=35% vs quetiapine=43% vs risperidone=43% HRs (95% CI) for pair-wise comparisons: Clozapine vs olanzapine=0.24 (0.07, 0.78) Clozapine vs quetiapine=0.16 (0.04, 0.54) Clozapine vs risperidone=0.16 (0.05, 0.54) PANSS Total Score Change at 3 mos (p-value represents pair-wise comparison to clozapine) Clozapine= -11.7 vs olanzapine= -3.2 (p=0.22) vs quetiapine= 2.5 (p<0.02) vs risperidone= 4.1 (p<0.03) CGI severity change in score at 3 mos Clozapine= -0.7 vs olanzapine= 0.1 (p<0.02) vs quetiapine= 0.2 (p=0.003) vs risperidone= 0.0 (p=6.18)

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Adverse effects reported
McCue, 2006 RCT, open-label, U.S. Inpatients Funding - NR	Proportion of patients reporting side-effects (week 2: P=0.14; week 3: P=0.72; end-point: P=0.49).
McEvoy, 2006 CATIE Phase 2E	Clozapine vs olanzapine vs quetiapine vs risperidone (%pts) (p-values are NS unless otherwise specified and come from a test with df=3 comparing all treatment groups) Any AE: 76% vs 74% vs 67% vs 56% Insomnia: 4% vs 16% vs 13% vs 31%, p=0.02 Hypersomnia/sleepiness: 45% vs 32% vs 33% vs 25% Urinary hesitancy/dry mouth/constipation: 20% vs 0 vs 47% vs 6%p=0.002 Sex drive/sexual arousal/sexual orgasm: 33% vs 11% vs 13% vs 25% Gynecomastia/galactorrhea: 2% vs 5% vs 0 vs 0 Menstrual irregularities: 0 for all Incontinence/nocturia: 10% vs 0 vs 13% vs 13% Sialorrhea: 33% vs 11% vs 0 vs 13, p<0.02 Orthostatic faintness: 12% vs 5% vs 27% vs 6% Skin rash: 4% vs 0 vs 7% vs 6% Weight gain from baseline ≥ 7%: 20% vs 13% vs 15% vs 18% Weight change (mean lb): 1.4 vs 6.2 vs 5.1 vs 3.9

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Extrapyramidal symptoms
McCue, 2006 RCT, open-label, U.S. Inpatients Funding - NR	Change in Simpson–Angus Scale ratings from baseline to end-point (F=0.61, .f.=5,307, P=0.69; age as co-variable). Change in score on the Barnes Akathisia Rating Scale from baseline to end-point (F=1.45, df.=5,307, P=0.20; age as co-variable).
McEvoy, 2006 CATIE Phase 2E	AIMS severity score ≥ 2: 21% vs 21% vs 10% vs 0 Barnes score ≥ 3: 5% vs 0% vs 23% vs 0 Simpson-Angus mean score ≥ 1: 5% vs 13% vs 17% vs 0

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Total withdrawals; withdrawals due to adverse events	Comments
McCue, 2006 RCT, open-label, U.S. Inpatients Funding - NR	18 WD 14 due to AEs	Age was significantly different between groups.
McEvoy, 2006 CATIE Phase 2E	See previous results	

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Eligibility criteria	Interventions (drug, dose, duration)	Allowed other medications	Age Gender Ethnicity	Other population characteristics
McEvoy, 2006 Patel 2009 USA CAFE: Comparison of Atypicals in First Episode of Psychosis	16–40 ys; DSM-IV criteria for schizophrenia, schizophreniform disorder, or schizoaffective disorder; be in the first episode of their psychotic illness and been continuously ill for at least 1 month - 5 ys. Patients were excluded if a prior psychotic episode had remitted for 3 months or more or if they had prior antipsychotic drug treatment > 16 cumulative wkss; ≥4 on at least one Positive and Negative Syndrome Scale (PANSS; 17) psychosis item and a score ≥4 (moderately ill) on CGI-S; women of childbearing potential had to be using a medically acceptable form of contraception. Exclusion- did not speak English; had a history of mental retardation; pregnant or nursing; had a serious, unstable medical illness; had a known allergy to one of the study medications; serious risk of suicide; or had participated in an investigational drug trial within 30 ds	olanzapine (2.5–20 mg/d) quetiapine (100–800 mg/d) risperidone (0.5–4 mg/d) Durartion=52 wks	adjunctive antidepressant or mood stabilizer during the first 8 wkss of treatment was not allowed unless approved by the project medical officer. Anticholinergic medications for acute extrapyramidal side effects were permitted for up to a total of 2 wkss over the course of the trial.	Mean age 24.5 ys 73% male 51.3% white 43.0% black 5.8% other	Schizophrenia 57.8% Schizophreniform disorder 28.8% Schizoaffective disorder 13.5% Age at onset 23.5 ys
McQuade, 2004 DB, RCT, multicenter Inpatients Meyer 2009	Schizophrenia, in acute relapse, requiring hospitalization, 18 ys of age and older, a Positive and Negative Syndrome Scale (PANSS) total score of >60 and a score of >4 on a least 2 of the following PANSS items: delusions, hallucinatory behavior, conceptual disorganization, suspiciousness.	N=317 aripiprazole (N=156): 15-30 mg/d olanzapine (N=161): 10-20 mg/d 26 week duration	lorazepam up to 4mg/d allowed, not within 4 hs of efficacy/safety assessments	Mean Age: 38.4 Male: 72% Ethnicity NR	In-Patient population: 100%

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Number screened/ eligible/ enrolled	Withdrawn/ Lost to follow-up/ Analyzed	Results
McEvoy, 2006 Patel 2009 USA CAFE: Comparison of Atypicals in First Episode of Psychosis	NR/NR/400	281/0/400	Overall discontinuation before 52 wkss 70% of patients; 68.4% olanzapine, 70.9% quetiapine, 71.4% risperidone. At 12 wkss mean change from baseline in the PANSS positive subscale scores showed greater reductions for olanzapine (–5.2) and risperidone (–5.1) than for quetiapine (–4.0; quetiapine vs olanzapine, p=0.017; quetiapine vs risperidone, p=0.031) Trmt response at any point in study olanzapine 64%, quetiapine 58% risperidone 65% Olanzapine vs risperidone vs quetiapine Weight gain at 12 wkss LSM (SE) in pounds 15.6 (1.1) vs 8.6 (1.1) vs 7.9 (1.1) Weight gain ≥7% from baseline: Olanzapine vs risperidone 59.8% vs 32.5%, p<0.001, vs Quetiapine 29.2% (p<0.0001) Changes in total PANSS and weight gain: NS at 12 wkss (p=0.936) Weight gain at 52 wkss in pounds 24.2 (1.9) vs 14.0 (1.9) vs 12.1 (1.8), p<0.001 Weight gain of ≥7% from baseline: Olanzapine vs risperidone: 80% vs 57.6%, p<0.05, vs quetiapine 50.0%, p<0.01 No statistically significant difference between changes in total PANSS score and changes in weight at 52 wkss (p=0.338)
McQuade, 2004 DB, RCT, multicenter Inpatients Meyer 2009	NR/NR/378	72%/approx.10%/317	At Week 26: % of Patients who had > 7% increase in body weight: O: 37% vs A: 14%; (p<.001) Mean Change in Body Weight from Baseline: O: +4.23 kg (9.40lb) vs A: -1.37 kg (3.04lb); (p<.001) Mean Changes in Fasting Triglyceride Levels: O: +79.4 mg/dL vs A: +6.5 mg/dL; (p<.05) Mean Changes in Fasting HDL Cholesterol Levels: O: -3.39 mg/dL vs A: +3.61 mg/dL; (p<.05) Reduction in Symptoms of Schizophrenia: "No clinically meaningful differences between the aripiprazole and olanzapine groups."

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Adverse effects reported
McEvoy, 2006 Patel 2009 USA CAFE: Comparison of Atypicals in First Episode of Psychosis	Olanzapine Quetiapine Risperidone (%) Weight gain 51.1 40.3 41.4 Increased sleep hs 33.8 41.8 27.1 Insomnia 38.4 29.1 33.8 Menstrual irregularities 31.3 23.8 47.1 Decreased sex drive 27.8 26.1 27.1 Akinesia 24.1 24.6 27.1 Dry mouth 21.8 34.3 15.8 Akathisia 20.3 18.7 22.6 Decreased sexual arousal 21.8 16.4 18.1 Decreased orgasm 16.5 15.7 18.8 Orthostatic faintness 11.3 19.4 12.8 Constipation 8.3 11.9 13.5 Sialorrhea 5.3 6.0 13.5 Skin rash 7.5 5.2 6.8 Gynecomastia 6.8 2.2 9.8 Urinary hesitancy 5.3 5.2 3.0 Incontinence or nocturia 3.8 3.7 3.0 Galactorrhea 2.3 0.0 2.3
McQuade, 2004 DB, RCT, multicenter Inpatients Meyer 2009	Headache: O: 32% vs A: 23% Insomnia: O: 30% vs A: 32% Anxiety: O: 25% vs A: 20% Somnolence: O: 23% vs A: 8% 6 mo data on ethnicity from Meyer 2009 Mean change in body weight from baseline (LSM, SE): A vs O White -1.44 (0.36) vs 3.37 (0.32), p=0.000 Black/Hispanic: 0.99(0.36) vs 4.57 (0.38), p=0.000

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Extrapyramidal symptoms
McEvoy, 2006 Patel 2009 USA CAFE: Comparison of Atypicals in First Episode of Psychosis	According to article "There were NSD across treatment" groups
McQuade, 2004 DB, RCT, multicenter Inpatients Meyer 2009	EPS-Related AEs: Low: O: 16% vs A: 17% Parkinsonism events: O: 12% vs A: 11% Akathisia: O: 3% vs A: 6%

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Total withdrawals; withdrawals due to adverse events	Comments
McEvoy, 2006 Patel 2009 USA CAFE: Comparison of Atypicals in First Episode of Psychosis		
McQuade, 2004 DB, RCT, multicenter Inpatients Meyer 2009	229 WD Approx. 30% due to AE	

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Eligibility criteria	Interventions (drug, dose, duration)	Allowed other medications	Age Gender Ethnicity	Other population characteristics
Meltzer 2011 DB RCT Multicenter	Schizophrenia, male and female, 18-75, have an illness duration at leasy 1 yr also hospitalized fo >2 wks, CGI-S score of >4 and PANSS score of >80.	Lurasidone = 120 mg. Max dose. Olanzapine = 15mg. Max dose. P Duration: 6wks	Benzoiazepines	Mean Age: 38 Male = 78% Ethnicity: White = 33% Black = 36% Asian = 25% Other = 7% Hispanic = 14%	• Age at onset of illness (ys) = 24 • Duration of illness (ys) = 13
Meltzer, 2008 DB RCT United States 3 outpatient centers	Men and women, 18-58 ys with schizophrenia or schizoaffective disorder who had failed to respond adequately to prior treatment with other antipsychotic drugs	Olanzapine (25-45 mg/d) n=19 and Clozapine (300-900 mg/d) n=21 for 6 mos	only during washout, haloperidol	Clozapine vs. olanzapine Age 37.2 vs. 36.4 % male 71.4 vs 63.2 % White 57.1 vs. 73.7 % African American 38.1 vs. 15.8 % Asian 0 vs. 10.5 % Other 4.8 vs. 0	Clozapine vs. olanzapine % schizophrenia 80.9 vs. 83.2 % schizoaffective disorder 19.1 vs. 16.8

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Number screened/ eligible/ enrolled	Withdrawn/ Lost to follow-up/ Analyzed	Results
Meltzer 2011 DB RCT Multicenter	781/478/478	75/3/473	Lurasidone, 40 mg vs. Lurasidone, 120 mg vs. Olanzapine, 15 mg vs. Placebo PANSS: (Estimate, SE) Total score changed –25.7 2.0 P<0.001 vs. –23.6 2.1 P=0.011 vs. –28.7 1.9 P<0.001 vs. . –16.0 2.1 Positive subscale score change –7.7 0.7 P= 0.018 vs. –7.5 0.7 P= 0.035 vs. –9.3 0.7 P<0.001 vs. –5.4 0.7 Negative subscale score change –6.0 0.5 P= 0.002 vs. –5.2 0.6 P= 0.045 vs. –6.2 0.5 P<0.001 vs. –3.6 0.5 General psychopathology score change –12.4 1.0 P= 0.001 vs. –11.1 1.0 P= 0.022 vs. –13.3 0.9 P<0.001vs. –7.8 1.0 Cognitive subscale (modified) score change: –4.2 0.3 P=0.005 vs. –4.0 0.4 vs. P=0.012 –4.6 0.3 P<0.001 vs. –2.7 0.4 CGI severity score change: –1.5 0.1 P=0.006 vs. –1.4 0.1 P=0.040 vs. –1.5 0.1 P<0.001 vs. –1.1 0.1 MADRS total score change: –3.5 0.5 P=0.324 –3.2 0.6 P=0.571 –5.0 0.5 P=0.003 vs. –2.8 0.6
Meltzer, 2008 DB RCT United States 3 outpatient centers	NR/NR /40	24 (60%) withdrawn Clozapine (11 (52.4%)) vs. olanzapine (5 (26.3%)) / NR/ 40	Clozapine vs. olanzapine PANSS total 72.1(3.4) vs. 71.7 (2.8) P = 0.92 PANSS positive 15.1 (1.1) vs. 17.8 (0.9) P = 0.07 PANSS negative 20.9 (1.2) vs. 19.1 (1.0) P = 0.28 GAF 62.4 (2.1) vs. 54.8 (1.8) P = 0.01 CGI 2.6 (0.8) vs. 2.3 (0.6) P = 0.76 CGI-S 3.6 (0.2) vs. 3.6 (0.2) P = 0.78

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Adverse effects reported
Meltzer 2011 DB RCT Multicenter	(Lurasidone, 40 mg vs. Lurasidone, 120 mg vs. Olanzapine, 15 mg vs. Placebo) N % At least one adverse event 90 75.6% vs. 97 82.2% vs. 100 82.0% vs. 84 72.4% Headache: 26 21.8% vs. 21 17.8% vs. 17 13.9% vs. 25 21.6% Akathisia: 14 11.8% vs. 27 22.9% vs. 9 7.4% vs. 1 0.9% Somnolence: 12 10.1% vs. 18 15.3% vs. 11 9.0% vs. 5 4.3% Insomnia: 15 12.6% vs. 14 11.9% vs. 13 10.7% vs. 13 11.2% Sedation: 11 9.2% vs. 16 13.6% vs. 18 14.8% vs. 4 3.4% Anxiety: 12 10.1% vs. 12 10.2% vs. 7 5.7% vs. 8 6.9% Nausea: 13 10.9% vs. 9 7.6% vs. 6 4.9% v5 4.3% Agitation: 14 11.8% vs. 7 5.9% vs. 8 6.6% vs. 6 5.2% Dyspepsia: 9 7.6% vs. 9 7.6% vs. 6 4.9% vs.7 6.0% Constipation: 6 5.0% vs. 9 7.6% vs. 8 6.6% vs. 6 5.2% Vomiting: 5 4.2% vs. 10 8.5% vs. 3 2.5% vs. 8 6.9% Back pain: 6 5.0% vs. 6 5.1% vs. 7 5.7% vs. 5 4.3% Dizziness: 5 4.2% vs. 6 5.1% vs. 3 2.5% vs. 2 1.7% Restlessness: 7 5.9% vs. 4 3.4% vs. 4 3.3% vs. 3 2.6% Salivary hypersecretion: 2 1.7% vs. 8 6.8% vs. 1 0.8% vs. 0 0.0% Musculoskeletal stiffness: 3 2.5% vs. 6 5.1% vs. 3 2.5% vs. 2 1.7% Appetite decreased: 6 5.0% vs. 1 0.8% vs.2 1.6% vs. 2 1.7% Appetite increased 1 0.8% vs. 3 2.5% vs.7 5.7% vs.4 3.4% Weight increased: 2 1.7% vs. 2 1.7% vs. 25 20.5% vs. 6 5.2% Toothache: 4 3.4% vs. 3 2.5% vs.12 9.8% vs.6 5.2% Dry mouth: 2 1.7%v s.3 2.5% vs.12 9.8% vs.1 0.9% Psychotic disorder: 2 1.7%vs. 4 3.4% vs. 4 3.3% vs. 8 6.9%
Meltzer, 2008 DB RCT United States 3 outpatient centers	Clozapine vs. olanzapine Weight 204.3 (3.3) vs. 217 (2.9) P = 0.01 BMI 30.6 (0.5) vs. 32.6 (0.4) P = 0.006

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Extrapyramidal symptoms
Meltzer 2011 DB RCT Multicenter	(Lurasidone, 40 mg vs. Lurasidone, 120 mg vs. Olanzapine, 15 mg vs. Placebo) N % Extrapyramidal adverse events: Parkinsonism 11 9.2% vs. 13 11.0% vs. 6 4.9% vs. 2 1.7% Tremor 2 1.7 % vs. 9 7.6 % vs. 7 5.7% vs. 5 4.3% Dystonia 4 3.4% vs. 9 7.6% vs 1 0
Meltzer, 2008 DB RCT United States 3 outpatient centers	Clozapine vs. olanzapine AIMS total 1.4 (0.7) vs. 2.3 (0.6) P = 0.3 SAS total 2.3 (0.6) vs. 1.6 (0.5) P = 0.4

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Total withdrawals; withdrawals due to adverse events	Comments
Meltzer 2011 DB RCT Multicenter	Withdrawals due to adverse events: 40	
Meltzer, 2008 DB RCT United States 3 outpatient centers	16 WD 0 due to AEs	

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Eligibility criteria	Interventions (drug, dose, duration)	Allowed other medications	Age Gender Ethnicity	Other population characteristics
Moller, 2008 DB RCT Multinational 74 centers	Outpatients aged 18–65 ys with a diagnosis of schizophrenia (including catatonic, disorganized, paranoid and undifferentiated)Patients with a Clinical Global Impressions of Severity of Illness (CGI-S) (National Institutes of Mental Health, 1970) score of 3 or lower were clinically stable	Quetiapine XR n=331 or Quetiapine IR n=166 400, 600 or 800 mg/d 6 wks	Antidepressants, anxiolytics, hypnotics, mood stabilizers or other psychoactive drugs and drugs that induce or inhibit cytochrome 3A4 enzymes were permitted if treatment had started at least 2 wks	Mean (SD) age (yrs) XR 39.8 (11.4) vs IR 39.9 (10.2) % male 50.9XR vs 57.8 IR Ethnicity (%) White XR 82.7 vs IR 84.9 Black XR 14.2 vs IR 10.8 Asian XR 1.2 vs IR 0.6	PANSS total XR 59.5 (14.3) IR 59.3 (14.7) CGI-S XR 2.6 (0.6) IR 2.7 (0.6)

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Number screened/ eligible/ enrolled	Withdrawn/ Lost to follow-up/ Analyzed	Results
Moller, 2008 DB RCT Multinational 74 centers	NR / NR / 630	38 9 496	Primary outcome - proportion of patients who discontinued study treatment owing to lack of efficacy or whose PANSS total scores increased by 20% or more from randomization to any visit (MITT population): 9.1% XR; 7.2% IR. The estimated difference MITT population was 1.86% (95% CI –3.78, 6.57; P=0.0431) PANSS score LSM change from baseline (95% CI): Total XR – 3.7 (– 5.2, – 2.3) vs. IR– 4.2 (– 6.0, – 2.5) Positive XR – 0.8 (– 1.2, – 0.4) vs. IR – 0.9 (– 1.4, – 0.4) Negative XR – 1.1 (– 1.5, – 0.6) vs. IR – 1.3 (– 1.8, – 0.8) CGI-I score, % of patients with no change or improvement (95% CI) XR 92.7 (89.4, 95.1) vs. IR 93.4 (88.5, 96.3) CGI-S score, mean change from baseline (SD) XR – 0.0 (0.6) vs. – 0.1 (0.6)

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Adverse effects reported
Moller, 2008 DB RCT Multinational 74 centers	XR vs IR n (%) Dry mouth 14 (4.2) vs. 2 (1.2) Somnolence 13 (3.9) vs. 4 (2.4) Fatigue 7 (2.1) vs. 3 (1.8) Sedation 6 (1.8) vs. 6 (3.6) Constipation 4 (1.2) vs. 3 (1.8) Tremor 3 (0.9) vs. 1 (0.6) Weight decreased 3 (0.9) vs. 0 Decreased appetite 2 (0.6) vs. 0 Dizziness 2 (0.6) vs 3 (1.8) Dysgeusia 2 (0.6) vs. 0 Headache 2 (0.6) vs. 1 (0.6) Increased appetite 2 (0.6) vs. 0 Muscle rigidity 2 (0.6) vs. 0 Psychotic disorder 2 (0.6) vs. 0 Tachycardia 2 (0.6) vs. 1 (0.6) Extrapyramidal disorder 0 vs. 2 (1.2) Insomnia 0 vs. 2 (1.2)

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Extrapyramidal symptoms
Moller, 2008 DB RCT Multinational 74 centers	SAS scores XR vs. IR Improved 20.7% vs. 21.1% Stayed the same 69.3% vs. 76.5% Worsened 10% vs. 2.4% MedDRA terms of tremor, akathisia, muscle rigidity, dyskinesia, hypokinesia, Parkinsonism, extrapyramidal disorder and restlessness: XR 3.3% and IR 2.4%

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Total withdrawals; withdrawals due to adverse events	Comments
Moller, 2008 DB RCT Multinational 74 centers	38 WD 7 due to AEs	

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Eligibility criteria	Interventions (drug, dose, duration)	Allowed other medications	Age Gender Ethnicity	Other population characteristics
Mori, 2004 Inpatients	Hoyu Mental Hospital inpatients being treated with typical antipsychotics and antiparkinsonian anticholinergic drugs and with symptoms corresponding to DSM-IV criteria for schizophrenia	N= 77 Final Doses: olanzapine (N=20): 16.5 mg/d perospirone (N=18) 37.3 mg/d quetiapine (N=4): 432.5 mg/d risperidone (N=19): 7.37 mg/d 4 wks duration	NR	Mean age: 59.9 ys 50.6% Male	Schizophrenia Diagnoses: Disorganized: 23(29.8%) Paranoid: 10(12.9%) Undifferentiated: 34(44.1%)
Mullen, 1999 (QUEST sub-group)	Psychosis and schizophrenia, schizoaffective disorder, bipolar disorder, major depressive disorder (MDD), delusional disorder, Alzheimer's Disease, schizophreniform disorder, vascular dementia, or substance abuse dementia.	quetiapine mean dose at completion: 253.9 mg/d; oral risperidone mean dose at completion: 4.4 mg/d; oral Duration: 4 mos	NR	Mean age: quetiapine 45.1 risperidone 46.2 quetiapine 50.9% male risperidone 54.3 % male Ethnicity NR	Special characteristics: included those > 65 ys Diagnosis: bipolar: 83/554;20/175 major depressive disorder: 75/554;26/175 schizoaffective: 158/554;57/175 schizophrenia: 218/554;67/175 all non-mood diagnoses: 316/554;103/17

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Number screened/ eligible/ enrolled	Withdrawn/ Lost to follow-up/ Analyzed	Results
Mori, 2004 Inpatients	NR/NR	NR/NR/77	Changes in percentages of correct responses in neutral DSDT tests: Mean at baseline vs Mean after switching antipsychotics vs Mean after WD of anticholinergics Olanzapine: 0.32 vs 0.34 vs 0.42 Perospirone: 0.39 vs 0.46 vs 0.44 Quetiapine: 0.43 vs 0.36 vs 0.44 Risperidone: 0.36 vs 0.37 vs 0.43 Changes in percentages of correct responses in distractibility DSDT tests: Mean at baseline vs Mean after switching antipsychotics vs Mean after WD of anticholinergics Olanzapine: 0.35 vs 0.39 vs 0.41 Perospirone: 0.43 vs 0.46 vs 0.47 Quetiapine: 0.42 vs 0.36 vs 0.41 Risperidone: 0.26 vs 0.32 vs 0.39 PANSS totals: Mean at baseline vs Mean after switching antipsychotics vs Mean after WD of anticholinergics Olanzapine: 82.1 vs 73.8 vs 69.4; P<0.0001 Perospirone: 72.4 vs 72.6 vs 77.2; P<0.05 Quetiapine: 78.8 vs 73.7 vs 72.9; P<0.001 Risperidone: 81.2 vs 74.9 vs 71.5; P<0.0001 General psychopathology: Mean at baseline vs Mean after switching antipsychotics vs Mean after WD of anticholinergics Olanzapine: 40.9 vs 37.2 vs 35.0; P<0.0001 Perospirone: 37.1 vs 36.8 vs 39.5; P<0.005 Quetiapine: 38.4 vs 36.2 vs 35.8; P<0.001 Risperidone: 40.0 vs 36.8 vs 35.1; P<0.0001
Mullen, 1999 (QUEST sub-group)	NR/NR/751 quetiapine 554 risperidone 175	NR	Outcome: % change from baseline Hamilton Rating Scale (depression) scores (schizoaffective; schizophrenia) Quetiapine:–41.6%;–41.6% Risperidone:–34.6%;–31.4% (no significant difference between groups) Quetiapine group had significantly (p= 0.028) greater improvement on Hamilton Rating Scale (depression) than risperidone group Higher percentage in quetiapine group had improvement in CGI at each visit compared with risperidone group No statistically significant differences between groups in PANSS scale

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Adverse effects reported
Mori, 2004 Inpatients	NR
Mullen, 1999 (QUEST sub-group)	NR

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Extrapyramidal symptoms
Mori, 2004 Inpatients	NR
Mullen, 1999 (QUEST sub-group)	Extrapyramidal events (EPS checklist) declined in both groups; no significant differences between groups in overall occurrence. Odds of risperidone-treated patient having treatment-emergent EPS requiring adjustment of medication or anti-EPS medication 5.6 times greater than odds of quetiapine-treated patient having similar event ($p< 0.001$). Extrapyramidal symptoms rated as 'at least moderate' (EPS checklist) occurred more frequently at each visit in risperidone participants.

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Total withdrawals; withdrawals due to adverse events	Comments
Mori, 2004 Inpatients	NR / NR	
Mullen, 1999 (QUEST sub-group)	NR / NR	

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Eligibility criteria	Interventions (drug, dose, duration)	Allowed other medications	Age Gender Ethnicity	Other population characteristics
Naber, 2001	Diagnosis of schizophrenia was confirmed by experienced clinicians relying on criteria according to DSM-IV	olanzapine(N=36): 12.92 mg, risperidone(N=28): 3.55mg, clozapine(N=36): 194.44mg	No	Mean age: 34.2 ys 54% male Ethnicity: NR	NR
Naber, 2005 DB, RCT, non-inferiority, multicenter (Germany) Inpatients x 2 wks and then outpatients (flexible dosing)	DSM-4 schizophrenia, a minimum BPRS score of 24. Documented failure to at least one antipsychotic other than clozapine and olanzapine or had experienced intolerable side effects during these prior antipsychotic treatments. Not pregnant or lactating women. No serious somatic illnesses, including alcohol and/or drug dependency. Not received olanzapine at any time or prior clozapine treatment within the last 3 mos.	Olanzapine 5-25 mg/d (mean dose 16.2mg) or clozapine 100-400 mg/d (mean dose 209mg) X 26 wks, followed by a 2 week taper period. Mean actual duration of treatment: 109 ds in olanzapine group and 101 ds in clozapine group.	benztropine for agitation (lorazepam up to 8mg/d, temazepam up to 30mg/d, diazepam up to 60mg/d, oxazepam up to 100mg/d); chloral hydrate up to 1500mg/d for insomnia, and biperiden up to 6mg.d for treatment-emergent EPS.	age, (range): 34.0 ± 10.6 (18-59) male: 69 (61%) Ethnicity: NR	Age at onset of disease ys (range): 26.9 ± 7.8 (11-55) Number of previous episodes, (range): 4.5 ± 4.7 (0-30) CGI Severity: Moderately ill: 11%, markedly ill: 53%, severely ill: 35%, most extremely ill. 2% SWN total score: (total score: 20 items) 73.1 ± 20.6; (total score: 38 items): 136.0 ± 37.6

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Number screened/ eligible/ enrolled	Withdrawn/ Lost to follow-up/ Analyzed	Results
Naber, 2001	Unclear / unclear / 100	NR/NR/100	Change in PANSS mean scores from admission to discharge: clozapine vs risperidone vs olanzapine Total scores: -25.5 vs -12.56 vs -23.55 Positive scores: -6.77 vs -5.29 vs -8.34 Negative: -6.06 vs -2.74 vs -5.23 Change in mean SWN scores, admission to discharge: clozapine vs risperidone vs olanzapine Total scores: +8.78 vs +8.40 vs +18.97 Mental Functioning: +1.78 vs +0.92 vs +3.77 Social Integration: +1.42 vs +1.34 vs +4.33 Emotional Regulation: +2.00 vs +2.04 vs +3.48 Physical Functioning: +1.58 vs +1.65 vs +4.86 Self-control: +1.6 vs +2.16 vs +2.83
Naber, 2005 DB, RCT, non-inferiority, multicenter (Germany) Inpatients x 2 wks and then outpatients (flexible dosing)	NR/ 122/114	36/27/43 (completed study)	Efficacy Mean changes, BL to endpoint (LOCF, ITT); Group difference (Olanzapine-clozapine) [95% CI] SWN total score change: (20 item): 3.2 [-4.2*, 10.5]; *p=0.002 SWN total score change (38 items): 8.3 [-5.4; 21.9] MLDL satisfaction change: -0.05 [-0.77; 0.67] PANSS total score change: -2.4 [-13.7; -8.4] BPRSO-6 total change:-2.8 [-9.7; -4.2] CGI Severity scores improvement: O 1.4 ± 1.2 vs. C: 1.3 ±1.5

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Adverse effects reported
Naber, 2001	NR
Naber, 2005 DB, RCT, non-inferiority, multicenter (Germany) Inpatients x 2 wks and then outpatients (flexible dosing)	AE possibly or probably related to study drug (spontaneously reported): C 75% vs. O 47%, RR 1.60 (95% CI: 1.26; 2.02) Proportion of patients with any AE: C 91% vs. O 77% RR 1.18 (95% CI: 1.04; 1.34) C> O: dizziness 13% vs. 2%; Increased salivation:18% vs. 0%; constipation: 21% vs. 0%; respectively O> C: Anxiety: 12% vs. 2% Mean Body weight gain (kg): C> O : 5.0 ± 6.8 vs. 3.5± 5.9, respectively Marked weight gain by at least 7% of body weight: C> O; 52% vs. 34% BL BMI < 23 kg/m2--weight gain was most pronounced C > O: 8.2 ± 8.1 vs. 9.0 ±8.9 BL BMI > 27 kg/m2: weight gain was less although still C> O 1.7± 2.4 vs. 3.5 ± 7.2 ECGs: unchanged in majority of pts (O 81%, C 88%)-No serious ECG changes reported. A prolongation of QT-time was reported for one C pt. Blood glucose remained within normal range in all but one C pt who had elevated non-fasting blood glucose levels CGI Therapeutic Index: O > C (mean index: Olanzapine: 2.17 ± 1.22, clozapine 1.63 ± 1.14). CGI Therapeutic Effect ratings were similar in both groups CGI Side Effects: no or no significant impairment by SE in 92% of olanzapine-treated pts vs. 79% clozapine group.

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Extrapyramidal symptoms
Naber, 2001	NR
Naber, 2005 DB, RCT, non-inferiority, multicenter (Germany) Inpatients x 2 wks and then outpatients (flexible dosing)	Simpson Angus Scale improved in both treatment groups: mean total scores decreased: O 2.7 ± 4.8 points with (n=50) and 2.1 ± 4.5 points in C group (n=54) (data not shown). Concomitant antiparkinsonian medications was used in 12% O pts (7/57), 5% C pts (3/57)

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Total withdrawals; withdrawals due to adverse events	Comments
Naber, 2001	NR / NR	There were two groups of patients, one group n=212 and was divided into typicals vs atypicals. The second group was n=100, and was divided between clozapine, risperidone, and olanzapine. It was unclear if the two groups were the same. Olanzapine and risperidone pts were pseudo-randomized; clozapine was given because of insufficient antipsychotic treatment or severe motor symptoms under previous medications. Olanzapine pts were significantly younger than risperidone.
Naber, 2005 DB, RCT, non-inferiority, multicenter (Germany) Inpatients x 2 wks and then outpatients (flexible dosing)	71 total WD 12 due to AEs	Recruitment problems. Overall retention rates were 69% after 6 wks, and 34% at 26 wks.

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Eligibility criteria	Interventions (drug, dose, duration)	Allowed other medications	Age Gender Ethnicity	Other population characteristics
Naber, 2005 DB, RCT Inpatients and outpatients	DSM-IV and ICD-10 criteria for schizophrenia, predominantly primary negative PANSS symptoms (negative subscale score ≥21 ; at least 1 pt greater than positive subscale score)	n=44 Risperidone (n=22): ds 1-2: 2 mg/d; ds 3-5: 4 mg/d; ds 6-7: 6 mg/d. Dose up to 8 gm/d allowed after d 7. Quetiapine (n=22): d 1: 50 mg; d 2: 100 mg; titrated up to 600 mg up to d 7. Dose up to 800 mg allowed after d 7.	lorazepam (≤4 mg/d) zopiclone (≤ 15 mg/d) biperiden hydrochloride (≤8 mg/d)	Mean age: 35 yrs (SD 11.6) 61% male Ethnicity NR	PANSS total mean score: 100.6 (SD 16.7) SANS total mean score: 59.2 (SD 20.9) SAS mean score: 0.35 (SD 1.2)
NCT00789698 PEARL 3 Extension Study DB, RCT, multicenter	PEARL 3 study criteria: 18-75 years, DSM-IV schizophrenia For extension: completed all required assessments on final study visit of PEARL 3, suitable for outpatient treatment	Lurasidone 40-160 mg/d flexible dose (original study patients were on Lurasidone 80 mg, lurasidone 160 mg, or placebo) Quetiapine XR 200-800 mg/d flexible dose	NR	Age: 37.6 Gender: 33.2% female Ethnicity: NR	NR
Newcomer, 2008 DB RCT Multinational Multicenter	Males and females, 18 to 65 yrs w/ schizophrenia or schizoaffective disorder on olanzapine for 1 to 24 mos, BMI 27 or more, CGI-S 4 or less.	Aripiprazole 10-30 mg/d n=88 Olanzapine 10-20 mg/d n=85 for 16 wks	Stable statins, antidepressants (except fluoxetine and paroxetine) benzodiazepines/anxiolytics, mood stabilizers, anti-convulsants, sleeping agents, propranolol and other B-adrenergic blockers	Mean age 39.2 yrs 64.2% male 68.2% Caucasian 24.3% black 2.3% Asian 0.6% Pacific Islander 4.6% other	76.9% schizophrenia 23.1% schizoaffective disorder Mean BMI 32.3

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Number screened/ eligible/ enrolled	Withdrawn/ Lost to follow-up/ Analyzed	Results
Naber, 2005 DB, RCT Inpatients and outpatients	NR/22/22	risperidone 2/0/efficacy NR; safety 22 quetiapine: 4/2/efficacy NR; safety 22	Mean change from baseline at week 12: PANSS total: R -29 vs Q -30 PANSS negative subscale: R -7 vs Q -11 PANSS positive subscale: R -8 vs Q -4 PANSS general psychopathy: R -15 vs Q -16 (all PANSS data interpolated from graph) No SS differences b/t drugs in PANSS subscales SANS total: R -15.5 vs Q -23 SANS affective blunting: R -4 vs Q -6.5 SANS alogia: R -2 vs Q -5; p=0.065 SANS avolition/apathy: R -4.75 vs Q -5.1 SANS anhedonia/asociality: R -4.9 v Q 5.2 SANS disturbance of attention: R -3 vs Q -3.1 (all SANS data interpolated from graph) No SS differences b/t drugs in SANS subscales CGI: R 1.5 (SD 1.6) v Q 1.7 (SD 1.4); p=0.767
NCT00789698 PEARL 3 Extension Study DB, RCT, multicenter	NR/NR/292	152/21/218	Lurasidone-Lurasidone group (either lurasidone dosing group during original study and lurasidone for extension study) vs. Quetiapine-Quetiapine group (quetiapine for original study and extension study) Relapse of Psychotic Symptoms: 29 vs. 21; HR, 0.728; 95% CI, 0.410 to 1.295 Change from baseline (95%CI) to Month 6, CogState Computerized Cognitive Scores: 0.22 (0.06 to 0.38) vs. -0.03 (-0.26 to 0.20) Change from baseline (95%CI) to Month 12, PANSS: -34.6 (-38.3 to -30.9) vs. -25.7 (-30.9 to -20.6) Change from baseline (95%CI) to Month 12, CGI-S: -1.9 (-2.1 to -1.7) vs. -1.6 (-1.9 to -1.4)
Newcomer, 2008 DB RCT Multinational Multicenter	NR/NR/244	54/0/173	Change in weight at 16 wks aripiprazole -1.8 kg vs olanzapine +1.41 kg; p < .001. CGI-I endpoint scores olanzapine (mean +/- SE = 3.09 +/- 0.16) vs aripiprazole (mean +/- SE = 3.74 +/- 0.15; p < .001),

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Adverse effects reported
Naber, 2005 DB, RCT Inpatients and outpatients	Weight gain: R 1.72 (SD 3.57) kg v Q 2.93 (SD 4.02); p=0.296 Cold: R 14 (8.2%) v Q 3 (13.6%)' p=0.680 Headache: 7 (31.8%) v Q 6 (27.3%); p=0.741 Tiredness: R 5 (22.7%) v Q 17 (77.3%); p<0.001 Insomnia: R 5 (22.7%) vs Q 6 (27.3%); p=0.728 Dizziness: R 6 (27.3%) vs Q 6 (27.3%); p=1.000 Nausea: R 2 (9.1%) vs Q 4 (18.2%); p=0.660 Intermediate (6 wk) serum measurements revealed a SS difference in prolactin levels (R 100 ug/L v Q -18 ug/L; p<0.001) and estrogen (R -21 ug/L v Q 12 ug/L; p<0.01). SS differences in testosterone and SHBG also reported (p<0.05) although graphical data impossible to interpolate (see Fig. 3 in paper)
NCT00789698 PEARL 3 Extension Study DB, RCT, multicenter	Groups from original study: Lurasidone 80mg vs. Lurasidone 160 mg vs. Placebo (extension study received lurasidone)vs. Quetiapine SAE (%): 12.5 vs. 7.59 vs. 3.57 vs. 20.0 Any AE, not SAE (%): 61.1 vs. 64.6 vs. 62.5 vs. 62.3 Weight increase (%): 4.17 vs 7.59 vs. 1.79 vs. 8.24
Newcomer, 2008 DB RCT Multinational Multicenter	Aripiprazole vs. olanzapine n(%) Any AE 56 (63.3) vs. 45 (53.6) Nausea 6 (6.8) vs. 1 (1.2) Weight increase 4 (4.5) vs. 5 (6.0) Headache 8 (9.1) vs. 3 (3.6) Insomnia 19 (21.6) vs. 9 (10.7)

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Extrapyramidal symptoms
Naber, 2005 DB, RCT Inpatients and outpatients	Akathisia: R 8 (36.4%) v Q 0; p=0.006 Parkinsonism: R 8 (36.4%) v Q 0; p=0.006 Use of anticholinergic medication: R 9 (40.9%) v Q 2 (9.1%); p=0.037
NCT00789698 PEARL 3 Extension Study DB, RCT, multicenter	Akathisia (%): 15.28 vs. 10.13 vs. 10.71 vs. 2.35 Dystonia (%): 5.56 vs. 1.27 vs. 3.57 vs. 1.18 Parkinsonism (%): 4.17 vs. 7.59 vs. 16.07 vs. 0
Newcomer, 2008 DB RCT Multinational Multicenter	Mean change from baseline Aripiprazole vs. olanzapine SAS -0.21 vs. -0.18 P = 0.822 AIMs -0.05 vs. -0.02 P = 0.914

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Total withdrawals; withdrawals due to adverse events	Comments
Naber, 2005 DB, RCT Inpatients and outpatients	19 total WD 3 due to AEs	
NCT00789698 PEARL 3 Extension Study DB, RCT, multicenter	WD: 152 Due to AE: 17	
Newcomer, 2008 DB RCT Multinational Multicenter	54 WD 15 due to AEs	

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Eligibility criteria	Interventions (drug, dose, duration)	Allowed other medications	Age Gender Ethnicity	Other population characteristics
Newcomer, 2009 Open label RCT Multinational, multicenter (58)	Inclusion: Male and female ; age 18-65 yrs; schizophrenia; no prior treatment or had shown inadequate response Exclusion: previous treatment with study agents, clozapine, chlorpromazine, valproic acid, lithium or antidepressants, agents that effect insulin sensitivity, diagnosis of diabetes, pregnancy, other Axis I disorders, clinically relevant disease or depot antipsychotic within 1 dosing interval	Quetiapine vs. Olanzapine vs. Risperidone Mean daily doses 607.0 mg vs. 15.2 mg vs. 5.2 mg 24 wks	Benzodiazepines and anticholigenerics	Mean age 39 yrs 90% male 73% white	BMI 25 kg/m 75% paranoid

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Number screened/ eligible/ enrolled	Withdrawn/ Lost to follow-up/ Analyzed	Results
Newcomer, 2009 Open label RCT Multinational, multicenter (58)	NR/NR/574	121/16/395 (those that had measurements at baseline and week 20 or later)	Quetiapine vs. Olanzapine vs. Risperidone CGI-S < 3 (%) 70.2 vs. 75.7 vs. 74.3 CGI-I much and vey much improved (%) 57.7 vs. 63.9 vs 55.6 Mean weight change (kg) +3.7 vs. +4.6 vs. +3.6 Mean change in AUC 0-2 h glucose 9.1 vs. 21.9 vs. 18.8

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Adverse effects reported
Newcomer, 2009 Open label RCT Multinational, multicenter (58)	Quetiapine vs. Olanzapine vs. Risperidone % AEs 59.8 vs 47.0 vs. 67.4 Serious AEs 10.1 vs. 2.4 vs. 7.6 Insomnia 6.5 vs. 4.2 vs. 14.5 Somnolence 10.1 vs. 3.6 vs. 4.7 Akathisia 1.2 vs. 1.8 vs. 12.8 Schizophrenia 7.1 vs. 1.2 vs. 4.7 Sedation 6.5 vs. 3.0 vs. 2.9 Dizziness 5.3 vs. 0 vs. 3.5

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Extrapyramidal symptoms
Newcomer, 2009 Open label RCT Multinational, multicenter (58)	Quetiapine vs. Olanzapine vs. Risperidone % Extrapyramidal disorder 1.8 vs. 1.8 vs. 24.4

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Total withdrawals; withdrawals due to adverse events	Comments
Newcomer, 2009 Open label RCT Multinational, multicenter (58)	121 WD 34 due to AEs	

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Eligibility criteria	Interventions (drug, dose, duration)	Allowed other medications	Age Gender Ethnicity	Other population characteristics
Pandina 2011 Alphs, 2013 DB RCT Multicenter	Schizophrenia, men and women, 18 and older, PANSS score between 60-120, BMI >17.0 kg/m2 and <40 kg/m2.	Risperidone-LAI = 50 mg. Max dose. Paliperidone palmitate = 150 mg. Max dose. P Duration: 13 wks	Antidepressants Benzodiazepines Lorazepam.	Mean Age: 39 Male = 58% Women = 42% Ethnicity: White = 79% Black = 16% Asian = 5% Other = 1%	Prior psychotropic medications • Atypical antipsychotics = 68% • Typical antipsychotics = 43% • Benzodiazepines = 35% • Anti-EPS = 26% • Antidepressants = 17%

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Number screened/ eligible/ enrolled	Withdrawn/ Lost to follow-up/ Analyzed	Results
Pandina 2011 Alphs, 2013 DB RCT Multicenter	1400/1220/1220	107/29/913	(Paliperidone palmitate vs. Risperidone-LAI) PSP score, mean (SD) Change from baseline: 8.5 (11.82) 8.8 (11.65) CGI-S, mean (SD) Change from baseline: −0.9 (0.97) −0.9 (0.93) SDS, mean (SD) Change from baseline: −1.9 (3.03) −1.8 (2.91) Positive symptoms, Mean (SD) Change from baseline:−5.6 (5.53) −5.3 (5.04) Negative symptoms, Mean (SD) Change from baseline: −3.8 (4.61) −3.8 (4.61) Disorganized thoughts, Mean (SD) Change from baseline: −3.4 (4.14) −3.2 (3.92) Uncontrolled hostility/excitement, Mean (SD) Change from baseline: −1.7 (3.01) −1.5 (2.97) Anxiety/depression, Mean (SD) Change from baseline: −2.7 (3.15) −2.4 (2.88) Efficacy outcomes, change from baseline to endpoint: Paliperidone palmitate vs. RLAI Prior Ris only (mean (SD)), Prior other AP (mean (SD)), No prior AP (mean (SD)) PANSS total: -18.7 (13.7), -18.5 (17.3), -19.5 (12.8) vs. -18.3 (13.2), -17.6 (14.1), -17.5 (16.1) PANSS positive sx: -5.6 (4.8), -6.2 (5.8), -6.2 (4.5) vs. -5.8 (4.7), -5.7 (4.8), -5.9 (4.9) PANSS negative sx: -4.6 (3.8), -4.0 (5.2), -3.9 (3.8) vs. -4.0 (4.3), -4.2 (4.2), -3.6 (4.8) PANSS disorganized thought: -3.7 (3.6), -3.5 (4.4), -4.1 (3.6) vs. -4.0 (3.5), -3.4 (3.5), -3.0 (4.5) PANSS uncontrolled hostility/excitement: -1.9 (2.8), -1.9 (3.0), -1.9 (2.4) vs. -2.1 (2.4), -1.6 (3.0), -1.7 (3.1) PANSS anxiety/depression: -3.0 (2.5), -2.8 (3.3), -3.4 (2.8) vs. -2.4 (2.5), -2.6 (2.8), -3.4 (2.6) CGI-S: -1.0 (0.9), -1.0 (1.0), -1.1 (0.9) vs. -1.0 (0.9), -0.9 (0.9), -0.9 (0.9) PSP: 9.9 (10.5), 9.7 (11.8), 8.6 (10.7) vs. 9.9 (10.7), 9.2 (11.2), 10.5 (10.5)

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Adverse effects reported
Pandina 2011 Alphs, 2013 DB RCT Multicenter	(Paliperidone palmitate vs. Risperidone-LAI) Overall rate of TEAEs:57.9% vs 52.8% . Individual TEAEs: ≥2% of patients in either treatment group Insomnia: 9.4% vs 6.7% Injection site pain: 5.1%: 0.8% Anxiety: 4.3% vs 2.1% Constipation: 0.8% vs 3.1% Tx-emergent adverse events: Paliperidone vs. RLAI Prior Ris only n (%), Prior other AP n (%), No prior AP n (%) Subjects with >=1 AE: 68 (54.0), 122 (61.3), 31 (55.4) vs. 56 (52.3), 109 (53.7), 29 (51.8) Most common AEs (>= 5% in any group): Headache: 8 (6.3), 18 (9.0), 5 (8.9) vs. 6 (5.6), 19 (9.4), 3 (5.4) Insomnia: 13 (10.3), 25 (12.6), 4 (7.1) vs. 6 (5.6), 17 (8.4), 4 (7.1) Injection site pain: 9 (7.1), 6 (3.0), 6 (10.7) vs. 0, 2 (1.0), 0 Somnolence: 5 (4.0), 12 (6.0), 3 (5.4) vs. 6 (5.6), 7 (3.4), 1 (1.8) Akathisia: 5 (4.0), 13 (6.5), 3 (5.4) vs. 4 (3.7), 7 (3.4), 1 (1.8) Schizophrenia: 3 (2.4), 11 (5.5), 1 (1.8) vs. 2 (2.8), 7 (3.4), 2 (3.6) Salivary hypersecretion: 1 (0.8), 7 (3.5), 3 (5.4) vs. 3 (2.8), 0, 1 (1.8) Weight increased: 5 (4.0), 3 (1.5), 3 (5.4) vs. 2 (1.9), 4 (2.0), 3 (5.4) Nasopharyngitis: 2 (1.6), 5 (2.5), 2 (3.6) vs. 2 (1.9), 4 (2.0), 3 (5.4) Lethargy: 2 (1.6), 2 (1.0), 0 vs. 0, 0, 4 (7.1) Tremor: 0, 8 (4), 3 (5.4) vs. 2 (1.9), 5 (2.5), 0 Subjects w/ >= 1 prolactin-related AE: 2 (1.6), 6 (3.0), 2 (3.6) vs. 2 (1.9), 5 (2.5), 4 (7.1) Most common prolactin-related AEs (>= 1% in any group): Amenorrhea: 0, 2 (1.0), 1 (1.8) vs. 1 (0.9), 2 (1.0), 1 (1.8) Anorgasmia: 0, 1 (0.5), 0 vs. 0, 0, 1 (1.8) Erectile dysfunction: 1 (0.8), 0, 0 vs. 1 (0.9), 1 (0.5), 1 (1.8) Galactorrhea: 0, 0, 0 vs. 0, 0, 1 (1.8) Ejaculation delayed: 0, 0, 1 (1.8) vs. 0, 0, 0 Libido decreased: 1 (0.8), 2 (1.0), 0 vs. 0, 1 (0.5), 0 Subjects with >=1 glucose-related AE: 0, 1 (0.5), 0 vs. 0, 0, 0

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Extrapyramidal symptoms
Pandina 2011 Alphs, 2013 DB RCT Multicenter	Extrapyramidal effects: NR Paliperidone palmitate vs. RLAI Prior Ris only n (%), Prior other AP n(%), No prior AP n (%) Subjects w/ >=1 EPS-related AE: 10 (7.9), 31 (15.6), 9 (16.1) vs. 9 (8.4), 22 (10.8), 2 (3.6) Most common EPS-related AEs (>= 2% in any group): Akathisia: 5 (4.0), 13 (6.5), 3 (5.4) vs. 4 (3.7), 7 (3.4), 1 (1.8) Muscle rigidity: 2 (1.6), 3 (1.5), 1 (1.8) vs. 3 (2.8), 3 (1.5), 0 Muscle tightness: 0, 1 (0.5), 2 (3.6) vs. 0, 1 (0.5), 0 Musculoskeletal stiffness: 2 (1.6), 1 (0.5), 2 (3.6) vs. 1 (0.9), 0, 0 Tremor: 0, 8 (4.0), 3 (5.4) vs. 2 (1.9), 5 (2.5), 0 Parkinsonism: 0, 5 (2.5), 1 (1.8) vs. 0, 2 (1.0), 0

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Total withdrawals; withdrawals due to adverse events	Comments
Pandina 2011 Alphs, 2013 DB RCT Multicenter	Withdrawals due to adverse events: 30 Paliperidone palmitate vs. RLAI Prior Ris only n (%), Prior other AP n (%), No prior AP n (%) Discontinuations due to AEs: 1 (0.8), 5 (2.5), 0 vs. 0, 2 (1.0), 2 (3.6)	

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Author, year Study design	Eligibility criteria	Interventions (drug, dose, duration)	Allowed other medications	Age Gender Ethnicity	Other population characteristics
Perez-Iglesias, 2007 Spain Goes with Crespo-Facorro 2006	Men and women 15 to 50 ys, living in region, experiencing their first episode of psychosis (DSM-IV codes 295, 297, and 298), and never treated with antipsychotic medication.	Haloperidol = 4.2 mg/d, Olanzapine = 12.7 mg/d, Risperidone = 3.6 mg/d for 12 wkss	Lormetazepam and clonazepam permitted for management of agitation, general behavior disturbances, and/or insomnia; if clinically significant EPS occurred, anticholinergic medication (biperiden at dose of up to 8 mg/d) was allowed.	Haloperidol vs. Olanzapine vs. risperidone Age 28.6 yrs vs 28.5 yrs vs 26.9 yrs % male 62.5 vs 61 vs 59.6 Ethnicity 96% white	Haloperidol vs. Olanzapine vs. Risperidone % Schizophrenia 70 vs. 53.7 vs. 53.2 Schizophreniform disorder 20 vs. 24.4 vs. 21.3 Weight 68.29 vs. 66.39 vs 65.26 BMI 24.33 vs. 22.92 vs 22.2
Potkin 2011 DB RCT Single center	Schizophrenia, schizoaffective, males and females, 18–70.	Lurasidone = 120 mg. Max dose. Ziprasidone = 160 mg. Max dose. P Duration: 3 wks	Beta-blockers Benzodiazepines Zolpidem Eszopiclone.	Mean Age: 43 Male = 70% Ethnicity: White = 35% Black = 52% Other = 13%	Number of previous acute episodes • 0-2 = 9% • 3-5 = 26% • 6 or more = 66% Hospitalized in the last 2 ys = 39% Most frequently reported prior antipsychotic medication • Quetiapine = 25% • Risperidone = 18% • Olanzapine = 14% • Aripiprazole = 13%

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Perez-Iglesias, 2007 Spain Goes with Crespo-Facorro 2006	193/147/145	17/8/128	Haloperidol vs. Olanzapine vs. Risperidone Weight gain (kg) 3.83 (4.89) vs. 7.46 (5.11) vs 5.58 (4.48) Haloperidol vs. Olanzapine P = 0.004, all other NS BMI gain 1.36 (1.59) vs. 2.62 (1.78) vs 1.87 (1.47) Haloperidol vs. Olanzapine P = 0.008, all other NS For other results see Crespo-Facorro 2006
Potkin 2011 DB RCT Single center	520/307/307	16/21/301	PANSS total: (N LS mean change SD P-value) Lurasidone 120 mg 139 −4.9 10.6 0.145 Ziprasidone 160 mg 143 −2.9 15.5 PANSS positive symptoms: (N LS mean change SD P-value) Lurasidone 120 mg 139 −1.5 3.8 0.464 Ziprasidone 160 mg 143 −1.2 5.0 PANSS negative symptoms: Lurasidone 120 mg 139 −1.3 3.2 0.046 Ziprasidone 160 mg 143 −0.6 4.2 PANSS general psychopathology: Lurasidone 120 mg 139 −2.1 5.9 0.218 Ziprasidone 160 mg 143 −1.2 7.9 CGI-S: Lurasidone 120 mg 139 −0.1 0.6 0.905 Ziprasidone 160 mg 144 −0.1 0.7

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Author, year Study design	Adverse effects reported
Perez-Iglesias, 2007 Spain Goes with Crespo-Facorro 2006	See Crespo-Facorro 2006
Potkin 2011 DB RCT Single center	Adverse event, N (%) (Lurasidone vs. Ziprasidone) Arthralgia: 0 (0) vs. 3 (2.0) Insomnia: 16 (10.7) vs. 14 (9.3) Vomiting: 12 (8.0) vs. 6 (4.0) Nausea: 11 (7.3) vs. 7 (4.6) Headache: 10 (6.7) vs7 (4.6) Somnolence: 10 (6.7) vs. 15 (9.9) Anxiety: 7 (4.7) vs5 (3.3) Sedation :7 (4.7) vs17 (11.3) Dry mouth: 6 (4.0) vs4 (2.6) Fatigue: 5 (3.3) vs. 6 (4.0) Dizziness: 4 (2.7) vs. 10 (6.6) Nasopharyngitis: 4 (2.7) vs. 3 (2.0) Restlessness: 4 (2.7) vs. 2 (1.3) Schizophrenia: 4 (2.7) vs. 3 (2.0) Constipation: 3 (2.0) vs. 3 (2.0) Cough: 3 (2.0) vs. 3 (2.0) Psychotic disorder: 3 (2.0) vs. 3 (2.0) Diarrhea: 2 (1.3) vs5 (3.3) Vision blurred: 0 (0) vs. 3 (2.0) Patients with at least one AE: 85 (56.7) vs. 99 (65.6) Proportion of AEs rated as severe: 10 (6.7) vs. 11 (7.3)

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Author, year Study design	Extrapyramidal symptoms
Perez-Iglesias, 2007 Spain Goes with Crespo-Facorro 2006	See Crespo-Facorro 2006
Potkin 2011 DB RCT Single center	Extrapyramidal effects: N (%) (Lurasidone vs Ziprasidone) Akathisia: 5 (3.3) vs 10 (6.6) Extrapyramidal disorder: 5 (3.3) vs 2 (1.3) Muscle spasm: 1 (0.7) vs 3 (2.0) Tremor: 0 (0) vs 4 (2.6)

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Author, year Study design	Total withdrawals; withdrawals due to adverse events	Comments
Perez-Iglesias, 2007 Spain Goes with Crespo-Facorro 2006		Goes with Crespo-Facorro 2006
Potkin 2011 DB RCT Single center	Withdrawals due to adverse events: N=33	

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Eligibility criteria	Interventions (drug, dose, duration)	Allowed other medications	Age Gender Ethnicity	Other population characteristics
Potkin 2007 DB RCT 21 sites United States Inpatient for first 3 wks	More than 18 yrs old with schizophrenia CGI-S of 4 or more, PANSS 60 or more, 2 items on PANSS-P of 4 or more.	Asenapine 5 mg bid it n= 58 Risperidone 3 mg bid it n=56 P it n=60 6 wks	Yes- zolpidem, zaleplon, chloral hydrate, benzodiazepines, lorazepam, anticholinergic agents	Asenapine vs. P vs. risperidone Age 38 vs. 42 vs. 43 % men 78 vs. 79 vs. 61 % White 42 vs. 32 vs. 42 % Black 47 vs. 52 vs. 44 % Other 10 vs. 16 vs. 14	Asenapine vs. P vs. risperidone Type of schizophrenia Paranoid 85% vs. 97% vs. 85% Disorganized 2% 0 vs. 5% Undifferentiated 12% vs. 2% vs. 7% Not specified or obtained 2% vs. 2% vs. 3% Baseline PANSS 96.5 vs. 92.4 vs. 92.2
Potkin, 2003b DB, RCT, P-controlled, parallel, multicenter Inpatients	Acute, psychosis in patients diagnosed with schizophrenia and schizoaffective disorder Exclusion criteria: psychiatric disorder other than schizophrenia, schizoaffective disorder requiring pharmacotherapy, history of violence, recent history of suicide ideation/attempts, clinically significant neurological abnormality other than tardive dyskinesia or EPS, current diagnosis of psychoactive substance dependence, history of alcohol/drug abuse, treatment with an investigational study drug within 4 wks before washout, acute/unstable medical condition	aripiprazole: 20 mg/d:(N=101) aripiprazole: 30 mg/d:(N=101) risperidone: 6 mg/d:(N=99) P:(N=103)	NR	Mean age: 38.9 ys 70% Male Ethnicity NR	100% inpatient

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Number screened/ eligible/ enrolled	Withdrawn/ Lost to follow-up/ Analyzed	Results
Potkin 2007 DB RCT 21 sites United States Inpatient for first 3 wks	NR / NR / NR	107 / NR / 180	Asenapine vs. P vs. risperidone Mean changes from baseline PANSS -15.9 vs. -5.3 vs. -10.9 Asenapine vs. P P < 0.005, risperidone vs. P P = NS CGI-S -0.74 vs. -0.28 vs. -0.75 Asenapine or risperidone vs. P P < 0.01. risperidone vs. P P < 0.005 PANSS-P -5.5 vs. -2.5 vs. -5.1 Asenapine vs. P P = 0.01. risperidone vs. P P < 0.05 PANSS-N -3.2 vs. -0.6 vs. -1.05 Asenapine vs. P P = 0.01, risperidone vs. P P = NS
Potkin, 2003b DB, RCT, P-controlled, parallel, multicenter Inpatients	NR/NR/404	162/0/242	PANSS score: P-value=drug vs P Total: A20: -14.5 (p=.001) vs A30: -13.9 (p=.003) vs R6: -15.7 (p<.001) vs P: -5.0 BPRS score: A20: -3.5 (p=.004) vs A30: -3.3 (p=.01) vs R6: -3.9 (p<.001) vs P: -1.7 CGI-score: A20: -0.2 (p=.03) vs A30: -0.6 (p=.006) vs R6: -0.7 (p<.001) vs P: -0.2 Body weight: Mean increase in body weight from baseline to endpoint: A20: 1.2 kg vs A30: 0.8 kg vs R6: 1.5 kg vs P: -0.3 kg Serum Prolactin Levels: Mean changes in serum prolactin levels from baseline to endpoint: A20: -6.6 ng/mL vs A30: -6.4 ng/mL vs R6: 47.9 ng/mL vs P: 0.1 ng/mL

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Author, year Study design	Adverse effects reported
Potkin 2007 DB RCT 21 sites United States Inpatient for first 3 wks	Asenapine vs. P vs. risperidone % Experienced one or more AEs 83 vs. 79 vs. 90 Insomnia 19 vs. 13 vs. 22 Somnolence19 vs. 13 vs. 15 Nausea 19 vs. 13 vs. 12 Anxiety 17 vs. 15 vs. 15 Agitation 15 vs. 24 vs. 19 Headache 14 vs. 27 vs. 22 Vomiting 14 vs. 11 vs. 5 Constipation 10 vs. 10 vs. 7 Psychosis 10 vs. 6 vs. 7 Dizziness 8 vs. 15 vs. 7 Dyspepsia 7 vs. 8 vs. 12 URTI 7 vs. 5 vs. 10 Pain 5 vs. 6 vs. 10 Fatigue 3 vs. 6 vs. 10 Hypertonia 0 vs. 3 vs. 12 Greater than 7% weight gain 4.3 vs. 1.9 vs. 17.0
Potkin, 2003b DB, RCT, P-controlled, parallel, multicenter Inpatients	Whole body: A20: 58% vs A30: 61% vs R6:53% vs P: 59% CV system: A20: 1% vs A30: 7% vs R6: 15% vs P: 1% Digestive System: A20: 65% vs A30: 52% vs R6: 66% vs P: 53% Musculoskeletal System: A20: 6% vs A30: 6% vs R6: 7% vs P: 5% Respiratory System: A20: 9% vs A30: 17% vs R6: 22% vs P: 8% Skin and appendages: A20: 7% vs A30: 11% vs R6: 8% vs P: 7% Blurred vision: A20: 3% vs A30: 5% vs R6: 8% vs P: 1% Urogenital System: A20: 1% vs A30: 4% vs R6: 1% vs P: 3%

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Extrapyramidal symptoms
Potkin 2007 DB RCT 21 sites United States Inpatient for first 3 wks	Asenapine vs. P vs. risperidone Mean change from baseline BAS -0.21 vs. 0.25 vs. 0.14 SAS -0.32 vs. -0.24 vs. 0.05 AIMS 0.04 vs. 0.46 vs. -0.02
Potkin, 2003b DB, RCT, P-controlled, parallel, multicenter Inpatients	Incidence of EPS-related AEs: A20: 32 vs A30: 31% vs R6: 31% vs p: 20% Mean change in Simpson-Angus Scale scores from baseline to endpoint: A20: -0.16 vs A30: -0.09 vs R6: -0.18 vs p: -0.29 Mean change in Barnes Akathisia Rating Scale Global Scores from baseline to endpoint: A20: 0.15 vs A30: 0.18 vs R6: 0.14 vs P: 0.11 Mean change in Abnormal Involuntary Movement Scale scores from baseline to endpoint: A20: -0.27 vs A30: -0.5 vs R6: -0.6 (p=.03 against p) vs p: 0.1

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Total withdrawals; withdrawals due to adverse events	Comments
Potkin 2007 DB RCT 21 sites United States Inpatient for first 3 wks	Asenapine vs.p vs. risperidone 107 (59%) (54% vs. 58% vs. 66%) WD 17 (9.4%) (10.2% vs. 6.8% vs. 11.3%) due to AEs	
Potkin, 2003b DB, RCT, P-controlled, parallel, multicenter Inpatients	162 total WD 44 due to AEs	

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Eligibility criteria	Interventions (drug, dose, duration)	Allowed other medications	Age Gender Ethnicity	Other population characteristics
Potkin, 2006 DB, RCT Rupnow 2007	18-64 ys of age; DSM-IV diagnosis of schizophrenia (paranoid, disorganized, or undifferentiated type) or schizoaffective disorder confirmed by M.I.N.I.-Plus; experiencing acute exacerbation of their illness of recent onset (within 4 wks) with prominent troublesome symptoms requiring hospitalization; score >/= 4 on at least two of the following items on the PANSS: Hostility, Excitement, Tension, Uncooperativeness, and Poor Impulse Control, and a total score on these 5 items >/= 17 Exclusion criteria: any Axis I diagnosis, except abuse/dependence disorders; an Axis II diagnosis of MR or borderline personality disorder; treatment-resistant schizophrenia; imminent risk for self harm; having received a depot antipsychotic within one dosing cycle prior to baseline; having received risperidone or quetiapine within 7 ds prior to baseline; known allergy or sensitivity to either drugs; evidence of a clinically significant or unstable disease, including a thyroid disorder not stabilized for at least 3 mos	Risperidone (n=153): titrated from 1 mg/d to target dose 4 mg/d (</= 70 kg) or 6 mg/d (> 70 kg) by d 5. Quetiapine (n=156): titrated from 50 mg/d to target dose of 400 mg/d (</= 70 kg) or 600 mg/d (>70 kg). P (n=73). After d 5, patients maintained on same dose except that investigators were able to increase dose of quetiapine to 600 mg/d (</= 70 kg) or 800 mg/d (>70 kg) on d 8. Mean (SD) doses at the additive therapy baseline: Risperidone: 4.7 (0.9) mg/d Quetiapine: 579.0 (128.9) mg/d	Use of other psychotropic medications prohibited during monotherapy phase (ds 1-14); however, short-acting, non-benzodiazepine hypnotics (e.g., zolpidem, zaleplon, zopiclone) for treating insomnia, and injectable lorazepam, sodium Amytal, or midazolam for treating agitation or restlessness permitted as needed. After d 14, investigator could prescribe any psychotropic medication deemed necessary, except specifically prohibited medications (drugs known to interact with the cytochrome P450 isoenzymes CYP2D6 and CYP3A4, and drugs with potential thyroid toxicity); benztropine mesylate or equivalent treatment for movement disorders permitted as needed	risperidone vs. quetiapine vs. P Mean age (SD): 34.7 (9.6) vs. 34.2 (9.8) vs. 36.1 (9.8) % male: 69% vs. 64% vs. 63% % white: 26% vs. 25% vs. 23% % Hispanic: 0.65% vs. 2% vs. 1% % Black: 14% vs. 13% vs. 15% % Asian: 59% vs. 60% vs. 60% Other: 0 vs. 0.64% vs. 0	risperidone vs. quetiapine vs. P Schizophrenia: 92% vs. 93% vs. 90% Schizoaffective disorder: 8% vs. 7% vs. 10% ds since onset of symptoms Mean (SD): 15.3 (6.6) vs. 15.6 (7.0) vs. 16.6 (6.9) Mean PANSS scores: Total: 95.0 (18.0) vs. 97.3 (19.1) vs. 94.3 (18.2) Total of 5 items for inclusion: 20.6 (2.7) vs. 20.7 (2.7) vs. 20.9 (2.6) Mean CGI-S: 5.4 (0.5) vs. 5.4 (0.5) vs. 5.4 (0.6)

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Author, year Study design	Number screened/ eligible/ enrolled	Withdrawn/ Lost to follow-up/ Analyzed	Results
Potkin, 2006 DB, RCT Rupnow 2007	400/382/382	Monotherapy phase (ds 1-14) ITT population: 379 Safety population: 382	Monotherapy Phase Endpoint risperidone vs. quetiapine vs. P (p-values risperidone vs. quetiapine): PANSS Total: -27.7 (1.5) vs. -20.5 (1.5) vs. -20.2 (2.0) ; P<0.01 Total of 5 items for inclusion: -9.4 (0.4) vs. -7.8 (0.4) vs. -6.9 (0.6); P<0.01 >/= 30% improvement [number (%) of subjects achieving this level of improvement: 76 (50%) vs. 56 (36%) vs. 26 (37%); P<0.01 PANSS-Marder Factors (LS mean change from baseline value): Positive symptoms: -8.7 (0.5) vs. -5.9 (0.5) vs. -5.3 (0.7); P<0.01 Negative symptoms: -4.0 (0.4) vs. -2.5 (0.4) vs. -3.5 (0.6); P<0.01 Disorganized thoughts: -4.1 (0.4) vs. -2.6 (0.4) vs. -3.0 (0.5); P<0.01 Hostility/excitement: -7.9 (0.4) vs. -6.5 (0.3) vs. -5.9 (0.5); P<0.01 Anxiety/depression: -3.1 (0.2) vs. -2.8 (0.2) vs. -2.6 (0.3) CGI: Mean change CGI-S: -1.8 (0.1) vs. -1.3 (0.1) vs. -1.1 (0.1); P<0.01 Mean (SE) CGI-C: 2.4 (0.1) vs. 2.9 (0.1) vs. 2.9 (0.1); P<0.01 Responders: 68 (45%) vs. 43 (28%) vs. 17 (24%); P<0.01 HAM-D-17: -5.6 (0.4) vs. -5.0 (0.4) vs. -4.4 (0.5); P=NR MSQ, mean (S.E.): 5.2 (0.1) vs. 4.7 (0.1) vs. 4.5 (0.2); P<0.01 RDQ yes: 84 (56%) vs. 59 (38%) vs. 22 (32%); P<0.01 Results from the 28 d additive therapy phase: Risperidone vs Quetiapine (Rupnow 2007) Mean (SD) change in PANSS total score: -34.5 (1.6) vs -30.9 (1.6), p=NS % with ≥30% improvement: 68% vs 62%, p=NS Mean(SD) change in CGI severity: -2.3 (0.1) vs -2.0 (0.1), p<0.05 Additional psychotropics received: 36% vs 53%, p<0.001 Antipsychotics: 33% vs 53% (risperidone vs quetiapine vs P p<0.01) Antidepressants: 5% vs 1% mood stabilizers: 2% vs 2% RR quetiapine vs risperidone of antipsychotic polypharmacy: 1.90 (p=0.001; 95% CI 1.29-2.80)

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Adverse effects reported
Potkin, 2006 DB, RCT	Monotherapy Phase (risperidone vs. quetiapine vs. P):
Rupnow 2007	At least one TEAE: 100 (65%) vs. 97 (62%) vs. 44 (60%) Insomnia: 29 (19%) vs. 22 (14%) vs. 17 (23%) Headache: 22 (14%) vs. 18 (12%) vs. 10 (14%) Sedation: 10 (7%) vs. 15 (10%) vs. 5 (7%) Somnolence: 4 (3%) vs, 16 (10%) vs. 2 (3%) Dizziness: 9 (6%) vs. 16 (10%) vs. 3 (4%) Cogwheel rigidity: 11 (7%) vs. 5 (3%) vs. 1 (1%) Akathisia: 11 (7%) vs. 1 (<1%) vs. 1 (1%) Constipation: 8 (5%) vs. 14 (9%) vs. 2 (3%) AE from the 28 d additive therapy phase: Risperidone vs Quetiapine (Rupnow 2007) Headache: 6% vs 4% Cogwheel rigidity: 5% vs 3% weight gain: 5% vs 3% tremor: 5% vs 4%

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Author, year Study design	Extrapyramidal symptoms
Potkin, 2006 DB, RCT	Monotherapy Phase (risperidone vs. quetiapine vs. p):
Rupnow 2007	AIMS total score (mean change from baseline): 0.3 (0.2) vs. -0.1 (0.2) vs. -0.1 (0.3) SAS total score (mean change from baseline): 0.8 (0.2) vs. -0.1 (0.2) vs. -0.1 (0.3); P<0.01 BAS-Global Severity of Akathisia, Change from baseline [N (%)]: Worsened: 22 (15) vs. 10 (7%) vs. 5 (8%) Unchanged: 114 (78%) vs. 115 (79%) vs. 51 (77%) Improved: 10 (7%) vs. 20 (14%) vs. 10 (15%)

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Total withdrawals; withdrawals due to adverse events	Comments
Potkin, 2006 DB, RCT Rupnow 2007	Risperidone vs. quetiapine vs. p 14 vs. 24 vs. 13 WD due to AEs NR for monotherapy phase (ds 1-14)	All results are for monotherapy phase (2 wks), not additive therapy phase, per Sujata's instructions.

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Eligibility criteria	Interventions (drug, dose, duration)	Allowed other medications	Age Gender Ethnicity	Other population characteristics
Purdon, 2000 David, 1999 Jones, 1998 DB, RCT, multicenter (Canada)	Schizophrenia; 'early phase'–first 5 ys of illness, PANSS < 90	Olanzapine: 5–20 mg/d; Risperidone: 4–10 mg/d; Haloperidol: 5–20 mg/d; Duration: 54 wks.	No other antipsychotics, but other meds allowed as needed	Mean age: 29 ys 71% male Ethnicity NR	Mean duration of disease 2.63 PANSS total: NR

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Number screened/ eligible/ enrolled	Withdrawn/ Lost to follow-up/ Analyzed	Results
Purdon, 2000 David, 1999 Jones, 1998 DB, RCT, multicenter (Canada)	NR/NR/65 olanzapine = 21 risperidone = 21 haloperidol = 23	37/NR/65 for symptoms, 55 for neurocognitive outcomes	Olanzapine/risperidone (p-value) Symptoms: Mean change PANSS total: NR Mean change PANSS positive:-2.14/-1.19 (0.72) Mean change PANSS negative: -2.76/-0.67 (0.72) Mean change PANSS gen psychopathology: -2.52/-1.33 (0.92) NR: QOL, resource utilization Cognitive outcomes: Cognitive Domains: olanzapine superior to risperidone on 2 of 6 domains: Motor skills: mean change o/r (p-value) 0.90/0.08 (p=0.04) Nonverbal fluency and construction: 0.81/-0.09 (p=0.006) Individual measures: olanzapine superior on 4 of 18 (grooved pegboard, verbal list learning, Hooper visual organization test, Rey-Taylor complex figure copy) General Cognitive Index: Comparison of change from baseline to wk 54: olanzapine superior to risperidone (data NR) p=0.004 Within group changes significant at: olanzapine: wk 6, 30 and 54 risperidone: wk 54

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Author, year Study design	Adverse effects reported
Purdon, 2000 David, 1999 Jones, 1998 DB, RCT, multicenter (Canada)	ESRS: olanzapine/risperidone (p-value) Total score NR Parkinsonism: -1.43/+1.33 (p=0.14) Dystonia: -0.05/-0.14 (p=0.91) Dyskinesia: -0.57/+0.19 (p=0.12) Receiving EPS meds within 48hrs of last visit: olanzapine: 3/20 (15%), risperidone: 9/20 (45%)

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Author, year Study design	Extrapyramidal symptoms
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Author, year Study design	Total withdrawals; withdrawals due to adverse events	Comments
Purdon, 2000 David, 1999 Jones, 1998 DB, RCT, multicenter (Canada)	Overall 37 (57%) olanzapine: 43% risperidone: 67% haloperidol 61% Due to AEs:12 (18%) olanzapine: 2 (9.5%) risperidone 3 (14%) haloperidol 7 (30%)	Analysis of effect of Anti-EPS meds on cognitive outcomes revealed one domain where significant effects were apparent at 6 and 54 wks (immediate recall).

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Eligibility criteria	Interventions (drug, dose, duration)	Allowed other medications	Age Gender Ethnicity	Other population characteristics
QUEST; Mullen, 2001	Psychosis and: schizophrenia, schizoaffective disorder, bipolar disorder, major depressive disorder (MDD), delusional disorder, Alzheimer's Disease, schizophreniform disorder, vascular dementia, or substance abuse dementia	Quetiapine 50-800 mg/d in divided doses (maximum mean dose=329 mg/d) Risperidone 1-3 mg/d in divided doses (maximum mean dose=5 mg/d at d 64, and 4.65 by d 112)	Any mood stabilizers or antidepressants prescribed must have been at a stable dose for at least 2 wks before randomization	Mean age=45.4 51.1% male 73.1% white 16.7% black 5.9% Hispanic 2.7% Asian 1.5% other	DSM-IV diagnosis Schizophrenia: 32.5% Schizoaffective disorder: 29.5% Bipolar I disorder: 13.3% Major depressive disorder: 10.4% Delusional disorder: 1.9% Alzheimer's dementia: 1.4% Schizophreniform disorder: 0.9% Other medical dementia: 0.7% Vascular dementia: 0.1% Substance abuse dementia: 0.1% Other: 7% Age at first diagnosis: 28.6 Psychiatric hospitalizations in last 4 mos: 0.3 Duration of current symptoms: 163 wks Use of illicit drugs Past use: 32.2% Current use: 4.1% Current alcohol problem: 6.2% Previous alcohol problem: 30.4%
Reinstein, 1999 (QUEST subgroup)	Psychosis and: schizophrenia, schizoaffective disorder, bipolar disorder, major depressive disorder (MDD), delusional disorder, Alzheimer's Disease, schizophreniform disorder, vascular dementia, or substance abuse dementia.	Quetiapine: flexible (mean 253.9 mg/d); oral Risperidone: flexible (mean 4.4 mg/d); oral Duration: 4 mos	NR	NR	adult outpatients with psychotic disorders

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Number screened/ eligible/ enrolled	Withdrawn/ Lost to follow-up/ Analyzed	Results
QUEST; Mullen, 2001	NR/NR/728	32.2% withdrawn/lost to fu NR/analyzed varied by outcome	Quetiapine, risperidone, p-value WD due to lack of efficacy: 57 (10.3%), 10 (5.8%) Mean changes: PANSS positive score: -3.2 vs -2.5, p=NS PANSS negative score: -3.1 vs -2.8, p=NS PANSS total score: -13 vs -11.8, p=NS HAM-D: -5.4 vs -4.0, p=0.028 CGI-I: quetiapine=risperidone (logistic regression model adjusting for differences in baseline EPS, diagnoses, age, and age at diagnosis p=0.087
Reinstein, 1999 (QUEST subgroup)	NR/NR/751	NR	CGI; PANSS; DAI-10 Both groups had improvements in all efficacy measures (NS). Higher percentage from quetiapine group had improvement in the CGI at each visit compared with risperidone group HAM-D: Quetiapine group had significantly greater improvement than risperidone group (p= 0.028)

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Adverse effects reported
QUEST; Mullen, 2001	Deaths: 0 vs 4 (2.3%) Any event 400 (72.3%), 107 (61.1%), NS Somnolence: 173 (31.3%), 27 (15.4%), p<0.05 Dry mouth: 80 (14.5%), 12 (6.9%), p<0.05 Dizziness: 70 (12.7%), 12 (6.9%), p<0.05 Insomnia: 65 (11.8%), 17 (9.7%), NS Headache: 52 (9.4%), 11 (6.3%), NS Agitation: 34 (6.1%), 3 (1.7%), p<0.05 WDs due to Dry mouth: 2 (0.4%), 1 (0.6%) Dizziness: 6 (1.1%), 0 Weight gain: 14 (2.5%), 6 (3.4%), p-value nr Weight loss: 4 (0.7%), 0
Reinstein, 1999 (QUEST subgroup)	NR

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Extrapyramidal symptoms
QUEST; Mullen, 2001	Quetiapine, risperidone Patients reporting EPS at LOCF: 38.6%, 39.2%, logistic regression model of the presence of any EPS in mos 1-4 showed odds of a risperidone-treated patient having any EPS event were 1.33 times the odds of a quetiapine-treated patient having any EPS event, p=NS At least moderate EPS during trial: 161 (29.8%), 70 (40.9%); 1.94 times the odds for risperidone, p=0.003 Substantial EPS: 38 (7%), 35 (20.5%); 3.5 time the odds for risperidone, p<0.001 Anti-EPS medication use in patients with baseline EPS: 93/293 (31.7%), 47/91 (51.6%), p<0.001
Reinstein, 1999 (QUEST subgroup)	EPS checklist: extrapyramidal events in both groups declined over treatment period, with no significant differences between groups in overall occurrence; risperidone group more likely to have extrapyramidal event and more likely (p < 0.001) to be one requiring adjustment of study medication or adjunctive medication than quetiapine group

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Total withdrawals; withdrawals due to adverse events	Comments
QUEST; Mullen, 2001	WD: 176 (31.8%), 59 (33.7%)WD due to AE: 48 (8.7%), 9 (5.1%)	
Reinstein, 1999 (QUEST subgroup)	NR / NR	

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Eligibility criteria	Interventions (drug, dose, duration)	Allowed other medications	Age Gender Ethnicity	Other population characteristics
Ritchie, 2003 Ritchie, 2010 Pragmatic RCT, multicenter (Australia)	Patients > 60 with schizophrenia taking typical antipsychotics (depot or oral).	Starting dose: Olanzapine 5mg/d; 10mg after washout complete mean dose after switch: 9.9mg Risperidone 0.5mg/d, 1mg after washout complete mean dose after switch: 1.7mg Doses titrated by unblinded clinicians Duration: "Completion of switch"; stable dose of atypical and not on typical for 2 consecutive visits. Visit schedule = 14 ds for those previously on oral neuroleptics, and "dose cycle: for depot drugs	NR	Mean age 70 19% male Ethnicity NR	Mean chlorpromazine equivalents Depot 326mg Oral 273mg 48.5% had TD at baseline Mean non-psychotropic drugs: 2.0/patient Mean major physical ailments: 1.2/patient Mean major surgical procedures (lifetime): 0.4

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Number screened/ eligible/ enrolled	Withdrawn/ Lost to follow-up/ Analyzed	Results
Ritchie, 2003 Ritchie, 2010 Pragmatic RCT, multicenter (Australia)	80/74/66 olanzapine: 34 risperidone: 32	14/0/61	Successful Switch: Crude OR 2.7(95% CI 0.7 to 10.2)* *Not based on an ITT population Recalculated crude RR based on ITT: O vs R 1.28 (95% CI 0.99 1.74) Mean time to complete switch: olanzapine 40.6 ds risperidone 40.4 ds Symptoms: NS difference between groups on change in BPRS, SANS, MADRS SS improvement within groups on BPRS, SANS, MADRS QOL: Olanzapine: within group SS change on physical, psychological well-being and health satisfaction Risperidone: within group changes NS O vs R: SS difference on change in psychological well-being score (p=0.002) (ANCOVA analysis) Cox regression estimate of the rate or progression to cessation of (a) originally radomized medication in patients assigned to olanzapine or risperidone and (b) in patients treated with oral medication over acute study phase: Adjusted OR (95% CI), P (a) Medication group Risperidone: 2.55 (0.91, 7.14), 0.075 (b) Pre-randomization Medication route Depot: 2.63 (0.97, 7.13), 0.057 Cox regression estimate of the rate of progression to cessation of (a) in patients treated with oral medication or depot, (b) originally randomized medication in patients assigned to olanzapine or risperidone, and compared to (c) baseline BPRS Adjusted OR (95% CI), P (a) Medication group Risperidone: 1.73 (0.79, 3.80), 0.170 (b) Pre-randomization Medication route Depot: 2.19 (0.99, 4.86), 0.054 (c) Baseline BPRS: 1.02 (0.99, 1.06), 0.210

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Adverse effects reported
Ritchie, 2003 Ritchie, 2010 Pragmatic RCT, multicenter (Australia)	SAS and BARS: SS change from baseline (reduction) in both groups NS difference between groups AIMS: SS change from baseline in olanzapine group, not in risperidone group; NS difference between groups Other: Sedation and hypotension/dizziness > olanzapine (NS) GI symptoms > risperidone (NS) Changes in libido (increases) > olanzapine (NS) Weight gain: SS within groups mean increase: olanzapine 2.8kg, risperidone 2.1kg (NS)

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Extrapyramidal symptoms
Ritchie, 2003 Ritchie, 2010 Pragmatic RCT, multicenter (Australia)	SAS and BARS: SS change from baseline (reduction) in both groups NS difference between groups AIMS: SS change from baseline in olanzapine group, not in risperidone group; NS difference between groups

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Total withdrawals; withdrawals due to adverse events	Comments
Ritchie, 2003	14 (21%) total WD	Not ITT.
Ritchie, 2010 Pragmatic RCT, multicenter (Australia)	3 (in risperidone arm = 9%) due to AEs	Only switch data presented, 6-mo and 1 y FU data to come.

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Eligibility criteria	Interventions (drug, dose, duration)	Allowed other medications	Age Gender Ethnicity	Other population characteristics
Ritchie, 2006 Open-label x 6 mos, multicenter (Australia)	> 60 ys of age, previously treated with a typical antipsychotic drug for schizophrenia, imperfect symptom control or troublesome side effects on the typical drug and have had to complete cross-over Richie, 2003 study.	O: (n = 34), [30 pts had successfully switched from a typical antipsychotic] R: (n = 32) [22 had successfully switched from a typical antipsychotic]	Concomitant medications were permitted throughout the trial, except for additional antipsychotic agents.	Mean age: O: 69.7 ± 7.3 R: 69.4 ± 5.0 p=0.973 Gender (%) male: O: 10 (29.4%) R: 8 (29.6%) % unmarried: O 28 (82.4%) R: 20 (74.1%)	"No clinical or demographic differences between the groups"

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Number screened/ eligible/ enrolled	Withdrawn/ Lost to follow-up/ Analyzed	Results
Ritchie, 2006 Open-label x 6 mos, multicenter (Australia)	NA/NA/61	8/0/61	BPRS Overall, between BL and 6 mo follow-up: O: p=0.001; R: p= 0.044 Between end of crossover and 6-mo follow-up: O: p=0.329; R: p=0.511 Group differences at 6-mo follow-up (ANCOVA); p=0.303 SANS Between BL and 6 mo follow-up: O: p= 0.002; R: p= 0.030 Between end of crossover and 6 mo follow-up: O: p=0.159; R: p=0.194 Group differences at 6 mo follow-up (ANCOVA): p= 0.212 MADRS Between BL and 6 mo follow-up: O: p=0.008; R: 0.p=114 Between end of crossover and 6 mo follow-up: O: p=0.549; R: p=0.156 Group differences at 6 mo follow-up (ANCOVA): p=0.402 WHO-QOL: O: (n=29); R (n=21) (adjusted mean group differences on 6 mo domains after co-varying for BL QOL. All effects favored Olanzapine Physical: p=0.034; Psychological: p=0.100 (NS) Social: p=0.015 Environmental: p=0.643 (NS) Overall QOL: p=0.040 Health Satisfaction p=0.031

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Adverse effects reported
Ritchie, 2006 Open-label x 6 mos, multicenter (Australia)	Weight gain between BL and 6 mo: O (n=34) gained an average of 4.3 kg (SD =4.6, median=3.0kg) vs. R: (n=27) average gain 1.7kg (SD=4.7; median 1.0kg) (difference p=NS) Between BL and 6 mo: O 24/34 (70.6%) gained mean increase 7.3 kg; median 6.0kg vs. R 14/27 (51.9%) gained mean increase =4.6kg; median =4.0 kg) (difference p=NS) MMSE scores stable (between BL and 6 mo follow-up) (mean difference, p=NS) AE occurring > 5%: O vs. R GI: 14 vs. 7 CNS: 9 vs. 4 Musculoskeletal 6 vs. 3 Psychiatric: 7 vs. 5 -- not captured specifically in study rating scales. Infection 8 vs. 6 CVS: 7 vs. 10 Renal: 0 vs. 5 Dermatological: 3 vs. 3 Endocrine: 6 vs. 0 Total AE: 61 vs. 36--"no significant differences observed between the two groups"

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Extrapyramidal symptoms
Ritchie, 2006 Open-label x 6 mos, multicenter (Australia)	AIMS At 6-mo after adjusting for BL: NS Overall, between BL and 6 mo follow-up: O: (p=0.054); R (p=0.964) Between end of crossover and 6-mo follow-up: O: (p=0.622); R: (p=0.055), Group differences at 6-mo follow-up (ANCOVA); p=0.190 SAS: Between BL and 6-mo followup: O: p=0.001; R: p<0.001 Between end of crossover and 6 mo follow-up: O: p=0.273; R: p=0.249 Between-group differences at 6 mos after controlling for BL scores; p=0.647 Akathisia: 6 mo: (R: n=9, 33.3%; O n=10, 29.4%)-experienced some degree of post-baseline akathisia (mostly mild/moderate in degree). Of the 19, 9 (O=6, 17.6%; R n=3, 11.1%) were new cases who had not experienced akathisia at baseline. NS

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Total withdrawals; withdrawals due to adverse events	Comments
Ritchie, 2006 Open-label x 6 mos, multicenter (Australia)	26 (O: 9 (26.5%); R 15 (46.9%) p=0.09 (NS)/6 (2 in the o arm and 4 in the R arm. In the O group, there were 61 Total AE (1.79 per patient) vs. 36 in the R group (1.33 per patient)	Unable to recruit target population of 80 patients...post-hoc power calculation --N was sufficient for analysis.

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Eligibility criteria	Interventions (drug, dose, duration)	Allowed other medications	Age Gender Ethnicity	Other population characteristics
Robinson, 2006 (Companion paper to Lieberman 2003, Green 2004, Perkins 2004) Sevy, 2011 USA- NY	Current diagnosis of DSMIV schizophrenia, schizophreniform disorder, or schizoaffective disorder; age 16 to 40; < 12 wkss of lifetime antipsychotic medication treatment; current positive symptoms or current negative symptoms; for women, a negative pregnancy test and agreement to use a medically accepted method of birth control Exclusion- meeting DSM-IV criteria for a current substance induced psychotic disorder, psychotic disorder due to a general medical condition, or mental retardation; medical condition/ treatment known to affect the brain; any medical condition requiring treatment with a medication with psychotropic effects; medical contraindications to treatment with olanzapine or risperidone; significant risk of suicidal or homicidal behavior.	olanzapine (2.5–20 mg/d) risperidone (1–6 mg/d). 4 mos	Benztropine for extrapyramidal symptoms and lorazepam or propranolol for akathisia.	Mean age 23.3 ys Male 70% "diverse ethnic backgrounds" no specifics reported	Onset of psychotic symptoms=slightly over 2 ys Antipsychotic medication naïve (% patients)=78% Diagnosis (% patients): Schizophrenia=75% Schizophreniform disorder=17% Schizoaffective disorder=8%
Robles, 2011 Spain	12-18 years; First episode psychosis diagnosed using the Kiddie-Sads-Present and Lifetime Version	Quetiapine: n, 24; mean dosage, 532.8mg/d; mean duration, 143.75±68 days Olanzapine: n, 26; mean dosage, 9.7mg/d; mean duration, 144.1±62.5 days study durartion=6 mo	Prior to Randomization, all patients: Risperidone 2-6mg for 3-5 days for stabilization. Adjunctive pharmacological treatments were allowed, but other antipsychotic medications were not allowed.	Age, mean years: 16 Gender: 22.4% female Ethnicity: 81.6% caucasian	Diagnosis: 32.7% Schizophrenia, 26.5% Bipolar disorder, 40.8% Other psychoses Time since first psychotic symptom: delusions, 5 months; hallucinations, 3 months Naïve to antipsychotics: 77.6% IQ, mean: 78.85

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Number screened/ eligible/ enrolled	Withdrawn/ Lost to follow-up/ Analyzed	Results
Robinson, 2006 (Companion paper to Lieberman 2003, Green 2004, Perkins 2004) Sevy, 2011 USA- NY	474/120/120	23/8/112	Response rates olanzapine (43.7%, 95% CI=28.8%–58.6%) and risperidone (54.3%, 95% CI=39.9%–68.7%). Response rates did ot differ between tx groups (survivial analysis): response rates @ 16 wks olanzapine (45%, 95% CI: 25-65%) and risperidone (54%, 95% CI: 29-79%); NSD (P=0.68) Comparison of baseline and 16 week positive and negative sx (Olanzapine vs. Risperidone): Olanzapine (baseline mean (SD), 16 wk mean (SD)) vs. Risperidone (baseline mean (SD), 16 wk mean (SD)), mixed model P Positive sx: Delusions: 5.5 (0.6), 2.7 (1.6) vs. 5.4 (0.6), 2.6 (1.7), 0.47 Hallucinations: 4.6 (1.6), 2.0 (1.6) vs. 5.0 (0.9), 1.8 (1.2), 0.23 Thought disorder: 7.3 (3.5), 4.5 (2.6) vs. 6.6 (3.7), 3.6 (0.8), 0.49 Total: 19.8 (4.3), 10.6 (4.3) vs. 19.2 (4.7), 9.1 (2.9), 0.84 Baseline negative sx: Affective flattening/blunting: 2.0 (1.1), 2.0 (1.0) vs. 2.1 (1.3), 2.5 (1.1), 0.12 Alogia: 2.0 (1.0), 1.8 (0.8) vs. 1.8 (1.1), 2.2 (1.1), 0.75 Avolition-apathy: 3.1 (1.2), 3.0 (1.1) vs. 3.0 (1.3), 2.9 (0.9), 0.81 Asociality-anhedonia: 3.1 (1.1), 2.7 (1.1) vs. 3.3 (1.0), 2.6 (1.1), 0.50
Robles, 2011 Spain	53/53/50	17/7/32	Symptom improvement over time (baseline vs. day 7 vs. day 15 vs. 30 vs. day 90 vs. 6 months): PANSS positive, mean (SD): Quetiapine: 22.3 vs. 17.2 vs. 14.8 vs. 13.5 vs. 13.3 vs. 13.6; W=-2.028, P=0.043 Olanzapine: 27.3 vs. 17.9 vs. 15.3 vs. 14.6 vs. 11.1 vs. 12.9; W=-2.366, P=0.018 PANSS negative, mean (SD): Quetiapine: 20.6 vs. 17.1 vs. 15.6 vs. 16.3 vs. 15.1 vs. 15.4; W=-2.533, P=0.011 Olanzapine: 26.1 vs. 23.1 vs. 21.1 vs. 18.5 vs. 18.4 vs. 20.9; W=-0.210, P=0.833 PANSS total, mean (SD): Quetiapine: 86.8 vs. 69.1 vs. 63.2 vs. 62.8 vs. 58.5 vs. 62.7; W=-2.197, P=0.028 Olanzapine: 107.3 vs. 83.8 vs. 73.7 vs. 64.9 vs. 59.7 vs. 65.2; W=-2.201, P=0.028 PANSS Quetiapine vs. Olanzapine after 6- months: NSD Cognitive domains, Quetiapine vs. Olanzapine, z-score mean (SD) at 6 months: Attention: 0.3851(0.51) vs. 0.0538 (0.91); U=64.00, P=0.12 Working Memory: 0.427 (1.18) vs. -0.183 (0.63); U=82.00, P=0.08 Learning and Memory: 0.534 (1.02) vs. 0.578 (1.12); U=109.50, P=0.68 Executive Functions: 0.3356 (0.70) vs. -0.07 (0.76); U=49.00; P=0.29

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Adverse effects reported
Robinson, 2006 (Companion paper to Lieberman 2003, Green 2004, Perkins 2004) Sevy, 2011 USA- NY	Weight gain olanzapine 17.3% (95% CI=14.2%–20.5%) vs. risperidone 11.3% (95% CI=8.4%–14.3%) Baseline mean weight and BMI in the olanzapine and risperidone tx groups were sig. increased @ week 16, although there was a time main effect for weight and BMI (P <0.001) Baseline mean weight (SD): olanzapine 155 lbs (29 lbs) and risperidone 140 lbs (24 lbs) Week 16 mean weight (SD): olanzapine 180 lbs (34 lbs) and risperidone 151 lbs (41 lbs) Baseline mean BMI (SD): olanzapine 23 (4) and risperidone 22 (4) Week 16 mean BMI (SD): olanzapine 26 (4) and risperidone 25 (5)
Robles, 2011 Spain	NR

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Extrapyramidal symptoms
Robinson, 2006 (Companion paper to Lieberman 2003, Green 2004, Perkins 2004) Sevy, 2011 USA- NY	Extrapyramidal symptom severity scores risperidone 1.4 (95% CI=1.2–1.6) vs. olanzapine 1.2 (95% CI=1.0–1.4) Parkinsonism risperidone 16.0% (95% CI=5.5%–26.6%) vs olanzapine 8.9% (95% CI=0.3%–17.6%)
Robles, 2011 Spain	NR

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Total withdrawals; withdrawals due to adverse events	Comments
Robinson, 2006 (Companion paper to Lieberman 2003, Green 2004, Perkins 2004) Sevy, 2011 USA- NY		
Robles, 2011 Spain		

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Eligibility criteria	Interventions (drug, dose, duration)	Allowed other medications	Age Gender Ethnicity	Other population characteristics
Sacchetti 2009 DB RCT 23 Italian departments of mental health. The MOZART Study	Inclusion: DSM-IV diagnosis of schizophrenia, a history of resistance and/or intolerance to at least three acute cycles with different antipsychotics given at therapeutic doses, PANSS score ≥80, and CGI-S score ≥4 Exclusion: current DSM-IV Axis I comorbid disorders; concomitant acute or unstable physical illnesses; clinically significant abnormal laboratory test values; a positive urine screen for substances of abuse; any contraindication to ziprasidone or clozapine; and treatment with the investigational drugs during the previous 3 mos; female patients of childbearing potential not using contraception	Ziprasidone (80–160 mg/d, n=73) vs. or clozapine (250–600 mg/d, n=74) Duration 18 wks	Benzodiazepines and anticholinergic agents	Mean age 40 yrs 69% male Ethnicity NR	Resistance only 40% Intolerance only 16% Both resistance and intolerance 44%
Sacchetti, 2008 The QUERISOLA trial DB RCT Italy	18 and 65 ys; diagnosis of schizophrenia ; a total score of ≥ 70 on the Positive and Negative Syndrome Scale (PANSS) ; and no exposure to depot antipsychotics in the previous 6 wks.	Risperidone 590.0 ± 175 mg n=25 Olanzapine 5.1 ± 1.5 mg n=25 Quetiapine 15.1 ± 5.8 n=25 8 wks	YES - zolpidem or flurazepam for insomnia , or anticholinergics or benzodiazepines for movement disorders	Mean age 39.94 56% male Ethnicity NR	PANSS Total Risperidone 96.0±20.5 Olanzapine 98.5±20.0 Quetiapine 101.3±20.0

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Number screened/ eligible/ enrolled	Withdrawn/ Lost to follow-up/ Analyzed	Results
Sacchetti 2009 DB RCT 23 Italian departments of mental health. The MOZART Study	162/157/147	56/NR/146	Ziprasidone (n=71) vs. Clozapine (n=73) Mean (±SD) change (LOCF) PANSS total score −25.0±22.0 vs. −24.2±22.5 PANSS-P −6.0±7.8, vs. −7.0±7.2 PANSS-N −7.6±6.7 vs. −6.1±6.5 PANSS general psychopathology subscale score −11.3±11.4 vs. −11.4±12.8 CGI-S score −0.6±0.9 vs. −0.6±0.9 CGI-I score endpoint 3.2±1.5 vs. 3.3±1.3
Sacchetti, 2008 The QUERISOLA trial DB RCT Italy	NR/NR/75	14/2/61 PP	Quetiapine vs. risperidone vs. olanzapine mean reductions PANSS total scores 37.0 vs. 32.1 vs. 34.4 ≥ 40% reduction from baseline in PANSS total score at Week 8 10/21 [48%] vs. 8/20 [40%] vs. 8/20 [40%]).

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Adverse effects reported
Sacchetti 2009 DB RCT 23 Italian departments of mental health. The MOZART Study	Ziprasidone(n=73) vs. Clozapine(n=73) Increased salivation 0% vs. 28.8% Tachycardia 2.7% vs. 28.8% Dizziness 4.1% vs. 9.6% Headache 6.8% vs. 4.1% Nausea 6.8% vs. 8.2% Somnolence 4.1% vs. 23.3% Insomnia 9.6% vs. 2.7% Any AE 71.2% vs. 79.5%
Sacchetti, 2008 The QUERISOLA trial DB RCT Italy	Five patients (6.7%) spontaneously reported an AE of moderate intensity during the trial: quetiapine group, no events; risperidone group, one event (parkinsonian symptoms); olanzapine group, four events (weight gain, anxiety, pneumonia, scrotal eczema). ≥ 7% increase in baseline body weight occurred in quetiapine 8%, risperidone 8%, olanzapine 29%

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Extrapyramidal symptoms
Sacchetti 2009 DB RCT 23 Italian departments of mental health. The MOZART Study	Ziprasidone vs. Clozapine Change score, mean [95% CI] Simpson–Angus Scale −0.21 [−0.30 to −0.12] vs. −0.06 [−0.14 to 0.02] Barnes Akathisia Scale −0.37 [−0.64 to −0.11] vs. −0.22 [−0.44 to 0.01] Abnormal Involuntary Movement Scale −0.15 [−0.08 to −0.22] vs. −0.08 [−0.18 to 0.03]
Sacchetti, 2008 The QUERISOLA trial DB RCT Italy	SAS scores (lower quartile, median, upper quartile) Week 8 Risperidone 1.00, 3.00, 10.25 Olanzapine 0.00, 0.50, 4.25 Quetiapine 0.0, 0.0, 1.0 Risperidone vs quetiapine P = 0.005, other comparisons NS

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Total withdrawals; withdrawals due to adverse events	Comments
Sacchetti 2009 DB RCT 23 Italian departments of mental health. The MOZART Study	56 WD 31 due to AEs	
Sacchetti, 2008 The QUERISOLA trial DB RCT Italy	14 WD 1 due to AEs	Completers analysis, ITT reported in graphs.

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Eligibility criteria	Interventions (drug, dose, duration)	Allowed other medications	Age Gender Ethnicity	Other population characteristics
Saddichha, 2007 India	Drug-naïve patients with a DSM-IV diagnosis of first episode schizophrenia.	Haloperidol n=15, 15.6 (2.6) mg Olanzapine n=29 , 17(5) mg Risperidone n=22. 4.5 (1.2) mg 6 wks	None that would effect weight or metabolism	Age 26.7 yrs % male 47 Ethnicity NR	Weight 48.3 (10.5) BMI 19.2
Saddichha, 2008 Saddichha 2008 "Predictors of antipsychotic…" Saddichha 2008 "Diabetes and Schizophrenia-effect of disease or drug.." India	Drug-naïve patients with a DSM-IV diagnosis of first episode schizophrenia.	35 on Olanzapine (16.5 ± 4.6 mg), 33 on Risperidone (4.4 ± 1.2 mg) a 31 on Haloperidol (13.4 ± 3.6 mg). 6 wks	None that would effect weight or metabolism	Age 26.0 (5.5) yrs % male 52.5%	66 (66.7%) paranoid schizophrenia 33 (33.3%) undifferentiated schizophrenia.
Sajatovic, 2002 (QUEST sub-group analysis, Mullen, 2001) RCT, open-label, multicenter	Psychosis and: schizophrenia, schizoaffective disorder, bipolar disorder, major depressive disorder (MDD), delusional disorder, Alzheimer's Disease, schizophreniform disorder, vascular dementia, or substance abuse dementia. No significant medical disorders, no current clozapine treatment or history of non-response to clozapine, and no history of drug-induced agranulocytosis. For this analysis, Mood Disorder was classified as: 1) schizoaffective disorder, 2) bipolar disorder, and 3) MDD	quetiapine 50-800mg/d risperidone 1-6 mg/d Duration: 4 mos	Any deemed medically necessary. Additional antipsychotics allowed only after attempt to stabilize on assigned drug for 1 mo. No depot drugs, clozapine or olanzapine allowed. Mood stabilizers and antidepressants could be continued if dose stable x 2 wks. Rescue meds allowed.	Mean age 45 73 % white 51% male	33.7% taking mood stabilizers 33.7 taking antidepressants 57% of total population classified as "mood disorder"

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Number screened/ eligible/ enrolled	Withdrawn/ Lost to follow-up/ Analyzed	Results
Saddichha, 2007 India	NR/NR/NR	NR/NR/66	Olanzapine vs. Risperidone vs. Haloperidol Weight gain (kg) 5.1 vs. 4.1 vs. 2.8 Treatment -emergent obesity WHO 10.3% vs. 9.1% vs. 0 IDF 44.8% vs. 36.4% vs. 0
Saddichha, 2008 Saddichha 2008 "Predictors of antipsychotic…" Saddichha 2008 "Diabetes and Schizophrenia-effect of disease or drug.." India	NR/NR/110	11/NR/99	Olanzapine vs. Risperidone vs. Haloperidol Mets by ATP IIIA 20.0% vs. 9.1% vs. 0% Mets by IDF 25.7% vs. 24.2% vs. 3.2%
Sajatovic, 2002 (QUEST sub-group analysis, Mullen, 2001) RCT, open-label, multicenter	NR/NR/729 Of these, 419 with mood disorders	NR/NR/419	Psychosis Efficacy: NS difference on PANSS or CGI, reported in Muller 2001 Depression: HAM-D Scores Change from baseline to LOCF: quetiapine ~5.6, risperidone ~4 (p=0.028) % Change from baseline: quetiapine, risperidone, p-value All patients: -44.6%, -34.4, p=0.0015 Mood disorders: -44.1, -35.7, p=0.0364 NS by individual diagnosis Non-mood disorders: -45.6, -31.1, p=0.0083 HAM-D score >/=20 Mood disorders: -47%, -34%, p=0.0051 Non-mood disorders: Q>R, p=0.008 HAM-D score 10-19, or <10 NS difference for either group.

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Adverse effects reported
Saddichha, 2007 India	NR
Saddichha, 2008 Saddichha 2008 "Predictors of antipsychotic…" Saddichha 2008 "Diabetes and Schizophrenia-effect of disease or drug.." India	% of patients with weight gain>7% above baseline: Olanzapine vs Risperidone: 77.1% vs 63.6%, p<0.001 Mean Weight gain at endpoint : Olanzapine: 5.0, Risperidone: 4.2, p<0.001 Increase in Fasting blood sugar at endpoint (mean (SD)) : Olanzapine 6.6(12.7), Risperidone: 4.3 (12.5), p=0.01 Increase in Post prandial blood sugar at endpoint: Olanzapine: 21.5 (32.2), Risperidone: 21.0 (23.4), p<0.001 Treatment emergent Diabetes: (WHO definition) Olanzapine vs Risperidone: 11.4% vs 9.1% (ADA definition) 2.9% vs 0%
Sajatovic, 2002 (QUEST sub-group analysis, Mullen, 2001) RCT, open-label, multicenter	Patients with Mood disorders: risperidone > quetiapine (p<0.001, numbers NR) Patients without Mood disorders: NS difference (p=0.063)

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Extrapyramidal symptoms
Saddichha, 2007 India	NR
Saddichha, 2008 Saddichha 2008 "Predictors of antipsychotic…" Saddichha 2008 "Diabetes and Schizophrenia-effect of disease or drug.." India	NR
Sajatovic, 2002 (QUEST sub-group analysis, Mullen, 2001) RCT, open-label, multicenter	NR

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Total withdrawals; withdrawals due to adverse events	Comments
Saddichha, 2007 India		
Saddichha, 2008 Saddichha 2008 "Predictors of antipsychotic…" Saddichha 2008 "Diabetes and Schizophrenia-effect of disease or drug.." India		
Sajatovic, 2002 (QUEST sub-group analysis, Mullen, 2001) RCT, open-label, multicenter	NR / NR	Analysis of effect of EPS on HAM-D scores by ANCOVA: subset of patients who had at worst mild akinesia, hypokinesia or akathisia at baseline and did not get worse during trial showed quetiapine superior to risperidone on HAM-D score (p=0.017) - not clear which group of patients, size of group, or timing of assessments.

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Eligibility criteria	Interventions (drug, dose, duration)	Allowed other medications	Age Gender Ethnicity	Other population characteristics
San, 2012 RCT Spain	18 years old, presence of psychotic symptoms at admission (4 or more on pANSS items 1,3,5 or 6 and 3, naïve to psychotropic drugs. Excluded: presence of major medical or neurological disease or mental retardation, suspician of substance use directly contributing to the symptoms	Haloperidol 1.5–8.5,olanzapine7.5–40,risperidone1.5–7.0,quetiapine100–1500 and ziprasidone40–240mg/day.	Benzodiazepines, anticholinergics	mean age 25.6 74.6% male Ethnicity NR	BMI 22.7 82.5% single 46.5% elementary school education 44.7% diagnosed with schizophrenia Duration of untreated psychosis: 52.5 weeks baseline PANSS: 91.0
Sato, 2012 Crossover study Japan	Inpatients at Kusatsu Hosptial with diagnosis of schizophrenia based on DSM-IV. Excluded were current suicidality, nuerological disorders, acute or unstable medical condition, clinically significan tlab test value, and alcohol or substance dependence within 3 months	Ariprazole or risperidone; dose determined by clinical response risperidone mean 2.61 mg/day aripiprazole mean 17.5 mg/day	NR	mean age 38.5 52% male Ethnicity NR	IQ 96.0 Duration of disorder mean 13.1 years Onset of disorder mean 25.9 years 39% were receiving no mediation prior to enrollment

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Number screened/ eligible/ enrolled	Withdrawn/ Lost to follow-up/ Analyzed	Results
San, 2012 RCT Spain	159/141/114	73/unclear/114	Proportion discontinuing treatment by 12 months: 40% olanzapine,56.5% quetiapine,64% risperidone,80% ziprasidone (no statistical analysis) Mean time to all-cause discontinuation: olanzapine 260 days; quetiapine 187 days; risperidone 206 days; ziprasidone 142 days (P =0.005)
Sato, 2012 Crossover study Japan	NR/NR/23	5/0/18	Risperidone versus Aripiprazole SF-36 total scores NR Bodily Pain 72.29 vs 77.29; P 0.27 General Health Perception 47.59 vs 48.50, P=0.75 Mental health 56.94 vs 56.00, P=0.87 Physical functioning 85.00 vs 85.88, P=0.71 Role-emotional 58.82 vs 60.78, P=0.85 social functining 67.65 vs 70.59, P=0.68 vitality 64.71 vs 61.47, P=0.54 PSQI sleep index: 5.29 vs 6.24, P=0.24 Schedule for Assessment of Insight: 11.65 vs 13.12, P=0.10

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Adverse effects reported
San, 2012 RCT Spain	Discontinuations due to adverse events: 20% olanzapine, 7.7% quetiapine; 6.2% risperidone; 25% ziprasidone Time to discontinuation due to adverse events: NR UKU scores were higher in halroperidol group compared to second generation drugs, and no differences were found between the other drugs. WEeight gain ranged from 3 kg with ziprasidone to 9 kg with olanzapine but no statistically significant differences were found.
Sato, 2012 Crossover study Japan	Epworth Sleepiness Scale: 3.18 vs 2.59, P=0.46 Weight (mean): 65.21 vs 64.51, P=0.42

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Extrapyramidal symptoms
San, 2012 RCT Spain	NR, noted to be higher in haloperidol group
Sato, 2012 Crossover study Japan	DIEPSS: 1.76 vs 2.06, P=0.21

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Total withdrawals; withdrawals due to adverse events	Comments
San, 2012 RCT Spain	Overall discontinuations: 40% olanzapine,56.5% quetiapine,64% risperidone,80% ziprasidone. Discontinuations due to adverse events: 20% olanzapine, 7.7% quetiapine; 6.2% risperidone; 25% ziprasidone	
Sato, 2012 Crossover study Japan	5 (22%); 0 due to adverse events (all due to lack of efficacy)	

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Eligibility criteria	Interventions (drug, dose, duration)	Allowed other medications	Age Gender Ethnicity	Other population characteristics
Schering-Plough 25517 DB RCT Multicenter: Russia, Australia, South Africa, 8 countries in Europe	Inclusion: Aged 18 or older with a DSM-IV TR diagnosis of schizophrenia or schizoaffective disorder; PANSS total score>=6 and a score of >=4 on at least 2 of 5 PANSS positive subscale items; CGI-S score >=4 at baseline; and have never received neuroleptic treatment before or shown a response with a neuroleptic other than clozapine. Exclusions: significant medical conditions or abnormal lab or physical exam diagnosis of residual type schizophrenia or coexisting Axis I substance abuse disorder; risk of harming self or others	Sublingual Asenapine 5 or 10 mg BID, flexible dose, 52 wks. Oral olanzapine 10 to 20 mg QD, flexible dose, 52 wks. Double-dummy design (active vs P). Patients were hospitalized for a minimum of 2 wks and then monitored on outpatient basis.	NR	Mean age 36.6 54% male 92.6% Caucasian 5.7% Black 0.9% Asian	77.8% Schizophrenia, paranoid subtype 13.1% Schizoaffective disorder Mean CGI-S at baseline 4.8
Schering-Plough 25543 DB RCT Multicenter: Australia, Romania, South Africa, 13 countries in Europe	Inclusion: Aged 18+ with DSM-IV TR diagnosis of schizophrenia of paranoid, disorganized, catatonic, residual, or undifferentiated subtype; PANSS negative subscale >=20 at screening and baseline with a score >=4 (moderate) on at least 3 of the Marder factors for negative symptoms; PANSS positive subscale score less than the PANSS negative subscale score at screening and at baseline; and stable disease in the last 5 mos. Exclusions: significant medical conditions or abnormal lab or physical exam; coexisting Axis I primary diagnosis including depression or substance abuse; risk of harming self or others	Asenapine 5 or 10 mg BID, flexible dose, 26 wks. Olanzapine 5 to 20 mg QD, flexible dose, 26 wks. Double-dummy design (active vs P). 30-d stable observation period followed by baseline visit. Active treatment period: 4 week AP switch period followed by 22-week monotherapy.	NR	Mean age 40.5 68.2% male 89.4% Caucasian 6.9% Black 0.2% Asian	62.6% paranoid subtype

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Number screened/ eligible/ enrolled	Withdrawn/ Lost to follow-up/ Analyzed	Results
Schering-Plough 25517 DB RCT Multicenter: Russia, Australia, South Africa, 8 countries in Europe	Screened NR Eligible NR 1215 randomized	691 (56.8%) withdrew 26 (2.1%) loss to follow-up 1166 (93%) analyzed	Asenapine vs Olanzapine: Mean change from baseline to endpoint: PANSS total score: -21.0 vs -27.5 (p<0.0001 in favor of olanzapine) CGI-S: -1.2 vs -1.6 Mean CGI-I score at endpoint: 2.9 v. 2.4 CGI-I score <3 (much or very much improved): 52% vs 66% CGI-I score >=3 (minimal improvement): 48% vs 34% No differences between groups on SWN or SF-12, or in living situations, employment, or level of functioning.
Schering-Plough 25543 DB RCT Multicenter: Australia, Romania, South Africa, 13 countries in Europe	Screened NR Eligible NR 481 enrolled	132 (27.4%) withdrew 5 (1%) lost to followup 433 (90%) analyzed	Asenapine vs olanzapine: Mean change from baseline to d 182 in NSA: -12.5 vs -12.5. Change in CDSS: -0.8 vs -0.2; P=0.0055. No differences between treatments in NSA global scores, QLS total score, PANSS total score, CGI-S score, CGI-I response rates, and Q-LES-Q social relations or leisure time activities scores.

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Adverse effects reported
Schering-Plough 25517 DB RCT Multicenter: Russia, Australia, South Africa, 8 countries in Europe	Asenapine vs olanzapine: Suicide attempts: 1.2 vs 1.9% Completed suicide: n=5 (<1%) vs n=1 (<1%) Weight increase: 12 vs 29% Mean (SD) change in weight: 0.9 (4.8) kg vs 4.2 (7.6) kg Schizophrenia/psychosis: 8 vs 5% Insomnia: 7 vs 5% Sedation: 8 vs 10% Somnolence: 9 vs 10% GI symptoms: 9 vs 7% Akathisia: 8 vs 4% Prolactin levels decreased in both treatment groups.
Schering-Plough 25543 DB RCT Multicenter: Australia, Romania, South Africa, 13 countries in Europe	Asenapine vs olanzapine, % of group: Gained >=7% of body weight: 7.9 vs 24.6 Abnormal increase in prolactin: 7 vs 3.5 Insomnia: 15.8 vs 10.8 Headache: 12.9 vs 9,.6 Somnolence: 12.4 vs 11.3 Anxiety: 9.5 vs 8.3 Schizophrenia: 7.1 vs 3.8 Agitation: 6.2 vs 1.3 Nausea: 5.4 vs 3.8 Fatigue: 4.6 vs 6.7 Weight increased: 4.6 vs 21.3

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Extrapyramidal symptoms
Schering-Plough 25517 DB RCT Multicenter: Russia, Australia, South Africa, 8 countries in Europe	Asenapine vs olanzapine EPS: 18% vs 8%, most commonly akathisia: 8% vs 4% Mean (SD) change from baseline to endpoint in EPS scales: SAS: -0.4 (2.5) vs -0.7 (2.7) BARS: -0.1 (1.9) vs -0.3 (1.5) AIMS 7 total score: -0.1 (1.3) vs -0.2 (1.2)
Schering-Plough 25543 DB RCT Multicenter: Australia, Romania, South Africa, 13 countries in Europe	Asenapine vs olanzapine: EPS: 8.3% vs 3.3% Akathisia: 2.9 vs 1.3% Parkinsonism 2.1 vs 1.7%

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Total withdrawals; withdrawals due to adverse events	Comments
Schering-Plough 25517 DB RCT Multicenter: Russia, Australia, South Africa, 8 countries in Europe	total N; % of asenapine vs olanzapine: 691 withdrew; 61.5% vs 42.8% 193 due to AE; 17.1% vs 12.2%	
Schering-Plough 25543 DB RCT Multicenter: Australia, Romania, South Africa, 13 countries in Europe	total N; % of asenapine vs olanzapine 132 withdrew; 35.3% vs 19.6% 54 due to AE; 14.9% vs 7.5%	

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Eligibility criteria	Interventions (drug, dose, duration)	Allowed other medications	Age Gender Ethnicity	Other population characteristics
Schering-Plough, Data on file. Study 041022 DB RCT Multicenter (USA, Ukraine, Russia)	Inclusion: 18 ys of age or older with a DSM-IV text-revised diagnosis of schizophrenia (of the paranoid, disorganized, catatonic, or undifferentiated subtypes) with an acute exacerbation of psychotic symptoms; positive response to previous antipsychotic medication other than clozapine; PANSS total score >60 and a score of >4 on at least 2 of 5 PANSS positive subscale items (delusions, conceptual disorganization, hallucinatory behavior, grandiosity, suspiciousness/persecution); CGI-S score >4 at baseline Exclusion: clinically significant medical conditions or abnormal laboratory or physical examination findings; diagnosis of residual type schizophrenia, schizoaffective disorder, or coexisting psychiatric disorder coded on Axis I; substance abuse; a >20% decline in PANSS total score from screening to baseline; those at risk of harming themselves or others	Asenapine (5mg or 10mg bid) sublingual P bid Olanzapine (10mg to 20mg qd) oral 6 wks	NR	Asenapine vs P vs Olanzapine Mean age (SD): 44 (9.03) vs 41.9 (9) vs 41.6 (10.41) Male: 74.4% vs 79.6% vs 78.3% Caucasian: 50% vs 45.2% vs 44.6% Black: 42.2% vs 46.2% vs 46.7% Asian: 2.2% vs 0 vs 2.2% Other: 5.6% vs 8.6% vs 6.5%	Asenapine vs P vs Olanzapine Current Principal Psychiatric Diagnosis Schizophrenia ---Catatonic subtype: 0 vs 0 vs 0 ---Disorganized subtype: 3.3% vs 3.2% vs 3.3% ---Of the paranoid subtype: 93.3% vs 90.3% vs 89.1% ---Undifferentiated subtype: 3.3% vs 6.5% vs 7.6%

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Number screened/ eligible/ enrolled	Withdrawn/ Lost to follow-up/ Analyzed	Results
Schering-Plough, Data on file. Study 041022 DB RCT Multicenter (USA, Ukraine, Russia)	NR/NR/277	142/21/259	"The study did not meet its primary endpoint, there was no significant difference between asenapine and P or olanzapine and P in the LS mean changes in the PANSS total score from baseline to endpoint or at any trial visit" "No statistically significant differences were observed between asenapine and P or between olanzapine and P in the LS mean change from baseline to endpoint in any secondary efficacy measure defined for this trial"

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Adverse effects reported
Schering-Plough, Data on file. Study 041022 DB RCT Multicenter (USA, Ukraine, Russia)	Asenapine vs P vs Olanzapine n (%) All AEs: 62 (68.9) vs 56 (60.2) vs 58 (63.0) All serious AEs: 6 (6.7) vs 3 (3.2) vs 8 (8.7) Headache: 18 (20.0) vs 15 (16.1) vs 11 (12.0) Anxiety: 10 (11.1) vs 7 (7.5) vs 9 (9.8) Insomnia: 10 (11.1) vs 11 (11.8) vs 8 (8.7) Agitation: 6 (6.7) vs 6 (6.5) vs 6 (6.5) Nausea: 6 (6.7) vs 11 (11.8) vs 5 (5.4) Constipation: 5 (5.6) vs 7 (7.5) vs 8 (8.7) Dyspepsia: 5 (5.6) vs 4 (4.3) vs 10 (10.9) Sedation: 5 (5.6) vs 4 (4.3) vs 12 (13.0) Weight Increased: 5 (5.6) vs 1 (1.1) vs 8 (8.7)

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Extrapyramidal symptoms
Schering-Plough, Data on file. Study 041022 DB RCT Multicenter (USA, Ukraine, Russia)	NR

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Total withdrawals; withdrawals due to adverse events	Comments
Schering-Plough, Data on file. Study 041022 DB RCT Multicenter (USA, Ukraine, Russia)	Asenapine vs P vs Olanzapine Total WDs: 48 vs 45 vs 49 WDs due to AEs: 6 vs 5 vs 11	

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Eligibility criteria	Interventions (drug, dose, duration)	Allowed other medications	Age Gender Ethnicity	Other population characteristics
Schering-Plough, Data on file. Study 7501012 DB RCT	Inclusion: 18 ys of age or older with a DSM-IV text-revised diagnosis of schizophrenia; receiving continuous antipsychotic treatment for at least 1 y; stable at time of entry with a history of >1 episode of acute schizophrenia in the 3 ys preceding screening Exclusion: a concurrent Axis 1 diagnosis other than schizophrenia at screening; a PANSS score >80 or a CGI-S score >4 at screening; MR or organic brain syndrome; a substance-induced psychotic disorder	All patients received 5 mg or 10 mg flexible dose asenapine during 4 wks open label phase 1 and 22 wks open-label phase 2 Patients were then randomized 1:1 to 26 wks DB treatment with arsenapine (5 or 10mg) BID or P Treatments administered sublingually	NR	Asenapine vs P Mean age (SD): 89 (45.9) vs 76 (39.6) ys Male: 54.1% vs 60.4% Caucasian: 72.7% vs 72.9% Black: 11.3% vs 9.4% Asian: 15.5% vs 17.2% Other: 0.5% vs 0.5%	Asenapine vs Placbo DSM-IV Diagnosis, n (%) Schizophrenia, catatonic subtype: 1% vs 0.5% Schizophrenia, disorganized subtype: 0 vs 0.5% Schizophrenia, of the paranoid subtype: 82% vs 81.3% Schizophrenia, undifferentiated subtype: 13.4% vs 13.5% Schizophrenia, residual type: 3.6% vs 4.2% Schizoaffective disorder: 0 vs 0

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Number screened/ eligible/ enrolled	Withdrawn/ Lost to follow-up/ Analyzed	Results
Schering-Plough, Data on file. Study 7501012 DB RCT	NR/NR/NR	179/6/ITT 382	Time to relapse was longer in the asenapine group compared with the P group (P<0.0001; RR, 0.26) Time to termination was significantly longer in the asenapine group compared with the P group throughout the double-blind treatment period (P<0.0001; RR, 0.47) Statistically significant difference in favor of asenapine in the change from baseline of the double-blind period to endpoint of the double-blind period for PANSS total score, PANSS Marder Factor scores, and CGI-S.

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Adverse effects reported
Schering-Plough, Data on file. Study 7501012 DB RCT	Asenapine vs P At least one treatment-related AE: 22.7% (44/194) vs 27.1% (52/192) Anxiety: 8.2% vs. 10.9% Weight increased: 6.7% vs. 3.6% Insomnia: 6.2% vs. 13.5% Mean (SD) change in weight: 0.0 (3.41) vs -1.2 (3.96) kg >7% gain from baseline: 4% vs 1% Markedly abnormal biochemistry values in creatinine kinase: 1.7% vs 1 0.6% Markedly abnormal biochemistry values in creatinine: 1.1% vs 0% Markedly abnormal biochemistry values in AST: 2.8% vs 0.6% Markedly abnormal biochemistry values in ALT: 1.7% vs 0.6% Markedly abnormal metabolic chemistry values in LDL: 0.6% vs 0% Markedly abnormal metabolic chemistry values in triglycerides: 1.5% vs 0.8% Markedly abnormal metabolic chemistry values in high glucose: 5.4% vs 3.3% Markedly abnormal metabolic chemistry values in HbA1c: 2.3% vs 0.6%

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Extrapyramidal symptoms
Schering-Plough, Data on file. Study 7501012 DB RCT	NR

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Total withdrawals; withdrawals due to adverse events	Comments
Schering-Plough, Data on file. Study 7501012 DB RCT	Asenapine vs P Total WD: 59 vs 120 WD due to AEs: 16 vs 53	

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Eligibility criteria	Interventions (drug, dose, duration)	Allowed other medications	Age Gender Ethnicity	Other population characteristics
Schering-Plough; Data on File. Study 041021 DB RCT Multicenter (USA, Ukraine, Russia)	Inclusion: 18 ys of age or older with a text-revision DSM-IV diagnosis of schizophrenia (of the paranoid, disorganized, catatonic, or undifferentiated subtypes) with an acute exacerbation of psychotic symptoms; positive response to previous antipsychotic medication other than clozapine; PANSS total score ≥60 and a score of ≥4 on at least 2 of 5 PANSS positive subscale items (delusions, conceptual disorganization, hallucinatory behavior, grandiosity, suspiciousness/persecution); CGI-S score ≥4 at baseline Exclusion: clinically significant medical conditions or abnormal laboratory or physical examination findings; diagnosis of residual type schizophrenia, schizoaffective disorder, or coexisting psychiatric disorder coded on Axis I; substance abuse; a ≥20% decline in PANSS total score from screening to baseline; those at risk of harming themselves or others	Asenapine 5mg BID vs Asenapine 10 mg BID vs P BID vs Olanzapine 15 mg BID 6 wks	NR	Mean age: 40.2 ys Male: 70.3% Caucasian: 46.3% Black: 44.9% Asian: 1.7% Other: 7.1%	Diagnosed with schizophrenia (paranoid subtype): 88.5%
Schoemaker, 2010 DB RCT; worldwide	≥18 years, DSM-IV-TR diagnosis of schizophrenia or schizoaffective disorder, PANSS total ≥60 and ≥4 on at least 2 of 5 PANSS positive items, CGI-S ≥4, treatment naïve or a history of a positive response to an antipsychotic other than clozapine. Excluded history of inadequate or intolerable response to olanzapine, greater than mild on any item of the abnormal involuntary movement scale	A. Asenapine 5mg sublingual, twice daily, dosage flexible to 5 or 10 mg twice daily after 7 days, + Matching placebo to olanzapine B. Olanzapine 10mg capsules, once daily, dosage flexible to 10 or 20 mg daily after 7 days, + Matching placebo to asenapine	hypnotics, anxiolytics, anticholinergics, andtidepressants other than tricyclics or monoamine oxidase inhibitors	Age: 36.65 y Gender: 46.1% female Ethnicity: 93% white, 6% black	Diagnosis: Schizoaffective disorder 13.1%, Schizophrenia 86.9%

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Number screened/ eligible/ enrolled	Withdrawn/ Lost to follow-up/ Analyzed	Results
Schering-Plough; Data on File. Study 041021 DB RCT Multicenter (USA, Ukraine, Russia)	NR/NR/417	189/20/386	Asenapine 5mg BID vs Asenapine 10 mg BID vs P BID vs Olanzapine 15 mg BID; P values are vs P Mean change in PANSS total score: -14.5 (P=0.2556) vs -13.4 (P=0.3046) vs -11.1 vs -16.5 (P=0.0168) Mean change in PANSS positive subscale score: -5.5 (P=0.0119) vs NR (P=NS) vs -3.6 vs -5.6 (P=0.0132) Asenapine 10 BID resulted in a statistically significantly greater LS mean increase from baseline to endpoint in the Q-LES-Q leisure time activities and social relations subscale scores. A statistically significant difference between olanzapine and P on the QOL Enjoyment and Satisfaction Questionnaire (Q-LES-Q) leisure time activities subscale at endpoint. No statistically significant difference between any active treatment and P in the CGI-I, CDSS, Fleming/Potkin Battery, cognitive function HAS, ISST-Modified, QOL scale or PETiT scales.
Schoemaker, 2010 DB RCT; worldwide	1377/NR/1225	697/NR/1166	Last observation carried forward, change from baseline: Asenapine vs. Olanzapine: PANSS total: -21.0 ± 22.8 vs. -27.5 ± 22.0, p<0.0001 PANSS positive: -7.9 ± 7.67 vs. -10.0 ± 7.75, p<0.001 PANSS negative: -4.6 ± 6.54 vs. -6.0 ± 6.23, p<0.001 PANSS disorganized thoughts: -4.4 ± 5.36 vs. -5.9 ± 5.29, p<0.001 PANSS hostility/excitement:-1.5 ± 4.11 vs. -2.4 ± 3.72, p<0.001 PANSS anxiety/depression: -2.7 ± 3.7 vs. -3.3 ± 3.79, p<0.001 CGI-S: -1.2 ± 1.35 vs. -1.6 ± 1.35, p<0.001

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Adverse effects reported
Schering-Plough; Data on File. Study 041021 DB RCT Multicenter (USA, Ukraine, Russia)	Asenapine 5mg BID vs Asenapine 10 mg BID vs P BID vs Olanzapine 15 mg BID Dizziness: 8.7% vs 4.9%vs 2.0% vs 7.8% Hypoesthesia oral: 2.9% vs 3.9% vs 0.0% vs 0.0% weight increased: 3.8%vs 2.9% vs 0.0% vs 4.9% Hyperprolactinemia (>4 times the upper limit of normal): 6.0% vs 3.1% vs 2.1% vs 0.0% Fasting glucose values (>1.5 times the upper limit of normal): 3.7% vs 0.0% vs 1.3% vs 5.1% Triglyceride levels (>5.65 mmol/L): 0.0% vs 1.3% vs 3.9% 5.1% Weight gain (>7%): 4.8% vs 5.9% vs 1.0% vs 16.7%
Schoemaker, 2010 DB RCT; worldwide	Asenapine vs. Olanzapine: Mortality: 7 (<1%) vs. 1 (<1%) Suicide: 5 (<1%) vs. 1 (<1%) Suicide Attempts: 11 (1.2%) vs. 6 (1.9%) Serious AEs: 174 (19%) vs. 36 (12%) All AEs: 749 (82%) vs. 254 (82%)

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Extrapyramidal symptoms
Schering-Plough; Data on File. Study 041021 DB RCT Multicenter (USA, Ukraine, Russia)	Asenapine 5mg BID vs Asenapine 10 mg BID vs P BID vs Olanzapine 15 mg BID Treatment-emergent extrapyramidal symptoms: 6.7% vs 11.8% vs 7.0% vs 6.9%
Schoemaker, 2010 DB RCT; worldwide	extrapyramidal-like symptoms: 18% vs. 8% akathisia: 89 (10%) vs. 11 (4%) tardive diskinesia: 3 vs. 0

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Total withdrawals; withdrawals due to adverse events	Comments
Schering-Plough; Data on File. Study 041021 DB RCT Multicenter (USA, Ukraine, Russia)	Total WD: 189 WD due to AEs: 39	
Schoemaker, 2010 DB RCT; worldwide	697/193	

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Eligibility criteria	Interventions (drug, dose, duration)	Allowed other medications	Age Gender Ethnicity	Other population characteristics
Schoemaker, 2012 DB RCT; worldwide	Patients completed the core study (Schoemaker 2010), benefited from treatment in opinion of investigator and/or patient, and wished to remain on double-blind treatment.	A. Asenapine, dosage flexible to 5 or 10 mg twice daily + Matching placebo to olanzapine, mean dose 13.4±4.05mg for core+extension study B. Olanzapine, dosage flexible to 10 or 20 mg daily + Matching placebo to asenapine, mean dose 13.4±4.09mg for core+extension study	No drugs prohibited, but CYP2D6 drugs used with caution	Age: 36.9 y Gender: 44.5% female Ethnicity: NR	Diagnosis: Schizoaffective disorder 12.3%, Schizophrenia 87.7
Schooler, 2005 Multi-national	16–45 y-old Structured Clinical Interview for DSM-IV criteria for schizophrenia, schizophreniform disorder, or schizoaffective disorder < 1 y; no more than two psychiatric hospitalizations for psychosis; <12 wkss of cumulative exposure to antipsychotics and required antipsychotic treatment upon enrollment Exclusions- meeting DSM-IV criteria for another axis I diagnosis, including substance dependence or abuse; needing another nonantipsychotic psychotropic medication at enrollment; having a serious or unstable medical illness.	Risperidone (1 to 8 mg/d) or haloperidol (1 to 8 mg/d)	Chloral hydrate, zolpidem, or flurazepam for sleep; and lorazepam for agitation.	Mean age 25 ys 70% male 74% White 13% African-American 3% Hispanic 10% Other	DSM-IV diagnosis (% patients): Schizophrenia=48.2 Schizoaffective disorder=7.6 Schizophreniform disorder=44.0 No previous antipsychotic exposure (% patients)=31.0 Age at onset of first episode=24.0 ys

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Number screened/ eligible/ enrolled	Withdrawn/ Lost to follow-up/ Analyzed	Results
Schoemaker, 2012 DB RCT; worldwide	528/NR/440	114/NR/414	Last observation carried forward, Asenapine vs. Olanzapine: PANSS total during first year of study: -37.0 vs. -35.3 Further change during extension study: 1.6 vs. -0.8
Schooler, 2005 Multi-national	NR/NR/559	218/0/528	Risperidone vs. haloperidol change from baseline in PANSS Total -21.0 vs. -20.6 p = 0.49 Positive -6.6 vs. -7.0 p = 0.13 Negative -4.8 vs. -4.2 p = 0.98 CGI change score 2.69 vs. 2.62 p = 0.45

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Adverse effects reported
Schoemaker, 2012 DB RCT; worldwide	Asenapine vs. Olanzapine, Aes started in extension study: Mortality: 3 vs. 0 Suicide: 0 Serious AEs:54 (18.6%) vs. 12 (8.0%) All AEs: 180 (62.1%) vs. 82 (54.7%)
Schooler, 2005 Multi-national	Weight gain at endpoint risperidone [N=211]: mean=7.5 kg, haloperidol [N=204]: mean=6.5 kg, p=0.26 Suicide ideation risperidone 7.2% (N=20) and no suicides vs. haloperidol 9.4% (N=26) with three completed suicides p = nr

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Extrapyramidal symptoms
Schoemaker, 2012 DB RCT; worldwide	Asenapine vs. Olanzapine, started during extension phase: Extrapyramidal-like symptoms: 4.5% vs. 3.3% Akathisia: 7 (2.4%) vs. 3 (2.0%)
Schooler, 2005 Multi-national	Risperidone vs. haloperidol Dyskinesia Baseline 1.1% vs 1.4% Emergent 8.3% vs. 13.4% Persistent 1.8% vs. 3.3% Extrapyramidal symptoms Total 3.72 vs 4.72 p = 0.04 Parkinsonism, dystonia 3.28 vs. 4.14 p = 0.05 Dystonia 0.34 vs. 0.35 p = 0.91 Parkinsonism 3.12 vs. 3.97 p = 0.05 Dyskinesia 0.82 vs. 1.11 p = 0.12 Akathisia 0.61 vs. 1.00 p < 0.0001

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Total withdrawals; withdrawals due to adverse events	Comments
Schoemaker, 2012 DB RCT; worldwide	Total WD: 114 WD due to AE, asenapine vs. olanzapine: 2.4% vs. 1.3%	
Schooler, 2005 Multi-national		

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Eligibility criteria	Interventions (drug, dose, duration)	Allowed other medications	Age Gender Ethnicity	Other population characteristics
Schreiner 2012 RCT	Schizophrenia, 18-65 ys, PANSS score range from 60-100, Patients using concomitant lipid-lowering therapy could be enrolled only if they had a stable dose of statins, niacin, ezetimble, and resins for 4 wks or longer or fibrates for 12 wks or longer.	Paliperidone ER = 9 mg. Max dose. Olanzapine = 15 mg. Max dose Duration: 12 mos	NR	NR	NR
Sethuraman, 2005 Sub-analysis of Tran 1997	Same as Tran 1997.	Same as Tran 1997	Same as Tran 1997	Same as Tran 1997	Same as Tran 1997

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Number screened/ eligible/ enrolled	Withdrawn/ Lost to follow-up/ Analyzed	Results
Schreiner 2012 RCT	NR/Nr/462	Analyzed: 459 Loss to fu: 2.5% and 1.8%	Improvements in psychotic symptoms: both treatments (P < 0.0001) TG/HDL ratio higher at end point versus baseline: olanzapine vs.paliperidone ER Mean end point change in TG/HDL ratio: 0.097 T 2.72 (P < 0.0001,worsening), vs. no significant change (-0.17 + 2.51)
Sethuraman, 2005 Sub-analysis of Tran 1997	Same as Tran 1997	Same as Tran 1997	Proportion of time spent in remission for olanzapine vs risperidone: Definition 1: 40% vs 31%, p=0.03 Definition 2: 18% vs 11%, p=0.01

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Author, year Study design	Adverse effects reported
Schreiner 2012 RCT	(Paliperidone ER vs. Olanzapine) N (%) Any TEAE: 130 (54.4) vs.114 (51.8) Serious TEAEs: 21 (8.8) vs.12 (5.5) TEAEs occurring in >5% of patients: Weight increase: 23 (9.6) vs. 40 (18.2) Somnolence: 8 (3.3) vs. 21 (9.5) Insomnia: 23 (9.6) vs. 3 (1.4) Schizophrenia: 12 (5.0) vs.4 (1.8) TEAE causally related to study drug: 77 (32.2) vs. 84 (38.2) Severity of TEAEs: Mild: 164 (54.7) vs.153 (61.7) Moderate: 119 (39.7) vs. 77 (31.0) Severe: 17 (5.7) vs.18 (7.3) Action taken because of TEAE: None: 257 (85.7) vs.226 (91.1) Dose adjustment: 23 (7.7) vs.17 (6.9) Temporary stop: 2 (0.7) vs. 0
Sethuraman, 2005 Sub-analysis of Tran 1997	NR

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Extrapyramidal symptoms
Schreiner 2012 RCT	Extrapyramidal effects: NR
Sethuraman, 2005 Sub-analysis of Tran 1997	NR

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Total withdrawals; withdrawals due to adverse events	Comments
Schreiner 2012 RCT	Withdrawals due to adverse events: Permanent discontinuation 18 (6.0) vs.5 (2.0)	
Sethuraman, 2005 Sub-analysis of Tran 1997	NR / NR	

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Eligibility criteria	Interventions (drug, dose, duration)	Allowed other medications	Age Gender Ethnicity	Other population characteristics
Simpson, 2004 DB, multicenter, parallel, flexible-dose Inpatients	Between Ages 18-55 yrs, females not of childbearing potential, hospitalized no more than 2 consecutive wks immediately before screening, schizophrenia/schizoaffective disorder, persistent psychotic symptoms for the week before hospitalization, score of >4 before screening on CGI, score of >4 on at least one of the Positive and Negative Syndrome Scale, normal laboratory results, normal ECG results, negative results on urine drug screen a entry.	Olanzapine (n= 133): daily mean dose- 11.3 mg Ziprasidone (n= 136): daily mean dose- 129.9 mg 6 wks duration	Lorazepam, benztropine.	Mean age: 37.7 ys Male: 176/269(65%) Female: 93/269(35%) White: 141/269(52%) Black: 65/269(24%) Asian: 6/269(2%) Hispanic: 28/269(10%) Other: 7/269(3%)	In-Patient population: 100%
Simpson, 2005 (Continuation of Simpson, 2004) Funding: Pfizer, Inc	1) completion of 6 wks' double-blind treatment with ziprasidone or olanzapine, 2) a CGI improvement score of ≤2 or a ≥20% reduction in Positive and Negative Syndrome Scale total score at acute-study endpoint, and 3) outpatient status.	ziprasidone mean dose 135.2 mg/d (range=78–162) olanzapine 12.6 mg/d (range=5–15) 6 mos	NR	NR - see earlier study	

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Number screened/ eligible/ enrolled	Withdrawn/ Lost to follow-up/ Analyzed	Results
Simpson, 2004 DB, multicenter, parallel, flexible-dose Inpatients	367/269/269	115 (42.6%)/NR/269	BPRS Total Scores: Difference at endpoint: p=0.77, CI=-2.36 to 3.18 CGI Severity Scale: p=0.95, CI -0.27 to 0.29 Positive and Negative Syndrome Scales: CI= -4.44 to 5.21 CGI Improvement Scale: Very much improved: Z: 15.1% vs O: 17.8% Much improved: Z: 34.1% vs O: 38.8% Calgary Depression Scale for Schizophrenia: p=0.38, 95% CI= -0.48 to 1.24 Serum lipid profile results- Median changes: Total cholesterol: O: +19.5 mg/dl vs Z: -1 mg/dl; p<0.0001 Triglycerides: O: +26 mg/dl vs Z: -2 mg/dl; p=0.77 LDL cholesterol: O: +13 mg/dl vs Z: -1 mg/dl; p=0.78 Homocystine levels: O: -1.06 mg/dl vs Z: -0.38 mg/dl; p<0.005 Apolipoprotein B levels: O: +9.0 mg/dl vs Z: -3.0 mg/dl; p<0.0001 Glucose metabolism results- Median changes: Fasting serum glucose levels: Z: 1.0 mg/dl vs O: 1.0 mg/dl Fasting serum insulin levels: O: +3.30 vs Z: +0.25; p=0.051 C-peptide levels: O: +0.46 vs Z: +0.16; p=0.07 Uric acid levels-Median changes: O: + 0.65 vs Z: +0.10; p<0.004
Simpson, 2005 (Continuation of Simpson, 2004) Funding: Pfizer, Inc	NA/NR/1236	0/0/126 when possible	Ziprasidone vs. olanzapine Change in LS mean (SE) BPRS -18.6 (2.1) vs. -20.5 (1.8) CGI-S -1.9 (0.2) vs. -2.0 (0.15) Total PANSS -32.6 (3.8) vs. -35.6 (3.3) Calgary -2.8 (0.7) vs. -3.0 (0.6)

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Adverse effects reported
Simpson, 2004 DB, multicenter, parallel, flexible-dose Inpatients	Body as a whole: Z: 52(38.2%) vs O: 39(29.3%) CV: Z: 7(5.1%) vs O: 10(7.5%) Digestive: Z: 55(40.4%) vs O: 41(30.8%) Endocrine: Z: 1(0.7%) vs O: 0(0%) Hematic and lymphatic: Z: 3(2.2%) vs O: 5(3.8%) Metabolic and nutritional: Z: 5(3.7%) vs O: 14(10.5%) Musculoskeletal: Z: 8(5.9%) vs O: 8(6.0%) Nervous: Z: 82(60.3%) vs O: 64(48.1%) Respiratory: Z: 24(17.6%) vs O: 16(12.0%) Skin and appendages: Z: 14(10.3%) vs O: 10(7.5%) Special senses: Z: 8(5.9%) vs O: 6(4.5%) Urogenital: Z: 9(6.6%) vs O: 5(3.8%) Weight change (kg): Z +0.8 vs O +3.4, p<0.001
Simpson, 2005 (Continuation of Simpson, 2004) Funding: Pfizer, Inc	Ziprasidone vs. olanzapine Weight changes –0.82 kg vs. 4.97 kg BMI changes -0.59 vs 1.31 fasting insulin (1.0 µU/ml) vs. (2.0 µU/ml) Total cholesterol -1.0 mg/dl vs 13.0 mg/dl Mean QTc (Bazett correction) 407.1msec vs. 394.4 msec

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Extrapyramidal symptoms
Simpson, 2004 DB, multicenter, parallel, flexible-dose Inpatients	Scales used: Extrapyramidal Symptom Rating Scale, Barnes akathisia scale, Abnormal Involuntary Movement Scale (AIMS).
Simpson, 2005 (Continuation of Simpson, 2004) Funding: Pfizer, Inc	Ziprasidone vs. olanzapine Change in LS mean (SE) EPS rating scale -0.4 (0.3) vs. -0.7 (0.3) Barnes Rating Scale -0.2 (0.4) vs. -0.9 (0.3) AIMS score -0.07 (0.09) vs. -0.07 (0.07)

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Total withdrawals; withdrawals due to adverse events	Comments
Simpson, 2004 DB, multicenter, parallel, flexible-dose Inpatients	115 total WD 5 due to AEs	
Simpson, 2005 (Continuation of Simpson, 2004) Funding: Pfizer, Inc	88 total WD 25 due to AEs	

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Eligibility criteria	Interventions (drug, dose, duration)	Allowed other medications	Age Gender Ethnicity	Other population characteristics
Sirota, 2006 RCT, DB(?)	PANSS negative subscale score ≥15; SANS total score ≥60. Excluded due to: concurrent Axis 1 DSM-IV diagnosis, history of seizure disorder, al clinically significant medical condition that would interfere with evaluations or efficacy or tolerability, pregnancy, use of depot antipsychotics within 1 dosing interval, participation in another investigational drug trial w/in 30 ds for study entry.	olanzapine 5-20 mg/d quetiapine 200-800 mg/d Titration schedule: olanzapine - d 1-5: 5 mg/d; d 6-10: 10 mg/d; d 11-end of study: 15 mg/d; up to 20 mg/d permitted during this period of sufficient response not achieved quetiapine - d 1: 50 mg/d; d 2: 100 mg/d: d 3-4: 200 mg/d; d 5-7: 300 mg/d; two wks: 400 mg/d; six wks: 600 mg/d; up to 800 mg/d permitted if sufficient response was not achieved	biperiden; 1 pt received citalopram	Mean age 37.2 yrs (SD 11.5) 80% male Ethnicity NR	Mean duration of illness: 14.5 yrs (SD 8.2) Previous antipsychotic use: >99%

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Number screened/ eligible/ enrolled	Withdrawn/ Lost to follow-up/ Analyzed	Results
Sirota, 2006 RCT, DB(?)	NR/NR/40	5/NR/unclear - presumably 40. Analysis based on "ITT" of all pts w/at baseline and at least one baseline measurement w/LOCF.	No SS between-group differences for SANS or PANSS scores (total and subscale) Median change in SANS from baseline at wk 12: Total SANS: O -11 v Q -12 Affective flattening and blunting: O -5 v Q -5 Attention impairment: O -2 v Q 0 Avolition: O -2 v Q -2 Alogia: O -1 v Q -2 Median change in PANSS from baseline at wk 12: Total PANSS: O -11.0 v Q -13.0 PANSS negative symptom score: O -5.0 v Q -5.0 PANNS positive symptom score: O -4.0 v Q -1.0

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Adverse effects reported
Sirota, 2006 RCT, DB(?)	Anxiety: O 7/21 (33.3%) v Q 7/19 (36.8%) Insomnia: O 6/21 (28.6%) v Q 6/19 (31.6%) Abdominal pain: O 2/21 (9.5%) v Q 1/19 (5.3%) Fever: O 2/21 (9.5%) v Q 1/19 (5.3%) Rhinitis: O 2/21 (9.5%) v Q 1/19 (5.3%) Conjunctivitis: O 2/21 (9.5%) v Q 0 Mean weight change at 12 wks: O +2.3kg v Q -0.9kg (p<0.01)

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Extrapyramidal symptoms
Sirota, 2006 RCT, DB(?)	No clinically significant changes in SAS, BAS or AIMS scores in either group. Akathisia: O 3/21 (14.3%) v Q 3/19 (15.8%) Parkinsonism: O 5/21 (23.8%) v Q 3/19 (15.8%) Use of biperiden: O 6/21 (28.6%) v Q 5/19 (26.3%)

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Total withdrawals; withdrawals due to adverse events	Comments
Sirota, 2006 RCT, DB(?)	5 (O=3; Q=2) total WD 1 (O - jaundice) due to AEs	

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Eligibility criteria	Interventions (drug, dose, duration)	Allowed other medications	Age Gender Ethnicity	Other population characteristics
Smith 2009 Smith 2010 Open-label RCT single-center, psychiatric hospital, USA	Inclusion: inpatients with chronic DSM-IV schizophrenia or schizoaffective psychosis; age 18-65 ys. Exclusion: currently treated with clozapine or antidiabetic drugs	Olanzapine (5-40, mean 25.2 mg/d) or risperidone (2-12, mean 6.1 mg/d) for 5 mos	Statins allowed if started 2+ mos prior to study and no recent dosage changes	Mean age 41.9 98% male 74% Black	Olanzapine vs. risperidone: PANSS 64.04 (17.0) vs. 61.78 (13.7) Duration of illness 21.26 (11.42) vs. 23.17 (11.7) ys ys hospitalized 2.47 (3.0) vs. 3.16 (5.25) BMI 29.96 (6.50) vs. 28.85 (5.71) N with glucose >100 mg/dL in last 3 ys 5 vs. 7. 13/23 (56.5%) on olanzapine and 11/23 (48%) on risperidone were on same drug at baseline. 8/46 (17%) were not on either drug at baseline.

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Number screened/ eligible/ enrolled	Withdrawn/ Lost to follow-up/ Analyzed	Results
Smith 2009 Smith 2010 Open-label RCT single-center, psychiatric hospital, USA	166/80/58	9/0/46 3 completed less than 2 mos of drug treatment and were excluded from analysis	Olanzapine (n=23) vs. risperidone (n=23) Mean (±SEM) change from 5 mos vs. baseline; P-values for change within group BMI 1.39±0.51; P<0.01 vs. 0.59±0.50; P=ns Prolactin fasting ng/mL -8.41±4.71; P=ns vs. 11.98±4.71; P<0.05 No differential drug effect on PANSS, results NR. There was no differential drug effect of olanzapine v. risperidone on change in BMI, weight, or waist circumference over time. Effects of olanzapine and risperidone on fasting lipid metabolism (metabolic or other measure): Difference (5 months vs. baseline) Olanzapine diff (SEM) vs. Risperidone diff (SEM), ANOVA P BMI: 1.39 (0.51) vs. 0.59 (0.50), 0.235 Cholesterol fasting (mg/dL): 3.16 (6.20) vs. 3.215 (6.06), 0.5916 Triglyceride fasting (mg/dL): -12.61 (17.10) vs. -18.09 (16.65), 0.2604 Free fatty acid fasting (uEq/L): -33.3 (49.0) vs. -43.5 (52.7), 0.7123 Leptin fasting (ng/ml): 1.09 (1.00) vs. -0.65 (1.02), 0.5427 HDL fasting (mg/dL): 0.99 (1.60) vs. 2.22 (1.55), 0.7405 LDL fasting (mg/dL): 4.99 (6.33) vs. -2.27 (6.14), 0.1280 Cholesterol/HDL ratio: -0.01 (0.23) vs. -0.41 (0.23), 0.6545 Triglyceride/HDL ratio: -0.64 (0.63) vs. -0.59 (0.62), 0.2738 Effects of olanzapine and risperidone on lipid metabolism after fatty meal: Difference (2 months vs. baseline) Olanzapine diff (SEM) vs. Risperidone diff (SEM), ANOVA P Glucose (mg/dL) (1 hr): 6.56 (4.77) vs. 1.41 (4.43), 0.4328 Insulin (uIU/mL) (1 hr): -2.11 (7.07) vs. -8.09 (6.71), 0.1488 FFA (uEq/L) (4 hr): -66.1 (32.3) vs. 41.9 (33.7), 0.0260 Cholestrol (mg/dL) (4 hr): 15.79 (7.16) vs. 6.48 (6.67), 0.3472 Triglycerides (mg/dL) (4 hr): 50.29 (19.20) vs. -4.82 (17.81), 0.0119 HDL (mg/dL) (4 hr): 2.70 (1.41) vs. 1.23 (1.28), 0.4453 LDL fasting (mg/dL) (4 hr): 5.24 (4.58) vs. -2.27 (6.14), 0.8674 VLDL cholesterol (mg/dL) (4 hr): 16.73 (5.21) vs. 6.33 (5.02), 0.0062 VLDL tryiglycerides (mg/dL) (4 hr): 39.70 (23.83) vs. -22.67 (24.79), 0.0591

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Adverse effects reported
Smith 2009 Smith 2010 Open-label RCT single-center, psychiatric hospital, USA	One patient assigned to olanzapine was withdrawn before 2 mos of treatment due to abnormal glucose/lipid profile and excessive weight gain.

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Extrapyramidal symptoms
Smith 2009 Smith 2010 Open-label RCT single-center, psychiatric hospital, USA	NR

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Total withdrawals; withdrawals due to adverse events	Comments
Smith 2009 Smith 2010 Open-label RCT single-center, psychiatric hospital, USA	9 WD 1 due to AEs	

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Eligibility criteria	Interventions (drug, dose, duration)	Allowed other medications	Age Gender Ethnicity	Other population characteristics
Strakowski, 2005 (companion to Lieberman 2003, Green 2004, Perkins 2004) US & Europe HGDH Research Group	Same as Lieberman et al 2003.	Haloperidol 2-6 mg/d Olanzapine 5-20 mg/d with adjustments for both during the first 12 wks of study	Same as Lieberman et al 2003	Mean age 25 yrs (SD 5) 80% male 55% White 35% African-American 10% Other	Diagnosis: 61% schizophrenia 30% schizophreniform 9% schizoaffective PANSS total: 81 (SD 15) PAS total: 0.33 (SD 0.16) Duration of illness: 65 wks (SD 62) Duration of previous antipsychotic use: 6 wks (SD 10) Substance abuse disorder: 8% Hospitalized at index: 57%
Stroup 2009 CATIE Phase 3	18 to 65 ys, diagnosis of schizophrenia and appropriateness for oral antipsychotic medication	flexibile doses of monotherapies with oral aripiprazole, clozapine, olanzapine, perphenazine, quetiapine, risperidone, ziprasidone, LA injectable fluphenazine decanoate or a combination of any two of these treatments	Concomitant medications were permitted throughout the trial, except for additional antipsychotic agents.	Mean age: 40.5 ys (SD11.0) 70% male 67% white 30% African american 3% other	ys since first antipsychotic medication prescribed, Mean (SD) Aripiprazole: 11.8 (9.6) Clozapine: 8.3 (8.5) Olanzapine: 15.1 (10.2) Quetiapine:15.9 (10.5) Risperiodne: 16.1 (11.4) Ziprasidone: (13.9 (11.1)
Stroup, 2006 CATIE Phase 2T	Schizophrenia patients who had just discontinued treatment because patients who poorly tolerated their previous treatment, and discontinued their previous treatment because of inefficacy and did not want to consider treatment with clozapine, and discontinued their previous treatment independently of their doctor's recommendation.	Olanzapine 7.5–30 mg/d [N=66]; quetiapine, 200–800 mg/d[N=63]; risperidone, 1.5–6.0 mg/d [N=69]; ziprasidone, 40–160 mg/d [N=135]) up to a total of 18 mos, overall or at least 6 mos for this phase	Concomitant medications were permitted throughout the trial, except for additional antipsychotic agents.	Mean age=40.8 ys 69% male 66% white 30% black/African American 3% All other race groups 13% Hispanic	patients who discontinued the previous phase - "patient decision" (18%, N=81 of 448). intolerability: 87% [N=168 of 193]; inefficacy: 58% [N=184 of 318]).

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Number screened/ eligible/ enrolled	Withdrawn/ Lost to follow-up/ Analyzed	Results
Strakowski, 2005 (companion to Lieberman 2003, Green 2004, Perkins 2004) US & Europe HGDH Research Group	NR/NR/195	107/NR/195	No significant time-to-treatment group effects; significant improvement over time observed for all patients for most SF-36 variables for both interventions No further data on treatment groups provided; all other results combined interventions
Stroup 2009 CATIE Phase 3	eligible:410 Enrolled: 270	106/NR/Differen	Mean (SD) change in PANSS score at 6 mo from baseline : Aripiprazole(N=18) -13.7 (14.0), p<0.001 Clozapine (N=24)-13.3 (21.3)p=0.006 Olanzapine (N=30) -9.7 (16.3), p=0.003 Quetiapine(N=23) -7.0 (19.6), p=0.100 Risperidone (N=24) -8.1 (13.9), p=0.009 Ziprasidone (N=21) -3.1 (15.7), p=0.371
Stroup, 2006 CATIE Phase 2T	1493/1052/444	395 withdrawn of which 106 were taken out because of changed protocol./289 LTF/338 analyzed	Median time until treatment discontinuation for any reason (mos) olanzapine=6.3 vs risperidone=7.0 vs quetiapine=4.0 mos vs ziprasidone=2.8 HRs (95% CI) for pair-wise comparisons: olanzapine vs risperidone=1.02 (0.67 - 1.55) p = NR olanzapine vs quetiapine=0.65 (0.43 - 0.97) p< 0.05 olanzapine vs ziprasidone=0.61 (0.43 - 0.87) p< 0.01 risperidone vs quetiapine =0.64 (0.43 - 0.95) p< 0.05 risperidone vs ziprasidone =0.60 (0.42 - 0.85) p< 0.01 quetiapine vs ziprasidone =0.94 (0.67 - 1.31) p = NR PANSS Total Score differences at 3 mos olanzapine vs quetiapine=6.8 (p=0.005 and ziprasidone = 5.9 (p=0.005)

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Adverse effects reported
Strakowski, 2005 (companion to Lieberman 2003, Green 2004, Perkins 2004) US & Europe HGDH Research Group	NR
Stroup 2009 CATIE Phase 3	Aripiprazole vs clozapine vs olanzapine vs quetiapine vs risperidone vs ziprasidone Weight gain>7%: 7% vs 32% vs 23% vs 16% vs 14% vs 7%,p=0.031
Stroup, 2006 CATIE Phase 2T	olanzapine vs risperidone vs quetiapine vs ziprasidone (%pts) (p-values are NS unless otherwise specified and come from a test with df=3 comparing all treatment groups) Any serious AE: 6% vs 11% vs 8% vs 15% Insomnia: 13% vs 23% vs 16% vs 31%, p=0.01 Hypersomnia/sleepiness: 28% vs 22% vs 23% vs 13% Urinary hesitancy/dry mouth/constipation: 21% vs 21% vs 27% vs 17%p=0.002 Sex drive/sexual arousal/sexual orgasm: 17% vs 29% vs 11% vs 15% Gynecomastia/galactorrhea: 1% vs 5% vs 0 vs 1% Incontinence/nocturia: 1% vs 3% vs 4% vs 4% Orthostatic faintness: 7% vs 6% vs 13% vs 4% Skin rash: 2% vs 6% vs 8% vs 4% Weight gain from baseline ≥ 7%: 27% vs 13% vs 13% vs 6% Weight change (mean lb): 1.3 vs -0.2 vs 0.1 vs -1.7

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Author, year Study design	Extrapyramidal symptoms
Strakowski, 2005 (companion to Lieberman 2003, Green 2004, Perkins 2004) US & Europe HGDH Research Group	NR
Stroup 2009 CATIE Phase 3	Aripiprazole vs clozapine vs olanzapine vs quetiapine vs risperidone vs ziprasidone AIMS severity index ≥2: 9% vs 8% vs 0% vs 105 vs 19% vs 12%, p=0.231 Barnes Global clinical assessment ≥ 3: 0% vs 3% vs 3% vs 7% vs 3% vs 15%, p=0.201 Simpson-Angus EPS mean scale score≥ 3% vs 7% vs 3% vs 10% vs 3% vs 4%p= 0.493
Stroup, 2006 CATIE Phase 2T	AIMS severity score ≥ 2: 9% vs 8% vs 17% vs 10% Barnes score ≥ 3: 6% vs 3% vs 6% vs 5% Simpson-Angus mean score ≥ 1: 4% vs 12% vs 7% vs 4%

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Author, year Study design	Total withdrawals; withdrawals due to adverse events	Comments
Strakowski, 2005 (companion to Lieberman 2003, Green 2004, Perkins 2004) US & Europe HGDH Research Group		
Stroup 2009 CATIE Phase 3	Aripiprazole vs clozapine vs olanzapine vs quetiapine vs risperidone vs ziprasidone Total WD: 33% vs 46% vs 41% vs 36% vs 44% vs 41% (P=NS between groups) WD due to AE: 3% vs 16% vs10% vs 6% vs 6% vs 8% (P=NS between groups)	
Stroup, 2006 CATIE Phase 2T	289 WD 40 due to AE	

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Author, year Study design	Eligibility criteria	Interventions (drug, dose, duration)	Allowed other medications	Age Gender Ethnicity	Other population characteristics
Stroup, 2007 CATIE Phase 1B	Patients who were assigned to treatment in phase 1 with perphenazine and who discontinued it then entered phase 1B	olanzapine, 7.5–30.0 mg/d quetiapine 200–800 mg/d risperidone 1.5–6.0 mg/d 18 mos or discontinuation	Concomitant medications were permitted throughout the trial, except additional antipsychotics	Mean age=40.8 ys 77% male 65% white 33% black/African American 3% Asian 14% Hispanic	patients who discontinued perphenazine in phase 1 because of inefficacy (55 of 65, 85%) intolerability (37 of 40, 93%) “patient decision” (21 of 77, 27%).
Suzuki, 2007 Open label RCT Japan	Older than 18 ys and were required to score more than 54 points in the 18-item Brief Psychiatric Rating Scale BPRS.	First assigned to Olanzapine (N=26) First assigned to Quetiapine (N=26) First assigned to Risperidone (N=26) OLZ→QTP→RIS, OLZ→RIS→QTP, QTP→OLZ→RIS, QTP→RIS→OLZ, RIS→OLZ→QTP, RIS→QTP→OLZ. Up to 8 wks each	Lorazepam	Mean age 44.9 45% male Ethnicity NR	85% inpatients BPRS 72.6 (SD 8.5) DIEPSS 5.59 (SD 5.15) Duration of illness 17.0 (SD 11.7)

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Number screened/ eligible/ enrolled	Withdrawn/ Lost to follow-up/ Analyzed	Results
Stroup, 2007 CATIE Phase 1B	1894/192/115	77(68%)/0/114	Median time until treatment discontinuation for any reason (mos) olanzapine=7.1 vs quetiapine=9.9 vs risperidone=3.6 mos HRs (95% CI) for pair-wise comparisons: olanzapine vs quetiapine=0.97 (0.53 - 1.75) p= 0.91 olanzapine vs risperidone=0.53 (0.31 - 0.91) p= 0.02 quetiapine vs risperidone=0.55 (0.32 - 0.95) p= 0.04 Discontinuations due to lack of efficacy (% pts) olanzapine=18 vs quetiapine=34 vs risperidone=34 mos HRs (95% CI) for pair-wise comparisons: olanzapine vs quetiapine=0.55 (0.22 - 1.39) p= 0.21 olanzapine vs risperidone=0.36 (0.14 - 0.92) p= 0.04 quetiapine vs risperidone=0.66 (0.30 - 1.45) p= 0.30 PANSS Total Score Change at 3 mos olanzapine=9.6 vs quetiapine=6.5 vs risperidone=5.3 CGI severity change in score at 3 mos olanzapine=0.4 (vs. risperidone p = 0.03) vs quetiapine=0.5 (vs. risperidone p = 0.005) vs risperidone=0.1
Suzuki, 2007 Open label RCT Japan	78 enrolled	7 dropouts	Thirty-nine patients (50%) responded to the first agent (OLZ, n=16; QTP, n=9; RIS, n=14), 14 to the second agent (OLZ, n=6; QTP, n=5; RIS, n=3), and only two to the third agent (RIS alone). Sixteen patients (21%) failed to respond to all three atypical antipsychotics. Results for first arm only BPRS Baseline to endpoint Olanzapine 71.6 to 56.6 vs Quetiapine 71.4 to 60.6 vs Risperidone 72.6 to 58.6 Global assessment of functioning Baseline to endpoint Olanzapine 30.2to 44.4 vs Quetiapine 31.6 to 40.8 vs Risperidone 30.6 to 42.7 Severity of illness Baseline to endpoint Olanzapine 5.62 to 4.75 vs Quetiapine 5.6 to 4.98 vs Risperidone 5.64 to 4.91 Global improvement Olanzapine 3.06 vs Quetiapine 3.55 vs Risperidone 3.13

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Adverse effects reported
Stroup, 2007 CATIE Phase 1B	Olanzapine vs quetiapine vs risperidone (%pts) (p-values are NS) Any serious AE: 5% vs 11% vs 8% Insomnia: 10% vs 18% vs 16% , Hypersomnia/sleepiness: 26% vs 42% vs 16% Urinary hesitancy/dry mouth/constipation: 33% vs 16% vs 24% Decreased sex drive/sexual arousal/sexual orgasm: 23% vs 18% vs 13% Gynecomastia/galactorrhea: 3% vs 0 vs 0 Menstrual irregularities: 10% vs 13% vs 11% Incontinence/nocturia: 0% vs 3% vs 3% Sialorrhea: 0% vs 3% vs 8% Orthostatic faintness: 8% vs 18% vs 3% Skin rash: 8% vs 3% vs 11% Weight gain from baseline ≥ 7%: 36% vs 24% vs 14% Weight change (mean lb): 11.9 vs 2.0 vs 2.8
Suzuki, 2007 Open label RCT Japan	3 serious AEs 1 risperidone neuroleptic malignant syndrome 1 olanzapine minor episode of cerebrovascular accident 1 quetiapine acute obstructive suppurative cholangitis owing to cholelithiasis

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Extrapyramidal symptoms
Stroup, 2007 CATIE Phase 1B	AIMS severity score ≥ 2: 7% vs 12% vs 0% Barnes score ≥ 3: 0 vs 0% vs 0 Simpson-Angus mean score ≥ 1: 50 vs 0% vs 0
Suzuki, 2007 Open label RCT Japan	Drug-induced extrapyramidal rating scale Baseline to endpoint Olanzapine (n=50) 5.26 to 5.38 Quetiapine (n=45) 5.98 to 5.64 Risperidone (n=50) 6.10 to 6.62

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Total withdrawals; withdrawals due to adverse events	Comments
Stroup, 2007 CATIE Phase 1B	Total WDs 77 Due to AEs 17	
Suzuki, 2007 Open label RCT Japan	7 WD Due to AEs NR	

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Eligibility criteria	Interventions (drug, dose, duration)	Allowed other medications	Age Gender Ethnicity	Other population characteristics
Swartz, 2007 CATIE Phase 1 QOL subgroup (n=455)	Patients who completed the QOL Scale at baseline of Phase 1 and were available at the primary 12-mo endpoint (n=455)	see above	see above	Mean age=41.9 ys 75.8% male 62% white	Alcohol abuse=29% Drug abuse=20.4%
Tollefson, 1999a; Tollefson, 1999b (Tran, 1997 sub-analysis) RCT, multicenter, multinational (6 European, South Africa and US) Post-hoc Analysis of Depression, Mood disturbance, QoL	Diagnosis: schizophrenia, schizophreniform or schizoaffective disorders (DSM-IV), age 18-65, Min score of 42 on BPRS as extracted from PANSS (items 1-7); inpatient or outpatient	olanzapine: 10–20 mg/d mean dose: 17.2 mg/d risperidone: 4–12 mg/d mean dose: 7.2 mg/d Duration: 28 wks	benzodiazepines (limited use for agitation), chloral hydrate, diperiden or benztropine (up to 6mg/d) for treatment of EPS only	Mean age 36 65% male 75% white	82% diagnosis = schizophrenia mean length of current episode: 154 ds 80% had <4 prior episodes Prominent negative symptoms: 80%

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Number screened/ eligible/ enrolled	Withdrawn/ Lost to follow-up/ Analyzed	Results
Swartz, 2007 CATIE Phase 1 QOL subgroup (n=455)	1493/1440/455	NA/NA/455	Mean change in QOL Scale (p-value represents within-group difference from baseline) Olanzapine (n=145): 0.19, p<0.05 Perphenazine (n=74): 0.19, p=NS Quetiapine (n=82): 0.09, p=NS Risperidone (n=107): 0.26, p<0.01 Ziprasidone (n=47): 0.26, p=NS Paired comparisons P vs O vs Q vs R: F=0.59, p=0.62 O vs Q vs R: F=0.64, p=0.53
Tollefson, 1999a; Tollefson, 1999b (Tran, 1997 sub-analysis) RCT, multicenter, multinational (6 European, South Africa and US) Post-hoc Analysis of Depression, Mood disturbance, QoL	NR/NR/339	161/11/339	Overall Results: see Tran 1997 (HTA report tables) PANSS Mood item (scored 1-7): At 8 wks mean change: olanzapine 1.13 risperidone 0.85 (p=0.006) At 28 wks: olanzapine > risperidone (p=0.004, data NR) PANSS Depression Cluster (PDC): At 8 wks: olanzapine: 59% improvement vs risperidone: 45% improvement (p=0.045) Of those with >/= 20% improvement in total PANSS, Kaplan-Meier analysis of maintenance of response to 28 wks: olanzapine > risperidone (p=0.001) Relapse Risk (from wk 8 to wk 28) If change from baseline < 7 points PDC: NS difference If change from baseline >/= 7 points: RR R vs O 8.55 (95% CI 2.99 to 24.47)

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Adverse effects reported
Swartz, 2007 CATIE Phase 1 QOL subgroup (n=455)	NR
Tollefson, 1999a; Tollefson, 1999b (Tran, 1997 sub-analysis) RCT, multicenter, multinational (6 European, South Africa and US) Post-hoc Analysis of Depression, Mood disturbance, QoL	See Tran 1997

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Extrapyramidal symptoms
Swartz, 2007 CATIE Phase 1 QOL subgroup (n=455)	NR
Tollefson, 1999a; Tollefson, 1999b (Tran, 1997 sub-analysis) RCT, multicenter, multinational (6 European, South Africa and US) Post-hoc Analysis of Depression, Mood disturbance, QoL	NR

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Total withdrawals; withdrawals due to adverse events	Comments
Swartz, 2007 CATIE Phase 1 QOL subgroup (n=455)	N/A	
Tollefson, 1999a; Tollefson, 1999b (Tran, 1997 sub-analysis) RCT, multicenter, multinational (6 European, South Africa and US) Post-hoc Analysis of Depression, Mood disturbance, QoL	See Tran 1997	Further analysis presented to show relationship of PANSS-mood items and QLS.

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Eligibility criteria	Interventions (drug, dose, duration)	Allowed other medications	Age Gender Ethnicity	Other population characteristics
Tollefson, 2001	Schizophrenia Diagnosis: DSM-IV	olanzapine 15 mg/d, after first 2 wks 15–25 mg/d mean 21 mg clozapine fixed dose escalation from 25 to 200 mg/d during ds 1–8 of therapy; after first 2 wks, 200–600 mg/d mean 303 mg Duration: 18 wks	benzodiazepine (up to 40 mg daily diazepam equivalent or 8 mg lorazepam equivalent) for agitation, choral hydrate for insomnia, and biperiden or benztropine mesylate (up to 4 mg daily) for EPS permitted	Mean age (SD): 38.6 (10.6) ys 63.9% male Ethnicity NR	Schizophrenia subtypes: catatonic 3/180; disorganized 34/180; paranoid 101/180; undifferentiated 34/180; residual 8/180 Schizophrenia course: residual symptoms 81/180; no residual symptoms 3/180; continuous 92/180; in partial remission 2/180; other pattern 2/180
Tran, 1997 Edgell, 2000	Diagnosis: schizophrenia, schizophreniform or schizoaffective disorders (DSM-IV), age 18-65, Min score of 42 on BPRS as extracted from PANSS (items 1-7); inpatient or outpatient	olanzapine, 10–20 mg/d; risperidone, 4–12 mg/	benzodiazepines (limited use for agitation), chloral hydrate, diperiden or benztropine (up to 6mg/d) for treatment of EPS only	Mean age=36.21 64.9% male 74.6% white	81.7% diagnosis of schizophrenia 55.5% paranoid subtype Course of illness 39.8% continuous 34.5% episodic with inter-episode residual symptoms Age of onset of illness: 23.7 ys Length of patients' current episodes: 153.8 ds 80.4% had less than 10 previous episodes before entry into the study 41.9% were inpatients

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Number screened/ eligible/ enrolled	Withdrawn/ Lost to follow-up/ Analyzed	Results
Tollefson, 2001	NR/NR/180 olanzapine: 90 clozapine: 90	olanzapine 36/2/90 clozapine 37/2/90	PANSS total (positive; negative subscales). Final equals change from baseline: Olanzapine: (n= 89) –25.6,25.5(–6.8,7.6;–7.1,7.4) Clozapine: (n= 87) –22.1,23.1,p= 0.888 (–6.4,7.2;–5.6,6.9) CGI-S;BPRS total. Final equals change from baseline: Olanzapine: (n= 89) –1.1,1.2;–15.2,15.3 Clozapine: (n= 87) –0.9,1.1;–14.0,13.3 BPRS+ CGI-S; PANSS total score (≥20%;≥30%;≥40%;≥50% improvement; no improvement): Olanzapine: (n= 89) 34/89;53/89;41/89;24/89;9/89;11/89 Clozapine: (n= 87) 30/87;47/87;28/87;14/87;9/87;14/87
Tran, 1997 Edgell, 2000	NR/NR/339 olanzapine 172 risperidone 167	Withdrawn=161 (47.5%)/Lost to fu=11 (3.2%)/analyzed=33 1 olanzapine 166 risperidone 165	Olanzapine, risperidone, p-value Mean changes: PANSS Total: -28.1, -24.9, p=NS PANSS positive: -7.2, -6.9, p=NS PANSS negative: -7.3, -6.2, p=NS PANSS general psychopathology: -13.5, -11.8, p=NS PANSS depression item: -1.1, -0.7, p=0.004 BPRS total score: -17.0, -15.2, p=NS SANS summary score: -4.3, -2.9, p=0.020 CGI-S score: -1.1, -1.0, p=NS Improvement in PANSS total score ≥20%: 102 (61.5%), 104 (63%), p=NS ≥30%: 88 (53%), 72 (43.6%), p=NS ≥40%: 61 (36.8%), 44 (26.7%), p=0.049 ≥50%: 36 (21.7%), 20 (12.1%), p=0.020 Mean changes in QOL Scale scores: Total score: 13.4, 8.8, p=NS Common objective and activities: 1.6, 1.2, p=NS Instrumental role: 1.7, 1.1, p=NS Interpersonal relations: 5.4, 2.8, p=0.011 Intrapsychic foundation: 4.8, 3.7, p=NS

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Adverse effects reported
Tollefson, 2001	Olanzapine: somnolence 12/90; agitation 10/90; headache 10/90; insomnia 7/90; constipation 6/90; weight gain 6/90; anxiety 5/90; rhinitis 5/90; dry mouth 4/90 (p = 0.043); vomiting 4/90; influenza syndrome 3/90; asthenia 2/90; increased salivation 2/90, sweating 2/90; dizziness 1/90; fever 1/90; leucopenia 1/90; nausea 1/90 Clozapine: somnolence 22/90; agitation 4/90; headache 5/90; insomnia 3/90; constipation 17/90 (p = 0.014); weight gain 6/90; anxiety 5/90; rhinitis 3/90; vomiting 5/90; influenza syndrome 5/90; asthenia 6/90; increased salivation 26/90 (p < 0.001); sweating 5/90; dizziness 8/90 (p = 0.017); fever 5/90; leucopenia 5/90; nausea 10/90 (p = 0.005); tooth disorder 4/90 (p = 0.043) AMDP-5 solicited AEs scale (statistically significant): Olanzapine: drowsiness 23/89; hypersalivation 13/89; dry mouth 24/89 (p = 0.019) dizziness 6/89; increased perspiration 8/89; hypotonia 2/89; tardive dyskinesia 5/89 (p = 0.026); Clozapine: drowsiness 41/86 (p = 0.003) hypersalivation 54/86 (p < 0.001); dry mouth 11/86; dizziness 26/86 (p = 0.001); increased perspiration 19/89 (p = 0.016); hypotonia 9/86 (p = 0.025); tardive dyskinesia 0/86 Mean weight change (SD): olanzapine 1.8 (5.0) kg; clozapine 2.3 (4.9) kg – no significant difference Mean decrease in orthostatic blood pressure (SD): olanzapine 0.5 (14.5) mmHg; 3.7 (18.1) mmHg – no significant difference
Tran, 1997 Edgell, 2000	Olanzapine, risperidone, p-value Mean change in weight (kg): 4.1, 2.3, p=0.015 Corrected QTc interval prolongation: -4.9 vs 4.4, p=0.019 Prolactin concentrations (% pts with elevation above standard reference ranges): 51.2%, 94.4%, p<0.001 Hospitalization rate (ds/mo): 3.9, 4.5, p=NS Weight gain: olanzapine > risperidone (data nr, p-value nr) Nausea, amblyopia, extrapyramidal syndrome, increased salivation, suicide attempt, abnormal ejaculation, back pain, creatine phosphokinase increases, and urinary tract infection: risperidone > olanzapine (data nr, p-value nr) Solicited treatment-emergent AEs (AMDP-5) Backache: 11 (6.6%), 22 (13.3%), p=0.040 Blurred vision: 16 (9.6%), 34 (20.6%), p=0.005 Breathing difficulties: 12 (7.2%), 24 (14.5%), p=0.031 Delayed ejaculation: 3 (1.8%), 12 (7.3%), p=0.016 Early waking: 20 (12%), 40 (24.2%), p-0.004 Increased dreams/nightmares: 19 (11.4%), 32 (19.4%), p=0.043

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Extrapyramidal symptoms
Tollefson, 2001	EPS rating scales: SAS total; AIMS non-global total; BAS global score. Final equals change from baseline Intervention: (n = 88) –3.2, 4.8; –0.8, 2.2; –0.3, 0.9 Control: (n = 84) –1.4, 3.3 (p = 0.006); –0.7, 2.5; –0.4, 1.0
Tran, 1997 Edgell, 2000	Olanzapine, risperidone, p-value Dystonic events: 1.7%, 6%, p=0.043 Parkinsonian events: 9.9%, 18.6%, p=0.022 Any EPS event: 18.6%, 31.1%, p=0.008 Akathisia events: 9.9%, 10.8%, p=NS Dyskinetic events: 2.3%, 3%, p=NS Residual events: 1.7%, 0.6%, p=NS Treatment-emergent dyskinetic symptoms (categorical analysis of AIMS according to Schooler and Kane criteria): 4.6%, 10.7%, p=0.049

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Total withdrawals; withdrawals due to adverse events	Comments
Tollefson, 2001	olanzapine 36/90 (40%) Due to AE 4 (4.4%) clozapine 37/90 (41%) Due to AE 13 (14.4%)	General comments: Using 'absolute' observed group mean changes from baseline, difference in means was 3.5 units in favor of olanzapine, and one-sided lower 95% confidence limit, –2.2, indicating no clinical difference between treatments. Using 'adjusted' group mean changes from baseline, difference in means was 3.8 units in favor of olanzapine and one-sided lower 95% confidence limit,–1.9. Post-hoc ANCOVA: adjusted endpoint least squares means, 80.3 olanzapine;83.4 clozapine, with one-sided CI of –3.7
Tran, 1997 Edgell, 2000	olanzapine, risperidone, p-value WD: 73 (42.4%), 88 (52.7%), NS WD due to AE: 17 (9.9%), 17 (10.2%), NS	

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Eligibility criteria	Interventions (drug, dose, duration)	Allowed other medications	Age Gender Ethnicity	Other population characteristics
van Bruggen, 2003 Inpatients	Adolescents/young adults aged 16-28, first or second psychotic episode, schizophrenia, schizophreniform, schizoaffective disorder	6-10 week study Median doses: olanzapine: 15 mg/d, risperidone: 4 mg/d	Antidepressants, benzodiazepines, mood stabilizers, anticholinergics	Mean age: 21 ys 79% Male Ethnicity NR	Adolescents/young adults aged 16-28
Van Nimwegen, 2008 DB RCT Netherlands 4 center	Male and female; 18 to 30 ys old, w/ schizophrenia, schizoaffective disorder, or schizophreniform disorder based on the Structured Clinical Interview for the DSM-IV, patient version.	Olanzapine (5,10, 15, or 20 mg/d) n=59 Risperidone (1.25, 2.5, 3.75, or 5 mg) n=63 6 wks	NR	Mean age 24.6 yrs 91.3% male Ethnicity NR	90% schizophrenia, 6% schizophreniform disorder, 4% schizoaffective disorder Baseline Y-BOCS score overall mean, 5.3 $\pm$ 8.1 Baseline PANSS scores (62.9 $\pm$ 18.8 in olanzapine vs 65.8 $\pm$ 20.2 in risperidone) Baseline CDSS scores (3.1 $\pm$ 5.8 in olanzapine vs 2.8 $\pm$ 12.3 in risperidone)

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Number screened/ eligible/ enrolled	Withdrawn/ Lost to follow-up/ Analyzed	Results
van Bruggen, 2003 Inpatients	NR/NR/44	NR/NR/31	Mean change in scores from baseline to endpoint: PANSS Total: O: -15.1 vs R: -15.0 Positive Symptoms: O: -0.3 vs R: -3.2 Negative Symptoms: O: -1.9 vs R: -1.9 Depression Symptoms: O: 2.1 vs R: 0.7 Agitation/excitement: O: -0.7 vs R: 0.4 Disorganization: O: 1.1 vs R: 0.8 General psychopathology: O: -6.6 vs R: -6.3 Achievement of remission at Endpoint: O: 28% vs R: 11%
Van Nimwegen, 2008 DB RCT Netherlands 4 center	Screened NR/ 201 eligible / 131 took one dose	9 / 9/ 122	Olanzapine vs. risperidone Y-BOCS total score total group (N = 122: –2.2 vs –0.3, z = –2.651, P < 0.01), Baseline Y-BOCS total score > 0 (n = 58: –5.1 vs –0.4, z = –2.717, P < 0.01), Baseline Y-BOCS total > 10 (n = 29: –7.1 vs –0.6, z = –2.138, P = 0.032).

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Adverse effects reported
van Bruggen, 2003 Inpatients	Somnolence: O: 25% vs R: 66% Excessive thirst: O: 17% vs R: 53% Decreased libido: O: 17% vs R: 53% Excessive appetite: O: 42% vs R: 42% Akathisia: O: 33% vs R: 32% Headache: O: 33% vs R: 5% Dry Mouth: O: 25% vs R: 32% Dizziness: O: 25% vs R: 26% Difficulty falling asleep: O: 25% vs R: 26% Heaviness in legs: O: 25% vs R: 21% Menstrual difficulties: O: 25% vs R: 0% Hypersalivation: O: 17% vs R: 26% Increased perspiration: O: 17% vs R: 21% Palpitations: O: 17% vs R: 16% Blurred vision: O: 17% vs R: 16% Decreased appetite: O: 8% vs R: 16% Nausea: O: 8% vs R: 16% Vomiting: O: 8% vs R: 16% Breathing difficulties: O: 0% vs R: 16% Backache: O: 0% vs R: 16% Chills: O: 8% vs R: 16%
Van Nimwegen, 2008 DB RCT Netherlands 4 center	NR

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Extrapyramidal symptoms
van Bruggen, 2003 Inpatients	Parkinsonism: O: 3% vs R: 3%
Van Nimwegen, 2008 DB RCT Netherlands 4 center	NR

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Total withdrawals; withdrawals due to adverse events	Comments
van Bruggen, 2003 Inpatients	NR/NR	
Van Nimwegen, 2008 DB RCT Netherlands 4 center	9 WD Due to AEs NR	

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Eligibility criteria	Interventions (drug, dose, duration)	Allowed other medications	Age Gender Ethnicity	Other population characteristics
Volavka, 2001 DB, RCT Inpatients	Treatment-resistant, inpatients with DSM-IV diagnosis of schizophrenia, or schizoaffective disorder	14 week trial: clozapine (N=40): target for wks 1-8: 500 mg/d, mean dose for wks 9-14: 526.6 mg/d olanzapine (N=39): target for wks 1-8: 20 mg/d, mean dose for wks 9-14: 30.4 mg/d risperidone (N=41): target for wks 1-8: 8 mg/d, mean dose for wks 9-14: 11.6 mg/d haloperidol (N=37): target for wks 1-8: 20 mg/d, mean dose for wks 9-14: 25.7 mg/d	Benztropine, propranolol, lorazepam, diphenhydramine hydrochloride, chloral hydrate	Mean age: 40.33 ys 84% Male 29% Caucasian 58.4% African-American 10.9% Hispanic 2% Asian-Pacific Islander	Schizophrenia: 135(86%) Schizoaffective disorder: 22(14%) 100% Male for testing of prolactin levels of plasma

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Number screened/ eligible/ enrolled	Withdrawn/ Lost to follow-up/ Analyzed	Results
Volavka, 2001 DB, RCT Inpatients	NR/167/157	0/0/157 22 analyzed with Total Aggression Severity (TAS) 101 analyzed for glucose and cholesterol levels and weight gain 16 analyzed for prolactin levels of plasma	PANSS mean scores- hostility item: baseline vs endpoint clozapine: 2.68 vs 2.24 olanzapine: 2.35 vs 2.24 risperidone: 2.40 vs 2.49 haloperidol: 2.42 vs 2.95 Superiority over haloperidol at 14 wks: clozapine: (p<0.007) olanzapine: (p<0.02) risperidone: (p=NR) haloperidol: (p=NR) Mean glucose level changes from baseline at 8 wks and 14 wks: clozapine: 17.1, 4.4; (p=NS) haloperidol: 8.4, 10.6; (p=NS) olanzapine: 1.9, 14.3; (p<0.02) risperidone: -1.3, 2.7; (p=NS) Mean change from baseline in cholesterol levels: 8 wks, 14 wks clozapine: 14.7, 16.3 mg/dl; (p=NS) haloperidol: -4.9, -4.4 mg/dl; (p=NS) olanzapine: 12.3, 20.1 mg/dl; (p<0.002) risperidone: 4.2, 9.2 mg/dl; (p=NS) Overall analysis of variance, effect of medication type on TAS: (p<0.013) Comparison of clozapine vs haloperidol: (p<0.007) Overall analysis of variance, effect of medication type on PANSS: (p=0.008) Negative relationship between TAS vs PANSS: (p=0.0004) Clozapine's efficacy increased with TAS, efficacy of risperidone and olanzapine decreased with TAS Olanzapine superior to haloperidol: (p<0.012), olanzapine superior to risperidone: (p<0.016), clozapine to haloperidol: (p<0.065)Risperidone: dose-dependent increased elevation of prolactin levels: (p<.05) Pair-wise comparisons significant increase in prolactin levels: Haloperidol vs clozapine: (p<.002) Haloperidol vs olanzapine: (p<.026) Olanzapine vs clozapine: (p=NS)

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Adverse effects reported
Volavka, 2001 DB, RCT Inpatients	Weight gain (kg), mean change from baseline olanzapine: 7.3 (7.6), p<0.0001 clozapine: 4.8(6.1), p<0.0003 risperidone: 2.4(6.3), p=0.09 haloperidol: 0.9(5.7), NS Association of cholesterol change and weight gain at endpoint four groups combined, p=0.0008 clozapine group, p=0.008 olanzapine group, p=0.035 after baseline cholesterol and weight were introduced as covariates in the analyses clozapine group, p<0.03 olanzapine group, p=0.06

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Extrapyramidal symptoms
Volavka, 2001 DB, RCT Inpatients	Mean Extrapyramidal Symptoms scores from baseline: clozapine: at 8 wks: 5.3; (p<0.03), at 14 wks: 5.1; (p<0.005) olanzapine: at 8 wks: 3.7; (p<<0.0008), at 14 wks: 3.8; (p<0.0001) risperidone: at 8 wks: 4.7; (p<0.002), at 14 wks: 4.8; (p<0.005) haloperidol: at 8 wks: 4.7; (p=NR), at 14 wks: 4.4; (p=NR)

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Total withdrawals; withdrawals due to adverse events	Comments
Volavka, 2001 DB, RCT Inpatients	0 WD 0 due to AEs	

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Eligibility criteria	Interventions (drug, dose, duration)	Allowed other medications	Age Gender Ethnicity	Other population characteristics
Voruganti, 2007 RCT, rater blinded, multicenter	Established diagnosis of schizophrenia (DSM-IV) confirmed through administration of SCID; male or female aged 18-65; treated with first generation antipsychotic drugs and in need of switch to a second generation antipsychotic drug due to unresolved symptoms or distressing side effects. Exclusion criteria: developmental disorders, epilepsy or acquired brain injury and significant substance abuse comorbidity; lack of competence to consent		Rescue medications included benzodiazepines (lorazepam or clonazepam for anxiety and agitation or sleep difficulties); and adjunctive medications or anti-Parkinsonian medications were added, if felt necessary by physician, and were recorded for every patient	Mean age yrs (SD): olanzapine: 41.33 (13.61) quetiapine: 38.72 (14.37) % male olanzapine: 83% quetiapine: 65% Ethnicity: NR	Duration of illness y (SD): olanzapine: 15.33 (11.31) quetiapine: 14.16 (11.76)
Wahlbeck, 2000 Open-label RCT	Diagnosis: schizophrenia (DSM-IV); Treatment-resistant: persistent psychotic symptoms for < 6 mos while on medication from ≥ 2 different classes of antipsychotic drugs in doses ≥ 1000 mg/d chlorpromazine for > 6 wks each; in addition, non-tolerance to haloperidol or non-response to haloperidol, > 40 mg/d	clozapine 400 mg/d for 2 wks; flexible thereafter 600 mg/ d mean 385 mg/d risperidone, 6 mg/d for 3 ds; flexible thereafter up to 10 mg/d mean 7.8 mg/d Duration: 10 wks preceded by 6-week treatment with haloperidol, ≤ 50 mg/d if no history of previous treatment with haloperidol, > 40 mg/d, or haloperidol intolerance	biperiden (EPS) and lorazepam (anxiety) as required	Mean age 35.9 ys; range, 24–55 ys 55% male Ethnicity NR	Duration of illness, ~ 12 ys, range 0.5–33 ys; treatment resistant* illness

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Number screened/ eligible/ enrolled	Withdrawn/ Lost to follow-up/ Analyzed	Results
Voruganti, 2007 RCT, rater blinded, multicenter	NR/NR/86	1 post-randomization exclusion/85 analyzed	Clinical outcomes at 12 mos (olanzapine vs. quetiapine) PANSS Total: 48.5 (9.9) vs. 49.4 (12.0); F=1.67 (df=1,79), P=0.28 Positive symptom subscale: 15.5 (4.58) vs. 11.4 (4.3); F=0.001 (df=1,79), P=0.97 Negative symptom subscale: 10.9 (3.15) vs. 14.8 (6.03); F=1.037 (df=1,79), P=0.31 General Psychopathology subscale: 22.3 (4.99) vs. 23.78 (6.2); F=1.772 (df=1,79), P=0.18 Cognitive cluster: 18.4 (5.41) vs. 15.64 (4.9); F=11.28 (df=1,79), P=0.02 DAI: 3.70 (1.50) vs. 6.26 (1.22); F=10.69 (df=1.79), P=0.002 PETiT (compliance subscale): 14.7 (3.1) vs. 16.34 (1.79); F=3.622 (df=1,67), P=0.06 BWISE: 10.95 (3.0) vs. 15.68 (3.1); F=52.73 (df=1,79), P=0.001 Functional outcomes at 12 mos (olanzapine vs. quetiapine) SSTICS: 30.2 (18.2) vs. 19.4 (12.4); F=10.54 (df=1,71), P=0.002 Muller-Lyer's Visual task: 71.3 (10.6) vs. 67.2 (10.5); F=1.36 (df=1,81), P=0.56 Size estimation task: 2.88 (1.15) vs. 2.39 (0.62); F=0.84 (df=1,81), P=0.36 Backward masking task: 21.0 (4.82) vs. 26.17 (5.4); F=10.81 (df=1,81), P=0.01 Asarnow's task: 13.16 (2.3) vs. 15.39 (2.4); F=12.73 (df=1,81), P=0.01 Wisconsin card sorting test Total score: 63.0 (11.6) vs. 65.4 (12.6); F=34.74 (df=1,80), P=0.001 Perseverative errors: 17.19 (3.7) vs. 12.12 (3.5); F=65.74 (df=1,81), P=0.001 Random errors: 17.42 (4.2) vs. 11.39 (3.9); F=35.4 (df=1,81), P=0.001 Psychosocial functioning SIP: 65.7 (13.7) vs. 64.8 (14.6); F=0.431 (df=1,78), P=0.51 GAF: 64.72 (7.8) vs. 66.1 (8.05); F=0.881 (df=1,79), P=0.35
Wahlbeck, 2000 Open-label RCT	9000/90/20	7/NR/19	20% improvement on PANSS: 50% clozapine, 67% risperidone (p=0.65) Hospital discharge: 60% clozapine, 78% risperidone (p=0.63) Mean Change in score (clozapine/risperidone, p-value) PANSS total: -10/-18 (NS) PANSS positive -4/-4 (NS) PANSS negative +1/-4 (p=0.056) CGI-S -0.6/-1.3 (NS) GAF: +4/+13 (NS) SFS: -13/-9 (NS) DAI: -0.8/-0.6 (NS)

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Adverse effects reported
Voruganti, 2007 RCT, rater blinded, multicenter	Outcomes at 12 mos (olanzapine vs. quetiapine): UKU-SR: 21.9 (10.7) vs. 16.14 (8.8); F=2.674 (df=1,79), P=0.1 Weight gain (kg): 7.24 (2.43) vs. 2.84 (1.72); F=5.679 (df-1,79), P=0.02 # of Dysglycemics: 13 vs. 4, P=0.001
Wahlbeck, 2000 Open-label RCT	NR

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Extrapyramidal symptoms
Voruganti, 2007 RCT, rater blinded, multicenter	Outcomes at 12 mos (olanzapine vs. quetiapine) SAS: 0.37 (1.21) vs. 0.26 (1.24); F=0.035 (df=1, 79), P=0.85 AIMS: 0.92 (1.50) vs. 0.75 (1.06); F=0.024 (df=1,75), P=0.62 BAS: 0.05 (0.32) vs. 0.13 (0.47); F=2.239 (df=1,79), P=0.13
Wahlbeck, 2000 Open-label RCT	NR

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Total withdrawals; withdrawals due to adverse events	Comments
Voruganti, 2007 RCT, rater blinded, multicenter	0 total WD 0 due to AEs	
Wahlbeck, 2000 Open-label RCT	6/20 ((30%) total WD 3 (15%) due to AE 11% risperidone 18% clozapine	Pilot study.

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Eligibility criteria	Interventions (drug, dose, duration)	Allowed other medications	Age Gender Ethnicity	Other population characteristics
Wampers, 2012 Non-randomized, open-label	Patients admitted to psychiatric center with schizophrenia, free of antipsychotic medications	A. Risperidone, mean dose 3.9±1.6 mg/d B. Olazapine, mean dose 17.1±6.7 mg/d	Anticholinergics, benzodiazepines, antidepressants, mood stabilizers, additional sedatives, somatic mediacations, antihypertensives	Age: 32.3±10.8 y Gender: 34.5% Ethnicity: NR	First episode patients: 18.6% DSM diagnosis: schizoaffective disorder, 24.8%; schizophrenia, paranoid 32.7%; schizophrenia, undifferentiated 23.9%

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Number screened/ eligible/ enrolled	Withdrawn/ Lost to follow-up/ Analyzed	Results
Wampers, 2012 Non-randomized, open-label	NR/NR/125	NR/NR/113	NR

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Adverse effects reported
Wampers, 2012 Non-randomized, open-label	Change in metabolic parameters from baseline, risperidone vs. olanzapine, p-value for time x medication group: Adiponectin, ng/mL: 970.4±5847.6 vs. -2291.9±4948.4, p=0.0015 Glucose, mg/dl: 1.2±7.5 vs. 2.3±9.8, p=NS Insulin, mIU/l: 0.6±9.5 vs. 2.3±22.7, p=NS TG, mg/dl: 11.0±59.7 vs. 17.2±65.7, p=NS Cholesterol, mg/dl: 11±28.8 vs. 21.1±37.5, p=NS NonHDL, mg/dl: 10±28.6 vs. 24.2±37.3, p=0.0247 HDL, mg/dl: 1±13.8 vs. -3.2±11, p=NS LDL, mg/dl: 6.2±35.8 vs. 18.33±35.7, p=NS HOMA-IR: -0.1±2.0 vs. 0.33±7.2, p=NS AUC insulin: -0.1±3.0 vs. -0.4±5.2, p=NS BMI: 1.0±1.9 vs. 2.3±1.7, p=0.0002 Weight, kg: 3.1±5.7 vs. 7.1±5.3, p=0.0002 Waist, cm: 3.2±6.4 vs. 6.9±6.1, p=0.0019

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Extrapyramidal symptoms
Wampers, 2012 Non-randomized, open-label	NR

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Total withdrawals; withdrawals due to adverse events	Comments
Wampers, 2012 Non-randomized, open-label	NR	

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Eligibility criteria	Interventions (drug, dose, duration)	Allowed other medications	Age Gender Ethnicity	Other population characteristics
Wang, 2006 RCT, DB	Diagnosed with schizophrenia spectrum disorder by SCID; judged by treating clinician to have been stable on conventional antipsychotic meds for at least 2 ys; no previous therapeutic trial with an atypical antipsychotic medication; had a reason for switching to atypical antipsychotic medication including desire for improved efficacy, improved side effect profile and/or reduced risk of developing or worsening Tardive dyskinesia Exclusion criteria: unstable psychiatric, metabolic, hematologic, CV, hepatic or renal function	risperidone (n=19): mean dose 5.3 mg/d olanzapine (n=17): mean dose 13.8 mg/d	NR for 12 week outcome phase	Age mean yrs (SD): 47.0 (9.3) risperidone: 45.2 (9.9) olanzapine: 48.9 (8.4) % male (risperidone vs. olanzapine): 42.1% vs. 52.9%, P=0.74 % African American (risperidone vs. olanzapine): 89.5% vs. 82.4%, P=0.65 % White: 10.5% vs. 17.6%	Schizophrenia: 63.2% vs. 70.6% Schizoaffective: 36.8% vs. 29.4% PANSS score at baseline: risperidone 59.3 (12.4) olanzapine: 55.9 (13.4) P=0.46

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Number screened/ eligible/ enrolled	Withdrawn/ Lost to follow-up/ Analyzed	Results
Wang, 2006 RCT, DB	NR/NR/36	13 withdrew; analysis based on ITT population (N=36) using LOCF	PANSS mean (SD) risperidone vs. olanzapine Total score Baseline: 59.3 (13.4) vs. 55.9 (13.7) Endpoint: 44.3** (9.8) vs. 46.9** (13.2) Factor Scores--Positive Baseline: 14.9 (5.3) vs. 14.0 (5.7) Endpoint: 10.4** (3.7) vs. 11.6* (4.9) Factor Scores--Negative Baseline: 16.4 (4.9) vs. 16.8 (4.0) Endpoint: 12.3** (3.7) vs. 13.3** (3.7) Disorganized thoughts Baseline: 14.1 (3.9) vs. 12.8 (3.9) Endpoint: 11.3** (2.6) vs. 10.7** (3.2) Uncontrolled hostility/excitement Baseline: 5.9 (2.0) vs. 5.3 (2.0) Endpoint: 4.4** (0.7) vs. 5.1 (1.7) Anxiety and depression Baseline: 8.1 (3.2) VS. 7.0 (3.0) Endpoint: 5.9** (2.8) vs. 6.2 (2.7) *Significantly lower than baseline (within group comparison, P<0.05) **Significantly lower than baseline (within group comparison, P<0.01)

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Adverse effects reported
Wang, 2006 RCT, DB	Both risperidone and olanzapine patients exhibited significant weight increase during study. Risperidone patients gained 3.4 lbs (SD 6.2) (t=2.4, df=18, P<0.05) vs. 7.6 lbs (SD 9.6) increase in olanzapine patients (t=3.3, df=16, P<0.01). Comparison of weight increases between groups revealed significantly higher gain in olanzapine treated group at 16 wks (t=2.3, df=34, P<0.05), however at 22 wks this difference was no longer significant (t=1.6, df=34, P=0.12). No other AEs reported

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Extrapyramidal symptoms
Wang, 2006 RCT, DB	Simpson-Angus scores decreased in both groups comparably over course of study (F[5,204]=4.2, P<0.01).

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Total withdrawals; withdrawals due to adverse events	Comments
Wang, 2006 RCT, DB	13 (36%) total WD risperidone: 8 olanzapine: 5 6 (16.7%) due to AEs risperidone: 4 olanzapine: 2	

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Eligibility criteria	Interventions (drug, dose, duration)	Allowed other medications	Age Gender Ethnicity	Other population characteristics
Weiden 2009 Open-label RCT 2 sites, USA	Target population: first-episode schizophrenia patients. Assessment phase inclusion: Aged 16-40; inpatients or outpatients with a provisional diagnosis of schizophreniform disorder, schizophrenia, or schizoaffective disorder; and <=16 wks of lifetime total AP medication exposure. Subjects were treated clinically for up to 12 wks before being assigned into the RCT. RCT inclusion: SCID-confirmed diagnosis of schizophrenia, schizophreniform disorder, or schizoaffective disorder; clinical indication for a long-term maintenance AP treatment; clinical response to oral AP medication during evaluation. phase; willingness to attend outpatient treatment services; and completion of at least 1 baseline psychoeducation session that included a key family member.	Compares risperidone LA injectable to oral risperidone. Assessment phase: study clinicians could prescribe any AAP except clozapine. RCT: subjects were randomized to remain on oral medication, or to change to risperidone long-acting injection (RLAI); both groups received up to 2 psychoeducation sessions. Those on RLAI received an initial injection of 25 mg RLAI with initial overlap with oral risperidone for at least 3 wks. The target maintenance dose for RLAI was 25 mg (allowable range 25-50 mg) every 2 wks. Reports on the first 12 wks of followup.	Adjunctive therapies for affective or anxiety symptoms were allowed. Oral supplementation was permitted for acute exacerbations of positive symptoms, but long-term use (>4 wks) of oral antipsychotic with risperidone LA injectable was not permitted in maintenance phase treatment.	Median age 23 ys 69% male 34% African American 57% Afro-Caribbean	At study entry, 81% (n=30) were on oral risperidone at study entry; 11% (n=4) on haloperidol; 5% (n=2) on olanzapine; 3% (n=1) on quetiapine.

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Number screened/ eligible/ enrolled	Withdrawn/ Lost to follow-up/ Analyzed	Results
Weiden 2009 Open-label RCT 2 sites, USA	74/46/37	0/0/37	26 assigned to risperidone LA injectable; 11 assigned to oral risperidone. 19 of 26 (73%) assigned to risperidone LA injectable accepted 9 (24%) of all 37 subjects experienced at least 1 GAP within 12 wks after randomization. In ITT analysis there were no differences between RLAI and Oral groups on adherence: At least 1 GAP by week 12: 6/26 (23%) on RLAI vs. 3/11 (27%) on Oral; P=1.0 In analysis of actual treatment (where oral group includes subjects assigned to RLAI but declined), RLAI accepters were more likely to remain adherent than remaining Oral group. Risperidone LA injectable vs. oral: At least 1 GAP by week 12: 2/19 (11%) vs. 7/18 (39%); P=0.063 Kaplan-Meier analysis, %Adherence: 89%; 95%CI,64%-97% vs. 59%; 95%CI, 32%-78%; P=0.035 Medication adherence attitudes were similar between groups for either ITT or AAT comparison.

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Adverse effects reported
Weiden 2009 Open-label RCT 2 sites, USA	Reports that there was no side-effect distress in either group at 12 wks.

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Extrapyramidal symptoms
Weiden 2009 Open-label RCT 2 sites, USA	NR

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Total withdrawals; withdrawals due to adverse events	Comments
Weiden 2009 Open-label RCT 2 sites, USA	0 WD 0 due to AEs	

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Eligibility criteria	Interventions (drug, dose, duration)	Allowed other medications	Age Gender Ethnicity	Other population characteristics
Weiden, 2003 open-label CCT (3 separate open-label studies on switching to Z from O, R, or Typicals)	Men or women aged 18 to 55, DSM-IV schizophrenia or schizoaffective disorder outpatients status for ≥ 3 mos; treatment with current antipsychotic within 25% of recommended dosage for ≥ 3 mos with at least partial response (CGI-I score <4 since the initiation of current antipsychotic); inadequate response to or poor tolerability of current medication; and 8th grade reading level.	Flexible dose of ziprasidone though week 6 (40-160mg/d) Mean ziprasidone daily dose: 91mg for those switched from conventional antipsychotic; 90mg for those switched from olanzapine; 92mg for those switched from risperidone 6-week duration	Other psychotropic agents were not allowed (except for anti-EPS agents)	Mean age: 37.6 ys Age range: 18-61ys 65.5% male Ethnicity: NR	Mean baseline PANSS total score Conventional: 67.5 (SD: 16.3) Olanzapine: 65.6 (SD: 16.7) Risperidone: 71.0 (SD: 19.0) Mean baseline CGI-S Conventional: 3.5 (SD: 0.74) Olanzapine: 3.5 (SD: 0.81) Risperidone: 3.7 (SD: 0.74)

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Number screened/ eligible/ enrolled	Withdrawn/ Lost to follow-up/ Analyzed	Results
Weiden, 2003 open-label CCT (3 separate open-label studies on switching to Z from O, R, or Typicals)	NR/ NR/ 270	Unclear: numbers analyzed changed depending on the test	All results were health indices

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Adverse effects reported
Weiden, 2003 open-label CCT (3 separate open-label studies on switching to Z from O, R, or Typicals)	Mean body weight change in patients from baseline to week 6; p-values for baseline vs wk 6: Olanzapine (n=99): -1.8 kg (estimated from figure), p<0.0001 Risperidone (n=55): - 0.86kg, p<0.002 Conventional antipsychotics (n=102): +0.27kg, p=0.3 Median change in prolactin levels baseline to wk 6 (approximated from figure; p-values for baseline vs wk 6) Olanzapine (n=92) : -2 mg/ml, p=0.6 Risperidone (n=49): -32 mg/ml, p<0.0001 Conventional antipsychotics (n=81): -4 mg/ml, p<0.05 Median change in triglyceride levels baseline to wk 6; p-values for baseline vs wk 6: Olanzapine (n=91): -50 mg/dL, p<0.0001 Risperidone (n=50): -29 mg/dL, p<0.01 Conventional antipsychotics (n=82): -17mg/dL, p=NS (estimated from graph) Median change in total nonfasting cholesterol levels baseline to wk 6; p-values for baseline vs wk 6: Olanzapine (n=91): -21 mg/dL, p<0.0001 (estimated from graph) Risperidone (n=50): -18mg/dL, p<0.01 (estimated from graph) Conventional antipsychotics (n=82): - 3 mg/dL, p= NS (estimated from graph)

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Extrapyramidal symptoms
Weiden, 2003 open-label CCT (3 separate open-label studies on switching to Z from O, R, or Typicals)	Mean Simpson-Angus scores: Significant % improvement after switching from: Conventional antipsychotics: 48% improvement, p<0.0001, effect size 0.493 Risperidone: 45% improvement, p<0.001, effect size: 0.381 Concomitant antiparkinsonian drug use decreased for patients who switched from conventional antipsychotics: 58% at baseline to 14.8% after 6 wks. Concomitant antiparkinsonian drug use decreased for prior risperidone pts from 26% to 8.6% at 6 wks.

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Total withdrawals; withdrawals due to adverse events	Comments
Weiden, 2003 open-label CCT (3 separate open-label studies on switching to Z from O, R, or Typicals)	The studies were completed by 72%, 79%, and 79% of patients switched from conventional antipsychotics, olanzapine, and risperidone, respectively. Discontinuations due to AEs after switching from: Conventional antipsychotics: 11% Olanzapine: 6% Risperidone: 9%	

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Eligibility criteria	Interventions (drug, dose, duration)	Allowed other medications	Age Gender Ethnicity	Other population characteristics
Wu, 2006 Wu, 2007 Randomized, unblinded, longitudinal study	Consistently referred patients, aged 18-45 with a first psychotic episode of schizophrenia diagnosed with DSM-IV criteria; to remain hospitalized for 8 wks; had same diets throughout trial; no use of any antipsychotics or other recreational drugs before enrollment; not involved in weight reduction diets or progs. Exclusion criteria: pregnant or lactating; MR; addictive disorder; specific systemic diseases or other medical conditions such as diabetes mellitus, dyslipidemia, CV diseases, and hypertension.	Clozapine (n=30): 200-400 mg/d Olanzapine (n=24): 10-20 mg/d Risperidone (n=29): 2-5 mg/d Sulpiride (n=29): 600-1,000 mg/d 8 week study duration	Only trihexyphenidyl for EPS or lorazepam for insomnia or agitation was allowed on a needed basis	Age, mean (SD) All: 34.87 (10.20) clozapine: 32.6 (8.4) olanzapine: 34.2 (10.3) risperidone: 33.4 (9.7) sulpiride: 32.9 (8.6) % female All: 50% clozapine: 53% olanzapine: 42% risperidone: 52% sulpiride:52% Ethnicity: NR (presumably 100% Chinese)	Schizophrenia, paranoid type clozapine: 47% olanzapine: 54% risperidone: 48% sulpiride: 48% Schizophrenia, catatonic type clozapine: 3% olanzapine: 0% risperidone: 4% sulpiride: 4% Schizophrenia, disorganized type clozapine: 7% olanzapine: 8% risperidone: 10% sulpiride: 7% Family history of type II diabetes clozapine: 10% olanzapine: 8.3% risperidone: 7% sulpiride: 7%
Yamashita, 2004 Inpatients	Schizophrenia	Olanzapine: 2.5-20.0 mg/d Perospirone: 4.0-48.0 mg/d Quetiapine: 50.0-750.0 mg/d Risperidone: 1.0-12.0 mg/d	NR	Mean age: 59.9 ys 52.1% Male Ethnicity NR	100% In-patient Schizophrenia Diagnoses: Disorganized: 29(31.5%) Paranoid: 11(11.9%) Undifferentiated: 52(56.5%)

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Number screened/ eligible/ enrolled	Withdrawn/ Lost to follow-up/ Analyzed	Results
Wu, 2006 Wu, 2007 Randomized, unblinded, longitudinal study	NR/NR/120	8/112	Difference between baseline and endpoint of metabolic profiles (clozapine vs. olanzapine vs. risperidone vs. sulpiride): BMI (kg/cm2): 1.49 (0.20) vs. 1.11 (0.13) vs. 0.19 (0.12) vs. 0.66 (0.12); P=0.009 WHR: 0.02 (0.007) vs. 0.01 (0.005) vs. 0.007 (0.002) vs. 0.008 (0.003); P=ns FG (mmol/l): -0.07 (0.03) vs. -0.05 (0.01) vs. -0.12 (0.06) vs. - 0.03 (0.02); P=ns TG (mmol/l): 0.48 (0.07) vs. 0.39 (0.08) vs. 0.11 (0.05) vs. 0.17 (0.05); P=0.02 CHOL (mmol/l): 0.63 (0.18) vs. 0.75 (0.14) vs. 0.12 (0.07) vs. 0.21 (0.06); P=0.005 Ins (10*3 mU/L): 16.54 (1.65) vs. 14.14 (1.62) vs. 5.43 (1.41) vs. 6.79 (1.07); P=0.005 CP (pmol/l): 262.69 (41.63(vs. 225.78 (42.50) vs. 49.34 (29.55) vs. 61.00 (25.85); P=0.001 IRI: 3.45 (0.50) vs. 2.80 (0.36) vs. 1.12 (0.30) vs. 1.57 (0.29); P=0.007 Subgroup analyses based on gender (male:female) for clozapine vs olanzapine vs risperidone vs sulpiride (within-group between-gender p-values NS unless otherwise specified) TG (mmol/100 mL): 62.88:25.68 (p=0.007) vs 46.94:8.85 (p=0.002) vs 15.05:10.62 vs 12.40:28.34 (p=0.035) No other within-group gender differences for clozapine, olanzapine, or risperidone for any other metabolic parameters
Yamashita, 2004 Inpatients	NR/92	NR	PSQI Results: Change in Score After Switched From Typical to Atypical Olanzapine vs Perospirone vs Quetiapine vs Risperidone Sleep quality: -.050 vs 0.2 vs -0.33 vs -0.35; P=.063 Sleep latency: -0.45 vs -0.22 vs -0.59 vs -0.35; P=.76 Sleep duration: -0.55 vs 0.69 vs -0.22 vs -0.25; .0009 Habitual sleep efficiency: -0.80 vs 0.47 vs -0.44 vs -0.65; P=.0024 Sleep disturbances: -0.20 vs 0.04 vs -0.11 vs -0.25; P=.36 Use of sleep medications: -0.05 vs 0.13 vs -0.07 vs -0.30; P=.50 dtime dysfunction: -0.65 vs 0.21 vs -0.15 -0.30; P=.0018

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Adverse effects reported
Wu, 2006 Wu, 2007 Randomized, unblinded, longitudinal study	NR
Yamashita, 2004 Inpatients	NR

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Extrapyramidal symptoms
Wu, 2006 Wu, 2007 Randomized, unblinded, longitudinal study	NR
Yamashita, 2004 Inpatients	NR

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Total withdrawals; withdrawals due to adverse events	Comments
Wu, 2006 Wu, 2007 Randomized, unblinded, longitudinal study	8 total WD 0 WD due to AEs	
Yamashita, 2004 Inpatients	NR	

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Eligibility criteria	Interventions (drug, dose, duration)	Allowed other medications	Age Gender Ethnicity	Other population characteristics
Zhang, 2012 China	18-65 y, first episode schizophrenia. Excluded current substance abuse, diabetes, thyroid, unstable psychiatric illness	A. Paliperidone (Invega), 6mg B. Aripiprzole (Abilify), 5mg C. Ziprasidone (Geodon), 20mg 52 weeks	NR	Age: 26.34 Female: 38.9% Ethnicity: NR	Duration of illness, months: 2.29
Zhong, 2004 Poster Only RCT	Men or women, aged 18-65 ys old, with a diagnosis of catatonic, disorganized, paranoid, or undifferentiated schizophrenia according to DSM-IV; PANSS total score of ≥ 60 at baseline (d 1); a baseline score of ≥ 4 on one or more of the PANSS items for delusions, conceptual disorganization, hallucinatory behavior, and suspiciousness/persecution; CGI-S score ≥ 4 at baseline	Quetiapine 50 mg/d, increased to 400 mg/d by d 5, then flexibly dosed in range of 200-880 mg/d (mean dose=525 mg) Risperidone 2 mg/d, increased to 4 mg/d by d 5, then flexibly dosed in range of 2-8 mg/d (mean dose=5.2 mg) Duration: 8 wks Setting: hospitalized for ≥ 7 ds following randomization	NR	Mean age 39.94 75.7% male 50.8% black 38.7% white 7.6% Hispanic 2.9% other ethnicity	Glucose (mg/dL): 99.7 Weight (kg): 86.6 Prolactin (ng/mL): 22.65 PANSS total scores: 92.5

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Number screened/ eligible/ enrolled	Withdrawn/ Lost to follow-up/ Analyzed	Results
Zhang, 2012 China	NR/NR/254	51/10/203	Paliperidone vs. Aripiprazole vs. Ziprasidone, mean (SD) PANSS, total Baseline: 87.1(12.8) vs. 89.8(14.5) vs. 88.0(11.6), p=0.369 13 weeks: 59.6(14.1) vs. 74.4(13.7) vs. 73.6(9.5), p=0.004 26 weeks: 55.1(10.4) vs. 71.4(13.7) vs. 72.9(8.5), p=0.002 52 weeks: 54.9(10.6) vs. 68.6(9.3) vs. 69.3(9.7), p=0.012 CGI-S, all NSD
Zhong, 2004 Poster Only RCT	NR/NR/673 quetiapine 338 risperidone 335	351 (52.1%) withdrawn/analyzed nr	Change from baseline to endpoint for PANSS total scores: quetiapine=risperidone, p-value NR Proportions of patients with ≥ 40 reduction in PANSS total, positive, negative, and general pathology scores: quetiapine=risperidone, p-values NR CGI-C (% patients who were "much" or "very much" improved by d 56): quetiapine=risperidone, p-values NR

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Adverse effects reported
Zhang, 2012 China	Anthropometric results, paliperidone vs. ariprazole vs. ziprasidone: Baseline Weight: 53.4 (6.3) vs. 54.3 (7.2) vs. 54.7(6.8), p=0.645 BMI: 21.5 (3.2) vs. 22.4 (3.7) vs. 21.9 (3.4) , p=0.322 Waist Circumference: 69.5 (12.4) vs. 67.3 (14.6) vs. 71.5 (13.8), p=0.248 13 weeks Weight: 52.3 (6.4) vs. 57.6 (7.7) vs. 52.7 (7.1), p= 0.039 BMI: 21.2 (3.1) vs. 23.7 (4.1) vs. 20.2 (3.3), p=0.115 Weight Circumference: 68.7 (15.3) vs. 70.5 (16.2) vs. 70.4 (15.8), p=0.331 26 weeks Weight: 53.1 (7.2) vs.58.8 (8.5) vs. 51.9 (7.2), p=0.034 BMI: 21.9 (5.2) vs. 24.3 (5.8) vs. 2 0.6 (5.1), p= 0.027 Waist Circumference: 68.4 (15.5) vs. 71.3 (16.6) vs. 69.7 (16.3), p=0.178 52 weeks later Weight: 53.6 (7.4) vs. 57.4 (8.2) vs. 50.5 (6.9), p=0.037 BMI: 21.5 (5.4) vs. 24.5 (5.9) vs. 20.3 (5.2), p=0.015 Waist Circumference: 68.5 (15.6) vs. 71.6 (17.6) vs. 70.3 (16.7), p=0.126
Zhong, 2004 Poster Only RCT	Quetiapine, risperidone, p-values not provided Somnolence: 89 (26.3%), 66 (19.8%) Headache: 51 (15.1%), 56 (16.8%) Dizziness: 48 (14.2%), 32 (9.6%) Dry mouth: 41 (12.1%), 17 (5.1%) Agitation: 5 (17%), 3 (10%) WDs due to somnolence: 2 (0.6%), 1 (0.3%) WDs due to akathisia: 0, 4 (1.2%) WDs due to dystonia: 0, 6 (1.8%) EPS-related AEs: 43 (12.7%) vs 73 (21.9%), p<0.01 BARS improvement: quetiapine > risperidone, p-value nr SAS and AIMS improvement: quetiapine=risperidone Sexual AEs: 2 (0.6%), 15 (4.5%), p-value nr Change in plasma prolactin (ng/mL) All patients: -11.5, +35.5, p<0.001 Females: -12, +63 (estimated from graph), p<0.001 Mean change in glucose levels (mg/dL): 3.9, 4.5 % pts with blood glucose levels ≥ 230: 1.8, 1.7 Mean change in weight (kg) : 1.6, 2.2 % pts with ≥ 7% gain: 10.4 vs 10.4

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Extrapyramidal symptoms
Zhang, 2012 China	NR
Zhong, 2004 Poster Only RCT	NR

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Total withdrawals; withdrawals due to adverse events	Comments
Zhang, 2012 China		
Zhong, 2004 Poster Only RCT	WD due to AE (# patients; population analyzed nr): 20 vs 23	

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Eligibility criteria	Interventions (drug, dose, duration)	Allowed other medications	Age Gender Ethnicity	Other population characteristics
Zhong, 2006 R, DB, MC, flexible-dose non-inferiority study 66 centers in US. Inpatients (minimum of 7 ds following randomization) then treated on an outpatient basis	18-65 ys of age; schizophrenia (DSM-IV); total score ≥ 60 on PANSS; score of ≥4 on 1 or more of the following PANSS items: delusions, conceptual disorganization, hallucinations, suspiciousness, or persecution; and CGI Severity or Illness score of ≥ 4 and clinical deterioration during the 3 wks preceding randomization.	Quetiapine 200-800mg/d (titrated schedule) (mean doses: 525 mg/d) Risperidone 2-8 mg/d- (titrated schedule) (mean dose 5.2mg/d) x 8 wks (Mean duration of treatment Q: 34.7 ds vs. Q: 36.5 ds)	Anticholinergics PRN.. Lorazepam up to and not beyond d 3	Age, mean (SD), y Q: 40.2 (10.8); R: 39.6 (10.8) Males: Q: 77.1%, R:74.4% Race, n (%) White: Q: 130 (38.4), R 131 (39.1%) African American: Q: 171 (50.6); R: 171, (50.9) Hispanic: Q: 25 (7.3); R:26 (7.8) Other: Q: 12 (3.6) R: 7 (2.2)	Both groups were moderately to severely ill (mean BL PANSS total scores > 92 and CGI-Severity of Illness of 4.6).

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Number screened/ eligible/ enrolled	Withdrawn/ Lost to follow-up/ Analyzed	Results
Zhong, 2006 R, DB, MC, flexible-dose non-inferiority study 66 centers in US. Inpatients (minimum of 7 ds following randomization) then treated on an outpatient basis	872/NR/673	62/65/322 Withdrew consent: Q: 28 (8.3%); R: 34 (10.2%) Lost to follow-up: Q: 25 (7.4%); R: 40 (11.9%)	Efficacy: PANSS total scores: MITT patients (LOCF; p<.05),among completers (p<.01) , or when pts with significant protocol violations or deviations were excluded (p<.02). Change from Baseline in PANSS Total Score: LOCF: p=NS OC: p=NS % ≥ 40% reduction in PANSS Scores: PANSS total scores, positive, negative, general at endpoint: LOCF: p=NS; completers: p=NS % ≥ 30% reduction in PANSS Scores: Q: 27.4% R: 27.7%; p=NS Q vs. R: Difference Least squares Mean PANSS subscale at wk 8 and last Observation: LOCF for Positive Symptoms; p=.03 LOCF for negative, general psychopathology, anxiety, depression; p=NS Completers for positive, negative, general psychopathology, anxiety, depression; (all p=NS) CGI-C scores: 8 wk: % of pts rated "much" or "very much" improved for LOCF and completers: p=NS Cognitive measures: (multivariate analysis of covariance (controlling for BL score and site): p=NS PEAT or SSPA: p=NS Changes from baseline within each group in phonological fluency, trail making, verbal learning, vigilance, and SSPA, but not PEAT scores, were "statistically significant" (data not shown but published in Harvey P et al Am J Psychiatry. (In Press)

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Adverse effects reported
Zhong, 2006 R, DB, MC, flexible-dose non-inferiority study 66 centers in US. Inpatients (minimum of 7 ds following randomization) then treated on an outpatient basis	Q: (n=338) vs. R: (n=334) All AE: Q: 76.3% vs. R: 76.6% Serious AEs : Q: 14 (4.1%) vs. R: 9 (2.7%) AEs Occurring in ≥ 5% of pts: Q n (%) vs. R n (%) Somnolence: 89 (26.3) vs. 66 (19.7), p=.044 Dry mouth 41 (12.1) vs. 17 (5.1), p<.01 Akathisia 13 (3.8) vs. 28 (.8.4), p=.016 Dystonia 1 (0.3) vs. 18 (5.4), p<.001 Headache, weight gain, dizziness, dyspepsia, nausea, pain, asthenia, agitation, pharyngitis, vomiting; all p=NS 8 wk Mean Prolactin levels change vs. BL (ng/mL) All patients: Q: -11.5 vs. R 35.5; p<.001 Mean Prolactin levels change from baseline for Females (ng/mL): Q:(n=42) -12.7 vs. R: (n=59) 60.9; p<.001 Mean Prolactin levels change from baseline for Men (ng/mL): Q: (n=167) -11.7 vs. R: (n=172) 8.4; p<.001 Final Mean prolactin levels (ng/L) in men and women in Q group (11-15); R 91 (women) and 31 (men) Prolactin: Q: mean change from BL: -25.98 ng/mL (doses < 200 mg/d) to -11.35 ng/mL (doses of > 600 mg/d); R: 9.33 ng/mL (doses of < 2 mg/d) to 36.98 ng/mL (doses of > 6 mg/d). Spontaneous reports of sexual and reproductive AE: R: 4.2% (lactation 2, menorrhagia 1, dysmenorrhea 4, vaginitis 1, abnormal sexual function 1, anorgasmia 1, impotence 3, ejaculatory dysfunction 1 vs. Q: 0.6% (dysmenorrhea 2; p=.002) Weight change: p=NS BMI: p=NS Mean change from BL in random serum glucose (mg/dL): LOCF and Completers: p= NS

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Extrapyramidal symptoms
Zhong, 2006 R, DB, MC, flexible-dose non-inferiority study 66 centers in US. Inpatients (minimum of 7 ds following randomization) then treated on an outpatient basis	Spontaneously reported EPS: Q: 12.7% vs. R: 21.8%; p=.002 AIMS and SAS total scores: greater improvements with Q than R; p= NS BARS score: Q> R; p<.05 % of pts taking anticholinergic medications on a prn basis: Q 5.6% , R 6.9%

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Total withdrawals; withdrawals due to adverse events	Comments
Zhong, 2006 R, DB, MC, flexible-dose non-inferiority study 66 centers in US. Inpatients (minimum of 7 ds following randomization) then treated on an outpatient basis	351/ 44 Leading to withdraw: Q:(5.9%) vs. R: (6.9%) Withdrew: Due to AE: Q 19, (5.6%); R 25, (7.5%) somnolence: Q: 2, R: 1 EPS: R= 13 (akathisia 4; dystonia 6; extrapyramidal syndrome 1; movement disorder 2). Q: 1 (tardive dyskinesia)	Mean median doses of quetiapine in responders and completers were 574 mg/d and 626 mg/d; respectively. Mean median dose in pts that withdrew due to lack of efficacy: Q: 429mg/d; R 4.7mg/d.

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Eligibility criteria	Interventions (drug, dose, duration)	Allowed other medications	Age Gender Ethnicity	Other population characteristics
Zimbroff, 2007 DB RCT 25 centers in US Inpatient	Men and women, 18–70 ys of age, primary diagnosis of schizophrenia or schizoaffective disorder: hospitalized for less than 14 consecutive ds prior to screening, scores > 4 (at least moderate severity) on the CGI-S, PANSS total score > 80, and a score > 4 on at least two of the PANSS-positive items assessing delusions, hallucinatory behavior or conceptual disorganization.	4 wks Ziprasidone 40 mg bid on d 1, 60 mg bid on d 2, and 80 mg bid on ds 3–14. ds 15–28: 40, 60 or 80 mg bid n=125 Aripiprazole 15mg every d on ds 1–14. ds 15–28: 10, 15 or 30 mg daily. n=128	NR	Mean age Ziprasidone 40.8 yrs Aripiprazole 39.8 yrs % Male Ziprasidone 71 Aripiprazole 63 % White, Black, Asian and other Ziprasidone 34, 56, 2 and 8 Aripiprazole 39, 46, 1 and 14	

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Number screened/ eligible/ enrolled	Withdrawn/ Lost to follow-up/ Analyzed	Results
Zimbroff, 2007 DB RCT 25 centers in US Inpatient	NR/371 screened/256 randomized	79 (31%) / 3 never took meds/ 253	LS mean change (SE) at 4 wks Ziprasidone CGI-S -1.12 ((0.09) BPRSd total -13.0 ((1.0) BPRSd core -4.3 (0.3) PANSS total -21.6 (1.7) PANSS-EC -2.9 (0.4) Aripiprazole CGI-S -1.15 (0.09) BPRSd total -15.2 (1.0) BPRSd core -5.2 (0.3) P < 0.05 for significant treatment difference favoring aripiprazole PANSS total -24.6 (1.7) PANSS-EC -3.4)

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Adverse effects reported
Zimbroff, 2007 DB RCT 25 centers in US Inpatient	Simpson Angus Scale total score (0.0 for ziprasidone and aripiprazole, P=0.99), Barnes Akathisia Scale total score (+0.1 for ziprasidone and – 0.1 for aripiprazole, P=0.50). Abnormal Involuntary Movement Scale total score, Ziprasidone showed no mean change (0, SE=0.1) from baseline to endpoint vs. aripiprazole decrease of – 0.4 (SE=0.1) (P=0.04). TEAEs n (%) Ziprasidone vs. Aripiprazole Asthenia 7 (5.6) vs. 3 (2.3) Headache 15 (12.0) vs. 22 (17.2) Pain 6 (4.8) vs. 8 (6.3) Constipation 10 (8.0) vs. 14 (10.9) Diarrhea 5 (4.0) vs. 7 (5.5) Dyspepsia 12 (9.6) vs. 23 (18.0) Nausea 8 (6.4) vs. 20 (15.6) Vomiting 12 (9.6) vs. 10 (7.8) Arthralgia 8 (6.4) vs. 5 (3.9) Agitation 14 (11.2) vs. 12 (9.4) Akathisia 7 (5.6) vs. 9 (7.0) Anxiety 7 (5.6) vs. 7 (5.5) Dizziness 9 (7.2) vs. 3 (2.3) Insomnia 8 (6.4) vs. 9 (7.0) Somnolence 33 (26.4) vs. 17 (13.3) Respiratory tract infection 9 (7.2) vs. 3 (2.3) Vaginitis 1 (2.8) vs. 3 (6.3)

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Extrapyramidal symptoms
Zimbroff, 2007 DB RCT 25 centers in US Inpatient	Ziprasidone vs. Aripiprazole n (%) Extrapyramidal syndrome 11 (8.8) 7 (5.5)

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year Study design	Total withdrawals; withdrawals due to adverse events	Comments
Zimbroff, 2007 DB RCT 25 centers in US Inpatient	79 WD 13 due to AEs	

Evidence Table 2. Quality assessment of trials in patients with schizophrenia

Author, year quality rating	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors masked?	Care provider masked?
Addington, 2004 RCT, multicenter, double-blind Fair	NR	NR	Yes	Yes	Yes	Yes
Akerele, 2007 Poor	NR	NR	N-higher mean ys of education, mean score on ASI, and # ds of cocaine use in past 30 ds in Olanzapine group	Yes	NR	Yes
Alvarez, 2006 Fair	Yes - computer generated	Yes - computerized randomization blocks	No - SS differences in baseline body weight (mean O 73.8 kg [SD 14.0] vs R 80.5 kg [SD 15.6 kg]; p=0.0005) and BMI (mean O 25.9 [SD 4.7] vs R 27.5 [SD 5.1]; p=0.007)	Yes	No - open label trial	No - open label trial
Andrezina, 2006 Fair	Yes - central call in	Yes - central call in	Yes	Yes	Yes	Yes
Apiquian, 2003 Poor	Not an RCT; Patients allocated consecutively	NA	Yes	Yes	NR	No ("open trial")
Arango, 2009	NR	No open label	No Olanzapine group: worse PANSS total & general psychopathology scores, >Hispanics	Yes	No	No

Evidence Table 2. Quality assessment of trials in patients with schizophrenia

Author, year quality rating	Patient masked?	Attrition?	Loss to follow-up: Differential/high?	Intention-to-treat analysis?	Quality rating	Comments
Addington, 2004 RCT, multicenter, double-blind Fair	Yes	Yes	No loss to follow-up	Unclear. "ITT" defined as "all randomized patients with a baseline and >/= 1 post-baseline evaluation	Fair	
Akerele, 2007 Poor	Yes	Yes O vs. R % patients completed: 43% vs. 71%	Described as "not interested" in Figure1., but described as " did not present for appointments" in text (p265) 7 vs. 3 -> 50% vs. 21%	Unclear; no info in Methods about analysis plans, raw Ns provided in Results, except for with HAM reported as using" last observation for each subject" and df=20-> means n=21, which excluded 7/28 14√3.0 = .21	Poor	
Alvarez, 2006 Fair	No - open label trial	NR	No	No: 235/250 evaluated for effectiveness; 247/250 evaluated for safety	Fair	
Andrezina, 2006 Fair	Yes	Yes	No	Yes	Good	
Apiquian, 2003 Poor	No ("open trial")	Yes, no, yes, no	No, No	No, excluded non completers (29%)	Poor (for a CCT as high attrition and only completers analyzed)	
Arango, 2009	No	Yes	No (14%), no	Unclear. ITT included all randomized, but cases with no data after baseline were "eliminated"	Poor	

Evidence Table 2. Quality assessment of trials in patients with schizophrenia

Author, year quality rating	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors masked?	Care provider masked?
AstraZeneca, 2010 5077IL/0089 RCT, Open-label multi-center USA	Unclear, method NR	Unclear, method NR	Unclear; statement of no differences, but data NR	Yes	Yes for opthalmology outcomes, unclear for others.	No; open-label
AstraZeneca #D1441C00112 RCT, DB Multicenter (43 international sites) Fair	Method NR; baseline characteristics seem evenly distributed	NR	Yes	Yes	Unclear	Stated to be DB
AstraZeneca #D1441C00132 2007	Method NR	Method NR	Yes	Yes	Yes but method not described	Yes but method not described
AstraZeneca #D1444C00133 RCT, DB Multicenter (40 sites in United States) Fair	Method NR; baseline characteristics seem evenly distributed	NR	Yes	Yes	Unclear	Stated to be DB
Atmaca, 2003 Fair	NR	NR	Yes	Yes	NR	Yes
Azorin, 2001 Anand, 1998 Double-blind, Multicenter (France and Canada) Fair	Method NR	Method NR	No, Significantly more women and lower baseline BPRS score in the risperidone arm	Yes	NR	Yes
Bai, 2006 Fair	Method NR	NR	Yes	Yes	Yes-SB study where raters were blinded	No-SB study
Beasley, 2003 Croatia, Poland, Romania, the Russian Federation, US, Yugoslavia Olanzapine Relapse Prevention Study Fair	Method NR	NR	Diagnosis schizophrenia 79% olanzapine vs 87% P; schizoaffective disorder 21% olanzapine vs 13% P (p=0.049)	Yes	Yes	NR

Evidence Table 2. Quality assessment of trials in patients with schizophrenia

Author, year quality rating	Patient masked?	Attrition?	Loss to follow-up: Differential/high?	Intention-to-treat analysis?	Quality rating	Comments
AstraZeneca, 2010 5077IL/0089 RCT, Open-label multi-center USA	No; open-label	No, Yes	NR	No	Fair	
AstraZeneca #D1441C00112 RCT, DB Multicenter (43 international sites) Fair	Yes	Incomplete - reports only withdrawals due to AE	NR / NR Withdrawals due to AE: P 2.7% Quetiapine 400 mg/d 6.9%; 800 mg/d 9.5%	Stated to be	Fair	
AstraZeneca #D1441C00132 2007	Yes	Yes	Yes/No	No 573/588 (97.4%) in MITT	Fair	
AstraZeneca #D1444C00133 RCT, DB Multicenter (40 sites in United States) Fair	Yes	Yes	High; not differential Completion overall 59%; by group: P 54% Quetiapine SR 400mg 65%; 600mg 58%; 800mg 60% Quetiapine IR 800 mg=54%	States "modified ITT": analysis excluded 20 (3.5%) of 564 randomized	Fair	
Atmaca, 2003 Fair	NR	Yes	No (1 in each treatment group)	No: 3 of 56 excluded from analysis	Fair	
Azorin, 2001 Anand, 1998 Double-blind, Multicenter (France and Canada) Fair	Yes	Yes	No	Yes	Fair	
Bai, 2006 Fair	No-SB study	Yes	LTFU- low/ Differential: low (only 1-patient withdrew)	Yes (98% completed); used LOCF	Fair	
Beasley, 2003 Croatia, Poland, Romania, the Russian Federation, US, Yugoslavia Olanzapine Relapse Prevention Study Fair	Yes	Attrition yes, adherence yes, crossovers and contamination no.	No	Not clear	Fair	

Evidence Table 2. Quality assessment of trials in patients with schizophrenia

Author, year quality rating	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors masked?	Care provider masked?
Bellack, 2004 Double-blind trial Substudy of unpublished trial Poor	NR if randomized	Method NR	NR	Yes	NR	Yes
Bitter, 2004 RCT Multi-center, Hungary & South Africa Fair	Method NR	stated to be "DB"	Stated to be, data NR	Yes	Unclear	Yes
Bondolfi, 1998 Single-center Double-blind RCT Fair	Method NR	Method NR	Similar, but number of mos in hospital: clozapine: 12.3, risperidone 24.3	Yes	NR	Yes
Bouchard, 2000 Bouchard, 1998 Fair	Method NR	Method NR	Yes	Yes	No	No
Breier, 1999 Single Center double-blind RCT (NIH Clinical Center) Unclear if Inpatient Fair	Method NR	Method NR	Some differences, NS: mos previously hospitalized: clozapine 8.8, risperidone 12.5 Length of illness (yrs): clozapine 13.9, risperidone 11.1	Yes	NR	Yes
Breier, 2005 Fair-Poor	1:1 ratio, unclear; stated as DB	NR	Yes OL slightly older than Zip; (p=0.04)	Yes	NR	NR
Buchanan 2012: NCT00145496 (WH study)	Unclear	Unclear	Yes	Yes	Yes	Yes

Evidence Table 2. Quality assessment of trials in patients with schizophrenia

Author, year quality rating	Patient masked?	Attrition?	Loss to follow-up: Differential/high?	Intention-to-treat analysis?	Quality rating	Comments
Bellack, 2004 Double-blind trial Substudy of unpublished trial Poor	Yes	Not by drug	Overall loss to follow-up very high (47-66%), differences by drug not apparent	No	Poor	
Bitter, 2004 RCT Multi-center, Hungary & South Africa Fair	Yes	Yes	Overall High: 58% NS difference between groups	Yes, using LOCF	Fair	
Bondolfi, 1998 Single-center Double-blind RCT Fair	Yes	Yes	No	Yes	Fair	
Bouchard, 2000 Bouchard, 1998 Fair	No	Attrition yes, crossovers yes	No/ no	No	Fair	
Breier, 1999 Single Center double-blind RCT (NIH Clinical Center) Unclear if Inpatient Fair	Yes	NR	NR	Yes	Fair	
Breier, 2005 Fair-Poor	NR	Yes	Yes; high and differential OL 40.4% vs. Zip 57.6%	Yes; stated not described	Fair-Poor	
Buchanan 2012: NCT00145496 (WH study)	Yes	DB phase: Overall-No (43.6%); differential: No (50.4% vs 36.2%)	No, No	Yes (3.4% not included in ITT, DB phase0	Fair	Those treated with Olanzapine within 5 mos of screening, had adequeate negative symptom response were excluded. Higher proportion of discontinuation from Asenapine group.

Evidence Table 2. Quality assessment of trials in patients with schizophrenia

Author, year quality rating	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors masked?	Care provider masked?
Buchanan 2012: NCT00202836 (EH study)	Unclear	Unclear	Yes	Yes	Yes	Yes
Byerly, 2008 Fair	NR	Unclear	Yes	Yes	NR	Blinding unclear
Canive, 2006 Poor	Unclear " done by computer"	NR	Unclear; this is a crossover study that did not report comparability of important characteristics at baseline of the first treatment period	Yes	Unclear	Unclear
Canuso 2009 (CR010498) Fair	Method not described	NR	Yes	Yes	NR	Stated to be DB
Canuso 2009 Fair	NR	NR	Yes	Yes	NR stated as DB	NR stated as DB
Chan, 2007 Fair	Unclear	NR	Yes	Yes	Unclear	Yes
Chan 2010 (J Clin Psychiatry)	Yes	Unclear (NR)	Yes (but anticholinergic drug use differed)	Yes	Yes	Unclear (Study described as double-blind but no details provided)
Chan, 2010 (Psychopharmacology)	Yes	Unclear (NR)	Yes (but baseline characteristic do not include weight measures)	Yes	Yes (raters)	Unclear (Study described as double-blind but no details provided)

Evidence Table 2. Quality assessment of trials in patients with schizophrenia

Author, year quality rating	Patient masked?	Attrition?	Loss to follow-up: Differential/high?	Intention-to-treat analysis?	Quality rating	Comments
Buchanan 2012: NCT00202836 (EH study)	Yes	DB phase: Overall-Yes; differential: No (35.3% vs 19.6%)	No, No	No, [10% not included in ITT (DB phase)]	Fair	Those treated with Olanzapine within 5 mos of screening, had adequeate negative symptom response were excluded. Higher proportion of discontinuation from Asenapine group.
Byerly, 2008 Fair	Blinding unclear	Yes	Completion rate: 75% Lost to follow-up: NR Withdrawals by group: NR	Yes	Fair	
Canive, 2006 Poor	Unclear	Yes; only 6/15 (40%) completed study	Unclear; discontinuations due to " noncompliance, failed drug screens, and geographic relocation"	No; precluded 60%	Poor, mostly due to high rate of exclusions of analyses.	
Canuso 2009 (CR010498) Fair	Yes	Yes	No; No Discontinuation rates (%): Paliperidone higher-dose 21.0% Lower-dose paliperidone 30.3% P 41.1%	Stated to be; analysis excluded 6 (1.9%) of 316 randomized.	Fair	
Canuso 2009 Fair	Yes	Yes	No 77.5% completed in P ER, 66.7% in quetiapine, 63.8% P	No 5/475 (1%) not included in ITT	Fair	
Chan, 2007 Fair	Yes	Yes- only 62 (75%) completed	None	Yes	Fair	
Chan 2010 (J Clin Psychiatry)	Unclear (Study described as double-blind but no details provided)	No, Overall 27%; Yes 30% for R and 23% for O.	No, No	Yes	Fair	
Chan, 2010 (Psychopharmacology)	Unclear (Study described as double-blind but no details provided)	Yes, Overall 18%; Yes 17% for O and 20% for R.	No, No	Yes (LOCF)	Fair	

Evidence Table 2. Quality assessment of trials in patients with schizophrenia

Author, year quality rating	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors masked?	Care provider masked?
Chin, 2006 Fair	NR	NR	Yes	Yes	NR	No-open
Chiu, 2006 Fair	NR	NR	Yes	Yes	NR	No-open
Chrzanowski, 2006	NR	NR	Yes, but more acute - phase relapsers randomized to olanzapine	Yes	Unclear, Open-study	No, Open
Chue, 2005 Fair	NR	NR	No- ILA risp group had greater number of previous hospitalizations	Yes	NR	Yes
Chue, 2005, RCT, multicenter, DB, double dummy Poor	NR	NR	No; oral risperidone group had a "marginally significant" greater number of previous hospitalizations	Yes	Yes	Yes
Citrome, 2001; Volavka, 2002, 2004b, 2004c; Lindenmayer, 2003, 2004 Fair	NR	NR	Yes	Yes	Yes	Yes
Citrome , 2012	Yes	Yes	Yes	Yes	No	Yes, double dummy
Conley, 2001 Double-blind, Multicenter Fair	Yes	Yes	Similar, but mean age: olanzapine 38.9 yr (SD 10.5); risperidone 41.0 yr (SD 11.0), p = 0.04	Yes	Yes	Yes

Evidence Table 2. Quality assessment of trials in patients with schizophrenia

Author, year quality rating	Patient masked?	Attrition?	Loss to follow-up: Differential/high?	Intention-to-treat analysis?	Quality rating	Comments
Chin, 2006 Fair	No-open	None-100% completion	None	Yes	Fair	
Chiu, 2006 Fair	No-open	None - 100% completion	None	Yes	Fair	
Chrzanowski, 2006	No, open	Yes, No, No, No	None	LOCF for 211/214 = 98%	Fair	
Chue, 2005 Fair	Yes	Yes-completion rate of 82%	Unclear-reasons for discontinuation NR	No-16% excluded	Fair	
Chue, 2005, RCT, multicenter, DB, double dummy Poor	Yes	Yes	NR	Unclear; number analyzed NR	Poor	
Citrome, 2001; Volavka, 2002, 2004b, 2004c; Lindenmayer, 2003, 2004 Fair	Yes	Yes: 42% withdrew	No.	Yes (LOCF)	Fair	
Citrome , 2012	Yes, double dummy	No,62% overall No, and 66% vs 56%	Yes, overall 10%, No, differential 3%	Yes	Fair	
Conley, 2001 Double-blind, Multicenter Fair	Yes	Yes	No	Yes	Good	

Evidence Table 2. Quality assessment of trials in patients with schizophrenia

Author, year quality rating	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors masked?	Care provider masked?
Conley, 2003 Kelly, 2003 Double-blind, single center, crossover Poor	NR	NR	No	Yes	NR	Yes
Conley, 2005 Fair	Yes	NR	Yes	Yes	NR	NR
Covington, 2000 Poor	Method NR	Method NR	NR	No	No	NR
Crespo-Facorro, 2006 Fair	NR	NR	Yes	Yes	No-open	No-open
Crespo-Facorro, 2011 Fair	Yes	Unclear (NR)	Yes (but longer duration of illness in R vs O (30.7 vs 17.9 mos)	Yes	NR	No (open)
Crespo-Facorro, 2013 Fair	Yes	Unclear	No, some potentially important differens at baseline, e.g. duration of illness, duration of psychosis	Yes	NR	No, open label
Csernansky, 2002 Fair	Method NR	Method NR	Yes	Yes	Yes but method not described	NR
Cutler, 2008 Fair	Yes	NR	Yes	Yes	NR	Stated to be DB

Evidence Table 2. Quality assessment of trials in patients with schizophrenia

Author, year quality rating	Patient masked?	Attrition?	Loss to follow-up: Differential/high?	Intention-to-treat analysis?	Quality rating	Comments
Conley, 2003 Kelly, 2003 Double-blind, single center, crossover Poor	Yes	Yes; 3 withdrew during olanzapine assigned as first drug (23%)	One publication states 3 withdrew during olanzapine assigned as first drug (23%), other publication states that 6 withdrew during olanzapine phase.	No	Fair	
Conley, 2005 Fair	NR	Yes	Yes; high and differential RIS 31% QU 42% FLU 64%	Yes	Fair	
Covington, 2000 Poor	NR	No	NR	NR	Poor	
Crespo-Facorro, 2006 Fair	No-open	Yes;7/172 (4%)	No/no	No; 10/182(5%) excluded	Fair	
Crespo-Facorro, 2011 Fair	No (open)	Yes overall (12.1%); unclear for differential (NR)	No, Unclear (NR)	Yes	Fair	
Crespo-Facorro, 2013 Fair	No, open label	Yes	No, yes	Yes	Fair	
Csernansky, 2002 Fair	Yes	Attrition yes NR Adherence yes NR	No/ no	No: 91.9%	Fair	
Cutler, 2008 Fair	Stated to be DB	Yes	No; 66% completed trial	Yes	Fair	

Evidence Table 2. Quality assessment of trials in patients with schizophrenia

Author, year quality rating	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors masked?	Care provider masked?
Cutter, 2006 Fair	NR	NR	Yes	Yes	Yes	Yes
Daniel, 1996 Crossover design Poor	Method NR	Method NR	Yes (crossover study)	Yes	NR	NR
Davidson, 2007 Fair	NR	NR	Yes	Yes	Yes	Yes
Deberdt, 2008	Method NR	Method NR	No Differences in PANSS total and BMI	Yes	NR Stated as DB	NR Stated as DB
Dollfus, 2005 Poor	Method NR	Method NR	Unclear only provided info regarding age, sex and illness duration	Yes	NR	NR
Emsley, 1999 International multicenter (does not include US) Fair	Method not described (just reports that patients were 'randomly' assigned to tx (study design not explicitly reported)	NR	Yes	Yes	Unclear, reported as DB	Unclear, reported as DB

Evidence Table 2. Quality assessment of trials in patients with schizophrenia

Author, year quality rating	Patient masked?	Attrition?	Loss to follow-up: Differential/high?	Intention-to-treat analysis?	Quality rating	Comments
Cutter, 2006 Fair	Yes	Yes; only 53% completed	No/no	N NR; efficacy sample included all patients who received ≥ 1 dose of study medication and had ≥ 1 post-baseline visit using LOCF. Note: Concern is that with such a high drop-out rate, there is potential for analysis population to also have excluded a large number of patients; with the N, we can't rule this out.	Fair	
Daniel, 1996 Crossover design Poor	NR	Yes	No	No	Poor	
Davidson, 2007 Fair	Yes	Yes; completion rate = 59%	No/no	No; exceeded 13/618	Fair	
Deberdt, 2008	NR Stated as DB	Yes	NR	No Included only those with ≥ 1 post baseline evaluation for a given analysis. Data not provided	Fair	76/160 planned N enrolled. Study not adequately powered.
Dollfus, 2005 Poor	NR	NR	NR	Unclear number of pts included in analysis. Endpoint analysis excluded non responders (7%)	Poor	
Emsley, 1999 International multicenter (does not include US) Fair	Unclear, reported as DB	Yes NR NR NR	LTFU was combined with other misc noncompletion factors (total 11% of noncompletion factors for each arm) Differential for total withdrawn: NR but there was a higher differential due to AE (~18%) bw risperidone and haloperidol	Yes (all enrolled patients were included)	Fair	

Evidence Table 2. Quality assessment of trials in patients with schizophrenia

Author, year quality rating	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors masked?	Care provider masked?
Fleischhacker, 2009 Fair	Yes	NR	Yes	Yes	NR	Stated to be DB
Fleischhacker, 2012	Yes	Yes	Yes	Yes	Yes	Yes
Gaebel, 2011	Unclear (Stated but not described)	Unclear (NR)	Yes	Yes	No (open)	No (open)
Gafoor, 2010	Unclear, (NR how sequence was generated)	Yes	Yes (but higher proportion living independently in quetiapine group [38% vs 27%])	Yes	Yes (raters)	No (patients and clinicians were not blinded to treatment)
Garyfallos, 2003 CCT Poor	NR	NR	Yes	No	No	No
Gothelf, 2003	No	No	Differences in gender distribution and duration of illness		No	No
Green, 2002 Marder, 2003 Fair	Method NR	Method NR		Yes	Yes but method not described	NR
Grootens, 2011	Unclear (NR - stated but not described)	Unclear (NR)	Yes (but moreschizoaffective in ziprasidone group)	Yes	Unclear; rater-blinding NR	Yes: double-dummy

Evidence Table 2. Quality assessment of trials in patients with schizophrenia

Author, year quality rating	Patient masked?	Attrition?	Loss to follow-up: Differential/high?	Intention-to-treat analysis?	Quality rating	Comments
Fleischhacker, 2009 Fair	Stated to be DB	Yes	No 77.9% completed in Olanzapine group 70.7% completed in Aripiprazole	Yes	Fair	
Fleischhacker, 2012	Yes	No, 55% overall Yes, (9% dif)	No, overall 3%, No, differential 3% vs 3%	Yes	Fair	
Gaebel, 2011	No (open)	No, 56% overall, No, difference between groups 10.3%	No, overall 3% No, 3% vs 3%	Yes (LOCF), for efficacy and harms	Fair	
Gafoor, 2010	No (patients and clinicians were not blinded to treatment)	Yes overall; unclear differential (Insufficient information provided to determine level of differential attrition)	No, No	Yes for mo 1 antipsychotic outcomes, No for others	Fair	
Garyfallos, 2003 CCT Poor	No	Yes	No	Yes	Poor	
Gothelf, 2003	No	Yes 39/43 (90.6%) completed	No, no	No	Poor	
Green, 2002 Marder, 2003 Fair	Yes but method not described	Attrition yes	NR	Yes	Fair	
Grootens, 2011	Yes, double-dummy	No, Overall 23%; Yes 17% vs 28% for differential	No, No	No KP: Add exclusion rate of 17%	Fair	

Evidence Table 2. Quality assessment of trials in patients with schizophrenia

Author, year quality rating	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors masked?	Care provider masked?
Hamilton, 1998 Fair	Method NR	Method NR	SARS score significantly higher in haloperidol group (p=0.0002)	Yes	Yes but method not described	No
Hardy, 2011	Unclear (NR - stated but not described)	Unclear (NR -stated bu not described)	Yes	Yes	Unclear (only for CTs)	Yes
Harvey, 2003a Harvey, 2002a Harvey, 2002b Harvey, 2002c RCT Multi-site; US, Austria, Israel, Norway, Poland and The Netherlands Fair	Method NR	Method NR	Yes	Yes	Not clear - states some outcomes masked, but not which or how.	Yes
Hatta 2009 Fair	NR	NR	Yes (see comments)	Yes	Yes	No
Hatta, 2008	Method NR	Method NR	Differences between groups in whether the same antipsychotic was assigned and received	Yes	Yes	No
Hertling, 2003 Fair	Method NR	Method NR	Yes	Yes	NR	NR
Hirsch, 2002 Fair	Yes	No: Envelope method	Yes	Yes	Yes but method not described	NR

Evidence Table 2. Quality assessment of trials in patients with schizophrenia

Author, year quality rating	Patient masked?	Attrition?	Loss to follow-up: Differential/high?	Intention-to-treat analysis?	Quality rating	Comments
Hamilton, 1998 Fair	Yes but method not described	Yes	No	Yes	Fair	
Hardy, 2011	Yes	No, Overall 44%; No, 62% for O and 50% for R.	Unclear	No, (N analyzed in the figures and tables less than enrolled)	Poor	
Harvey, 2003a Harvey, 2002a Harvey, 2002b Harvey, 2002c RCT Multi-site; US, Austria, Israel, Norway, Poland and The Netherlands Fair	Yes	Yes	Overall 38% Not differential	Stated LOCF methods, but numbers reported vary by test applied.	Fair	
Hatta 2009 Fair	No	Yes	No loss to follow-up 75% risperidone, 88% olanzapine, 45% quetiapine, and 52% of aripiprazole completed.	No 78/80 in ITT	Fair	
Hatta, 2008	No	No	No, no	No 2/80 (2.5%) excluded	Fair	Lack of randomization, allocation concealment, blinding along with lack of baseline characteristics or ITT indicate potential for important bias
Hertling, 2003 Fair	Yes but method not described	No	NR	No	Fair	
Hirsch, 2002 Fair	Yes but method not described	Attrition yes	NR	No	Fair	

Evidence Table 2. Quality assessment of trials in patients with schizophrenia

Author, year quality rating	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors masked?	Care provider masked?
Huang, 2005 Poor	Method NR	NR	No, baseline characteristics of patients NR by drug.	No (few exclusion criteria listed but no explicit inclusion criteria reported)	Unclear (study design NR)	Unclear (study design NR)
Ingole, 2009	Method NR	Method NR	No, differences in BMI	Yes	No	No
InterSePT; Meltzer, 2003 Meltzer, 2002 (AO), Potkin, 2003 Meltzer, 1996 RCT - open label, masked ratings Multi-site - 67 sites, 11 countries (US, Europe, South Africa, South America) Good	Yes	Method NR	Yes, data on alcohol and drug abuse missing	Yes	Yes, for most outcomes. Blinding for reporting of AE's not clear	No
Jerrel, 2002 Open-label RCT with economic analysis Fair	Method NR	Method NR	Although randomization stratified, and an adaptive randomization procedure used, SS difference on baseline atypical antipsychotic use present. Four other variables NS	Yes	No	No
Jeste, 2003 Jeste, 2002 Jeste, 2001 RCT Multinational (US, Israel, Poland, Norway, The Netherlands, Austria) 1 full paper, 2 conference procedures FAIR	Method NR	Method NR	Yes	Yes	Yes; method NR	Yes; method NR

Evidence Table 2. Quality assessment of trials in patients with schizophrenia

Author, year quality rating	Patient masked?	Attrition?	Loss to follow-up: Differential/high?	Intention-to-treat analysis?	Quality rating	Comments
Huang, 2005 Poor	Unclear (study design NR)	NR	LTFU-NR WDrates NR but 97/126 (77%) completed blood sampling and final assessment of severity	No	Poor	
Ingole, 2009	No	NR	NR	NR	Poor	
InterSePT; Meltzer, 2003 Meltzer, 2002 (AO), Potkin, 2003 Meltzer, 1996 RCT - open label, masked ratings Multi-site - 67 sites, 11 countries (US, Europe, South Africa, South America) Good	No	Yes	Overall high: 39%, but similar in groups	Yes, but method not clearly described	Good for efficacy, Poor for AE	
Jerrel, 2002 Open-label RCT with economic analysis Fair	No	Yes	Overall 69% - entirely due to refusals after randomization Due to adaptive randomization, unclear if differences between groups existed	Yes	Fair	
Jeste, 2003 Jeste, 2002 Jeste, 2001 RCT Multinational (US, Israel, Poland, Norway, The Netherlands, Austria) 1 full paper, 2 conference procedures FAIR	Yes; method NR	Yes	No; No	Yes	Fair	

Evidence Table 2. Quality assessment of trials in patients with schizophrenia

Author, year quality rating	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors masked?	Care provider masked?
Jones, 1998 Purdon, 2000 David, 1999 Multicenter, Canada Double-blind RCT Fair	Yes	Method NR	Yes	Yes	Not clear	Not clear (dose adjustments)
Josiassen, 2010	No (Assignment based on clinical judgment)	N/A - nothing to conceal	Yes (but baseline weight and BMI higher in risperidone group)	Yes	Yes (raters)	No (Clinicians made medication and dosing decisions)
Kahn, 2007 RCT, multi-center, international, double-blind, P-controlled Fair	Unclear, "dual-matched P used to maintain blinding"	Unclear	Yes; Patients taking medication for insomnia was higher in the P compared to the quetiapine groups (at wk 1 and end of study)	Yes	NR	NR
Kahn, 2009	Method NR	Method NR	NR	Yes	No	No
Kane 2009 Fair	NR	NR	Yes	Yes	NR stated as DB	NR stated as DB
Kane, 2003 Nasrallah, 2004 Fair	Method NR	NR	Similar, but only report baseline on patients receiving at least 1 injection of risperidone.	Yes	Yes	Not clear
Kane, 2006 Fair	Method NR	Method NR	Yes	Yes	NR	Yes but method not described

Evidence Table 2. Quality assessment of trials in patients with schizophrenia

Author, year quality rating	Patient masked?	Attrition?	Loss to follow-up: Differential/high?	Intention-to-treat analysis?	Quality rating	Comments
Jones, 1998 Purdon, 2000 David, 1999 Multicenter, Canada Double-blind RCT Fair	Yes	Yes	Overall 57% olanzapine 43% risperidone 67% haloperidol 61%	Yes	Fair	
Josiassen, 2010	Unclear (Study described as single-blind but no details provided)	Unclear, Unclear (Insufficient information provided to determine level of attrition)	Unclear, Unclear (Insufficient information provided to determine loss to follow-up)	Unclear	Poor	High rate of noncompliance, missing compliance data
Kahn, 2007 RCT, multi-center, international, double-blind, P-controlled Fair	Yes	Attrition, yes (approx. 76% completed the study); Adherence for all tx groups except Quetiapine XR; crossovers and contamination, no.	No/No	Yes' Modified intention-to-treat (MITT); see page 834 'statistical analysis' section	Fair	
Kahn, 2009	No	Yes	Yes/Yes	NR	Poor	
Kane 2009 Fair	NR stated as DB	Yes	Yes 57% of olanzapine completed 49% of aripiprazole completed	No those with 1 post-baseline measure stated to be included	Fair	
Kane, 2003 Nasrallah, 2004 Fair	Yes	Attrition and adherence (withdrawals due to) yes, others no.	6% in P and 75 mg group vs 2% in 25 mg and 3% in 50 mg group.	No. Efficacy evaluation only in patients with at least one post-baseline assessment.	Fair	Authors mention that a study site was audited and they ran their #s with and without 43 patients--there was no difference
Kane, 2006 Fair	Yes but method not described	Attrition reported yes; high, no	Some/ Not differential CHL 12%; ZIP 11%	Yes	Fair	Allocation imbalance, baseline differences

Evidence Table 2. Quality assessment of trials in patients with schizophrenia

Author, year quality rating	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors masked?	Care provider masked?
Kane, 2007 Fair	Method NR	Method NR	Unclear; difference in the # with disorganized vs. undifferentiated type schizophrenia	Yes	Unclear; reported as double-blind	Unclear, reported as double-blind
Kane, 2007 Fair	Yes; per computer generated code and was balanced by using permitted blocks and stratified by site	NR	Yes	Yes	Unclear, reported as double-blind	Unclear, reported as double-blind
Kane, 2010	Unclear	Unclear	Mostly but some statistically significant differences were observed for baseline severity, particularly, difference between oral and very low dose of LA-I for CGI-I, between oral dose and medium dose of LAI. These differences were not considered clinically significant.	Yes	Yes	Yes
D1050234, NCT00789698	Unclear; described as randomized, but no details provided	Unclear	Higher proportion of male in the lurasidone group compared to quetiapine treatment group	Yes	Unclear, reported as double-blind	Unclear, reported as double blind
Karagianis 2009 Fair	NR	NR	Unclear: 3.6% ODO group schizoaffective vs.18.5% of SOT; 8.31% schizophreniform vs. 3.1%; 32.1% bipolar vs. 21.5%	Yes	NR stated as DB	NR stated as DB

Evidence Table 2. Quality assessment of trials in patients with schizophrenia

Author, year quality rating	Patient masked?	Attrition?	Loss to follow-up: Differential/high?	Intention-to-treat analysis?	Quality rating	Comments
Kane, 2007 Fair	Unclear, reported as double-blind	Attrition-yes	LTFU-NR ~25% total withdrawn Differential: overall low, but there was a 6% difference between aripiprazole and perphenazine for those who discontinued due to AE	Yes (98% included in ITT); LOCF	Fair	
Kane, 2007 Fair	Unclear, reported as double-blind	Yes	LTFU- low ~34% total withdrawn Differential: moderate-high when comparing P to active treatments; low-moderate differential when comparing among active treatments	Yes (628/630 included as ITT); ANCOVA with LOCF	Fair	
Kane, 2010	Yes	Overall: yes 29.3% , Differential: yes	No, No	Yes, 3 patients excluded from ITT analysis	Fair	Randomization questionable as patients assigned to oral olanzapine continued to receive their previously stabilized dose whereas those assigned to LAI could be assigned a suboptimal dose
D1050234, NCT00789698	Yes	Overall: yes 52%, differential: yes	No, No	No,56/292 (19.2%) excluded from primary efficacy analysis.	Fair	
Karagianis 2009 Fair	Yes	Yes	No	Yes	Fair	

Evidence Table 2. Quality assessment of trials in patients with schizophrenia

Author, year quality rating	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors masked?	Care provider masked?
Kasper, 2003 Fair	Method NR	Method NR	Yes	Yes	Yes but method not described	NR
Kaushal, 2012	Yes	NR	Yes	Yes	Unclear (NR)	No (open)
Keefe, 2006 OL v RIS v Poor	1:1:1 ratio, stated as DB	NR	Y	Y	NR	NR
Keks, 2007 Poor	Yes	Yes	Unclear - only provided for 88% of patients	Yes	Unclear - open study	no- open study
Kelly, 2008 Fair	NR	NR	Yes	Yes	NR	Stated to be DB
Kern, 2006 FDA Study 98213 RCT, multicenter, open label Fair	NR	NR	Small differences, favoring aripiprazole, on age (younger), IQ tests (with exception of NAART scores) and PANSS scores (Total, Positive, Negative)	Yes	NR	No
Kern, 2006 Poor	NR	NR	Unclear, baseline characteristics only provided for 66% included in analysis	Yes	Unclear- open study	No - open Study

Evidence Table 2. Quality assessment of trials in patients with schizophrenia

Author, year quality rating	Patient masked?	Attrition?	Loss to follow-up: Differential/high?	Intention-to-treat analysis?	Quality rating	Comments
Kasper, 2003 Fair	Yes but method not described	Attrition yes NR NR NR	No/ extent NR (maximum 22% in aripiprazole; 26% in haloperidol)	No: 99.1%	Fair	
Kaushal, 2012	No (open)	NR	NR	Unclear	Fair	
Keefe, 2006 OL v RIS v Poor	NR	Y	Y; high and differential OL 43%* RIS 34 % HAL 28%* *stat sign	Y	Poor; due to attrition & 26% randomized to drug they were on before the study	
Keks, 2007 Poor	no- open study	Yes	None	378/618 = 61% analyzed for short-term efficacy 362/618 = 58% analyzed for long-term efficacy	Poor	
Kelly, 2008 Fair	Stated to be DB	Yes	No 71.8% completed risperidone group 77.2% completed olanzapine group	Unclear	Fair	
Kern, 2006 FDA Study 98213 RCT, multicenter, open label Fair	No	NR	NR	Unclear - some reported as LOCF, others not.	Fair (based on poster and published abstract only)	
Kern, 2006 Poor	No- Open study	Yes, no, yes, no	N/N	169/255 = 66% analyzed	Poor	High number of patients taking anti-depressants concurrently during the study [comparable in the tx groups, 52.8%]

Evidence Table 2. Quality assessment of trials in patients with schizophrenia

Author, year quality rating	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors masked?	Care provider masked?
Kim, 2010	Unclear	Unclear	Yes	Yes	Unclear (NR)	Unclear (NR)
Kim, 2012	Yes	Unclear (Insufficient details)	Yes	Yes	Yes	No (Open)
Kinon, 2006a RCT, multi-center, double-blind, parallel Poor	Method NR	Method NR	Y; Zip group had > use of antipsychotics at or within 20 ds before baseline tests [Zip 82.3% vs. Olan 70.8]; accounted for in analysis.	Yes	NR	NR
Kinon, 2006b MC, R, DBT Fair	Yes; per computer generated code and was balanced by using permitted blocks and stratified by site	Yes; identical med blister packs administered by study site personnel	Yes	No (general inclusion criteria were specified but exclusion criteria were not specified)	Unclear, reported as double-blind	Unclear, reported as double-blind
Klieser, 1995; Heinrich, 1994 Double-blind, single center, parallel Fair	NR	NR	Unclear; more males and patients older in clozapine group	Yes	Yes	Yes
Kluge, 2007 Fair	NR	Unclear	Yes	Yes	NR	Stated to be DB
Knegtering, 2004 Open, single center, parallel Poor	NR	NR	Yes	Yes	No	No

Evidence Table 2. Quality assessment of trials in patients with schizophrenia

Author, year quality rating	Patient masked?	Attrition?	Loss to follow-up: Differential/high?	Intention-to-treat analysis?	Quality rating	Comments
Kim, 2010	Unclear (NR)	Unclear, Unclear (Insufficient information provided to determine level of attrition)	Unclear, Unclear (Insufficient information provided to determine loss to follow-up)	Unclear	Poor	
Kim, 2012	No (Open)	Yes, overall (14%); No, differential 9% vs. 19%)	Unclear (NR - state only that drop out rates are not stat. sig. P=.45), No	Yes	Fair	
Kinon, 2006a RCT, multi-center, double-blind, parallel Poor	NR	Yes	High; differential Higher in the Zip group than Olan group (Zip 70.3 vs. Olan 55.4%, p=0.003).	Yes, using MMRM and LOCF	Poor	
Kinon, 2006b MC, R, DBT Fair	Yes; all study meds were identical in appearance; med blister packs given	Yes	LTFU-low ~45% total withdrawn; larger proportion of subjects in quetiapine arm (32%) discontinued due to psychiatric AE compared to olanzapine arm (12.9%)	Not true ITT though authors report it as ITT; used LOCF	Fair	
Klieser, 1995; Heinrich, 1994 Double-blind, single center, parallel Fair	Yes	Yes: 28/59 (47.5%) withdrew.	No	Yes for some outcomes, unclear for others	Fair	
Kluge, 2007 Fair	Stated to be DB	Yes	No 86% completed trial	Yes	Fair	
Knegtering, 2004 Open, single center, parallel Poor	No	All 51 patients who were analyzed completed the 6-wk study period	No loss to follow-up	Not clear - 51 patients "whose data could be analyzed" are reported on	Poor	

Evidence Table 2. Quality assessment of trials in patients with schizophrenia

Author, year quality rating	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors masked?	Care provider masked?
Knegtering, 2006 OL v RIS Fair	unclear; open label, says randomized.	Yes	Yes	Yes	No	No
Krakowski, 2006 CLO v OL v HOL Fair	Yes; block randomization scheme	Yes	Yes	Yes	Yes	Yes
Kramer, 2007 Study was terminated early Fair	Yes; computer generated randomization and stratification scheme	Yes, assigned by an interactive voice-response system	Yes; appears that there may be differences between the arms when looking at prior atypical & typical antipsychotics	Yes	Unclear, reported as DB	Unclear, reported as DB

Evidence Table 2. Quality assessment of trials in patients with schizophrenia

Author, year quality rating	Patient masked?	Attrition?	Loss to follow-up: Differential/high?	Intention-to-treat analysis?	Quality rating	Comments
Knegtering, 2006 OL v RIS Fair	No	No	NR; says all subjects initially randomized finished 6 wks of meds, did not measure compliance	No	Fair; short study (6 wks); 13 of 46 (28%) subjects had missing data	
Krakowski, 2006 CLO v OL v HOL Fair	Yes	Yes	Yes; moderate CLO 35% OL 30% HAL 44%	Yes	Fair; discontinuation was somewhat high for the Hal group, however the study was executed well; inpatient setting, short duration	
Kramer, 2007 Study was terminated early Fair	Unclear, reported as DB	Yes NR NR NR	LTFU- low ~13.5% (28/207) 'drop-outs' Differential: ~8% difference between those in P and paliperidone ER arm (more in paliperidone withdrew due to WDof consent)	Study terminated early. Efficacy analyses based on those who received at least 1-dose of tx and 1-postbaseline assessment	Fair	I think this might have been a gray area regarding the threshold for attrition levels - in your email to us on 3/27 I think you mentioned that overall attrition for short term studies (6-12 wks) would be considered high at 20% - this study is 13 wks so it was kind of on the edge. I am happy to change it to "No, No" though. Let me know what you want us to use for studies >12 and but < 6 mos. Perhaps anything under 6 mos is in the 20% range? That would make sense.

Evidence Table 2. Quality assessment of trials in patients with schizophrenia

Author, year quality rating	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors masked?	Care provider masked?
Kusumi, 2011	Unclear (Stated but not described)	No	Unclear	Yes	Unclear (NR)	No (Open)
Lee, 1999 Fair	Method NR	Method NR	Yes	Yes	No	No
Li, H., 2011	Yes	Unclear (NR)	Yes	Yes	Yes	No (Open)
Li, Y., 2012	Unclear (Stated but not described)	Unclear (NR)	Yes	Yes	Yes	No (Open)
Liberman, 2002 Poor	Method NR	Method NR	Yes	Yes	NR	NR
Lieberman, 2003 Green, 2004 Fair	Method NR	Method NR	No	Yes	Yes but method not described	NR
Lieberman, 2003 US and Europe Good	Method NR	NR	Yes	Yes	Yes	Yes
Lieberman, 2005 (CATIE Study) Good	Yes	Yes, "done under DB conditions"	Few minor differences	Yes	Yes	Yes
Lindenmayer, 1998 Open-label Pragmatic trial Poor	Not randomized- patients assigned to treatment based on their willingness to accept wkly blood drawings.	No	No significant differences in characteristics, N=21 clozapine, 14 risperidone.	Yes	No, "independent", but open label	No

Evidence Table 2. Quality assessment of trials in patients with schizophrenia

Author, year quality rating	Patient masked?	Attrition?	Loss to follow-up: Differential/high?	Intention-to-treat analysis?	Quality rating	Comments
Kusumi, 2011	No (Open)	Yes,Yes	No, No (no loss to follow-up reported)	Yes	Fair	
Lee, 1999 Fair	No	Attrition yes	No	No	Fair	
Li, H., 2011	No (Open)	No overall (23%) No differential (28% vs 17%)	No, (4% vs. 6%); No, overall (5%)	No	Fair	
Li, Y., 2012	No (Open)	Yes, Yes	No, No (only 1 pt. lost to follow-up)	Yes	Fair	
Liberman, 2002 Poor	NR	NR	NR	NR	Poor	
Lieberman, 2003 Green, 2004 Fair	Yes but method not described	Attrition yes	NR	No	Fair	
Lieberman, 2003 US and Europe Good	Yes	No/No/No/No	NR	Yes	Good	
Lieberman, 2005 (CATIE Study) Good	Yes	Yes (74%)	Yes Yes	Yes	Good	
Lindenmayer, 1998 Open-label Pragmatic trial Poor	No	Yes: 5 clozapine vs 2 risperidone withdrawn (24% vs 14%)	No	No: 32/35 analyzed (2 clozapine, 1 risperidone patient not analyzed)	Poor	

Evidence Table 2. Quality assessment of trials in patients with schizophrenia

Author, year quality rating	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors masked?	Care provider masked?
Lindenmayer, 2008	Method NR	Method NR	Unclear QXR 300 mg group had higher % paranoid, lower % undifferentiated	Yes	Yes but method not described	Yes but method not described
Lublin, 2009	Unclear (Stated but not described)	Unclear (NR)	Yes	Yes	Unclear (NR)	No (Open)
Luthringer, 2007 Fair	Yes, computer generated	Yes, central call center	N-paliperidone patients younger, only gave baseline characteristics of completers (86%)	Yes	Yes	Yes
Macfadden, 2010	Unclear (Stated but not described)	Unclear (NR)	Yes	Yes	Yes (rater)	No (Open)
Malla, 2004 Canada Poor	Not randomized	No - authors state allocation was influenced by availability based on state-funded reimbursement	Unclear - data only available for those completing treatment	Yes	No	No
Marder, 2007 Good	Yes, computer generated	Yes	Yes	Yes	Yes	Yes
McCue, 2006 Fair	Yes	Yes	Some; mean age varied by up to 6.7 ys across groups	Yes	No	No
McEvoy, 2007 Fair	NR	NR	Yes	Yes	Yes	Yes

Evidence Table 2. Quality assessment of trials in patients with schizophrenia

Author, year quality rating	Patient masked?	Attrition?	Loss to follow-up: Differential/high?	Intention-to-treat analysis?	Quality rating	Comments
Lindenmayer, 2008	Yes	Yes	Yes/Yes	No 498/532 (94%) in efficacy analysis	Fair	
Lublin, 2009	No (Open)	Yes, No differential (31% Tx vs. 17%, 23%, and 23% Comp)	Yes, (0% for all groups except Q [11%]); No, overall (~10%)	No, 14% from analysis	Fair	
Luthringer, 2007 Fair	Yes	Attrition-14%	No/No	Unclear for PANSS, but assume No, as with sleep outcomes	Fair	
Macfadden, 2010	No (Open)	Yes, Yes	No (10% vs. 5%); No overall (<10%)	Yes (although not 100%, meets criteria)	Fair	
Malla, 2004 Canada Poor	No	Yes/Yes/No/No	NR	No - 32/84 enrolled patients analyzed	Poor	
Marder, 2007 Good	Yes	Yes, No, No, No	No, No	432/444 = 97% analyzed	Good	
McCue, 2006 Fair	No	Yes	No No	No	Fair	
McEvoy, 2007 Fair	Yes	Attrition-66%	No/No	LOCF of patients who received >= 1 dose of medication and had >= 1 post baseline measurement	Fair	

Evidence Table 2. Quality assessment of trials in patients with schizophrenia

Author, year quality rating	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors masked?	Care provider masked?
McEvoy, 2007 Good	NR	NR	Yes	Yes	Yes	Yes
McQuade, 2004 RCT, multicenter, double-blind Fair	NR	NR	Yes	Yes	NR	Yes
Meltzer, 2008 Fair	Yes	Unclear	Yes	Yes	NR	Double-dummy
Meltzer, 2011	Yes	Yes	Yes	Yes	Unclear (NR)	Yes
Moller, 2008 Fair	NR	Unclear	Yes	Yes	NR	Double-dummy
Naber, 2001 Poor	NR - O vs R described as pseudo-randomized, C assignment not random	NR	No - differences in treatment refractoriness, and gender at baseline	Yes	Not blinded	Not blinded
Naber, 2005 Poor	Unclear; states computer prog with no details	NR	Yes, small differences (sign NR)	Yes	NR	NR

Evidence Table 2. Quality assessment of trials in patients with schizophrenia

Author, year quality rating	Patient masked?	Attrition?	Loss to follow-up: Differential/high?	Intention-to-treat analysis?	Quality rating	Comments
McEvoy, 2007 Good	Yes	Yes, No, No, No	No, No	Efficacy Sample = 410/420 (98%) Safety sample = 415/420 (99%)	Good	
McQuade, 2004 RCT, multicenter, double-blind Fair	Yes	Yes; 72% early discontinuation	No/No	8 patients excluded from "incidence of weight gain" analysis; 3 because they didn't receive study meds and other 5 because they did not have on-treatment weight measurements	Fair	
Meltzer, 2008 Fair	Double-dummy	Yes	Yes 73.7% completed in olanzapine group 47.6% completed in clozapine group	Unclear	Fair	
Meltzer, 2011	Yes	No, overall (38%); No, 36% for lurasidone 40 mg, 44% for 120 mg, 32% for O and 39% for P	No (1% vs. 2% vs. 2%); No, overall (1%)	Yes	Fair	
Moller, 2008 Fair	Double-dummy	Yes	No 92.4% completed study	Yes	Fair	20 in primary and 26 in safety analyses were excluded post-randomization because they were randomized despite meeting exclusion criteria
Naber, 2001 Poor	Not blinded	Unclear	Unclear	Unclear	Poor	
Naber, 2005 Poor	NR	Yes	Y; high and differential Overall 75% lost to follow-up; Lack of efficacy of tx: OL 12% vs. CLO 26% (sign NR)	Yes	Poor	

Evidence Table 2. Quality assessment of trials in patients with schizophrenia

Author, year quality rating	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors masked?	Care provider masked?
Newcomer 2009 Fair	Yes	Yes	Yes	Yes	No	No
Newcomer, 2008 Fair	NR	NR	Yes	Yes	NR	Stated to be DB
Nicolai-Costa, 2007 Poor	No- reported as 'by allotment'	No-open	Yes	Yes	No-open; but those who interviewed and collected data for the DGSFi were blinded to the treatment	No-open
Pandina, 2011	Yes	Yes	Yes	Yes	Yes	Yes, double dummy
Perez-Iglesias 2007 Fair	Yes	NR	Mostly, except for haloperidol group has significantly more users of anticholinergics than either the olanzapine or risperidone groups	Yes	Unclear	Stated to be DB
Peuskens 2007 Fair	Method NR	Method NR	Yes, some differences, with the P group being younger (4 ys mean), shorter disease duration (0.8 ys, mean), and fewer schizophrenic episodes (mean 1.1 fewer).	Yes	Yes	Yes
Peuskens, 1999 Fair	Method NR	Method NR	Yes	Yes	Yes but method not described	NR
Potkin, 2003 Fair	NR	NR	Yes	Yes	NR	Yes

Evidence Table 2. Quality assessment of trials in patients with schizophrenia

Author, year quality rating	Patient masked?	Attrition?	Loss to follow-up: Differential/high?	Intention-to-treat analysis?	Quality rating	Comments
Newcomer 2009 Fair	No	Yes	Yes 65% of olanzapine completed 86% of quetiapine completed 77% of risperidone completed	No those randomly assigned who were given study treatment per random assignment were included.	Fair	
Newcomer, 2008 Fair	Yes	Yes	No: loss to follow-up 7% in both groups	Unclear	Fair	
Nicolai-Costa, 2007 Poor	No-open	Attrition-yes (~14%); No patient changed their allocated group	LTFU-low (1-patient) 14% total withdrawn Differential: NR	NR	Poor	
Pandina, 2011	Yes, double dummy	No, overall (24%); No, (25% vs. 23%)	No (2% vs. 3%); No, overall (11%)	No	Fair	
Perez-Iglesias 2007 Fair	Stated to be DB	Yes	No: 88% completed study 2 lost to follow-up in haloperidol group 1 lost to follow-up in olanzapine group 5 lost to follow-up in risperidone group	Stated they analyzed using an ITT analysis, but give explanation for why they present only the per-protocol analysis	Fair	
Peuskens 2007 Fair	Yes	Yes	Yes/No. WDrate was 67% compared to 17% in treatment group.	Yes	Fair	
Peuskens, 1999 Fair	Yes	Attrition yes	No/ no	No	Fair	
Potkin, 2003 Fair	Yes	Yes	Unable to determine, groups NR.	No: 392/404 analyzed	Fair	

Evidence Table 2. Quality assessment of trials in patients with schizophrenia

Author, year quality rating	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors masked?	Care provider masked?
Potkin, 2006 Good	NR	Yes - centralized interactive voice response system (IVRS)	Yes	Yes	Yes	Yes
Potkin, 2007 Fair	NR	NR	Yes	Yes	NR	Stated to be DB
Potkin, 2011	Yes	Unclear	Yes	Yes	Unclear (NR)	Yes
QUEST; Mullen, 2001 Mullen, 1999 Reinstein, 1999 Fair	Method NR	Method NR	Yes	Yes	No	No
Riedel, 2005 Fair	Method NR	Method NR	No Higher PANSS Negative SANS alogia SANS avolition-apathy and SANS Total in quetiapine group (page 434)	Yes	Unclear, reported as double-blind	Unclear, reported as double-blind
Ritchie, 2003, 2000 Pragmatic RCT Multicenter, Australia Fair	Yes	Yes	Small differences in mean baseline doses of typical antipsychotics, baseline rate of TD and # in residential care	Yes	No	No
Robinson, 2006 Fair	NR	NR	Yes	Yes	Yes	No
Robles, 2011	Unclear	Unclear	Unclear	Yes	Yes (SB)	No
Rosenheck, 1997 Fair	Method NR	Method NR	Yes	Yes	Yes but method not described	NR

Evidence Table 2. Quality assessment of trials in patients with schizophrenia

Author, year quality rating	Patient masked?	Attrition?	Loss to follow-up: Differential/high?	Intention-to-treat analysis?	Quality rating	Comments
Potkin, 2006 Good	Yes	Yes - 51/382 (13%)	Higher in P group (15%) compared to risperidone (3%) and quetiapine (6%)	no-excluded 3 patients (0.8%)	Good	
Potkin, 2007 Fair	Yes	Yes	Yes: 34% completed in P group, 46% completed in asenapine group, 42% completed in risperidone group	Unclear: 8 patients not included in analysis	Fair	
Potkin, 2011	Yes	No, overall (32%); Yes (33% vs. 31%)	No, (1% vs. 5%); No, overall (4%)	No, 6% excluded	Fair	
QUEST; Mullen, 2001 Mullen, 1999 Reinstein, 1999 Fair	No	No	NR	Yes, using LOCF	Fair	
Riedel, 2005 Fair	Yes	Yes	No: loss to follow-up: Q 2/22 (9%) v R 0	Efficacy analysis based on pts w/baseline and at least one postbaseline measurement w/LOCF; all pts included in safety analysis	Fair	
Ritchie, 2003, 2000 Pragmatic RCT Multicenter, Australia Fair	No	Yes	No	Stated to use LOCF, but 5 risperidone patients not included	Fair	
Robinson, 2006 Fair	No	Yes, No, No, No	None	Analysis excluded 8 (7%) of patients due to protocol violations or refusal of treatment	Fair	
Robles, 2011	No	No, Yes	No, No	No, analyzed completers only	Fair	
Rosenheck, 1997 Fair	Yes	Attrition yes; crossovers yes	No/ no	No	Fair	

Evidence Table 2. Quality assessment of trials in patients with schizophrenia

Author, year quality rating	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors masked?	Care provider masked?
Rosenheck, 2003 Fair	Method NR	Yes	Yes, except mean PANSS negative subscale 23.2 in olanzapine vs 21.7 in haloperidol (p=0.02)	Yes	Yes but method not described	NR
Rubio, 2006 Poor	No-allocated alternately	No	Yes	Yes	Yes	No
Sacchetti, 2008 Fair	Yes	Unclear	Pretty much: Risperidone group slightly older than olanzapine and quetiapine groups	Yes	Yes	No
Sacchetti, 2009 Fair	Method NR	Method NR	Differences in DAI-10 scores, historical causes of refractoriness	Yes	NR stated as DB	NR stated as DB
Saddichha 2008 Fair	NR	NR	Risperidone vs olanzapine: Lower baseline HDL (33.8 vs 40.0). Age comparison NR. Similar for gender and weight and glucose parameters.	Yes	Yes	Yes
Sayers, 2005 Fair-Poor	Method NR	Yes	Unclear; only age, smoking and cocaine use given	Yes	Yes	NR
San, 2012 Fair	Method-NR	Unclear	Some differences at baseline in PANSS scores, number ultimately diagnosed with schizophrenia	yes	No	No
Sato, 2012 Poor	Method-NR	Unclear	Unclear	Yes	Unclear	Unclear

Evidence Table 2. Quality assessment of trials in patients with schizophrenia

Author, year quality rating	Patient masked?	Attrition?	Loss to follow-up: Differential/high?	Intention-to-treat analysis?	Quality rating	Comments
Rosenheck, 2003 Fair	Yes	Attrition yes	No/ no	Yes	Fair	
Rubio, 2006 Poor	No	Yes 4/66	No/No	N-4/66 excluded	Poor	
Sacchetti, 2008 Fair	Yes	Yes	No; No	Yes	Fair	
Sacchetti, 2009 Fair	Yes	Yes 90/147 completed (61.2%)	No/ no 90/147 completed (61.2%)	No All randomized with ≥ 1 dose + baseline measure + ≥ 1 valid post-baseline PANSS	Fair	
Saddichha 2008 Fair	Yes	Yes	Dropouts NR by group 90% completed study	No, excluded non completers (10%)	Fair	
Sayers, 2005 Fair-Poor	Yes	Attrition yes	High/Not differential 42% in each group	Yes	Fair-Poor Rating, small study,	
San, 2012 Fair	No	Yes	Unclear	Yes	Fair	
Sato, 2012 Poor	Unclear	Yes 22%; not reported by assigned drug	Slighlty high; not reported by group	No	Poor	

Evidence Table 2. Quality assessment of trials in patients with schizophrenia

Author, year quality rating	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors masked?	Care provider masked?
Schering-Plough #041023 RCT, DB Multicenter (USA, Canada, India, Russia, Romania) Fair	Yes	NR	Yes, except fewer females on asenapine	Yes	Unclear	Yes
Schering-Plough #7501012 RCT, DB Multicenter (Croatia, India, Latvia, Russia, United States) Fair	Unclear	NR	NR for DB phase between groups (asenapine v. P)	Yes	Unclear	Stated to be DB
Schering-Plough Study 041021	Unclear Central interactive voice response system	Unclear Central interactive voice response system	Unclear; inadequate data provided	Yes	Unclear; reported as DB	Unclear; reported as DB
Schering-Plough Study 041022	Unclear Central interactive voice response system	Unclear Central interactive voice response system	Unclear; inadequate data provided	Yes	Unclear; reported as DB	Unclear; reported as DB
Schering-Plough Study 25517	Unclear Central interactive voice response system	Unclear Central interactive voice response system	Unclear; inadequate data provided	Yes	Unclear; reported as DB	Unclear; reported as DB
Schering-Plough Study 25543	Unclear Interactive voice response system	Unclear Interactive voice response system	Unclear; inadequate data provided	Yes	Unclear; reported as DB	Unclear; reported as DB
Schering-Plough Study 25544	Unclear Interactive voice response system	Unclear Interactive voice response system	Unclear; inadequate data provided	Yes	Unclear; reported as DB	Unclear; reported as DB
Schreiner , 2012	Yes	Unclear	Yes	Yes	Unclear (NR)	No (open)

Evidence Table 2. Quality assessment of trials in patients with schizophrenia

Author, year quality rating	Patient masked?	Attrition?	Loss to follow-up: Differential/high?	Intention-to-treat analysis?	Quality rating	Comments
Schering-Plough #041023 RCT, DB Multicenter (USA, Canada, India, Russia, Romania) Fair	Yes	Yes	High; not differential Completion rates: Asenapine 5 mg = 63%; 10 mg = 67% P = 57% Haloperidol 4 mg = 59%	Stated to be; Analysis excluded 10 (2%)of 458 randomized	Fair	
Schering-Plough #7501012 RCT, DB Multicenter (Croatia, India, Latvia, Russia, United States) Fair	Stated to be DB	Yes	High; differential NR. Overall completion, DB phase: 37.5% Attrition NR between groups (asenapine v. P)	Stated to be; analysis excluded 1 of 192 randomized	Poor	
Schering-Plough Study 041021	Yes	Yes	No/Yes 42.3% vs. 50% vs. 50% vs. 43.1% withdrawals	No 386/417 (93%) in ITT	Fair	
Schering-Plough Study 041022	Yes	Yes	No/Yes 53% vs. 48% vs. 53% withdrawals	No 259/277 (94%) in ITT	Fair	
Schering-Plough Study 25517	Yes	Yes	Yes/Yes 62% vs. 43% withdrawals	No 1166/1225 (95%) in ITT	Fair	Patients with history of inadequate response to olanzapine excluded.
Schering-Plough Study 25543	Yes	Yes	Yes/Yes 35% vs. 20% withdrawals	No 433/481(90%) in ITT	Fair	
Schering-Plough Study 25544	Yes	Yes	No/No	No 279/306 (91%) in ITT	Fair	
Schreiner , 2012	No (open)	No, 25% overall No, 30% vs 20%	No, overall <10%, No 2.5% vs 1.8%	No, (n=45 excluded for primary outcome)	Fair	

Evidence Table 2. Quality assessment of trials in patients with schizophrenia

Author, year quality rating	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors masked?	Care provider masked?
Schoemaker, 2010	Unclear	Unclear	Yes	Yes	Unclear	Yes-double dummy
Schooler, 2005 Fair	Method NR	Method NR	Yes	Yes	Unclear; reported as DB	Unclear; reported as DB
Sechter, 2002 Fair	Method NR	Method NR	Yes	Yes	Yes but method not described	NR
Shopsin, 1979 Fair	Method NR	Method NR	NR	Yes	Yes	Yes
Shrivastava, 2000 Poor	Method NR	Method NR	Unclear	No	No	No
Silva de Lima, 2005 Fair	Performed centrally	Investigators received sealed, numbered ,coded envelopes from a person who had no contact w/the persons evaluation.	Yes	Yes	Yes-blinded to allocation, no contact with doctors or patients' records	No-open
Simpson, 2004 Fair	NR	NR	69% olanzapine vs 62% ziprasidone male (NS); otherwise similar	Yes	NR (states double-blind, but no details)	Used masked blister packs, and included "A, B, or C" corresponding to low, medium, or high dose.
Sirota, 2006 Fair	Method NR	Method NR	Yes, although quetiapine points had a slightly longer duration of illness (15.9 yrs [SD 9.1] vs 13.3 yrs [SD 7.4] for olanzapine)	Yes	Unclear, stated as "rater-blinded"	Unclear, stated as "rater-blinded"

Evidence Table 2. Quality assessment of trials in patients with schizophrenia

Author, year quality rating	Patient masked?	Attrition?	Loss to follow-up: Differential/high?	Intention-to-treat analysis?	Quality rating	Comments
Schoemaker, 2010	Yes-double dummy	Overall, No (56.9% excluded), differential: asenapine completers 38%, olanzapine completers: 57%)	No loss to follow-up	Yes,(4.8% excluded)	Fair	
Schooler, 2005 Fair	Unclear; reported as DB	Yes (36.5%), no, no, no	Overall withdrawals 36.5%; p=0.40 between groups	Yes	Fair	
Sechter, 2002 Fair	Yes but method not described	Attrition yes	No/ no	No	Fair	
Shopsin, 1979 Fair	Yes	Unclear	Differential loss to f/u in P group	No	Fair	
Shrivastava, 2000 Poor	No	Yes	NR/No (33%)	No	Poor	
Silva de Lima, 2005 Fair	No-open	Yes-13%	No/no	Unclear-provided results for 'completers' and 'LOCF', but did not provide any Ns; presume LOCF is ITT	Fair	Random assignment, open label
Simpson, 2004 Fair	Used masked blister packs, and included "A, B, or C" corresponding to low, medium, or high dose.	Yes	High- 37/136 (27.2%) ziprasidone, 25/133 (18.8%) olanzapine (p=0.10)	Yes	Fair	
Sirota, 2006 Fair	NR	Yes	No loss to follow-up (all 5 withdrawals accounted for)	Unclear # analyzed NR	Fair	

Evidence Table 2. Quality assessment of trials in patients with schizophrenia

Author, year quality rating	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors masked?	Care provider masked?
Smelson, 2006 Fair	NR	NR	Yes	Yes	Yes	Yes
Smith, 2009	Yes	Method NR	Differences in type and number of antipsychotics used. Not statistically significant. Analysis adjustment used to control for bias.	Yes	No	No
Suzuki, 2007 Poor	NR	NR	Yes	Yes	Open label	Open label
Tollefson, 1997 Breier, 1999 Gilmore, 2002 Goldstein, 2002 Gomez, 2001 Hamilton, 2000 Kennedy, 2003 Kinon, 2001 Revicki, 1999 Sanger, 1999 Tohen, 2001 Tollefson, 1998 Tollefson, 1999 Tran, 1999 Tunis, 1999 Fair	Method NR	Method NR	Yes	Yes	Yes but method not described	NR
Tollefson, 2001 Beasley, 1999 Beuzen, 1998 Fair	Method NR	Method NR	Some differences. Proportion with disorganized type Schizophrenia 23% in O group, 14% in C, while undifferentiated = 13% in O, 24% in C. Also, those with continuous course = 54% in O, 48% in C. Mean age, and other important characteristics NR per group.	Yes	Yes	Yes
Tran, 1997 Fair	Method NR	Method NR	Unclear - not well reported	Yes	NR	Yes

Evidence Table 2. Quality assessment of trials in patients with schizophrenia

Author, year quality rating	Patient masked?	Attrition?	Loss to follow-up: Differential/high?	Intention-to-treat analysis?	Quality rating	Comments
Smelson, 2006 Fair	Yes	Yes - 12/31 (39%) dropped out	Unclear- Reasons for drop-outs NR	No- Excluded 39% (completers only)	Fair	
Smith, 2009	No	Yes 44/49 (89.8%) completed	No; no	No 46/49 (93.9%) in ITT	Fair	
Suzuki, 2007 Poor	Open label	Yes	No; No	No	Poor	
Tollefson, 1997 Breier, 1999 Gilmore, 2002 Goldstein, 2002 Gomez, 2001 Hamilton, 2000 Kennedy, 2003 Kinon, 2001 Revicki, 1999 Sanger, 1999 Tohen, 2001 Tollefson, 1998 Tollefson, 1999 Tran, 1999 Tunis, 1999 Fair	Yes but method not described	Attrition yes	No/ no	No	Fair	
Tollefson, 2001 Beasley, 1999 Beuzen, 1998 Fair	Yes	Yes	No	Yes (LOCF methods)	Fair	
Tran, 1997 Fair	Yes	Yes	Overall 47.5% olanzapine 57.6% risperidone 47.3%	Yes	Fair	

Evidence Table 2. Quality assessment of trials in patients with schizophrenia

Author, year quality rating	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors masked?	Care provider masked?
Tran-Johnson, 2007 Fair	Method NR	Method NR	Yes	Yes	NR	Stated to be DB
Tunis 2006 Fair	Method NR	Method NR	Yes	Yes	No	No
Tzimos, 2008	Method NR	Method NR	18% of Paliperidone group over age 75 vs. 5% of P group	Yes	Stated to be DB	Stated to be DB
van Bruggen, 2003 Poor	NR	NR	Yes (but appears baseline characteristics exclude 2 patients not analyzed). Groups imbalanced: 18 randomized to O, 26 to R.	Yes	Not clear (states "independent")	NR
van Nimwegen, 2008 Fair	NR	Unclear	NR	Yes	Unclear	Stated to be DB
Vanelle, 2006 Good	Yes - Computer generated	Yes - Kept by Sanofi-Synthelabo	Yes	Yes	Yes	Yes
Velligan, 2003 Fair	Method NR	Method NR	Yes	Yes	Yes	No
Voruganti, 2007 Fair	NR	NR	Yes	Yes	Yes	NR
Wahlbeck, 2000 Open-label RCT Fair	Yes	Method NR	No, Significantly more women in the risperidone arm	Yes	No, open-label	No, open-label
Wampers, 2012	N/A	N/A	Unclear	Yes	Unclear (NR)	No (open)

Evidence Table 2. Quality assessment of trials in patients with schizophrenia

Author, year quality rating	Patient masked?	Attrition?	Loss to follow-up: Differential/high?	Intention-to-treat analysis?	Quality rating	Comments
Tran-Johnson, 2007 Fair	Stated to be DB	Yes	No/no	Yes (LOCF)	Fair	
Tunis 2006 Fair	No	Yes	No/No	Yes	Fair	
Tzimos, 2008	Stated to be DB	Yes 79% completed DB phase	No, yes(84%) of drug group completed 26/38 (68%) of P group completed	No included those who had baseline +≥ 1 postbaseline efficacy assessment	Poor	
van Bruggen, 2003 Poor	NR	NR	Yes- 2/26 risperidone vs 0/18 olanzapine not included in analysis	No: 2 risperidone patients excluded	Poor	
van Nimwegen, 2008 Fair	Stated to be DB	Yes	No; No	Excluded 3 patients from analysis because they had no postrandomization observable scores	Fair	
Vanelle, 2006 Good	Yes	Yes - 14/85 early discontinuation	No/No	No - Excluded 2/85 (0.02%)	Good	Small number of patients.
Velligan, 2003 Fair	No	Attrition yes	No/ no	No	Fair	Prospective randomized controlled design
Voruganti, 2007 Fair	NR	Yes- 1/86 early discontinuation	No/No	No - 1/86 (1%) excluded	Fair	Physiologic measures only, no data on psychiatric improvement; investigators not blinded to treatment; only 8 wks long.
Wahlbeck, 2000 Open-label RCT Fair	No, open-label	Yes	Overall = 35% Differential drop-out: clozapine 50%, risperidone 11%	Yes	Fair	
Wampers, 2012	No (open)	Unclear (NR)	Unclear (NR)	Yes	Poor	

Evidence Table 2. Quality assessment of trials in patients with schizophrenia

Author, year quality rating	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors masked?	Care provider masked?
Wang, 2006 RCT, double-blind Fair	Unclear; pharmacists maintained '"randomization schedules", no details provided	Unclear	Yes	Yes	NR	NR
Weiden, 2009	Method NR	Method NR	NR	Yes	Adherence attitude assessor blinded	No
Wu, 2006 Fair	NR	NR	Yes	Yes	No	NR
Yamashita, 2004 Mori, 2004 RCT, single center, blinding unclear Fair	NR	NR	No	Yes	NR	Blinding unclear
Zhang, 2012	Unclear	Unclear	Unclear, baseline characterstics reported on completer population	Yes	Open label	Open label
Zhong, 2006 Fair	Not stated	Unclear	Yes	Yes	NR	NR
Zimbroff, 2007 Fair	Yes	Yes	Yes	Yes	Unclear	Stated to be DB

Evidence Table 2. Quality assessment of trials in patients with schizophrenia

Author, year quality rating	Patient masked?	Attrition?	Loss to follow-up: Differential/high?	Intention-to-treat analysis?	Quality rating	Comments
Wang, 2006 RCT, double-blind Fair	Yes	Yes	Yes; 42% (8) Risp vs. 29% (5) Olan [study states these were similar, no statistics reported]	Yes, using LOCF	Fair	
Weiden, 2009	No	Unclear 19/26 (73%) in RLAT accepted random assignment	Unclear	Yes	Poor	
Wu, 2006 Fair	NR	Yes; 8 of 120	No/no	NR	Fair	
Yamashita, 2004 Mori, 2004 RCT, single center, blinding unclear Fair	Blinding unclear	Yes	No loss to follow-up	Unclear if analysis included 2 patients (2.2%) who discontinued early	Fair	
Zhang, 2012	Open label	Yes, Yes	No, No	No, excluded 20%, completers only	Fair	
Zhong, 2006 Fair	Yes	Yes	Yes; high, not differential Completion rates: approx 48% Lost to follow-up; QU v RIS, 7.4 vs 11.9; RIS higher WD due to AE compared to QU	Y	Fair	
Zimbroff, 2007 Fair	Yes	Yes	No; 68% completed in ziprasidone group 69.5% completed in aripiprazole group	Stated to be, but 6 patients excluded from analysis	Fair	

Evidence Table 3. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Data source	Prospective Retrospective Unclear	Sampling frame	Exposure period
Advokat, 2003	Eastern Louisiana Mental Health System	Retrospective	1995-2001	5 ys
Advokat, 2004 United States	Hospital charts and medical records from the Eastern Louisiana Mental Health System	Retrospective	September 1996 through September 2001	NR

Evidence Table 3. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Interventions mean dose	Population	Age Gender Ethnicity
Advokat, 2003	olanzapine 332 ds risperidone 376 ds quetiapine 558 ds clozapine 583 ds	Schizoaffective/Bipolar Type, Paranoid Schizophrenia, or Schizophrenia Undifferentiated	Mean age=40.6 ys 31% male 50% Africa American
Advokat, 2004 United States	Olanzapine: 20.6mg/d Risperidone: 5.3mg/d Quetiapine: 320.6mg/d Clozapine: 375mg/d	Patients reporting initial baseline value of 35 or greater on the Brief Psychiatric Rating Scale (BPRS) and had at least 3 successive moly BPRS ratings	Olanzapine/Risperidone/Quetiapine/ Clozapine Mean age (ys): 39.8/41.2/43.3/ 38.7 %male: 37/22/36/29 %African-American: 50/47/45/71

Evidence Table 3. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Exposed Eligible Selected	Withdrawn Lost to follow-up Analyzed	Effectiveness outcomes
Advokat, 2003	398/100/100	NR/NR/100	length of hospitalization: olanzapine (n=18) vs risperidone (n=9) = 634 ds vs 1017 ds, p=0.038 >20% decline from baseline in BPRS score: olanzapine = 33/46 (72%) risperidone = 16/36 (44%) clozapine = 52/59 (88%) clo vs ris, p<0.01; ola vs ris, p=0.012; clo vs ola, p=0.034 responders that retained or improved their BPRS scores: olanzapine vs risperidone, NS Latencies from responders: olanzapine vs risperidone = 1.67 vs 1.47 mos
Advokat, 2004 United States	NR/NR/100	NR/NR/100	Maximum daily dosages 28 of 46 patients on olanzapine received 15mg or less per d as max dose 21 of 36 patients on risperidone received 4mg or less per d as max dose 8 of 11 patients on quetiapine received 400mg or less per d as max dose 7 of 7 patients on clozapine received 450mg or less per d as max dose Average Length of stay in hospital Olanzapine: 332 ds Risperidone: 376 ds Quetiapine: 558 ds Clozapine: 583 ds 20% or more change from baseline on BPRS Olanzapine: 33 of 46 (72%) patients Risperidone: 16 of 36 (44%) patients Quetiapine: 4 of 11 (36%) patients Clozapine: 5 of 7 (71%) patients Response latency Olanzapine: 1.67 mos Risperidone: 1.47 mos Quetiapine: 2.00 mos Clozapine: 2.75 mos

Evidence Table 3. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Safety outcomes	Comments
Advokat, 2003	NR	
Advokat, 2004 United States	NR	

Evidence Table 3. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Data source	Prospective Retrospective Unclear	Sampling frame	Exposure period
Agelink, 2001 Germany	Evangelical Hospital Gelsenkirchen, Germany	Retrospective	Mean: 14.1 ds	NR
Akkaya 2007 Turkey	Medical record review: Psychiatry Outpatient Clinic of Uludag University Medical Faculty	Retrospective	January 1998 to October 2005	Risperidone/Haloperidol/Olanzapine Mean duration of treatment (d): 430.7±536.7/761.5±836.7/754.5±818.9
Al-Zakwani, 2003 United States	Multicenter, United States	Retrospective	24 mos	18 mos

Evidence Table 3. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Interventions mean dose	Population	Age Gender Ethnicity
Agelink, 2001 Germany	amisulpride: 400 mg/d, olanzapine: 20 mg/d, sertindole: 12 mg/d, clozapine: 100 mg/d	Medication-free inpatients with schizophrenia	Mean age: 33.7 ys 68.8% Male Ethnicity NR
Akkaya 2007 Turkey	Risperidone/Haloperidol/Olanzapine Mean dose (mg): 3 ±1.4/5.4±5.1/11.7±5.4	Patients diagnosed with schizophrenia and placed on drug treatment	Risperidone/Haloperidol/Olanzapine Age (y): 34.5±13.5/34.6±12.5/32.5±14.8 Gender (% male): 57.1/58.2/60 Ethnicity: NR
Al-Zakwani, 2003 United States	Doses NR. Interventions-Typical Antipsychotics: chlorpromazine, haloperidol, thioridazine, perphenazine, other; Atypical Antipsychotics: risperidone, olanzapine, quetiapine, clozapine	Psychosis, neurotic, personality and sexual disorders, drug/alcohol dependence, psychological malfunction arising from mental disorders, depressive disorder, childhood emotional disturbance/developmental delays, MR/Alzheimer's/Parkinson's diseases	Mean age: 38.5 ys 59% Male Ethnicity NR

Evidence Table 3. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Exposed Eligible Selected	Withdrawn Lost to follow-up Analyzed	Effectiveness outcomes
Agelink, 2001 Germany	NR/NR/51	0/0/51	NR
Akkaya 2007 Turkey	NR 407 274	NR NR 189 (63 risperidone, 91 haloperidol, 35 olanzapine)	Risperidone/Haloperidol/Olanzapine Rates of discontinuation (%) over 18 mos 68.3/51.6/54.3 Relapse under treatment (%) No: 81/68.1/65.7 Yes: 19/31.9/34.3 Relapse resulting in hospitalization (%) No: 33.3/44.6/41.7 Yes: 66.7/55.2/58.3 Reason of treatment discontinuation (%) Compliance issues: 74.6/72.5/60 Side effect: 4.8/5.5/8.6 Relapse: 4.8/11/5.7 Hospitalization: 1.6/3.3/8.6 Treatment continued: 14.3/7.7/17.1
Al-Zakwani, 2003 United States	2710/833/469	NR/NR/469	Typical Antipsychotics: # dose adjustments: 14(16.5%) # treatment augmentation: 1(1.2%) # requiring treatment switch: 11(12.9%) # receiving mixed therapy: 1(1.2%) Atypical Antipsychotics: # dose adjustments: 128(30.4%) # treatment augmentation: 3(0.8%) # requiring treatment switch: 70(18.2%) # receiving mixed therapy: 7(1.5%)

Evidence Table 3. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Safety outcomes	Comments
Agelink, 2001 Germany	clozapine, olanzapine, sertindole had a prolonged mean frequency-corrected QTc times; P<0.05 HRr at endpoint: A: 77.2 vs O: 84.6 vs S: 88.7 vs C: 95.9 CVr at endpoint: A: 3.9 vs O: 3.9 vs S: 5.2 vs C: 2.3	
Akkaya 2007 Turkey	Risperidone/Haloperidol/Olanzapine Side effects that caused treatment discontinuation (authors do not report if this figure is n or %) EPS: 0/5/2 Prolactin increase: 2/0/0 Weight gain: 0/0/1 Sedation: 1/0/0	
Al-Zakwani, 2003 United States	NR	

Evidence Table 3. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Data source	Prospective Retrospective Unclear	Sampling frame	Exposure period
Ascher-Svanum 2008 US (21 sites in multiple states)	Data from a randomized, open-label study of the cost effectiveness of olanzapine, risperidone, and typical antipsychotics. Twenty sites in the US.	Retrospective	May 1998-September 2002	One y
Ascher-Svanum, 2004 Faries, 2005 USA	U.S. Schizophrenia Care and Assessment Prog (US SCAP)	Prospective	July 1997 to 2003	One y
Barak, 2004 Israel	Abarbamel Mental Health Center, Bat-Yam	Retrospective	January 1998 to December 2002	5 ys

Evidence Table 3. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Interventions mean dose	Population	Age Gender Ethnicity
Ascher-Svanum 2008 US (21 sites in multiple states)	olanzapine 13.3 mg risperidone 4.85 mg typical antipsychotics: perphenazine, haloperidol, loxapine, thiothixene, fluphenazine, trifuloperazine, mesoridazine, thioridazine, chlorpromazine, molindone	18 ys of age or older, DSM-IV criteria for schizophrenia, schizoaffective or schizophreniform disorders, minimum scoreof 18 on BPRS.	Mean age 43 ys 63% male 54% white, 34% African American, 12% other race/ethnicity
Ascher-Svanum, 2004 Faries, 2005 USA	Olanzapine Risperidone	DSM-IV criteria for schizophrenia, schizoaffective, or schizophreniform disorder; > 18 ys; and understood and provided informed consent. Excluded if participation in a controlled clinical drug trial in past mo .	Age at enrollment, Olanzapine 43.5 Risperidone 39.3 Male, Olanzapine 62.9% Risperidone 54.5% Ethnicity White Olanzapine 52.8% Risperidone 49.1% Black Olanzapine 41.5% Risperidone 39.1% Other Olanzapine 5.7% Risperidone 11.8%
Barak, 2004 Israel	clozapine 445mg for 575 ds olanzapine 17.8mg for 492 ds risperidone 4.6mg for 466 ds	Schizophrenia or schizoaffective disorder with attempted suicide in the 4 WK preceding admissions	Mean age=39.1 ys 84.7% male Ethnicity: NR

Evidence Table 3. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Exposed Eligible Selected	Withdrawn Lost to follow-up Analyzed	Effectiveness outcomes
Ascher-Svanum 2008 US (21 sites in multiple states)	664 664 648 (222 olanzapine, 217 risperidone, 209 typical antipsychotics)	None reported None reported 648	Mean time (SD) to all-cause medication discontinuation: Olanzapine: 277.2 ds (123.9); p<0.001 vs typical antipsychotics; p<0.001 vs risperidone; Risperidone: 231.9 ds (142.2) Typical antipsychotics: 193.5 ds (137.9) Perphenazine: 277.2 ds (123.9) One-y survival rates (SD): Olanzapine: 55.3% (3.6%); p=0.007 vs risperidone Risperidone: 46.8* (3.5%) Typical antipsychotics: 31.7% (3.3%); p <0.001 vs olanzapine; p=0.002 vs risperidone Perphenazine: 30.8% (6.8%); p<0.001 vs olanzapine; p=0.060 vs risperidone
Ascher-Svanum, 2004 Faries, 2005 USA	NA	NR/NR/Olanzapine n = 159 Risperidone n = 112	Adherent group (n = 271) Hospitalization rates risperidone 24.1% vs. olanzapine 14.4% P = 0.040 Hospitalization ds risperidone 14.5 ds vs. olanzapine 9.9 ds P = 0.035. Adherent and non-adherent groups combined (n = 516) Hospitalization rates risperidone 31.5% vs. olanzapine 23.6% P = 0.045 Hospitalization ds risperidone 17.6 ds vs. olanzapine 19.1 ds P = 0.755. Odds of staying on monotherapy during the 1-y period (vs initiating polytherapy) (Faries 2005) Olanzapine vs quetiapine: OR 2.08 (95% CI 1.30, 3.31) Olanzapine vs risperidone: OR 1.36 (95% 1.01, 1.84)
Barak, 2004 Israel	68000/4486/378	NR/NR/378	NR

Evidence Table 3. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Safety outcomes	Comments
Ascher-Svanum 2008 US (21 sites in multiple states)	NA	
Ascher-Svanum, 2004 Faries, 2005 USA	NR	
Barak, 2004 Israel	suicide group vs control group exposed to second generation antipsychotics: 16% vs 37%, p=0.0001 protective effect: OR (p, 95% CI) overall: 3.54 (p=NR, 2.4-5.3) risperidone: 3.16 (p=0.001, 1.9-5.3) olanzapine: 1.76 (p=0.02, 1.2-3.3)	

Evidence Table 3. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Data source	Prospective Retrospective Unclear	Sampling frame	Exposure period
Barner, 2004 United States	Database: Central Texas Veterans Health Care System	Retrospective	Duration of treatment NR. Mean number of persistent ds (total number of continuous ds the patient took an antipsychotic agent without a gap, I.e. a 15-d lapse in therapy): AAPs: 3.9-5.6 mos Typical APs: 4.7-7.3 mos	NR
Bitter, 2005 Africa, the Middle East, Asia, Central and Eastern Europe, Latin America IC-SOHO Study (6-mo data) Hostile/aggressive behavior outcomes	same as Dossenbach 2004	same as Dossenbach 2004	same as Dossenbach 2004	same as Dossenbach 2004
Bond, 2004 United States	A psychiatric rehabilitation agency and four community mental health centers.	Prospective	March 1999 to January 2001	9 mos

Evidence Table 3. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Interventions mean dose	Population	Age Gender Ethnicity
Barner, 2004 United States	Any AAP or typical AP, dose and duration NR	Included subjects aged 18+ who had not received a typical AP or AAP 6 mos prior to the dispensing of a typical AP or AAP, and had not been diagnosed with DM or used an antidiabetic drug 12 mos before being prescribed a typical AP or AAP.	Mean age 59.4 94.3% male 69.9% white
Bitter, 2005 Africa, the Middle East, Asia, Central and Eastern Europe, Latin America IC-SOHO Study (6-mo data) Hostile/aggressive behavior outcomes	same as Dossenbach 2004	Subset of patients who sustained monotherapy and had hostile/aggressive outcome data available at 3- and 6-mos	Mean age=35.2 ys 54% male Ethnicity NR
Bond, 2004 United States	Olanzapine 12.9 mg Risperidone 5.4 mg	Schizophrenia or schizoaffective disorder	Mean age=40.8 ys 59% male 45% Caucasian; 42% Africa American; 3% other

Evidence Table 3. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Exposed Eligible Selected	Withdrawn Lost to follow-up Analyzed	Effectiveness outcomes
Barner, 2004 United States	6735 3469 3469	NR NR 3469	NR
Bitter, 2005 Africa, the Middle East, Asia, Central and Eastern Europe, Latin America IC-SOHO Study (6-mo data) Hostile/aggressive behavior outcomes	7655/5828/3135	NR/NR/3135	Change in proportions of patients with hostile/aggressive behavior from baseline to 6 mos: Clozapine: -16.8% Olanzapine: -23.1% Quetiapine: -18.3% Risperidone: -22.7% ORs for improvement of hostility over time (95% CI): Risperidone vs clozapine: 1.83 (1.05, 3.20) Olanzapine vs clozapine: 1.67 (1.01, 2.75)
Bond, 2004 United States	551/124/90	NR/NR/90	work outcomes: olanzapine (n=39) vs risperidone (n=27) vs first-generation anti-psychotics (n=24) paid employment at any time; 29(74%) vs 17(63%) vs 13(54%), NS integrated employment at any time: 16(41%) vs 8(30%) vs 8(33%), NS second generation vs first generation: vocational activities: 76% vs 50%, p<0.05 increase in vocational activities: higher vs lower, p<0.001 moly rate of paid employment: higher vs lower, NS moly rate of integrated employment: greater vs lower, p=0.001

Evidence Table 3. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Safety outcomes	Comments
Barner, 2004 United States	Frequency of new-onset diabetes mellitus among patients taking AAPs: AAP group (n=2477) 7.2% (ns) Typical AP group (n=992) 7.0% (ns) Risperidone 7.5% (ns) Quetiapine 5.8% (ns) Olanzapine 6.4% (ns) Adjusted OR of new-onset diabetes mellitus (95% CI): Olanzapine 0.976 (0.594-1.605) Quetiapine 1.149 (0.531-2.485) Risperidone 0.926 (0.544-1.579)	Dose and duration of treatment are not controlled for in this analysis
Bitter, 2005 Africa, the Middle East, Asia, Central and Eastern Europe, Latin America IC-SOHO Study (6-mo data) Hostile/aggressive behavior outcomes	NR	
Bond, 2004 United States	NR	

Evidence Table 3. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Data source	Prospective Retrospective Unclear	Sampling frame	Exposure period
Brown, 2005 United States	Review of charts of VA patients	Retrospective	June 2001 to March 2003	NR
Buse, 2003 United States	AdvancePCS Inc	Retrospective	>2 ys	NR

Evidence Table 3. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Interventions mean dose	Population	Age Gender Ethnicity
Brown, 2005 United States	Ziprasidone Olanzapine	Schizophrenia or other psychoses	Mean age (ys): Ziprasidone=47.3; Olanzapine=53.9 Gender: Ziprasidone=90.9% male; Olanzapine=96.1% male Ethnicity: NR
Buse, 2003 United States	Clozapine: 183.1 mg/d Olanzapine: 5.1 mg/d Quetiapine: 79.9 mg/d Risperidone: 1.2 mg/d Haloperidol: 2.5 mg/d Thioridazine: 43.9 mg/d	Schizophrenia	Mean age: 52 ys 63% male

Evidence Table 3. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Exposed Eligible Selected	Withdrawn Lost to follow-up Analyzed	Effectiveness outcomes
Brown, 2005 United States	NR/NR/191	NR/NR/191	Weight changes Patients gained an average of 3.9kg on olanzapine (P<0.001) Patients lost on average 1.5kg on ziprasidone (P>0.05) Patients switched from olanzapine to ziprasidone lost an average of 3.4kg over the course of therapy (P=0.002) Metabolic changes Olanzapine was associated with an 8% increase in total cholesterol (P=0.01), an 11% increase in LDL, a 4% decrease in HDL, a 27% increase in triglycerides (P=0.05) and a 6% increase in HbA1c (P<0.05) Ziprasidone was associated with a 7% reduction in total cholesterol, a 14% decrease in LDL, an 8% increase in HDL, a 7% decrease in triglycerides and a 9.4% reduction in HbA1c
Buse, 2003 United States	5,816,473 58,751 58,751	Withdrawn=N/A (retrospective) Lost to follow-up=N/A (retrospective) Analyzed=58,751	Risk of Diabetes Mellitus: olanzapine: P=0.479 clozapine: P=0.496 quetiapine: P=0.033 haloperidol: P=0.040

Evidence Table 3. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Safety outcomes	Comments
Brown, 2005 United States	NR	
Buse, 2003 United States	Hazard ratio of developing diabetes comparing antipsychotics to haloperidol group: olanzapine: risperidone: P=0.479 quetiapine: P=0.040 clozapine: P=0.496	

Evidence Table 3. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Data source	Prospective Retrospective Unclear	Sampling frame	Exposure period
Bushe 2013 (Combined data from IC and European SOHO)	Worldwide Schizophrenia Outpatient Health Outcomes database	Prospective	5 years	3 years
Caro, 2002 Quebec	Database: Regie de l'Assurance Maladie du Quebec	Retrospective	1/1/97 to 12/31/99	NR

Evidence Table 3. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Interventions mean dose	Population	Age Gender Ethnicity
Bushe 2013 (Combined data from IC and European SOHO)	Clozapie Olanzapine Quetiapine Risperidone	Schizophrenia	Mean age: 37.91 (SD 12.91) Male: 54.6% Ethnicity: NR
Caro, 2002 Quebec	Olanzapine Risperidone	Psychotic disorders ≥ 1 prescription for olanzapine or risperidone	Mean age NR 47.2% male Race NR

Evidence Table 3. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Exposed Eligible Selected	Withdrawn Lost to follow-up Analyzed	Effectiveness outcomes
Bushe 2013 (Combined data from IC and European SOHO)	12,763 11088 4626	NR, NR, 4626	NR
Caro, 2002 Quebec	NR 34,692 33,946 Olanzapine= 19,153 Risperidone= 14,793	NR NR 33,946	NR

Evidence Table 3. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Safety outcomes	Comments
Bushe 2013 (Combined data from IC and European SOHO)	Mean weight gain in Kg at 3 years (95% CI) Quetiapine: 2.5 (1.4-3.6) Risperidone: 3.1 (2.6-3.6) Clozapine: 3.3 (2.3-4.3) Olanzapine: 4.2 (3.9-4.5) Mean change in BMI (kg/m2) at 3 years (95% CI) Quetiapine: 0.9 (0.5 -1.3) Risperidone: 1.2 (1.0 -1.3) Clozapine: 1.2 (0.8- 1.6) Olanzapine: 1.6 (1.5 - 1.7) Proportion of patients gaining ≥7% of body weight,(95% CI) Clozapine: 33% (26-41%) Quetipaine: 35% (28-44%) Risperidoe: 40% (37-44%) Olanzapine: 45% (43-48%) Proportion of patients who lost ≥7% of body weight, (95% CI) Quetiapine: 10% (7-16%) Risperdione: 8% (6-11%) Clozapine: 8% (5-13%) Olanzapine:7% (6-8%)	
Caro, 2002 Quebec	Diabetes Olanzapine=319/17 Risperidone=217/16 p=0.43 (Cases/rate per 1000 patient ys)	

Evidence Table 3. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Data source	Prospective Retrospective Unclear	Sampling frame	Exposure period
Castro 2007 Brazil	Chart review: Institute of Psychiatry, Universidade de Sao Paulo	Retrospective	NR	12/1/97-12/31/99

Evidence Table 3. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Interventions mean dose	Population	Age Gender Ethnicity
Castro 2007 Brazil	NR	Patients with schizophrenia who were discharged on a regimen of either haloperidol, risperidone or clozapine Exclusion criteria: patients discharged on two or more antipsychotics, patients with another axis 1 disorder and diagnosis of neurological disorders	Haloperidol/Risperidone/Clozapine Mean age: 38.28±10.17/37.59±11.72/35.55±9.48 Male (n): 17/10/21 Ethnicity: NR

Evidence Table 3. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Exposed Eligible Selected	Withdrawn Lost to follow-up Analyzed	Effectiveness outcomes
Castro 2007 Brazil	NR NR 96 (43 haloperidol, 22 risperidone, 31 clozapine)	NR NR 96	Haloperidol/Risperidone/Clozapine Mean time to hospital readmission (d): 395±318 (range 54-1015)/284±200 (range 6-596)/264±157 (range 88-427) Median time to hospital readmission (d):286/271/303 *No significant difference in time to rehospitalization between groups (ANOVA F=0.66; df=2; p=0.53) Mean length of follow-up for patients who were not readmitted (d): 718±483 (range 14-1095)/879±421 (range 22-1095)/1053±210 (range 26-1095) Percentage of patients remaining non-hospitalized: 12 mos: 84/73/90 24 mos: 79/59/84 36 mos: 74/59/84 Rehospitalization rates (%): 12 mos: 16/27/10 24 mos: 21/41/16 36 mos: 26/41/16 *No significant difference in rehospitalization rates between treatment groups; P-value=NR

Evidence Table 3. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Safety outcomes	Comments
Castro 2007 Brazil	NR	

Evidence Table 3. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Data source	Prospective Retrospective Unclear	Sampling frame	Exposure period
Cianchetti, 2011 Italy	Prospective cohort from Clinic of Child and Adolescent Neuropsychology, Hospital-University of Cagliari, Italy	Prospective	1990-2005	11 years
Citrome 2004 US (New York State)	Integrated Research Database, containing patient information and drug prescription information for every inpatient within the 17 adult civil facilities of the NY State psychiatric hospital system	Retrospective	January 1, 2000-December 31, 2002	Case group: mean 121 + 60.9 ds Control group: mean 133 + 55 ds
Conley, 1999 United States	Record review: Maryland state psychiatric facilities	Prospective	3/14/94 to 12/31/95	NR

Evidence Table 3. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Interventions mean dose	Population	Age Gender Ethnicity
Cianchetti, 2011 Italy	Haloperidol, 3-8 mg/d Risperidone, 3-6 mg/d Olanzapine, 10-20 mg/d Quetiapine, 250-450 mg/d Aripiprazole, 10-20 mg/d Clozapine, 200-500 mg/d Mean doses NR	10-17 years, Schiophrenia or Schizoaffective disorder	Age: 15.5 Gender: NR Ethnicity: 100% Caucasian
Citrome 2004 US (New York State)	clozapine risperidone olanzapine quetiapine Mean doses NR	Case group: those who received new prescription of antidiabetic medication. Required to have at least a 30-d period of hospitalization before the start of the prescription. Control group: Those who did not receive a prescription of antidiabetic medication, matched to those in case group on calendar y,then length of stay, then race, then age group, then diagnosis.	Case group: Mean age 43.3 ys (SD 11.4) 61% male 32% white Control group: Mean age 43.7 ys (SD 12.8) 71% male 32% white
Conley, 1999 United States	Clozapine Risperidone	Schizophrenia	Mean age=40.4 60.5% male Race NR

Evidence Table 3. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Exposed Eligible Selected	Withdrawn Lost to follow-up Analyzed	Effectiveness outcomes
Cianchetti, 2011 Italy	NR/58/47	28/NR/47 at 3 years, 41 at 5 years, 30 at 8 years, 19 at 11 years	Haloperidol vs. Risperidone vs. Olanzapine vs. Quetiapine vs. Aripiprazole vs. Clozapine Positive Response at 3-years, n=47 (%): 10.0 vs. 37.5 vs. 8.3 vs. 50.0 vs. 75.0 vs. 81.5 Positive Response at 5-years, n=41 (%): 13.8 vs. 25.0 vs. 0 vs. 55.5 vs. 42.9 vs. 76.0 Z scores for clinical improvement at 5-years, Haloperidol vs. Risperidone vs. Olanzapine vs. Clozapine PANSS total: 4.37, p<0.0001 vs. 4.72, p<0.0001 vs. 2.80, p<0.05 vs. 4.54, p<0.0001 PANSS positive: 4.04, p<0.0001 vs. 4.37, p<0.0001 vs. 2.01, p<0.05 vs. 4.44, p<0.0001 PANSS negative: 3.99, p<0.0001 vs. 4.74, p<0.0001 vs. 2.38, p<0.05 vs. 4.17, p<0.0001 C-GAS/GAF: 3.95, p<0.0001 vs. 4.78, p<0.0001 vs. 2.38, p<0.05 vs. 4.45, p<0.0001 Clozapine vs. All other drugs combined: GAF, mean increase at 8-years: 93±50% vs. 60±34%, P=NS GAF, mean increase at 11- years: 87±41% vs. 54±31%, P<0.05
Citrome 2004 US (New York State)	13,611 8,461 1,629	NR NR 1,629	
Conley, 1999 United States	NR NR 124 (clozapine=49, risperidone=75)	NR NR unclear	NR

Evidence Table 3. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Safety outcomes	Comments
Cianchetti, 2011 Italy	Suicide attempts: 0 Adverse Events Causing discontinuation: Haloperidol: Neurodysleptic crises, 1 Risperidone: Excessive weight gain, 2; Amenorrhea, 2; Adenoma of hypophysis, 1; Parkinsonism, 1; Neurdysleptic crises, 2; Seizures, 1 Olanzapine: Excessive weight gain, 3; Amenorrhea, 2 Aripiprazole: Amenorrhea, 1 Clozapine: Excessive weight gain, 1; Neutropenia <1500/mmc, 3; Seizures, 1	
Citrome 2004 US (New York State)	Adjusted OR (95% CI) for development of diabetes vs typical antipsychotic use: Clozapine only: 2.06 (1.07, 3.99) Olanzapoine only: 1.57 (0.87, 2.82) Quetiapine only: 3.09 (1.59, 6.03) Risperidone only: 1.50 (0.81, 2.79) More than one atypical antipsychotic: 2.86 (1.57, 5.20)	
Conley, 1999 United States	Hospitalization Readmission rates (% patients) y 1=13% vs 17%; p=NS y 2=13% vs 34%; p=NS Mean time to readmission (ds)=360 vs 319	

Evidence Table 3. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Data source	Prospective Retrospective Unclear	Sampling frame	Exposure period
Cooper, 2005 Canada	Database: Quebec health insurance database and Quebec database for hospitalizations	Retrospective	July 1, 1996 through August 31, 2006	1 y
Cooper, 2007 Canada	Database: Quebec health insurance board and Quebec registry of hospitalizations	Retrospective	January 1, 1997 to August 31, 1999	1 y
Coulter, 2001 International	Database: Uppsala Monitoring Centre in Sweden	Unclear	NR	NR
de Haan, 2002 Netherlands	Academic Medical Center, University of Amsterdam	Prospective	6 WK	NR

Evidence Table 3. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Interventions mean dose	Population	Age Gender Ethnicity
Cooper, 2005 Canada	Olanzapine Risperidone	Schizophrenia	Age: 8% 0-24 ys; 50% 25-44 ys; 32% 45-64 ys; 10% 65 ys and over Gender: 57% male
Cooper, 2007 Canada	Low intensity: Olanzapine= <9.7mg/d; Risperidone= <1.9mg/d; Clozapine= <300mg/d; Quetiapine= <100mg/d Medium intensity: Olanzapine= >9.7mg/d but <10.0mg/d; Risperidone= >1.9mg/d but <4.0mg/d; Clozapine= >300mg/d but <425mg/d; Quetiapine= >100mg/d but <300mg/d High intensity Olanzapine= >10mg/d; Risperidone= >4mg/d; Clozapine= >425mg/d; Quetiapine= >300mg/d	Schizophrenia	Age: 27% 0-34 ys; 63% 35-64 ys; 10% 65 ys or older Gender: 57% male Ethnicity: NR
Coulter, 2001 International	Clozapine Olanzapine Quetiapine Risperidone	NR	NR NR NR
de Haan, 2002 Netherlands	Olanzapine(N=39): 14.2mg Risperidone(N=23): 4.1mg	N=113 Schizophrenia, 15% OCD disorder, drug class naïve	Mean age: 22.4 ys

Evidence Table 3. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Exposed Eligible Selected	Withdrawn Lost to follow-up Analyzed	Effectiveness outcomes
Cooper, 2005 Canada	38,048/6,405/6,405	NR/NR/6,405	Mean ds of use before discontinuation olanzapine=233 risperidone=142 (60.5% of individuals discontinued use of initial treatment prior to one-y) Concomitant use Of those who stayed on their initial treatment for at least one y: 738 (47.3%) of olanzapine users and 435 (48.5%) of risperidone users received at least one concomitant antipsychotic prescription during treatment
Cooper, 2007 Canada	NR/NR/6662	NR/NR/6662	<u>Persistence</u> Individuals started on clozapine were more likely to be persistent than those on olanzapine, however those on olanzapine were more likely to be persistent than those on risperidone Individuals who received a dosage in the low or medium intensity were more likely to be persistent than those receiving the high intensity dosage
Coulter, 2001 International	NR NR NR	NR NR Reports analyzed: Clozapine=24730, Olanzapine=6,135, Quetiapine=709, Risperidone=10,746	NR
de Haan, 2002 Netherlands	NR/113/113	NR/NR/62	YBOCS Mean Scores: At Admission: R: 2.4 vs O: 2.4 At Endpoint (6 WK): R: 2.2 vs O: 1.9

Evidence Table 3. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Safety outcomes	Comments
Cooper, 2005 Canada	NR	
Cooper, 2007 Canada	NR	
Coulter, 2001 International	Cardiomyopathy or myocarditis (# cases/%) Clozapine=231/0.9% Olanzapine=8/0.1% Quetiapine=2/0.3% Risperidone=16/0.1%	
de Haan, 2002 Netherlands	NR	

Evidence Table 3. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Data source	Prospective Retrospective Unclear	Sampling frame	Exposure period
De Hert, 2008, Belgium	Records and patients from University Psychiatric Centre Catholic University Leuven	Retrospective (including a subsample of prospective data for matched group)	NR	Historic cohort: 1984-1995 (FGAs) Current cohort: 2000-2005 (SGAs) (At least 1 y treatment exposure; average 3 ys treatment exposure)
Dinakar, 2002 United States	Rockland Psychiatric Center, NY	Retrospective	3 mos	NR

Evidence Table 3. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Interventions mean dose	Population	Age Gender Ethnicity
De Hert, 2008, Belgium	Amisulpride Aripiprazole Clozapine Olanzapine Risperidone Quetiapine	First-episode patients with schizophrenia treated with FGAs matched with first-episode schizophrenia patients treated with SGAs Historic cohort was derived from a cohort of schizophrenic patients admitted between 1973 and 1992	Historic cohort/Current cohort: Age: 22.3±3.2 / 22.1±3.1 Gender (% male): 65.5 / 71.6 Ethnicity: both cohorts were > 95% Caucasian and of native Belgian origin
Dinakar, 2002 United States	At endpoint: olanzapine: 52.75 risperidone: 52.53	Schizophrenia	Mean age: 55.5 ys Gender and Ethnicity NR

Evidence Table 3. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Exposed Eligible Selected	Withdrawn Lost to follow-up Analyzed	Effectiveness outcomes
De Hert, 2008, Belgium	Historic cohort: 1119 301 148 Current cohort: NR NR 148	NR NR 296 (148 in historic cohort, matched with 148 in current cohort)	N/A
Dinakar, 2002 United States	NR/79/79	0/0/79	BPRS scores: baseline vs endpoint O: 67.03 vs 52.75 R: 62.70 vs 52.53

Evidence Table 3. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Safety outcomes	Comments
De Hert, 2008, Belgium	MetS per antipsychotic in the SGA group (Baseline/Follow-up) (%): Amisulpride: 12.5 / 25 Aripiprazole: 10 / 10 Clozapine: 8.3 / 58.3 Olanzapine: 5.8 / 47.1 Risperidone: 4.1 / 16.7 Quetiapine: 4.8 / 15 Mortality: Historic cohort: 5% died (4.3% suicides, 0.7% CV) Current cohort: 0% died Historic cohort (data available on 130 patients up-to-date): 6 deaths (5 suicide, 1 cancer) Two deaths while still on an FGA and 6 when treated with an SGA later in the course of illness (4 on clozapine, of which 2 with ketoacidosis; 1 on olanzapine, and 1 on risperidone)	
Dinakar, 2002 United States	NR	

Evidence Table 3. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Data source	Prospective Retrospective Unclear	Sampling frame	Exposure period
Dolder, 2002 United States	Database: VA San Diego Healthcare System	Retrospective	NR	12 mos

Evidence Table 3. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Interventions mean dose	Population	Age Gender Ethnicity
Dolder, 2002 United States	Haloperidol 8mg/d Perphenazine 12mg/d Risperidone 4mg/d Olanzapine 12.5mg/d Quetiapine 400mg/d	Schizophrenia, schizoaffective disorder, mood disorder with psychotic features, or psychosis not otherwise specified	Age=49.7 89.9% male Ethnicity (%) Caucasian=61.8 African American=18.4 Hispanic=9.4 Other=5.5

Evidence Table 3. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Exposed Eligible Selected	Withdrawn Lost to follow-up Analyzed	Effectiveness outcomes
Dolder, 2002 United States	629/NR/288	Withdrawn=N/A (retrospective) Withdrawn=N/A (retrospective) Analyzed=288	Adherence Rates-cumulative mean gap ratio Those treated with atypical antipsychotics had significantly smaller gaps in therapy compared to those treated with typical antipsychotics at 6-mos (p=0.001) and at 12-mos (p=0.001). Olanzapine had a significantly lower gap ratio compared to haloperidol at 6-mos (p=0.008), no other significant differences between individual medications was observed at either 6-mos or 12-mos. Adherence Rates-compliant fill rate Those treated with atypical antipsychotics had significantly higher adherence rates at 6-mos compared to those treated with typical antipsychotics (p=0.05), at 12-mos the trend was similar, though not at the significant level.

Evidence Table 3. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Safety outcomes	Comments
Dolder, 2002 United States	NR	

Evidence Table 3. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Data source	Prospective Retrospective Unclear	Sampling frame	Exposure period
Dossenbach 2008 IC-SOHO study (36 mo data)	Dossenbach 2004	Same as Dossenbach 2004	36 mos	NR

Evidence Table 3. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Interventions mean dose	Population	Age Gender Ethnicity
Dossenbach 2008 IC-SOHO study (36 mo data)	Same as Dossenbach 2004	Schizophrenia	same as Dossenbach 2004

Evidence Table 3. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Exposed Eligible Selected	Withdrawn Lost to follow-up Analyzed	Effectiveness outcomes
Dossenbach 2008 IC-SOHO study (36 mo data)	Same as Dossenbach 2004	2293/NR/3835	Olanzapine vs risperidone vs quetiapine % responding to treatment at 36 mos 78% vs 65% vs 47% Median time to response (95% CI) mo: 5.2 (5.0 to 5.5) vs 6.3 (6.0 to 6.7) vs 11.3 (6.3 to 17.5) Olanzapine as a reference HR (95% CI): vs risperidone 0.8 (0.7 to 0.8), p<0.001, Number needed to treat (95% CI) at 36 mo 15 (10-31) HR (95% CI): vs quetiapine 0.6 (0.4 to 0.7), p<0.001, nmber needed to treat (95% CI) at 36 mo 8 (4 to 50) Risperidone as a reference HR (95% CI): vs quetiapine 0.8 (0.6 to 1.0), p=0.037, Number needed to treat (95% CI) at 36 mo 12 (5 to -23) % patients relapsed following treatment response: 12% vs 14% vs 18%

Evidence Table 3. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Safety outcomes	Comments
Dossenbach 2008 IC-SOHO study (36 mo data)	**EPS** Olanzapine as reference Adjusted OR (95% CI) vs Risperidone 5.63 (4.27 to 7.40), p<0.001, Number needed to treat (95% CI)at 36 mo 5 (5 to 7) Adjusted OR (95% CI) vs Quetiapine 0.23 (0.07 to 0.75), p=0.015, Number needed to treat(95% CI at 36 mo -18 (-57 to -11) Risperidone as a reference Adjusted OR (95% CI) vs Qutiapine: 0.04 (0.01 to 0.13), p<0.001, Number needed to treat (95% CI) at 36 mo -4 (-5 to -4) **Tardive dyskinesia** Olanzapine as reference Adjusted OR (95% CI) vs Risperidone: 4.15 (2.37 to 7.27), p<0.001, Number needed to treat at 36 mo 42 (26 to 105) Adjusted OR (95% CI) vs Quetiapine : 1.37 (0.39 to 4.72), p=0.623, Number needed to treat at 36 mo 138 (30 to -53) Risperidone as a reference Adjusted OR (95% CI vs Quetiapine: 0.33 (0.09 to 1.16), p=0.084, Number needed to treat at 36 mo -59 (81 to -22) **Sexual dysfunction** Olanzapine as a reference Adjusted OR (95% CI) vs Risperidone 2.14 (1.70 to 2.70), p<0.001, Number needed to treat (95% CI) at 36 mo 10 (7 to 22) Adjusted OR (95% CI) vs Quetiapine 1.43 (0.78 to 2.60), p=0.246, Number needed to treat at 36 mo 39 (7 to -10) Risperidone as a reference Adjusted OR (95% CI) vs Quetiapine 0.67 (0.36 to 1.23), p=0.196, Number needed ot treat at 36 mo -14 (17 to -5) **Weight gain>7% from baseline** Olanzapine as reference Adjusted OR (95% CI) vs risperidone 0.63 (0.54 to 0.73), p<0.001, number needed to treat (95% CI) at 36 mo -9 (48 to -4) Quetiapine as reference Adjusted OR (95% CI) vs quetiapine 0.81 (0.55 to 1.21), p=3.00, number needed to treat at 36 mo (95% CI) -18 (12 to -5)	

Evidence Table 3. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Data source	Prospective Retrospective Unclear	Sampling frame	Exposure period
Dossenbach et al, 2004 27 countries in Africa, Asia, Europe, Central and South America and the Middle East IC-SOHO Study (6 mo data)	Prospectively collected, multicenter study data	Prospective	6 mos (interim data - planned exposure 3 yrs)	NR

Evidence Table 3. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Interventions mean dose	Population	Age Gender Ethnicity
Dossenbach et al, 2004 27 countries in Africa, Asia, Europe, Central and South America and the Middle East IC-SOHO Study (6 mo data)	Mean doses at 6 mos: olanzapine 10.9 mg/d (SD 4.8) quetiapine 339.5 mg/d (SD 188.9) risperidone 4.0 mg/d (SD 2.1) haloperidol 12.2 mg/d (SD 9.3)	Schizophrenia	Mean age 35.5 yrs (SD 12.2) 54% male Ethnicity NR

Evidence Table 3. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Exposed Eligible Selected	Withdrawn Lost to follow-up Analyzed	Effectiveness outcomes
Dossenbach et al, 2004 27 countries in Africa, Asia, Europe, Central and South America and the Middle East IC-SOHO Study (6 mo data)	7658/NR/5833	NR/NR/unclear; according to the text "as a result of missing data, the number of patients in each subgroup may differ for each comparison"	CGI-Severity of Illness Scale score, mean change from baseline at 6 mos: Overall: O -1.44 (SE 0.04) v Q -1.02 (SE 0.09) v R -1.24 (SE 0.05) v H -0.87 (SE 0.08) Statistically significant difference (p≤0.001) for the following comparisons: O v Q, R, & H; R v H Positive: O -1.44 (SE 0.05) v Q -1.01 (SE 0.10) v R -1.27 (SE 0.06) v H -1.07 (SE 0.09) Statistically significant difference (p≤0.001) for the following comparisons: O v Q, R, & H Negative: O-1.21 (SE 0.04) v Q -0.82 (SE 0.09) v R -0.98 (SE 0.05) v H -0.65 (SE 0.08) Statistically significant difference (p≤0.001) for the following comparisons: O v Q, R & H; R v H Depressive: O -1.11 (SE 0.04) v Q -0.83 (SE 0.09) v R -0.91 (SE 0.05) v H -0.67 (SE 0.08) Statistically significant difference (p≤0.001) for the following comparisons: O v Q, R & H Cognitive: O -1.05 (SE 0.04) v Q -0.61 (SE 0.09) v R -0.83 (SE 0.05) v H -0.54 (SE 0.08) Statistically significant difference (p≤0.001) for the following comparisons: O v Q, R & H; R v H

Evidence Table 3. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Safety outcomes	Comments
Dossenbach et al, 2004 27 countries in Africa, Asia, Europe, Central and South America and the Middle East IC-SOHO Study (6 mo data)	Weight change: significantly higher with olanzapine use compared to all other interventions (p<0.0001) O 2.57 kg (SE 0.21) Q 0.58 kg (SE 0.44) R 1.49 kg (SE 0.26) H 0.73 (SE 0.40)	Data on pts remaining on monotherapy or switching therapies not abstracted

Evidence Table 3. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Data source	Prospective Retrospective Unclear	Sampling frame	Exposure period
Dossenbach et al, 2005 Dossenbach 2006 for sexual dysfunction results 27 countries in Africa, Asia, Europe, Central and South America and the Middle East IC-SOHO Study (12 mo data)	Same as Dossenbach 2004	Same as Dossenbach 2004	12 mos	NR
Eriksson, 2012 Sweden	Medical record review	Retrospective	July 2009-September 2010	NR

Evidence Table 3. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Interventions mean dose	Population	Age Gender Ethnicity
Dossenbach et al, 2005 Dossenbach 2006 for sexual dysfunction results 27 countries in Africa, Asia, Europe, Central and South America and the Middle East IC-SOHO Study (12 mo data)	Same as Dossenbach 2004	Schizophrenia	Same as Dossenbach 2004
Eriksson, 2012 Sweden	Quetiapine IR, 335 mg/d Quetiapine XR, 494 mg/d	18-65 years, ICD-10 schizophrenia, hospitalized for psychotic symptoms, at least one dose of drug.	Age: Quetiapine XR, 44.1 y; Quetiapine IR, 42.3 Gender: XR, 47%; IR, 50% Ethnicity: NR

Evidence Table 3. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Exposed Eligible Selected	Withdrawn Lost to follow-up Analyzed	Effectiveness outcomes
Dossenbach et al, 2005 Dossenbach 2006 for sexual dysfunction results 27 countries in Africa, Asia, Europe, Central and South America and the Middle East IC-SOHO Study (12 mo data)	Same as Dossenbach 2004	1007/225/3551 (from Figure 1 in text)	CGI-Severity of Illness Scale score, least squares mean change from baseline at 12 mos: Overall: O -1.80 (SE 0.04) v Q -1.62 (SE 0.06) v R -1.39 (SE 0.11) v H -1.04 (SE 0.11) Statistically significant difference (p≤0.001) for the following comparisons: O v Q, R, & H; R v H Positive: O -1.74 (SE 0.05) v Q -1.64 (SE 0.06) v R -1.44 (SE 0.12) v H -1.16 (SE 0.11) Statistically significant difference (p≤0.001) for the following comparisons: O v H; R v H Negative: O -1.58 (SE 0.05) v Q -1.38 (SE 0.06) v R -1.25 (SE 0.12) v H -0.88 (SE 0.11) Statistically significant difference (p≤0.001) for the following comparisons: O v R & H; R v H Depressive: O -1.38 (SE 0.05) v Q -1.21 (SE 0.06) v R -1.06 (SE 0.12) v H -0.73 (SE 0.11) Statistically significant difference (p≤0.001) for the following comparisons: O v R & H; R v H Cognitive: O -1.34 (SE 0.05) v Q -1.17 (SE 0.06) v R -1.05 (SE 0.12) v H -0.64 (SE 0.11) Statistically significant difference (p≤0.001) for the following comparisons: O v R & H; R v H Relapse rates at 12 mos among previous responders: O 7.7% v R 9.0% (OR 1.07 [0.68-1.68] vs olanzapine) v Q 12.5% (OR 1.76 [0.66-4.74] vs olanzapine) v H 30.0% (OR 6.57 [3.10-13.93] vs olanzapine) Proportion of patients who had worsened at 12 mos: O 20.2% v R 24.8% (OR 1.29 [1.04-1.59] vs olanzapine) v Q 37.0% (OR 2.28 [1.47-3.54] vs olanzapine) v H 37.1% (OR 2.37 [1.60-3.52] vs olanzapine)
Eriksson, 2012 Sweden	NR/NR/178	NA/NA/178	Quetiapine XR vs. Quetiapine IR: GAF changes during hospitalization: LSM 14.9 vs. 15.7, p=0.70 Length of hospitalization, days: 45.8 vs. 33.2, p=0.08 ECT treatment, n: 8 vs. 1, p=0.11

Evidence Table 3. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Safety outcomes	Comments
Dossenbach et al, 2005 Dossenbach 2006 for sexual dysfunction results 27 countries in Africa, Asia, Europe, Central and South America and the Middle East IC-SOHO Study (12 mo data)	Weight gain, least squares mean: O 3.4kg (CI 2.9-4.0); p<0.001 v R; R 2.2kg (CI 1.5-3.0); Q 1.9kg (CI 0.5-3.3); H 2.2kg (CI 0.9-3.4) Patients with weight gain >7% of baseline: O 760/1963 (39%) v R 153/549 (28%) v Q 20/80 (25%) v H 27/105 (26%) Relapse mos 3-12, based on subset of initial responders (total n=1682): O 99/1292 (7.7%) R 28/310 (9.0%); OR 1.07 (0.68-1.68) vs olanzapine Q 5/40 (12.5%); OR 1.76 (0.66-4.74) vs olanzapine H 12/40 (30.0%); OR 6.57 (3.10-13.93) vs olanzapine p<0.001: O v H; R v H Compliance (based on patient perception): O 1637/1916 (85.4%) v R 445/547 (81.4%) v Q 61/84 (72.6%) v H 72/121 (59.5%) p<0.001: O v H; R v H Sexual dysfunction-related AE's during 12-mo treatment period for olanzapine vs risperidone vs quetiapine vs haloperidol/OR (95% CI) for comparison to olanzapine Patient perception of sexual dysfunction: 55.7% vs 67.8% (OR 2.02, 95% CI 1.63, 2.49) vs 60.2% (OR 0.88, 95% CI 0.56, 1.39) vs 71.1% (OR 2.47, 95% CI 1.61, 3.77) Loss of libido: 46.4% vs 60% (OR 2.05, 95% CI 1.67, 2.52) vs 54.6% (OR 1.16, 95% CI 0.72, 1.85) vs 68.1% (OR 3.25, 95% CI 2.14, 4.92) Impotence/sexual dysfunction: 32% vs 46% (OR 2.17, 95% CI 1.72, 2.73) vs 43% (OR 1.26, 95% CI 0.74, 2.14) vs 52.3% (OR 3.04, 95% CI 1.94, 4.74) Amenorrhea/menstrual disturbances: 29.5% vs 42.1% (OR 2.26, 95% CI 1.63, 3.15) vs 20.9% (OR 0.46; 95% CI 0.20, 1.05) vs 53.8% (OR 4.06, 95% CI 2.20, 7.51)	
Eriksson, 2012 Sweden	NR	

Evidence Table 3. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Data source	Prospective Retrospective Unclear	Sampling frame	Exposure period
Etminan, 2003 Ontario	Database: Ontario Drug Benefit (ODB) claims database	Unclear	NR	NR
Feldman, 2004 United States	AdvancePCS Inc	Retrospective	6-9 mos	NR
Feng, 2012	Prospectively collected cohort	Prospective	2001-2010	NR
Fleischhaker, 2006, Germany	Four child and adolescent psychiatric departments in four mental heath centers in Germany	Prospective	NR	Mean = 7.4 WK
Fuller, 2003 Ohio	Database: Veteran's Integrated Service Network 10	Retrospective	1/1/97 to 12/31/00	NR

Evidence Table 3. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Interventions mean dose	Population	Age Gender Ethnicity
Etminan, 2003 Ontario	Olanzapine Quetiapine Risperidone	Schizophrenia	Mean age=84.2 34.2% male Race NR
Feldman, 2004 United States	NR	Geriatric	Mean age: 79.2 ys 60.8% female Ethnicity NR
Feng, 2012	Clozapine, 405 mg Olanzapine, 12mg Mean doses reported for those treated all 8 years	Schizophrenia, paranoid 34%, disorganized 4%, undifferentiated 46%; Schizoaffective disorder 16%	Mean age: 41.92 Gender: 44% female Ethnicity: NR
Fleischhaker, 2006, Germany	Clozapine/Olanzapine/Risperidone Mean dose (mg): 321.9±156.5/16.6±7.1/3.9±1.7 Dose range (mg): 125.0-600.0/7.5-30.0/1.0-6.0	Adolescent inpatients (n=51) who started treatment with clozapine (n=16), olanzapine (n=16), and risperidone (n=19) in open clinical trials 31 adolescents had a diagnosis of schizophrenia	Clozapine/Olanzapine/Risperidone Mean age (y±SD): 17.2±1.8/15.8±1.4/15.6±2.6 Gender (n male): 11/9/13 Ethnicity: NR
Fuller, 2003 Ohio	Risperidone 2.8 mg Olanzapine 10.0 mg Fluphenazine 12.2 mg Haloperidol 8.4 mg	Range of psychiatric diagnoses: Schizophrenia=61% Depression=47% Bipolar Disorder=26% Dementia=8%	Mean age=53 Gender NR 73% White

Evidence Table 3. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Exposed Eligible Selected	Withdrawn Lost to follow-up Analyzed	Effectiveness outcomes
Etminan, 2003 Ontario	NR NR 3250	NR NR 2984 (individual group n's NR)	NR
Feldman, 2004 United States	NR/NR/1,836,799	NR/NR/30,953	Development of Diabetes Mellitus (Risk Ratio): All combined conventional antipsychotics: 3.2; P<0.001 All combined atypicals: 3.3; P<0.001 clozapine: 5.8; P=0.002 olanzapine: 3.5; P<0.001 quetiapine: 2.5; P<0.001 risperidone: 3.4; P<0.001
Feng, 2012	NR/NR/50	15/NR/35	NR
Fleischhaker, 2006, Germany	NR NR 51	NR NR 51	NA
Fuller, 2003 Ohio	NR NR 5837	NR NR 5837	NR

Evidence Table 3. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Safety outcomes	Comments
Etminan, 2003 Ontario	Diabetes Diabetic events (% patients): Olanzapine=2.1 Quetiapine=1.0 risperidone 2.1	Age - older adults
Feldman, 2004 United States	NR	
Feng, 2012	Developed diabetes, olanzapine vs. clozapine: 7/27 (26%) vs. 0/23, p=0.01 Mean (SD) glucose levels, baseline vs. 8-year follow up: clozapine, 5.7 (0.7) vs. 6.5 (1.5), p=0.01; olanzapine, 5.5(0.7) vs. 5.5(0.5), p=0.94 Cholesterol, triglycerides, no change from baseline	
Fleischhaker, 2006, Germany	Clozapine/Olanzapine/Risperidone Tardive dyskinesia (n,(%)): 0(0)/0(0)/0(0) Weight gain (n,(%)): 9(56.3)/11(68.8)/7(36.8); p=0.16 Mean weight gain after 6 WK (kg): 2.5/4.6/2.8	Comedication
Fuller, 2003 Ohio	Risk (Hazard Ratio, 95% CI) of developing diabetes for olanzapine vs risperidone: Univariate analysis=HR 1.29, 95% CI 1.00 to 1.67; Multivariate analysis=HR 1.37, 95% CI 1.06 to 1.76	

Evidence Table 3. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Data source	Prospective Retrospective Unclear	Sampling frame	Exposure period
Ganguli, 2001 United States	Multiple sources	Retrospective	4 mos	NR
Garcia-Cabeza, 2003 Montes, 2003 Spain Subjective Response Analysis from Estudio Farmacoepidemiologico en la Esquizofrenia con Olanzapine (EFESO)	Multicenter Controlled	See above	See above	NR
Gasquet, 2005 Europe (Denmark, France, Germany, Greece, Ireland, Italy, The Netherlands, Portugal, Spain and UK) SOHO (secondary publication)	Prospectively collected, multicenter study data	Prospective	6 mo (interim analysis of planned 3-yr term)	NR

Evidence Table 3. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Interventions mean dose	Population	Age Gender Ethnicity
Ganguli, 2001 United States	NR	Schizophrenia	Mean age: 41.3 ys 56.5 Males Caucasian: 57% African-American:38% Other: 5%
Garcia-Cabeza, 2003 Montes, 2003 Spain Subjective Response Analysis from Estudio Farmacoepidemiologico en la Esquizofrenia con Olanzapine (EFESO)	Overall mean dose: Olanzapine: 13 mg/d Risperidone: 5.4 mg/d Haloperidol: 13.6 mg/d	Paranoid schizophrenia: 65.1% Undifferentiated schizophrenia: 13.5% Residual schizophrenia: 12.3% Subjective response and compliance with antipsychotic treatment using 10 Item Drug Attitude Inventory (DAI-10)	Mean age: 35.4 63.9% male Ethnicity NR
Gasquet, 2005 Europe (Denmark, France, Germany, Greece, Ireland, Italy, The Netherlands, Portugal, Spain and UK) SOHO (secondary publication)	Olanzapine 11.1 mg/d (SD 5.0) Risperidone 4.6 mg/d (SD 2.6)	Previously untreated schizophrenics	Mean age 33.6 yrs 60% male Ethnicity NR

Evidence Table 3. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Exposed Eligible Selected	Withdrawn Lost to follow-up Analyzed	Effectiveness outcomes
Ganguli, 2001 United States	NR/NR/100	0/0/100	NR
Garcia-Cabeza, 2003 Montes, 2003 Spain Subjective Response Analysis from Estudio Farmacoepidemiologico en la Esquizofrenia con Olanzapine (EFESO)	NR/ 2967/ 2657	Unclear; unclear; 2348 for safety at 6 mos and 2189 for DAI-10 score at 6 mos	From Montes 2003: Mean changes in scale scores for olanzapine vs risperidone vs conventional antipsychotics (p-value is NS unless otherwise specified and represents comparison to conventional antipsychotics group) CGI-S: -1.8 vs -2.0 vs -1.5 GAF: 29.2 vs 32.2 vs 22.6 EuroQol-1:0.35 vs 0.36 vs 0.25 Visual Analogue Scale (0=worst state of health possible to 100=best state of health possible): 26 ($p<0.05$) vs 28 ($p<0.05$) vs 17.5 AWAD scale (subjective attitude towards medication; positive score=positive subjective response, negative score=negative response): 4.7 vs 3.1 vs 1.3
Gasquet, 2005 Europe (Denmark, France, Germany, Greece, Ireland, Italy, The Netherlands, Portugal, Spain and UK) SOHO (secondary publication)	1033/NR/919	134/NR/919	EQ-5D VAS at 6 mos: O 64.4 (SD 18.1) v R 61.1 (SD 18.8); adjusted mean difference O v R: -3.73 (CI -1.48 to -5.97); p=0.001

Evidence Table 3. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Safety outcomes	Comments
Ganguli, 2001 United States	Change in Mean Body Weight/BMI at Endpoint: risperidone: 82.8kg, P=NS	
Garcia-Cabeza, 2003 Montes, 2003 Spain Subjective Response Analysis from Estudio Farmacoepidemiologico en la Esquizofrenia con Olanzapine (EFESO)	Subjective Response : Mean DAI-10 Score (range: -10 to +10) , baseline vs 6 mos: olanzapine: +0.17 vs +4.63 risperidone: +0.32 vs +3.42, p<0.001 vs Olz haloperidol: -1.25 vs +1.68, p <0.001 vs Olz and p=0.003 vs Ris Compliance with principal antipsychotic treatment, % of pts at each level data given as Olz vs Ris vs Hal High compliance: 84.8% vs 74.2% vs 69.8% (p=0.001 for Olz vs Ris) Moderate compliance: 11.1% vs 19.4% vs 27.1% (p=0.022 for Olz vs Hal) Low compliance: 2.5 % vs 5% vs 2.1% Nil: 1.6% vs 1.4% vs 1% % of pts with EPS, baseline vs 6 mo data, p=NR: Olz: 35.8% vs 31.9% Ris: 48.3% vs 44.6% Hal: 69.2% vs 66.3%	
Gasquet, 2005 Europe (Denmark, France, Germany, Greece, Ireland, Italy, The Netherlands, Portugal, Spain and UK) SOHO (secondary publication)	Weight gain at 6 mos: O 3.1kg (SD 4.9) v R 2.1 (SD 4.6); adjusted mean difference O v R: -1.0 (CI -1.8 v -0.1)	

Evidence Table 3. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Data source	Prospective Retrospective Unclear	Sampling frame	Exposure period
Gianfrancesco, 2002 United States	Database: Two mixed indemnity and managed care health plans located in the northeastern and southeastern United States (unspecified)	Retrospective	January 1996 through December 1997	Risperidone=6.8 mos Olanzapine=6.1 mos High-potency conventionals=7 mos Low-potency conventionals=7.1 mos Clozapine=9.4 mos
Gianfrancesco, 2003a United States	Database: Blue Cross/Blue Shield claims database	Retrospective	April 1997 through October 2000	Risperidone=9.1 mos Olanzapine=8.7 mos Quetiapine=7.1 mos Conventionals=12.1 mos

Evidence Table 3. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Interventions mean dose	Population	Age Gender Ethnicity
Gianfrancesco, 2002 United States	Mean dosages in form of risperidone equivalents: Risperidone=2.3 mg Olanzapine=3.6 mg High-potency conventionals=1.7 mg Low-potency conventionals=1.7 mg Clozapine=2.5 mg	Psychosis diagnosis (schizophrenia, bipolar and manic, major depressive, dementia, other psychoses)	Untreated vs treated (restricted to those WITHOUT Type 2 Diabetes at 4 mos prior to observation) Mean age=41.9 vs 45.3 % male=40.4% vs 36.6% Race nr
Gianfrancesco, 2003a United States	Risperidone Olanzapine Quetiapine Conventionals Mean doses NR	Schizophrenia=14% Bipolar and manic=35%, Major depressive=38%, Other psychoses=13%	Mean age=37.5 41% male Race NR

Evidence Table 3. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Exposed Eligible Selected	Withdrawn Lost to follow-up Analyzed	Effectiveness outcomes
Gianfrancesco, 2002 United States	NR NR NR	NR NR NR	NR
Gianfrancesco, 2003a United States	NR NR 6582 patients Treatment episodes: Risperidone= 2860, Olanzapine=2703, Quetiapine=922, Conventional antipsychotics=2756	NR NR Analyzed=6582 patients (Treatment episodes: Risperidone=2860, Olanzapine=2703, Quetiapine=922, Conventional antipsychotics=2756)	NR

Evidence Table 3. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Safety outcomes	Comments
Gianfrancesco, 2002 United States	OR (vs Risperidone) for 12 mos of treatment (extrapolated from 1-mo treatment rates) (excluded patients with pre-existing Type II Diabetes identified at 8-mo screening): Olanzapine=3.53, p<0.05 Clozapine=8.45, p<0.05 Frequency of Type 2 Diabetes after at least 12 mos' treatment (excluding patients with pre-existing Type II Diabetes identified at 8-mo screening): Risperidone=2/90 (2.2%) Olanzapine=4/56 (7.1%) Clozapine=1/4 (25%)	
Gianfrancesco, 2003a United States	Frequency of Type II Diabetes at 4-8 mos/8-12 mos/>12 mos: Risperidone=0.2/0.0/0.6 Olanzapine=0.2/1.3/3.0 Quetiapine=0.5/1.2/0.9 Conventional=0.0/1.9/1.4 One-mo ORs (95% CI) converted to 12-mos for each drug vs no antipsychotic treatment: Risperidone=0.660 (0.311 to 1.408) Olanzapine=1.426 (1.046 to 1.955) Quetiapine=0.976 (0.422-2.271) Conventionals=1.049 (0.688-1.613)	

Evidence Table 3. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Data source	Prospective Retrospective Unclear	Sampling frame	Exposure period
Gianfrancesco, 2003b United States	Database: Two mixed indemnity and managed care health plans located in the northeastern and southeastern United States (unspecified)	Retrospective	January 1996 through December 1997	Patients not taking antipsychotics=13.7 mos Risperidone=6.1 mos Olanzapine=5.4 mos High-potency Conventional Antipsychotics=6.5 mos Low-potency conventional antipsychotics=6.5 mos
Gianfrancesco, 2006a United States	Database: PharMetrics	Retrospective	January 1999 through August 2003	NR

Evidence Table 3. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Interventions mean dose	Population	Age Gender Ethnicity
Gianfrancesco, 2003b United States	(Risperidone equivalents) Risperidone 2.1 mg Olanzapine 3.4 mg High-potency conventional antipsychotics 1.6 mg Low-potency conventional antipsychotics 1.6 mg	% patients NOT taking antipsychotics/% patients TAKING antipsychotics: Bipolar=48.1%/30.6% MDD=39.7%/664.5% Manic=12.2%/4.9%	Patients NOT taking antipsychotics/Patients TAKING antipsychotics: Mean age=41.8/42.2 % male=38.9%/31.8% Race NR
Gianfrancesco, 2006a United States	Atypical Antipsychotics Risperidone: 3.0mg/d Olanzapine: 11.4mg/d Quetiapine: 264mg/d Ziprasidone: 86mg/d Typical Antipsychotics Haloperidol: 10.5mg/d Perphenazine: 13.5mg/d Thioridazine: 128mg/d Thiothixene: 11.2mg/d	Schizophrenia or schizoaffective disorder	Mean age (ys): 41.5 % male: 48.9

Evidence Table 3. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Exposed Eligible Selected	Withdrawn Lost to follow-up Analyzed	Effectiveness outcomes
Gianfrancesco, 2003b United States	NR NR 5723	NR 5236 patients (Patients NOT taking antipsychotics=2644; Risperidone=849, Olanzapine=656, High-potency conventional antipsychotics=785, Low-potency antipsychotics=302) (excludes those found to have pre-existing Type II diabetes at the 4-mo screening period)	NR
Gianfrancesco, 2006a United States	NR/NR/5683	NR/NR/5683	Comparisons of treatment duration Treatment duration for risperidone, olanzapine, and ziprasidone were NSly different from the typical antipsychotics, but quetiapine demonstrated a nonsignificant trend for shorter treatment durations compared with the combined group of typical agents (P=0.091). Quetiapine had significantly shorter treatment durations than risperidone (P=0.024) and olanzapine (P=0.004). Differences between other atypical agents were NS. Patient characteristics with significant increasing associations with treatment duration included age, switch from another antipsychotic, substance dependence/abuse, more vs less managed form of coverage, and earlier date for start of treatment episode (all P<0.05).

Evidence Table 3. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Safety outcomes	Comments
Gianfrancesco, 2003b United States	12-mo ORs (converted from 1-mo estimates) that excludes patients found to have pre-existing Type II diabetes at 8-mo screening: Relative to Untreated Risperidone=1.024 (0.351-3.015) Olanzapine=4.289 (2.102-8.827) Olanzapine vs risperidone-4.189, p=0.02958	
Gianfrancesco, 2006a United States	NR	

Evidence Table 3. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Data source	Prospective Retrospective Unclear	Sampling frame	Exposure period
Gianfrancesco, 2006b United States	Medical and prescription claims data for commercially insured patients	Retrospective	1999 to August 2003	Unclear
Gibson, 2004 United States	Database: Michigan Medicaid administrative claims data set from Michigan's Department of Community Health (MDCH)	Retrospective	January 1996 through September 1997	1 y
Gomez, 2000 Spain Estudio Farmacoepidemiologico en esquizofrenia con Olanzapine (EFESO)	Multicenter Controlled	Schizophrenia patients were included when a change of medication was indicated or a new antipsychotic drug treatment was being initiated for whatever reason. Choice of new drug was made by the treating physician.	6 mos	Olanzapine 13.01 mg Risperidone 5.39 mg Haloperidol 13.64 mg

Evidence Table 3. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Interventions mean dose	Population	Age Gender Ethnicity
Gianfrancesco, 2006b United States	Risperidone, olanzapine, quetiapine, ziprasidone mean dosages NR	Schizophrenia	Mean age=42 43% male Ethnicity NR
Gibson, 2004 United States	Mean initial dosages: olanzapine 9.9mg risperidone 3.8mg haloperidol 18.2mg	Schizophrenia	Haloperidol/Risperidone/Olanzapine: Mean age=39.7/40.5/40.7 ys Women (%)=53/48/53 Ethnicity=NR
Gomez, 2000 Spain Estudio Farmacoepidemiologico en esquizofrenia con Olanzapine (EFESO)	NR	Death Weight gain	Mean age=35.4 63.6% male Race NR

Evidence Table 3. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Exposed Eligible Selected	Withdrawn Lost to follow-up Analyzed	Effectiveness outcomes
Gianfrancesco, 2006b United States	NR/NR/3807	NR/NR/3807	Hazard ratios (95% CI) for risk of hospitalization Olanzapine vs risperidone=1.34 (1.03, 1.74) Risperidone vs quetiapine=1.05 (0.71, 1.55) Risperidone vs ziprasidone=1.14 (0.55, 2.37) Olanzapine vs quetiapine=1.40 (0.94, 2.07) Olanzapine vs ziprasidone=1.52 (0.73, 3.15) Ziprasidone vs quetiapine=0.92 (0.42, 2.02)
Gibson, 2004 United States	3,642/1191/1191	NR/NR/1191	Patterns of use changes: individuals increased usage of olanzapine as their only antipsychotic medication from 41% to 46% individuals decreased usage of risperidone as their only antipsychotic medication from 61% to 42% individuals decreased usage of haloperidol as their only antipsychotic medication from 81% to 39% Cost reduction: Olanzapine was associated with $2552 lower total cost than risperidone and $2323 lower costs than haloperidol
Gomez, 2000 Spain Estudio Farmacoepidemiologico en esquizofrenia con Olanzapine (EFESO)	NR NR 2949	798 (25.7%) WDs 506 (17.1%) lost to fu 2949 analyzed	NR

Evidence Table 3. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Safety outcomes	Comments
Gianfrancesco, 2006b United States	NR	
Gibson, 2004 United States	NR	
Gomez, 2000 Spain Estudio Farmacoepidemiologico en esquizofrenia con Olanzapine (EFESO)	<u>Death</u> Olanzapine: 3 (0.1%) Control group: 1 (0.1%) <u>Suicide</u> Olanzapine: 1 (0.05%) Control group: 1 (0.1%) <u>Weight gain</u> Olanzapine: 146 (6.9%) Risperidone: 8 (1.9%) Haloperidol: 1 (0.9%) Olanzapine vs. risperidone: p<0.001 Olanzapine vs. haloperidol: p=NS	

Evidence Table 3. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Data source	Prospective Retrospective Unclear	Sampling frame	Exposure period
Guo, 2011 China	Prospective, multi-site, open-label study	Prospective	January 2005 - October 2007	12 months
Gupta, 2004 United States	Olean General Hospital at the SUNY Upstate Medical University at Syracuse	Prospective	NR	10 WK

Evidence Table 3. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Interventions mean dose	Population	Age Gender Ethnicity
Guo, 2011 China	Chlorpromazine, 334.7 mg/d Sulpiride, 724.3 mg/d Clozapine, 266.5 mg/d Risperidone, 3.6 mg/d Olanzapine, 12.1 mg/d Quetiapine, 516.8 mg/d Aripiprazole, 18.6 mg/d	Outpatient psychiatric patients, age 16-50, DSM-IV criteria for schizophrenia or schizophreniform disorder	Mean age: 26.1 Gender: 45.6% female Ethnicity: NR
Gupta, 2004 United States	Quetiapine 4 WK 392.5 mg/d	Schizophrenia, schizoaffective disorder, bipolar disorder, psychotic disorder, or major depression with psychotic features.	Mean age =46.6 ys 56% male Ethnicity: NR

Evidence Table 3. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Exposed Eligible Selected	Withdrawn Lost to follow-up Analyzed	Effectiveness outcomes
Guo, 2011 China	NR/1357/1133	459/151/1133	Mean (SE) change from baseline, chlorpromazine vs. sulpiride vs. clozapine vs. risperidone vs. olanzapine vs. quetiapine vs. aripiprazole: PANSS score: -2.5 (1.5) vs. -4.9 (1.2) vs. -4.9 (1.0) vs. -5.9 (1.0) vs. -5.5 (0.9) vs. -2.0 (1.1) vs. -6.7 (1.2); p=0.068 CGI-S score: −0.3 (0.1) vs. −0.8 (0.1) vs. −0.6 (0.1) vs. −0.5 (0.1) vs. −0.6 (0.1) vs. −0.5 (0.1) vs. −0.8 (0.1); p=0.054 Insight and Treatment Attitudes Questionnaire: 3.3 (0.5) vs. 3.3 (0.5) vs. 4.1 (0.5) vs. 3.8 (0.5) vs. 3.9 (0.5) vs. 3.3 (0.6) vs. 3.7 (0.6); p=0.884 GAS score: 1.2 (0.9) vs. 3.8 (0.9) vs. 5.2 (0.9) vs. 6.3 (0.8) vs. 4.8 (0.7) vs. 4.5 (0.9) vs. 6.7 (1.0); chlorpromaine vs. clozapine, p=0.001, chlorpromazine vs. risperidone, p<0.001, chlorpromazine vs. aripiprazole, p<0.001
Gupta, 2004 United States	NR/NR/16	2/2/NR	Positive and Negative Syndrome Scale (PANSS): NS Simpson-Angus-Scale (SAS): NS

Evidence Table 3. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Safety outcomes	Comments
Guo, 2011 China	Chlorpromazine vs. Sulpiride vs. Clozapine vs. Risperidone vs. Olanzapine vs. Quetiapine vs. Aripiprazole Extrapyramidal side effects (%): 42.0 vs. 41.4 vs. 8.5 vs. 32.7 vs. 10.7 vs. 13.1 vs. 24.2; P<0.001: chlorpromazine vs clozapine, chlorpromazine vs olanapine, chlorpromazine vs quetiapine; ; sulpiride vs clozapine, sulpiride vs olanapine, sulpiride vs quetiapine, risperidone vs olanapine, risperidone vs quetiapine, risperidone vs clozapine; P=0.001, chlorpromazine vs aripiprazole; P=0.002, sulpiride vs aripiprazole Weight gain, mean (SE) lbs: 4.2 (0.8) vs. 4.1 (1.0) vs. 6.6 (1.0) vs. 4.4 (0.9) vs. 8.3 (1.0) vs. 3.4 (1.1) vs. 2.9 (1.1); olanapine vs chlorpromazine, p=0.004; olanapine vs sulpiride, p=0.003; olanapine vs risperidone,p=0.005; olanapine vs quetiapine, p=0.001; olanapine vs aripiprazole, p<0.001; clozapine vs quetiapine, p=0.027; clozapine vs aripiprazole, p=0.011	
Gupta, 2004 United States	Mean weight loss=2.25kg, p=0.03 BMI declined to 34.4kg/m2, p=0.065 fasting glucose, lipid profile, hemoglobin A1c, serum triglycerides: NS	Patients switched from olanzapine to quetiapine

Evidence Table 3. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Data source	Prospective Retrospective Unclear	Sampling frame	Exposure period
Haro, 2005 Europe SOHO (primary publication)	Prospectively collected, multicenter study data	Prospective	6 mo (interim analysis of planned 3-yr term)	NR

Evidence Table 3. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Interventions mean dose	Population	Age Gender Ethnicity
Haro, 2005 Europe SOHO (primary publication)	Olanzapine 12.1 mg/d (SD 5.9) Risperidone 4.9 mg/d (SD 2.8) Quetiapine 391 mg/d (SD 216) Clozapine 238 mg/d (SD 140)	Schizophrenia	Mean age 40 yrs 59.4% male Ethnicity NR

Evidence Table 3. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Exposed Eligible Selected	Withdrawn Lost to follow-up Analyzed	Effectiveness outcomes
Haro, 2005 Europe SOHO (primary publication)	NR/NR/10972	1944/NR/9028 (at 6 mos)	Outcomes at 6 mos- EQ-5D VAS rating (mean): O 63.2 (SD 19.5) R 61.2 (SD 18.8); OR -2.3 (-3.4 to -1.2) vs olanzapine; p<0.0001 Q 59.9 (SD 19.9); OR -3.0 (-4.5 to -1.4) vs olanzapine; p<0.0001 C 61.0 (SD 20.3); OR 0.5 (-1.7 to 2.6) vs olanzapine Socially active: O 3990/4716 (84.6%) R 1410/1711 (82.4%); OR 1.27 (1.05 to 1.54) vs olanzapine; p<0.05 Q 544/690 (78.9%); OR 1.67 (1.29 to 2.16) vs olanzapine; p<0.001 C 246/301 (81.6%); OR 1.25 (0.87 to 1.80) vs olanzapine Relationship with spouse or partner: O 1467/4716 (31.1%) R 532/1711 (31.1%); OR 1.06 (0.81 to 1.39) vs olanzapine Q 206/690 (29.9%); OR 1.06 (0.72 to 1.57) vs olanzapine C 61/301 (20.3%); OR 1.23 (0.72 to 2.09) vs olanzapine Paid employment: O 1080/4716 (22.9%) R 370/1711 (21.6); OR 1.15 (0.88 to 1.51) vs olanzapine Q 206/690 (29.9%); OR 1.21 (0.81 to 1.81) vs olanzapine C 61/301 (20.3%); OR 1.66 (0.99 to 2.78) vs olanzapine Suicide attempt since baseline visit: O 75/4716 (1.6%) R 41/1711 (2.4%); OR 0.77 (0.47 to 1.25) vs olanzapine Q 10/690 (1.4%); OR 1.17 (0.52 to 2.66) vs olanzapine C 4/301 (1.4%); OR 0.92 (0.32 to 2.66) vs olanzapine

Evidence Table 3. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Safety outcomes	Comments
Haro, 2005 Europe SOHO (primary publication)	NR	Only data abstracted for olanzapine, risperidone, quetiapine, clozapine arms

Evidence Table 3. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Data source	Prospective Retrospective Unclear	Sampling frame	Exposure period
Haro, 2006 SOHO (secondary publication) 12-mo medication maintenance outcomes Europe	Same as Haro 2005	Same as Haro 2005	NR	12 mos
Haro, 2006 SOHO (secondary publication) 3-y effectiveness Europe	Same as Haro 2005	Same as Haro 2005	NR	3 ys

Evidence Table 3. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Interventions mean dose	Population	Age Gender Ethnicity
Haro, 2006 SOHO (secondary publication) 12-mo medication maintenance outcomes Europe	Same as Haro 2005	Same as Haro 2005	Mean age 40 ys 56.9% male Ethnicity NR
Haro, 2006 SOHO (secondary publication) 3-y effectiveness Europe	Same as Haro 2005	Same as Haro 2005; only patients with none or 1 missing visit	Mean age 39.8 ys 56.7% male Ethnicity NR

Evidence Table 3. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Exposed Eligible Selected	Withdrawn Lost to follow-up Analyzed	Effectiveness outcomes
Haro, 2006 SOHO (secondary publication) 12-mo medication maintenance outcomes Europe	8519/NR/7186	NR/NR/7186	Medication maintenance at 12 mos (% pts): Highest frequencies: Clozapine=79.5% and Olanzapine=77% Lowest frequencies: Quetiapine=51.4% and amisulpride=58.2% Frequencies for other cohorts NR ORs (95% CI) of associated with maintenance compared to olanzapine: Risperidone: 0.72 (0.62, 0.83) Quetiapine: 0.36 (0.29, 0.44) Amisulpride: 0.53 (0.39, 0.71) Clozapine: 1.65 (1.20, 2.28) Oral typical: 0.56 (0.45, 0.70) Depot typical: 0.58 (0.46, 0.75)
Haro, 2006 SOHO (secondary publication) 3-y effectiveness Europe	9857 8072 7728	nr/nr/7728	Patients maintaining treatment for 36 mos Olanzapine 1851, Risperidone 619 , Quetiapine 126, Amisulpride 85, Clozapine 123, Oral typical NR Depot typical NR Patient discontinuing for any reason (%) Olanzapine 36.4, Risperidone 42.7 , Quetiapine 66.1, Amisulpride 50.4, Clozapine 33.8, Oral typical 53.1 Depot typical 50.2 Patient discontinuing for lack of efficacy (%) Olanzapine 18.4, Risperidone 22.7 , Quetiapine 48.3, Amisulpride 28.7, Clozapine 17.8, Oral typical 33.8, Depot typical 31.4 Patient discontinuing for intolerability(%) Olanzapine 6.4, Risperidone 10.1 , Quetiapine 14.2, Amisulpride 13.7, Clozapine 7.2, Oral typical 13.3, Depot typical 9.2

Evidence Table 3. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Safety outcomes	Comments
Haro, 2006 SOHO (secondary publication) 12-mo medication maintenance outcomes Europe	NR	
Haro, 2006 SOHO (secondary publication) 3-y effectiveness Europe	Hospitalization for exacerbation of schizophrenia Hazard ratio (95% CI) Olanzapine 1 Risperidone 1.04 (0.88, 1.23) Quetiapine 1.64 (1.31, 2.05) *** Amisulpride 1.39 (1.01, 1.92) * Clozapine 1.13 (0.83, 1.53) Oral typicals 1.39 (1.08, 1.79) ** Depot typicals 1.44 (1.10, 1.88) ** Suicide attempt % Olanzapine 2.1, Risperidone 1.9 , Quetiapine 1.4, Amisulpride 3.1, Clozapine , Oral typical 0.4, Depot typical 3.5 EPS % Olanzapine 14.7, Risperidone 32.2 , Quetiapine 13.4, Amisulpride 16.8, Clozapine 17.2, Oral typical 31.4, Depot typical 42.8 Tardive dyskinesia % Olanzapine 5.9, Risperidone7.8 , Quetiapine 6.0, Amisulpride 9.8, Clozapine 6.2, Oral typical 8.7, Depot typical 12.9 Loss of libido/impotence Olanzapine 46.9, Risperidone 52.2 , Quetiapine 39.8, Amisulpride 49.2, Clozapine 48.5, Oral typical 50.7, Depot typical 49.7 Gynecomastia, galactorrhea, amenorrhea Olanzapine 11.5, Risperidone 16.7 , Quetiapine 12.4, Amisulpride 18.0, Clozapine 16.4, Oral typical 14.9, Depot typical 13.8 Mean (SD) weight change (kg) Olanzapine 3.6(8.9), Risperidone 2.5(8.5) , Quetiapine 0.6(7.9), Amisulpride 0.5(10.8), Clozapine 3.0(11.5), Oral typical 1.5(6.3), Depot typical 2.6(10.3) * $p \leq 0.05$. ** $p \leq 0.01$. *** $p \leq 0.001$.	

Evidence Table 3. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Data source	Prospective Retrospective Unclear	Sampling frame	Exposure period
Haro, 2006 SOHO (secondary publication) 3-y remission/relapse outcomes Europe	Same as Haro 2005	Same as Haro 2005	NR	3 ys

Evidence Table 3. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Interventions mean dose	Population	Age Gender Ethnicity
Haro, 2006 SOHO (secondary publication) 3-y remission/relapse outcomes Europe	Same as Haro 2005	Same as Haro 2005; only patients with none or 1 missing visit	Mean age 40.2 ys 57.6% male Ethnicity NR

Evidence Table 3. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Exposed Eligible Selected	Withdrawn Lost to follow-up Analyzed	Effectiveness outcomes
Haro, 2006 SOHO (secondary publication) 3-y remission/relapse outcomes Europe	10,218/7112/6516	NR/NR/6516	Remission=Scores of 3 or below on the CGI overall severity, positive symptoms score, negative symptoms score, AND cognitive symptoms score ORs (95% CI) of remission compared to olanzapine: Amisulpride: 0.72 (0.56, 0.94) Clozapine: 0.78 (0.65, 0.95) Depot typical: 0.59 (0.50, 0.69) Oral typical: 0.64 (0.55, 0.74) Quetiapine: 0.65 (0.56, 0.76) Risperidone: 0.74 (0.66, 0.83) ORs (95% CI) of relapse compared to olanzapine: Amisulpride: 1.37 (0.99, 1.90) Clozapine: 1.09 (0.78, 1.53) Depot typical: 1.69 (1.31, 2.18) Oral typical: 1.65 (1.32, 2.08) Quetiapine: 2.15 (1.71, 2.69) Risperidone: 1.30 (1.09, 1.54)

Evidence Table 3. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Safety outcomes	Comments
Haro, 2006 SOHO (secondary publication) 3-y remission/relapse outcomes Europe	NR	

Evidence Table 3. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Data source	Prospective Retrospective Unclear	Sampling frame	Exposure period
Haro, 2008 10 European countries	Data from the SOHO (Schizophrenia Health Outcomes) study	Prospective observational study	3 y follow-up	3 ys

Evidence Table 3. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Interventions mean dose	Population	Age Gender Ethnicity
Haro, 2008 10 European countries	Olanzapine Is the reference medication Other medications include risperidoen, quetipine, amisulpride, clozapine, depot typicals	Patients at least 18 ys of age with initiating or changing antipsychotic medication for the treatment of schizophrenia; presenting within the normal course of care in the outpatient setting or in the hospital when admission was planned for the initiation or change of antipsychotic medication and discharge planned within 2 WK 5950 patients analyzed Mean duration of illness: 11.9 ys 9% never treated for schizophrenia Concomitant medication: 19% on anticholinergics; 18% on antidepressants; 9% on mood stabilizers; 37% on anxiolytics CGI overall (SD): 4.4 (1.0)	Mean age: 40.3 ys Male: 58% Ethnicity: NR

Evidence Table 3. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Exposed Eligible Selected	Withdrawn Lost to follow-up Analyzed	Effectiveness outcomes
Haro, 2008 10 European countries	NR/NR/5950	NR/NR/5950	Remission was defined as a score of 3 (mild severity) or less on the CGI overall severity score, the CGI positive symptoms score, the CGI negative symptoms score and the CGI cognitive symptoms score that was maintained for a period of six mos or more 2301 (38.7%) never achieved remission during the 3-y follow-up (prolonged course), 933 (15.7%) achieved remission but relapsed (remission and relapse) and 2716 (45.7%) achieved and maintained remission (persistent remission). "Patients prescribed risperidone, quetiapine or depot typicals at the baseline visit had a lower chance of achieving remission compared with those prescribed olanzapine" Relationship between independent variables (age of onset, ys since onset, male, never treated before baseline, has a spouse/partner, paid employment, socially active, CGI overall, CGI positive, CGI negative, CGI cognitive, hostile behaviours, BMI, anxiolytics, and ood stabilizers) given in table. "Females, patients with better social functioning at baseline (living independently, in paid employment, socially active or having a spouse or partner) and with a shorter duration of illness had a more favourable course"

Evidence Table 3. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Safety outcomes	Comments
Haro, 2008 10 European countries	NR	

Evidence Table 3. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Data source	Prospective Retrospective Unclear	Sampling frame	Exposure period
Haro, 2009 SOHO (secondary publication) 36-mo data from treatment discontinuation	Same as Haro 2005	Same as Haro 2005	36 mos analysis	NR
Alonso 2009 SOHO(secondary publication)HRQOL data				
Novick 2009 SOHO (secondary publication) Recovery data in the outpatient setting				
Novick 2009 SOHO (Tolerability of outpatient antipsychotic treatment.."				
Usall 2007 SOHO				

Evidence Table 3. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Interventions mean dose	Population	Age Gender Ethnicity
Haro, 2009 SOHO (secondary publication) 36-mo data from treatment discontinuation Alonso 2009 SOHO(secondary publication)HRQOL data Novick 2009 SOHO (secondary publication) Recovery data in the outpatient setting Novick 2009 SOHO (Tolerability of outpatient antipsychotic treatment.." Usall 2007 SOHO	Mean endpoint doses olanzapine: 11.8 mg/d risperidone:4.5 mg/d quetiapine: 320mg/d	Schizophrenia	Mean age: 34y 59% male Ethnicity: NR

Evidence Table 3. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Exposed Eligible Selected	Withdrawn Lost to follow-up Analyzed	Effectiveness outcomes
Haro, 2009 SOHO (secondary publication) 36-mo data from treatment discontinuation	NR/NR/1009	NR/236*/931 * lost to Follow-up before changing medication	% of patients discontinuing treatment by 36 mo Olanzapine vs Risperidone vs typicals vs other atypicals 28.9% vs 36.2% vs 44.5% vs 34.7%
Alonso 2009 SOHO(secondary publication)HRQOL data			Cox proportional HR for discontinuation of treatment by 36 mos- Higher than olanzapine for Risperidone and typical Typicals: HR 1.76; 95% CI 1.11-2.78
Novick 2009 SOHO (secondary publication) Recovery data in the outpatient setting			Risperidone: HR 1.36 95% CI 1.02-1.82 HR for atypicals similar to olanzapine: Atypicals: HR 1.43 (95% CI, 0.85-2.40)
Novick 2009 SOHO (Tolerability of outpatient antipsychotic treatment.."			Patients with higher CGI-score at baseline had higher risk of discontinuing treatment at 36 mos HR 1.18, 95% CI 1.06-1.30 EuroQOL-5D mean (SD) score at 36 mo: 0.80 (0.25)
Usall 2007 SOHO			Factors associated with achieving long lasting symptomatic remission vs functional remission vs adequate QOL during 3 y follow-up OR with respect to Olanzapine Risperidone (OR): 0.785, p= 0.0062 vs 0.795 (p=0.795) vs 0.639 (p<0.0001) Quetiapine (OR)0.456 (p<0.0001) vs 0.760 (p=0.2121) vs 0.443 (p<0.0001) Clozapine (OR) 0.944 (p=7514) vs 0.555 (p0.0881) vs 1.101 (p=0.6098) Response overall CGI: OR for gender (female reference category) 95% CI, p-Value Olanzapine cohort 0.88 (0.78 to 1.00), p=0.040 Risperidone cohort 0.90 (0.74 to 1.10), p=0.2969 Clozapine 0.56 (0.34 to 0.93) p=0.252, p=0.0252 EQ-VAS change from baseline Difference in rating by gender (female reference category), 95% CI, p-value Olanzapine cohort: -1.52 (-2.53 to -0.50), p=0.0033 Risperidone cohort: 0.27 (-1.28 to 1.83), p=0.7300 Clozapine cohort: -2.03 (-6.06 to 2.00), p=0.3243

Evidence Table 3. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Safety outcomes	Comments
Haro, 2009 SOHO (secondary publication) 36-mo data from treatment discontinuation Alonso 2009 SOHO(secondary publication)HRQOL data Novick 2009 SOHO (secondary publication) Recovery data in the outpatient setting Novick 2009 SOHO (Tolerability of outpatient antipsychotic treatment.." Usall 2007 SOHO	% of patients with AEs Olanzapine vs risperidone vs other typicals vs typicals EPS: 3.6% vs 17.1% vs 9.9% vs 13.7% TD: 0.4% vs 1.1% vs 1.7% vs 1.2% loss of libido/impotence: 25.5% vs 38.9% vs 37.9% vs 41.3% Prolactin-related: 3.8% vs 9.2% vs 10% vs 3.1% 7% weight gain: 30.8% vs 23.2% vs 22.7% vs 10.7% Tolerability (Novick 2009)Olanzapine vs risperidone vs quetiapine vs clozapine EPS % of patients with EPS at 36 mo 9.4% vs 15.6% vs 11.9% vs 12.9% OR (95% CI) in comparison to olanzapine Risperidone: 2.55 (2.16 to 3.02), Quetiapine 1.36 (1.02 to 1.81), Clozapine 1.19 (0.81 to 1.74) Tardive dyskinesia % of patients with tardive dyskinesia at 36 mo: 3.4% vs 4.8% vs 5.3% vs 7.1% OR (95 % CI) in comparison to olanzapine Risperidone: 2.47 (1.56 to 3.94), Quetiapine 1.77 (0.89 to 3.51) Clozapine 2.37 (0.96 to 5.85) Loss of libido/impotence % of patients with loss of libido/impotence at 36 mo 32.5% vs 36.5% vs 34.2% vs 40.9 OR (95% CI) in comparison to olanzapine Risperidone 1.38 (1.20 to 1.60), quetiapine 1.07 (0.86 to 1.33) vs 1.39 (1.04 to 1.86) mean (SD) Weight change from baseline to 36 mo: 4.2 (8.7) vs 2.7 (7.6) vs 1.7 (8.4) vs 2.6 (9.5) % of patients with >7% weight gain at 36 mo from baseline: 40.6% vs 33.7% vs 30.9% vs 29.5%	

Evidence Table 3. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Data source	Prospective Retrospective Unclear	Sampling frame	Exposure period
Haukka 2008 Finland	National Hospital Discharge Register, Statistics Finland, and a nationwide prescription register.	Retrospective	January 1, 1997-December 31, 2003	NR
Hedenmalm, 2002 International	WHO database	Retrospective	Median treatment duration: R: 13 ds, C: 52 ds, O: 115 ds	NR

Evidence Table 3. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Interventions mean dose	Population	Age Gender Ethnicity
Haukka 2008 Finland	clozapine olanzapine typical antipsychotics (haloperidol zuclopenthixol, other or mixed) antidepressants (fluoxetine, citalopram, paroxetine, sertraline, mianserin, other or mixed)	All individuals in Finland who (a) had been hospitalized with a diagnosis of attempted suicide, (b) had at least one hospitalization registered in the National Hospital Discharge Register with a schizophrenia diagnosis and (c) were at least 16 ys of age when the index hospitalization began.	Median age 35.63 (males), 41.05 (females) 51% male Race NR
Hedenmalm, 2002 International	Risperidone Clozapine Olanzapine	Schizophrenia	NR NR NR

Evidence Table 3. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Exposed Eligible Selected	Withdrawn Lost to follow-up Analyzed	Effectiveness outcomes
Haukka 2008 Finland	NR NR 1,611	NR NR 1,611	Propensity-score adjusted hazard ratios (95% CI) vs no antipsychotic use <u>Suicide attempts</u> Clozapine: 0.74 (0.35, 1.57) Olanzapine: 1.37 (0.87, 2.14) Haloperidol: 0.92 (0.46, 1.83) Perphenazine: 1.73 (0.89, 3.34) Other or mixed: 1.34 (1.10, 1.62) <u>Suicides</u> Clozapine: 0.67 (0.16, 2.85) Olanzapine: 0.40 (0.11, 1.44) Haloperidol: 1.03 (0.18, 5.98) Perphenazine: 0.27 (0.01, 4.73) Other or mixed: 0.62 (0.39, 0.98) <u>All-cause mortality</u> Clozapine: 0.57 (0.19, 1.71) Olanzapine: 0.31 (0.12, 0.79) Haloperidol: 0.50 (0.15, 1.65) Perphenazine: 0.20 (0.04, 1.06) Other or mixed: 0.54 (0.40, 0.74)
Hedenmalm, 2002 International	NR/NR/868	0/0/868	NR

Evidence Table 3. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Safety outcomes	Comments
Haukka 2008 Finland	NA	
Hedenmalm, 2002 International	74% of cases of discontinuation, glucose tolerance improved after discontinuation. After rechallenge (N=24) , following resulted in recurrence of glucose intolerance: clozapine: 18, olanzapine: 5, risperidone: 1	

Evidence Table 3. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Data source	Prospective Retrospective Unclear	Sampling frame	Exposure period
Hennessy, 2002 United States	3 US Medicaid progmes	Retrospective	NR	NR
Herceg, 2008	Vrapce Psychiatric Hospital, Zagreb, Croatia	Retrospective	Jan 1, 2003-Dec 31, 2004	2 yrs

Evidence Table 3. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Interventions mean dose	Population	Age Gender Ethnicity
Hennessy, 2002 United States	Quarter 1, Quarter 2, Quarter 3, Quarter 4 clozapine: <243, 243-385, 386-543, >543 risperidone: <2.8, 2.8-5.0, 5.1-6.5, >6.5 haloperidol: <3.5, 3.5-7.5, 7.6-15.0, >15.0 thioridazine: <51, 51-102, 103-204, >204	Schizophrenia, control group of patients with psoriasis	71.5% over 34 yrs of age 54% Female Ethnicity NR
Herceg, 2008	Risperidone vs olanzapine vs clozapine Newly diagnosed schizophrenia Mg/d, median, Interquartile (IQ) range 4 (4-6) vs 10 (10-15) vs 250 (200-300) Chronic schizophrenia Mg/d, median, IQ range: 4(3-6) vs 15 (10.0-17.5) vs 200 (150-300)	Newly diagnosed schizophrenia and Chronic schizophrenia	risperidone vs olanzapine vs clozapine Newly diagnosed schizophrenia Age median, (IQ range): 24 (20-32) vs 27 (22-39) vs 33 (27-46) % male: 64.0% vs 44.0% vs 77.0% Chronic Schizophrenia Age, median (IQ range):38 (30-35) vs 36 (28.5-44.0) vs 40 (33.5-47.5) % male: 64.0% vs 53.0% vs 60.0%) Ethnicity: NR

Evidence Table 3. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Exposed Eligible Selected	Withdrawn Lost to follow-up Analyzed	Effectiveness outcomes
Hennessy, 2002 United States	NR/NR/NR	NR/NR/NR	Adjusted rate ratios; 95% Cis Patients with glaucoma: cardiac arrest/ventricular arrhythmia; death: clozapine: 1.7 (1.0-2.9); 3.4 (2.1-5.5) haloperidol: 2.2 (1.7-3.0); 4.5 (3.6-5.7) risperidone: 3.1 (2.2-4.5); 5.8 (4.3-8.0) thioridazine: 2.2 (1.6-3.); 4.0 (3.1-5.2) Patients with psoriasis: cardiac arrest/ventricular arrhythmia; death: clozapine: 1.9 (1.0-3.7); 2.6 (1.5-4.5) haloperidol: 2.4 (1.5-3.9); 3.2 (2.2-4.8) risperidone: 3.2 (1.9-5.4); 4.1 (2.7-6.4) thioridazine: 2.4 (1.4-3.9); 2.9 (2.0-4.4)
Herceg, 2008	NR/831/533	298/NR/533	Newly diagnosed schizophrenia risperidone vs olanzapine vs clozapine % rehospitalized taking atypical antipsychotics:17.3% vs 19.2% vs 11.5, p=NS Time to first rehospitalization at 2 ys: longest for olanzapine (difference with other groups, NS) chronic schizophrenia % rehospitalized taking atypical antipsychotics by the 2nd y follow-up: 13% vs 12% vs 14%, p=NS Time to first rehospitalization: longest for risperidone (Difference with other groups, NS)

Evidence Table 3. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Safety outcomes	Comments
Hennessy, 2002 United States	Those with treated schizophrenia has higher rates of cardiac arrest and ventricular arrhythmia over those non-treated: ratio: 1.7-3.2	
Herceg, 2008	NR	

Evidence Table 3. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Data source	Prospective Retrospective Unclear	Sampling frame	Exposure period
Herrman et al, 2004 Canada	Database: administrative health care databases in Ontario, Canada	Retrospective	April 1, 1997 through March 31, 2002	NR

Evidence Table 3. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Interventions mean dose	Population	Age Gender Ethnicity
Herrman et al, 2004 Canada	Risperidone Olanzapine Typical antipsychotics	Patients over age 65 who were given at least 2 successive prescriptions and received enough drug for at least 30 ds of observation.	Mean age approximately 82 ys (SD 7.5) 69% female Ethnicity NR

Evidence Table 3. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Exposed Eligible Selected	Withdrawn Lost to follow-up Analyzed	Effectiveness outcomes
Herrman et al, 2004 Canada	NR NR 11,400	NR NR 11,400	NR

Evidence Table 3. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Safety outcomes	Comments
Herrman et al, 2004 Canada	Hospital admission for stroke: typical antipsychotic users: N=10 risperidone users: N=58 olanzapine users: N=24 Crude stroke rate per 1.000 person ys: typical antipsychotic users: 5.7 risperidone users: N=7.8 olanzapine users: N=5.7 (NS) RR relative to typical antipsychotic use: olanzapine: 1.1 (95% CI 0.5, 2.3) risperidone: 1.4 (95% CI 0.7, 2.8) RR of risperidone relative to olanzapine: 1.3 (95% CI 0.8, 2.2)	

Evidence Table 3. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Data source	Prospective Retrospective Unclear	Sampling frame	Exposure period
Ho, 1999 United States	Mental Health Clinical Research Center, University of Iowa	Retrospective	4 WK	6 mos
Hodgson, 2005 England	Case Notes: 26 consultant psychiatrists	Retrospective	1994 to 2001	NR

Evidence Table 3. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Interventions mean dose	Population	Age Gender Ethnicity
Ho, 1999 United States	Risperidone 6.0 mg/d (N=21) Olanzapine 13.7 mg/d (N=21)	Schizophrenia	Mean age: 31.5 ys 76.2% male Ethnicity NR
Hodgson, 2005 England	Clozapine=332.3mg/d Olanzapine=12.1mg/d Risperidone=4.7mg/d	Schizophrenia or schizoaffective disorder	Clozapine/Olanzapine/Risperidone Mean age (ys)=37.3/41.8/39.4 % male=82/60/65

Evidence Table 3. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Exposed Eligible Selected	Withdrawn Lost to follow-up Analyzed	Effectiveness outcomes
Ho, 1999 United States	NR/NR/42	NR/NR/26	olanzapine vs risperidone, change from baseline, p value At discharge Symptom score: negative symptom dimension: -2.8(0.76)* vs -1.8(0.61)*, p=0.49 psychotic symptom dimension: -1.3(0.55)* vs -1.9(0.53)*, p=0.82 disorganized symptom dimension: -1.8(0.68)* vs -2.1(0.77)*, p=0.68 Total SANS/SAPS: -5.8(1.58)* vs -5.9(1.46)*, p=0.69 Total BPRS: -9.0(2.91)* vs -6.5(2.47)*, p=0.14 GAS score: 8.9(2.18)* vs 6.2(1.4)*, p=0.09 (*p<0.05 vs baseline, within group comparison) At follow-up Symptom score: negative symptom dimension: -1.5(0.94) vs -1.5(1.18), p=0.84 psychotic symptom dimension: -1.4(0.5)* vs -3.9(0.64)*, p=0.03 disorganized symptom dimension: -0.8(0.7) vs -3.2(1.1)*, p=0.36 Total SANS/SAPS: -3.7(1.23)* vs -8.6(2.39)*, p=0.3 GAS score: 8.8(4.01)* vs 13.9(2.43)*, p=0.52 QOL scores: occupational impairment: -0.5(0.43) vs 0.5(0.27), p=0.06 financial dependence: 0.7(0.27) vs 0.7(0.26), p=0.49 impairment in performance of household duties:-0.7(0.24)* vs -0.6(0.4), p=0.91 relationship impairment with family member: -0.01(0.27) vs -0.4(0.2), p=0.27 relationship impairment with friends: -0.4(0.29) vs -0.2(0.25), p=0.37 enjoyment of recreational activities: -0.8(0.36) vs -0.3(0.38), p=0.77 satisfaction: -0.5(0.22) vs -0.8(0.30), p=0.67 overall psychosocial functioning:-0.7(0.31) vs -1.15(0.22)*, p=0.24 (*p<0.05 vs baseline, within group comparison)
Hodgson, 2005 England	550/261/253	NR/NR/253	Patients treated with risperidone and clozapine were 1.3 and 0.56 times, respectively, more likely to discontinue compared to olanzapine Median time to discontinuation Risperidone=274 ds Olanzapine=522 ds Clozapine=6 ys

Evidence Table 3. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Safety outcomes	Comments
Ho, 1999 United States	EPS at discharge: SAS: 0(0.19), 0.4(0.56), p=0.31 BAS: -0.1(0.15) vs 0.6(0.20)*, p=0.001 (*p<0.05 vs baseline, within group comparison)	
Hodgson, 2005 England	One serious AE was reported: intussusception in a patient taking clozapine. Side effects were not a common primary reason for medication discontinuation and therefore were NR by the authors.	

Evidence Table 3. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Data source	Prospective Retrospective Unclear	Sampling frame	Exposure period
Hrdlicka, 2009	patients receiving routine clinical care at the department of child psychiatry	Retrospective	1997-2007	6 WK
Jerrell, 2007 United States	Medical and pharmacy claims information	Retrospective	July 1, 2002 to June 30, 2004	NR
Joyce, 2005 United States	Medical and pharmaceutical claims from the PharMetrics Patient-Centric Database	Retrospective	March 1, 2001 and August 31, 2003	>12 mos

Evidence Table 3. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Interventions mean dose	Population	Age Gender Ethnicity
Hrdlicka, 2009	Risperidone vs olanzapine vs ziprasidone vs clozapine Mean dose (SD) at week 6: 2.7 mg(1.3) vs 15.0mg (6.1) vs 80.0 mg(0.0) vs 247.5 mg(118.0)	Schizophrenia, schizoaffective disorder and other schizophrenic disorders	Mean age, yrs (SD)15.8 (1.6) range (10.5-18.8) yrs % male: 47.7%
Jerrell, 2007 United States	Atypical antipsychotics: Aripiprazole Ziprasidone Quetiapine Risperidone Olanzapine Clozapine Typical antipsychotics: Haloperidol Fluphenazine	Primary or secondary diagnosis of schizophrenia	51% of sample was >40 ys of age 51% male 62% African American
Joyce, 2005 United States	Risperidone: between 0.5mg and 8mg daily Olanzapine: between 2.5mg and 40mg daily Quetiapine: between 100mg and 800mg daily Ziprasidone: between 40mg and 160mg daily	Schizophrenia or Schizoaffective disorders	Ziprasidone/Risperidone/ Olanzapine Mean age (ys): 40.1/43.4/45.3 % male: 36.9/42/44.9

Evidence Table 3. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Exposed Eligible Selected	Withdrawn Lost to follow-up Analyzed	Effectiveness outcomes
Hrdlicka, 2009	NR/109/109	52/NR/109	Risperidone vs olanzapine vs clozapine mean change in weight between baseline and week 6 (Kg): +3.6 (2.6) vs +4.4 (2.5) vs + 2.1 (4.0), p=0.286
Jerrell, 2007 United States	NR/NR/2231	NR/NR/2231	Health Outcomes For cerebrovascular conditions, there were no significant differences between groups For heart disease conditions, aripiprazole had a lower estimate for myocardial infarctions and ischemic heart disease compared to both typical antipsychotics (P=0.006), risperidone had a lower incidence rate for arrhythmias compared to both typical antipsychotics (P=0.007). The incidence rate for cardiomyopathy was significantly lower for aripiprazole than for both typical antipsychotics (P=0.02). The incidence of being diagnosed with incident hypertension was significantly higher for those taking ziprasidone compared to both typical antipsychotics (P=0.01)
Joyce, 2005 United States	NR/NR/1810	NR/NR/1810	Compliance and Persistence Compliance was significantly higher among those prescribed ziprasidone compared with the other treatment groups (P<0.01) Persistence in the first y was 30 ds longer among those prescribed ziprasidone compared with the other treatment groups, though NS (persistence in ds: ziprasidone=228; risperidone=193; and olanzapine=201) Health Care Costs Ziprasidone treatment group had the highest total annual cost compared to the other two treatment groups. Though change in cost from pre- to post index periods was NSly different among the treatment groups. Psychiatric-related costs decreased significantly more for the ziprasidone treatment group than the other two groups (risperidone, P=0.0116 and olanzapine, P=0.0021)

Evidence Table 3. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Safety outcomes	Comments
Hrdlicka, 2009	NR	Weight gain data from ziprasidone not available at week 6 for statistical analysis because of early discharges and drop outs
Jerrell, 2007 United States	See outcomes column	
Joyce, 2005 United States	NR	

Evidence Table 3. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Data source	Prospective Retrospective Unclear	Sampling frame	Exposure period
Karagianis, 2009 HOCCC study	9 Canadian provinces	Prospective	NR	1 y
Kasper, 2001 9 countries in Europe and Australasia	Riverview Hospital , British Columbia	Retrospective	4 mos	NR

Evidence Table 3. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Interventions mean dose	Population	Age Gender Ethnicity
Karagianis, 2009 HOCCC study	Mean doses(SD) at 12 mo (mg/d) Olanzapine: 12.8 (8.2) Risperidone: 2.9 (1.7) Quetiapine:375.6 (SD 293.6) Clozapine: 332.8 (172.9)	schizophrenia or other related disorders	Olanzapine vs risperidone vs quetiapine vs clozapine Age (yrs), mean (SD) 43.4(11.6) vs 43.7 (11.5) vs 41.9 (11.1) vs 43.1 (12.4) % female: 48% vs 48.4% vs 45.8% vs 14.3% % Caucasian: 88.1% vs 84.7% vs 86.1% vs 94.7%
Kasper, 2001 9 countries in Europe and Australasia	Risperidone (N=30) : 4.89 mg/d vs. olanzapine (N=30): 17.19 mg/d	Aged 18-60, schizophrenia-types: paranoid, schizoaffective--disorder, Bipolar affective disorder, undifferentiated	Mean Age: 35.7 ys Male: 62% Ethnicity: NR

Evidence Table 3. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Exposed Eligible Selected	Withdrawn Lost to follow-up Analyzed	Effectiveness outcomes
Karagianis, 2009 HOCCC study	NR/NR/929	266/NR/796	Olanzapine vs risperidone vs quetiapine v clozapine Proportion of treatment completers: 67.4% vs 62% vs 63.7% vs 55.6%, p=0.15
Kasper, 2001 9 countries in Europe and Australasia	NR/NR/60	NR/NR/37	Percentage of Patients Discharged on Original Therapy: R: 40% vs O: 13.3%; P<0.05 Treatment success: R: 40% vs O: 27%; P<0.01 Switched due to lack of efficacy: R: 37% vs O: 57%; P=NS Switched due to side effects: R: 10% vs O: 63%; P<0.05

Evidence Table 3. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Safety outcomes	Comments
Karagianis, 2009 HOCCC study	Olanzapine vs risperidone vs quetiapine v clozapine % of serious AEs: 11.7% vs 8.9% vs 15.7% vs 21% 5 deaths in olanzapine group vs 1 from the other SGA group. Olanzapine vs risperidone vs quetiapine LS mean changes from baseline BMI were 0.7 (95% CI 0.1 to 1.2), 0.6 (95% CI -0.3 to 1.5) and -1.2 (95% CI -2.3 to -0.13). Olanzapine and risperidone groups had significantly higher increases in BMI(LS mean treatment effect 1.91 (95% CI: 0.41 to 3.42) and 1.86 (95% CI 0.13 to 3.58) respectively compared to quetiapine LS mean weight change from baseline(Kg): 2.0 (95% CI 0.4 to 3.6) vs 1.2 (95% CI -1.3 to 3.8) and -2.8 (95% CI -6.1 to 0.4). Olanzapine and risperidone significantly ore likely to gain weight compared to quetiapine (LS mean difference 4.8 and 4.0 respectively)	
Kasper, 2001 9 countries in Europe and Australasia	Treatment-emergent side effects: Total # of patients with side effects: R: 43.3% vs O: 40% EPS symptoms: 6/30 (20%) Akathisia: R: 5 vs O: 1 Stiffness: R: 2 vs O: 0 Tremor: R: 2 vs O: 1 Parkinsonism: R: 1 vs O: 0 Agitation: R: 1 vs O: 5 Increased prolactin level: R: 0 vs O: 1 Blurred vision: R: 0 vs O: 1 Increased salivation: R: 0 vs O: 1 Anxiety: R: 1 vs O: 0 Sedation: R: 5 vs O: 3 Hypotension: R: 2 vs O: 0 Dizziness: R: 1 vs O: 1 Weight Gain: R: 1 vs O: 1 Difficulty swallowing: O:1 vs R: 0 Sexual dysfunction: O: 1 vs O: 0	

Evidence Table 3. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Data source	Prospective Retrospective Unclear	Sampling frame	Exposure period
Kelly, 2010 USA	State of Maryland Clozapine Authorization and Monitoring Program, administrative database of inpatient second generation antipsychotics in Maryland, and the Social Security Death Index	Retrospective	1994-2000	NR
Killian, 2012	Multi-center prospective study	Prospective	January 2005- November 2008	2 years

Evidence Table 3. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Interventions mean dose	Population	Age Gender Ethnicity
Kelly, 2010 USA	Clozapine Risperidone Doses NR	20-69 years, DSM-III or DSM-IV diagnosis of schizophrenia, schizoaffective disorder or psychosis not otherwise specified	Age: 39.8 years Gender: 37.2% female Ethnicity: clozapine group: 62.9% white, 33.2 African American; risperidone group: 47.8% white, 49.7 African American
Killian, 2012	Quetiapine: 588 mg/d Olanzapine: 15 mg/d Risperidone: 3.9 mg/d	18+ years, schizophrenia or schizoaffective disorder	Age: 39.98 years Gender: 47.6% female Ethnicity: NR

Evidence Table 3. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Exposed Eligible Selected	Withdrawn Lost to follow-up Analyzed	Effectiveness outcomes
Kelly, 2010 USA	NR/NR/1686	NA/NA/1686	NR
Killian, 2012	NR/530/374	117/NR/257	Hospital readmission, average rate: Olanzapine vs. Qutiapine: OR, 0.40; p=0.017 Olanzapine vs. Risperidone: OR, 0.25; p=0.000 Regression models: GAF, b=1.350, p=0.000; Quality of Life, b=0.628, p=0.006; Cognitive performance, b=0.270, p=0.000

Evidence Table 3. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Safety outcomes	Comments
Kelly, 2010 USA	Risk of Cardiovascular Disease Mortality, clozapine vs. risperidone: HR, 1.20; 95%CI, 0.59-2.44; p=0.613	
Killian, 2012	NR	

Evidence Table 3. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Data source	Prospective Retrospective Unclear	Sampling frame	Exposure period
Kilzieh 2008 United States	Electronic medical records database transformed into a data "warehouse" for data extraction	Retrospective	January 1999 through December 2000	NR
Kim 2008 Korea	Comprehensive medical histories were collected from all available sources including patients, informants, and hospital medical records	Prospective	NR	2 ys

Evidence Table 3. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Interventions mean dose	Population	Age Gender Ethnicity
Kilzieh 2008 United States	NR	Schizophrenia or schizoaffective disorder	Mean Age (y): 48.4±11.6 % Male: 91 Ethnicity: NR
Kim 2008 Korea	Mean modal dose (mg/d) Clozapine: 423.6±107.4 Risperidone: 7.6±2.9	Schizophrenia and comorbid alcohol use disorders (AUD) Exclusion criteria: subjects with substance abuse other than alcohol, those with significant physical problems or organic mental disorders, and those with MR	Clozapine/Risperidone Age (y): 39.5±9.4/38.7±10.5 Gender (% male): 100/100 Ethnicity: NR

Evidence Table 3. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Exposed Eligible Selected	Withdrawn Lost to follow-up Analyzed	Effectiveness outcomes
Kilzieh 2008 United States	NR NR 495 (221 Olanzapine, 274 Risperidone)	NR NR 495	Discontinuation rates: Index medication trials: 73% Olanzapine: 70% Risperidone: 76% (P=0.12) Higher discontinuation rate of risperidone: hazards ratio = 1.23; 95% CI 0.99-1.5 Median time (d) to discontinuation: 120 (95% CI 105-135) Median time (d) to discontinuation (olanzapine): 150 (95% CI 120-180) Median time (d) to discontinuation (risperidone): 90 (95% CI 71-109) olanzapine compared to risperidone, P=0.04 Self-discontinuation was the main method of discontinuation occurring in 48% of index trials, with no significant difference between olanzapine (50%) and risperidone (46%) (OR 0.86, 95% CI 0.60-1.23) Switching between 2 agents as a form of discontinuation: 25% of index trials More switching in risperidone (30%) than olanzapine (20%) (P=0.01; OR 1.72, 95% CI 1.13-2.61) Of patients who switched medication, 44% did so in the first mo of trial. Observed more in risperidone (50%) than olanzapine (32%) (P=0.05)
Kim 2008 Korea	NR 67 67	6 NR 61 (25 clozapine, 36 risperidone)	Clozapine/Risperidone Community survival (%): 52/25 Mean survival (d): 526.5 (95% CI 435.0-498.6)/420.4 (95% CI 342.2-498.6) The survival curve for the clozapine group was significantly different from that of the risperidone group (log-rank test, *df* =1, P= .045)

Evidence Table 3. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Safety outcomes	Comments
Kilzieh 2008 United States	NR	
Kim 2008 Korea	NR	Study subjects were 100% male

Evidence Table 3. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Data source	Prospective Retrospective Unclear	Sampling frame	Exposure period
Kim, 2008, South Korea	Department of Psychiatry, Bundang CHA General Hospital, South Korea	Prospective	December 2004 - July 2007	NR
Koro, 2002 UK	England and Wales-based General Practice Database, Bristol-Myers Squibb, MEDTAP	Retrospective	30 mos	NR
Koro, 2002b UK	United Kingdom based General Practice Research Database	Retrospective	NR	NR

Evidence Table 3. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Interventions mean dose	Population	Age Gender Ethnicity
Kim, 2008, South Korea	Risperidone LA!, Oral Risp 85.9±77.7 / 241.8±108.3	Patients with first-episode schizophrenia or schizoaffective disorder, between 17 and 60 ys of age, with an IQ above 80, and receiving treatment of long-acting injectable or oral risperidone as outpatients	RLAI/Oral Age (ys): 32.5±10.6/31.0±10.1 Gender (%male): 32/40 Ethnicity: NR
Koro, 2002 UK	Olanzapine: dose range NR Risperidone: dose range NR Conventional antipsychotics	Schizophrenia	Mean age: 51 ys 60% Male
Koro, 2002b UK	Olanzapine: dose range NR Risperidone: dose range NR Conventional antipsychotics	Patients with prescriptions for both schizophrenia and diabetes	Mean age: 51 ys 62.5% Female

Evidence Table 3. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Exposed Eligible Selected	Withdrawn Lost to follow-up Analyzed	Effectiveness outcomes
Kim, 2008, South Korea	NR 55 (25 assigned to risperidone long-acting injection (RLAI) group, 30 assigned to oral risperidone group)/ 50 (22 assigned to RLAI group, 28 assigned to oral risperidone group)	NR NR 50	1-y medication compliance (%mean±SD): RLAI = 85.7±21.4 Oral risperidone = 54.3±32.8 2-y medication compliance (%mean±SD): RLAI = 81.4±26.6 Oral risperidone = 54.6±32.1 Non- or partial adherence (%): RLAI = 32% Oral risperidone = 68% Good adherence (%): RLAI = 68% Oral risperidone = 32% 1-y relapse (%): RLAI = 18% Oral risperidone = 50% 2-y relapse (%): RLAI = 23% Oral risperidone = 75%
Koro, 2002 UK	3.5 million /18,309/8866	0/0/8866	NR
Koro, 2002b UK	3.5 million/3.5 million/19,637	0/0/19,637	NR

Evidence Table 3. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Safety outcomes	Comments
Kim, 2008, South Korea	Tardive dyskinesia was observed in one patient in the RLAI group	N was small
Koro, 2002 UK	Odd of developing hyperlipidemia: compared with no antipsychotic exposure: olanzapine: (OR, 4.65; 95% CI, 2.44-8.85); P<.001 vs risperidone: (OR, 1.12; 95% CI, 0.60-2.11); P=.72 compared with use of conventional antipsychotics: olanzapine: (OR, 3.36; 95% CI, 1.77-6.39); P<.001 vs risperidone: (OR, 0.81; 95% CI, 0.44-1.52); P=.52	
Koro, 2002b UK	OR of risk of developing diabetes: Olanzapine vs non-treated 5.8; 95%CI: 2.0-16.7 Olanzapine vs typical APs: 4.2; 95%CI: 1.5-12.2 Risperidone vs non-treated : 2.2; 95%CI: 0.9-5.2 Risperidone vs typical APs: 1.6; 95%CI: 0.7-3.8	

Evidence Table 3. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Data source	Prospective Retrospective Unclear	Sampling frame	Exposure period
Kozma, 2004 (poster) United States	Database: Medstat's Medicaid database	Retrospective	1999-2002	NR
Kraus, 1999 Germany	Max Planck Institute of Psychiatry	Retrospective	4 WK	1 week
Kreyenbuhl, 2011 USA	VA mid-Atlantic pharmacy and health care utilization databases	Retrospective	2004 through September 2006	Mean (SD): 22.9 (8.8)

Evidence Table 3. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Interventions mean dose	Population	Age Gender Ethnicity
Kozma, 2004 (poster) United States	Atypical antipsychotics overall Olanzapine Risperidone Quetiapine Haloperidol Benzodiazepines	Age 60 or older, evidence of dementia treatment (2 or more claims containing a primary or secondary diagnosis of dementia), initial use (I.e., following a 6-mo or longer period of no use) of 1 of 3 classes of drugs: atypical antipsychotics (risperidone, olanzapine, or quetiapine), haloperidol, or benzodiazepines.	Median age 78-82 among groups; Among patients taking atypical antipsychotics, 56% were Caucasian, 17% African American; among patients taking conventional antipsychotics, 45% were Caucasian and 21% African American.
Kraus, 1999 Germany	Clozapine: 170 mg/d Olanzapine: 13 mg/d Haloperidol: 5 mg/d	Schizophrenia	Mean age: 37 ys 43% Female
Kreyenbuhl, 2011 USA	Mean dosages NR Aripiprazole Olanzapine Quetiapine Risperidone Ziprasidone Chlorpromazine Haloperidol	Schizophrenia, VA patient, new start of study medication during study period	Age: 19-34: 5.6%, 35-49: 36.4% vs. 50-64: 45.9%, 65+: 12.2% Gender: 7.4% female Ethnicity: 28.3% White, 47% Non-white, 24.6% Missing data

Evidence Table 3. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Exposed Eligible Selected	Withdrawn Lost to follow-up Analyzed	Effectiveness outcomes
Kozma, 2004 (poster) United States	NR NR 26,456	NR NR 26,456	NR
Kraus, 1999 Germany	NR/NR/NR	NR/NR/44	Mean scores at endpoint; p value from baseline clozapine: weight: 71.0 kg; P=0.001 leptin: 10.7 ng/ml; P=0.004 olanzapine: weight: 70.6 kg; P<0.001 leptin: 10.1 ng/ml; P=0.006 haloperidol: weight: 64.2 kg; P=0.94 leptin: 7.0 ng/ml; P=0.54 no treatment: weight: 69.1 kg; P=0.63 leptin: 7.3 kg; P=0.86
Kreyenbuhl, 2011 USA	2613/2479/2138	NA/NA/2138	Aripiprazole vs. Olanzapine vs. Quetiapine vs. Risperidone vs. Ziprasidone vs. Chlorpromazine vs. Haloperidol Median time to discontinuation, days: 93 vs. 90 vs. 87 vs. 76 vs. 114 vs. 164 vs. 95 Risk of discontinuation, HR; 95%CI; p-value (Olanzapine reference): Aripiprazole: HR, 0.94; 95%CI, 0.79-1.12; p=0.501 Quetiapine: HR, 1.02; 95%CI, 0.89–1.18; p=0.746 Risperidone: HR, 1.15; 95%CI, 1.02–1.30; p= 0.025 Ziprasidone: HR, 0.88; 95%CI, 0.71–1.09; p= 0.255 Chlorpromazine: HR, 0.89; 95%CI, 0.64–1.24; p= 0.489 Haloperidol: HR, 1.01; 95%CI, 0.80–1.26; p= 0.947

Evidence Table 3. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Safety outcomes	Comments
Kozma, 2004 (poster) United States	Stroke-related event (defined as an acute inpatient hospital admission for a stroke-related event within 90 ds following initiation of treatment with the index medication): Unadjusted rates were not statistically significant, reporting is unclear: states rates were: 0.87%, 0.97%, 0.88%, 0.58%, 1.19%, 1.11% 1.04% for atypical antipsychotics overall, olanzapine, risperidone, quetiapine, haloperidol, and benzodiazepine groups, respectively.	
Kraus, 1999 Germany	NR	
Kreyenbuhl, 2011 USA	NR	

Evidence Table 3. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Data source	Prospective Retrospective Unclear	Sampling frame	Exposure period
Lambert, 2005 Australia	Medical record review	Retrospective	1998 to 2000	18 mos
Lambert, 2005 SOHO (secondary publication) 6-mo tolerability results Europe (Denmark, France, Germany, Greece, Ireland, Italy, the Netherlands, Portugal, Spain, and the UK)	Same as Haro 2005	Same as Haro 2005	Initial recruitment period of 9/1/00-12/31/01	6 mos

Evidence Table 3. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Interventions mean dose	Population	Age Gender Ethnicity
Lambert, 2005 Australia	Risperidone: 2.7mg/d (non-affective psychosis) and 2.5mg/d (affective psychosis) Olanzapine: 10.3mg/d (non-affective psychosis) and 9.8mg/d (affective psychosis)	Experiencing an episode of psychosis, non-affective psychosis, or affective psychosis	Mean age (ys): 21.7 66% male
Lambert, 2005 SOHO (secondary publication) 6-mo tolerability results Europe (Denmark, France, Germany, Greece, Ireland, Italy, the Netherlands, Portugal, Spain, and the UK)	Same as Haro 2005	Subset of patients who were only receiving one antipsychotic after the baseline visit	Mean age=40 56.6% male Ethnicity NR

Evidence Table 3. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Exposed Eligible Selected	Withdrawn Lost to follow-up Analyzed	Effectiveness outcomes
Lambert, 2005 Australia	NR/NR/367	NR/NR/367	Treatment variables Within affective group, those taking olanzapine had a significantly longer duration of treatment than those taking risperidone (p=0.02) Outcome measures (non-affective psychosis) No significant differences were noticed between groups on the CGI-S, GAF, and SOFAS 112 people (56.6%) in the risperidone group and 28 people (58.3%) in the olanzapine group reached full remission of positive symptoms Outcome measures (affective psychosis) There was a significantly better response to olanzapine compared to risperidone measured by the CGI-S score at endpoint (p=0.002), however scores on the CGI-BP, GAF, and SOFAS were NSly different
Lambert, 2005 SOHO (secondary publication) 6-mo tolerability results Europe (Denmark, France, Germany, Greece, Ireland, Italy, the Netherlands, Portugal, Spain, and the UK)	10,972/8400/7436	NR/NR/7436	NR

Evidence Table 3. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Safety outcomes	Comments
Lambert, 2005 Australia	Extrapyramidal side effects overall (p<0.001), especially parkinsonism (p<0.001) and akathisia (p=0.015) occurred more often in the risperidone group. More patients on risperidone experienced prolactin elevation (p=0.014), while weight gain was more prevalent with olanzapine users (p<0.001)	
Lambert, 2005 SOHO (secondary publication) 6-mo tolerability results Europe (Denmark, France, Germany, Greece, Ireland, Italy, the Netherlands, Portugal, Spain, and the UK)	<u>Mean weight change (kg)/adjusted difference compared to olanzapine (95% CI)</u> Olanzapine: 2.4 Risperidone: 1.4/-1.0 (-1.3, -0.7) Quetiapine: 0.6/-1.2 (-1.6, -0.7) Amisulpride: 1.4/-0.7 (-1.4, 0.0) Clozapine: 2.3/0.1 (-0.6, 0.7)) Oral typical: 1.1/-1.3 (-1.8, -0.8) Depot typical: 1.1/-0.9 (-1.5, -0.3) <u>Mean BMI change (kg/m^2)/adjusted difference compared to olanzapine (95% CI)</u> Olanzapine: 0.9 Risperidone: 0.5/-0.4 (-0.5, -0.3) Quetiapine: 0.2/-0.4 (-0.6, -0.2) Amisulpride: 0.5/-0.2 (-0.5/0.0) Clozapine: 0.8/0.0 (-0.3, 0.2) Oral typical: 0.4/-0.5 (-0.7, -0.3) Depot typical: 0.4/-0.4 (-0.6, -0.1)	

Evidence Table 3. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Data source	Prospective Retrospective Unclear	Sampling frame	Exposure period
Lambert, 2005 United States	California Medicaid	Retrospective	July 1, 1997 to December 31, 2000	More than 12 weeks
Lambert, 2006 United States	Veterans Health Administration of the Department of Veterans Affairs (VA)	Retrospective	October 1, 1996 to September 30, 2001	NR
Lasser, 2004 United States	NR	Prospective	NR	8 WK

Evidence Table 3. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Interventions mean dose	Population	Age Gender Ethnicity
Lambert, 2005 United States	clozapine olanzapine quetiapine risperidone	Schizophrenia	NR
Lambert, 2006 United States	Olanzapine Risperidone Quetiapine Haloperidol	Schizophrenia	Olanzapine/Risperidone/ Quetiapine/Haloperidol Mean age (ys): 50.3/51.1/50.6/52 % male: 94.1/93.2/91.7/95.1 % African American: 28.8/30.8/21.2/39.4 % Hispanic: 6.8/4.8/4.1/5.4
Lasser, 2004 United States	Olanzapine or risperidone for 8 WK	Schizophrenia or schizoaffective disorders	Mean age=49.9 ys 60.8% male 63.6% white

Evidence Table 3. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Exposed Eligible Selected	Withdrawn Lost to follow-up Analyzed	Effectiveness outcomes
Lambert, 2005 United States	129341/34337/12637	NR/NR/12637	NR
Lambert, 2006 United States	NR/NR/15767	NR/NR/15767	There were no significant differences between groups in regards to increased risk of developing diabetes. When analyses were reproduced, including those excluded previously due to having been exposed to antipsychotic agents during the prior 12-week period, there was an increased RR of developing diabetes for all second-generation antipsychotics except for quetiapine. In this analysis, the RR associated with olanzapine was significantly greater than that associated with risperidone (P=0.02).
Lasser, 2004 United States	NR/NR/552	NR/NR/375	NR

Evidence Table 3. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Safety outcomes	Comments
Lambert, 2005 United States	ORs for conditional logistic regression model predicting development of hyperlipidemia 12-week exposure: n, OR, p(95% CI) clozapine: 879, 1.16, 0.07(0.99-1.37) olanzapine: 3322, 1.20, 0.00 (1.08-1.33) quetiapine: 322, 1.01, 0.92(0.78-1.32) risperidone: 2612, 1.00, 0.98(0.90-1.12) 24-week exposure: n, OR, p(95% CI) clozapine: 766, 1.22, 0.03(1.03-1.45) olanzapine: 2935, 1.24, <0.0001 (1.12-1.38) quetiapine: 243, 0.83, 0.25(0.61-1.13) risperidone: 2365, 1.01, 0.91(0.90-1.13) 52-week exposure: n, OR, p(95% CI) clozapine: 603, 1.20, 0.06(0.99-1.46) olanzapine: 2036, 1.17, 0.01 (1.04-1.32) quetiapine: 140, 0.80, 0.27(0.53-1.20) risperidone: 1819, 0.94, 0.34(0.83-1.27)	
Lambert, 2006 United States	NR	
Lasser, 2004 United States	patients with >= 7% weight increase olanzapine adult smokers: 25/82(30.5%) olanzapine adult nonsmokers: 16/55(29.1%) olanzapine elderly smokers: 4/27(14.8%) olanzapine elderly nonsmokers: 4/35(11.4%) risperidone adult smokers: 11/82(13.4%) risperidone adult nonsmokers: 7/43(16.3%) risperidone elderly smokers: 0/20(0%) risperidone elderly nonsmokers: 3/31(9.7%) Pearson's correlation analysis between smoking and weight: risperidone-treated patients: r = -0.037 olanzapine-treated patients: r = 0.029	

Evidence Table 3. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Data source	Prospective Retrospective Unclear	Sampling frame	Exposure period
Lee, 2002 United States	Database: Protocare Sciences' administrative claims and enrollment info	Retrospective	Index dates of patients occurred during a 27-mo period (1997-1999). Mean duration of therapy: AAPs: 126.1 ds Typical APs: 108.34 ds	Patients were observed 365 ds after their index dates.
Lee, 2006 IC-SOHO sub-study in Asian country participants 12-mo outcomes Korea, Taiwan and Malaysia	Same as Dossenbach 2004	Same as Dossenbach 2004	NR	12 mos
Leon, 1979 Colombia	Hospital Psiquiatrico, Colombia	Retrospective	6 WK	3-4 ys
Leslie, 2004 United States	Department of Veteran Affairs	Retrospective	3 mos	NR

Evidence Table 3. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Interventions mean dose	Population	Age Gender Ethnicity
Lee, 2002 United States	Clozapine Olanzapine Quetiapine Risperidone Typical APs Mean doses NR	Patients aged 18-65 selected by first (index) AP/AAP prescription between Sept 1997-Dec 1999; excluded those who filed a claim for an AP/AAP within 180 ds, or filled a Rx for a diabetes medication or had a DM diagnosis within 365 ds before index date. Also excluded patients using concomitant AP meds on index date.	Mean age 44 41.4% male Ethnicity NR
Lee, 2006 IC-SOHO sub-study in Asian country participants 12-mo outcomes Korea, Taiwan and Malaysia	Same as Dossenbach 2004	IC-SOHO patients from participating Asian countries	Mean age=34.7 ys 50% male 100% Asian
Leon, 1979 Colombia	NR	Schizophrenia	Mean age: 30.6 ys 58% male Ethnicity NR
Leslie, 2004 United States	Clozapine, olanzapine, quetiapine, risperidone: mean doses NR	Schizophrenia	NR/NR/NR

Evidence Table 3. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Exposed Eligible Selected	Withdrawn Lost to follow-up Analyzed	Effectiveness outcomes
Lee, 2002 United States	NR 2315 2315 AAPs n=1334 Olanzapine n=513 Risperidone n=750 Clozapine n=5 Quetiapine n=66 Typical APs n=981	NR NR 2315 analyzed	NR
Lee, 2006 IC-SOHO sub-study in Asian country participants 12-mo outcomes Korea, Taiwan and Malaysia	1256/NR/898	100 (11%)/0 lost to fu/analyzed unclear	Response rates (overall CGI-S score improved by ≥ 2 points from a baseline score of ≥ 4, or improved by ≥ 1 point from a baseline score of 3): Olanzapine=76.3% Risperidone=72.7% Typical antipsychotics=50% OR of response for typical agent vs olanzapine: 0.38 (p=0.010) (CI NR)
Leon, 1979 Colombia	NR/NR/50	NR/NR/39	Mean number of required re-hospitalizations: clozapine: 1.89 vs chlorpromazine: 3.52; P<0.01 Average time spent in hospital: clozapine: 44.8 ds vs chlorpromazine: 272.8 ds; P<0.05 Average mean time for re-admission: clozapine: 260 ds vs chlorpromazine: 229
Leslie, 2004 United States	56,849/56,849/56,849	0/0/56,849	NR

Evidence Table 3. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Safety outcomes	Comments
Lee, 2002 United States	Adjusted odds (95%CI) of diabetes onset within 1-y after index date: Atypicals vs typicals: 1.01 (0.61-1.67) Olanzapine vs typicals: 0.86 (0.43-1.73) Risperidone vs typicals: 1.07 (0.61-1.89) Olanzapine vs risperidone 0.79 (0.38-1.61)	
Lee, 2006 IC-SOHO sub-study in Asian country participants 12-mo outcomes Korea, Taiwan and Malaysia	<u>Tardive dyskinesia</u> % patients: olanzapine=7.9% risperidone=13.3% typicals=13% OR (95% CI): risperidone vs olanzapine=1.04(0.34-3.14) typicals vs olanzapine=4.23(1.02, 17.47) typicals vs risperidone=4.08(0.83, 19.94)	
Leon, 1979 Colombia	NR	
Leslie, 2004 United States	7.3% diagnosed with diabetes will on treatment Highest risk: clozapine: 2.03%, quetiapine: 0.80%, olanzapine: 0.63%, risperidone: 0.05%	

Evidence Table 3. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Data source	Prospective Retrospective Unclear	Sampling frame	Exposure period
Lin, 2006 Taiwan	Chart reviews	Retrospective	7/1/01-6/30/02	2 ys
Lindstrom, 2007, Sweden	Patients enrolled in a national, multicenter, point-prevalence, 5-y longitudinal Phase IV trial	Prospective	1995-2000	Variable

Evidence Table 3. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Interventions mean dose	Population	Age Gender Ethnicity
Lin, 2006 Taiwan	Clozapine, risperidone, typical antipsychotics	Schizophrenia	82% male Mean age=39.2 ys 100% Taiwanese
Lindstrom, 2007, Sweden	NR	Patients with schizophrenia or a related disorder according to DSM-IV and treated with risperidone as the main antipsychotic drug for at least 1 mo. During the following 5 ys, some patients were switched to other antipsychotic compounds or were drug-free Males and females >18y; in- and out-patients; responders or partial responders to antipsychotic drugs	Background variables of all included patients (n=225) Age (y): 38.5±11.7 (range 18-79) Gender (n male): 132 Ethnicity: NR

Evidence Table 3. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Exposed Eligible Selected	Withdrawn Lost to follow-up Analyzed	Effectiveness outcomes
Lin, 2006 Taiwan	NR/NR/382	83 (22%)/NR/382	Typical antipsychotic vs clozapine vs risperidone: 360 ds follow-up period Mean time to rehospitalization (ds): 244 vs 240 vs 262, p=NS Event rate: 49.6% vs 44.3% vs 43%, NS 720-d follow-up period Mean time to rehospitalization (ds): 378 vs 403, vs 426, NS Event rate: 57.7% vs 49.2% vs 53.1%, NS
Lindstrom, 2007, Sweden	Exposed:225 Eliglble:225 Selected:101	Withdrawn: NR Lost to FU: NR Analyzed: 101	

Evidence Table 3. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Safety outcomes	Comments
Lin, 2006 Taiwan	NR	
Lindstrom, 2007, Sweden	Frequency of Parkinsonism/dystonia according to the ESRS instrument over 5 ys (Score 0-1 / Score 2-4 / Score 5-6 / n): 495/574 / 240/158 / 10/13 / 745 Abnormal involuntary movements: 23 of 166 patients (14%) had TD Social Outcomes: Mean number of ds in hospital decreased from 41 to 10 ds Mean number of ds in sheltered accommodations increased from 28 to 63 Net decrease in the number of patients who lived independently from 83% to 71% One patient (of 101) had 365 hospital ds during y 5, and 9 others had any hospital ds (range 3-138) 15-26% of patients had no social contacts (except with health service staff) 29-37% reported meeting friends or peers <1 time per week 12% of patients worked or studied full-time 14% worked or studied half-time 75% were on sick leave or had disability pension Mortality: 8 patients died during the 5 y trial	

Evidence Table 3. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Data source	Prospective Retrospective Unclear	Sampling frame	Exposure period
Liperoti 2009 USA	SAGE database containing MDS; data is from 1581 nursing homes in 5 US states	Retrospective	Jan 1998-Dec 2000	6 mos following first use of any antipsychotic.
Lucey, 2003 Ireland	Irish Risperidone Olanzapine Drug Outcomes in Schizophrenia	Retrospective	Mean duration: 37.8-40.5 ds	NR
Lund, 2001 United States	Database: Iowa Medicaid prog claims/PD	Unclear	1990 to 1994	Clozapine=25.5 mos Typical APs =24.5 mos
Madhusoodanan, 1999 United States	St. John's Episcopal Hospital	Retrospective	4 mos	NR

Evidence Table 3. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Interventions mean dose	Population	Age Gender Ethnicity
Liperoti 2009 USA	Atypical antipsychotics (N=6524) Risperidone: n=4406 Olanzapine N=1563 Quetiapein N=497 Clozapine N=59 Conventional antipsychotics (N=3205), most frequently haloperidol (N=1413) and phenothiazines (N=546) Mean dose NR.	Nursing home residents with dementia, aged 65+ who were new users of antipsychotics. Excluded comorbid schizophrenia.	Mean age: 84 72% male 90.7% White 8.4% Black
Lucey, 2003 Ireland	risperidone: 4.2 mg/d olanzapine: 12.9 mg/d	Schizophrenia, schizoaffective disorder	Mean age: 37 ys 55.5% Male Ethnicity NR
Lund, 2001 United States	Clozapine Typical Antipsychotics	Schizophrenia	Mean age=41.9 59.2% male Race NR
Madhusoodanan, 1999 United States	Mean daily doses: risperidone(N=114): 3mg olanzapine(N=37): 10mg	schizophrenia, schizoaffective disorder, dementia, bipolar disorder, major depressive w/psychotic features, delusional disorder	Mean age: 71 ys 60.5% Female Ethnicity NR

Evidence Table 3. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Exposed Eligible Selected	Withdrawn Lost to follow-up Analyzed	Effectiveness outcomes
Liperoti 2009 USA	61,781 exposed 9,729 eligible (1st-time monotherapy users) All 9729 eligible were included.	No WDs. Loss to followup NR. 9729 analyzed.	NR
Lucey, 2003 Ireland	NR/396/394	0/0/396	Hospital Stay: % discharged on or before d 120: R 95% vs O 94% (NS) Mean length of study duration: O 30 ds vs R 26 d (p=0.27) Duration of hospital stay: O 40.5 vs R 37.8 (p=0.90) Distribution function curve of time to discharge: 'similar', p = 0.0.54
Lund, 2001 United States	NR 4770 3013	NR NR 3013 (clozapine=552, CAPD=2461)	NR
Madhusoodanan, 1999 United States	NR/NR/151	22%/NR/151	% of patients who responded to treatment: R: 78% vs O: 75% CGI scores: Very much/much improved: R: 78% vs O: 75% Minimally improved: R: 56% vs O: 24% No change: R: 20% vs O: 8%

Evidence Table 3. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Safety outcomes	Comments
Liperoti 2009 USA	Risk of mortality is 26% greater with haloperidol vs atypical antipsychotics. Effect of conventional APs on increased mortality seen only in non-Alzheimer's dementia; absent among those with Alzheimer's dementia. Mortality during 6 mos after index prescription, crude incidence per 100 person-ys: Atypical antipsychotics: 40.0 Conventional antipsychotics: 54.3 HR for conventional vs atypical APs adjusted for age, race/ethnicity, gender, BMI, ADL score, Cognitive Performance Scale score, severity of behavioral symptoms, CV and cerebrovascular comorbidities, and use of concomitant medications (including CV drugs, aspriin/sntiplatelets/anticoagulants, benzodiazepines, and antidepressants: Residents with Alzheimer's Disease, HR = 1.02 (95%CI 0.75-1.39) Residents with other dementias (non-Alzheimer's), HR = 1.31 (95%CI 1.14,1.50) Haloperidol vs risperidone, adjusted HR: 1.31 (95%CI 1.13-1.53). Mortality was similar among AAPs.	
Lucey, 2003 Ireland	NR	
Lund, 2001 United States	Diabetes Total cohort 21 (4%) vs 78 (3.4%); p=0.62 Patients aged 20-34 11/222 (5%) vs 15/768 (2%) RR 2.5, 95% CI 1.2 to 5.4	
Madhusoodanan, 1999 United States	AEs reported: R: 20%; EPS, tremor, sedation, hypotension, diarrhea, tardive dyskinesia, chest pain, anxiety, restlessness, itching, insomnia and fall O: 16%; sedation, EPS, postural hypotension	

Evidence Table 3. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Data source	Prospective Retrospective Unclear	Sampling frame	Exposure period
McIntyre, 2003 Williams, 2006 Canada Canadian National Outcomes Measurement Study in Schizophrenia (CNOMSS)	Naturalistic: 32 university and community sites across Canada	Prospective	June 1999 and November 2000	
Medved , 2009 Croatia	cohort of patients admitted to the Department of Psychiatry, Zagreb University Hospital Centre	Prospective	2004 to 2007	3 mos

Evidence Table 3. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Interventions mean dose	Population	Age Gender Ethnicity
McIntyre, 2003 Williams, 2006 Canada Canadian National Outcomes Measurement Study in Schizophrenia (CNOMSS)	Olanzapine 14.7 mg Quetiapine=324mg Risperidone=3.5 mg	Consecutive outpatients with schizophrenia, schizophreniform disorder, schizoaffective disorder, or psychosis NOS	Mean age=36.8 67.9% male Race NR
Medved , 2009 Croatia	Orally administered olanzapine 5-20 mg/d or risperidone 2-5 mg/d for 3 mos (±1 week) during 3-6 WK of hospital treatment and followed by outpatient treatment. Mean olanzapine dose (SD): 11.51 (3.9) Mean Risperidone dose (SD): 3.16 (1.09)	Patients who were previously unmedicated (no antipsychotic medication) prior to admission and were diagnosed with DSM-IV schizophrenia spectrum disorders (DSM-IV criteria met for schizophrenia, schizoaffective disorder or delusional disorder, and no other neurological diseases, mental disorders, drug and alcohol abuse and eating disorders). Patients with menstrual cycle irregularities, pregnant, lactating or required treatment with medications other than diazepam and clonazepam for occasional insomnia were not included.	Mean age (SD): 31.07 (7.86) 100% female 100% Caucasian

Evidence Table 3. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Exposed Eligible Selected	Withdrawn Lost to follow-up Analyzed	Effectiveness outcomes
McIntyre, 2003	NR	NR	Admission to hospital for any reason: n/N (%)
Williams, 2006	NR	NR	Initial assessment to y 1; y 2
Canada	243	243 analyzed	
	(Olanzapine=109,		Clozapine: 9/59 (15.2%); 12/51 (23.5%)
Canadian National	Quetiapine=23,		Olanzapine: 7/87 (8%); 9/70 (12.8%)
Outcomes Measurement	Risperidone=111)		Quetiapine: 5/20 (25%); 5/16 (31%)
Study in Schizophrenia			Risperidone: 10/97 (97%); 14/80 (17.5%)
(CNOMSS)			
Medved , 2009	NR/NR/94	0/0/94	NR
Croatia			

Evidence Table 3. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Safety outcomes	Comments
McIntyre, 2003 Williams, 2006 Canada Canadian National Outcomes Measurement Study in Schizophrenia (CNOMSS)	Mean weight gain (kg) Olanzapine=3.72 Quetiapine=7.55 Risperidone=1.62 ≥ 7% weight gain (% pts) Olanzapine=24.1% Quetiapine=55.6% Risperidone=23.7% Quetiapine vs risperidone=OR 3.62, 95% CI 1.02 to 12.83 ≥ 10% weight gain (% pts) Olanzapine=18.5% Quetiapine=38.9% Risperidone=13.2% Quetiapine vs risperidone=OR 3.91; 95% CI 1.02 to 15.08	
Medved , 2009 Croatia	Olanzapine: 10 (19%) drowsiness; 1 (2%) extrapyramidal syndrome (EPS); 1 (2%) edema Risperidone: 6 (16%) drowsiness; 2 (5) galactorhea; 1 (2.4%) EPS 27% patients with metabolic syndrome after 3-mo compared to 15% of patients at baseline. Increase in BMI (SD) of 2.44 (3.01). "BMI was found to be a significant predictor of metabolic syndrome after second-gereration antipsychotics treatment"; P<0.001	

Evidence Table 3. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Data source	Prospective Retrospective Unclear	Sampling frame	Exposure period
Meyer, 2002 United States	Oregon State Hospital	Retrospective	July and August 1999	1 y
Miller, 1998 United States	Innsbruck University Clinics, Austria	Retrospective	>3 mos	NR
Mladsi, 2004 United States	Three acute care inpatient mental health facilities	Retrospective	May 1, 1998 and June 30, 2000	Length of stay- less than 30 ds
Mohamed, 2009 United States	Database: National ADs; and the Veterans Affairs Drug Benefit Management System files	Retrospective	2006	2 y follow-up

Evidence Table 3. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Interventions mean dose	Population	Age Gender Ethnicity
Meyer, 2002 United States	risperidone (N=47): 4.5 mg/d olanzapine (N=47): 16.7 mg/d	Schizophrenia, schizoaffective disorder	Mean age:44.5 ys 41% 87% Male Ethnicity NR
Miller, 1998 United States	clozapine: 425.6 mg/d risperidone: 4.7 mg/d conventional antipsychotics: 476.5 mg/d	Schizophrenia, schizoaffective disorder, personality disorder, paranoid subtype	Mean age: 36.6 ys 57.5% Male White: 71.7% Black: 2.6% Hispanic: 3.8% Asian: 1.9%
Mladsi, 2004 United States	Risperidone 4.45 mg Olanzapine 14.04 mg Quetiapine 350.33 mg	Schizophrenia 59% Schizoaffective 41%	Mean age 40 ys 62% male 52% white 39% black 9% other
Mohamed, 2009 United States	Long-acting injectable risperidone or oral antipsychotics	All veterans seen at Veterans Affairs medical centers nationally who received a prescription for any new antipsychotic medication during fiscal y 2006 and had a diagnosis of schizophrenia. Prescriptions were considered new if there were no prescriptions for the drug during the last 6 mos of fiscal y 2005.	32.4% at age 40-49 ys 48.9% at age 50-64 ys 8.6% at age >65 ys 93.4% male 21.5% Black 5.1% Hispanic 1.1% Other 20% unknown race

Evidence Table 3. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Exposed Eligible Selected	Withdrawn Lost to follow-up Analyzed	Effectiveness outcomes
Meyer, 2002 United States	NR/396/394	Withdrawn=N/A (retrospective) Lost to follow-up=N/A (retrospective) Analyzed=94	Fasting triglyceride levels at one y: R: mean increase of 29.7 mg/dL vs O: 88.2 mg/dL Weight increases at one y: R: 11.7-13.9lb vs O: 15.0-26.0lb
Miller, 1998 United States	NR/NR/NR	0/0/106	Simpson-Angus Scale scores: Akinesia>0: C: 17.1% vs R: 30.4% vs Conventionals: 38.1% Arm dropping>0: C: 12.2% vs R: 30.4% vs Conventionals: 35.4% Gait>0: C: 4.9% vs R: 21.7% vs Conventionals: 23.8% Salivation>0: C: 36.6% vs R: 8.7 vs Conventionals: 4.8% Tremor>0: C: 19.5 vs R: 21.7% vs Conventionals: 40.5%
Mladsi, 2004 United States	NR NR 327	NA NA 327	Mean length of stay was 12.4 ds (SD 6.5) for risperidone patients, 11.3 ds (SD 5.7) for olanzapine patients, and 13.7 ds (SD 6.5) for quetiapine GAF scores at discharge (45.9 [SD 10.3] for risperidone, 46.2 [SD 10.1] for olanzapine, and 44.3 [12.2] for quetiapine)
Mohamed, 2009 United States	11821/11821/11821	0/0/11821	Hazard ratio for discontinuing antipsychotics as compared to LA injectiable risperidone: Aripiprazole: 2.76; P=0.0001 Clozapine: 0.37; P=0.0001 Conventional: 0.83; P=0.0003 Olanzapine: 0.83; P=0.0017 Quetiapine: 0.78; P=0.0001 Risperidone: 0.83; P=0.0002 Ziprasidone: 0.96; P=0.5516

Evidence Table 3. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Safety outcomes	Comments
Meyer, 2002 United States	Triglycerides: O: + 104.8 mg/dL vs R: +31.7 mg/dL (P=.037) Cholesterol: O: +30.7 mg/dL vs R: +7.2 mg/dL (P=.004) Glucose: O: +10.8 mg/dL vs R: +0.74 mg/dL (P=.030)	
Miller, 1998 United States	Point prevalence of Akathisia: C: 7.3% vs R: 13% vs Conventionals: 23.8% Point prevalence of Rigidity: C: 4.9% vs R: 17.4% vs Conventionals: 35.7% Point prevalence of Cogwheeling: C: 2.4% vs R: 17.4% vs Conventionals: 26.2%	
Mladsi, 2004 United States	NR	
Mohamed, 2009 United States	NR	

Evidence Table 3. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Data source	Prospective Retrospective Unclear	Sampling frame	Exposure period
Moisan, 2005 Canada	Database from the Prescription Drug Insurance Plan administered by the Quebec Health Insurance Board	Retrospective	January 1, 1997-August 31, 1999	NR

Evidence Table 3. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Interventions mean dose	Population	Age Gender Ethnicity
Moisan, 2005 Canada	Olanzapine Risperidone	All drug beneficiaries who had received at least one prescription of an atypical antipsychotic drug during the time period and was under the age of 65.	% in each age group: 0-29 ys=20.4 30-44 ys=43.8 45-59 ys=29.9 60-64 ys=6.0 % male: 51.5

Evidence Table 3. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Exposed Eligible Selected	Withdrawn Lost to follow-up Analyzed	Effectiveness outcomes
Moisan, 2005 Canada	38043/19582/19582	NR/NR/19582	Those taking olanzapine were more likely to need to be started on a diabetic and/or lipids medication than those taking risperidone

Evidence Table 3. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Safety outcomes	Comments
Moisan, 2005 Canada	NR	

Evidence Table 3. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Data source	Prospective Retrospective Unclear	Sampling frame	Exposure period
Montes, 2003 Spain Sub-group Analysis from Estudio Farmacoepidemiologico en la Esquizofrenia con Olanzapine (EFESO)	Multicenter Controlled	Subjects that required antipsychotic treatment for a first episode of schizophrenia, with an evolution of the illness of less than one y and who were not over the age of 40. Choice of new drug was made by the treating physician.	6 mos	
Mullins 2008 Maryland	All pharmacy and medical service encounter and fee-for-service claims from the Maryland Medicaid FFS and HealthChoice progs	Retrospective	January 1, 2001 to December 31, 2003	

Evidence Table 3. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Interventions mean dose	Population	Age Gender Ethnicity
Montes, 2003 Spain Sub-group Analysis from Estudio Farmacoepidemiologico en la Esquizofrenia con Olanzapine (EFESO)	Olanzapine 13.5 mg Risperidone 5.4 mg Haloperidol 12.4 mg	Weight gain	Mean age=24.2 64.8% male Race NR
Mullins 2008 Maryland	NR	Maryland Medicaid recipients aged 18-64 having a claim for schizophrenia any time during the three y study period for any of the 5 atypicals (aripiprazole, olanzapine, quetiapine, risperidone, or ziprasidone)	Aripiprazole/Olanzapine/Quetiapine/Risperidone/ Ziprasidone Age Group (%) 18-39: 39.9/43.5/41.9/41.7/49.9 40-54: 48.4/44.5/47.1/46.5/42.1 55-64: 11.7/12.0/11.0/11.8/8.0 Gender (% male) 52.2/54.1/47.6/46.9/49.1 Ethnicity White: 53.6/39.1/47.5/38.5/48.7 Black: 46.4/60.9/52.5/61.5/51.3

Evidence Table 3. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Exposed Eligible Selected	Withdrawn Lost to follow-up Analyzed	Effectiveness outcomes
Montes, 2003 Spain Sub-group Analysis from Estudio Farmacoepidemiologico en la Esquizofrenia con Olanzapine (EFESO)	NR NR 182	45 (24.7%) withdrawn 24 (13.2%) lost to fu 182 analyzed	NR
Mullins 2008 Maryland	NR NR 5898 (1705 olanzapine, 1580 risperidone, 1467 quetiapine, 700 ziprasidone, 466 aripiprazole)	NR NR 5898 (1705 olanzapine, 1580 risperidone, 1467 quetiapine, 700 ziprasidone, 466 aripiprazole)	Hazard ratios of discontinuation (95% CI), P value: Olanzapine: reference Aripiprazole: 1.047 (0.919-1.193), 0.4911 Quetiapine: 1.130 (1.039-1.230), 0.0044 Risperidone: 0.973 (0.897-1.055), 0.5014 Ziprasidone: 0.990 (0.891-1.100), 0.8514 Age: 0.997 (0.994-1.000), 0.0348 Black: 1.058 (0.994-1.127), 0.785 Male: 0.899 (0.845-0.957),0.0008 Psychiatric hospitalization: 1.276 (1.192-1.367), <0.0001 Concurrent medications: 0.225 (0.210-0.241), <0.0001 Adjusted medication continuation/discontinuation rates: Median time to discontinuation (d)/180-d continuation rate (%)/365-d continuation rate (%) Aripiprazole: 58/19.1/9.0 Olanzapine: 59/20.6/10.0 Quetiapine: 54/16.8/7.4 Risperidone: 61/21.5/10.7 Ziprasidone: 59/20.9/10.3

Evidence Table 3. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Safety outcomes	Comments
Montes, 2003 Spain Sub-group Analysis from Estudio Farmacoepidemiologico en la Esquizofrenia con Olanzapine (EFESO)	Weight gain (% patients) Olanzapine=15 (13.2%) Risperidone=1 (3.2%) Haloperidol= 0 p<0.05 for olanzapine > risperidone and haloperidol groups	First Episodes
Mullins 2008 Maryland	NR	

Evidence Table 3. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Data source	Prospective Retrospective Unclear	Sampling frame	Exposure period
Novick, 2005 SOHO (secondary publication) Europe	Prospectively collected, multicenter study data	Prospective	6 mo (interim analysis of planned 3-yr term)	NR
Ollendorf, 2004 United States	Database: PharMetrics Patient-Centric Database	Retrospective	1995-2001 Mean duration of therapy was 9 mos in both typical AP and AAP groups; mean number of prescriptions was higher in AAP group: 8.5 vs 6.6, p<0.0001	Minimum of 3 mos; mean 435 ds
Opolka, 2003 United States	Medical claims data from the Texas Medicaid Management Information System and pharmacy claims data from the Texas Vendor Drug Prog paid prescription claims database	Retrospective	January 1, 1996 to August 31, 1999	NR

Evidence Table 3. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Interventions mean dose	Population	Age Gender Ethnicity
Novick, 2005 SOHO (secondary publication) Europe	Olanzapine 11.8 mg/d (SD 5.7) Risperidone 4.9 mg/d (SD 2.7) Quetiapine 375 mg/d (SD 201) Clozapine 235 (SD 134)	Schizophrenics receiving antipsychotic monotherapy	Mean age 39.6 yrs 57% male Ethnicity NR
Ollendorf, 2004 United States	Olanzapine n=937 Risperidone n=690 Quetiapine n=164 Clozapine n=35 Mean dose NR	Patients with ≥1 medical claims with a diagnosis of schizophrenia, as well as ≥1 paid pharmacy claims for an AP medication during 1996-2001; the first observed antipsychotic pharmacy claim in this period was the index date. All medical and pharmacy claims were then compiled for these patients for the exposure period. Patients who used an AP or typical AP in the 6 mos prior to the index date, or had evidence of DM within 12 mos prior to the index date were excluded.	Mean age 39.1 48.2% male Ethnicity NR
Opolka, 2003 United States	Haloperidol Risperidone Olanzapine	Schizophrenia, schizoaffective disorder	Mean age: NR Gender: NR 45% White 39% African American

Evidence Table 3. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Exposed Eligible Selected	Withdrawn Lost to follow-up Analyzed	Effectiveness outcomes
Novick, 2005 SOHO (secondary publication) Europe	10972/8057/6931 (olanzapine, risperidone, quetiapine and clozapine cohorts only)	765/NR/6931 (olanzapine, risperidone, quetiapine and clozapine cohorts only)	NR
Ollendorf, 2004 United States	18,134 2443 2443	NR NR 2443	NR
Opolka, 2003 United States	NR/NR/3583	NR/NR/3583	Adherence to index antipsychotic Risperidone users were 15% less adherent than olanzapine users (30 ds less use/study period, P<0.001) Haloperidol users were 33% less adherent than olanzapine users (65 ds less use/study period, P<0.001) and 21% less adherent than risperidone users (35 ds less use/study period, P<0.001) African Americans were 12% less adherent than whites (24 ds less use/study period, P<0.001) Mexican Americans were 13% less adherent than whites (25 ds less use/study period, P=0.003) and 1% less adherent than African Americans (2 ds less use/study period, P=0.838)

Evidence Table 3. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Safety outcomes	Comments
Novick, 2005 SOHO (secondary publication) Europe	Proportion of pts reporting weight gain: O 2993/4428 (67.6%) v R 946/1617 (58.5%) v Q 300/610 (49.2%) v C 157/276 (56.9%) Subgroup: concomitant medication use - proportion of pts reporting weight gain: O 1772/2546 (69.6%) v R 581/972 (59.8%) v Q 183/373 (49.1%) v C 118/183 (64.5%)	
Ollendorf, 2004 United States	Patients treated with AAPs had an increased risk of diabetes mellitus after 1 y, compared with typical APs: hazard ratio 1.17, 95% CI 1.06-1.30 No differences between olanzapine, risperidone, quetiapine, and clozapine were found on risk of diabetes.	This analysis controlled for total duration of therapy and number of prescriptions. Actual mean doses are NR.
Opolka, 2003 United States	NR	

Evidence Table 3. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Data source	Prospective Retrospective Unclear	Sampling frame	Exposure period
Pelagotti, 2004 Italy	Inpatients to a hospital Psychiatric Unit or as outpatients to a Psychiatric Ambulatory Clinic.	Retrospective	15 May 2002 to 20 August 2002	Median 11.9 mos
Perez, 2008, Spain	77 acute hospital units in Spain	Prospective	March 2002 - October 2004	Acute: admission to discharge, and Long-term: discharge to 12 mos

Evidence Table 3. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Interventions mean dose	Population	Age Gender Ethnicity
Pelagotti, 2004 Italy	Olanzapine daily dose (mg) 13.3 (n=283) Risperidone daily dose (mg) 5.7 (n=170)	Diagnosis of schizophrenia; > 18 ys; treatment with either olanzapine or risperidone at the date of enrollment; ''Stable'' therapy over the previous 4 mos; Cumulative dose in this period of at least 80% of the respective defined daily doses (DDD values: olanzapine, 10 mg/d; risperidone, 5 mg/d).	Mean age 40 ys 61.8% male Race NR
Perez, 2008, Spain	Mean doses at discharge: quetiapine = 719.6 mg/d risperidone = 8.0 mg/d Mean doses at 12 mos: quetiapine = 718.5 mg/d risperidone = 7.0 mg/d	Patients admitted to an acute unit with schizophrenia, schizophreniform or schizoaffective disorder who were prescribed quetiapine or risperidone within the first week of treatment	**Quetiapine/Risperidone:** Mean age: 37.2/36.4 Gender (% male): 63.6/67.8 Ethnicity: NR

Evidence Table 3. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Exposed Eligible Selected	Withdrawn Lost to follow-up Analyzed	Effectiveness outcomes
Pelagotti, 2004 Italy	454/NR/144	NR/NR/144	Dropout rate in the primary analysis (with a follow-up of 7 mos: 4 switches from olanzapine to risperidone vs 11 switches from risperidone to olanzapine, P = 0.01) and in the secondary analysis (with a follow-up longer than 7 mos: 9 switches from olanzapine vs risperidone and 17 switches from risperidone to olanzapine; P = 0.004).
Perez, 2008, Spain	NR 492 Selected: Intent to Treat population: 466 (quetiapine=345, risperidone=121) Per protocol population: 422 (quetiapine=311, risperidone=111) Safety population: 470 (quetiapine=349, risperidone=121)	**Quetiapine/Risperidone:** **Withdrawn: NR** **Lost to FU:** **time of discharge: 43/9** **6-mo follow-up: 89/28** **12-mo follow-up: 31/13** **Analyzed:** **baseline: 345/121** **time of discharge: 324/116** **6-mo follow-up: 235/88** **12-mo follow-up: 204/75**	

Evidence Table 3. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Safety outcomes	Comments
Pelagotti, 2004 Italy	NR	
Perez, 2008, Spain		

Evidence Table 3. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Data source	Prospective Retrospective Unclear	Sampling frame	Exposure period
Peuskens 2009 Belgium	Participants were recruited from university hospitals, general and psychiatric hospitals and ambulatory practice	Prospective	2 ys	Haloperidol/Olanzapine/Risperidone Mean treatment duration (d) based on 294 patients: 476±248/545±232/513±257
Philippe, 2005 France	Principal public psychiatric care units in France	Prospective	1993 to 2002	Nine ys

Evidence Table 3. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Interventions mean dose	Population	Age Gender Ethnicity
Peuskens 2009 Belgium	Haloperidol/Olanzapine/Risperidone Mean dose (mg/d) based on 294 patients: 8.9±6.8/14±6/4.2±1.9	Adults diagnosed with schizophrenia or schizophreniform disorder and stabilized with haloperidol/haloperidol decanoate, olanzapine or risperidone monotherapy ≤ 1 mo following discharge from full-time (maximum 6 mo) hospitalization due to first episode of schizophrenia or psychotic relapse	Haloperidol/Olanzapine/Risperidone Age (y): 41.8±14.4/37.2±13.1/35.7±13.2 Gender (% male): 81/66/59 Ethnicity: NR
Philippe, 2005 France	Conventional antipsychotics Risperidone Olanzapine Clozapine Amisulpride	ICD-10 criteria for schizophrenia and to be between 18 and 64 ys old Patients hospitalized for more than 1 y were excluded	Mean age 39.4 ys Male 64% Ethnicity NR

Evidence Table 3. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Exposed Eligible Selected	Withdrawn Lost to follow-up Analyzed	Effectiveness outcomes
Peuskens 2009 Belgium	NR NR 323	7 84 273 (1-y follow-up), 219 (2-y follow-up)	294/323 patients (91%) had ≥1 follow-up visit Mean follow-up time of these 294 patients was 597±219 ds (haloperidol), 630±186 ds (olanzapine), and 640±200 ds (risperidone), P=0.026 Haloperidol/Olanzapine/Risperidone Continuation rates (%) after 2 ys: ≥1 post-baseline visit: 88/92/92 Completers: 59/66/71 Stable: 47/68/61 Stable completers: 31/50/43 Allocated to treatment group but longer on another drug: 13/10/15 Switches: 39 (1-2 switches per patient)/23 (1-5 switches per patient)/31 (1-4 switches per patient) Of 323 patients, 63% had no antipsychotic treatment switch or addition (stable patients) There were 328 hospitalizations in 150 patients, of which 47 were hospitalized once (15%), and 83 were hospitalized 2-8 times (26%) 165 were never hospitalized (51%); 28 had no follow-up data (9%) Full-time hospitalization (%): 50/44/35 (NS) Time to first rehospitalization (d): 123±168/215±189/209±184 (NS) Duration of full-time hospitalization: 94±166/48±91/55±122 Social status, living environment and employment all remained stable over the 2-y study
Philippe, 2005 France	NR/NR/3470	NA/NA/3470	At baseline, 2.2% of schizophrenic patients in the study cohort already had a diagnosis of diabetes vs.. an age and gender matched sample of the general population (1.5%). Incidence of diabetes from 1993 to 2002 Conventional antipsychotic 2.8% Risperidone 2.4% Olanzapine 2.7% Clozapine 2.1% Amisulpride 2.4%

Evidence Table 3. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Safety outcomes	Comments
Peuskens 2009 Belgium	Haloperidol/Olanzapine/Risperidone AEs Weight gain Mean baseline weight (kg): 79.2±12.5/74.9±13.9/75.3±14.2 Overall weight gain (kg): NR/2.6/2.6 P<0.05 (olanzapine and risperidone) Patients with weight gain >7% (%): 19/29/33 Weight gain of patients who dropped out from study: 1.5±4.1 kg/y Weight gain of patients who remained in study: 1.7±9.0 kg/y 5 patients died	N for haloperidol group was small, plus the group differed from the other groups in marital, institutionalized, and educational status
Philippe, 2005 France	The standard mortality ratio was 3.6 (95% CIs: 3.3 and 4.0), indicating a risk of death for schizophrenic patients in the study between three and four times higher than that of the general population.	

Evidence Table 3. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Data source	Prospective Retrospective Unclear	Sampling frame	Exposure period
Procyshyn, 1998 Canada	Chart review from Riverview Hospital in British Columbia	Retrospective	6 WK	NR
Rascati, 2003 United States	Database: Texas Department of Health Medicaid Prog	Retrospective	January 1996 through August 1999	1 y
Remington, 2001 Canada	Hospital records from the Schizophrenia and Continuing Care Prog at the Centre for Addiction and Mental Health	Retrospective	>18 mos (1993-1995)	NR

Evidence Table 3. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Interventions mean dose	Population	Age Gender Ethnicity
Procyshyn, 1998 Canada	Mean Doses: risperidone: 5.3mg/d vs olanzapine: 14.5mg/d	Aged < 65 ys, schizophrenia or schizoaffective disorder, discharged from hospital or >120 ds follow-up in hospital, Types of Schizophrenia: catatonic, disorganized, paranoid, undifferentiated, residual, schizoaffective disease, other schizophrenia	Mean Age: 37 ys 57.5% Male Ethnicity NR
Rascati, 2003 United States	olanzapine: 12.87mg/d risperidone 4.40mg/d	Schizophrenia or schizoaffective disorder	Mean age: 41.43 ys 53% female 42% Caucasian, 34% African-American, 14% Hispanic, 0.97% Asian, 0.24% Native American, & 8.32% other
Remington, 2001 Canada	Oral or depot conventional antipsychotic Clozapine Risperidone	Schizophrenia	Oral Conventional/ Depot Conventional/Clozapine/ Risperidone Mean age (ys): 31.7/36.5/33.4/31.7 % male: 55/55/66/53

Evidence Table 3. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Exposed Eligible Selected	Withdrawn Lost to follow-up Analyzed	Effectiveness outcomes
Procyshyn, 1998 Canada	2339/1901/1345 Risperidone: N=924, Olanzapine: N=977	300/0/1345	NR
Rascati, 2003 United States	NR/NR/2885	NR/NR/2885	% who discontinued medication: olanzapine=8.87% risperidone =14.5% Affects on medication choice: Region: Increase likelihood of being prescribed olanzapine by 3% to 5% when in Austin, Lubbock or Dallas vs decreased likelihood by 3% when in San Antonio or Houston Comorbid diagnosis: Having nonorganic mental illness as a comorbid diagnosis decreased likelihood of being prescribed olanzapine by 2% and having diabetes as a comorbid diagnosis also decreased likelihood of being initiated on olanzapine by 3% Previous medication use: for each antipsychotic used in the pre-period the likelihood of being started on olanzapine increased by 3.5%. If an atypical was used in the pre-period the likelihood of being initiated on olanzapine increased by 8% Schizophrenia related costs: History of clozapine use was associated with an increase of $3158 (US) per y History of depot antipsychotic use was associated with an increase of $1645 (US) per y Total health care costs: Previous hospitalization or history of clozapine use was associated with an increase of $3424 (US) per y and $2451 (US) per y, respectively
Remington, 2001 Canada	314/66/66	NR/NR/NR	No significant differences were found between groups for number of hospital visits, ds in hospital, or emergency room visits. Clozapine takers had a higher number of doctor visits compared to those taking either form of conventional antipsychotic, while risperidone takers had a higher number of doctor visits compared only to those taking oral conventional antipsychotics. CGI scores were significantly improved over the 18 mos for those treated with clozapine, risperidone, and depot conventional antipsychotics vs oral conventional antipsychotics.

Evidence Table 3. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Safety outcomes	Comments
Procyshyn, 1998 Canada	Number of Patients Discontinued: Due to Side Effects: R: 36(4%) vs O: 23(2%); P=0.70 Number of patients who experienced AE: R: 123(13%) vs O: 109(11%); P=0.20 Body as a whole: R: 8(0.9%) vs O: 13(1.3%); P=0.30 Central and peripheral nervous system: R: 73(7.9%) vs O: 56(5.7); P=0.06 Psychiatric: R: 45(4.9%) vs O: 40(4.1); P=0.40 GI: R: 21(2.3%) vs O: 13(1.3%); P=0.10 Metabolic and nutritional: R: 1(0.1%) vs O: 17(1.7%); P=0.04 Others: 27(2.9%) vs O: 17(1.7%);	
Rascati, 2003 United States	NR	
Remington, 2001 Canada	NR	

Evidence Table 3. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Data source	Prospective Retrospective Unclear	Sampling frame	Exposure period
Ren, 2006 United States	Database: VA National administrative data and VA pharmacy benefits management strategic healthcare group	Retrospective	October 1, 1998 through September 30, 1999	1 y
Rettenbacher, 2006 Austria	Laboratory measurements of included subjects	Prospective	NR	4 WK
Rettenbacher, 2011 Austria	Laboratory measurements of included subjects	Prospective	NR	Mean(SD) duration of treatment: 14.6 (9.5) weeks

Evidence Table 3. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Interventions mean dose	Population	Age Gender Ethnicity
Ren, 2006 United States	Olanzapine Risperidone	Schizophrenia either paranoid type, disorganized type, catatonic type, undifferentiated type, residual type, schizophreniform disorder or schizoaffective disorder	Olanzapine/Risperidone: Mean age (ys)=50/50.5 % male=94.7/94.7 % Caucasian=43.7/43.9 % African-American=31.5/33.9 % Hispanic=6.9/4.7 % other ethnicity=17.9/17.6
Rettenbacher, 2006 Austria	Olanzapine Clozapine Amisulpride Ziprasidone	Schizophrenia	Age range: 18-65 ys
Rettenbacher, 2011 Austria	Clozapine, 263 mg/d Olanzapine, 16 mg/d Amisulpride, 459 mg/d Risperidone, 3.9 mg/d Quetiapine, 386 mg/d Ziprasidone, 111 mg/d Sertindole, 16.3 mg/d Zotepine, 148 mg/d Aripiprazole, 19.5 mg/d	Schizophrenia ICD-10 code, 18-65 years	Age: 35.0 Gender: 34.1% female Ethnicity NR

Evidence Table 3. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Exposed Eligible Selected	Withdrawn Lost to follow-up Analyzed	Effectiveness outcomes
Ren, 2006 United States	NR/NR/7144	NR/NR/NR	Incidence of comorbid conditions: Those initiated on risperidone had more overall comorbid conditions (2.79 vs 2.68; P<0.05) and more medical comorbid conditions (1.53 vs 1.44; P<0.05) than olanzapine initiators Incidence of concomitant medications Those initiated on olanzapine used more mood stabilizers (14.45% vs 12.42%; P<0.05) and more overall number of drugs for psychiatric conditions (0.78 vs 0.73; P<0.05) than risperidone Incidence of hospitalizations No difference was found between the treatment groups regarding individuals having at least one psychiatric hospitalization Incidence of discontinuation Initiating with olanzapine decreased the incidence of discontinuation by 12%, when adjusted for sociodemographic and clinical information
Rettenbacher, 2006 Austria	NR/NR/NR	NR/NR/35	No significant differences were found between clozapine and olanzapine-treated patients regarding changes in scores of BMI and serum lipids (P>0.2).
Rettenbacher, 2011 Austria	NR/NR/132	NR/NR/132	NR

Evidence Table 3. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Safety outcomes	Comments
Ren, 2006 United States	NR	
Rettenbacher, 2006 Austria	NR	
Rettenbacher, 2011 Austria	Clozapine vs. Risperidone vs. Olanzaapine vs. Quetiapine vs. Amisulpride vs. Ziprasidone Neutropenia, corrected incidence rates (%): 11.8 vs. 6.3 vs. 13.6 vs. 31.8 vs. 5.9 vs. 18.5; p=0.096 Eosinophilia, corrected incidence rates (%): 11.9 vs. 11.5 vs. 14.1 vs. 12.5 vs. 0 vs. 0; p=0.564	

Evidence Table 3. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Data source	Prospective Retrospective Unclear	Sampling frame	Exposure period
Ritsner, 2006 Ritsner, 2004 Israel	Sha'ar Menashe Mental Health Center Case Register	Prospective	NR	1 y
Schillevoort, 2001 Netherlands	PHARMO-database	Retrospective	90 ds	NR

Evidence Table 3. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Interventions mean dose	Population	Age Gender Ethnicity
Ritsner, 2006 Ritsner, 2004 Israel	Olanzapine 15.2 mg/d Risperidone 4.4mg/d Typical antipsychotics mean dose NR	Schizophrenia diagnosed based on DSM-IV criteria; age 18-60 ys	ITT population: Mean age=39.6 ys 76.7% male Race NR PP population (n=124) Mean age=40.0 ys 78.2% male Race NR
Schillevoort, 2001 Netherlands	haloperidol: 2.2 mg/d, risperidone: 54 mg/d, olanzapine mg/d	Schizophrenia	Mean age: 35.3 ys 48.6% Male Ethnicity NR

Evidence Table 3. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Exposed Eligible Selected	Withdrawn Lost to follow-up Analyzed	Effectiveness outcomes
Ritsner, 2006 Ritsner, 2004 Israel	150/136/133	9 (6.8%) withdrawn 4 (3%) lost to fu 124 analyzed	**Q-LES-Q index** (% change from baseline estimated from Figure 2): risperidone= +3.5% vs olanzapine= +14% vs first-generation agents= +6% vs combined therapy= -4%; 2-way ANCOVA test of treatment group effect: F=3.1, p=0.029; effect size for risperidone vs olanzapine= -0.57 **Physical health index** (% change estimated from Figure 2): risperidone= +5% vs olanzapine= +17% vs first-generation agents= +14% vs combined therapy= -2%; 2-way ANCOVA test of treatment group effect: F=2.1, p=0.15; effect size for risperidone vs olanzapine= -0.51 **Subjective feelings** (% change estimated from Figure 2): risperidone= +9.5% vs olanzapine= +20% vs first-generation agents= +7.5% vs combined therapy= -2%; 2-way ANCOVA test of treatment group effect: F=2.7, p=0.050; effect size for risperidone vs olanzapine= -0.29 **Leisure time activities** (% change estimated from Figure 2): risperidone= +13% vs olanzapine= +20.5% vs first-generation agents= +4% vs combined therapy= -2%; 2-way ANCOVA test of treatment group effect: F=3.2, p=0.026; effect size for risperidone vs olanzapine= -0.18 **Social relationships** (% change estimated from Figure 2): risperidone= +6% vs olanzapine= +14% vs first-generation agents= +8% vs combined therapy= +0.5%; 2-way ANCOVA test of treatment group effect: F=0.6, p=0.64; effect size for risperidone vs olanzapine= -0.28 **General activity** (% change estimated from Figure 2): risperidone= -3% vs olanzapine= +6% vs first-generation agents= +3.5% vs combined therapy= +4%; 2-way ANCOVA test of treatment group effect: F=0.3, p=0.84; effect size for risperidone vs olanzapine= -0.52 **Life satisfaction** (% change estimated from Figure 2): risperidone= +3.5% vs olanzapine= +26.5% vs first-generation agents= +22% vs combined therapy= +2%; 2-way ANCOVA test of treatment group effect: F=0.2, p=0.88; effect size for risperidone vs olanzapine= -0.42
Schillevoort, 2001 Netherlands	450,000/NR/848	0/0/848	NR

Evidence Table 3. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Safety outcomes	Comments
Ritsner, 2006 Ritsner, 2004 Israel	NR	
Schillevoort, 2001 Netherlands	Use of antiparkinsonian medication at baseline: R: 36.2% vs O: 40.3% vs H: 4.5%; p<0.001No significant differences found at endpoint for use of antiparkinsonian medication with antipsychotic	

Evidence Table 3. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Data source	Prospective Retrospective Unclear	Sampling frame	Exposure period
Sernyak, 2002 United States	Veterans Health Administration of the Department of Veterans Affairs (VA)	Retrospective	October 1, 1999 to September 30 1999	4 mos
Shajahan, 2009, Scotland	Chart Review: Lanarkshire, Scotland	Retrospective	2002-2007	≤5 ys
Sharif, 2000 United States	Creedmoor Psychiatric Center, Columbia University	Retrospective	12 WK	4 WK
Snaterse, 2000 Canada	Alberta Hospital Edmonton	Retrospective	12 mos	12 mos
Soholm, 2003 Denmark	Patient records from the Psychiatric University Clinic, Rigshospitalet, Copenhagen University Hospital, Denmark	Retrospective	>1997	NR

Evidence Table 3. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Interventions mean dose	Population	Age Gender Ethnicity
Sernyak, 2002 United States	Clozapine, olanzapine, risperidone, quetiapine	Patients prescribed to study drugs	Mean age: 52.6 ys 5.2% Female African-American: 25% Hispanic: 4.3%
Shajahan, 2009, Scotland	Aripiprazole (N=89): starting dose: 10.2 mg/d, max dose 18.7 mg/d; Quetiapine (N=132): starting dose 91 mg/d, max dose 422 mg/d	Diagnosed schizophrenia and related psychoses, onset of treatment with either drug after 2002, and more than one mental health contact	Mean age (Aripiprazole/Quetiapine): 39.6 ys/36.7 ys; % Male (Aripiprazole/Quetiapine): 58%/52%; Ethnicity: NR
Sharif, 2000 United States	Clozapine: 520 mg/d Risperidone: 7.5 mg/d	Schizophrenia, schizoaffective disorder	Mean age: 35.9 ys 54% Male White: 63% Black: 21% Hispanic: 13% Asian: 4%
Snaterse, 2000 Canada	Risperidone(N=35): 4.17 mg/d Olanzapine(N=21): 15.24 mg/d	Schizophrenia, schizoaffective disorder	Mean age: 38.8 ys 40.5% Female Ethnicity NR
Soholm, 2003 Denmark	1st line of treatment: conventional antipsychotic or clozapine 2nd line of treatment: atypical antipsychotic	Schizophrenia, schizotypal disorder, or schizoaffective disorder	Mean age (ys): 38.7 % male: 63

Evidence Table 3. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Exposed Eligible Selected	Withdrawn Lost to follow-up Analyzed	Effectiveness outcomes
Sernyak, 2002 United States	NR/NR/38,632	NR/NR/38,682	Analysis of Association Between Atypicals vs Typicals: 95% CI; p-value clozapine: 1.07-1.46; P<0.005 olanzapine: 1.04-1.18; P<0.002 quetiapine: 1.11-1.55; P<0.002 risperidone: 0.98-1.12; P=0.15
Shajahan, 2009, Scotland	NR/22000/221	NR NR 221 (89 aripiprazole, 132 quetiapine)	Medication discontinuation rates (Aripiprazole/Quetiapine): 45%/42% ; Time to discontinuation (Aripiprazole/Quetiapine): 103 ds/175 ds
Sharif, 2000 United States	NR/NR/24	NR/NR/24	Patients classified as responders to treatment: clozapine: 14(58%) vs risperidone: 6(25%) Response rates: Positive symptoms: clozapine: 38% vs risperidone: 17% Negative symptoms: clozapine: 29% vs risperidone: 8% Aggressive symptoms: clozapine: 71% vs risperidone: 41%
Snaterse, 2000 Canada	NR/NR/56	NR/NR/56	Time to initial response: R: 14.3 ds vs O: 30.9 ds; P<0.00001 Time to discharge: R: 36.6 ds vs 58.2 ds; P=0.0201
Soholm, 2003 Denmark	NR/71/57	NR/NR/57	Significantly more individuals were in the olanzapine group than in the risperidone group (P=0.0001) Most common diagnosis of individuals was schizophrenia 67% of those treated with newer atypical antipsychotics as the first line of treatment, stayed on treatment for the duration Those taking olanzapine had significantly fewer ds in the hospital (P=0.001)

Evidence Table 3. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Safety outcomes	Comments
Sernyak, 2002 United States	NR	
Shajahan, 2009, Scotland	NR	
Sharif, 2000 United States	Response rates: Clinical Global Impressions-Improvement scores ≤2: Global rating: R: 25% vs C: 58% Positive symptoms: R: 17% vs C: 38% Negative symptoms: R: 8% vs C: 29% Aggressivity: R: 41% vs C: 71%	
Snaterse, 2000 Canada	Re-admission rate at 12 mos: R: 31.4% vs O: 61.9%; P=0.026	
Soholm, 2003 Denmark	No significant differences were found between groups for adverse effects. The severity of extrapyramidal symptoms was generally reduced in all groups.	

Evidence Table 3. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Data source	Prospective Retrospective Unclear	Sampling frame	Exposure period
Still, 1996 United States	a 400-bed state psychiatric hospital	Prospective	April to August 1994	12 WK
Strous, 2006 Israel	Clinic visits	Prospective	NR	12 WK
Su, 2005 Taiwan	Clinic visits	Prospective	NR	3 mos
Sumiyoshi, 2004 United States	Outpatient community mental health center (Mental Health Cooperative at Nashville, TN)	Prospective (with retrospective epidemiologic survey of clinical and demographic information)	February 2001 to May 2002	NR

Evidence Table 3. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Interventions mean dose	Population	Age Gender Ethnicity
Still, 1996 United States	Patients switched from clozapine to risperidone. Risperidone titrated a week to 3mg bid. The mean dosage for the five subjects who completed 12 WK treatment is 7.6 mg at week 9 and 8 mg at week 12.	Schizophrenia or schizoaffective disorder	Mean age=41.2 ys 60% male Ethnicity: NR
Strous, 2006 Israel	Risperidone, olanzapine, clozapine	Schizophrenia or schizoaffective disorders	Mean age=36.7 58.0% male Race NR
Su, 2005 Taiwan	Olanzapine 7.9mg, risperidone 2.5mg	DSM-IV criteria for schizophrenia; poor or partial response to current antipsychotic (olanzapine or risperidone) for at least 3 mos	Mean age=35.7 53% male Ethnicity NR
Sumiyoshi, 2004 United States	Clozapine, Risperidone, Olanzapine or Quetiapine	Patients who visited the mental health center during the sampling frame and if he or she was receiving clozapine, risperidone, olanzapine or quetiapine 46.6% diagnosed with schizophrenia spectrum disorders	Mean age (SD): 42.9 (10.6) ys 56.9% male 60.3% white; 39.7% non-white

Evidence Table 3. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Exposed Eligible Selected	Withdrawn Lost to follow-up Analyzed	Effectiveness outcomes
Still, 1996 United States	NR/NR/10	5/0/5	No subjects improved after being switched to risperidone PANSS, LPCF increased from baseline, but no significant changes: patients who were switched from clozapine tended to worsen when taking risperidone (data NR) The mean total scores on the PANSS, the PANSS positive symptom subscale and the BPRS met the study's 20% criterion for a clinically significant change at week 6 through week 12 (data NR) CGI scores: 2 no change; 3 minimally worse; 4 much worse; 1 very much worse
Strous, 2006 Israel	NR/NR/131	0/0/131	NR
Su, 2005 Taiwan	NR/30/15	NR/NR/15	NR
Sumiyoshi, 2004 United States	NR/NR/116	NR/NR/116	NR

Evidence Table 3. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Safety outcomes	Comments
Still, 1996 United States	3 decreased concentration 3 impaired memory 4 irritability 3 akathisia, confusion Akathisia scale showed significant different worsening of symptoms	
Strous, 2006 Israel	Proportional increase in weight: Clozapine=6.9% Olanzapine=2.7% Risperidone=2.1% 2x3x2 ANOVA results (gender and group as between-subjects and time as within subjects factors): F(2,128)=8.52, p<0.0001 Post-hoc Tukey-HSD 2x2 comparisons: Clozapine vs olanzapine (p<0.05) and vs risperidone (p<0.05)	
Su, 2005 Taiwan	Change in Mean Body Weight in kg: Baseline/endpoint (% change) Olanzapine (after switch from risperidone): 70.1/66.1 (-6%), p=0.049 Risperidone (after switch from olanzapine): 65.9/69.9 (+6%), p=0.008 Change in BMI: Baseline/endpoint (% change) Olanzapine (after switch from risperidone): 25.7/24.2 (-6%), p=0.04 Risperidone (after switch from olanzapine): 24.8/25.9 (+4%), p=NS	
Sumiyoshi, 2004 United States	Nonparametric survival analysis indicated no statistically signifcant difference in time to onset of type 1 and type 2 diabetes mellitus between clozapine (median: 112 ds; mean (SD): 495.6 (738.4) ds), risperidone (median: 502 ds; mean (SD): 789.8 (829.9) ds), and olanzapine (median: 399 ds; mean (SD): 602.8 (574) ds). P=0.43	

Evidence Table 3. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Data source	Prospective Retrospective Unclear	Sampling frame	Exposure period
Swanson, 2004 United States	Medical records from the North Carolina site of the Schizophrenia Care and Assessment Prog	Retrospective	1997 to 1999	3 ys
Tadger, 2008, Israel	Inpatients and their files from inpatient rehabilitation and d care units	Prospective (some data was collected retrospectively, however)	NR	One y or longer for patients treated with second-generation antipsychotic agents; NR for patients treated with first-generation antipsychotics

Evidence Table 3. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Interventions mean dose	Population	Age Gender Ethnicity
Swanson, 2004 United States	Olanzapine Risperidone	Schizophrenia-related disorders	Mean age (ys): 46.1 % male: 56 % African-American: 67.7
Tadger, 2008, Israel	Typical antipsychotics, risperidone, olanzapine	Inpatients treated with second-generation antipsychotics for 1+ y (n=70), and inpatients treated with first-generation antipsychotics (n=30). 91% of subjects were diagnosed with schizophrenia, 9% were diagnosed with other psychiatric disorders.	Mean age: 47.4±12.4 ys Gender: 60% male Ethnicity: NR

Evidence Table 3. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Exposed Eligible Selected	Withdrawn Lost to follow-up Analyzed	Effectiveness outcomes
Swanson, 2004 United States	NR/NR/124	NR/NR/124	Olanzapine takers had a reduced probability of violence over time Trend toward greater compliance with medication among those who remained on olanzapine therapy for > 12 mos (OR=1.94, p=0.07)
Tadger, 2008, Israel	NR NR 100 (risperidone N=40, olanzapine N=30, typical N=30)	NR NR NR	N/A

Evidence Table 3. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Safety outcomes	Comments
Swanson, 2004 United States	NR	
Tadger, 2008, Israel	**Increase/decrease in BMI (%):** -1.00 (lost weight): typical=23.3 risperidone=17.9 olanzapine=6.9 0.00 (maintained weight): typical=50.0 risperidone=59.0 olanzapine=48.3 1.00 (gained weight): typical=26.7 risperidone=17.9 olanzapine=37.9 2.00 (gained weight): typical=N/A risperidone=5.1 olanzapine=3.4 3.00 (gained weight): typical=N/A risperidone=N/A olanzapine=3.4	

Evidence Table 3. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Data source	Prospective Retrospective Unclear	Sampling frame	Exposure period
Taylor, 2006 UK- Scotland	NR	Prospective	2002 plus 6 mo follow-up	6 mos
Taylor, 2003 UK	U.K. Risperidone Olanzapine Drug Outcomes Studies in Schizophrenia prog (RODOS-UK)	Retrospective	4 mos	NR
Taylor, 2008, Scotland	Case record review: Lankshire, Scotland	Retrospective	February 2002-June 2005	NR

Evidence Table 3. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Interventions mean dose	Population	Age Gender Ethnicity
Taylor, 2006 UK- Scotland	At 6 mos mean doses were amisulpride (n=16) 487.5mg, for clozapine (n=12) 429 mg, for olanzapine (n=65) 13.7 mg, for quetiapine (n=8) 350 mg, and for risperidone (n=56) 3.4 mg.	All patients from adolescent, adult, and old age psychiatry in the Greater Glasgow area (population -1.0 million) with a clinical diagnosis (from a senior psychiatrist) of schizophrenia or schizophreniform disorder.	Mean age 45.9 ys 51% male Ethnicity- NR
Taylor, 2003 UK	risperidone: 5.5+2.4 mg/d olanzapine: 14.1+4.7 mg/d	Schizophrenia, schizoaffective disorder	Mean age: 36.2 ys 68.5% male Ethnicity NR
Taylor, 2008, Scotland	Mean Dose for Schizophrenia (Amisulpride/Olanzapine/Quetiapine/Risperidone /Clozapine): 589/15.5/441/6.0/427 mg/d	Schizophrenia or related psychoses (aged 16-65), and initiation of treatment with SGAs after EPR reviews commenced	Mean age (Amisulpride/Olanzapine/Quetiapine/Risperidone /Clozapine): 41/40/41/43/37 ys; % Male (Amisulpride/Olanzapine/Quetiapine/Risperidone /Clozapine): 63/64/38/62/65%; Ethnicity: NR

Evidence Table 3. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Exposed Eligible Selected	Withdrawn Lost to follow-up Analyzed	Effectiveness outcomes
Taylor, 2006 UK- Scotland	NR study started with 373 patients	81/ NR/ 101	Mean change from baseline and % change CGI Amisulpride 0.85 19% Clozapine 1.80 34% Olanzapine 1.18 33% Quetiapine 0.83 11% Positive symps Amisulpride 0.55 30% Clozapine1.50 54% Olanzapine 0.9 51% Quetiapine 0.67 26% Negative symps Amisulpride 0.40 24% Clozapine 0.40 20% Olanzapine 0.26 11% Quetiapine 1.00 39% Side effects, Amisulpride 0.87 54% (1.5) Clozapine 0.10 13% Olanzapine 0.90 51% Quetiapine 1.50 53% QOL, Amisulpride 0.38 15% Clozapine 1.10 34% (1.7)Olanzapine 0.96 36% Quetiapine 1.17 31%
Taylor, 2003 UK	NR/NR/501	NR/NR/499	% of effectiveness: R: 78% vs O: 74%; P=.39 Mean time to onset of effectiveness: R: 17.6 ds vs O: 22.4 ds; P=.01 Mean ds in hospitalization: R: 58 ds vs R: 49 ds; P=.007
Taylor, 2008, Scotland	NR 11250 1464	NR NR 1464	Medication discontinuation rates (Amisulpride/Olanzapine/Quetiapine/Risperidone/Clozapine): 51/41/36/28/18%; Adjusted discontinuation rates (Amisulpride/Olanzapine/Quetiapine/Risperidone/Clozapine): 0.71/0.64/0.54/0.53/0.25; Medication discontinuation rate due to side effects (Amisulpride/Olanzapine/Quetiapine/Risperidone/Clozapine): 35/32/46/0/14%; Medication discontinuation rate due to inefficacy (Amisulpride/Olanzapine/Quetiapine/Risperidone/Clozapine): 33/28/36/73/0%; Medication discontinuation rate due to 'other' (Amisulpride/Olanzapine/Quetiapine/Risperidone/Clozapine): 32/40/18/27/86%; Mean number of ds to discontinuation (Amisulpride/Olanzapine/Quetiapine/Risperidone/Clozapine): 232/256/191/152/427 ds

Evidence Table 3. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Safety outcomes	Comments
Taylor, 2006 UK- Scotland	NR	
Taylor, 2003 UK	% of patients discontinued due to side effects: R: 3.7% vs O: 2.3% Events reported: body as a whole, central/peripheral nervous system, psychiatric, GI, metabolic/nutritional, heart rate/rhythms	
Taylor, 2008, Scotland	NR	Max doses were NR but results were discussed

Evidence Table 3. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Data source	Prospective Retrospective Unclear	Sampling frame	Exposure period
Taylor, 2009, UK	Pharmacy computer records	Retrospective	Clozapine group: March 2002-October 2006 Risperidone group: August 2002-October 2004	Clozapine/Risperidone Mean duration of treatment (mos) (mean±SD): 12.3±18.6/5.9±8.7
Tihonen, 2011 Finland	National Hospital Discharge Register	Retrospective	2000-2007	Mean: 2 years

Evidence Table 3. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Interventions mean dose	Population	Age Gender Ethnicity
Taylor, 2009, UK	Clozapine/Risperidone: Mean dose at cessation (mg/d) (mean±SD): 360±159/34.5±12.2	161 Clozapine discontinuers matched with 161 Risperidone discontinuers	Clozapine/Risperidone Age at discontinuation (mean±SD) (y): 40.0±12.6/39.9±13.1 Gender (n male): 99/99 Ethnicity (n): White: 72/61 Black (African/Caribbean): 61/79 Asian: 13/9 Mixed 15/12
Tihonen, 2011 Finland	Median doses: Haloperidol injection, 6.6 mg Olanzapine, 17mg Clozapine, 360mg Risperidone injection, 4.1mg Quetiapine, 560mg Perphenazine injection, 7.7mg Zuclopenthixol injection, 18mg Risperidone oral, 4.5mg Zuclopenthixol oral, 36mg Haloperidol oral, 5.6mg Perphenazine, 24mg	Schizophrenia, first hospitalization	Age, mean (SD): 37.8 (13.7) Gender: 38% female Ethnicity NR

Evidence Table 3. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Exposed Eligible Selected	Withdrawn Lost to follow-up Analyzed	Effectiveness outcomes
Taylor, 2009, UK	Clozapine/Risperidone Exposed: 592/277 Eligible: 224/250 Selected: 161/161	Clozapine/Risperidone Withdrawn: NR/NR Lost to FU: NR/27 Analyzed: 161/161	
Tihonen, 2011 Finland	1507/1507/1507	NA/NA/1507	Adjusted HR for All-Cause Discontinuation of antipsychotic: Any injection vs. any oral: HR, 0.41; 95%CI, 0.27-0.61; p<0.0001 Haloperidol injection vs. oral: HR, 0.27; 95% CI, 0.08-0.88; p=0.03 Perphenazine injection vs. oral: HR, 0.32; 95% CI, 0.19-0.53; p<0.0001 Risperidone injection vs. oral: HR, 0.44; 95% CI, 0.31-0.62; p<0.0001 Zuclopenthixol injection vs. oral: HR, 0.75; 95% CI, 0.29-1.89; p=0.54 Adjusted HR for Rehospitalization, injection vs. oral: Any injection vs. any oral: HR, 0.36; 95%CI, 0.17-0.75; p=0.007 Haloperidol injection vs. oral: HR, 0.12; 95% CI, 0.01-1.13; p=0.06 Perphenazine injection vs. oral: HR, 0.53; 95% CI, 0.22-1.28; p=0.16 Risperidone injection vs. oral: HR, 0.57; 95% CI, 0.30-1.08; p=0.09 Zuclopenthixol injection vs. oral: HR, 0.49; 95% CI, 0.11-2.14; p=0.35 Adjusted HR for Rehospitalization (oral risperidone reference): Haloperidol, injection: HR, 0.21; 95%CI, 0.03–1.60; p= 0.13 Clozapine: HR, 0.48; 95%CI, 0.31–0.76; p=0.001 Olanzapine: HR, 0.54; 95%CI, 0.40–0.73; p <0.0001 Risperidone, injection: HR, 0.57; 95%CI, 0.30–1.08; p=0.09 Perphenazine, injection: HR, 0.59; 95%CI, 0.31–1.12; p=0.11 Zuclopenthixol, injection: HR, 0.95; 95%CI, 0.37–2.44; p=0.92 Perphenazine, oral: HR, 1.11; 95%CI, 0.57–2.18; p=0.76 Quetiapine: HR, 1.11; 95%CI, 0.75–1.64; p=0.60 Haloperidol, oral: HR, 1.79; 95%CI, 0.63–5.09; p=0.28 Zuclopenthixol, oral: HR, 1.93; 95%CI, 0.57–6.58; p=0.29

Evidence Table 3. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Safety outcomes	Comments
Taylor, 2009, UK	Death as a reason for discontinuation (n, (%)): Clozapine/Risperidone/OR (95% CI)/McNemar's x2, df=1 21 (13.0)/3 (1.9)/7 (2.09-23.5)/13.5 (p=0.0003) Clozapine/Risperidone: Mortality rate: 8.5 (95%CI 5.53-13.07) per 1000 patient ys/5.3 (95% CI 1.7-16.61) per 1000 patient ys	Funder: Janssen-Cilag, Novartis, IVAX
Tihonen, 2011 Finland	NR	

Evidence Table 3. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Data source	Prospective Retrospective Unclear	Sampling frame	Exposure period
Tiihonen, 2006 Finland	Community care	Prospective	1996-2001	3.6 ys
Tiihonen, 2009 Finland	National Hospital Discharge Register	Retrospective	January 1, 1996 to 2006 (because prescription data are available only after 1995)	11-y follow-up with average of 8.6 ys

Evidence Table 3. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Interventions mean dose	Population	Age Gender Ethnicity
Tiihonen, 2006 Finland	Olanzapine, clozapine, risperidone, oral perphenazine, thioridazine, perphenazine depot, chlorprothixene, chlorpromazine, haloperidol, and levomepromazine	All people in Finland who were hospitalized because of a diagnosis of schizophrenia or schizoaffective disorder; index ages 15-45 ys	Mean age 30.7 ys 62% male Ethnicity or race NR
Tiihonen, 2009 Finland	First generation and second generation antipsychotic drugs either as monotherapy or combinations, as well as no therapy	All patients in Finland who were admitted with a diagnosis of schizophrenia from Jan 1, 1973, to Dec 31, 2004	Mean age: 51 ys 46.1% male

Evidence Table 3. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Exposed Eligible Selected	Withdrawn Lost to follow-up Analyzed	Effectiveness outcomes
Tiihonen, 2006 Finland	NA- all were included that were hospitalized in Finland	0/0/2230	Hospitalization- Drug and crude RR/adjusted RR (sex, calendar y, age at onset of follow-up, number of previous relapses, duration of index hospitalization, and length of follow-up) Perphenazine depot 0.54 (0.41 to 0.70) 0.54 (0.41 to 0.70) Clozapine 0.79 (0.66 to 0.95) 0.64 (0.53 to 0.77) Olanzapine 0.81 (0.67 to 0.97) 0.67 (0.56 to 0.80) Thioridazine 0.73 (0.59 to 0.91) 0.75 (0.60 to 0.93) Perphenazine oral 0.66 (0.54 to 0.80) 0.77 (0.63 to 0.94) Chlorpromazine 0.83 (0.66 to 1.04) 0.89 (0.71 to 1.12) Chlorprothixene 0.85 (0.68 to 1.06) 0.90 (0.72 to 1.13) Mixed or rare 1.05 (0.89 to 1.25) 0.91 (0.76 to 1.08) Haloperidol oral 1.00 1.00 Levomepromazine 1.53 (1.22 to 1.93) 1.01 (0.80 to 1.27) Risperidone 0.89 (0.74 to 1.06) 0.87 (0.73 to 1.05)
Tiihonen, 2009 Finland	NA: all patients in Finland admitted with a diagnosis of schizophrenia	NA/NA/66881	NR

Evidence Table 3. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Safety outcomes	Comments
Tiihonen, 2006 Finland	84 patients died during follow-up, no significant differences between drugs but, mortality was more than 10 times higher in patients not taking drugs than in patients currently taking antipsychotic drugs: 75 patients not taking drugs died (3362 person ys) and nine patients taking drugs died (4664 person ys) (adjusted RR 12.3) Twenty six suicides occurred in patients not taking drugs compared with one suicide in patients taking drugs (crude RR 36.1, 4.9–266)	
Tiihonen, 2009 Finland	Overall risk of death was lower during the current use of any antipsychotic drug than it was with no antipsychotic use; adjusted HR, 0.68; 95% CI, 0.65 to 0.71; P<0.0001). Risk of death significantly lower in patients with long term (7-11 ys) antipsychotic treatment than in those who had not used any antipsychotic drugs during follow-up; HR, 0.81; 95% CI, 0.77 to 0.84; P<0.0001) Life expentancy of patients with schizohrenia had not declined during the study period compared with the general population (32.5 ys vs 57.5 ys in 1996 respectively; 37.4 ys vs 59.9 ys in 2006 respectively)	

Evidence Table 3. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Data source	Prospective Retrospective Unclear	Sampling frame	Exposure period
Usall, 2009 SOHO (Secondary publication) Reporting on gender differences in Schizophrenia	Same as Haro 2005	Same as Haro 2005	6 mo analysis	NR
van Winkel, 2008, Belgium	University Psychiatric Center of the Katholieke Universiteit Leuven in Kortenberg, Belgium	Prospective	November 2003-January 2007	3 mos

Evidence Table 3. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Interventions mean dose	Population	Age Gender Ethnicity
Usall, 2009 SOHO (Secondary publication) Reporting on gender differences in Schizophrenia	Male vs female Olanzapine: 11.08 (5.37) vs 10.19 (4.99) Risperidone: 4.67 (2.57) vs 4.09 (2.54) Clozapine: 159.68 (125.03) vs 148.01 (125.63)	Schizophrenia	age: 39.7 % male: 56.7 Ethnicity: NR
van Winkel, 2008, Belgium	amisulpride = 26.5, 27.9 aripiprazole = 28.4, 27.3 clozapine = 24.8, 26.5 olanzapine = 23.5, 25.8 quetiapine = 25.2, 26.8 risperidone = 24.9, 25.8	Patients with schizophrenia or schizoaffective disorder, newly started on or switched to specific atypical antipsychotic medication therapy, with OGTT-confirmed non-diabetic status	Mean age: 33.7 ys; % Male: 60.7%; Ethnicity: NR

Evidence Table 3. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Exposed Eligible Selected	Withdrawn Lost to follow-up Analyzed	Effectiveness outcomes
Usall, 2009 SOHO (Secondary publication) Reporting on gender differences in Schizophrenia	NR/NR/7990	NR/NR/7990	Overall CGI response OR for gender [Female reference category], 95% CI, p-value Olanzapine: 0.88 (0.78 to 1.00), p=0.0460 Risperidone: 0.90 (0.74 to 1.10), p=0.2969 Clozapine: 0.56 (0.34 to 0.93), p=0.0252 Typical cohort: 0.62 (0.48 to 0.82), p=0.0006 EQ-VAS change from baseline, differences in rating by gender (female reference category) Olanzapine: -1.52(-2.53 to -0.50), p=0.0033 Risperidone: 0.27 (-1.28 to 1.83), p=0.7300 Clozapine: -2.03 (-6.06 to 2.00), p=0.3243 Typical cohort: -2.16 (-4.33 to 0.01), p=0.0505
van Winkel, 2008, Belgium	NR/415/183	NR	NR

Evidence Table 3. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Safety outcomes	Comments
Usall, 2009 SOHO (Secondary publication) Reporting on gender differences in Schizophrenia		
van Winkel, 2008, Belgium	8 patients developed diabetes within 3 mos after the start of the atypical antipsychotic, resulting in a 3-mo incidence rate of 4.4% . Initiation of clozapine 9.5% of patients initiated on clozapine, 8.0% of patients initiated on olanzapine, 4.2% of patients initiated on quetiapine, and 2.1% of patients initiated on risperidone developed new-onset diabetes, whereas no new cases developed in patients initiated on aripiprazole and amisulpride. 5 of the 8 (62.5%) had prediabetic abnormalities at baseline; 3 (37.5%) had no glucose abnormalities. Type of initiation (start or switch) did not affect the metabolic parameters. BMI (kg/m2)at baseline and after 3 mos: amisulpride = 26.5, 27.9 aripiprazole = 28.4, 27.3 clozapine = 24.8, 26.5 olanzapine = 23.5, 25.8 quetiapine = 25.2, 26.8 risperidone = 24.9, 25.8	N (183) was small for assessing the low incidence rates typically reported for diabetes. Study was naturalistic: there was no random allocation of antipsychotic medication which resulted in treatment cohorts of different sizes.

Evidence Table 3. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Data source	Prospective Retrospective Unclear	Sampling frame	Exposure period
Verma, 2001 United States	Houston VA Medical Center	Retrospective	Average: 25 ds	NR
Voruganti, 2000 Voruganti, 2002 Canada	Western Ontario schizophrenia research prog	Retrospective	NR	>6 mos

Evidence Table 3. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Interventions mean dose	Population	Age Gender Ethnicity
Verma, 2001 United States	risperidone: 2.2 mg olanzapine: 13.2 mg	Schizophrenia	Mean age: 71.4 ys 100% male 71% Caucasian, 23% African-American, 6% Hispanic
Voruganti, 2000 Voruganti, 2002 Canada	Risperidone(N=50): 2-8 mg Olanzapine(N=50): 15-40 mg Quetiapine(N=50): 200-800 mg Switched from following conventional drugs (CAPD): chlorpromazine, fluphenazine, flupenthixol, haloperidol, methotrimeprazine, perphenazine, pimozide, Pipothiazine, trifluoperazine	Schizophrenia	Mean age: 32.1 ys 68.7% male

Evidence Table 3. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Exposed Eligible Selected	Withdrawn Lost to follow-up Analyzed	Effectiveness outcomes
Verma, 2001 United States	NR/NR/NR	NR/NR/34	Changes in scores at discharge: Positive and negative symptoms (PANSS): R: 56.90 vs O: 59.0; P=0.735 Extrapyramidal side-effect rating scale (ESRS): R: 23.46 vs O: 20.54; P=0.557 Rating scale for side effects (RRSE): R: 8.14 vs O: 7.71; P=0.817
Voruganti, 2000 Voruganti, 2002 Canada	NR/230/150	15 WDs or lose to FU/135	85% of patients benefitted from switching from conventional to novel antipsychotics 8(6%) preferred conventional treatment Remained on maintenance treatment: risperidone 82% olanzapine 86% quetiapine 82% CAPD (n=44) vs risperidone (n=50) vs olanzapine (n=48) vs quetiapine (n=42) vs clozapine (n=46) Psychosocial functioning and QOL: Sickness impact profile (SIP): 35.3(13.2)* vs 26.9(14.3) vs 29.1(14.8) vs 28.2(10.6) vs 32.1(18.1) QOL (QLS): 58.8(22.6) vs 63.3(15.3) vs 60.8(15.4) vs 61.4(14.2) vs 58.2(14.8) Global assessment of functioning scale (GAF): 59.8(14.5) vs 61.9(10.5) vs 59.4(8.9) vs 56.8(12.6) vs 57.8(10.6) (*p<0.05 on Tukey tests) Mean change in scores after a switch from conventional to the novel antipsychotic drugs risperidone (n=43) vs olanzapine (n=44) vs quetiapine (n=31) Symptoms 1. PANSS: -23.63 vs -23.67 vs -21.43 a. positive symptoms cluster: -5.18 vs -4.11 vs -4.67 b. negative symptoms cluster: -8.2* vs -6.3 vs -5.0 c. excited symptoms cluster: -3.68 vs 2.79 vs -1.03 d. depressive symptoms cluster: 2.68 vs -6.09* vs -1.70 e. cognitive symptoms cluster: -3.89 vs -4.38 vs -9.03* QOL 1. QLS: 10.30 vs 9.97 vs 9.87 2. GAF: 16.0 vs 15.18 vs 14.67 3. SIP: -22.32 vs -20.40 vs -21.20 (*p<0.05 on post hoc Tukey tests)

Evidence Table 3. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Safety outcomes	Comments
Verma, 2001 United States	NR	
Voruganti, 2000 Voruganti, 2002 Canada	CAPD (n=44) vs risperidone (n=50) vs olanzapine (n=48) vs quetiapine (n=42) vs clozapine (n=46) Drug attitude inventory scores: 1. DAI-30 total: 12.9(10.5) vs 19.4(9.1)* vs 18.9(8.9)* vs 18.2(10.2)* vs 16.2(11.0) 2. subjective positive: 3.1(4.2) vs 5.4(3.3)* vs 5.5(2.7)* vs 5.8(3.8)* vs 4.9(3.6) 3. subjective negative: 2.4(3.5) vs 3.2(2.8) vs 3.5(2.5) vs 2.7(3.2) vs 2.4(3.3) 4. health/illness: 1.7(1.1) vs 1.7(1.8) vs 1.6(1.6) vs 1.5(1.2) vs 1.2(1.9) 5. professionals: 1.6(0.9) vs 1.7(0.7) vs 1.1(1.5) vs 1.6(0.9) vs 1.5(1.0) 6. control issues: 0.6(1.3) vs 1.4(1.1) vs 1.3(1.2) vs 0.9(1.2) vs 1.2(1.2) 7. prevention: 1.1(1.0) vs 1.6(0.9) vs 1.3(1.2) vs 1.5(1.1) vs 1.4(1.7) 8. harmful effects: 0.4(1.3) vs 0.9(1.3) vs 0.9(1.2) vs 0.8(1.0) vs 0.6(1.5) Proportion of dysphoric responders:7(17%)* vs 3(6%) vs 2(5%) vs 3(7%) vs 3(6.5%) Severity of side effects 1. Simpson-Angus EPS rating scale: 3.4(2.3)* vs 1.34(2.4) vs 0.9(2.0) vs 1.1(2.2) vs 0.4(1.4) 2. BAS: 1.2(1.4) vs 0.8(0.9) vs 0.2(0.6) vs 1(1.2) vs 0.6(1.0) 3. AIMS: 1.6(2.1) vs 1.2(2.4) vs 1.4(2.8) vs 1.2(3.2) vs 3.5(5.8) 4. LUNSERS: 21.1(9.6)* vs 13.4(9.4) vs 13.4(4.0) vs 12.8(7.2) vs 25.4(15.7)* (*p<0.05 on Tukey tests) Mean change in scores after a switch from conventional to the novel antipsychotic drugs risperidone (n=43) vs olanzapine (n=44) vs quetiapine (n=31) Side effects 1. AIMS: -0.21 vs -0.75 vs -0.12 2. BAS: 3.40 vs -4.52 vs -3.96 3. SAS: -6.02 vs -6.75 vs -6.67 4. LUNSERS: -21.86 vs -23.18 vs -30.7* Subjective tolerability: 1. DAI: 11.86 vs 14.6* vs 12.12 2. proportion of dysphoric responders in the group (%): -6.9 vs -13.6 vs -9.7 (*p<0.05 on post hoc Tukey tests)	

Evidence Table 3. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Data source	Prospective Retrospective Unclear	Sampling frame	Exposure period
Wang, 2002 U.S.	Databases: NJ Medicaid prog & NJ Pharmaceutical Assistance to the Aged & Disabled prog plus Medicare	Retrospective	6 mos before date of 1st prescription for insulin or oral hypoglycemic agent	6 mos
Weiser, 2000 Israel	Tel-Aviv University Medical School	Retrospective	NR	NR
Wirshing, 2002 United States	VA Greater Los Angeles Healthcare System	Retrospective	Mean duration: clozapine: 43.3 mo olanzapine: 13.5 mo risperidone: 28.6 mo quetiapine: 33.o mo haloperidol: 37.1 mo fluphenazine: 47.0 mo	NR

Evidence Table 3. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Interventions mean dose	Population	Age Gender Ethnicity
Wang, 2002 U.S.	clozapine vs other psychiatric agents (includes typical APs and risperidone); Dose and duration of treatment during the 6-mo observation period were included in the analysis	Patients with psychiatric disorders, age>20, enrolled in government-sponsored drug benefit progs in New Jersey. Cases were patients with a 1st prescription (index date) for insulin or oral hypoglycemics between 1990-1995. Controls were patients without diabetes, matched on age, gender, and a randomly assigned index date. Subjects were then selected for analysis if they had a psychiatric diagnosis in the previous 6 mos.	Mean age 62.5 31.8% male 64% white
Weiser, 2000 Israel	Haloperidol(N=23): 10 mg/d Olanzapine(N=26): 10.56 mg/d Risperidone(N=27): 4.35 mg/d	Schizophrenia, schizophreniform disorder	Mean age: 30.9 ys 68% Male Ethnicity NR
Wirshing, 2002 United States	Clozapine, olanzapine, risperidone, quetiapine, haloperidol, fluphenazine/mean doses NR	Schizophrenia	Mean age: 51.3 ys 94.4% Male 47.9% White 36.7% African-American

Evidence Table 3. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Exposed Eligible Selected	Withdrawn Lost to follow-up Analyzed	Effectiveness outcomes
Wang, 2002 U.S.	NR NR 14007	NR NR 14007 analyzed Cases with diabetes mellitus n=7227 Controls without diabetes mellitus n=6780	NR
Weiser, 2000 Israel	NR/NR/NR	NR/NR/76	Cognitive functioning as measured by VMT: Higher for olanzapine and risperidone vs haloperidol: P=0.002 CPT scores: R: 0.541 vs O: 0.516 vs H: 0.300; F=1.003 Calgary Depression Scale: R: 6.73 vs O: 4.53 vs H: 7.75; F=1.974 Rey VLT: R: 38.0 vs O: 40.3 vs H: 36.0; F=0.674 PANSS: R: 66.8 vs O: 63.3 vs 68.2; F=0.568
Wirshing, 2002 United States	NR/590/215	0/0/215	NR

Evidence Table 3. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Safety outcomes	Comments
Wang, 2002 U.S.	Adjusted odds of diabetes mellitus associated with clozapine use: 0.98 (95% CI 0.74-1.31) Adjusted odds of DM associated with use of other antipsychotics: 1.13 (95% CI 1.05-1.22) Adjusted odds of DM associated with specific antipsychotics (95% CI): risperidone 0.90 (0.96-1.18) chlorpromazine 1.31 (1.09-1.56) perphenazine 1.34 (1.11-1.62) haloperidol 1.06 (0.96-1.18)	Duration of treatment and previous treatment with clozapine, prior to the 6-mo window of observation were not included in the analysis.
Weiser, 2000 Israel	Haloperidol and risperidone suffered more severe EPS vs olanzapine: P=0.023	
Wirshing, 2002 United States	Increase in glucose levels from baseline: clozapine: +14%; p=.05 olanzapine: +21%; p=.03 haloperidol: +7%; p=.04 Increase/decrease in total cholesterol levels from baseline: risperidone: -6%, p=.04 fluphenazine: -6%; p=.04 13% of olanzapine patients (4) required increases in doses of lipid-lowering agents after beginning treatment	

Evidence Table 3. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Data source	Prospective Retrospective Unclear	Sampling frame	Exposure period
Yood, 2009 U.S.A.	3 sites: Kaiser Permanente Health Plan, Northern California; HealthCore Integrated Research Network; PharMetrics	Retrospective	Nov 2002 through March 2005	minimum 45 ds

Evidence Table 3. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Interventions mean dose	Population	Age Gender Ethnicity
Yood, 2009 U.S.A.	% of inception cohort (N=56,037) Aripiprazole 4.5% Clozapine 0.1% Olanzapine 22.2% Quetiapine 18.2% Risperidone 19.6% Ziprasidone 2.9% Typical antipsychotics 10.5% Mean dose NR	Inception cohort subset: all patients aged 18 and older exposed to typical or atypical antipsychotics for at least 45 ds and continuously enrolled in the database for at least 3 mos before and 6 mos after the index date with no evidence of diabetes anytime before the index date, and no previous antipsychotic prescription filled within 3 mos before the index date.	Mean (SD) age: 45.1 (19.4) 39.7% male Ethnicity NR

Evidence Table 3. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Exposed Eligible Selected	Withdrawn Lost to follow-up Analyzed	Effectiveness outcomes
Yood, 2009 U.S.A.	77946 = simple cohort 56037 eligible as inception cohort All eligible were included in analysis.	No WDs, no loss to followup: subjects selected based on continuous enrollment for 6 mos after index date. 56,037 analyzed.	NR

Evidence Table 3. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Safety outcomes	Comments
Yood, 2009 U.S.A.	Olanzapine and clozapine were associated with increased risk of diabetes. Aripiprazole, ziprasidone, risperidone, and quetiapine did not show an increased risk. HR (95% CI) for incident diabetes adjusted for sex, study site, history of AP use, exposure to other pharmacotherapy, overweight, schizophrenia and bipolar disorder code: (Typical antipsychotic = referent) Aripiprazole: 0.93 (0.50, 1.76) Clozapine: 2.58 (0.76, 8.80); p=0.13 (based on 3 events in 147 exposed patients) Olanzapine: 1.71 (1.12, 2.61); p=0.01 (based on 139 events in 17119 exposed patients) Quetiapine: 1.04 (0.67, 1.62) Risperidone: 0.85 (0.54, 1.36) Ziprasidone: 1.05 (0.54, 2.08) Multiple: 1.29 (0.64, 2.62)	The effect estimate for clozapine is imprecise due to the small N's

Evidence Table 3. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Data source	Prospective Retrospective Unclear	Sampling frame	Exposure period
Yu, 2008 U.S.A.	Pennsylvania Medicaid claims data.	Retrospective	4 ys: 1999-2003	12 mos after index prescription.
Yu, 2009 USA	Pennsylvania Medicaid claims data.	Retrospective	1999-2003	2 years

Evidence Table 3. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Interventions mean dose	Population	Age Gender Ethnicity
Yu, 2008 U.S.A.	Olanzapine (N=6929) or quetiapine (n=2321) monotherapy for 30 ds or longer, classified based on the initial atypical antipsychotic received during the observation period, regardless of switching pattern. Dose NR.	Adult schizophrenia patients aged 18-64 who were continuously enrolled at least 1 y before and 1 y after the index prescription date, received a do-d monotherapy of either olanzapine or quetiapine after a 90-d washout period during June 2000 to June 2002. Excluded patients who had a managed care organization claim on or after the index prescription date.	Quetiapine (N=2321) vs. olanzapine (6929) // olanzapine cohort (N=2321) matched on propensity score: Mean age: 41.3 vs 42.8 // 41.6 % male: 39.9% vs 52.8% // 40.2% % White: 65.5% vs 55.2% // 64.3% % Black: 28.3% vs 36.7% // 29.1% % Hispanic: 2.0% vs 3.2% // 1.9%
Yu, 2009 USA	Olanzapine Quetiapine Mean dose, NR	Schizophrenia, 18-64 years, new prescription for olanzapine or quetiapine	Age: 42.4 Gender: 50.5% female Ethnicity: 57.8% White, 34.6% Black, 2.9% Hispanic, 4.7% Other

Evidence Table 3. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Exposed Eligible Selected	Withdrawn Lost to follow-up Analyzed	Effectiveness outcomes
Yu, 2008 U.S.A.	Exposed: 22167 had a pharmacy claim for either drug within index window (2000-2002) Eligible: 9250 met all criteria Selected: all eligible were included	No WDs, no loss to followup: subjects selected based on continuous enrollment for 12 mos 4642 analyzed.	Compared with quetiapine, patients treated with olanzapine had significantly fewer psychiatric hospitalizations, lower pharmacy utilization, and lower medical service costs. Olanzapine (N=2321) vs quetiapine (N=2321): % any psychiatric hospitalization: 28.8% vs 34.0%; p=0.0001 % any emergency visit: 47.0% vs 52.0%: p=0.0007 Any use of clozapine: 4.6% vs 7.1%; p=0.0003 Any use of antidepressants: 65.0% vs 71.3%; p<0.0001 Any use of mood stabilizers: 51.9% vs 57.9%; p<0.0001 Any use of benzodiazepines/hyptnotics/anxiolytics: 47.6% vs 52.1%; p=0.0020 Mean (SD) psychiatric costs, $: 7352 (14,282) vs 9037 (16,904); p=0.0002 Mean (SD) psychiatric hospitalization costs, $: 3149 (10,638) vs 4220 (13,838); p=0.0024 Mean (SD) psychotropic drug costs excluding index drug, $: 1828 (2131) vs 2459 (2477); p<0.0001 Total mean (SD) costs: 16,028 (19,182) vs 17,232 (19,162); p=0.0279 Reduction in costs (postindex minus preindex), adjusted for baseline characteristics: Medical service cost: $2106 vs $869 p=0.0046 Psychiatric cost: $2017 vs $587; p=0.0004 Psychiatirc hospitalization cost: $1566 vs $574; p=0.0043 Drug cost: $3578 vs $3304; p=0.0059 Psychotropic drug cost: $3097 vs $2736; p<0.0001 Total costs: $1473 vs $2435; p=0.0320
Yu, 2009 USA	29265/9250/9250	NA/NR/9250	Olanzapine vs. Quetiapine Adherence, Medication Possession Ratio: 0.47 vs. 0.43, p<0.0001 6-month discontinuation: 65.6% vs. 63.7%, p=0.6666 6-month switch to other antipsychotic: 11.0% vs. 10.6%, p=0.6691

Evidence Table 3. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Safety outcomes	Comments
Yu, 2008 U.S.A.	Use of antiparkinsonian medication during 12-mo postindex period was slightly but significantly lower with olanzapine vs quetiapine: 25.9% vs 28.9%; p=0.0214	
Yu, 2009 USA	NR	

Evidence Table 3. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Data source	Prospective Retrospective Unclear	Sampling frame	Exposure period
Zhang, 2007, China	Randomly recruited inpatients from Beijing Hui-Long-Guan Hospital, Beijing City, China	Both? (cross-sectional)	NR	7.5 ± 6.5 ys
Zhao, 2002 United States	IMS Health Lifelink: Integrated Claims Solutions	Retrospective	Average: 181-217 ds	NR
Zhao, 2002 United States	Database: IMS Health Life Link: Integrated Claims Solutions	Retrospective	October 1, 1996 through December 31, 1998	1 y

Evidence Table 3. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Interventions mean dose	Population	Age Gender Ethnicity
Zhang, 2007, China	Mean dose (in chlorpromazine equivalents): 419 ± 337.6 mg/d	Chronic schizophrenic patients (chronically treated with clozapine, risperidone or typical antipsychotics) and healthy control subjects	Subjects/Controls Mean age (ys): 47.3/46.2 % male: 73.4/72% Ethnicity: 100% Han Chinese for both subjects and controls
Zhao, 2002 United States	risperidone(N=985): 4.02 mg olanzapine(N=348): 10.49 mg	Schizophrenia	Mean age: 48.6 ys 53.5% male Ethnicity NR
Zhao, 2002 United States	Olanzapine= 10.45mg/d Risperidone= 3.32mg/d	Schizophrenia	Olanzapine/Risperidone: Mean age (ys)=48.9/52.4 % female=44.4/52.2

Evidence Table 3. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Exposed Eligible Selected	Withdrawn Lost to follow-up Analyzed	Effectiveness outcomes
Zhang, 2007, China	NR/NR/124patients and 50 controls	Withdrawn: NR Lost to FU: NR Analyzed: 124 schizophrenic patients (clozapine n=57, risperidone n=23, typical antipsychotics n=44) 50 healthy controls	NA
Zhao, 2002 United States	NR/NR/1333	0/0/1333	Average ds of treatment: O: 217 vs R: 181; P<.0001
Zhao, 2002 United States	745/670/670	NR/NR/670	Duration of treatment: Olanzapine= 213 ds Risperidone= 162 ds After controlling for patient demographics, patients initiated on olanzapine stayed on therapy 29.4% longer than those initiated on risperidone (P<0.0001) # of patients with >80% of ds of receiving medication of interest: Olanzapine= 176 of 423 (41.6%) Risperidone= 64 of 247 (25.9%) Incidence of switching: Patients in olanzapine group were significantly less likely to switch to risperidone than vice versa (OR=0.275, P<0.0001, 95% CI 0.43-0.95) Use of concomitant medications: Olanzapine group significantly less likely to be prescribed an anti-Parkinsonian medication than risperidone group (OR=0.639, P=0.03, 95% CI 0.43-0.95) and had fewer treatment ds with such medications (27.4% fewer ds, P<0.0001)

Evidence Table 3. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Safety outcomes	Comments
Zhang, 2007, China	BMI values: subjects (male/female): 23.9 ± 3.5/25.8 ± 3.6 BMI values: controls (male/female): 21.5 ± 1.9/22.4 ± 2.1 BMI values when matched for BMI on a 1:1 basis: subjects (male/female): 21.5 ± 1.9/22.5 ± 1.9 BMI values when matched for BMI on a 1:1 basis: controls (male/female): 21.2 ± 1.8/22.4 ± 2.0 BMI/BMI gain (kg/m^2)by drug class: Typical: 23.7 ± 3.2/2.5 ± 3.1 Clozapine: 25.4 ± 3.4/3.9 ± 3.2 Risperidone: 22.9 ± 4.1/1.5 ± 3.7	Limited number of female patients
Zhao, 2002 United States	NR	
Zhao, 2002 United States	NR	

Evidence Table 4. Quality assessment of observational studies in patients with schizophrenia

Author, year	Non-biased selection?	Low overall loss to follow-up?	Outcomes pre-specified and defined?	Ascertainment techniques adequately described?	Non-biased and adequate ascertainment methods?
Advokat, 2004	No, excluded patients with incomplete data	No withdrawals reported	Yes	Yes	No, ratings probably unblinded because performed by psychologists/ psychiatrists on staff at hospital
Advokat, 2004	Yes for overall group; but unclear for subset for which length of stay was determined, which was only those who were discharged during study period and N was NR	Unclear; implied that length of stay not available for all patients, but N=NR	Yes for some, no for length of stay.	No	Unclear
Agelink, 2001	Method NR, unable to determine.	Yes (9%)	Yes	Yes	Yes
Akkaya, 2007	Yes	NA: retrospective analysis excluded 32.7% of pts with an initial admission and diagnosis but no follow-up visit	Yes	Yes	Possible missing data inherent in chart review - AEs not gathered uniformly - but direction of potential bias is unknown.
Alvarez, 1997 Spain	No: AE withdrawals during first 3 weeks not included	NR	Yes	Yes	Yes
Al-Zakwani, 2003	No, excluded patients who had a behavioral health benefit carve-out and those who were not continuously enrolled for 18 mos	No withdrawals reported.	Yes	Yes	NR

Evidence Table 4. Quality assessment of observational studies in patients with schizophrenia

Author, year	Statistical analysis of potential confounders?	Adequate duration of follow-up?	Overall quality assessment	Comments
Advokat, 2004	No and only baseline demographic data reported; unclear if differences in prognostic factors	Yes	Poor	
Advokat, 2004	No and there were differences between groups in rates of patents taking concomitant typical AP's : olanzapine= 57%, risperidone=38%, quetiapine = 64%, and clozapine = 14%	No; ≥ 3 mos	Poor	
Agelink, 2001	Yes	Yes	Fair	
Akkaya, 2007	Yes; bivariate comparisons	N/A	Fair	
Alvarez, 1997 Spain	NR	Yes	Fair	
Al-Zakwani, 2003	Yes	Yes	Fair	

Evidence Table 4. Quality assessment of observational studies in patients with schizophrenia

Author, year	Non-biased selection?	Low overall loss to follow-up?	Outcomes pre-specified and defined?	Ascertainment techniques adequately described?	Non-biased and adequate ascertainment methods?
Ascher-Svanum, 2004 US-SCAP Study Interim Results	Not entirely clear. Broad range of patients enrolled, with few exclusion criteria but method of obtaining participants not described well enough to determine. Also, for this sub-study, patients discontinuing treatment prior to 1 year were excluded.	None	Yes	Yes	No. Data extracted from medical records. Methods not described (e.g. blinding, validation).
Ascher-Svanum, 2008	Yes	Yes	Yes	Yes	Yes
Atkin, 1996 UK/Ireland	Yes	NR	Yes	Yes	Yes
Barak, 2004	No, excluded patients without treatment charts	Yes (retrospective study)	Yes	Yes	Unclear if database/patient chart reviewer was blind to suicide status
Bobes, 2003b	Unclear if the inception cohort (n=901) represented ALL patients hospitalized for an acute psychotic episode during the specified time period; unclear how sample narrowed down to 158	Unclear for the process of narrowing the sample from 901 to 158; low for LTFU among the 158	Yes	Yes	Unclear if the person(s) that administered the instruments were blinded
Bond, 2004	No, excluded patients: (1) didn't express goal of employment; (2) were noncompliant with medications; (3) didn't complete baseline interview; (4) discontinued early; (5) switched medications during the study	Withdrawals not reported	Yes	Yes	Unclear; no information about how the Vocational Placement Scale was administered

Evidence Table 4. Quality assessment of observational studies in patients with schizophrenia

Author, year	Statistical analysis of potential confounders?	Adequate duration of follow-up?	Overall quality assessment	Comments
Ascher-Svanum, 2004 US-SCAP Study Interim Results	Yes	Yes	Fair	
Ascher-Svanum, 2008	Yes	Yes	Fair	
Atkin, 1996 UK/Ireland	NR	Yes	Fair	
Barak, 2004	No; only commented regarding similarities in gender, age, distribution of diagnoses	Unclear	Fair	
Bobes, 2003b	Partial; only covariates were baseline score and years since diagnosis	Yes	Poor	
Bond, 2004	No; only attempted adjustment for the few baseline differences in concomitant medication use, indicated adjustment didn't materially change the results, so presented unadjusted results	Yes	Poor	

Evidence Table 4. Quality assessment of observational studies in patients with schizophrenia

Author, year	Non-biased selection?	Low overall loss to follow-up?	Outcomes pre-specified and defined?	Ascertainment techniques adequately described?	Non-biased and adequate ascertainment methods?
Brown, 2005	No, excluded people who died during follow-up	There was differential loss to F/U Loss to F/U reported as 6/88 (6.8%) for ziprasidone; 27/103 (26%) for olanzapine	Yes	Yes	Unclear; chart review not duplicated
Buckman, 1999 United States	Unclear	NR	No	No	Unclear
Caro, 2002 Quebec	Yes	NR	Yes	Yes	Yes
Castro 2007	Unclear	Yes	Yes	Unclear	Unclear
Castro, 2007	Yes; see comment.	Yes; length of followup was significantly higher with clozapine than haloperidol or risperidone	Yes	Yes	Yes
Chen, 2008	Yes	NR	Yes	Yes	Yes
Cianchetti, 2011	Yes	No (29% excluded)	Yes	Yes	Unclear (blinding NR)

Evidence Table 4. Quality assessment of observational studies in patients with schizophrenia

Author, year	Statistical analysis of potential confounders?	Adequate duration of follow-up?	Overall quality assessment	Comments
Brown, 2005	No	Unclear	Poor: no adjusting for confounders; F/U interval unclear	retrospective, 2-group cohort
Buckman, 1999 United States	NR	Unclear	Poor	
Caro, 2002 Quebec	Yes	Yes	Fair	Between-group differences in age, gender, other characteristics
Castro 2007	Some	Yes	Poor	
Castro, 2007	Yes	Yes	Fair	Authors note that patients may differ between treatment groups in their level of treatment resistance and disease severity
Chen, 2008	Yes	Yes	Fair	It is not clear what % of patients included may have lost MediCal eligibility and were therefore lost to follow-up
Cianchetti, 2011	No, for discontinuation outcome patients had trials of ≥ 2 different AP's and were counted multiple times in the d/c analysis	Yes	Poor	

Evidence Table 4. Quality assessment of observational studies in patients with schizophrenia

Author, year	Non-biased selection?	Low overall loss to follow-up?	Outcomes pre-specified and defined?	Ascertainment techniques adequately described?	Non-biased and adequate ascertainment methods?
Citrome, 2004	Unclear Lower % of males in case group vs. control	NR	Yes	Yes	No Risk factors of BMI and activity level not assessed or controlled for. No assessment of baseline risk for diabetes and how that may have influenced choice of antipsychotic medication
Conley, 1999 United States	Yes	NR	Yes	Yes	Yes
Cooper, 2005 Cooper, 2007	Unclear: groups differed but did adjust	NA (retrospective study including persons with available data only)	Yes	Yes	Yes; database tested for accuracy
Coulter, 2001 International	Unclear	NR	Yes	No	Unclear
de Haan, 1999	Yes	Yes (retrospective study)	No; not defined	No	No
de Haan, 2002	No; excluded 15 (6.2%) due to noncompliance and crossover	Withdrawals NR	yes	Yes	No; raters were unblinded

Evidence Table 4. Quality assessment of observational studies in patients with schizophrenia

Author, year	Statistical analysis of potential confounders?	Adequate duration of follow-up?	Overall quality assessment	Comments
Citrome, 2004	Partial	Yes	Fair	
Conley, 1999 United States	Yes	Yes	Fair	
Cooper, 2005 Cooper, 2007	Yes	Yes, 365-d study period	Fair	retrospective, 2-group cohort in pub #1 4 drugs compared in pub #2
Coulter, 2001 International	NR	Unclear	Poor	
de Haan, 1999	No; only commented regarding between-groups comparability for sex, age at admission and diagnosis	Yes	Poor	
de Haan, 2002	No; there was no information about between-groups comparability of baseline characteristics	Yes	Poor	

Evidence Table 4. Quality assessment of observational studies in patients with schizophrenia

Author, year	Non-biased selection?	Low overall loss to follow-up?	Outcomes pre-specified and defined?	Ascertainment techniques adequately described?	Non-biased and adequate ascertainment methods?
De Hert 2008	Unclear; Historical cohort: Consisted of only 148/301 (49%) of patients with complete laboratory data. But, no significant differences between patients with and without complete laboratory data. Current cohort: No details provided on matching process. Significantly higher glucose in historic cohort (89 vs 84 mg/dl (*P*= 0.0055).	No; analysis excluded 22% overall (historic=21% vs current=37%)	Yes	Yes	Yes in "current" cohort of second-generation antipsychotics; unclear in historical cohort due to use of conversion factor for missing waist circumference measurements
Deliliers, 2000 Italy	Yes	NR	Yes	Yes	Yes
Devinsky, 1991 United States	Yes	NR	Yes	No	Unclear
Dinakar, 2002	Method NR, unable to determine.	Yes	Yes	Yes	Not reported if blind or independent assessment of outcomes.
Dolder, 2002	Yes	NA (pharmacy database with all records available)	Yes	Yes	Yes
Drew, 2002 Australia	Yes	NR	Yes	Yes	Yes

Evidence Table 4. Quality assessment of observational studies in patients with schizophrenia

Author, year	Statistical analysis of potential confounders?	Adequate duration of follow-up?	Overall quality assessment	Comments
De Hert 2008	No and no information reported about comparability of baseline characteristics between groups of patients based on individual atypical antipsychotic agent	Yes	Poor	
Deliliers, 2000 Italy	NR	Unclear	Fair	
Devinsky, 1991 United States	Yes	Unclear	Fair	
Dinakar, 2002	No	Yes	Poor- no control for confounding factors, not reported if outcome assessors blinded or independent, unable to determine if selection was unbiased.	
Dolder, 2002	No, although baseline groups were similar for known confounders	Yes; 12 mos	Fair	2-group cohort study; appears to be retrospective
Drew, 2002 Australia	NR	Yes	Fair	

Evidence Table 4. Quality assessment of observational studies in patients with schizophrenia

Author, year	Non-biased selection?	Low overall loss to follow-up?	Outcomes pre-specified and defined?	Ascertainment techniques adequately described?	Non-biased and adequate ascertainment methods?
Eberhard, 2006	NA (single-group study)	No (completers 166/223)	Yes	Yes	Yes (validated rating scale for TD)
Eriksson, 2012 Sweden	Yes	NA	Yes	No	NR methods beyond "chart review"
Etminan, 2003 Ontario	No	NR	Yes	Yes	Yes
Feldman, 2004 Buse, 2003	No- only included patients who maintained coverage with AdvancePCS were followed- those who discontinued coverage not analyzed; also excluded those missing information on sex or year of birth.	Yes (for those maintaining coverage)	Yes	Yes	Not reported if independent assessment of outcomes (but outcome was new prescription, so may be objective)
Feng, 2012	Unclear (hospitalized patients but selection methods NR)	Yes (<10% at 8 years)	Yes	Yes	Unclear (likely performed by psychologists/ psychiatrists on staff at hospital, so not blinded)
Fuller, 2003	Yes	NR	Yes	No	Yes
Ganguli, 2001	Yes- consecutive patients	Not reported	Yes	Yes	Not reported if independent assessment of outcomes (outcome was weight gain from chart review, objective, but several sources used, and judgment made about which of multiple weights recorded to use)

Evidence Table 4. Quality assessment of observational studies in patients with schizophrenia

Author, year	Statistical analysis of potential confounders?	Adequate duration of follow-up?	Overall quality assessment	Comments
Eberhard, 2006	NA (single-group study)	Yes: 5 years	Fair	this is an observational study of AE only (not efficacy); single-group cohort
Eriksson, 2012 Sweden	Yes	Yes	Fair	
Etminan, 2003 Ontario	Yes	NR	Poor	Diabetic events NR for 266 patients (reason NR)
Feldman, 2004 Buse, 2003	Yes	Yes	Fair	
Feng, 2012	Yes	Yes	Fair	
Fuller, 2003	Yes	Yes	Fair	
Ganguli, 2001	No	Yes (4 mos)	Fair	

Evidence Table 4. Quality assessment of observational studies in patients with schizophrenia

Author, year	Non-biased selection?	Low overall loss to follow-up?	Outcomes pre-specified and defined?	Ascertainment techniques adequately described?	Non-biased and adequate ascertainment methods?
Gianfrancesco, 2002 United States	Yes	NR	Yes	No	Yes
Gianfrancesco, 2003a United States	Yes	NR	Yes	No	Yes
Gianfrancesco, 2003b United States	Yes	NR	Yes	No	Yes
Gianfrancesco, 2006	Yes	None	Yes	Yes	Yes
Gianfrancesco, 2006 (Hospitalization Risks in the Treatment of Schizophrenia)	Yes	NA (retrospective; only patients with data were analyzed)	Yes	Yes	Unclear, don't know reliability of the database
Gibson, 2004	Unclear: groups differed but did adjust	NA (retrospective study including persons with available data only)	Yes	Yes, from Medicaid data	Unclear, don't know reliability of the database
Gomez, 2000 Spain Estudio Farmacoepidemio-logico en esquizofrenia con Olanzapine (EFESO)	Yes	Yes	Yes	No	Unclear
Guo 2011	Unclear; 13% were excluded because of refusal to participate or for "other reasons"	No, (40%)	Yes	Yes	No, "open label"
Hagg, 1998 Sweden	Yes	NR	Yes	Yes	Yes
Haro, 2008	Yes	No 58.2% included	Yes	Yes	Yes
Haukka 2008	Yes	Yes (retrospective study)	Yes	Yes	Yes

Evidence Table 4. Quality assessment of observational studies in patients with schizophrenia

Author, year	Statistical analysis of potential confounders?	Adequate duration of follow-up?	Overall quality assessment	Comments
Gianfrancesco, 2002 United States	Yes	Yes	Fair	
Gianfrancesco, 2003a United States	Yes	Yes	Fair	
Gianfrancesco, 2003b United States	Yes	Yes	Fair	
Gianfrancesco, 2006	Some	Yes	Fair	
Gianfrancesco, 2006 (Hospitalization Risks in the Treatment of Schizophrenia)	Yes	Unclear; mean treatment episode duration NR	Fair	
Gibson, 2004	No, there were many baseline differences, but clinical significance of the differences was unclear	Yes, 1 year	Fair	retrospective, 3-group cohort
Gomez, 2000 Spain Estudio Farmacoepidemio-logico en esquizofrenia con Olanzapine (EFESO)	Yes	Yes	Fair	
Guo 2011	Unclear; baseline differences in SES and EPS with no adjustment	Yes	Fair	
Hagg, 1998 Sweden	No	N/A, cross-sectional study	Fair	
Haro, 2008	Yes	Yes	Fair	
Haukka 2008	Yes	Yes	Good	

Evidence Table 4. Quality assessment of observational studies in patients with schizophrenia

Author, year	Non-biased selection?	Low overall loss to follow-up?	Outcomes pre-specified and defined?	Ascertainment techniques adequately described?	Non-biased and adequate ascertainment methods?
Hedenmalm, 2002	Yes	Yes (retrospective study)	Yes	Yes	Not stated if blinded or independent assessment of outcomes
Henderson, 2000 United States	Yes	NR	Yes	Yes	Yes
Henderson, 2005	Unclear; only information about sampling frame was observation period	NA (retrospective; only patients with data were analyzed)	Yes	Yes	Unclear, don't know reliability of the research psychiatrist in determining cause of death from autopsy reports and medical records
Hennessy, 2002	Not clear	Yes (retrospective study)	Yes	Yes	Not reported if independent assessment of outcomes
Herceg 2008	Not clear	Yes (retrospective study)	Yes	Not clear	Not clear
Ho, 1999	Unclear	No	Yes	Yes for group in the Longitudinal Study of Recent-Onset Psychosis, No for others	unclear, blinding NR
Hodgson, 2005	Unclear: groups differed but did adjust	NA (retrospective study including persons with available data only)	Yes	Yes, from pharmacy records	Unclear
Honigfeld, 1996 United States	Yes	NR	Yes	Yes	Yes
Hrdlicka 2009	Unclear; eligibility required "medical record quality sufficient to evaluation the patient" and no information reported on comparison between patients with and without "sufficient record quality"	No; 57/109 (52%) did not complete the 6-week study period	Yes	Yes	Yes

Evidence Table 4. Quality assessment of observational studies in patients with schizophrenia

Author, year	Statistical analysis of potential confounders?	Adequate duration of follow-up?	Overall quality assessment	Comments
Hedenmalm, 2002	No	Yes	Fair	
Henderson, 2000 United States	Yes	Yes	Fair	
Henderson, 2005	NA (single-group study)	Yes, 10 years	Poor	
Hennessy, 2002	Yes	Yes	Fair	
Herceg 2008	Some	Yes	Fair	
Ho, 1999	Partially, ANCOVA analysis was done to assess impact of differences at baseline in EPS, GAS, and QOL measures but other confounders not assessed.	Yes	Poor	
Hodgson, 2005	Yes	Unclear: study interval 1994-2001 but unclear if all three groups had same median observation period	Fair	retrospective, 3-group cohort
Honigfeld, 1996 United States	NR	Yes	Fair	
Hrdlicka 2009	No	No - 6 weeks	Poor	

Evidence Table 4. Quality assessment of observational studies in patients with schizophrenia

Author, year	Non-biased selection?	Low overall loss to follow-up?	Outcomes pre-specified and defined?	Ascertainment techniques adequately described?	Non-biased and adequate ascertainment methods?
Iqbal 2011	Unclear; eligibility criteria NR	No, only 37% analyzed at 3 mos, and only 29% at 12 mos.	Yes	Unclear (NR)	Unclear (NR)
Javitt, 2002	Unclear; indicates that data was obtained but doesn't indicate how	No loss to follow-up	Yes	No	No
Jerrell, 2007	NA (single-group study)	NA (retrospective; only patients with data were analyzed)	Yes	Yes	Yes
Jeste, 1999 United States	Yes	NR	Yes	Yes	Yes
Joyce, 2005	No, multiple exclusions applied depending on data most available.	None	Yes	Yes	Yes
Kane, 1993 United States	No	NR	Yes	Yes	Yes

Evidence Table 4. Quality assessment of observational studies in patients with schizophrenia

Author, year	Statistical analysis of potential confounders?	Adequate duration of follow-up?	Overall quality assessment	Comments
Iqbal 2011	Unclear (NR)	Yes	Poor	Mixed population
Javitt, 2002	Yes	Yes	Fair	
Jerrell, 2007	NA (single-group study)	Unclear (follow-up 3 years); for vascular outcomes longer follow-up would be more useful	Fair	this is an observational study of AE only (not efficacy); single-group cohort (retrospective)
Jeste, 1999 United States	Partial: univariate regressions for baseline scores, age race, education, neuroleptic type, and daily dose on risk of TD. Subjects were matched for age, diagnosis, and length of neuroleptic exposure at study entry.	Yes	Fair	
Joyce, 2005	No	Yes	Poor	
Kane, 1993 United States	No and there were nonsignificantly more females (38% vs 24%) and schizoaffective patients (17% vs 8%) in control group and clozapine-treated patients were significantly older (32.4 vs 26.4 years) and had significantly longer exposure to neuroleptics at baseline (6.4 vs 2.3 years)	Yes	Poor	Between group differences in gender and diagnosis

Evidence Table 4. Quality assessment of observational studies in patients with schizophrenia

Author, year	Non-biased selection?	Low overall loss to follow-up?	Outcomes pre-specified and defined?	Ascertainment techniques adequately described?	Non-biased and adequate ascertainment methods?
Karagianis, 2009	Yes	Yes	Yes	Yes	No Interrater reliability not assessed. Open label - possible rater bias
Kasper, 2001	No; selected patients in reverse chronological order with 33 from each center; also only included data from centers that completed data collection and verification by a certain date	Yes (retrospective study)	Yes	No	Unclear; blinding NR
Killian 2012	Unclear; 29% eligible patients refused participation overall and consent rates for each group not separately reported.	Yes	Yes	No	Unclear; methods for ascertaining rehospitalization NR
Kilzieh, 2008	Yes	Yes	Yes	Yes	Yes
Kim, 2008 (Effectiveness…)	Yes	Not reported	Yes	Yes	Yes
Kim, 2008 (Time…)	Yes	Yes	Yes	Yes	Interrater reliability unclear
Koller, 2003	Yes	Yes	Yes	Yes	Not reported if independent assessment of outcomes.
Kopala, 2005	Unclear	No (49% drop-out at 2 years)	yes	Yes	Yes
Koro, 2002a	Yes	Yes (retrospective study)	Yes	Yes	Not reported if independent assessment of outcomes
Koro, 2002b	Yes	Yes	Yes	Yes	Not reported if independent assessment of outcomes.

Evidence Table 4. Quality assessment of observational studies in patients with schizophrenia

Author, year	Statistical analysis of potential confounders?	Adequate duration of follow-up?	Overall quality assessment	Comments
Karagianis, 2009	Yes	Yes	Fair	More than half of included patients were using more than 1 antipsychotic medication concurrently
Kasper, 2001	Yes	Yes	Fair	
Killian 2012	Yes (propensity scores)	Yes	Fair	
Kilzieh, 2008	Yes	Yes	Good	
Kim, 2008 (Effectiveness…)	No analysis of treatment visit frequency as a potential confounder. Frequency for RLAI group was every 2 weeks; oral was moly	Yes	Fair	
Kim, 2008 (Time…)	Yes	Yes	Fair	
Koller, 2003	No- descriptive summary statistics only.	Yes	Fair	
Kopala, 2005	No	Yes	Poor	
Koro, 2002a	Yes	Yes (3 at least mos)	Fair	
Koro, 2002b	Yes	Yes (mean 5.2 years)	Fair	

Evidence Table 4. Quality assessment of observational studies in patients with schizophrenia

Author, year	Non-biased selection?	Low overall loss to follow-up?	Outcomes pre-specified and defined?	Ascertainment techniques adequately described?	Non-biased and adequate ascertainment methods?
Kozma, 2004 (poster) United States	Yes	NR	Yes	Yes	Yes
Kraemer 2012	Yes (consecutive enrollment)	Yes; OC=14%, OD=15%	Yes	No	Unclear
Kraus, 1999	Yes	Not reported	Yes	Yes	Not reported if independent assessment of outcomes (but outcome was weight, so may be objective)
Kreyenbuhl 2011	Yes	Yes	Yes	No	Unclear (NR)
Lambert, 2005	Yes; baseline data similar between groups	NA (retrospective; only patients with data were analyzed)	Yes	Yes	Unclear: 2 authors examined charts without blinding, but did have high inter-rater reliability
Lambert, 2005	No, excluded patients that were not continuously eligible for Medi-Cal benefits	Yes: 5.4% at 24 weeks, 20.1% at 52 weeks	Yes	Yes	Yes
Lambert, 2006	Yes	None	Yes	Yes	Yes
Lee, 2002 United States	Yes	NR	Yes	Yes	Yes
Leslie, 2004	Not clear	Yes (retrospective study)	Yes	No	Not reported if blind or independent assessment of outcomes.

Evidence Table 4. Quality assessment of observational studies in patients with schizophrenia

Author, year	Statistical analysis of potential confounders?	Adequate duration of follow-up?	Overall quality assessment	Comments
Kozma, 2004 (poster) United States	Yes	Unclear	Fair	
Kraemer 2012	Yes, some	Yes (1 year)	Fair	
Kraus, 1999	No	4 weeks- not sure	Poor: unclear if all patients analyzed at all time points (no info on dropouts), no control for confounding factors.	
Kreyenbuhl 2011	Yes		Fair	
Lambert, 2005	No, although baseline groups were similar for known confounders	Yes, 18 mos	Fair	Two-group cohort; retrospective
Lambert, 2005	No	Yes	Poor	
Lambert, 2006	Yes	Yes	Good	
Lee, 2002 United States	Partial: Adjusted for age, sex, geographic region, diagnosis, hypertension, heart disease, and length of AP therapy. Did not adjust for dose.	Yes	Fair	79% of patients were only prescribed the index antipsychotic during the study period.
Leslie, 2004	No	Yes? (3 mos)	Poor- No control for confounding factors, not reported if outcome assessor blinded, definition of outcomes and ascertainment techniques not adequately described, unable to determine if selection was unbiased.	

Evidence Table 4. Quality assessment of observational studies in patients with schizophrenia

Author, year	Non-biased selection?	Low overall loss to follow-up?	Outcomes pre-specified and defined?	Ascertainment techniques adequately described?	Non-biased and adequate ascertainment methods?
Lieberman, 1992 Alvir 1993 United States	Yes	NR	No	No	Unclear
Lin, 2006	Yes	Unclear	Yes	Yes	Unclear; 2 senior psychiatrists (first and second authors) verified data but no information provided about inter-rater reliability or overall reliability
Lindstrom, 1989	NA (single-group study)	Yes (attrition 3/96)	Yes	No	Unclear
Lindstrom, 2007	Yes	Yes	Yes	No	Unclear
Lublin, 2003	Yes	None	Yes	No	Unclear
Lucey, 2003	Unclear. 396 patients charts reviewed, but selection of these not stated	Yes (retrospective study)	Yes	Yes	Yes
Lund, 2001 United States	Yes	NR	Yes	Yes	Yes
McIntyre, 2003 Canada Canadian National Outcomes Measurement Study in Schizophrenia (CNOMSS)	Yes	NR	Yes	No	Unclear

Evidence Table 4. Quality assessment of observational studies in patients with schizophrenia

Author, year	Statistical analysis of potential confounders?	Adequate duration of follow-up?	Overall quality assessment	Comments
Lieberman, 1992 Alvir 1993 United States	Yes	Yes	Fair	
Lin, 2006	Yes	Yes	Fair	
Lindstrom, 1989	NA (single-group study)	Yes, 13 years	Fair-poor	Single-group cohort, retrospective; unclear how outcomes were ascertained
Lindstrom, 2007	Partial	Yes	Poor	
Lublin, 2003	No	12 weeks	Poor	
Lucey, 2003	Partially, analysis took into account mean dose and center.	Yes, for the outcome measure of time to discharge	Fair	
Lund, 2001 United States	Yes	Yes	Good	
McIntyre, 2003 Canada Canadian National Outcomes Measurement Study in Schizophrenia (CNOMSS)	Yes	Yes	Fair	

Evidence Table 4. Quality assessment of observational studies in patients with schizophrenia

Author, year	Non-biased selection?	Low overall loss to follow-up?	Outcomes pre-specified and defined?	Ascertainment techniques adequately described?	Non-biased and adequate ascertainment methods?
Medved 2009	Unclear	Yes	Yes for metabolic features; no for metabolic syndrome	Yes	Yes
Meyer, 2002	No- excluded patients with incomplete data	Yes (retrospective study)	Yes	Yes	Not reported if independent assessment of outcomes
Miller, 1998	Not clear- identified patients from chart review.	Yes	Yes	Yes	Yes- blinded assessment of EPS
Mladsi 2004 Fair	Unclear	NR	Unclear	Yes	Yes
Modai, 2000 Israel	Yes	NR	Yes	Yes	Yes
Mohamed, 2009	Yes	NR	Yes	Yes	Yes
Moisan, 2005	Yes	None	Yes	Yes	Yes
Montes, 2003 Spain Sub-group Analysis from EFESO	Yes	Yes	Yes	No	Unclear

Evidence Table 4. Quality assessment of observational studies in patients with schizophrenia

Author, year	Statistical analysis of potential confounders?	Adequate duration of follow-up?	Overall quality assessment	Comments
Medved 2009	Yes for age or duration of illness; higher baseline triglyceride levels for olanzapine (1.91 vs 1.41 mmol; *P*= 0.017), but none of the clinical features tested as predictors in logistic regression on metabolic syndrome before SGA admission was significant.	No-3 mos	Fair	
Meyer, 2002	No	Yes (one year)	Poor- may be biased selection, independent outcome assessment not reported, no control for potential confounding factors.	
Miller, 1998	Yes	Yes, but time period on medications varied (45.3 mos clozapine, 13.4 mos risperidone, 92.5 mos conventional antipsychotics)	Fair	
Mladsi 2004 Fair	Yes	Yes	Fair	
Modai, 2000 Israel	Yes	Unclear	Fair	
Mohamed, 2009	Partial	Yes	Fair	
Moisan, 2005	Yes	6 mos	Good	
Montes, 2003 Spain Sub-group Analysis from EFESO	Yes	Yes	Fair	

Evidence Table 4. Quality assessment of observational studies in patients with schizophrenia

Author, year	Non-biased selection?	Low overall loss to follow-up?	Outcomes pre-specified and defined?	Ascertainment techniques adequately described?	Non-biased and adequate ascertainment methods?
Mullins, 2008	Yes	Yes	Yes	Yes	Unclear
Naber, 2001	Method NR, unable to determine.	No (4% missing SWN data, 3% missing PANSS data)	Yes	Yes	Not blinded
Ollendorf, 2004 United States	Yes	NR	Yes	Yes	Yes
Opolka, 2003	Unclear: groups differed but did adjust	NA (retrospective study including persons with available data only)	Yes	Yes	Unclear, don't know reliability of the database
Ostbye, 2004 United States	Yes	NR	Yes	Yes	Yes
Peacock, 1996 Denmark	No	NR	No	No	Not clear
Pelagotti, 2004	Yes	None	Yes	No	Unclear
Perez 2008	Unclear; groups differed but did adjust (e.g., quetiapine group had significantly greater proportions of comorbid mood disorders, previous hospitalizations, lower proportions of first episode status, and higher mean Calgary Depression Scale (CDSS) scores)	No; 50% for quetiapine and 42% for risperidone	Yes	Yes	Yes

Evidence Table 4. Quality assessment of observational studies in patients with schizophrenia

Author, year	Statistical analysis of potential confounders?	Adequate duration of follow-up?	Overall quality assessment	Comments
Mullins, 2008	Partial	Yes	Fair	
Naber, 2001	Yes	Yes	Fair	
Ollendorf, 2004 United States	Yes	Yes	Fair	
Opolka, 2003	Yes	Yes, 1 year	Fair	retrospective, 3-group cohort
Ostbye, 2004 United States	Partial: does not control for dose and duration of treatment	Yes	Poor	
Peacock, 1996 Denmark	NR	Yes	Poor	
Pelagotti, 2004	No	Minimal (4-7 mos) for Primary outcome 72 mos for secondary outcomes	Poor	
Perez 2008	Adjusted means analysis using ANCOVA performed for efficacy outcomes (i.e., adjusted for unspecified clinical relevant and unbalanced baseline variables); no adjustment for weight gain or rehospitalization, but neither demonstrated a significantly significant difference	Yes	Poor	

Evidence Table 4. Quality assessment of observational studies in patients with schizophrenia

Author, year	Non-biased selection?	Low overall loss to follow-up?	Outcomes pre-specified and defined?	Ascertainment techniques adequately described?	Non-biased and adequate ascertainment methods?
Peuskens 2009	Unclear; some differences in baseline disease history, e.g., lower proportion of "first antipsychotic prescription" with olanzapine than risperidone (18% vs 30%)	No, 33% in olanzapine group and 29% in risperidone group did not complete the study	Yes	No	Unclear whether weight was self-reported or measured and whether outcome assessor was blinded
Phillippe, 2005	Yes	No, n = 3470 at enrollment, n = 1574 at analysis	Not clearly	Survey	Not clear
Procyshyn, 1998	Yes	None (retrospective)	Yes	No	No; method of determining classification as "responder" from physician note NR; blinding of chart reviewer NR
Rascati, 2003	Yes, Used instrumental variables to adjust for differences	NA (retrospective study including persons with available data only)	Yes	Yes	Unclear, don't know reliability of the database
Ray 2009	Yes	Yes	Yes	No; who ascertained NR	Unclear; use of blinded, independent assessment NR; reliability of assessments NR
Reid, 1998 United States	Unclear	NR	Yes	No	Unclear
Remington, 2001	Unclear	None	Yes	No	No
Ren, 2006	Unclear: groups differed but did adjust	NA (retrospective study including persons with available data only)	Yes	Yes	Unclear, don't know reliability of the database
Rettienbacher 2010	Unclear (how pts selected not clearly described)	Unclear (132 were "included into the analysis").	Yes	Unclear (NR)	Unclear (NR)
Rettienbacher, 2006	Unclear	Unclear	Yes	No	No

Evidence Table 4. Quality assessment of observational studies in patients with schizophrenia

Author, year	Statistical analysis of potential confounders?	Adequate duration of follow-up?	Overall quality assessment	Comments
Peuskens 2009	No	Yes	Poor	
Phillippe, 2005	Yes	Yes	Fair	
Procyshyn, 1998	No	Yes	Fair	
Rascati, 2003	Yes, used instrumental variables	Yes, 365-d study period	Good	retrospective, 2-group cohort
Ray 2009	Yes	Yes	Fair	
Reid, 1998 United States	NR	Unclear	Poor	
Remington, 2001	No	Yes	Poor	
Ren, 2006	Yes	Yes, 6-mo	Fair	retrospective, 2-group cohort
Rettienbacher 2010	Yes	Unclear (f/u for at least 6 mos but unclear if this is long enough for this outcome)	Fair	Not sure what a clinically significant amount of time of f/u is for neutropenia.
Rettienbacher, 2006	No	Unclear	Poor	

Evidence Table 4. Quality assessment of observational studies in patients with schizophrenia

Author, year	Non-biased selection?	Low overall loss to follow-up?	Outcomes pre-specified and defined?	Ascertainment techniques adequately described?	Non-biased and adequate ascertainment methods?
Sax, 1998	Method NR, unable to determine.	No	Yes	Yes	Not reported if blind or independent assessment of outcomes.
Schillevoort, 2001a	Yes	Yes	Yes	Yes	Not reported (outcome assessor not specified)
Schillevoort, 2001b	Yes	Yes (retrospective study)	Yes	Yes	Not reported if blind or independent assessment of outcomes.
Sernyak, 2002	Yes	Yes	Yes	Yes	Not reported (outcome assessor not specified)
Shajahan, 2009	Yes	NA: Retrospective chart review	Yes	Yes	Probably OK. Investigators assigned CGI scores retrospectively based on medical record notes. Author states the validity of this method has been previously established.
Sharif, 2000	Yes	None (retrospective)	Yes	No information about the method the research assistant used to "assess symptom domain response" when reviewing the charts	No; after filling out structured rating forms during chart review, same unblinded research assistant blacked out identifying in formation, randomly assigned "X" or "O" to the blacked out forms and gave to research psychiatrists for interpretation
Snaterse, 2000	Unclear if chart review included ALL potential patients during the specified time period	None (retrospective)	Yes	No	Unclear; blinding NR

Evidence Table 4. Quality assessment of observational studies in patients with schizophrenia

Author, year	Statistical analysis of potential confounders?	Adequate duration of follow-up?	Overall quality assessment	Comments
Sax, 1998	No	Yes	Poor- no control for confounding factors, not reported if outcome assessors blinded or independent, unable to determine if selection was unbiased.	
Schillevoort, 2001a	Yes	Yes	Fair	
Schillevoort, 2001b	Yes	Yes	Fair	
Sernyak, 2002	Yes	Not sure- 4-mo period studied.	Fair	
Shajahan, 2009	Yes	Yes	Fair	
Sharif, 2000	No	Yes	Poor	
Snaterse, 2000	Yes; but no demographics	Yes	Fair	

Evidence Table 4. Quality assessment of observational studies in patients with schizophrenia

Author, year	Non-biased selection?	Low overall loss to follow-up?	Outcomes pre-specified and defined?	Ascertainment techniques adequately described?	Non-biased and adequate ascertainment methods?
Spivak, 1998 Israel	Yes	NR	Yes	Yes	Yes
Strassnig, 2007	Yes	None	Yes	Yes	Yes
Strous, 2006	Unclear; referrals from treating physicians and sampling frame time period NR	None	Yes	Yes	Unclear, details about weight measurement methods NR
Su, 2005	Not clear	Unclear - only states that 15 completed the study	Not clear	Yes	Unclear
Sumiyoshi 2004	Unclear; "on randomly assigned ds, all patients who visited the mental health center were contacted" and ultimately, "clinical data were obtained from 116 subjects meeting the study criteria"	Yes	Yes	Yes	Yes
Swanson, 2004	Unclear: groups differed but did adjust	75% retention both groups over 3 years; unclear if varied between groups	Yes	Yes	Yes; had multiple ascertainment methods
Tadger 2008	Unclear; selection methods NR	Yes; 4/70 excluded from analysis of increase/ decrease in BMI from risperidone/olanzapine groups	No	No	Unclear
Taylor, 2003	Unclear if sample of charts that were reviewed represent those of ALL potentially eligible charts; also excluded 2 charts with inadequate dosing information	None (retrospective)	Yes	No description of how "documented positive statement of treatment effectiveness" was defined	No, efficacy outcome very subjective and blinding NR
Taylor, 2005	Unclear	Yes	Yes	Yes	No

Evidence Table 4. Quality assessment of observational studies in patients with schizophrenia

Author, year	Statistical analysis of potential confounders?	Adequate duration of follow-up?	Overall quality assessment	Comments
Spivak, 1998 Israel	NR	Yes	Fair	
Strassnig, 2007	Some	Yes	Fair	
Strous, 2006	Some	No - 12 weeks	Fair	
Su, 2005	No	3 mos	Poor	
Sumiyoshi 2004	Yes for length of treatment, gender, age and race	Yes	Fair	
Swanson, 2004	Yes	Yes (3 years)	Fair	Prospective, 2-group cohort
Tadger 2008	No	Yes	Poor	
Taylor, 2003	Yes	Yes	Fair	
Taylor, 2005	No	No - 6 mos	Poor	

Evidence Table 4. Quality assessment of observational studies in patients with schizophrenia

Author, year	Non-biased selection?	Low overall loss to follow-up?	Outcomes pre-specified and defined?	Ascertainment techniques adequately described?	Non-biased and adequate ascertainment methods?
Taylor, 2008	Yes	N/A: Retrospective chart review	Yes	Yes	Yes
Taylor, 2009	Yes	Yes	Yes	Yes	Yes
Tiihonen 2009	Yes	Yes	Yes	Yes	Yes
Tiihonen 2011	Yes	Yes Unclear; data completeness NR	Yes	Unclear (NR)	Unclear (NR)
Tilhonen, 2006	Yes	None	Yes	Yes	Yes
Umbricht, 1994 United States	No	NR	Yes	Yes	Yes

Evidence Table 4. Quality assessment of observational studies in patients with schizophrenia

Author, year	Statistical analysis of potential confounders?	Adequate duration of follow-up?	Overall quality assessment	Comments
Taylor, 2008	Bivariate only	Yes	Fair	Unclear whether a patient that switched AAPs would occur multiple times in the analysis, potentially contributing discontinuation data to more than one drug.
Taylor, 2009	Insufficient. Matched on age and gender, but was not able to adjust for smoking; there were 3 lung cancer deaths in clozapine.	Yes	Fair	Unclear how meaningful the mortality difference is. In risperidone there were only 3 deaths (ages 45, 65, 81), so the 95%CI's for observed and expected mortality were large and overlapped with the clozapine mortality estimates.
Tiihonen 2009	Yes	Yes	Good	
Tiihonen 2011	Yes	Yes	Fair	
Tilhonen, 2006	Yes	Yes	Good	
Umbricht, 1994 United States	Yes	Yes	Fair	

Evidence Table 4. Quality assessment of observational studies in patients with schizophrenia

Author, year	Non-biased selection?	Low overall loss to follow-up?	Outcomes pre-specified and defined?	Ascertainment techniques adequately described?	Non-biased and adequate ascertainment methods?
Van Winkel 2008	Yes	Yes	Yes	Yes	Yes
Verma, 2001	No	Yes	Yes	Yes	No, unblinded raters
Voruganti, 2000	No, convenience sample probably does not represent all of the patients among the 600 that would meet inclusion criteria	No withdrawals reported.	No	Yes	Yes
Wang, 2002 U.S.	Yes	n/a	Yes	Yes	Yes
Weiser, 2000	Yes ("recruited randomly")	No withdrawals reported.	Yes	Yes	No- raters of ESRS not blinded; other assessments computerized
Wirshing, 2002	No- included only records with adequate laboratory data, and excluded those with a lack of compliance (excluded 63.6% of charts reviewed).	Yes (retrospective study)	Yes	Yes	Not stated if blinded or independent assessment of outcomes (but lab test, may be objective)
Kelly 2010	Unclear; numbers and reasons for exclusions NR	Unclear; racial distinction missing on 14%	Yes	Yes	Unclear how cause of death was adjudicated
Yood 2009	Yes	Yes (retrospective study)	Yes	Unclear	Unclear
Yu 2008	Yes	Yes	Yes	Yes	Unclear
Yu 2009	Yes	Unclear; completeness of data NR.	Yes	Yes	Unclear (lack of information about a validation study for accuracy)
Yu, 2009	Yes	N/A: Subjects were selected on minimum 1-year enrollment after prescription date	Yes	Yes	Yes

Evidence Table 4. Quality assessment of observational studies in patients with schizophrenia

Author, year	Statistical analysis of potential confounders?	Adequate duration of follow-up?	Overall quality assessment	Comments
Van Winkel 2008	No, and BMI was significantly greater for aripiprazole than olanzapine (28.4 vs 23.5 kg/m^2; $P<0.05$)	No - 3 mos	Poor	
Verma, 2001	No	Unclear, follow-up ended at discharge, but mean duration of inpatient stay not reported	Poor	
Voruganti, 2000	No, and there were baseline differences in disease severity (clozapine patients were sicker)	Yes	Poor	
Wang, 2002 U.S.	Yes	N/A (case-control)	Fair	
Weiser, 2000	Controlled for age only.	Yes	Fair	
Wirshing, 2002	Yes	Yes (tests within 2 1/2 years included)	Fair	
Kelly 2010	Unclear; higher proportion of smokers in clozapine group (61% vs 48%; $P=0.0002$) and no adjustment	Yes	Fair	
Yood 2009	Yes	Yes	Fair	
Yu 2008	Yes - propensity score matching	Yes	Fair	
Yu 2009	Yes (propensity scores)	Yes	Good	
Yu, 2009	Yes	Yes; followup fixed at 12 mos by design	Good	

Evidence Table 4. Quality assessment of observational studies in patients with schizophrenia

Author, year	Non-biased selection?	Low overall loss to follow-up?	Outcomes pre-specified and defined?	Ascertainment techniques adequately described?	Non-biased and adequate ascertainment methods?
Zhang 2007	Yes, recruited randomly	Yes	No; no specification of primary outcome variable or whether both endpoint BMI and BMI gain were pre-planned	Yes	Yes
Zhao, 2002	Unclear: groups differed but did adjust	NA (retrospective study including persons with available data only)	Yes	Yes	Unclear, don't know reliability of the database
Zhao, 2002	Yes	No withdrawals reported	No	Yes	No

Evidence Table 4. Quality assessment of observational studies in patients with schizophrenia

Author, year	Statistical analysis of potential confounders?	Adequate duration of follow-up?	Overall quality assessment	Comments
Zhang 2007	Unclear; states "where there was a significance in ANOVA, the effect of age, sex, duration of illness and neuroleptic dose were tested by adding these variables to the analysis model as co-variate", but no mention of results of these tests of co-variate regarding impact on significance of difference in BMI and BMI change between clozapine and risperidone	Yes	Poor	
Zhao, 2002	Yes	Yes, 1 year	Fair	retrospective, 2-group cohort
Zhao, 2002	Yes	Yes	Fair	

Evidence Table 5. Randomized controlled trials in patients with bipolar I disorder

Author, Year Country Trial name	Study design Setting	Eligibility criteria	Therapy type Interventions Duration
Berwaerts 2012 U.S.	RCT, DB, parallel Multicenter	Patients 18-65 years with DSM-IV criteria for bipolar disorder with most recent manic or mixed episides with or without psychotic features at the time of screening.≥2 previous documented mood episodes, one of which had to be manic or mixed episode) requiring treatment within 3 years before screening and a score of ≥20 on YMRS	Monotherapy Paliperidone ER 3-12 mg/d Olanzapine: 5-20 mg/d 3 week acute treatment, 12 week continuation phase, maintenance phase till at least 140 recurrences occurred among patients originally assigned to paliperidone ER
Bobo, 2011 USA	Randomized, open-label	18-60 years, principal diagnosis of bipolar I, II or NOS, MADRS score ≥15, BMI 21-32 Exclusions: diabetes, fasting blood glucose >124, random blood glucose >240, history of non-affective psychotic disorder	Olanzapine orally disintegrating tablets, titrated to 10-20 mg/d, mean dose 13.3 mg/d Olanzapine solid oral tablets, titrated to 10-20 mg/d, mean dose 16.5 mg/d 8 weeks

Evidence Table 5. Randomized controlled trials in patients with bipolar I disorder

Author, Year Country Trial name	Allowed other medications/ interventions	Age Gender Ethnicity	Other population characteristics	Number screened/ eligible/ enrolled	Number withdrawn/ lost to follow-up/ analyzed
Berwaerts 2012 U.S.	Benzodiazepine upto 8mg/day, clonazepam upto 4mg/ day, or diazepam upto 80mg/day allowed as rescue medications . Nonbenzodiazapine hypnotics at standard doses allowed for insomnia, beta adrenergic blockers for the relief of treatment emergent akathisia, and antiparkinsonianism medications for the relief of extrapyramidal symptoms allowed at any time during DB phases.	Acute/continuation phase Mean age (SD): 40 years (11.9) Women: 52% White: 62% Black: 12% Asian: 25% Other: 1% American Indian or Alaska Native:,1% Maintenance phase Mean age (SD): 20 (12.5) years Female: 55% White: 61% Black: 6% Asian: 31% Other: 1% American Indian or Alaska native: 1%	Acute/continuation phase Mean (SD)baseline BMI (kg/m2): 27 (6.5) Region North Americana nd European Union: 41% Rest of the world: 59% Prior antipsychotic use: 60% Primary diagnosis Manic: 80%, mixed: 20% Mean (SD) baseline YMRS score: 28.4 (5.75) Mean (SD) baseline MADRS score: 9.1 (7.32) Maintenance phase Mean (SD)baseline BMI (kg/m2): 27 (6.4) Region North Americana nd European Union:27% Rest of the world: 73% Prior antipsychotic use: 63% Primary diagnosis Manic: 85%, mixed: 15% Mean (SD) baseline YMRS score: 28.2 (5.63) Mean (SD) baseline MADRS score: 7.6 (6.35)	NR/NR/766	acute/continuation phase: 372/30/750 maintennace phase: 147/23/372
Bobo, 2011 USA	Non-benzodiazepine sleep-promoting agents	Mean age: 37.83 Gender: 56.5% female Ethnicity: 65.2% white, 34.8% African American	Diagnosis: Bipolar I, depressed: 47.8% Bipolar II, depressed: 30.4% Bipolar I, mixed: 13.0% Bipolar, NOS: 8.7%	39/27/23	4/4/2023

Evidence Table 5. Randomized controlled trials in patients with bipolar I disorder

Author, Year Country Trial name	Results	Adverse effects reported
Berwaerts 2012 U.S.	Paliperidone vs risperidone vs placebo Mood symptoms Patients with recurrence: 45% vs 23% vs 54% Time to recurrence of mood symptoms significantly longer with paliperidone ER vs placebo (p=0.017) Median time to recurrence (days): 558 vs NA (23% reported recurrence of any mood symptoms) vs 283. Post-hoc pairwse comparison time to recurrenvce significantly longer with olanzapine vs either treatment group (p≤0.001 vs either treatment group) Recurrence rate, NNT (95% CI) for prevention of recurrence of any mood symptoms at 12 months 38.6 %vs 15.8% vs 51.6%, NNT-Paliperidone: 8 (4 to 885), olanzapine 3 (2 to5) at 24 months: 58.2% vs 34.3% vs 71.9%, NNT Paliperidone: 8 (4 to -322), Olanzapine: 3 (2 to 5) Manic symptoms Time to recurrence significantly longer in paliperidone Er grup vs placebo (p<0.001), HR (placebo paliperidone ER) 2.06 (95% CI 1.32 to 3.22). time to recurrence based on post-hoc pairwise comparison olanzapine with placebo(p≤0.001), olanzapine with paliperidone ER (p=0.014) Depressive symptoms Placebo vs paliperidone ER: [HR (95% CI0: 0.88 (0.53 to 1.46), p=NS mean (SD) change from maintenance phase baseline in YMRS at endpoint, (p vs placebo): 4.2 (9.33) p<0.001, vs 1.3 (6.26) vs 9.0 (11.78), LSM (SE) minus placebo for paliperidone -4.5 (1.25) 95% CI (-6.92 to -1.98) mean (SD) hange from maintenance phase baseline in MADRS endpoint, (p vs placebo): 6.1 (10.10), p=0.763, vs 2.5 (7.10) vs 6.0 (9.16)LSM difference (SE) minus placebo 0.3 (1.12) 95% CI (-1.87 to 2.55)	Paliperidone ER vs olanzapine Acute phase Patients with TEAE: 61% vs 56% TEAE leading to death: <1% vs 0 Serious TEAE: 7% vs 7% Insomnia: 14% vs 10% Akathisia: 14% vs 7% Somnolence: 12% vs 16% Extrapyramidal disorder: 9% vs 3% Weight increased: 8% vs 12% Dizziness: 7% vs 3% Sedation: 6% vs 17% Tremor: 6% vs 3% Depression: 3% vs 3% Dry mouth: 5% vs 9% Increased appetite: 4% vs 9% Mania: 2% vs 5% Weight decreased: 1% vs 0 Maintenance phase Paliperidone ER vs Olanzapine vs Placebo Patients with TEAE: 55% vs 64% vs 59% TEAE leading to death: 1% vs 0 vs 0 Serious TEAE: 11% vs 10% vs 22% Insomnia: 9% vs 8% vs 10% Akathisia: 1% vs 2% vs 1% Somnolence: 3%vs 1%vs 0 Extrapyramidal disorder:1% vs 1% vs 1% Weight increased: 8% vs 8% vs 7% Dizziness: 3% vs 0 vs 1% Sedation: 0 vs 2% vs 0 Tremor: 1% vs 4% vs 0 Depression: 5% vs 2% vs 5% Dry mouth: 1% vs 1% vs 1% Increased appetite:1% vs 0% vs 0% Mania: 5% vs 6% vs 18% Weight decreased: 3% vs 1% vs 6%
Bobo, 2011 USA	NR	Orally disintegrating tablets vs. solid oral tablets, LS Mean (SE) Weight, kg: Week 1: 77.4(0.6) vs. 77.6(0.7); Week 2: 77.8(0.6) vs. 78.3(0.7); Week 4: 78.6(0.6) vs. 78.7(0.7); Week 6: 78.9(0.7) vs. 79.4(0.7); Week 8: 79.1(0.7) vs. 80.1(0.7); NSD betwee

Evidence Table 5. Randomized controlled trials in patients with bipolar I disorder

Author, Year Country Trial name	Total withdrawal; withdrawal due to averse events	Comment
Berwaerts 2012 U.S.	Acute phase Paliperidone ER vs olanzapine Total withdrawals: 50% vs 42% Withdrawals due to AE: 10% vs 9% Maintenance phase Paliperidone ER vs olanzapine vs placebo Total withdrawals: 37% vs 47% vs 35% Withdrawals due to AE: 3% vs 8% vs 3%	
Bobo, 2011 USA	4;0	

Evidence Table 5. Randomized controlled trials in patients with bipolar I disorder

Author, Year Country Trial name	Study design Setting	Eligibility criteria	Therapy type Interventions Duration
Harvey, 2007 USA	Randomized, DB cross-over	18-55 ys old DSM-IV diagnosis of bipolar I disorder in partial or full remission and a Young Mania Rating Scale score <or= 8 Exclusion- use of sedating medications; current diagnosis of MDD, mania, hypomania, psychosis, dysthymia, or catatonic behaviors.	Risperidone-quetiapine sequence received 2 mg of risperidone with dinner and P with breakfast during period 1 and 100 mg of quetiapine with dinner and 100 mg with breakfast during period 2.
Kwentus; Ortho NCT00309699-2007 U.S., Europe, Asia	DB RCT Multicenter	Men and women aged 18-65 with DSM-IV-diagnosed Bipolar I disorder, most recent episode manic or mixed, currently experiencing an acute manic or mixed episode; history of at least 1 previously documented manic or mixed episode requiring medical treatment within 3 ys, and a total score ≥ 20 on YMRS at screening and baseline.	Oral paliperidone XR, 3 to 12 mg/d Oral quetiapine 400 to 800 mg/d P 3-week DB acute phase, subjects hospitalized for first 7 ds; 9-week DB maintenance phase Subjects randomized to active treatment acute phase remained on same treatment in maintenance phase. Subjects initially on P crossed over to paliperidone ER (blinded) in maintenance phase.

Evidence Table 5. Randomized controlled trials in patients with bipolar I disorder

Author, Year Country Trial name	Allowed other medications/ interventions	Age Gender Ethnicity	Other population characteristics	Number screened/ eligible/ enrolled	Number withdrawn/ lost to follow-up/ analyzed
Harvey, 2007 USA	Yes if they were stable for the proceeding 8 weeks.	Mean age 40.9 ys 71% male 32% white 61% black 7% other	DSM-IV diagnosis (patients) Hypomanic or manic episode: Partial remission: 1 (3.6%) Full remission: 3 (10.7%) Major depressive episode Partial remission: 1 (3.6%) Full remission: 19 (67.8%) Mixed episode in full remission: 2 (7.1%) Current or most recent episode in full remission: 2 (7.1%) ys since diagnosis: 10.0 YMRS total score: 2.9 MADRS total score: 5.6	NR/NR/30	2/NR/28
Kwentus; Ortho NCT00309699-2007 U.S., Europe, Asia	NR	NR	NR	NR/NR/493	37/0/491

Evidence Table 5. Randomized controlled trials in patients with bipolar I disorder

Author, Year Country Trial name	Results	Adverse effects reported
Harvey, 2007 USA	see AEs	Risperidone vs. Quetiapine Total AEs 18 vs. 36 at least 1 AE 14 vs. 25 p < 0.05 vs. risperidone Somnolence 9 vs. 24 p < 0.05 vs. risperidone Fatigue 4 vs. 6 Dry mouth 0 vs. 3 Headache 2 vs. 0 Carpal tunnel 1 vs. 0 Dystonia 1 vs. 0 Nausea 1 vs. 0 Blurred vision 0 vs. 1 Nasal congestion 0 vs. 1
Kwentus; Ortho NCT00309699-2007 U.S., Europe, Asia	Paliperidone ER vs quetiapine vs P: % of responders: 55.8 vs 49.0 vs 34.6 Mean (SD) change from baseline to 3-week endpoint (LOCF); P-value for paliperidone vs P: YMRS total score: -13.2 (8.68) vs -11.7 (9.28) vs -7.4 (10.74); p<0.001 GAF 12.2 (11.17) vs 11.6 (11.96) vs 6.7 (13.56); p<0.001 P-value for paliperidone ER relative to P at 3 weeks, results NR: CGI-BP-S: p<0.001 PANSS: p=0.002 Sleep VAS: p<0.001 Paliperidone ER v. quetiapine, mean (SD) change from baseline to 12-week endpoint (LOCF): YMRS total score -15.2 (10.26) vs -13.5 (11.02); p=NS	1 suicide in quetiapine during maintenance phase; 1 suicide in P/paliperidone ER group 5 ds after WDal from study (timing of WDal NR). Depression: 5 (5%) in P/paliperidone ER and 14 (7%) in paliperidone ER; 0 in quetiapine Paliperidone ER vs quetiapine vs P: % of subjects with abnormally high heart rate: 20 vs 19 vs 10 % of subjects with ≥7% weight increase at end of maintenance phase: 8 v 17 v 6 EPS: akathisia, hypertonia, drooling, extrapyramidal disorder, and muscle spasms more frequent in paliperidone ER than P, results NR. % of subjects receiving anticholinergic medications during acute treatment phase: 17 vs 7 vs 5. % of subjects with prolactin-related AEs during combined acute and maintenance phases: 5 vs 3 vs 2. Mean (SD) increases in prolactin (ng/mL) at 3-week endpoint: Paliperidone ER: 24.61 (23.98) in males; 89.77 (81.47) in females. P: -1.03 (14.08) in males; 7.15 (31.82) in females Quetiapine: No increase in mean prolactin.

Evidence Table 5. Randomized controlled trials in patients with bipolar I disorder

Author, Year Country Trial name	Total withdrawal; withdrawal due to averse events	Comment
Harvey, 2007 USA	WD 2 due to AEs 0	
Kwentus; Ortho NCT00309699-2007 U.S., Europe, Asia	Total WD NR; 37 WD due to AEs	

Evidence Table 5. Randomized controlled trials in patients with bipolar I disorder

Author, Year Country Trial name	Study design Setting	Eligibility criteria	Therapy type Interventions Duration
McIntyre 2009 Olympia Clinical Trial Program United States, India, Russia, Ukraine, Korea, Bulgaria, Philippines, Romania, Turkey, Malaysia	RCT, DB Multicenter (55)	Inclusion: Patients ≥18 ys old with DSM-IV diagnosed bipolar I disorder; with current manic or mixed bipolar I episode that began ≤3 mos before screening visit; YMRS total score ≥20; history of >1 previous episode. Exclusion: women who were or could become pregnant; psychotic disorder; rapid-cycling bipolar disorder during past y; DSM-IV substance dependence; positive screen for psychomotor stimulants; seizure disorder; HIV; unstable medical condition or lab abnormality; previously participated in asenapine trial; clozapine within 12 weeks; investigational drug within 30 ds of baseline.	Asenapine sublingual, flexible dose (5 or 10 mg BID; mean 18.2 mg/d), N=194 Oral olanzapine (5-20 mg QD, mean 15.8 mg/d), N=191. P, N=104. 3 weeks
McIntyre, 2009 Bulgaria, India, Malaysia, Philippines, Republic of Korea, Romania, Russia, Turkey, Ukraine, and the United States	DB extension trial Multicenter	Patients who completed one of the 3-week trials (Ares 7501004, Ares 7501005) were eligible for the extension study if they wished to participate, if they had no major protocol violations, and if the investigator judged that continued treatment could be of clinical benefit; those who did not complete a 3-week trial were excluded from the extension study.	Flexible dose Sublingual asenapine (5-10 mg) BID vs oral olanzapine (5-20mg) QD extended for 9 weeks Note: Patients who had received P in the 3-week trials were blindly switched to asenapine (labelled as P/asenapine group)

Evidence Table 5. Randomized controlled trials in patients with bipolar I disorder

Author, Year Country Trial name	Allowed other medications/ interventions	Age Gender Ethnicity	Other population characteristics	Number screened/ eligible/ enrolled	Number withdrawn/ lost to follow-up/ analyzed
McIntyre 2009 Olympia Clinical Trial Program United States, India, Russia, Ukraine, Korea, Bulgaria, Philippines, Romania, Turkey, Malaysia	EPS medications, benzodiazepines, and non-benzodiazepine sedative-hypnotics allowed only for first 7 ds. Allowed hormonal birth control, anti-hypertensives, diuretics, and oral hypoglycemics. Aspirin and NSAIDS as needed.	Mean age 39.4 57.4% male White 60.5% Black 16.6% Asian 18.0% Other 4.9%	Type of episode: Mania 69.3% Mixed 30.7%	654 screened / NR eligible / 489 enrolled	151/9/488
McIntyre, 2009 Bulgaria, India, Malaysia, Philippines, Republic of Korea, Romania, Russia, Turkey, Ukraine, and the United States	Lorazepam up to 4 mg/d for agitation, aspirin or nonsteroidal anti-inflammatory drugs for pain, and antiparkinsonian medications for EPS; hypnotics/ benzodiazepines (zolpidem 10 mg/d, zaleplon 20 mg/d, or temazepam up to 30 mg/d for no more than 3 nights per week) were permitted for insomnia.	P/Asenapine vs Asenapine vs Olanzapine Mean age (SD): 40 (13.1) vs 39.1 (13.0) vs 39.6 (11.9) ys Male: 48% vs 54% vs 59% White: 59 (63) vs 108 (60) vs 131 (57) Black: 19 (20) vs 20 (11) vs 27 (12) Asian or other: 16 (17) vs 53 (29) vs 71 (31)	Asenapine vs Olanzapine Mean YMRS total score (SD): 29.0 (6.1) vs 28.8 (5.9) Mean MADRS (SD): 9.7 (7.3) vs 10.3 (7.1)	680/NR/504	196/42/397 (see comments)

Evidence Table 5. Randomized controlled trials in patients with bipolar I disorder

Author, Year Country Trial name	Results	Adverse effects reported
McIntyre 2009 Olympia Clinical Trial Program United States, India, Russia, Ukraine, Korea, Bulgaria, Philippines, Romania, Turkey, Malaysia	Asenapine vs. olanzapine vs. P: Change in total score from baseline to d 21, mean ± SD; P-value vs. P: YMRS: -10.8 ± 0.8 vs. -12.6 ± 0.8 vs. -5.5 ± 10; both treatments P<0.0001. CGI-BP: -1.2 ± 0.1; P ≤0.01 vs. -1.4 ± 0.1; P ≤0.0001 vs. -0.7 ± 0.13 MADRS: -3.2 ± 0.5; P=ns vs. -4.2 ± 0.5; P ≤ 0.01 vs. -1.8 ± 0.7 Response rate: 42.3% vs. 50% vs. 25.2% Proportion of remitters: 40.2% vs. 39.4% vs. 22.3%	Asenapine (N=194) vs P (N=105) vs olanzapine (N=189), % of group: Mania 3.1 vs 2.9 vs 1.1 Agitation 1 .0 vs 0 vs 1.1 Sedation 18.6 vs 4.8 vs 18.5 Dizziness 11.9 vs 3.8 vs 8.5 Somnolence 8.8 vs 1.9 vs 7.4 Fatigue 6.2 vs 1.0 vs 4.8 Oral hypoesthesia 5.2 vs 1.0 vs 1.1 Dry mouth 4.1 vs 1.0 vs 14.3 Weight increase 3.1 vs 1.0 vs 6.9 Any EPS related AE 7.2 vs 2.9 vs 7.9 AIMS score ≥2: 1.1 vs 1.0 vs 1.6 BARS global score ≥2: 7.4 vs 5.2 vs 7.9 SAS mean total score >0.3: 5.5 vs 2.0 vs 2.8 Mean weight change, kg: 1.6 vs 0.3 vs 1.9
McIntyre, 2009 Bulgaria, India, Malaysia, Philippines, Republic of Korea, Romania, Russia, Turkey, Ukraine, and the United States	asenapine vs olanzapine Mean change YMRS total score (SD): -20.1 (10.7) vs -21.3 (9.6) Response rate: 77% vs 82% Remission rate: 75% vs 79% Mean change MADRS (SE): -3.6 (0.69) vs -2.4 (0.61); *P* =NS	P/Asenapine vs Asenapine vs Olanzapine Mean change in SAR-S (SD): -0.2 (1.07) vs 0.1 (1.3) vs -0.1 (1.74) Mean change in BARS (SD): -0.4 (1.55) vs 0.1 (1.3) vs -0.1 (1.13) Mean change in AIMS (SD): 0 (0.33) vs 0 (0.31) vs 0 (0.23) n (%) All AEs: 72 (77) vs 139 (77) vs 178 (78) All serious AEs: 13 (14) vs 22 (12) vs 22 (10) Sedation: 8 (9) vs 26 (14) vs 40 (18) Dizziness: 7 (7) vs 24 (13) vs 15 (7) Insomnia: 8 (9) vs 23 (13) vs 23 (10) Headache: 13 (14) vs 21 (12) vs 34 (15) Somnolence: 13 (14) vs 21 (12) vs 33 (14) Nausea: 11 (12) vs 15 (8) vs 7 (3) Weight gain: 3 (3) vs 14 (8) vs 33 (14) Constipation: 10 (11) vs 10 (6) vs 10 (4) Dry mouth: 3 (3) vs 7 (4) vs 25 (11) Akathisia: 4 (4) vs 13 (7) vs 20 (9) Parkinsonism: 3 (3) vs 10 (6) vs 4 (2) Dystonia: 3 (3) vs 6 (3) vs 5 (2) Bradykinesia: 0 vs 4 (2) vs 3 (1)

Evidence Table 5. Randomized controlled trials in patients with bipolar I disorder

Author, Year Country Trial name	Total withdrawal; withdrawal due to averse events	Comment
McIntyre 2009 Olympia Clinical Trial Program United States, India, Russia, Ukraine, Korea, Bulgaria, Philippines, Romania, Turkey, Malaysia	151 WD 35 due to AEs	
McIntyre, 2009 Bulgaria, India, Malaysia, Philippines, Republic of Korea, Romania, Russia, Turkey, Ukraine, and the United States	Total WD: 196 WD due to AEs: 64	Patients who had received P in the 3-week trials were blindly switched to asenapine and these patients were included in the safety analyses only.

Evidence Table 5. Randomized controlled trials in patients with bipolar I disorder

Author, Year Country Trial name	Study design Setting	Eligibility criteria	Therapy type Interventions Duration
Nejtek 2008 Texas, USA	DB RCT 2 psychiatric centers	Men and women, 20-50 ys, concurrent DSM-IV-defined bipolar I or II disorder and cocaine or methamphetamine dependence.	Monotherapy quetiapine 303.6 +/- 151.9 mg/d risperidone 3.1 +/- 1.2 mg/d . 20 weeks
Perlis, 2007 USA	RCT, DB. Multicenter	18-70 ys old; YMRS => 20; DSM-IV criteria for bipolar I disorder, manic or mixed episode, without psychotic features. Exclusion- serious suicide risk; DSM-IV substance abuse w/in 2 mos (except caffeine and nicotine); current hospitalization > 3 weeks; >= 90 ds current manic or mixed episode: previous failure to study drugs in past.	Olanzapine (5-20 mg/d; N = 165) and risperidone (1-6 mg/d; N = 164) 3 weeks

Evidence Table 5. Randomized controlled trials in patients with bipolar I disorder

Author, Year Country Trial name	Allowed other medications/ interventions	Age Gender Ethnicity	Other population characteristics	Number screened/ eligible/ enrolled	Number withdrawn/ lost to follow-up/ analyzed
Nejtek 2008 Texas, USA	Allowed to enter study with up to 2 psychotropics and treatments for general medical condition i.e. hypertension treatments, acute antibiotics and OTC cold and allergy medications	Quetiapine vs. Risperidone Age 52 (25) vs.. 54 (25) White (%) 71 vs.. 70 Black (%) 29 vs. 24 Hispanic (%) 0 vs. 6	Quetiapine vs. Risperidone Bipolar 1 79% vs. 89% Bipolar 2 21% vs. 11% Duration of illness yrs 24.7 vs.. 23.3	651/NR/124	80 (32 quetiapine and 34 risperidone)/25/80
Perlis, 2007 USA	Benztropine mesylate and lorazepam	Mean age 38 ys 45.3% male 73.6 white	Bipolar subtypes (% patients) Mixed: 58.7 Rapid cycling: 45.3 Mean scale scores CGI-BP=4.4 YMRS=26.6 HAM-D-21: 15.8 MADRS=16.3	NR/329/329	90/16/329

Evidence Table 5. Randomized controlled trials in patients with bipolar I disorder

Author, Year Country Trial name	Results	Adverse effects reported
Nejtek 2008 Texas, USA	Most results in graphs Kaplan -Meier survival analyses Quetiapine vs. Risperidone YMRS <9 at 3 weeks 40% vs. 24% IDS-C-30 remission by 6 weeks 40% vs. 50% 51% abstained from drug use during the intervention	Quetiapine vs. Risperidone Dizziness 2 vs. 1 Clumsiness 2 vs. 2 Blurred vision 1 vs. 3 Headache 3 vs. 3 Nervousness 7 vs. 3 Nausea or vomiting 2 vs. 1 Sexual difficulties 3 vs. 3 Diarrhea 1 vs. 1 Constipation 1 vs. 0 Dry mouth 3 vs. 1 Decreased appetite 3 vs 3 Increased appetite 6 vs 2 Tiredness 9 vs 6 Increased perspiration 1 vs 1 dtime sleepiness 6 vs 5
Perlis, 2007 USA	Between treatments, there was no difference in mean change in the YMRS, MADRS, CTD, PGWB, or SF-12 measures or in remission or response rates Olanzapine vs. risperidone Study completers 78.7% vs. 67.0%; p = .019	Olanzapine vs. risperidone (%) Sedation 31.5 vs. 27.4 Headache 12.7 vs. 15.2 Dry mouth 28.5 vs. 14.0 Appetite increase 13.9 vs. 11.0 Dizziness 13.9 vs 11.0 Akathisia 7.9 vs. 10.4 Weight increase 16.4 vs. 3.7

Evidence Table 5. Randomized controlled trials in patients with bipolar I disorder

Author, Year Country Trial name	Total withdrawal; withdrawal due to averse events	Comment
Nejtek 2008 Texas, USA	80 WD, none due to AEs	
Perlis, 2007 USA	Total WD 90 due to AEs 23	

Evidence Table 5. Randomized controlled trials in patients with bipolar I disorder

Author, Year Country Trial name	Study design Setting	Eligibility criteria	Therapy type Interventions Duration
Schering-Plough, Data on File, Study 7501004 United States, Bulgaria, India, Korea, Malaysia, Philippines, Romania, Russia, and Ukraine	DB RCT Multicenter	Inclusion: adult patients (>18 ys of age) with a primary diagnosis of bipolar I disorder; a YMRS score >20 at screening and baseline; a manic or mixed episode that began within 3 mos of screening; at least one previous moderate to severe mood episode, with or without psychotic features. .	Flexible dose Sublingual asenapine (5-10 mg) BID vs P BID vs Olanzapine (5-20mg) QD 3 weeks
Vieta, 2010 Worldwide	RCT, DB Hospitalized ≥7 days	18-65 years, DSM-IV diagnoses of bipolar I disorder, experiencing acute manic or mixed episodes, ≥1 manic or mixed episode requiring treatment in prior 3 years, Young Mania Rating Scale of ≥20. Excluded DSM-IV criteria for rapid cycling, shizoaffective disorder, known or suspected antisocial personality disorder or history of substance abuse.	A. Paliperidone ER, 3-12 mg/d flexible dose B. Quetiapine, 400-800 mg/d initially titrated, then flexible dose C. Placebo Placebo patients switched to Paliperidone after 3 week acute treatment phase, but remained blinded

Evidence Table 5. Randomized controlled trials in patients with bipolar I disorder

Author, Year Country Trial name	Allowed other medications/ interventions	Age Gender Ethnicity	Other population characteristics	Number screened/ eligible/ enrolled	Number withdrawn/ lost to follow-up/ analyzed
Schering-Plough, Data on File, Study 7501004 United States, Bulgaria, India, Korea, Malaysia, Philippines, Romania, Russia, and Ukraine	NR	asenapine vs P vs olanzapine Mean age (SD): 39.1 (12.26) vs 38.1 (12.49) vs 38.4 (10.82) ys Female: 50.3% vs 51% vs 42.9% Caucasian: 56.2% vs 56.1% vs 53.7% Black: 20.5% vs 16.3% vs 20% Asian: 21.6% vs 22.4% vs 21.5% Other: 1.6% vs 5.1% vs 4.9%	asenapine vs P vs olanzapine Diagnosed with Bipolar I disorder, manic: 69.7% vs 67.3% vs 68.8% Diagnosed with Bipolar I disorder, mixed: 30.3% vs 32.7% s 31.2%	NR/NR/488	146/11/480
Vieta, 2010 Worldwide	lorazepam, diazepam, anticholinergics and antihistamines	Age: 39.18 Gender: 42.4% female Ethnicity: White, 67.9%; Black, 21.2%; Asian, 9.87%; Other, 1.03	Bipolar disorder, Manic, 64.8% Bipolar disorder, Mixed, 35.2% Duration of current episode: 23.69 days	643/NR/493	261/36/486

Evidence Table 5. Randomized controlled trials in patients with bipolar I disorder

Author, Year Country Trial name	Results	Adverse effects reported
Schering-Plough, Data on File, Study 7501004 United States, Bulgaria, India, Korea, Malaysia, Philippines, Romania, Russia, and Ukraine	asenapine vs P vs olanzapine Mean change in YMRS score (SE): -11.5 (0.8) vs -7.8 (1.11) vs -14.6 (0.76); P<0.007 for asenapine vs P and P<0.0001 for olanzapine vs P YMRS response rate: 42.6% vs 34% vs 54.7%; P=0.001 for olanzapine vs P YMRS remission rate: 35.5% vs 30.9% vs 46.3%; P=0.016 for olanzapine vs P	asenapine vs P vs olanzapine n (%) ≥1 treatment-emergent AE: 140 (75.7) vs 55 (56.1) vs 136 (66.3) Somnolence: 22 (11.9) vs 3 (3.1) 23 vs (11.2) Dizziness: 19 (10.3) vs 2 (2.0) vs 13 (6.3) Sedation: 16 (8.6) vs 3 (3.1) vs 29 (14.1) Weight Increase: 12 (6.5) vs 0 (0.0) vs 19 (9.3) Vomiting: 10 (5.4) vs 2 (2.0) vs 4 (2.0) Increased appetite: 7 (3.8) vs 1 (1.0) vs 13 (6.3) Extrapyramidal symptoms: 19 (10.3) vs 3 (3.1) vs 14 (6.8) --Akathisia: 10 (5.4) vs 3 (3.1) vs 10 (4.9) Mean changes from baseline in laboratory values, metabolic parameters, and vital signs were not of clinical significance.
Vieta, 2010 Worldwide	Change from baseline, placebo vs. paliperidone vs. quetiapine; p-values vs. placebo 3-weeks: PANSS: -5.3 (11.90) vs. -9.2 (11.13), p=0.002 vs. -8.1 (10.77), p=0.015 CGI-BP-S: -0.5 (-3 to 2) vs. -2.0 (-4 to 2), p<0.001 vs. -1.0 (-4 to 2), p<0.001 12-weeks, placebo/paliperidone vs. paliperidone vs. quetiapine: PANSS: -4.8 (12.15) vs. -8.7(12.46) vs. -9.9(12.48), p=0.227 CGI-BP)-S: -1.0 (-4 to 2) vs. -2.0 (-5 to 1) vs. -2.0 (-5 to 2), p=0.723 Responders at 12-weeks, paliperidone vs. quetiapine: 64.7% vs. 57.8%	Acute treatment phase, placebo vs. paliperidone vs. quetiapine: All AEs: 66 vs. 127 vs. 147 EPS-related AEs ≥3% more frequently in paliperidone group vs. placebo: Treatment and Maintenence phases: akathisia, hypertonia, drooling, Treatment phase only: extrapyramidal disorder, and muscle spasm Maintenence phase, placebo/paliperidone vs. paliperidone vs. quetiapine: Death: 1 vs. 0 vs. 1

Evidence Table 5. Randomized controlled trials in patients with bipolar I disorder

Author, Year Country Trial name	Total withdrawal; withdrawal due to averse events	Comment
Schering-Plough, Data on File, Study 7501004 United States, Bulgaria, India, Korea, Malaysia, Philippines, Romania, Russia, and Ukraine	Total WD: 146 WD due to AEs: 34	Inconsistency in reporting of discontinuation due to AEs: reported 28 cases (page 51) and reported 34 cases (Table 1; page 53). The higher number was extracted.
Vieta, 2010 Worldwide	261/38	

Evidence Table 6. Quality assessment of randomized controlled trials of patients with bipolar disorder

	Internal validity						
Author, year	**Randomization adequate?**	**Allocation concealment adequate?**	**Groups similar at baseline?**	**Eligibility criteria specified?**	**Outcome assessors masked?**	**Care provider masked?**	**Patient masked?**
Altamura, 2003	NR	NR	Yes	Yes	Unclear	No	No
Amsterdam, 2005	Method not described	NR	No; differences in illness duration among the arms (range 15-24 years) and episode duration (12-30 months)	Yes	Unclear, reported as DB	Unclear, reported as DB	Unclear, reported as DB
AZ-D1447C00144	Method not described	Method not described	Yes	Yes	Stated as double-blind	Stated as double-blind	Yes
AZ-D144CC00004	Method not described	Method not described	Yes	Yes	Stated as double-blind	Stated as double-blind	Yes
Berwaerts, 2012	Yes	Yes, IVRS	Yes	Yes	Yes	Yes	Yes
Bobo, 2011	Yes	Unclear	Mostly, slightly more bipolar 1 patients in the orally disintegrating tablet group	Yes	NR	No, open label	No, open label

Evidence Table 6. Quality assessment of randomized controlled trials of patients with bipolar disorder

Author, year	Reporting of attrition, crossovers, adherence, and contamination	Loss to follow-up: differential/high	Intent-to-treat analysis	Maintenance of comparable groups	Quality rating	Comments
Altamura, 2003	NR, NR, NR, NR	NR NR	Unclear		Poor	
Amsterdam, 2005	Yes, NR, NR, NR	~41% discontinued before end of trial Differential: NR	NR; preliminary efficacy analyses were descriptive; did not specify which population they used for their analyses and how missing data were to be handled		Poor	Is 8 weeks long enough time to assess whether fluoxetine doesn't induce mania?
AZ-D1447C00144	Yes, NR, NR, Yes	NR NR	No 1172/1226 (95.6%) included	NR	Fair	
AZ-D144CC00004	NR, NR, NR, NR	NR NR	No Not all randomized were evaluated. Reported 96.1% and 98.8% in efficacy ITT	NR	Fair	
Berwaerts, 2012	Crossover-unclear adherence-yes contamination-unclear	Overall-Yes 59% overall, 37% from the maintenance phase, Differential-No	No; analysis excluded 6% in the maintenance phase	Yes	Fair	
Bobo, 2011	Yes, NR, NR, NR	Differential: Yes, 31% from orally disintegrating tablets group vs. 0%, Overally: No	Yes	Unclear, completers and noncompleters did not differ but NR for each group.	Fair	

Evidence Table 6. Quality assessment of randomized controlled trials of patients with bipolar disorder

Internal validity

Author, year	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors masked?	Care provider masked?	Patient masked?
Brecher, 2003 Poster	NR	NR	Yes	Yes	Yes	Yes	Yes
Brown 2008	NR	NR	Mostly, quetiapine group had more white participants than the placebo group and YMRS scores were higher in the placebo group	Yes	NR	Stated as double-blind	Yes
Calabrese, 2004 Poster	NR	NR	Yes	Yes	Yes	Yes	Yes
Cutler; Ortho - NCT00299715-2007	NR	NR	Sample characteristics NR	Yes	NR	Stated as double-blind	Yes
Harvey, 2007	Method not described	NR	Yes	Yes	Unclear, reported as DB	Unclear, reported as DB	Unclear, reported as DB

Evidence Table 6. Quality assessment of randomized controlled trials of patients with bipolar disorder

Author, year	Reporting of attrition, crossovers, adherence, and contamination	Loss to follow-up: differential/high	Intent-to-treat analysis	Maintenance of comparable groups	Quality rating	Comments
Brecher, 2003 Poster	Yes, NR, NR, NR	No No	LOCF		Fair	
Brown 2008	Yes, No, No, No	No No	Yes; only (13; 11%) excluded participants from analysis without a postbaseline assessment		Fair	
Calabrese, 2004 Poster	Yes, NR, NR, NR	NR NR	LOCF		Fair	
Cutler; Ortho - NCT00299715-2007	Partially: reported attrition due to AEs No No No	No No	Yes; 2 (0.4%) subjects excluded from efficacy analysis	NR	Fair	
Harvey, 2007	Yes, Yes, Adherence-subjects stayed at the testing site to ensure compliance, NR	~7% (2/30) withdrew Differential: low	No, but 93% completed the study		Fair	Evaluating cognitive fxn is important but this study did not evaluate the long-term effects. The duration of the study needs to longer in

Evidence Table 6. Quality assessment of randomized controlled trials of patients with bipolar disorder

	Internal validity						
Author, year	**Randomization adequate?**	**Allocation concealment adequate?**	**Groups similar at baseline?**	**Eligibility criteria specified?**	**Outcome assessors masked?**	**Care provider masked?**	**Patient masked?**
Hirschfeld, 2004	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Houston, 2009	NR	NR	Yes	Yes	Stated as DB	Stated as DB	Stated as DB
Keck 2009	NR	NR	Mostly; placebo group had more white participants	Yes	NR	Stated as double-blind	Stated as double-blind
Keck, 2003	NR	NR	Yes	Yes	Yes	Yes	Yes

Evidence Table 6. Quality assessment of randomized controlled trials of patients with bipolar disorder

Author, year	Reporting of attrition, crossovers, adherence, and contamination	Loss to follow-up: differential/high	Intent-to-treat analysis	Maintenance of comparable groups	Quality rating	Comments
Hirschfeld, 2004	Yes, NR, NR, NR	No No	No; 12 (4.6%) excluded from endpoint analysis; 3 because they didn't have "at least two efficacy assessments", and 9 from one site due to GCP noncompliance or protocol violations ("repeat patients"); no mention of results from "worst case scenario" sensitivity analysis that included those 12 patients; data on file, submitted 11/9/04 was included in this consideration.		Fair	
Houston, 2009	Yes, No, No, No	No, No	NR Reported ITT was conducted but data to support ITTY not provided	Yes	Fair	
Keck 2009	Yes, No, No, No	No; No	Yes; only people (8) excluded from analysis were those without a postbaseline assessment		Fair	
Keck, 2003	Yes, NR, NR, NR	NR NR	No		Fair	

Evidence Table 6. Quality assessment of randomized controlled trials of patients with bipolar disorder

Internal validity

Author, year	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors masked?	Care provider masked?	Patient masked?
Keck, 2006	Method not described	NR	No; more males were randomized to aripiprazole than placebo; more patients with mania randomized to placebo arm and more subjects with mixed-type BPAD randomized to aripiprazole arm	Yes	Unclear reported as DB. Note: 'experienced raters' administered efficacy scales and effort was made to ensure that same raters were used but the authors did not specify whether they were blinded to treatment allocation	Unclear, reported as DB	Unclear, reported as DB
Khanna, 2003	NR	NR	Yes	Yes	Yes	Yes	Yes
Kwentus; Ortho NCT00309699-2007	NR	NR	Sample characteristics NR	Yes	NR	Stated as double-blind	Yes
Macfadden 2009	NR	NR	No RLAT group older at 1st diagnosis of bipolar I	Yes	Yes for relapse (independent relapse monitoring board)	Stated as double-blind	Yes
McElroy 2010 (EMBOLDEN II)	NR	Yes	Yes	Yes	Yes	Yes	Yes
McIntyre 2009	NR	NR	Yes Very little comparison data provided	Yes	Stated as double-blind	Stated as double-blind	Yes

Evidence Table 6. Quality assessment of randomized controlled trials of patients with bipolar disorder

Author, year	Reporting of attrition, crossovers, adherence, and contamination	Loss to follow-up: differential/high	Intent-to-treat analysis	Maintenance of comparable groups	Quality rating	Comments
Keck, 2006	Yes, NR, NR, NR	58.4% withdrew Differential: ~16% difference between placebo and aripiprazole arm	Yes		Fair	
Khanna, 2003	Yes, NR, NR, NR	No No	LOCF		Fair	
Kwentus; Ortho NCT00309699-2007	Yes No No No	No No	Yes; analyses only excluded 2 (0.4%) patients who discontinued before receiving study medication	NR	Fair	
Macfadden 2009	Yes, No, Yes, No	No No	No Patients with > 1 dose study medication included. Data not reported	NR	271 (240 enrolled in stabilization phase)/183/124	
McElroy 2010 (EMBOLDEN II)	Yes, No, No, No	No, Yes (36%)	Yes, 95% included in analysis using LOCF	Yes	Fair	
McIntyre 2009	Yes, No, No, No	No No	No 480/489 (98.2%) included	Yes	654/NR/489	

Evidence Table 6. Quality assessment of randomized controlled trials of patients with bipolar disorder

Internal validity

Author, year	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors masked?	Care provider masked?	Patient masked?
McIntyre 2009 3-week	Method not described	NR	No MADRS, ALT,AST,CK higher in placebo group	Yes	Stated as double-blind	Stated as double-blind	Yes
McIntyre 2009 Asenapine vs. olanzapine	Method not described	NR	Yes	Yes	Stated as double- blind	Stated as double-blind	Stated as double-blind
Morozova; Ortho NCT00132678-2007	NR	NR	NR between treatment groups	Yes	NR	Stated as double-blind	Yes
Muzina 2008	NR	NR	Mostly, placebo group had more white participants	Yes	NR	Stated as double-blind	Yes
Nejtek 2008	Assigned in blocks of 10	No	Yes	Yes	Yes	Yes	Yes
Nierenberg, 2006	No. Equipoise randomization - considering which options were acceptable to patient. 3 subjects included in more than one group.	NR	Some differences; Bipolar I range 16.7% to 68.8%, Bipolar II range 31.2% to 83.3%.	Yes	No	No	No

Evidence Table 6. Quality assessment of randomized controlled trials of patients with bipolar disorder

Author, year	Reporting of attrition, crossovers, adherence, and contamination	Loss to follow-up: differential/high	Intent-to-treat analysis	Maintenance of comparable groups	Quality rating	Comments
McIntyre 2009 3-week	Yes, No, No, No	No No	No 480 /489 (98%) included	Yes	Fair	
McIntyre 2009 Asenapine vs. olanzapine	Yes, No, No, No	No No	No 491/504 (97%) included	Yes	Fair	
Morozova; Ortho NCT00132678-2007	Partially: reported attrition due to AEs No No No	No NR	No; excluded 9.2% of subjects from efficacy analysis	NR	Fair	Excluded 28 of 303 from efficacy analysis, reasons not stated. All 303 included in safety analysis.
Muzina 2008	Yes, No, No, No	No No	Used a last observation cared forward approach		Fair	
Nejtek 2008	Yes No No No	31% lost to follow-up (32% in risperidone group and 31% in quetiapine group)	Yes		Fair	
Nierenberg, 2006	Yes NR NR NR	Unclear.	Yes; but 3 patients crossed over into more than one group and were accounted for twice in the analysis		Poor	

Evidence Table 6. Quality assessment of randomized controlled trials of patients with bipolar disorder

	Internal validity						
Author, year	**Randomization adequate?**	**Allocation concealment adequate?**	**Groups similar at baseline?**	**Eligibility criteria specified?**	**Outcome assessors masked?**	**Care provider masked?**	**Patient masked?**
Paulsson, 2003	NR	NR	Yes	Yes	Yes	Yes	Yes
Perlis, 2006	Unclear- "1:1 fashion"	NR	Yes	Yes	NR	NR	NR
Potkin, 2005	Yes	Yes	Some differences; >\# manic in Placebo, >\# mixed in ziprasidone groups	Yes	Yes	Yes	Yes
Riesenberg; Ortho NCT00309686-2007	NR	NR	NR between treatment groups	Yes	NR	Stated as double-blind	Yes
Sachs, 2004	NR	NR	Yes	Yes	Yes	Yes	Yes

Evidence Table 6. Quality assessment of randomized controlled trials of patients with bipolar disorder

Author, year	Reporting of attrition, crossovers, adherence, and contamination	Loss to follow-up: differential/high	Intent-to-treat analysis	Maintenance of comparable groups	Quality rating	Comments
Paulsson, 2003	Yes NR NR NR	No No	No, 2 (0.6%) excluded for unspecified reasons		Fair	
Perlis, 2006	Yes NR NR NR	Yes reported; > in olanzapine group (21.3%) vs. risperidone group (33%) (p= 0.019) Differential, not high	Yes		Fair	
Potkin, 2005	Yes NR NR NR	41% discontinued study overall 39% ziprasidone 46% placebo	Yes; LOCF for missing data		Fair	
Riesenberg; Ortho NCT00309686-2007	Partially: reported attrition due to AEs No No No	No No	Yes; 1 subject (0.3%) did not receive the DB medication and was excluded from analysis	NR	Fair	
Sachs, 2004	Yes NR NR NR	No No	No, 21 (11%) were excluded (includes patients with no post baseline assessments and patients from one complete center due to protocol violations)		Fair	

Evidence Table 6. Quality assessment of randomized controlled trials of patients with bipolar disorder

	Internal validity						
Author, year	**Randomization adequate?**	**Allocation concealment adequate?**	**Groups similar at baseline?**	**Eligibility criteria specified?**	**Outcome assessors masked?**	**Care provider masked?**	**Patient masked?**
Sachs, 2005	NR	NR	Yes	Yes	NR	Yes	Yes
Schering-Plough 7501004	Yes	NR	Yes	Yes	Yes	Stated as double-blind	Yes
Schering-Plough 7501008	Yes	NR	Yes	Yes	Yes	Stated as double-blind	Yes
Sheehan 2009	NR	NR	No Risperidone gp higher proportion of mixed mood state & current depression and > patients with lifetime panic disorder, higher Simpson Angus Scale scores	Yes	Stated as double-blind	Stated as double-blind	Yes
Suppes 2009	NR	NR	Yes	Yes	NR	Stated as double-blind	Stated as double-blind

Evidence Table 6. Quality assessment of randomized controlled trials of patients with bipolar disorder

Author, year	Reporting of attrition, crossovers, adherence, and contamination	Loss to follow-up: differential/high	Intent-to-treat analysis	Maintenance of comparable groups	Quality rating	Comments
Sachs, 2005	Yes NR Yes NR	NR NR	No, 4 (1.4%) patients excluded from efficacy analysis, and 3 (1.1%) patients excluded from safety analysis		Fair	
Schering-Plough 7501004	Yes No No No	No / No Completion rates (%) Asenapine v. placebo v. Olanzapine: 67 v. 58.2 v. 78.5	Stated to be. Analysis excluded 8 (1.6%) of 488 randomized	NR	Fair	
Schering-Plough 7501008	Yes No No No	High, not differential. Completion rates (%) Asenapine v. placebo: 38.4 v. 32.9	Stated to be. Analysis excluded 8 (2.5%) of 326 randomized.	NR	Fair	
Sheehan 2009	Yes, No, No, No	No No	No 103/111 (92.8%) in ITT	Yes 9 with no post baseline data excluded from analysis	NR/NR/111	
Suppes 2009	Yes No No No	No No	Yes		Fair	

Evidence Table 6. Quality assessment of randomized controlled trials of patients with bipolar disorder

Internal validity

Author, year	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors masked?	Care provider masked?	Patient masked?
Suppes 2010	NR	NR	Yes	Yes	Unclear, described as double-blind	Unclear, described as double-blind	Unclear, described as double-blind
Thase, 2006	Unclear; "interactive voice-response central randomization service"; 2:1 ratio for bipolar diagnosis, (1:1:1 for placebo, 300 mg or 600 mg groups).	Unclear	Yes	Yes	Unclear	Unclear	Yes
Thase, 2008	Yes	NR	Yes	Yes	Yes	Yes	Yes
Tohen 2008	Yes	Yes	Yes	Yes	Unclear	Yes	Yes

Evidence Table 6. Quality assessment of randomized controlled trials of patients with bipolar disorder

Author, year	Reporting of attrition, crossovers, adherence, and contamination	Loss to follow-up: differential/high	Intent-to-treat analysis	Maintenance of comparable groups	Quality rating	Comments
Suppes 2010	Yes, Yes, No, No	No Yes, 33%	Yes, 270 (96%) analyzed using LOCF	Yes	Fair	
Thase, 2006	Yes NR NR NR	Yes reported; Overall non-completion rates: 34.5% placebo, 41.3% in quetiapine 300mg group, 46.7% in quetiapine 600 mg group. Highest in 600 mg group.	Yes; stating using LOCF		Fair	
Thase, 2008	Yes No No No	Discontinuations were high and differential in both Study 1 and 2 Study 1: aripiprazole=46.8% vs placebo=35.1% Study 2: aripiprazole=41.2% vs placebo=29.8%	Efficacy sample: Study 1: aripiprazole=164 (88.2%) vs placebo=177 (94.1%) Study 2: aripiprazole=176 (94.1%) vs placebo=178 (94.5%)		Fair	
Tohen 2008	Yes No No No	No No	Yes		Good	"Olanzapine versus divalproex versus placebo in the treatment of mild to moderate mania: a randomized, 12-week, double-blind study"

Evidence Table 6. Quality assessment of randomized controlled trials of patients with bipolar disorder

Internal validity

Author, year	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors masked?	Care provider masked?	Patient masked?
Tohen 2008	Yes	Yes	Somewhat	Yes	NR	Stated as double-blind	Yes
Tohen, 1999	NR	NR	NR	Yes	Yes	Yes	Yes
Tohen, 2000	Yes	No; personnel at the site assigned a patient to the next available kit	Yes	Yes	Yes	Yes	Yes
Tohen, 2003	NR	Yes	No; Mean length of current depressive episode shorter for olanzapine group	Yes	Yes	Yes	Yes
Tohen, 2004	NR	Yes	Yes	Yes	Yes	Yes	Yes
Tohen, 2006	NR	NR	Yes for demographics, however randomization ratio of 2:1 in favor of olanzapine	Yes	NR	NR	Yes

Evidence Table 6. Quality assessment of randomized controlled trials of patients with bipolar disorder

Author, year	Reporting of attrition, crossovers, adherence, and contamination	Loss to follow-up: differential/high	Intent-to-treat analysis	Maintenance of comparable groups	Quality rating	Comments
Tohen 2008	Yes No No No	No No	Yes		Fair	"Olanzapine plus carbamazepine v. carbamazepine alone in treating manic episodes"
Tohen, 1999	Yes NR NR NR	NR NR	No, 3 (2.2%) patients excluded due to not having a post-baseline assessment		Fair	
Tohen, 2000	Yes NR NR NR	No No	No, 5 (4.3%) patients excluded due to not having a post-baseline assessment		Fair	
Tohen, 2003	Yes NR NR NR	No No	No		Fair	
Tohen, 2004	Yes NR NR NR	NR NR	Yes		Fair	
Tohen, 2006	Yes NR Yes NR	Yes/7.1% open-label phase, 8.4% olanzapine double-blind phase, 3.7% placebo double-blind phase	Yes for both open-label and double-blind phase		Fair	

Evidence Table 6. Quality assessment of randomized controlled trials of patients with bipolar disorder

	Internal validity						
Author, year	**Randomization adequate?**	**Allocation concealment adequate?**	**Groups similar at baseline?**	**Eligibility criteria specified?**	**Outcome assessors masked?**	**Care provider masked?**	**Patient masked?**
Vieta 2008	NR	NR	Yes	Yes	Unclear	Stated as double-blind	Stated as double-blind
Vieta 2008	NR	NR	Yes	Yes	Unclear	Stated as double-blind	Stated as double-blind
Vieta, 2010	Yes	Unclear	Imbalance in manic, mixed episodes	Yes	Unclear	Yes	Yes

Evidence Table 6. Quality assessment of randomized controlled trials of patients with bipolar disorder

Author, year	Reporting of attrition, crossovers, adherence, and contamination	Loss to follow-up: differential/high	Intent-to-treat analysis	Maintenance of comparable groups	Quality rating	Comments
Vieta 2008	Yes No No No	No No	Unclear		Fair	"Efficacy and safety of quetiapine in combination with lithium or divalproex for maintenance of patients with bipolar I disorder (international trial 126)"
Vieta 2008	Yes No No No	No No	Yes		Fair	"Efficacy of Adjunctive Aripiprazole to Either Valproate or Lithium in Bipolar Mania Patients Partially Nonresponsive to Valproate/Lithium Monotherapy: A Placebo-Controlled Study"
Vieta, 2010	unclear	Overall: Yes 25% Differential: Yes, >10% between drugs in maintenance phase	acute phase; yes for primary outcome and no for secondary outcomes. Maintenance phase: No, PP population 411/493 included	Yes	Fair	Benzodiapines were taken as recue upto 14 days of acute treatment phase. 2 deaths related to study drugs

Evidence Table 6. Quality assessment of randomized controlled trials of patients with bipolar disorder

	Internal validity						
Author, year	**Randomization adequate?**	**Allocation concealment adequate?**	**Groups similar at baseline?**	**Eligibility criteria specified?**	**Outcome assessors masked?**	**Care provider masked?**	**Patient masked?**
Yatham, 2003 International	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Yatham, 2007	NR; larger portion received Li vs DVP - investigators were asked to choose the appropriate med for each patient based on clinical history/condition	NR	Yes	Yes	NR	NR	Yes
Young 2009	NR	NR	Yes	Yes	NR	Stated as double-blind	Stated as double-blind
Young 2010	NR	Yes	Yes	Yes	Yes	Yes	Yes

Evidence Table 6. Quality assessment of randomized controlled trials of patients with bipolar disorder

Author, year	Reporting of attrition, crossovers, adherence, and contamination	Loss to follow-up: differential/high	Intent-to-treat analysis	Maintenance of comparable groups	Quality rating	Comments
Yatham, 2003 International	Yes NR NR NR	No No	No; 10 (6.7%) excluded from endpoint analysis; 8 because they didn't have "at least two efficacy assessments", and reasons for other 2 not specified; no mention of results from "worst case scenario" sensitivity analysis that included those 10 patients; data on file, submitted 11/9/04 was included in this consideration		Fair	
Yatham, 2007	Yes NR NR NR	Yes reported; overall discontinuation rates: 39.8% placebo vs. 33% quetiapine group (significance not reported).	Yes		Fair [not sure how investigator choice of Li or DVP may change study results]	
Young 2009	Yes No No No	No No	Yes		Fair	
Young 2010	Yes, No, No, No	No, No	Yes; analysis included 783 (98%) using LOCF	Yes	Good	

Evidence Table 6. Quality assessment of randomized controlled trials of patients with bipolar disorder

	Internal validity						
Author, year	**Randomization adequate?**	**Allocation concealment adequate?**	**Groups similar at baseline?**	**Eligibility criteria specified?**	**Outcome assessors masked?**	**Care provider masked?**	**Patient masked?**
Zimbroff 2007	NR	NR	Yes	Yes	Yes	Yes	Yes

Evidence Table 6. Quality assessment of randomized controlled trials of patients with bipolar disorder

Author, year	Reporting of attrition, crossovers, adherence, and contamination	Loss to follow-up: differential/high	Intent-to-treat analysis	Maintenance of comparable groups	Quality rating	Comments
Zimbroff 2007	Yes No No No	No No	Yes; analyses only excluded 10 (3%) patients who discontinued before receiving study medication		Fair	

Evidence Table 7. Observational studies in patients with bipolar disorder

Author, year Country	Data source	Prospective Retrospective Unclear	Sampling frame time period	Mean duration of follow-up	Interventions Mean dose	Population
Bhalerao, 2012 USA	VA registries	Retrospective	Fiscal years 2001-2008	180 days	Olanzapine, mean dose: 6.615 mg/d Quetiapine, mean dose: 72.691mg/d Risperidone, mean dose: 1.082mg/d Valproic acid and derivatives, mean dose: 776mg/d	≥65 years VA patients
Chengappa, 2005 Hennen, 2004 United States	Patients in an Eli Lilly RCT doing a 1-year follow-up with Olanzapine (follow-up to Tohen 1999)	Prospective	1 year	52 weeks total: 3 weeks DB, 49 weeks open label (OL) mean: 27.9 weeks Mean duration of participation: 30.0 (+/- 19.8) weeks	Quetiapine or ziprasidone	Bipolar I mania episode or mixed state

Evidence Table 7. Observational studies in patients with bipolar disorder

Author, year Country	Age Gender Ethnicity	Exposed Eligible Selected	Withdrawn Lost to follow-up Analyzed	Effectiveness outcomes
Bhalerao, 2012 USA	Age: 65-69: 33.2%, 70-74: 24.9%, 75-79: 22.2%, 80-84: 14.0%, 85+: 5.7% Gender: 3.2% female Ethnicity: 80.6% White, 7.0% Black	NR/NR/4717	NA/NA/4717	Olanzapine vs. Quetiapine vs. Risperidone vs. Valproic acid and derivatives Death rate (95% CI) per 100 person-years: 10.3 (7.5-3.9) vs. 5.3 (3.6-7.7) vs. 11.8 (9.0-15.3) vs. 4.6 (3.2-6.3) Propensity Weighted Hazard ratios of 180-day Mortality, vs. Risperidone: Olanzapine: HR, 0.67; 95%CI, 0.36-1.25; p=0.2073 Quetiapine: HR, 0.27; 95%CI, 0.13-0.55; p=0.0003 Vlaproic acid and derivatives: HR, 0.36; 95%CI, 0.17-0.75; p=0.0061
Chengappa, 2005 Hennen, 2004 United States	Mean age: 39.4 years 51.7% male Ethnicity NR (values from Hennen a little different in Chengappa)	NR NR 139	NR NR 113	Symptomatic remission of mania during 1 year: 79 (69.9%) remission by week 8: 50% CGI-BP: remitted vs not remitted = 4.38 (0.76) vs 4.85 (0.85), p=0.006 plausible, nearly ninefold, greater rate of trial completion: remitted vs not remitted = 53% vs 6%, p<0.001 Of the 79 subjects who achieved symptomatic remission: became symptomatic again: 82.3% (65/79) failed to sustain remission for at least 2 months: 49.4% (39/79) Achieved sustained recovery: 35.4% (40/113) Time-in-remission: 19.3(15.3) weeks, 52.2 (26.5)% patients Time-in-sustained-recovery: 31.65 (13.7) weeks

Evidence Table 7. Observational studies in patients with bipolar disorder

Author, year Country	Safety outcomes	Comments
Bhalerao, 2012 USA	NR	Is there an addendum or correction? 95% CI for deaths per 100 person years is reported incorrectly.
Chengappa, 2005 Hennen, 2004 United States	Only 15% (3 women and 3 men = 6/40) who recovered did so without weight gain Body weight increase (SD) at the endpoint: +6.53 (8.9) kg Increase of BMI: 2.17 (3.0) kg/m2 to 31.0 (6.1) kg/m2 50.4% of subjects had BMI ≥30 kg/m2 (i.e., reached obesity criteria) at endpoint 33.9% of subjects experienced increases of BMI of ≥10%	30.1% of OL patients were obese to begin with (BMI ≥30 kg/m2)

Evidence Table 7. Observational studies in patients with bipolar disorder

Author, year Country	Data source	Prospective Retrospective Unclear	Sampling frame time period	Mean duration of follow-up	Interventions Mean dose	Population
Dennehy, 2003 United States	NR	Prospective	1998-1999	8 weeks	Olanzapine 5-12 mg	Bipolar I disorder
Gianfrancesco, 2007 United States	PharMetrics database; medical and prescription claims data	Retrospective	1999 through August 2003	NR	Risperidone 1.7mg, olanzapine 8.3mg, quetiapine 160mg, ziprasidone 70mg	Bipolar and manic disorders

Evidence Table 7. Observational studies in patients with bipolar disorder

Author, year Country	Age Gender Ethnicity	Exposed Eligible Selected	Withdrawn Lost to follow-up Analyzed	Effectiveness outcomes
Dennehy, 2003 United States	Mean age: 39 years 26.7% male Ethnicity NR	NR NR 15	5 3 15	YMRS scores decreased: 14(93%) YMRS mean scores: 9.86, 2-30 point deduction IDS-C depressive symptoms: average 4.47 points reduction HAM-D: average 4 points reduction IDS-C depressive symptoms: 8 patients experienced a reduction of 1-37 points 7 patients experienced a increase of 3-16 points HAM-D: 2 patients experienced increased depression and contributed to the early withdrawal GAF: no significant change over the 8 weeks trial
Gianfrancesco, 2007 United States	Mean age=36 years 50% male Ethnicity NR	NR/NR/10,037	NA/NA/10,037	Hazard Ratio (95% CI) for hospitalization: Olanzapine vs risperidone: 1.00 (0.88, 1.15) Risperidone vs quetiapine: 1.19 (1.01, 1.40) Risperidone vs ziprasidone: 1.44 (0.99, 2.12) Olanzapine vs quetiapine: 1.19 (1.01, 1.40) Olanzapine vs ziprasidone: 1.45 (0.99, 2.12) Quetiapine vs ziprasidone: 1.22 (0.82, 1.81) <u>Subgroup analyses:</u> Age: 0.986 (0.982, 0.990) Gender (male vs female): 0.931 (0.827, 1.048) Substance dependence/abuse (yes vs no): 2.596 (2.307, 2.922)

Evidence Table 7. Observational studies in patients with bipolar disorder

Author, year Country	Safety outcomes	Comments
Dennehy, 2003 United States	Side effects: 80% moderate to severe dry mouth 60% mild dizziness 53% edema 53% mild to moderate drowsiness 47% constipation Weight gain: Of 13 patients with more than one weight measurement: 10(77%) patients range from 0.91-7.26 kg Of 7 patients who completed at least 7 visits: average gain 2.2 kg 1 patient with a weight loss of 10.89 kg in 3 weeks, putatively due to stimulant use 6 patients who gained weights: gained average 4.39kg	
Gianfrancesco, 2007 United States	NR	

Evidence Table 7. Observational studies in patients with bipolar disorder

Author, year Country	Data source	Prospective Retrospective Unclear	Sampling frame time period	Mean duration of follow-up	Interventions Mean dose	Population
Guo, 2006 United States	Multi-site managed care claims database	Retrospective	January 1, 1998 to December 31, 2002	NR	Atypical Antipsychotics: Olanzapine Risperidone Quetiapine Ziprasidone Clozapine Conventional antipsychotics: Haloperidol Chlorpromazine Fluphenazine Loxapine Molindone Perphenazine Thioridazine Trifluoperazine Thiothixene Pimozide	An affective disorder or cyclothymia: controls and diabetics
Hassan, 2007 USA	Medicaid administrative claims database	Retrospective	January 1, 1999, to December 31, 2001	2 years	Risperidone, olanzapine, quetiapine, or typical antipsychotic	Under 65 years Medicaid recipients

Evidence Table 7. Observational studies in patients with bipolar disorder

Author, year Country	Age Gender Ethnicity	Exposed Eligible Selected	Withdrawn Lost to follow-up Analyzed	Effectiveness outcomes
Guo, 2006 United States	Age: 4.47% were ≤12 years 9.74% 13-17 years 29.13% 18-34 36.65% 35-49 17.64% 50-64 2.36% ≥65 39.34% males	NR/NR/920 cases and 5258 controls	NR/NR/920 cases and 5258 controls	Of the 920 cases, 41% received atypical antipsychotics: 20% olanzapine; 14% risperidone; 9% quetiapine; and 1% ziprasidone. Risk of developing diabetes was greatest among clozapine users, ziprasidone users, olanzapine users, risperidone users, patients receiving switched atypical antipsychotics, and patients receiving conventional antipsychotics. Compared to conventional antipsychotics, risk of developing diabetes was greatest among those taking clozapine, olanzapine, risperidone and quetiapine.
Hassan, 2007 USA	NR NR NR	NR/832/825	NA/NA/825	Medication Possession Ratio = (total days supplied for index drug) / (total days from index to date of last prescription of index drug + days supplied for last fill) olanzapine 0.68 ±0.27 risperidone 0.68 ± 0.29 quetiapine 0.71 ± 0.25 typical antipsychotics 0.46 ± 0.34 Persistence - total days from the index prescription fill date until the occurrence of a filled prescription for any other index or nonindex antipsychotic or until discontinuation of therapy with the index drug. risperidone 194.8 ± 127.8 days olanzapine 200.9 ± 130.4 quetiapine 219.8 ± 128.9 days typical antipsychotic 179.2 ± 123.0 days for the cohort.

Evidence Table 7. Observational studies in patients with bipolar disorder

Author, year Country	Safety outcomes	Comments
Guo, 2006 United States	NR	
Hassan, 2007 USA	NR	

Evidence Table 7. Observational studies in patients with bipolar disorder

Author, year Country	Data source	Prospective Retrospective Unclear	Sampling frame time period	Mean duration of follow-up	Interventions Mean dose	Population
Iqbal, 2011 Pakistan	Aga Khan University Hospital	Retrospective	2003-2007	NR	Median dose: Risperidone: 2 mg/d Olanzepine: 10 mg/d Quetiapine: 200 mg/d Haloperidol: 10 mg/d Trifluoperazine: 2 mg/d	outpatient psychiatry patients
Jing, 2011 USA	Thomson Reuters MarketScan® Multi-State Medicaid Database	Retrospective	2003 through June 2008	NR	Aripiprazole, 13.7 Olanzapine, 9.6 Quetiapine, 194 Risperidone, 1.7 Ziprasidone, 94.4	18-64 years, Medicaid, bipolar disorder
Kim, 2009 USA	Ingenix I3/LabRx claims dataset	Retrospective	2003-2006	NR	Mean maximum dose: Aripiprazole, 12.4mg/d Ziprasidone, 100.2mg/d Olanzapine, 10.2mg/d Quetiapine, 169.8mg/d Risperidone1.8mg/d	18-65 years, ICD-9 code for bipolar disorder, manic, mixed or hypomanic

Evidence Table 7. Observational studies in patients with bipolar disorder

Author, year Country	Age Gender Ethnicity	Exposed Eligible Selected	Withdrawn Lost to follow-up Analyzed	Effectiveness outcomes
Iqbal, 2011 Pakistan	Age, mean (SEM): 34.61(1.44) Gender: 44% female Ethnicity: NR	NR/NR/124	NR/NR/29 at 1 year	Adjusted mixed model analyses showed weight significantly different over various follow up times (p=0.001) Maximum weight gain: olanzapine (29%), trifluoperazine (28%), quetiapine (24%), haloperidol (13%)
Jing, 2011 USA	Age: 36.13 years Gender: 69.1% female Ethnicity: 80.5% Caucasian, 12.8% African American, 0.7% Hispanic	1,102,270/NR/22479	NA/NA/22479	Aripiprazole vs. Olanzapine vs. Quetiapine vs. Risperidone vs. Ziprasidone Psychiatric hospitalizations per 1000 patient years: 234 vs. 321 vs. 349 vs. 288 vs. 315 Hazard ratio for time to psychiatric hospitalization: Aripiprazole vs. Olanzapine: HR, 1.52; 95%CI, 1.22-1.89 Aripiprazole vs. Quetiapine: HR, 1.40; 95% CI, 1.40-1.17 Aripiprazole vs. Ziprasidone: HR, 1.33; 95% CI, 1.02-1.73
Kim, 2009 USA	Age: 37.65 Gender: 35.4% female Ethnicity NR	198,919/6,162/Propensity score matched samples: 431 aripiprazole vs. 431 ziprasidone; 690 aripipraole vs. 690 olanzapine; 840 aripiprazole vs. 840 quetiapine; 829 aripiprazole vs. 829 risperidone	NA/NA/431 aripiprazole vs. 431 ziprasidone; 690 aripipraole vs. 690 olanzapine; 840 aripiprazole vs. 840 quetiapine; 829 aripiprazole vs. 829 risperidone	Aripiprazole vs. ziprasidone vs. olanzapine vs. quetiapine vs. risperidone: Hopitalization rate (propensity-matched sample): 6.5% vs. 10.2% vs. 8.7% vs. 8.5% vs. 8.6% Hazard ratios for hospitalization vs. aripiprazole: Ziprasidone: HR, 1.7; p=0.04 Olanza

Evidence Table 7. Observational studies in patients with bipolar disorder

Author, year Country	Safety outcomes	Comments
Iqbal, 2011 Pakistan	NR	
Jing, 2011 USA	NR	
Kim, 2009 USA	NR	

Evidence Table 7. Observational studies in patients with bipolar disorder

Author, year Country	Data source	Prospective Retrospective Unclear	Sampling frame time period	Mean duration of follow-up	Interventions Mean dose	Population
Kim, 2011 USA	Ingenix I3/LabRx claims dataset	Retrospective	2003 through 2006	NR	Aripiprazole Ziprasidone Olanzapine Quetiapine Risperidone Mean dose NR	18-65 years, ICD-9 code for bipolar disorder, manic, mixed or hypomanic

Evidence Table 7. Observational studies in patients with bipolar disorder

Author, year Country	Age Gender Ethnicity	Exposed Eligible Selected	Withdrawn Lost to follow-up Analyzed	Effectiveness outcomes
Kim, 2011 USA	Propensity score-matched samples: Aripiprazole vs. Ziprasidone: Age: 37.65 Gender: 27.3% female Aripiprazole vs. Olanzapine: Age: 37.6 Gender: 35.5% female Aripiprazole vs. Quetiapine: Age: 36.8 Gender: 31.4% female Aripiprazole vs. Risperidone: Age: 37.1 Gender: 33.5% female Ethnicity NR	198,919/7,169/2,739	NA/NA/2739	Aripiprazole vs. Ziprasidone Psychiatric hospitalization: 7.6% vs. 12.8% Medical hospitalization: 1.7% vs. 2.4% Risk of hospitalization (aripiprazole reference): HR, 1.962; 95%CI, 1.269-3.033); p<0.01 Aripiprazole vs. Olanzapine Psychiatric hospitalization: 6.4% vs. 9.0% Medical hospitalization: 1.5% vs. 1.9% Risk of hospitalization (aripiprazole reference): HR, 1.554; 95%CI, 1.035-1.333; p<0.05 Aripiprazole vs. Quetiapine Psychiatric hospitalization: 6.2% vs. 10.1% Medical hospitalization: 1.3% vs. 1.0% Risk of hospitalization (aripiprazole reference): HR, 1.556; 95%CI, 1.078-2.245; p<0.05 Aripiprazole vs. Risperidone Psychiatric hospitalization: 6.4% vs. 9.3% Medical hospitalization: 1.4% vs. 1.8% Risk of hospitalization (aripiprazole reference): HR, 1.368; 95%CI, 0.940-1.989; p=NS

Evidence Table 7. Observational studies in patients with bipolar disorder

Author, year Country	Safety outcomes	Comments
Kim, 2011 USA	NR	

Evidence Table 7. Observational studies in patients with bipolar disorder

Author, year Country	Data source	Prospective Retrospective Unclear	Sampling frame time period	Mean duration of follow-up	Interventions Mean dose	Population
Kraemer, 2012 Germany, Greece, France	Prospective, multi-site, open-label study	Prospective	April 2007-May 2009	1 year	Olanzapine-coated tablets: schizophrenia, 11.2 mg/d; bipolar, 9.7 mg/d Olanzapine-orodispersibile formulation: schizophrenia, 15.1 mg/d; bipolar, 15 mg/d	Adult outpatient, DSM-IV schizophrenia or bipolar disorder
Pelletier 2013 US	Medical and pharmacy claims data from the IMS PharMetrics Database	Retrospective	January 2007 through December 2008	6 months	NR	Age ≥ 18 to < 65 years; ≥ 2 diagnoses of bipolar disorder based on ICD-9-CM codes on 2 separate days within 6 months prior to or on index date

Evidence Table 7. Observational studies in patients with bipolar disorder

Author, year Country	Age Gender Ethnicity	Exposed Eligible Selected	Withdrawn Lost to follow-up Analyzed	Effectiveness outcomes
Kraemer, 2012 Germany, Greece, France	Age: Schizophrenia, 39.2; Bipolar, 44.6 Gender: 44.9% female Ethnicity: NR	NR/927/903	128/43/903	Schizophrenia Change from baseline, Coated vs. Orodispersible CGI: -0.9 (1) vs. -1.5 (1.2), p <0.001 GAF: 9.8 (14) vs. 14 (15.6), p <0.001 Psychological General Well-being Index (PGWBI): 12.2 (20) vs. 22.3 (23.4), p <0.001 Therapeutic Alliance Questionnaire (WAI): 5.4 (18.9) vs. 7.6 (22.5), p=0.32 Patients with at least one relapse: 19% vs. 15%, p=0.28 Bipolar Disorder Change from baseline, Coated vs. Orodispersible CGI: -1.1 (1.4) vs. -1.8 (1.6), p <0.001 GAF: 11.9 (15) vs. 16.8 (18.5), p=0.018 Psychological General Well-being Index: 14.4 (24.6) vs. 16.0 (23.4), p=0.027 Therapeutic Alliance Questionnaire: 2.0 (17.8) vs. 6.8 (18.8), p=0.060 Patients with at least one relapse: 21% vs. 26%, p=0.58
Pelletier 2013 US	Age: 42.1 32% male Ethnicity NR	NR/NR/4841	NR/NR/NR	Quetiapine XR vs aripiprazole Time to first hospitalization in days: 93.4 vs 77.3, *P*= NR Change in proportion of patients with ≥ admission: -16.4% vs -11.3%, *P*= NR Change in mean length of stay in days: -1.4 vs -0.2; *P*= NR

Evidence Table 7. Observational studies in patients with bipolar disorder

Author, year Country	Safety outcomes	Comments
Kraemer, 2012 Germany, Greece, France	Coated vs. Orodispersible Schizophrenia Hospitalization: 10% vs. 6% At least one suicide attempt, n: 9 vs. 4 Weight change greater than 7% from baseline: 20% vs. 25%, p=0.15 Bipolar Disorder Hospitalization: 10% vs. 7% At least one suicide attempt, n: 7 vs. 6 Weight change greater than 7% from baseline: 26% vs. 31%, p=0.43	
Pelletier 2013 US	NR	

Evidence Table 7. Observational studies in patients with bipolar disorder

Author, year Country	Data source	Prospective Retrospective Unclear	Sampling frame time period	Mean duration of follow-up	Interventions Mean dose	Population
Rascati, 2011 USA	Texas Medicaid Vendor Drug, Texas Medicaid Medical Services, and Thomson Reuters MarketScan databases	Retrospective	July 2002 through December 2007	1 year	Aripiprazole, mean dose: 20.4 mg/d Olanzapine: 20.2 mg/d Quetiapine: 206.8 mg/d Risperidone: 7.7 mg/d Ziprasidone: 106.8 mg/d	18-64 years, Medicaid, bipolar disorder
Ulcickas Yood, 2010 USA	Kaiser Permanente Health Plan of Northern California, HealthCore Integrated Research Network, Henry Ford Health System	Retrospective	November 2002 - December 2005	NR	Aripiprazole Clozapine Olanzapine Quetiapine Risperidone Ziprasidone	Schizophrenia or bipolar disorder, ≥18 years
Van Dorn, 2011 USA	Florida Medicaid, Florida Department of Children and Families (treatment provided), Florida Department of Law Enforcement (arrests)	Retrospective	July 2002 through March 2008	NR	First-generation antipsychotics (any not on list of second generation list) Second-generation antipsychotics (aripiprazole, clozapine, olanzapine, paliperidone, quetiapine, risperidone, RLAT, ziprasidone)	Schizophrenia, schizoaffective disorder, bipolar I and II disorders

Evidence Table 7. Observational studies in patients with bipolar disorder

Author, year Country	Age Gender Ethnicity	Exposed Eligible Selected	Withdrawn Lost to follow-up Analyzed	Effectiveness outcomes
Rascati, 2011 USA	Age: 37 Gender: 74% female Ethnicity: 76% white	NR/NR/2446	NA/NA/2446	Ziprasidone vs. Aripiprazole vs. Olanzapine vs. Quetiapine vs. Risperidone Adherence: 62% vs. 60% vs. 58% vs. 55% vs. 58% Likelihood of nonadherence (ziprasidone reference), OR(95%CI): 1.06 (0.70-1.63) vs. 1.12 (0.66-1.89) vs. 1.30 (0.84-2.00) vs. 1.09 (0.70-1.71) Persistence for 1 year: 17% vs. 18% vs. 14% vs. 19% vs. 18% Likelihood of nonpersistence (ziprasidone reference), OR (95%CI): 1.04 (0.83-1.31) vs. 1.34 (1.02-1.76), p=0.04 vs. 0.93 (0.74-1.17) vs. 1.05 (0.87-1.12)
Ulcickas Yood, 2010 USA	Age: 39.1 Gender: 60.4% female Ethnicity: NR	NR/NR/20489	NA/NA/20489	NR
Van Dorn, 2011 USA	Age: 42 years Gender: 51.9% female Ethnicity: 51.2% White, 19.9% African American, 19.6% Hispanic	NR/NR/36519	NA/NA/36518	Hazard Ratio for Arrest (Second Genreation Antipsychotics vs. First Generation Antipsychotic): HR, 0.91; 95% CI, 0.81-1.02; p=0.11 Interaction of first generation antipsychotic and at least 80% of 30-day periods during episode with outpatient visit: HR, 0.81; 95% CI, 0.60-1.10; p, NS Interaction of second generation antipsychotic and at least 80% of 30-day periods during episode with outpatient visit: HR, 0.68; 95% CI, 0.50-0.93; p=0.02

Evidence Table 7. Observational studies in patients with bipolar disorder

Author, year Country	Safety outcomes	Comments
Rascati, 2011 USA		
Ulcickas Yood, 2010 USA	Suicide events (attempts, completed), rate per 1000 patient-years: Aripiprazole: 20.69 Clozapine: 0 Olanzapine: 23.99 Quetiapine: 32.33 Risperidone: 19.69 Ziprasidone: 48.52 Multiple antipsychotics: 31.24 Older antipsychotics: 21.26 Adjusted HR for suicide events, aripiprazole vs. other SGAs: HR, 0.69; 95% CI, 0.42-1.14	
Van Dorn, 2011 USA	NR	

Evidence Table 7. Observational studies in patients with bipolar disorder

Author, year Country	Data source	Prospective Retrospective Unclear	Sampling frame time period	Mean duration of follow-up	Interventions Mean dose	Population
Yang 2013 Taiwan	Psychiatric Inpatient Medical Claims database of the National Health Insurance Research Database (NHIRD)	Retrospective	July 1, 1998 and December 31, 2006		Defined Daily Dose Equivalents from the Anatomic Therapeutic Chemical Classification System (e.g., 10 mg olanzapine or 300 mg of clozapine was equivalent to 1 defined daily dose): Clozapine: 0.1-0.3 Olanzapine: 0.6-0.9 Quetiapine: 0.8-0.9 Risperidone: 0.6-0.7	Stable diagnosis of bipolar disorder for ≥ 2 years
Zarate, 1995 United States	McLean Hospital records	Retrospective recruitment prospective follow up	Unclear	At least 3 months	Clozapine at discharged: 182 mg/day follow-up: 304.4 mg/day	Refractory bipolar disorder
Zhu, 2007 United States	PharMetrics Integrated Database for medical and pharmacy claims	Retrospective	January 2003 to December 2004	1 year	Olanzapine 11.0 ± 7.1 mg/day, quetiapine 192.6 ±183.1 mg/day risperidone 2.1 ± 1.7 mg/day, ziprasidone 101.2 ± 60.8 mg/day	Bipolar disorder

Evidence Table 7. Observational studies in patients with bipolar disorder

Author, year Country	Age Gender Ethnicity	Exposed Eligible Selected	Withdrawn Lost to follow-up Analyzed	Effectiveness outcomes
Yang 2013 Taiwan	Age: 44 61% male Ethnicity NR	NR/NR/Cases=571, Controls=2,277	NR/NR/Cases=571, Controls=2,277	NR
Zarate, 1995 United States	Mean age: 38.6 years 53% male Ethnicity NR	193 17 17	0 0 17	CGI responders, very much or much improved: at discharged: 11(64%) follow-up: 15(88%) CGI mean score: at discharged: 2.3(0.2) follow-up: 1.8(2.2) at discharged vs follow-up, p=0.02
Zhu, 2007 United States	Mean age 37 years 32% male Ethnicity NR	NR NR 1516	NA NA 1516	Initiation of monotherapy olanzapine 51% vs. quetiapine- (36%, p < 0.01), ziprasidone- (25%, p < 0.01), and risperidone-initiated patients (40%, p < 0.01) For one year olanzapine initiated patients used this index antipsychotic as monotherapy for significantly more days (73.4) than patients initiating quetiapine (56.2, p < 0.01), risperidone (52.9, p < 0.01) or ziprasidone (36.6, p < 0.01) Annual healthcare costs $15 208 for olanzapine, $14 216 for risperidone, $18 087 for quetiapine (vs. olanzapine p < 0.01) to $18 729 for ziprasidone (vs. olanzapine p < 0.01)

Evidence Table 7. Observational studies in patients with bipolar disorder

Author, year Country	Safety outcomes	Comments
Yang 2013 Taiwan	Pneumonia, adjusted risk ratio (95% CI): Clozapine: 2.59 (1.46-4.63) Olanzapine: 2.97 (1.90-4.66) Quetiapine: 2.12 (1.48-3.03) Risperidone: 1.74 (1.21-2.50)	
Zarate, 1995 United States	Side effects: 30% sedation 23% vertigo or dizziness 24% weight gain 18% salivation 6% constipation 6% tachycardia Rehospitalization rate: before starting clozapine: 0.8(1.2) follow-up during clozapine: 0.4(1.2) before vs follow-up, p=0.025	
Zhu, 2007 United States	NR	

Evidence Table 8. Quality assessment of observational studies in patients with bipolar disorder

Author, year	Non-biased selection?	Low overall loss to follow-up?	Outcomes prespecified and defined	Adverse events pre-specified and defined?	Ascertainment techniques adequately described?	Non-biased and adequate ascertainment methods?	Statistical analysis of potential confounders?	Adequate duration of follow-up?	Adequate sample size?	Overall adverse event assessment quality	Comments
Bahlerao 2012	Yes	Unclear	Yes	Yes	No, "data obtained", no information about how	Unclear; NR	Yes (propensity scores)	Yes (180 days)	Unclear - 4717	Fair	
Gianfrancesco, 2007	Yes	NA (case-control study)	Yes	NA	Yes	Unclear; limitations of using ICD-9 for diagnosis of bipolar disorder	Yes	Unclear; mean treatment episode duration NR	Yes; N=10,037	Fair	
Guo, 2006	Yes: case-control study: controls matched on age, sex, bipolar diagnosis	NA (case-control study)	Yes; drug exposure and diabetes were pre-specified	Yes	Yes, for diabetes diagnosis and for drug consumption	Unclear; limitations of using ICD-9 for diagnosis of diabetes	yes	Unclear; exposure examined over 4 years; perhaps prior exposure could have effect	Yes (cases 920, controls 5258)	Fair	Case control study
Hassan, 2007	Yes	Yes	Yes	NA	Yes	Yes	Yes	12 months	Unclear - 825	Fair	
Jing 2011	Yes; eligibility criteria described and #'s and reasons for exclusions reported.	Unclear; completeness of data NR	Yes	N/A, no harms	Yes KP: No	(Unclear, blinding NR) KP: Agree with unclear, but would also mention database reliability NR	Yes, (propensity score)	Yes	Yes? 22,479 (for hospitalization outcome)	Fair	
Kim 2011	Yes; eligibility criteria described and #'s and reasons for exclusions reported.	Unclear; completeness of data NR	Yes	N/A	No	Unclear; blinding and database reliability NR	Yes	Yes	Yes	Fair	

Evidence Table 8. Quality assessment of observational studies in patients with bipolar disorder

Author, year	Non-biased selection?	Low overall loss to follow-up?	Outcomes prespecified and defined	Adverse events pre-specified and defined?	Ascertainment techniques adequately described?	Non-biased and adequate ascertainment methods?	Statistical analysis of potential confounders?	Adequate duration of follow-up?	Adequate sample size?	Overall adverse event assessment quality	Comments
Rascati 2011	Yes (included all patients in claims data base with eligible RX and ICD-9 code.	Unclear; completeness of data NR	Yes	NA	No	Unclear (NR)	Yes (controlled for proxy measures for disease severity including baseline comorb conditions and pre index cost [utilization])	Yes	Unclear - 1,102	Fair	
Ulcickas Yood 2010	Unclear; eligibility criteria specified, but #'s and reasons for exclusions NR	Unclear; completeness of data NR	Yes	Yes	Yes (DX codes and death certificates)	Yes	Yes	Unclear, NR	Yes, N=20,489	Good	Mixed pop (85% bipolar). Note: this was funded by industry.
Van Dorn 2011	Yes	Unclear; completeness of data NR	Yes	NA? (not looking at AE?)	No	Unclear (NR)	Yes	Unclear (TX ranged from 60 days to 1,552)	Yes; 85,572 episodes	Fair	
Vieta, 2001	Yes	Yes	No, definition of "weight gain" was not specified	No	No	No	NR	Yes	No, 23	Fair	
Zhu 2007	Yes	Yes	Yes	NA	Unclear how 'total number of days used' was calculated and how gaps in refills were handled	Unclear; limitations of using ICD-9 for diagnosis of diabetes	Yes	12 months	Unclear - 1516	Fair	

Evidence Table 9. Systematic reviews of atypical antipsychotics in youths

Author Year	Aims	Literature search dates	Population included	Drugs included	Study designs included	Additional study eligibility criteria
Canitano, 2008	To review the use of risperidone in children and adolescents with autistic spectrum disorders, particularly regarding the treatment of associated behavioral disorders	Through February 2007	Autism spectrum disorders	Risperidone only	Randomized, placebo controlled trials, observational or retrospective studies and case reports.	Not reported
Dinca, 2005	To report a systematic review of the randomized or quasi-randomized controlled trials concerning the effectiveness of atypical antipsychotics and SSRIs in the treatment of behavioral problems associated with pervasive developmental disorders.	1966-2004	Diagnosed with a pervasive developmental disorder, excluding Rett's disorder and Childhood Disintegrative Disorder. Diagnosis must have been made using established diagnostic criteria (DSM-III-R, DSM-IV, DSM-IV-R, ICD-10, and/or using a standardized diagnostic instrument.	Oral atypical antipsychotics (also SSRIs): Trials of risperidone, amisulpride and olanzapine identified	Random or quasi-random trials, control group with placebo or alternative medication	At least one standardized measure such as a behavior checklist used for the intervention and control group
Jensen, 2007	To provide a descriptive review of treatment studies of atypical antipsychotics in pediatric psychiatric disorders	January 1994 through March 2006	Pediatric psychiatric disorders	Quetiapine, risperidone, olanzapine, aripiprazole, clozapine, ziprasidone: Trials of olanzapine and risperidone were identified for disruptive behavior disorders and pervasive developmental disorders.	Double-blind or open label clinical trials of >=8 weeks duration with >=20 patients	Unpublished data or abstracts not included

Evidence Table 9. Systematic reviews of atypical antipsychotics in youths

Author Year	Main results	Subgroups	Adverse events	Quality assessment
Canitano, 2008	Qualitative synthesis only. Moderate efficacy and safety of risperidone for treating maladaptive behaviors, including aggression, hyperactivity, self injury and irritability.	Efficacy and tolerabiliy of risperidone in the various types of pervasive developmental disorders, including different degress of severity of core symptoms, are still undetermined.	Weight gain most frequent adverse event, ranging from 1 to 10 kg. Weight gain stabilized over time, was more pronounced in first 2 to 3 months of therapy.	1. Report clear review question, state inclusion and exclusion criteria of primary studies? No 2. Substantial effort to find relevant research? No 3. Adequate assessment of validity of included studies? No 4. Sufficient detail of individual studies presented? Yes 5. Primary studies summarized appropriately? Yes Overall quality rating=Fair
Dinca, 2005	No quantitative synthesis. No information on long-term effectiveness and safety. No data on quality of life. Risperidone (2 studies: McCracken 2002, McDougle 1998) effective in moderate-to-severe behavioral problems in children and adolescents with autistic disorder. Olanzapine (1 study: Malone 2001) at low dosage effective for behavioral problems in children with autism and PDD-NOS.	Effectiveness of risperidone and olanzapine cannot be generalized to children with other forms of PDDs.	Risperidone well tolerated, low risk of EPS. Weight gain in children. Olanzapine well tolerated, with no EPS. Weight gain.	1. Report clear review question, state inclusion and exclusion criteria of primary studies? Yes 2. Substantial effort to find relevant research? Yes 3. Adequate assessment of validity of included studies? Yese 4. Sufficient detail of individual studies presented? Yes 5. Primary studies summarized appropriately? Yes Overall quality rating=Good
Jensen, 2007	No quantitative synthesis. Olanzapine (10.7 mg/day) and risperidone (0.49-1.8 mg/day) demonstrated efficacy in reducing symptoms in children with PDD. Risperidone: Effect size vs placebo in 2 studies, based on change from baseline in Aberrant Behavior Checklist-Irritability subscale=-1.2 (McCracken) and -0.8 (Shea) Olanzapine: 1 observational study (Kemner, before-after study) found improvement in ABC and CGI scores.	No information	Risperidone: most common side effects were mild transient somnolence and weight gain. Caregiver-reported tremor or "abnormal movements" (p=0.06 vs placebo) Olanzapine: EPS that resolved with dose adjustment reported.	1. Report clear review question, state inclusion and exclusion criteria of primary studies? Partially 2. Substantial effort to find relevant research? Yes 3. Adequate assessment of validity of included studies? Partially 4. Sufficient detail of individual studies presented? Yes 5. Primary studies summarized appropriately? Yes Overall quality rating=Fair

Evidence Table 9. Systematic reviews of atypical antipsychotics in youths

Author Year	Aims	Literature search dates	Population included	Drugs included	Study designs included	Additional study eligibility criteria
Jesner, 2007 (Cochrane Review)	To determine the efficacy and safety of risperidone for people with autism spectrum disorder	1966-April 2006	Autism spectrum disorders	Risperidone only	Randomized controlled trials of risperidone vs placebo	Trials had to have at least one standardized outcome measure used for both intervention and control group
Parikh, 2008	To systematically and critically examine the evidence for the pharmacological management of aggression and self-injurious behavior in children with autism spectrum disorders.	Searched from beginning of PubMed; end date of searches not reported	Children and adolescents with autism or autism spectrum disorders	Risperidone, others (no other atypical antipsychotics)	Randomized controlled trials of agent versus placebo or active agent	The use of at least one primary outcome measure with a standardized assessment of aggression and self-injury.

Evidence Table 9. Systematic reviews of atypical antipsychotics in youths

Author Year	Main results	Subgroups	Adverse events	Quality assessment
Jesner, 2007 (Cochrane Review)	Overall conclusion: Risperidone beneficial for some features of autism, but limited data available from studies with small sample sizes. Meta-analysis for ABC, CGI, and weight gain ABC mean score vs placebo (Shea 2004 and RUPP 2002): Irritability subscale: -8.09 (95% CI -12.99, -3.19) Social withdrawal/lethargy: -3.00 (95% CI -5.03, -0.97) Hyperactivity: -8.98 (95% CI -12.01, -5.94) Stereotypy: -1.71 (95% CI -2.97, -0.45) Inappropriate speech: -1.93 (95% CI -3.79, -0.07) CGI (McDougle 1998, RUPP 2002, Shea 2004): Relative risk of improvement vs placebo 4.83 (95% CI 2.21, 10.59); significant heterogeneity	No information	Most frequent AEs were somnolence, URTI, rhinitis, and increased appetite. Meta-analysis of weight gain (RUPP 2002, Shea 2004): Risperidone +1.78 kg (95% CI 1.15, 2.41) Placebo 1.0 kg	1. Report clear review question, state inclusion and exclusion criteria of primary studies? Yes 2. Substantial effort to find relevant research? Yes 3. Adequate assessment of validity of included studies? Yes 4. Sufficient detail of individual studies presented? Yes 5. Primary studies summarized appropriately? Yes Overall quality rating=Good
Parikh, 2008	Qualitative synthesis only. Risperidone decreased aggression and self-injurious behavior in 3 placebo-controlled trials	Not addressed	Weight gain associated with risperidone treatment	1. Report clear review question, state inclusion and exclusion criteria of primary studies? Yes 2. Substantial effort to find relevant research? Yes 3. Adequate assessment of validity of included studies? Partially 4. Sufficient detail of individual studies presented? Yes 5. Primary studies summarized appropriately? Yes Overall quality rating=Fair

Evidence Table 10. Quality assessment of trials in youths

	Internal validity						
Author, year Country	**Randomization adequate?**	**Allocation concealment adequate?**	**Groups similar at baseline?**	**Eligibility criteria specified?**	**Outcome assessors masked?**	**Care provider masked?**	**Patient masked?**
Aman et al, 2002 Risperidone Disruptive Behavior Study Group US	Method not reported	Not reported	Differences in IQ, but controlled for in analysis	Yes	Yes	Yes	Yes
Armenteros, 2007 US	Yes	Not reported	Yes	Yes	Yes	Yes	Yes
Buitelaar, 2001 Netherlands	Yes	Not reported	Yes	Yes	Yes	Yes	Yes
Connor 2008	NR	NR	Yes	Yes	NR (described as double-blind)	Yes	Yes
Findling et al, 2000 US	Yes	Yes	Trends: risperidone group older (p=0.006) and weighed more (p=0.12)	Yes	Yes	Yes	Yes

Evidence Table 10. Quality assessment of trials in youths

Author, year Country	Reporting of attrition, crossovers, adherence, and contamination?	Loss to follow-up: Differential/ high?	Intent-to-treat analysis?	Quality rating	Funding	Comments
Aman et al, 2002 Risperidone Disruptive Behavior Study Group US	Attrition and adherence yes, others no.	Yes- 78% risperidone, 70% placebo.	No- 3 risperidone patients with no efficacy data not included in analysis.	Fair	Supported by the Janssen Research Foundation.	
Armenteros, 2007 US	Yes, No, No, No	None	Yes	Good	First author has received research support and is on speakers panel of Janssen	
Buitelaar, 2001 Netherlands	Yes	No	Yes (LOCF)	Fair	Janssen-Cilag, The Netherlands	
Connor 2008	Yes, No, No, No	Differential: Yes High: Yes 8/9 (88%) completed in Quetiapine group 3/10 (30%) completed in placebo group (most dropped due to lack of efficacy; N=5)	Yes	Fair	AstraZeneca	
Findling et al, 2000 US	Attrition and adherence yes, others no.	Withdrawals- 40% risperidone, 70% placebo	Yes	Fair	Supported in part by the Janssen Research Foundation, the Stanley Foundation, and NICHD Pediatric Pharmacology Research Unit contract.	

Evidence Table 10. Quality assessment of trials in youths

	Internal validity						
Author, year Country	**Randomization adequate?**	**Allocation concealment adequate?**	**Groups similar at baseline?**	**Eligibility criteria specified?**	**Outcome assessors masked?**	**Care provider masked?**	**Patient masked?**
Hollander, 2006 US double blind placebo-controlled Olanzapine Poor	Method not reported	Method not reported	Yes	Yes	NR	NR	Yes
Kent 2013 U.S.	Unclear	Yes	Unclear; proportion of caucasians higher in high dose risperidone group	Yes	Yes	Yes	Yes
Luby, 2006 US Randomized, placebo-controlled Risperidone Fair	Yes	Yes	Yes on most measures; tx group greater severity of autism symptoms at baseline, poorer language skills, and poorer motor skill development.	Yes	Yes	No	Yes
Marcus 2009	Method not reported	Method not reported	No Placebo group heavier	Yes	NR (described as double-blind)	NR (described as double-blind)	NR (described as double-blind)

Evidence Table 10. Quality assessment of trials in youths

Author, year Country	Reporting of attrition, crossovers, adherence, and contamination?	Loss to follow-up: Differential/ high?	Intent-to-treat analysis?	Quality rating	Funding	Comments
Hollander, 2006 US double blind placebo-controlled Olanzapine Poor	Attrition, Yes Cross over, NA Adherence, No Contamination, No	6 tx; 4 completed 5 placebo; 4 completed	No	Poor	This study was supported by an investigator- initiated research grant from Lilly Research Laboratories. Olanzapine and matching placebo were supplied by Lilly Research Laboratories. We acknowledge Charles Cartwright, M.D., and Sallie Jo Hadley, M.D.	Small study, No ITT, No details on randomization
Kent 2013 U.S.	Yes, no, no no	Overall: no 19.8% withdrawal Differential: no	Yes	Fair	Janssen	
Luby, 2006 US Randomized, placebo-controlled Risperidone Fair	Attrition, Yes Cross over, NA Adherence, No Contamination, No	No/No 1 subject of 24 total	No; may not be applicable since only one did not complete?	Fair	Funded by Janssen Pharmaceutica	small study
Marcus 2009	Yes, No, Yes, No	No, no	No 3/218 excluded from efficacy sample	Fair		

Evidence Table 10. Quality assessment of trials in youths

	Internal validity						
Author, year Country	**Randomization adequate?**	**Allocation concealment adequate?**	**Groups similar at baseline?**	**Eligibility criteria specified?**	**Outcome assessors masked?**	**Care provider masked?**	**Patient masked?**
McCracken et al, 2002 Arnold et al, 2003 Research Units on Pediatric Psychopharmacology Autism Network RUPP	Method not reported	Not reported	Yes	Yes	Yes	Yes	Yes
Nagaraj, 2006 India double blind placebo-controlled Risperidone Fair	Yes	Yes	Yes	Yes	Yes	NR	Yes
Owen 2009	Yes	Yes	No Drug group older and heavier	Yes	Yes	NR (described as double-blind)	NR (described as double-blind)
Pathak 2013 US	Unclear, no information about sequence generation	Yes	Unclear; Overt Aggression Scale-Modified total scores higher in quetiapine groups	Yes	Unclear	Yes	Yes

Evidence Table 10. Quality assessment of trials in youths

Author, year Country	Reporting of attrition, crossovers, adherence, and contamination?	Loss to follow-up: Differential/ high?	Intent-to-treat analysis?	Quality rating	Funding	Comments
McCracken et al, 2002 Arnold et al, 2003 Research Units on Pediatric Psychopharmacology Autism Network RUPP	Attrition yes, others no.	No	Yes	Fair	Supported by contracts from the National Institute of Mental Health, General Clinical Research Center grants from the National Institutes of Health, and a grant from the Korczak Foundation. Study medication donated by Janssen Pharmaceutica.	
Nagaraj, 2006 India double blind placebo-controlled Risperidone Fair	Attrition, Yes Cross over, NA Adherence, No Contamination, No	No/No 1 of 20 placebo	No; may not be applicable since only one did not complete?	Fair-Good	Funding provided by Department of Pediatrics and the institute's internal finances. [Sun Pharmaceuticals, Mumbai, India, provision of the drug and placebo in the required format for the study.]	
Owen 2009	Yes, No, No, No	No, no	No 2/98 excluded from efficacy sample	Fair		A high fair - if all had been included in ITT, rating would be good
Pathak 2013 US	Yes, no. yes, no	Yes for high overall=22%; No for differential	No	Fair	Astra Zeneca	

Evidence Table 10. Quality assessment of trials in youths

	Internal validity						
Author, year Country	**Randomization adequate?**	**Allocation concealment adequate?**	**Groups similar at baseline?**	**Eligibility criteria specified?**	**Outcome assessors masked?**	**Care provider masked?**	**Patient masked?**
Reyes, 2006 International [8 countries, non-US] double blind placebo-controlled Risperidone Fair-Poor	Unclear; the randomization code was generated by the study sponsor, with treatment numbers allocated at each investigative center in chronological order.	Yes	Yes	Yes	NR	NR	Yes
Shea et al, 2004 Pandina et al, 2004 (subgroup analysis) Canada	Method not reported	Not reported	Yes	Yes	Yes	Not reported	Yes
Snyder et al, 2002 Risperidone Conduct Study Group Canada, US, South Africa	Method not reported	Not reported	Yes	Yes	Yes	Yes	Yes

Evidence Table 10. Quality assessment of trials in youths

Author, year Country	Reporting of attrition, crossovers, adherence, and contamination?	Loss to follow-up: Differential/ high?	Intent-to-treat analysis?	Quality rating	Funding	Comments
Reyes, 2006 International [8 countries, non-US] double blind placebo-controlled Risperidone Fair-Poor	Attrition, Yes Cross over, NR Adherence, NR Contamination, NR	Discontinuation due to adverse effects 1.7% with risperidone, 0.6% with placebo (maintenance phase).	No	Fair-Poor	This study was supported by Johnson & Johnson Pharmaceutical Research and Development	3 phases in the study, acute, continuation, and maintenance. Only patients who responded to initial treatment phase were randomized, Adverse events reported in 47.7% with risperidone; versus 36.2% with placebo in continuation phase of study. During the maintenance phase, 21% of Tx group and 22% were on concomitant psychostimulants, the effect of these on outcomes not assessed.
Shea et al, 2004 Pandina et al, 2004 (subgroup analysis) Canada	Attrition yes, others no.	No	Yes (1 not analyzed)	Fair	Supported by Janssen-Ortho Inc, Canada, and Johnson & Johnson Pharmaceutical Research and Development.	
Snyder et al, 2002 Risperidone Conduct Study Group Canada, US, South Africa	Attrition yes, others no.	Yes- 33.3% placebo, 11.3% risperidone withdrew (p=0.006)	No	Fair	Funded by Janssen Research Foundation	

Evidence Table 11. Placebo-controlled trials in youths

Author, year Country Trial name (Quality score)	N	Duration	Study design setting	Population	Eligibility criteria
Aman et al, 2002 Risperidone Disruptive Behavior Study Group US (FAIR) Biederman 2006 (post hoc subgroup analysis)	118	6 weeks	Double-blind, multicenter	Disruptive Behavior Disorders	Healthy and ages 5 to 12 years with symptoms sufficiently severe that the investigator felt there was a need for antipsychotic treatment; DSM-IV axis I diagnosis of conduct disorder, oppositional defiant disorder, or disruptive behavior disorder not otherwise specified; and axis II diagnosis of subaverage IQ (36-84), and a Vineland Adaptive Behavior Scale score 84 or less. Total rating of 24 or higher on the conduct problem subscale of the Nisonger Child Behavior Rating Form. Individuals with attention deficit hyperactivity disorder were also eligible if they met all other inclusion criteria.
Buitelaar, 2001 The Netherlands (FAIR)	38	6 weeks	Double-blind, single center	Disruptive Behavior Disorders	Adolescent inpatients with subaverage cognitive skills. Included if their overt aggressive behavior persisted during hospitalization, as reflected in a score of at least 1 on the modified Overt Aggression Scale (OAS-M) rated by nurses in the ward at the end of the baseline phase; their aggressive behavior failed to responds to behavioral treatment approaches; there was a clinical indication for drug treatment; they were between 12 and 18 years old; they had a principal diagnosis of conduct disorder, oppositional defiant disorder, or ADHD according to DSM-IV, and a full-scale IQ between 60 and 90 on the WISC-R.

Evidence Table 11. Placebo-controlled trials in youths

Author, year Country Trial name (Quality score)	Exclusions	Interventions	Allowed other medications/interventions
Aman et al, 2002 Risperidone Disruptive Behavior Study Group US (FAIR) Biederman 2006 (post hoc subgroup analysis)	Diagnosis of pervasive developmental disorder, schizophrenia, or other psychotic disorder; head injury as a cause of intellectual disability; or a seizure disorder requiring medication. Known hypersensitivity to risperidone or neuroleptics, history of tardive dyskinesia or neuroleptic malignant syndrome, serious or progressive illnesses, presence of HIV, and use of an investigational drug within the previous 30 days; previous treatment with risperidone.	Risperidone mean dose 1.16 mg/day (range 0.006-0.092 mg/kg/day)	Use of other antipsychotics, anticonvulsants, antidepressants, lithium, carbamazepine, valproic acid, or cholinesterase inhibitors was not permitted. Use of consistent doses of psychostimulants permitted if the dose had been stable for at least 30 days. Behavioral therapy permitted if initiated at least 30 days before the start of the study. No changes to psychostimulant use or behavioral therapy were allowed, no medications for sleep or anxiety were to be initiated during the trial. Subjects receiving antihistamines, chloral hydrate, or melatonin for sleep before the screening visit could continue use unchanged. Medications commonly used to treat EPS were discontinued at study entry. If EPS arose during the study, dose of study medication was decreased. If this resulted in deterioration of conduct disorder symptoms or failed to improve the EPS, anti-EPS medication could be considered.
Buitelaar, 2001 The Netherlands (FAIR)	Neurologic, cardiac, pulmonary, or hepatic diseases, primary mood disorders, schizophrenia or other active psychosis, or suicidality, comorbid substance abuse disorder according to DSM-IV; if female, pregnant or used inadequate contraception; major change in treatment strategy (such as transition to another ward) was expected in the near future; or it was not considered feasible to discontinue current psychotropic medication.	risperidone 1 mg or placebo	Concomitant medication for acute or chronic somatic illnesses was allowed at the discretion of the clinician in charge.

Evidence Table 11. Placebo-controlled trials in youths

Author, year Country Trial name (Quality score)	Age Gender Ethnicity	Other population characteristics	Number screened/ eligible/enrolled	Number withdrawn/ lost to follow-up/ analyzed
Aman et al, 2002 Risperidone Disruptive Behavior Study Group US (FAIR) Biederman 2006 (post hoc subgroup analysis)	Mean age 8 years (SD 2 years) 82% male 57% white, 34% black, 5% Hispanic, <1% Asian, 3% other ethnicity.	DSM-IV axis I diagnosis: 21% oppositional defiant disorder 32% oppositional defiant disorder plus ADHD 18% conduct disorder 22% conduct disorder plus ADHD 2% disruptive behavior disorder not otherwise specified 5% disruptive behavior disorder plus ADHD DSM-IV axis II diagnosis: 51% borderline intellectual disability 32% mild intellectual disability 17% moderate intellectual disability	142 screened/119 eligible/118 enrolled	12 risperidone, 19 placebo patients withdrew, 115 analyzed (3 in risperidone group had no efficacy data, not analyzed).
Buitelaar, 2001 The Netherlands (FAIR)	14.0 86.8% male Ethnicity NR	Principal diagnosis: Conduct disorder: 78.9% Oppositional defiant disorder: 15.8% Disruptive behavior disorder NOS: 5.3%	145/48/38	2 (placebo)/NR/38

Evidence Table 11. Placebo-controlled trials in youths

Author, year Country Trial name (Quality score)	Results	Overall withdrawals/ Withdrawals due to adverse events	Adverse events
Aman et al, 2002 Risperidone Disruptive Behavior Study Group US (FAIR)	Change in Nisonger Child Behavior Rating Form conduct problem subscale score at 6 weeks (risperidone vs placebo): -15.2 vs -6.2 (p<0.001)	3/118 (2.5%)/ 2/118 (1.7%)	No serious adverse events Most common adverse events, placebo vs risperidone: somnolence:10% vs 51%, headache: 14% vs 29%, vomiting: 6% vs 20%, dyspepsia: 6% vs 15%, weight increase: 2%
Biederman 2006 (post hoc subgroup analysis)	CGI change score (risperidone vs placebo): improved: 76.9% vs 33.4% (p<0.0001) much to very much improved: 7.9% vs 53.8% (p<0.001) Biederman 2006 analysis of affective symptoms: Risperidone effective in treating factors explosive irritability; agitated/expansive/grandiose; and depression. No difference from placebo on factors		vs 15%, elevated serum prolactin: 2% vs 13%, increased appetite: 6% vs 11%, and rhinitis: 5% vs 11%. Amount of weight gain not reported.
Buitelaar, 2001 The Netherlands (FAIR)	risperidone vs placebo Markedly or severely disturbed: 21% vs 84% Mean (SD) CGI-Severity score: 2.7 (1.2) vs 4.4 (1.0)	2 overall/ 0 due to AEs	Extrapyramidal symptoms were absent or very mild during risperidone treatment. Transient tiredness in 11/19 (58%) drug-treated subjects. Weight gain: mean 3.5% of body weight in risperidone group

Evidence Table 11. Placebo-controlled trials in youths

Author, year Country Trial name (Quality score)	N	Duration	Study design setting	Population	Eligibility criteria
Connor 2008 USA	19	6 weeks plus 1 week screening	Double-blind, single center	Adolescents with conduct disorder	12 and 17 years inclusive and to meet criteria for a primary psychiatric diagnosis of conduct disorder; patients had to have a moderate-to-severe degree of aggressive behavior as documented by an overt aggression scale score > 25 and at least moderate severity of symptoms as documented by a Clinical Global Impressions–Severity (CGI-S) score > 4 .
Findling et al, 2000 US (FAIR)	20	10 weeks	Double-blind, single, inner-city, academic medical center.	Disruptive Behavior Disorders	Outpatients who met DSM-IV criteria for conduct disorder as a primary diagnosis; ages 5 to 15 years, with at least a moderate degree of overall symptom severity as based on the CGI Scale, and an Aggression subscale T score 2 SD or more above the mean for age- and gender-matched peers on the Child Behavior Checklist (CBCL).

Evidence Table 11. Placebo-controlled trials in youths

Author, year Country Trial name (Quality score)	Exclusions	Interventions	Allowed other medications/interventions
Connor 2008 USA	Co-morbid psychiatric diagnosis of schizophrenia, schizoaffective disorder, psychotic disorder not otherwise specified(NOS), bipolar disorder, psychotic depression, or bipolar disorder NOS; alcohol or substance abuse or dependence within 3 months: significantly subaverage IQ ; lenticular abnormality or juvenile cataracts; seizure disorder; concurrent administration of any psychoactive medication, including stimulants; pregnant or lactating females; and any unstable medical disease	Mean quetiapine was 294 ± 78 mg/day (range 200–600 mg/day) vs.. Placebo	Oral benztropine was permitted for EPS.
Findling et al, 2000 US (FAIR)	Moderate or severe attention deficit/hyperactivity disorder, significant psychiatric comorbidity (including mood disorders), treatment with a psychotropic medication within one week of initiating double-blind therapy, a positive toxicology screen, suicide attempt within the past month, clinically significant general medical condition, organic mental syndromes, pregnant or nursing females, females of childbearing potential who were not using an acceptable method of birth control, and a standard score equivalent to <70 on the Peabody Picture Vocabulary Test-Revised.	Risperidone 0.25 mg if weight less than 50 kg; 0.50 mg if weight 50 kg or greater. Starting dose was 1 tablet per day; dose could be increased by 1 tablet per day each week to a maximum daily dose of 6 tablets per day. All dose adjustments were to occur during the first 6 weeks of the study.	For patients in whom EPS developed, treatment with oral benztropine was available.

Evidence Table 11. Placebo-controlled trials in youths

Author, year Country Trial name (Quality score)	Age Gender Ethnicity	Other population characteristics	Number screened/ eligible/enrolled	Number withdrawn/ lost to follow-up/ analyzed
Connor 2008 USA	Mean age 14.1 (1.6) yrs 74% male 76% Caucasian 16% Hispanic 10% African American	Conduct disorder 100% Oppositional defiant disorder (ODD) 95% ADHD 79%	NR/68/20	8/0/19
Findling et al, 2000 US (FAIR)	Mean age 9.2 years (SD 2.9), range 6-14 19/20 (95%) male 50% white (no other ethnicity information reported)	9 patients had not improved with treatments with other psychotropic medications (methylphenidate). Other medications previously prescribed included dextroamphetamine (n=4), clonidine (n=3), an antidepressant (n=5), divalproex sodium (n=2), and thioridazine (n=1).	Number screened, eligible not reported/20 enrolled	4/10 risperidone, 6/10 placebo patients withdrew/1 placebo patient lost to followup/20 analyzed

Evidence Table 11. Placebo-controlled trials in youths

Author, year Country Trial name (Quality score)	Results	Overall withdrawals/ Withdrawals due to adverse events	Adverse events
Connor 2008 USA	Baseline/endpoint CGI-S Quetiapine 5.9 (0.6) / 3.4 (1.1) Placebo 5.5 (1.2)/ 5.0 (0.6) OAS Quetiapine 73.2 (34.3) / 43.3 (55.6) Placebo 40.4 (23.8) / 49.4 (27.8) CPRS-CP Quetiapine 17.1 (5.1) / 11.3 (7.7) Placebo 11.4 (3.6) / 12.2 (4.4) Q-LES-Q Quetiapine 36.9 (8.6) 48.2 (10.2) Placebo 39.3 (9.5) 35.2 (8.0)	8 overall 1 due to AEs	Quetiapine vs. placebo n (%) Agitation 6 (66) vs. 9 (90) Anxiety 6 (66) 7 vs. (70) Decreased energy 3 (33) vs. 5 (50) Decreased mental alertness 3 (33) vs. 9 (90) P = 0.01 Diminished emotional expression 1 (11) vs. 7 (70) P = 0.009 Diminished facial expression 1 (11) vs. 6 (60) P = 0.03 Drooling 2 (22) vs. 0 (0) Irritability 7 (78) vs. 8 (80) Muscle stiffness 1 (11) vs. 2 (20) Overeating 1 (11) vs. 2 (20) Pacing 4 (44) vs. 5 (50) Restlessness 7 (78) vs. 7 (70) School refusal 2 (22) vs. 4 (40) Sedation 6 (67) vs. 9 (90) Social withdrawal 4 (44) vs. 5 (50) Tremor 0 (0)0 vs. 3 (30) Weight gain 3 (33) vs. 1 (10)
Findling et al, 2000 US (FAIR)	Rating of Aggression Against People and/or Property Scale (RAAPP) score Difference from baseline, weeks 7-10: risperidone: -1.91 placebo: -0.70 (p=0.0007) Difference from baseline, week 10: risperidone: -1.65 placebo: -0.16 (p=0.03) Mean CGI-I score at weeks 7-10: risperidone: 1.80 placebo: 3.19 (p=0.0006) Mean CGI-I score at week 10: risperidone: 1.80 placebo: 3.60 (p=0.002)	5/17 (29.4%) withdrew overall, no withdrawals due to AEs	No extrapyramidal symptoms

Evidence Table 11. Placebo-controlled trials in youths

Author, year Country Trial name (Quality score)	N	Duration	Study design setting	Population	Eligibility criteria
Hollander, 2006 US (FAIR)	11	8 weeks	Double-blind, RCT, single center	Children and adolescents with pervasive developmental disorders	Between ages of 6 and 17 years, fulfilling DSM-IV and ADI-R criteria with a rating of at least moderate (4 or greater) on the CGI. Patients were not selected for particular scores of aggressive or disruptive behaviors on study measures.
Kent, 2013 US	96	6 weeks	Double-blind randomized, multi center	Children and adolescents with autistic disorder	Aged 5-17 years, weighing at least 20kg with a diagnosis of autistic disorder using DSM-IV criteria, score of at least 4 on CGI-S at baseline, mental age of more than 18 months,seizure free for at least 6 consecutive months or a stable dosage of antiepileptic drugs for 4 weeks before screening.No psychotropic medications for at least 1 week.

Evidence Table 11. Placebo-controlled trials in youths

Author, year Country Trial name (Quality score)	Exclusions	Interventions	Allowed other medications/interventions
Hollander, 2006 US (FAIR)	Patients who were responding well to prior pharmacological treatment; psychotic disorders and a history of any clinically significant medical illness (with the exception of a stable seizure disorder).	Olanzapine, titrated according to weight up to a maximum of 20 mg/day vs placebo Mean doses 10 (SD 2.04) mg/day; range 7.5 mg-12.5 mg	None of the patients was taking any concomitant medications during the study.
Kent, 2013 US	DSM-IV diagnosis of psychotic disorder or pervasive developmental disorder other than autism, neurological disorders, moderate or severe extrapyramidal symptoms or tardive dyskinesia and lack of response to risperidone treatment in the past.	Risperidone low dose: 0.125mg/d, 0.175 mg/d Risperidone high dose: 1.25mg/d, 1.75mg/d Placebo	Anticholinergics, antihistamines for the treatment of emergent EPS restricted to the lowest dose and for shortest duration possible.Lorazepam 0.25-2mg, dyphenhydramine upto 50mg were allowed if the patient was had been stable on a particular dose for at least 30 days before study start.

Evidence Table 11. Placebo-controlled trials in youths

Author, year Country Trial name (Quality score)	Age Gender Ethnicity	Other population characteristics	Number screened/ eligible/enrolled	Number withdrawn/ lost to follow-up/ analyzed
Hollander, 2006 US (FAIR)	Mean age 9.1 years (range 6.0-14.8) 81.8% male 63.6% white, 18.2% black, 9.1% Hispanic, 9.1% Asian	6/11 autism, 1 Asperger's syndrome, 4 PDD-NOS 36.4% normal cognitive functioning, 45.5% mild mental retardation, 0% moderate, 18.2% severe, 0% profound	20/NR/11	3/0/NR
Kent, 2013 US	Mean age: 9 years (SD 3.1) 88% male White: 70% Black: 20% Asian: 7% Other: 3%	Baseline BMI(kg/m2): 19.7 (SD 5.05) Median age at first diagnosis of autism: 3 (range 2-14) Previous antipsychotic use: 9%	145/NR/96	19/2/96

Evidence Table 11. Placebo-controlled trials in youths

Author, year Country Trial name (Quality score)	Results	Overall withdrawals/ Withdrawals due to adverse events	Adverse events
Hollander, 2006 US (FAIR)	Response on CGI-I: 50% risperidone and 20% placebo No evidence for significant change on other outcome measures	3 overall/ 0 due to AEs	Weight gain: 7.5 (SD 4.8) lbs olanzapine vs 1.5 (SD 1.5) lb placebo; p=0.028 66.6% olanzapine vs 20% placebo subjects had a more than 7% weight gain. Most common side effects were increased appetite and sedation No abnormal movements, dyskinesias, or EPS
Kent, 2013 US	RIS low dose vs RIS high dose vs placebo Mean (SD) change from baseline in ABC-irritability subscale score: -7.4 (8.12) vs -12.4 (6.52) vs -3.5 (10.67), p-values vs placebo for low dosep= 0.164, for high dose p<0.001) Mean(SD) change from baseline in CGI-severity: -0.4 (0.73) vs -1.0 (0.78) vs -0.3 (0.79), p-values vs placebo for low dose p=0.769, for high dose p<0.001 Response rates: 52% vs 83% vs 41%, p values vs placebo for low dose p=0.817, for high dose p<0.004 Proportion of patients with much or very much improvement on CGI: 17% vs 63% vs 15%, p-values vs placebo for low dose p=0.985, for high dose p=<0.001 ABC subscale on hyperactivity: high dose p=0.019 vs placebo. No other data provided. ABC stereotypic behavior subscale: low dose p=0.008 vs placebo. No other data provided. ABC inappropriate speech or social withdrawal subscale score: low dose p=0.716 vs placebo, high dose: 0.511 vs placebo	RIS low dose vs RIS high dose vs placebo Total withdrawal: 5 (17%) vs 6 (19%) vs 8 (23%) Withdrawal due to AE: 0 vs 1 (3%) vs 1 (3%)	RIS low dose vs RIS high dose vs placebo TEAE: 60% vs 87% vs 80% Mean(SD) weight(kg) gain from baseline: 1.2 (1.3) vs 2.4 (2.7) vs 0.7 (1.19) AE occuring in at least 2 people high dose group and with twice the freqency Increased appetite: 35% vs 17% Sedation: 26% vs 3% Somnolence: 23% vs 0% weight gain: 11% (both groups combined) EPS- most frequently reported in ris high dose group: 16% (akathisia 13%) No meaningful change from baseline in AIMS total score, BARS or SARS rating scales

Evidence Table 11. Placebo-controlled trials in youths

Author, year Country Trial name (Quality score)	N	Duration	Study design setting	Population	Eligibility criteria
Luby, 2006 US (FAIR)	24	6 months	Double-blind, RCT, single center	Preschool children with autism spectrum disorders	Preschool children between age 2.5 and 6.0 years who met DSM-IV criteria for autism or PDD-NOS, previously diagnosed and referred by a clinician.
Nagaraj, 2006 India (FAIR)	40	6 months	Double-blind, RCT, single center	Children with autism	Consecutive children up to 12 years of age, diagnosed with autism according to the DSM-IV criteria. Referred with varying symptoms, including hyperactivity, aggression, stereotypes, and language difficulties.

Evidence Table 11. Placebo-controlled trials in youths

Author, year Country Trial name (Quality score)	Exclusions	Interventions	Allowed other medications/interventions
Luby, 2006 US (FAIR)	Other known significant CNS disorders; significant medical problems or other psychiatric disorders requiring pharmacotherapy.	Risperidone 0.5-1.5 mg or placebo Mean dose 1.14 mg (SD 0.32)	Participating families were strongly encouraged to minimize the use of adjunctive medications and/or supplements (hormones, vitamins, diets) over the duration of treatment.
Nagaraj, 2006 India (FAIR)	Severe mental retardation, any significant coexisting disease or illness (neurologic, cardiovascular, respiratory, genetic), or severe malnutrition (weight for age <60% of National Center for Health Statistics median)	risperidone 1 mg vs placebo	None

Evidence Table 11. Placebo-controlled trials in youths

Author, year Country Trial name (Quality score)	Age Gender Ethnicity	Other population characteristics	Number screened/ eligible/enrolled	Number withdrawn/ lost to follow-up/ analyzed
Luby, 2006 US (FAIR)	49 months 17/23 male (73.9%) 92% Caucasian	All were receiving behavioral therapy (risperidone 21.2 hours per week, placebo 11.3 hours per week; p=0.13)	NR/NR/24	1/NR/23
Nagaraj, 2006 India (FAIR)	Mean age 5 years 92.3% male	43.6% borderline IQ, 28.2% mild mental retardation, 28.2% moderate mental retardation	NR/NR/40	1/0/39

Evidence Table 11. Placebo-controlled trials in youths

Author, year Country Trial name (Quality score)	Results	Overall withdrawals/ Withdrawals due to adverse events	Adverse events
Luby, 2006 US (FAIR)	CARS total score at endpoint: risperidone 33.0 (SD 4.3) placebo 31.5 (SD 5.1) p=0.059 Controlled for motor development: p=0.12 Controlled for language skills: p=0.67	0/0	No deaths or serious treatment-related adverse events. Mean weight change (SD) from baseline to endpoint, risperidone vs placebo: 2.96 kg (2.53) vs 0.61 kg (1.10); p=0.008. Most common adverse events were transient sedation (n=5), increased appetite (n=6), and hypersalivation (n=2). One child had transient staring spells and periods of apparent waxy flexibility (after minor head injury, not attributed to medication)
Nagaraj, 2006 India (FAIR)	CARS: 63% risperidone vs 0% placebo had improvement of at least 20% Median score (range) at end of treatment, risperidone vs placebo: 39.5 (32.5-46) vs 38.5 (31.5-43); p<0.001 Children's Global Assessment Scale Score: 89% risperidone vs 10% placebo had improvement of at least 20% Mean score (SD) at end of treatment, risperidone vs placebo: 40.94 (7.83) vs 35.2 (9.38); p=0.035	1 withdrew/ 0 due to AEs	Increased appetite and improved eating habits in 17/19 children receiving risperidone (89.5%) Mean weight change, risperidone vs placebo: 2.81 kg (SD 2.04, 17% increase) vs 1.71 kg (1.3, 9.3% increase); NS

Evidence Table 11. Placebo-controlled trials in youths

Author, year Country Trial name (Quality score)	N	Duration	Study design setting	Population	Eligibility criteria
Pandina, 2007 Canada Subgroup analysis of Shea, 2004 Previously included as an abstract only (FAIR)	55	8 weeks	Double-blind, multicenter	Children with autism	Physically healthy male and female outpatients ages 5 to 12 years with a DSM-IV of autistic disorder and a total score of 30 or more on the Childhood Autism Rating Scale (CARS).

Evidence Table 11. Placebo-controlled trials in youths

Author, year Country Trial name (Quality score)	Exclusions	Interventions	Allowed other medications/interventions
Pandina, 2007 Canada Subgroup analysis of Shea, 2004 Previously included as an abstract only (FAIR)	Schizophrenia or other psychotic disorders; history of drug or alcohol abuse, tardive dyskinesia, neuroleptic malignant syndrome, seizure within the previous 3 months, or previous intolerance or unresponsiveness to risperidone.	Risperidone oral solution 0.01 mg/kg/day on treatment days 1 and 2 and increased to 0.02 mg/kg/day on day 3. Depending on therapeutic response at day 8, the dose could be increased by a maximal increment of 0.02 mg/kg/day. Thereafter, the dose could be adjusted at the investigator's discretion at weekly intervals by increments/decrements not to exceed 0.02 mg/kg/day. The maximal allowable dose was 0.06 mg/kg/day. In case of drowsiness, the study medication could be administered once daily in the evening, or the total daily dose could be divided and administered on a morning and evening schedule.	Medications that are used to treat EPSs were to be discontinued at the time of entry into the trial. However, during the trial, anticholinergics could be initiated to treat emergent EPSs after the ESRS had been completed. Prohibited medications included antipsychotics other than the study medication, antidepressants, lithium, alpha-2 antagonists, clonidine, guanfacine, cholinesterase inhibitors, psychostimulants, and naltrexone. A single anticonvulsant and/or medications for sleep or anxiety were permitted only in the case in which the subject was already taking them at a stable dose for the 30 days before enrollment. Similar restrictions were placed on the use of behavior intervention therapy. Medications for preexisting organic disorders were allowed provided that the dose and schedule of administration were kept as constant as possible.

Evidence Table 11. Placebo-controlled trials in youths

Author, year Country Trial name (Quality score)	Age Gender Ethnicity	Other population characteristics	Number screened/ eligible/enrolled	Number withdrawn/ lost to follow-up/ analyzed
Pandina, 2007 Canada Subgroup analysis of Shea, 2004 Previously included as an abstract only (FAIR)	Mean age 7.2 years 78.2% male 61.8% white, 18.2% black, 20% other race	0% risperidone vs 25% placebo patients had an IQ>84 (p=0.02); mean IQ (SD) 50.8 (19.8) risperidone vs 60.1 (26.9) placebo; p=0.213	NR NR 55	6/0/55/52

Evidence Table 11. Placebo-controlled trials in youths

Author, year Country Trial name (Quality score)	Results	Overall withdrawals/ Withdrawals due to adverse events	Adverse events
Pandina, 2007 Canada Subgroup analysis of Shea, 2004 Previously included as an abstract only (FAIR)	Mean score at endpoint (SD), risperidone vs placebo; p-value for mean change between group difference): ABC (Irritability): 7.2 (5.9) vs 14.1 (11.3); p=0.002 ABC (Lethargy/social withdrawal): 4.7 (4.4) vs 8.2 (8.9); p=0.020 ABC (Stereotypic behavior): 3.9 (4.2) vs 6.9 (6.9); p=0.053 ABC (Hyperactivity/noncompliance): 13.3 (8.7) vs 26.4 (12.8); p=0.001 ABC (Inappropriate speech): 1.9 (2.2) vs 3.1 (3.5); p=0.058 N-CBRF (Adaptive/social): 5.3 (2.4) vs 4.3 (2.4); p=0.072 N-CBRF (Compliant/calm): 8.7 (3.3) vs 6.9 (2.9); p=0.072 N-CBRF (Conduct problem): 6.5 (5.7) vs 15.5 (11.9); p=0.0025 N-CBRF (Hyperactive): 9.4 (5.4) vs 14.9 (8.4); p=0.021 N-CBRF (Insecure/anxious): 3.2 (4.3) vs 5.4 (4.8); p=0.217 N-CBRF (Overly sensitive): 2.8 (2.3) vs 4.3 (3.3); p=0.029 N-CBRF (Self-injurious/stereotypic): 2.2 (3.1) vs 2.8 (3.9); p=0.0183 N-CBRF (Self-isolated/ritualistic): 2.4 (2.5) vs 4.5 (5.5); p=0.078 Change from baseline in VAS for most troublesome symptom (least squares mean estimate, SE): -40.2 (6.6) vs -24.9 (6.4); p=0.066 Improvement as assessed by the CGI-C: 58.3% vs 21.4% (p=0.008)	2 of 55 (4%)/ 1 risperidone, 1 placebo	Mean weight (SD) at baseline and end point: risperidone: 30.4 (11.8); 32.8 (12.6) kg placebo: 27.3 (8.9); 28.4 (9.8) kg p=0.276 1 case of hyperkinesia and 1 case of extrapyramidal disorder in patients receiving risperidone.

Evidence Table 11. Placebo-controlled trials in youths

Author, year Country Trial name (Quality score)	N	Duration	Study design setting	Population	Eligibility criteria
Pathak, 2013 USA	284	3 weeks	Randomized, DB, PCT, multicenter, inpatient and outpatient	10-17 years, DSM-IV bipolar I with manic episodes	10-17 years, DSM-IV criteria for bipolar I with manic episodes, YMRS total score ≥20, permitted to have secondary diagnosis of ADHD
Reyes, 2006 International [8 countries, non-US] Risperidone (FAIR-POOR)	335	6 months	Randomized, single-blind, multicenter; Maintenance vs withdrawal	Children and adolescents with disruptive behavior disorders who had responded to risperidone treatment over 12 weeks	Children and adolescents (ages 5-17 years) without moderate or severe intellectual impairment (IQ>=55), who met DSM-IV criteria for conduct disorder, oppositional defiant disorder, or disruptive behavior disorder not otherwise specified, with the diagnosis confirmed by the K-SADS-PL. Inclusion required that the conduct problem be serious enough to warrant clinical treatment with risperidone and be associated with a score >+24 on the conduct problem subscale of the Nisonger Child Behavior Rating Form-parent version at both screening and treatment initiation. Children and adolescents with comorbid ADHD were not excluded.

Evidence Table 11. Placebo-controlled trials in youths

Author, year Country Trial name (Quality score)	Exclusions	Interventions	Allowed other medications/interventions
Pathak, 2013 USA	DSM-IV diagnosis of other Axis I disorder, history of serious suicide attempts, current risk of suicide or homicide	Quetiapine 400 mg/d, in 2 or 3 doses, titrated over 5 days Quetiapine 600 mg/d, in 2 or 3 doses, titrated over 7 days Placebo	Psychostimulant at stable dose for ADHD, Diphenhydramine, hydroxyzine, lorazepam, benztropine for treatment-emergent EPS (not prophylactic)
Reyes, 2006 International [8 countries, non-US] Risperidone (FAIR-POOR)	Serious medical or psychiatric conditions such as schizophrenia or bipolar disorder.	risperidone vs placebo (maintenance vs withdrawal). Flexible dose depending on body weight. Maximum dose 0.75 mg (patients <50 kg) or 1.5 mg (those >=50 kg)	Concomitant therapy with stable psychostimulant dosing was permitted. Treatment with additional antipsychotics, lithium, anticonvulsants, or antidepressants was not permitted.

Evidence Table 11. Placebo-controlled trials in youths

Author, year Country Trial name (Quality score)	Age Gender Ethnicity	Other population characteristics	Number screened/ eligible/enrolled	Number withdrawn/ lost to follow-up/ analyzed
Pathak, 2013 USA	Age: 43.7% 10-12 years, 56.3% 13-17 years Gender: 43.7% female Ethnicity: 76.5% White, 13.7% Black	Current or past history of ADHD: 44.8%	393/289/284	61/3/277 ITT; 283 safety
Reyes, 2006 International [8 countries, non-US] Risperidone (FAIR-POOR)	Mean age 10.9 years 86.6% male 87% Caucasian	36.7% Conduct disorder, 60.9% Oppositional defiant disorder, 2.4% Disruptive behavior disorder, NOS	575/NR/335	49/0/335

Evidence Table 11. Placebo-controlled trials in youths

Author, year Country Trial name (Quality score)	Results	Overall withdrawals/ Withdrawals due to adverse events	Adverse events
Pathak, 2013 USA	Quetiapine 400 mg/d vs. Quetiapine 600 mg/d vs. Placebo YMRS, Least squares mean change at day 21 (95%CI): -14.25 (-16.15 to -12.35) vs. -15.60 (-17.51 to -13.70) vs. -9.04 (-11.24 to -6.84), p<0.001 treatment vs. placebo CDRS-R mean (SD) changes at day 21: -5.2 (8.47) vs. -6.2 (7.56) vs. -3.8 (8.02), 600mg/d vs. placebo: p<0.05 CGI-BP Severity, least squares mean change at day 21(95%CI): -1.55 (-1.83 to -1.27) vs. -1.62 (-1.88 to -1.37) vs. -0.98 (-1.26 to -0.71), P=0.005 for 400mg vs. placebo, P<0.001 for 600mg vs. placebo	61/26	Quetiapine 400mg/d vs. Quetiapine 600mg/d vs. Placebo Weight gain >7%: 14.5% vs. 9.9% vs. 0% EPS: 4.2% vs. 3.1% vs. 1.1% Suicidal ideation, n: 1 vs. 0 vs. 0 SAE: 7 vs. 4 vs. 3 Total cholesterol ≥170mg/dL after normal baseline: 15 vs. 15 vs. 2 Triglycerides ≥150mg/dL after normal baseline: 14 vs. 15 vs. 8 Prolactin >26 ng/mL females or >20ng/mL males: 12 vs. 10 vs. 2
Reyes, 2006 International [8 countries, non-US] Risperidone (FAIR-POOR)	Risperidone vs placebo Time to symptom recurrence shorter with placebo (p=0.002) Symptom recurrence occurred in 25% of patients after 119 days with risperidone vs 37 days with placebo Rate of symptom recurrence: 27.3%, N=47 vs 42.3%, N=69 (p=0.002) Change from beginning to end of maintenance phase: Mean (SD), risperidone vs placebo Nisonger Child Behavior Rating Form Conduct problems: 5.0 (9.5) vs 8.8 (11.2); p<0.001 Insecure/anxious: 1.9 (6.2) vs 2.7 (6.5); p=0.20 Hyperactive: 0.8 (4.4) vs 2.4 (5.4); p=0.007 Self-injury/stereotypic behavior: 0.3 (1.5) vs 0.5 (1.8); p=0.34 Self-isolated/ritualistic: 0.8 (2.6) vs 0.9 (2.8); p=0.67 Overly sensitive: 0.4 (2.8) vs 1.0 (3.19); p=0.054 Compliant/calm: -1.5 (3.8) vs -2.8 (4.4); p<0.001 Adaptive/social: -0.9 (2.5) vs -1.7 (2.9); p=0.006 VAS rating of most troublesome symptom: 7.2 (26.9) vs 14.1 (27.8); p=0.01 CGI Severity: 0.6 (1.2) vs 1.2 (1.4); p<0.001 CGI Change: 3.6 (1.8) vs 4.3 (1.9); p<0.001 Children's Global Assessment Scale score: -3.5 (12.4) vs -10.2 (14.5); p<0.001	49/335 (14.6%)/ 8/335 (2.4%)	Most frequent adverse events were headache, rhinitis, URTI, pharyngitis, abdominal pain, somnolence, fatigue, increased appetite, and weight gain Risperidone vs placebo: Serious adverse events: 3.5% vs 3.1% Weight gain: 1.2% vs 0.6% Mean weight gain from beginning to end of maintenance phase: 2.1 kg (SD 2.7) vs -0.2 kg (SD 2.2)

Evidence Table 11. Placebo-controlled trials in youths

Author, year Country Trial name (Quality score)	N	Duration	Study design setting	Population	Eligibility criteria
RUPP Trial McCracken, 2002 Arnold, 2003 Aman 2005 Arnold 2010 US (FAIR)	101	8 weeks	Double-blind, multicenter.	Autism	Ages 5 to 17 years, weight at least 15 kg, mental age of at least 18 months; meeting criteria for autistic disorder described in DSM-IV, with tantrums, aggression, self-injurious behavior, or a combination of these.

Evidence Table 11. Placebo-controlled trials in youths

Author, year Country Trial name (Quality score)	Exclusions	Interventions	Allowed other medications/interventions
RUPP Trial McCracken, 2002 Arnold, 2003 Aman 2005 Arnold 2010 US (FAIR)	Serious medical disorders and other psychiatric disorders requiring medication; receiving a psychotropic drug that was deemed effective for the treatment of aggression, tantrums, or self-injurious behavior.	Children 20 to 45 kg: risperidone 0.5 mg, increased to 1 mg on day 4. Dose gradually increased in 0.5 mg increments to a maximum of 2.5 mg per day by day 29 Children over 45 kg: slightly accelerated dose schedule used, maximum dose of 3.5 mg. Children less than 20 kg: initial dose 0.25 mg. Scheduled dose increases could be delayed because of adverse effects or because of marked improvement at a lower dose. Dose reductions to manage side effects were allowed at any time, but there were no dose increases after day 29.	Treatment with an anticonvulsant agent for seizure control was allowed if the dose had been unchanged for at least 4 weeks and if there had been no seizures for at least 6 months.

Evidence Table 11. Placebo-controlled trials in youths

Author, year Country Trial name (Quality score)	Age Gender Ethnicity	Other population characteristics	Number screened/ eligible/enrolled	Number withdrawn/ lost to follow-up/ analyzed
RUPP Trial McCracken, 2002 Arnold, 2003 Aman 2005 Arnold 2010 US (FAIR)	Mean age 8.8 (SD 2.7), range 5-17 81% male 66% white, 11% black, 7% Hispanic, 8% Asian, 8% other ethnicity	Mental development (risperidone vs placebo) Average or above-average IQ: 7% vs 4% Borderline IQ: 17% vs 9% Mild or moderate retardation: 43% vs 51% Severe retardation: 33% vs 36% (NS)	270 screened/158 eligible/101 enrolled	18 withdrawn/3 lost to followup/101 analyzed/

Evidence Table 11. Placebo-controlled trials in youths

Author, year Country Trial name (Quality score)	Results	Overall withdrawals/ Withdrawals due to adverse events	Adverse events
RUPP Trial McCracken, 2002 Arnold, 2003 Aman 2005 Arnold 2010 US (FAIR)	Change in mean Irritability score from baseline to 8 weeks risperidone: -14.9 (56.9% decrease) placebo: -3.6 (14.1% decrease) (p<0.001) Positive response (at least 25% improvement on Irritability subscale and rating of much improved or improved on CGI-I) risperidone: 34/49 (69%) placebo: 6/52 (12%) (p<0.001) Moderator analysis: Mean decrease in ABC irritability subscale score from baseline at 8 weeks [reported as mean, (SD)] Placebo vs risperidone sex: interaction: x2=2.21, p=0.14, Pool variance=78.61 male: 5.17 (7.43) vs 15.25 (10.34), female: 0.83 (8.98) vs 18.33 (7.48) Age: interaction: x2=0.16, p=0.69, pooled variance=79.75 >8.15 years: 2.87 (8.10) vs 14.61 (10.81), <8.15 years: 6.05 (7.34) vs 16.70 (9.24) Education: interaction x2=1.61, p=0.20, pooled variance: 77.18 university degree: 3.70 (7.00) vs 13.00 (7.87), <university degree 4.86 (8.66) vs 18.61 (10.87) Ethnicity: intercation x2=0.01, p=0.91, pooled variance=81.56 non-caucasian: 4.67 (10.53) vs 15.50 (8.82), caucasian: 4.11 (6.10) vs 16.03 (10.39) Income: interaction x2=0.09, p=0.91, pooled variance: 81.56 High: 5.20 (5.01) vs 15 (10.43), low: 4.48 (8.87) vs 16.32 (8.98)	3/49 (6%) risperidone 18/52 (35%) placebo (p=0.001)/ No withdrawals due to AEs	Mean weight gain at 8 weeks: risperidone: 2.7 kg (SD 2.9) placebo: 0.8 kg (SD 2.2) (p<0.001) No extrapyramidal symptoms in either group. No serious adverse events in risperidone group. Parents reported 5 neurological side effects, of these, tremor was significantly more common in the risperidone group (p=0.06) 60 different adverse events recorded, 29 of which occurred in 5% or more of patients. Adverse events with a significantly different incidence (risperidone vs placebo) Increased appetite (mild): 49% vs 25% (p=0.03) Increased appetite (moderate): 24% vs 4% (p=0.01) Fatigue: 59% vs 27% (p=0.003) Drowsiness: 49% vs 12% (p<0.001) Drooling: 27% vs 6% (p=0.02) Dizziness: 16% vs 4% (p=0.05)

Evidence Table 11. Placebo-controlled trials in youths

Author, year Country Trial name (Quality score)	N	Duration	Study design setting	Population	Eligibility criteria
Shea, 2004 Canada (FAIR)	80	8 weeks	Double-blind, multicenter	Pervasive developmental disorders	Physically healthy male and female outpatients ages 5 to 12 years with a DSM-IV Axis I diagnosis of pervasive developmental disorder and a total score of 30 or more on the Childhood Autism Rating Scale (CARS), with or without mental retardation.
Snyder et al, 2002 Risperidone Conduct Study Group Canada (FAIR)	110	6 weeks	Double-blind, multicenter	Disruptive Behavior Disorders	DSM-IV diagnosis of conduct disorder, oppositional defiant disorder, or disruptive behavior disorder, not otherwise specified; rating (parent/caregiver) of 24 or higher on the Conduct Problem subscale of the Nisonger Child Behavior Rating Form (NCBRF); IQ between 36 and 84; Vineland Adaptive Behavior Scale score of 84 or less; healthy on the basis of a pretrial physical examination, medical history, and ECG; and consent by parent/caregiver.

Evidence Table 11. Placebo-controlled trials in youths

Author, year Country Trial name (Quality score)	Exclusions	Interventions	Allowed other medications/interventions
Shea, 2004 Canada (FAIR)	Schizophrenia, other psychotic disorders, clinically relevant nonneurologic disease, clinically significant laboratory abnormalities, or a seizure disorder for which they were receiving >1 anticonvulsant or if they had had a seizure in the last 3 months. History of hypersensitivity to neuroleptics, tardive dyskinesia, neuroleptic malignant syndrome, drug or alcohol abuse, or HIV infection. Also excluded subjects who had used risperidone in the last 3 months, had been previously unresponsive or intolerant to risperidone, or were using a prohibited medication.	Risperidone oral solution 0.01 mg/kg/day on treatment days 1 and 2 and increased to 0.02 mg/kg/day on day 3. Depending on therapeutic response at day 8, the dose could be increased by a maximal increment of 0.02 mg/kg/day. Thereafter, the dose could be adjusted at the investigator's discretion at weekly intervals by increments/decrements not to exceed 0.02 mg/kg/day. The maximal allowable dose was 0.06 mg/kg/day. In case of drowsiness, the study medication could be administered once daily in the evening, or the total daily dose could be divided and administered on a morning and evening schedule.	Medications that are used to treat EPSs were to be discontinued at the time of entry into the trial. However, during the trial, anticholinergics could be initiated to treat emergent EPSs after the ESRS had been completed. Prohibited medications included antipsychotics other than the study medication, antidepressants, lithium, alpha-2 antagonists, clonidine, guanfacine, cholinesterase inhibitors, psychostimulants, and naltrexone. A single anticonvulsant and/or medications for sleep or anxiety were permitted only in the case in which the subject was already taking them at a stable dose for the 30 days before enrollment. Similar restrictions were placed on the use of behavior intervention therapy. Medications for preexisting organic disorders were allowed provided that the dose and schedule of administration were kept as constant as possible.
Snyder et al, 2002 Risperidone Conduct Study Group Canada (FAIR)	Diagnosis of pervasive developmental disorder, schizophrenia, or other psychotic disorder; head injury as a cause of impaired IQ; seizure condition requiring medication; females who were sexually active without a reliable form of birth control; serious or progressive illness or clinically abnormal laboratory values; history of tardive dyskinesia, neuroleptic malignant syndrome, or hypersensitivity to any antipsychotic drug; known presence of HIV; and previous treatment with risperidone.	Risperidone oral solution beginning at 0.01 mg/kg for the first 2 days and at 0.02 mg/kg for the next 5 days. Physician could increase the dosage weekly by 0.02 mg/kg per day to a maximum of 0.06 mg/kg per day, or decrease the dose by any amount for the remainder of the trial. 6 weeks	Patients taking previously prescribed stable dosages of concomitant medication (e.g., medication for preexisting medical conditions, psychostimulants for comorbid ADHD, and sleep medication [antihistamines, chloral hydrate, and melatonin]) for 30 days prior to trial entry were included provided the medication was expected to remain stable for the duration of the trial. No other medication was allowed with the exception of anticholinergic medication to treat EPS shout it occur during the trial.

Evidence Table 11. Placebo-controlled trials in youths

Author, year Country Trial name (Quality score)	Age Gender Ethnicity	Other population characteristics	Number screened/ eligible/enrolled	Number withdrawn/ lost to follow-up/ analyzed
Shea, 2004 Canada (FAIR)	Mean age (range): 7.6 years (5-12) risperidone 7.3 years (5-12 placebo) 72.5% risperidone, 82.1% placebo males 15% risperidone, 15.4% placebo black; 67.5% risperidone, 71.8% placebo white; 17.5% risperidone, 12.8% placebo other race.	DSM-IV Axis I diagnosis, risperidone vs placebo: Autistic disorder: 67.5% vs 71.8% Asperger's disorder: 12.5% vs 17.9% Childhood disintegrative disorder: 2.5% vs 0% PDD not otherwise specified: 17.5% vs 10.3% 78% of risperidone and 90% of placebo patients had an IQ test performed. Of these (risperidone vs placebo): Normal, score > 85: 9.7% vs 31.4% Borderline, score 71-84: 19.4% vs 11.4% Mild, score 50-70: 38.7% vs 22.9% Moderate, score 35-49: 32.3% vs 34.3%	NR NR 80	3 withdrawn/0 lost to followup/77 analyzed
Snyder et al, 2002 Risperidone Conduct Study Group Canada (FAIR)	Mean age 8.7 (SD 0.27) years 75% male 75% white, 7% black, 16% other ethnicity	DSM-IV diagnoses: 9% conduct disorder 31% conduct disorder plus ADHD 15% oppositional defiant disorder, destructive behavior disorder 53% oppositional defiant disorder, destructive behavior disorder plus ADHD 26% combined/no ADHD 76% combined plus ADHD 48% borderline IQ (70-85) 38% mild mental retardation (IQ 50-69) 14% moderate mental retardation (IQ 35-49)	Number screened not reported/133 eligible/110 enrolled (23 placebo responders not randomized)	24 withdrawn/1 lost to followup/110 analyzed

Evidence Table 11. Placebo-controlled trials in youths

Author, year Country Trial name (Quality score)	Results	Overall withdrawals/ Withdrawals due to adverse events	Adverse events
Shea, 2004 Canada (FAIR)	Change from baseline to endpoint, risperidone vs placebo: ABC (Irritability): -12.1 vs -6.5 (p<0.001) ABC (Hyperactivity/noncompliance): -14.9 vs 7.4 (p<0.001) ABC (Inappropriate speech): -2.6 vs -1.6 (p<0.05) ABC (Lethargy/social withdrawal): -8.6 vs -5.7 (p<0.01) ABC (Stereotypic behavior): -4.3 vs -2.4 (p<0.05) N-CBRF (Conduct problem): -10.4 vs -6.6 (p<0.001) N-CBRF (Hyperactive): -8.1 vs -5.6 (p<0.05) N-CBRF (Self-isolated/ritualistic): -4.8 vs -3.6 (NS) N-CBRF (Insecure/anxious): -4.6 vs -3.5 (p<0.05) N-CBRF (Overly sensitive): -3.8 vs -2.7 (p<0.05) N-CBRF (Self-injurious/stereotypic): -2.6 vs -1.3 (NS) VAS (most troublesome symptom): -38.4 vs -26.2 (p<0.05) Improvement as assessed by the CGI-C: 87.2% vs 39.5%	8.9% (2 risperidone, 5 placebo)/ 1 risperidone, 1 placebo.	Mean weight gain at 8 weeks: risperidone: 2.7 kg (SD 2.0) placebo 1.0 kg (SD 1.6) (p<0.001 vs placebo Most common adverse events among risperidone-treated subjects were somnolence (72.5%), upper respiratory tract infection (37.5%), rhinitis (27.5%), and increased appetite (22.5%). 5 (12.5%) risperidone-treated subjects experienced adverse events categorized as severe and related to study medication (1 hyperkinesia and somnolence and 1 case each of weight gain, somnolence, aggressive reaction with impaired concentration, and extrapyramidal disorder as a result of an accidental overdose). Five cases of mild to moderate tachycardia in the risperidone group were reported as adverse events. Changes from baseline in EKG recordings were deemed to be clinically important for one subject in risperidone group; changes included tachycardia and a possible mild conduction anomaly.
Snyder et al, 2002 Risperidone Conduct Study Group Canada (FAIR)	Change in Nisonger Child Behavior Rating Form conduct problem subscale score at 6 weeks (risperidone vs placebo): -15.8 vs -6.8 (p<0.001)	24 overall	Most common side effects included somnolence, headache, appetite increase, and dyspepsia. Side effects related to extrapyramidal symptoms were reported in 7 (13.2%) and 3 (5.3%) of the subjects in the risperidone and placebo groups, respectively (p = .245)

Evidence Table 11. Placebo-controlled trials in youths

Author, year Country Trial name (Quality score)	N	Duration	Study design setting	Population	Eligibility criteria
Troost, 2005 The Netherlands	24	8 weeks (placebo-controlled discontinuation phase)	Double-blind, single center	Pervasive developmental disorders	DSM-IV criteria for a pervasive developmental disorder. Patients were required to demonstrate clinically significant tantrums, aggression, self-injurious behavior, or a combination of these problems. Age 5 to 17 years, a weight of at least 15 kg, and a mental age of at least 18 months. Only short-term responders to risperidone as judged within the first 8 weeks of treatment cold complete the protocol. Short-term response was defined as at least a 25% ABC Irritability score reduction and a rating of "much improved" or "very much improved" on the CGI-S.

Evidence Table 11. Placebo-controlled trials in youths

Author, year Country Trial name (Quality score)	Exclusions	Interventions	Allowed other medications/interventions
Troost, 2005 The Netherlands	On effective psychotropic drug treatment for disruptive behavior	Children on effective psychotropic drug treatment for disruptive behavior were excluded.	Anticonvulsants used for the treatment of a seizure disorder were permitted if the dose had been stable for at least 4 weeks and the patient was seizure free for at least 6 months.

Evidence Table 11. Placebo-controlled trials in youths

Author, year Country Trial name (Quality score)	Age Gender Ethnicity	Other population characteristics	Number screened/ eligible/enrolled	Number withdrawn/ lost to follow-up/ analyzed
Troost, 2005 The Netherlands	Mean age 9.1 years 91.7% male 91.7% white, 0% black, 8.3% other race	25% Autistic disorder, 8.3% Asperger's disorder, 66.7% pervasive developmental disorder, NOS	36 entered 8-week open label phase/26 classified as responders after 24-week open-label treatment/24 enrolled in 8-week discontinuation phase	2 withdrew before randomization in discontinuation phase 24 analyzed

Evidence Table 11. Placebo-controlled trials in youths

Author, year Country Trial name (Quality score)	Results	Overall withdrawals/ Withdrawals due to adverse events	Adverse events
Troost, 2005 The Netherlands	3/12 (25%) risperidone vs 8/12 (67%) placebo relapsed (p=0.049) Increase in ABC Irritability scores at study endpoint: 14% risperidone vs 60% placebo (p=0.043). No differences between groups in other ABC subscales.	2 for unacceptable weight gain	Increased appetite and weight gain (5.7 ± 2.8 kg in 24 weeks, range 1.2–11.7 kg; p < .0001). No changes on Simpson-Angus scale or AIMS. Neurological side effects included tremor (once), muscle rigidity (twice), and restlessness (twice).

Evidence Table 12. Randomized controlled trials in patients with bipolar I disorder

Author, Year Country Trial name	Study design Setting	Eligibility criteria	Therapy type Interventions Duration	Allowed other medications/ interventions
AstraZeneca, 2011 D144AC00001	DB RCT Multi-center	10-17 years, bipolar I or bipolar II with most recent episode depressed, CDRS-R score ≥45 and YMRS score ≥16	Quetiapine XR 150-300 mg/d vs. Placebo 8 Weeks	NR
Biederman 2005 USA	Open-label, randomized if they had not received treatments previously, however if they had then they were put on the other. Single center	Male or female subjects, aged 4–6 ys, DSM-IV bipolar I disorder, DSM-IV bipolar II disorder, or bipolar disorder not otherwise specified (NOS) and were currently displaying manic, hypomanic, or mixed symptoms (with or without psychotic features)	Risperidone mean 1.4+ 0.5 mg/d, Olanzapine mean 6.3+2.3 mg/d.	Stimulants if on stable dose for at least 30 ds (none were on this), benztropine mesylate for EPS and lorazepam
Delbello 2002 USA	DB RCT Single center	12–18 ys old, met DSM-IV criteria for bipolar I disorder currently mixed or manic, and had a Young Mania Rating Scale (YMRS) score of ≥20.	Adjunctive to divalproex (DVP) quetiapine, 450 mg/d or P 6 weeks	2 mg of lorazepam per d

Evidence Table 12. Randomized controlled trials in patients with bipolar I disorder

Author, Year Country Trial name	Age Gender Ethnicity	Other population characteristics	Number screened/ eligible/ enrolled	Number withdrawn/ lost to follow-up/ analyzed	Results
AstraZeneca, 2011 D144AC00001	Mean age: 14.0 ys Gender: 49.5% female Ethnicity: 65.1% White	NR	NR/262/193	49/6/NR	Least squares mean reduction in CDRS-R score, quetiapine vs. placebo: -29.6 vs. -27.3, difference = -2.29 (95%CI, -6.22 to 1.65), p=0.252 NSD remission or response rates, reducing depression severity on CGI-BP-S or CGI-BP-C, improvement in overall bipolar illness on CGI-BP-C
Biederman 2005 USA	Mean age 5 ys 71% male 97% Caucasian	27 met criteria for bipolar I disorder and 4 met criteria for bipolar disorder NOS Mania 100% Major depression 73% Conduct disorder 42% ADHD 94%	NR/NR/31	7 (6 olanzapine, 1 risperidone)/2 LTF/31	Risperidone vs. olanzapine YMRS 30% reduction 69% vs. 53% P = 0.4 YMRS 50% reduction 53% vs. 33% P = 0.3 Risperidone baseline/endpoint vs. olanzapine baseline/endpoint **YMRS** 35.2(8.2)/16.4(12.0) vs. 34.2(6.4)/22.1(8.3) P = 0.2 Increased motor activity 3.5(.5)/1.8(1.5) vs. 3.3(.5)/ 2.7(1.2) P = 0 .04 Pressured speech 5.1(1.4)/2.7(2.0) vs. 4.5(1.9)/3.7(2.1) P = 0.04 **BPRS** 46.4(12.4)/33.3(10.6) vs. 46.7(13.5)/37.8(11.9) P = 0.4 **CDRS** 39.7 10.5 27.0 6.3a 42.4 14.8 34.1 11.5 F(1,30) .8, p .4
Delbello 2002 USA	Mean age 14.3 ys % male 53 % Caucasian 83	% mixed 77 % psychosis 47 % ADHD 60	50/30/30	7 (DVP+quetiapine 6, DVP+P 1) WD, 0 LTF (though one moved away), 30 analyzed	DVP + quetiapine group vs. DVP + P YMRS response rate 87% vs. 53% P = 0.05 Other results reported graphically and there were no between group differences

Evidence Table 12. Randomized controlled trials in patients with bipolar I disorder

Author, Year Country Trial name	Adverse effects reported	Total withdrawal; withdrawal due to adverse events	Comments
AstraZeneca, 2011 D144AC00001	Quetiapine XR vs. Placebo: Overall AEs: 73.9% vs. 66.0% SAE: 1 vs. 4 Discontinuation due to AE: 3.3% vs. 12.0% EPS-related AE: 1.1% vs. 0 Suicide: 0 Suicidality: 1.1% vs. 0 Diabetes: 3.3% vs. 0 Weight change >7%: 15.2% vs. 10.0%	49/15 Quetiapine: 3 vs. Placebo: 12	
Biederman 2005 USA	Results shown in graph, authors state, "...the rate of spontaneously reported side effects did not differ between risperidone- and olanzapine treated subjects. In both groups, the most commonly reported side effects were increased appetite, common cold symptoms, headaches, and sedation."	7 WD (olanzapine 6 vs.. Risperidone 1 P = 0.03) 1 due to Aes	
Delbello 2002 USA	DVP + quetiapine group vs. DVP + P Change in EPS ratings, mean (SD) AIMS 0 (0) vs. 0 (0) Barnes Akathisia Scale –0.1 (0.3) vs. 0.1 (0.3) Simpson-Angus Scale 0 (0.8) vs. –0.1 (1.1) Sedation 12 (80) vs. 5 (33) P = 0.03 Nausea/vomiting 4 (27) vs. 6 (40) Dizziness 5 (33) vs. 3 (20) Headache7 (47) vs. 7 (47) GI irritation 7 (47) vs. 5 (33) Joint pain 2 (13) vs. 2 (13) Dry mouth 5 (33) vs. 2 (13	7 WD , none due to AEs	

Evidence Table 12. Randomized controlled trials in patients with bipolar I disorder

Author, Year Country Trial name	Study design Setting	Eligibility criteria	Therapy type Interventions Duration	Allowed other medications/ interventions
DelBello, 2009 USA	DB RCT two-site study	Adolescents (ages 12-18 ys) with a depressive episode associated with bipolar I disorder according to DSM-IV, text revised and determined by the Washington University at St. Louis Kiddie Schedule for Affective Disorders and Schizophrenia interview; screening and baseline Children's Depression Rating Scale-Revised Version score ≥ 40, a standard score that is considered consistent with clinically significant depression	Quetiapine vs P 8 weeks 100 mg quetiapine IR (or P) on d 1, 300 mg/d on d 3, with flexible titration to 600 mg/d in the evening	The use of lorazepam (a maximum of 4 mg/d for ds 0-7 and 2 mg/d for ds 8-14) was permitted during the study for agitation or anxiety.

Evidence Table 12. Randomized controlled trials in patients with bipolar I disorder

Author, Year Country Trial name	Age Gender Ethnicity	Other population characteristics	Number screened/ eligible/ enrolled	Number withdrawn/ lost to follow-up/ analyzed	Results
DelBello, 2009 USA	Quetiapine vs P	Quetiapine vs P	49/32/32	12/1 lost to FU/32	Quetiapine vs P
	Mean age (SD): 16 (2) vs 15 (2) ys Females: 71% vs 67% White: 82% vs 80%	Length of current episode (SD): 7 (2) vs 5 (4) weeks Age at onset of bipolar disorder (SD): 12 (2) vs 11 (3) ys Psychosis: 12% vs 7% ADHD: 12% vs 13% Anxiety disorders: 29% vs 20% Disruptive behavior disorders: 35% vs 13%			Mean change in Children's Depression Rating Scale-Revised Version score (SD): -19 (14) vs -20 (17); P=0.89 Change in Hamilton Anxiety Rating Scale: -4 vs -5; P=0.74 Change in YMRS: -5 vs -4; P=0.76 Change in Clinical Global Impression Bipolar Disorder Version Severity scores for overall illness: -1.8 vs -1.6; P=0.9

Evidence Table 12. Randomized controlled trials in patients with bipolar I disorder

Author, Year Country Trial name	Adverse effects reported	Total withdrawal; withdrawal due to adverse events	Comments
DelBello, 2009 USA	Quetiapine (n=17) vs P (n=15) GI upset: 11 (65%) vs 5 (33%) Sedation: 10 (59%) vs 5 (33%) Dizziness: 7 (41%) vs 1 (7%) Cold symptoms: 4 (24%) vs 3 (20%) Tooth pain: 3 (18%) vs 0 Headaches: 3 (18%) vs 5 (33%) Shortness of breath: 3 (18%) vs 0 Fast heart rate: 3 (18%) vs 0 Dry mouth: 2 (12%) vs 0 Increased appetite: 2 (12%) vs 0 Difficulty swallowing: 2 (12%) vs 0 Chest pain or pressure: 2 (12%) vs 0 Back and/or neck pain: 2 (12%) vs 5 (33%) EPS: NS between groups Mean change in prolactin levels (SD): 2.47 (8.53) vs 0.05 (4.27) ng/ml; P=0.3 Mean change in supine blood pressure (SD): 6 (9) vs -6 (9) mm Hg; P=0.001 Mean change in pulse (SD): 11 (13) vs -3 (11) beats/min; P=0.003	Total WD: 12 WD due to AE: 2	The mean (SD) quetiapine dose at endpoint was 403 (133) mg/d. For P, the mean dose at endpoint was 413 (141) mg/d.

Evidence Table 12. Randomized controlled trials in patients with bipolar I disorder

Author, Year Country Trial name	Study design Setting	Eligibility criteria	Therapy type Interventions Duration	Allowed other medications/ interventions
Findling, 2009 USA	DB RCT multicenter (59 sites)	Aged 19 to 17 ys with a confirmed DSM-IV diagnosis of bipolar I disorder with current maniac or mixed episodes, with or without psychotic features, and a YMRS total score ≥20 at baseline. Subjects with comorbid ADHD, conduct disorder, oppositional defiant disorder, or anxiety disorders (except posttraumatic stress disorder or obsessive-compulsive disorder) were eligible.	Aripiprazole 10mg/d vs Aripiprazole 30 mg/d vs P 4 weeks	Benzodiazepine and anticholinergic therapy was permitted as rescue medication and for extrapyramidal symptom relief, although not within 4 or 12 hs of efficacy or safety assessments, respectively.
Findling, 2012 USA	DB RCT Single center	4-9 ys old, who met DSM-IV for bipolar I and bipolar II disorders.	Aripiprazole = 15 mg, max dose vs.. P 72 weeks	• Adjunctive psychostimulants • Open-label methylphenidate & amphetamine Other psychotropic medications were not permitted in the study.

Evidence Table 12. Randomized controlled trials in patients with bipolar I disorder

Author, Year Country Trial name	Age Gender Ethnicity	Other population characteristics	Number screened/ eligible/ enrolled	Number withdrawn/ lost to follow-up/ analyzed	Results
Findling, 2009 USA	Mean age (SD): 13.4 (2.2) ys Male: 53.7% White: 65.2%	Mean age at onset (SD): 12.1 (3.0) ys Mean duration of bipolar disease (SD): 1.3 (2.2) ys Mean YMRS total score (SD): 30.0 (6.5) Treatment with antipsychotics within past mo: 12.2% Family history of bipolar I disorder: 44.3%	413/NR/296	59/11/289	Aripiprazole 10 mg vs Aripiprazole 30 mg vs P Mean changes in YMRS total score from baseline: -14.2 vs -16.5 vs -8.2; P<0.001 for aripiprazole vs P Mean changes in CGAS score: 15.1 vs 17.3 vs 5.8; P<0.001 for aripiprazole vs P Mean changes in Clinical Global Impressions Scale-Bipolar Version severity score-mania: -1.6 vs -2.1 vs -0.8; P<0.001 for aripiprazole vs P Mean changes in Clinical Global Impressions Scale-Bipolar Version-depression: -0.9 vs -0.9 vs -0.6; P=NS Mean changes in Clinical Global Impressions Scale-Bipolar Version-overall bipolar illness: -1.6 vs -2.0 vs -0.8; P<0.001 for aripiprazole vs P Mean changes in Children's' Depression Rating Scale-Revised score: -7.2 vs -6.1 vs -4.9; P=NS Mean changes in General Behavior Inventory total scores-parent/guardian (mania): -9.9 vs -9.5 vs -4.0; P<0.001 for aripiprazole vs P Mean changes in General Behavior Inventory total scores-parent/guardian (depression): -5.9 vs -4.1 vs -3.8; P=0.04 for 10 mg vs P; P=NS for 30 mg vs P Mean changes in General Behavior Inventory total scores-patient (mania): -6.4 vs -6.6 vs -4.6; P<0.05 for aripiprazole vs P Mean changes in General Behavior Inventory total scores-patient (depression): -3.4 vs -3.3 vs -3.4; P=NS Mean changes in ADHD-Rating Scale-Version IV total scores: -12.5 vs -11.9 vs -3.7; P<0.001 for aripiprazole vs P
Findling, 2012 USA	Mean age: 7 ys Male: 70% Female: 30% Ethnicity: NR	Bipolar disorder NOS: 55% Bipolar I disorder: 35%			

Evidence Table 12. Randomized controlled trials in patients with bipolar I disorder

Author, Year Country Trial name	Adverse effects reported	Total withdrawal; withdrawal due to adverse events	Comments
Findling, 2009 USA	Aripiprazole 10mg vs Aripiprazole 30 mg vs P Serious AEs: 5.1% vs 2% vs 5.2% Any AEs: 73.5% vs 27.3% vs 3.1% Any extrapyramidal symptom event: 23.5% vs 39.4% vs 7.2% Change in Simpson-Angus Scale scores: 0.6 vs 1.2 vs -0.1; P=0.03 for 10 mg vs P; P<0.001 for 30 mg vs P Change from baseline on the physician-rated BARS and AIMS did not differ from P at week 4. No deaths or suicides during the study. No clinically meaningful changes from baseline in fasting serum glucose, total cholesterol, triglycerides, HDL-cholesterol, heart rate, blood pressure, ECG parameters.	Total WD: 59 WD due to AE: 12	AEs resulting in study discontinuation in the 10 mg group were fatigue (n=2), sedation (n=2), akathisia (n=1), aggression (n=1), and suicidal ideation (n=1). In the 30 mg group, extrapyramidal disorder (n=3), exacerbation of bipolar disorder (n=2), vomiting (n=1), dystonia (n=1), and somnolence (n=1) led to study WDal (1 subject discontinued because of aggression and fatigue). Anxiety (n=1) and exacerbation of bipolar disorder (n=1) were AEs leading to discontinuation in the P group.
Findling, 2012 USA			

Evidence Table 12. Randomized controlled trials in patients with bipolar I disorder

Author, Year Country Trial name	Study design Setting	Eligibility criteria	Therapy type Interventions Duration	Allowed other medications/ interventions
Findling 2013 USA (26-week double-blind extension phase of Findling 2009)	DB RCT multicenter	Aged 19 to 17 ys with a confirmed DSM-IV diagnosis of bipolar I disorder with current maniac or mixed episodes, with or without psychotic features, and a YMRS total score ≥20 at baseline. Subjects with comorbid ADHD, conduct disorder, oppositional defiant disorder, or anxiety disorders (except posttraumatic stress disorder or obsessive-compulsive disorder) were eligible.	Aripiprazole 10mg/d vs Aripiprazole 30 mg/d vs P 4 weeks	Benzodiazepine and anticholinergic therapy was permitted as rescue medication and for extrapyramidal symptom relief, although not within 4 or 12 hs of efficacy or safety assessments, respectively.

Evidence Table 12. Randomized controlled trials in patients with bipolar I disorder

Author, Year Country Trial name	Age Gender Ethnicity	Other population characteristics	Number screened/ eligible/ enrolled	Number withdrawn/ lost to follow-up/ analyzed	Results
Findling 2013 USA (26-week double-blind extension phase of Findling 2009)	Mean age: 13.2 years Male: NR White: 66%	Mean YMRS total score: 30.0 CDRS-R suicidal ideation score: 1.1 Previous treatment for bipolar disorder	296/296/210	228/10/296	Aripiprazole 10mg vs Aripiprazole 30 mg vs Placebo Median weeks to discontinuation: 15.6 vs 9.5 vs 5.3 Response, % patients with ≥ 50% reduction from baseline YMRS total score: 58.7% vs 64.8% vs 29.7% Pediatric Quality of Life Enjoyment and Satisfaction Questionnaire overall global assessment (PQ-LES-Q): No statistically significant differences (data NR)

Evidence Table 12. Randomized controlled trials in patients with bipolar I disorder

Author, Year Country Trial name	Adverse effects reported	Total withdrawal; withdrawal due to adverse events	Comments
Findling 2013 USA (26-week double-blind extension phase of Findling 2009)	Aripiprazole 10mg vs Aripiprazole 30 mg vs Placebo Serious AE's: 1.3% vs 7.0% vs 3.1% Suicide attempts: None Deaths: None Mean weight gain, kg: 6.5 vs 6.6 vs 3.0, both $P<0.05$ Transition from non-obese to obese based on weight: 2.9% vs 9.1% vs 0% Transition from non-obese to obese based on BMI: 8.8% vs 13.6% vs 0% Extrapyramidal disorder, % patients: 13.3% vs 25.4% vs 3.1%	Total WD: 228=77% WD due to AE: 14=5%	

Evidence Table 12. Randomized controlled trials in patients with bipolar I disorder

Author, Year Country Trial name	Study design Setting	Eligibility criteria	Therapy type Interventions Duration	Allowed other medications/ interventions
Haas, 2009 USA	DB RCT Multicenter (21)	Children and adolescents (10–17 ys, inclusive) without known intellectual impairment were eligible for enrollment as inpatients or outpatients if they met criteria from the DSM-IV for bipolar I disorder, current episode manic or mixed, and were medically stable as determined by the investigator; scored ‡ 20 on the scale at screening and baseline	Dose-titration risperidone 0.5–2.5 mg/d, risperidone 3–6 mg/d, or P 3 weeks	Medications for treatment-emergent movement disorders [extrapyramidal symptoms (EPS)] were allowed. Use of sedatives/hypnotics such as lorazepam and diphenhydramine was allowed, but strictly for the control of agitation, irritability, restlessness, insomnia, and hostility during washout and the double-blind treatment phase (week 1 only).

Evidence Table 12. Randomized controlled trials in patients with bipolar I disorder

Author, Year Country Trial name	Age Gender Ethnicity	Other population characteristics	Number screened/ eligible/ enrolled	Number withdrawn/ lost to follow-up/ analyzed	Results
Haas, 2009 USA	Median age (range): 13 (10-17) ys 49% male 77% White 17% Black or African American 4% Mixed 2% American Indian／ Native Alaskan 1% Asian	36% bipolar I disorder, manic episode (DSM-IV) 64% bipolar 1 disorder, mixed episode (DSM-IV) 50% ADHD 58% with euphoria/elation (YMRS) 70% with irritability (YMRS)	237/170/170	32/3/166	risperidone 0.5-2.5 mg/d vs risperidone 3-6 mg/d vs P Mean change in YMRS total score (SD): -18.5 (9.7) vs -16.5 (10.3) vs -9.1 (11.0); P<0.001 for both risperidone doses vs P Clinical response rate at endpoint: 59% vs 63% vs 26%; P=0.002 for risperidone 0.5-2.5 mg/d vs P; P<0.001 for risperidone 3-6 mg/d vs P Remission rates, defined as YMRS score ≤12: 43% vs 43% vs 16%

Evidence Table 12. Randomized controlled trials in patients with bipolar I disorder

Author, Year Country Trial name	Adverse effects reported	Total withdrawal; withdrawal due to adverse events	Comments
Haas, 2009 USA	risperidone 0.5-2.5 mg/d vs risperidone 3-6 mg/d vs P Mean change in AIMS: -0.02 (0.43) vs -0.08 (0.59) vs 0.11 (1.39) Mean change in SAR-S: 0.3 (0.11) vs 0.10 (0.32) vs -0.04 (0.16) n(%) Total prolactin-related AEs: 2 (4) vs 3 (5) vs 1 (2) Total AEs: 45 (90) vs 58 (95) vs 44 (76) Somnolence: 21 (42) vs 34 (56) vs 11 (19) Headache: 20 (40) vs 23 (38) vs 19 (33) Fatigue: 9 (18) vs 18 (30) vs 2 (3) Abdominal pain: 9 (18) vs 9 (15) vs 3 (5) Dizziness: 8 (16) vs 8 (13) vs 3 (5) Rhinitis: 7 (14) vs 8 (13) vs 6 (10) Nausea: 8 (16) vs 8 (13) vs 4 (7) Vomiting: 6 (12) vs 6 (10) vs 4 (7) Dyspepsia: 8 (16) 3 (5) vs 2 (3) Agitation: 2 (4) vs 7 (11) vs 6 (10) Pharyngitis: 5 (10) vs 2 (3) vs 3 (5) Total serious AEs: 3 (6) vs 5 (8) vs 3 (5) Psychosis manic-depressive: 1 (2) vs 4 (7) vs 2 (3) Suicide attempt: 2 (4) vs 2 (3) vs 1 (2) Manic reaction: 0 vs 0 vs 1 (2) Allergic reaction 0 vs 1 (2) vs 0 Asthma: 1 (2) vs 0 vs 0 Bronchospasm: 1 (2) vs 0 vs 0	Total WD: 32 WD due to AEs: 17	

Evidence Table 12. Randomized controlled trials in patients with bipolar I disorder

Author, Year Country Trial name	Study design Setting	Eligibility criteria	Therapy type Interventions Duration	Allowed other medications/ interventions
Pathak, 2013 U.S.	Randomized, DB, PCT, multicenter, inpatient and outpatient	10-17 years, DSM-IV criteria for bipolar I with manic episodes, YMRS total score ≥20, permitted to have secondary diagnosis of ADHD	Quetiapine 400 mg/d, in 2 or 3 doses, titrated over 5 days Quetiapine 600 mg/d, in 2 or 3 doses, titrated over 7 days Placebo Duration=3 weeks	Psychostimulant at stable dose for ADHD, Diphenhydramine, hydroxyzine, lorazepam, benztropine for treatment-emergent EPS (not prophylactic)
Tohen 2007 USA and Puerto Rico	DB RCT Multicenter (24)	13-17 ys old, inpatient or outpatient, with manic or mixed bipolar episodes (with or without psychotic features)	Switch olanzapine (2.5–20.0 mg/d, mean 8.9 mg/d) or P. 3 weeks	No
Tramontina 2009 Brazil	DB RCT Single center	Children and adolescents were extensively assessed according to DSM-IV criteria for bipolar disorder comorbid with ADHD in acutely manic or in mixed states	Stand alone treatment Aripiprazole vs.. P 6 weeks	No

Evidence Table 12. Randomized controlled trials in patients with bipolar I disorder

Author, Year Country Trial name	Age Gender Ethnicity	Other population characteristics	Number screened/ eligible/ enrolled	Number withdrawn/ lost to follow-up/ analyzed	Results
Pathak, 2013 U.S.	Age: 43.7% 10-12 years, 56.3% 13-17 years Gender: 43.7% female Ethnicity: 76.5% White, 13.7% Black	Current or past history of ADHD: 44.8%	393/289/284	61/3/277 ITT; 283 safety	Quetiapine 400 mg/d vs. Quetiapine 600 mg/d vs. Placebo YMRS, Least squares mean change at day 21 (95%CI): -14.25 (-16.15 to -12.35) vs. -15.60 (-17.51 to -13.70) vs. -9.04 (-11.24 to -6.84), p<0.001 treatment vs. placebo CDRS-R mean (SD) changes at day 21: -5.2 (8.47) vs. -6.2 (7.56) vs. -3.8 (8.02), 600mg/d vs. placebo: p<0.05 CGI-BP Severity, least squares mean change at day 21(95%CI): -1.55 (-1.83 to -1.27) vs. -1.62 (-1.88 to -1.37) vs. -0.98 (-1.26 to -0.71), P=0.005 for 400mg vs. placebo, P<0.001 for 600mg vs. placebo
Tohen 2007 USA and Puerto Rico	Mean age 15.3 53% male 70% Caucasian	89% mixed 18% psychotic 36% ADHD 31% Oppositional defiant disorder	214/177/161	41/0/161	Olanzapine vs.. P Mean change in - YMRS –17.65 vs –9.99, P < 0 .001 Clinical Global Impressions— Bipolar Version overall –1.63 vs –0.99, P < 0.001 Clinical Global Impressions—Bipolar Version severity of mania –1.73 vs –1.05, P < 0.001 Response: 48.6% vs 22.2%, P = 0.002 Remission: 35.2% vs 11.1%, P = 0.001
Tramontina 2009 Brazil	Mean age 12 ys 47% male 91% white	BP I 81% BP II 19% 37% psychosis	710/NR/43	2 WDn/ 0 LTF/ 43 analyzed	Aripiprazole vs.. P Change in YMRS 27.22 vs. 19.52 P = 0.02 Response 88.9% vs. 52% Remission 72% vs. 32% P = 0.01 Change in SNAP-IV 0.79 vs. 0.55 P = 0.39

Evidence Table 12. Randomized controlled trials in patients with bipolar I disorder

Author, Year Country Trial name	Adverse effects reported	Total withdrawal; withdrawal due to adverse events	Comments
Pathak, 2013 U.S.	Quetiapine 400mg/d vs. Quetiapine 600mg/d vs. Placebo Weight gain >7%: 14.5% vs. 9.9% vs. 0% EPS: 4.2% vs. 3.1% vs. 1.1% Suicidal ideation, n: 1 vs. 0 vs. 0 SAE: 7 vs. 4 vs. 3	61/26	
Tohen 2007 USA and Puerto Rico	Incidence of treatment-emergent AEs frequency ≥5% significantly higher in the olanzapine group for appetite increase, weight increase, and somnolence and sedation items. Abnormal Involuntary Movement Scale (olanzapine, –0.10 [SD=0.71] vs P, 0.00 [SD=0.19], p=0.289), Simpson-Angus (olanzapine, 0.02 [SD=0.93] vs P,–0.02 [SD=0.14], p=0.769), Barnes scales (olanzapine, –0.04 [SD=0.44] vs P, 0.06 [SD=0.60], p=0.264)	41 WD 4 due to AEs	
Tramontina 2009 Brazil	Aripiprazole vs. P Incidence of AEs shown in graph	2 WD 1 due to AEs	

Evidence Table 13. Quality assessment of randomized controlled trials in pediatrics with bipolar disorder

Author, Year Country	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors masked?	Care provider masked?	Patient masked?
AstraZeneca, 2011 D144AC00001	Unclear, states randomized but no description of method	Unclear, no description of method	Unclear, reported that there were no differences in demographics but data NR	Yes	NR (described as double-blind)	NR (described as double-blind)	NR (described as double-blind)
Biederman 2005	NR	NA	Yes	Yes	Open-label	Open-label	Open-label
DelBello 2002	Unclear, used random number generator	Unclear	Yes	Yes	Yes	Yes	Yes
Delbello 2009	Unclear, used random number generator	NR	Yes	Yes	Yes	Yes	Yes
Findling 2009	NR	NR	Unclear Missing data on some clinical chartactoristics. Reported data shows differences in age, % non-Hispanic/Latino, % without psychotic features,% without ADHD	Yes	NR (described as double-blind)	NR (described as double-blind)	Yes
Findling 2012	Unclear	Unclear	Yes	Yes	Unclear, described as double-blind	Yes	Yes

Evidence Table 13. Quality assessment of randomized controlled trials in pediatrics with bipolar disorder

Author, Year Country	Reporting of attrition, crossovers, adherence, and contamination	Loss to follow-up: differential/high	Maintenance of comparable groups	Intent-to-treat analysis	Funding	Quality rating
AstraZeneca, 2011 D144AC00001	Yes, No, No, No	Differential: No High: Yes	Unclear	Unclear, states modified ITT but numbers NR	AstraZeneca	Fair
Biederman 2005	Yes, No, No, No	Differential: Yes High: No	Unclear	Yes	Center grant from the Stanley Medical Research Institute	Fair
DelBello 2002	Yes, No, No, No	Differential: Yes High: No	Unclear	Yes	AstraZeneca	Fair
Delbello 2009	Yes, No, No, No	No/No	Yes	Yes	AstraZeneca Pharmaceuticals	Fair
Findling 2009	Yes, No, Yes, No	No/No	Yes	No	Otsuka Pharmaceutical Co., Ltd.	Fair
Findling 2012	Yes, no, no, no	Overall: Yes 90% Differential: Yes 20%	unclear	Yes	Clinical Research Center Grant, Grant from the Stanley Medical Research Institute, NIMH grant MH P20 MH-66054, Bristol Myers Squibb, Otsuka Pharmaceuticals	Fair

Evidence Table 13. Quality assessment of randomized controlled trials in pediatrics with bipolar disorder

Author, Year Country	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors masked?	Care provider masked?	Patient masked?
Findling 2013	Unclear	Unclear	Yes	Yes	Unclear	Yes	Yes
Haas 2009	NR	NR	Yes	Yes	NR (described as double-blind)	NR (described as double-blind)	NR (described as double-blind)
Pathak, 2013 USA	Unclear, no information about sequence generation	Yes	Unclear; Overt Aggression Scale-Modified total scores higher in quetiapine groups	Yes	Unclear	Yes	Yes
Tohen 2007	NR	NR	Yes	Yes	NR (described as double-blind)	NR (described as double-blind)	NR (described as double-blind)
Tramontina 2009	Yes	Yes	Mostly: SES was significantly different, placebo group having more in the upper middle than aripiprazole	Yes	Yes	Yes	Yes

Evidence Table 13. Quality assessment of randomized controlled trials in pediatrics with bipolar disorder

Author, Year Country	Reporting of attrition, crossovers, adherence, and contamination	Loss to follow-up: differential/high	Maintenance of comparable groups	Intent-to-treat analysis	Funding	Quality rating
Findling 2013	Yes, No, No, No	Overall: Yes, 77% Differential: Yes, aripiprazole 10 mg=65%, 30 mg=78%, placebo=77%	Unclear	Yes	Otsuka Pharmaceutical Co., Ltd.	Fair
Haas 2009	Yes, No, Yes, No	No/No	Yes	No 169/170 included	Johnson & Johnson Pharmaceutical Research and Development, LLC.	Fair
Pathak, 2013 USA	Yes, No, Yes, No	Yes for high overall=22%; No for differential	Yes	No	AstraZeneca	Fair
Tohen 2007	Yes, No, No, No	79.4% compeleted olanzapine group 64.8% completed placebo group	Unclear	Yes	Eli Lilly & Co.	Fair
Tramontina 2009	Yes, No, No, No	No/No	Yes	Yes	Bristol-Myers Squibb	Good

Evidence Table 14. Observational studies in patients with major depressive disorder

Author, year Country	Study design	Time period covered Data source	Sample size	Population characteristics
Barbee 2004	Retrospective chart review	Time period covered: NR Data source: Charts from a fee-for-service psychiatric outpatient clinic	76 medication trials in 49 patients	Patients treated with 1+ doses of olanzapine, risperidone, quetiapine, or ziprasidone as augmentation for treatment-resistant, nonpsychotic MDD after being treated with an established antidepressant medication regimen for a minimum of 6 weeks % Male: 30.6
Seo 2009	Prospective cohort study	Time period covered: 2002-2006 Data source: patients admitted to a psychiatric inpatient unit for the treatment of MDD at two university hospitals in Seoul and Daejeon, Korea	AAP group: n=100 Non-AAP group: n=172	Patients with MDD who were treated with only one antidepressant during the admission period (non-AAP group) or were treated with augmentation with an APP for >2 weeks (AAP group) Sex (% male): 22 Mean age (y ± SD): 51.9±16.5 Duration of illness (y ± SD): 7.4±8.2

Evidence Table 14. Observational studies in patients with major depressive disorder

Author, year Country	Efficacy/effectiveness outcomes	Harms
Barbee 2004	Mean treatment duration (w): Olanzapine: 19.59 ± 21.66 (range 1-92 w) Risperidone: 35.86 ± 32.08 (range 4-94 w) Quetiapine: 17.94 ± 21.94 (range 2-74 w) Ziprasidone: 9.40 ± 10.97 (range 1-28 w)	Withdrawals (%) due to weight gain: Olanzapine: 43 Risperidone: 0 Quetiapine: 10 Ziprasidone: 14
Seo 2009	NR	Comparisons of weight changes in subjects of the AAP group using different combination therapies: n (%)/Change in weight (kg ± SD)/Statistics*/P-value SSRIs + olanzapine: 25 (25.0)/4.21±1.90/21.934/<0.001** SSRIs + quetiapine: 15 (15.0)/2.89±1.40/0.002/0.962 SSRIs + risperidone: 11 (11.0)/2.40±2.38/2.356/0.128 Mirtazapine + olanzapine: 10 (10.0)/2.44±1.26/1.734/0.191 Mirtazapine + quetiapine: 9 (8.3)/1.99±1.46/5.242/0.024** Venlafaxine + quetiapine: 8 (8.0)/3.16±1.81/0.017/0.896 Venlafaxine + olanzapine: 16 (16.0)/-/-/- Others: *ANCOVA was performed with duration of AAP prescription and duration of illness as covariates. P-value was derived from t-statistic based on the change in weight according to each type medications versus all others combined **P<0.05

Evidence Table 14. Observational studies in patients with major depressive disorder

Author, year Country	Comments	Funder
Barbee 2004	Does not report all-cause discontinuations and did not analyze between-drug differences in duration of treatment	Eli Lilly and Co.
Seo 2009		Korea Health 21 R&D Project, Ministry of Health, Welfare and Family Affairs, Republic of Korea

Evidence Table 15. Quality assessment of observational studies in major depressive disorder

Author Year Country	Non-biased selection?	High overall loss to follow-up or differential loss to follow-up?	Outcomes pre-specified and defined?	Ascertainment techniques adequately described?	Non-biased and adequate ascertainment methods?	Statistical analysis of potential confounders?	Adequate duration of follow-up?	Overall quality rating
Barbee 2004	Yes	No	No	No	Unclear	No	No for olanzapine, quetiapine, and ziprasidone. Yes for risperidone.	Poor
Seo 2009	Unclear whether 272 enrolled represented all eligible patients admitted between 2002 and 2006	Yes	Yes	Yes	Yes	Yes for duration of atypical antipsychotic treatment and illness duration	No	Fair

Evidence Table 16. Observational studies in youths

Author, year Country	Study design	Time period covered Data source	Sample size	Population characteristics
Correll, 2009 Queens, New York	Non-randomized prospective cohort study	Between December 2001 and September 2007 Patients recruited from pediatric inpatient and outpatient clinics	338 patients enrolled (aripiprazole n=47; olanzapine n=52; quetiapine n=45; risperidone n=168; comparison group n=20) analyzed patients n=272	Youth naive to antipsychotic medication and a psychiatric comparison group consisting of patients who refused or discontinued taking antipsychotic medications within 4 weeks of starting. Age of 4 to 19 years and 1 week or less of lifetime antipsychotic treatment; psychiatric illness prompting antipsychotic medication initiation; and consent, or baseline anthropometric and biochemical assessments obtained within 7 days of antipsychotic medication initiation Mean age (SD): 13.9 (3.6) years Male: 57% White: 48.5% Black: 25.9% Hispanic: 8.9% Asian: 4.1% Mixed: 12.5% Mean weight: 53.5 kg
Fleischhaker, 2008 Germany	Prospective Cohort Study	From July 1999 to October 2003 Four child and adolescent psychiatric departments in four mental health centers in Germany (Aachen, Freiburg, Marburg, and Wuerzburg)	61 inpatients considered for inclusion Final study sample n=33 (clozapine n=15; olanzapine n=8; risperidone n=10)	clozapine vs olanzapine vs risperidone Age: 17.2 vs 15.7 vs 1.3 years Males: 33.3% vs 15.2% vs 24.2% Medication dose (SD): 311.7 (137.5) vs 10.2 (3.5) vs 2.6 (1.7) mg

Evidence Table 16. Observational studies in youths

Author, year Country	Efficacy/ effectiveness outcomes	Harms	Funder
Correll, 2009 Queens, New York	NR	Antipsychotic medication was associated with increased weight, fat mass, BMI and waist circumference (*P* <0.001) aripiprazole vs olanzapine vs quetiapine vs risperidone vs untreated Weight change over time: 4.4 vs 8.5 vs 6.1 vs 5.3 vs 0.2 kg Weight % change of baseline: 8.1 vs 15.2 vs 10.4 vs 10.4 vs 0.7 Fat mass over time: 2.4 vs 4.1 vs 2.8 vs 2.5 vs 0.4 kg BMI change over time 1.7 vs 3 vs 2.1 vs 1.9 vs -0.003 BMI % change: 7.2 vs 14 vs 9.3 vs 9.1 vs 0.1 Waist circumference: 5.4 vs 8.6 vs 5.3 vs 5.1 vs 0.7 cm Metabolic parameter (*P <0.05) Glucose change: 0.54 vs 3.14* vs 2.64 vs 1.14 vs 0.69 mg/dL Total cholesterol change: 3.75 vs 15.58* vs 9.05* vs 3.46 vs 2.38 mg/dL LDL cholesterol change: 7.38 vs 11.54* vs 3.88 vs 0.21 vs 2.99 mg/dL HDL cholesterol change: 0.29 vs -1.27 vs -1.47 vs 0.33 vs 1.49 mg/dL Triglycerides change: -2.4 vs 24.34* vs 36.96* vs 9.74* vs -11.84 mg/dL	Supported in parts by National Institute of Health, National Alliance for Research in Schizophrenia and Depression Award, Feinstein Island Jewish Health System General Clinical Research Center, National Center for Research Resources
Fleischhaker, 2008 Germany	NR	clozapine vs olanzapine vs risperidone All 3 groups experienced significant weight gain from baseline Weight change (SD) from baseline in kg: 9.5 (10.4); *P* <0.004 vs 16.2(8.8); *P* <0.002 vs 7.2 (5.3); *P* <0.002 The absolute (±SD) and percentage (±SD) average weight gains were significantly higher for the olanzapine group (16.2 ± 8.8 kg; 30.1 ± 18.9%) than for the clozapine (9.5 ± 10.4 kg; 14.8 ± 15.8%) and the risperidone (7.2 ± 5.3 kg; 11.5 ± 6.0%) groups. (Mean proportional weight change over the 45 weeks of study shown as figure)	Non-restricted grant from Janssen-Cilag, Neuss, Germany

Evidence Table 16. Observational studies in youths

Author, year Country	Study design	Time period covered Data source	Sample size	Population characteristics
Fraguas, 2008	Prospective Cohort Study	Time period covered: March 2005-October 2006 Data source: The adolescent unit of the Psychiatric Department at Hospital General Universitario Gregorio Maranon, Madrid, Spain	n=66 (risperidone n=22, olanzapine n=20, quetiapine n=24)	Children and adolescents treated with a new prescription of risperidone, olanzapine, or quetiapine within the 30 days prior to enrollment and who had no history of prior lifetime antipsychotic treatment and who were treated with the new medication for 6 months Sex (% male): 66.7 Mean age (y ± SD): 15.2 ±2.9

Evidence Table 16. Observational studies in youths

Author, year Country	Efficacy/ effectiveness outcomes	Harms	Funder
Fraguas, 2008	NR	**Baseline and outcome measurements after 6 months of antipsychotic treatment (baseline/change):** Risperidone (Mean ±SD) Weight (kg): 57.5±20.3/5.0±4.8** BMI (kg/m2): 21.8±4.5/1.4±1.8** BMI z score: 0.56±1.41/0.48±0.73** Olanzapine (Mean ±SD) Weight (kg): 61.7±15.1/11.1±7.8** BMI (kg/m2): 22.7±5.2/3.7±2.7** BMI z score: 0.26±1.49/1.10±0.82** Quetiapine (Mean ±SD) Weight (kg): 60.5±11.4/2.5±6.8 BMI (kg/m2): 21.5±3.2/0.9±2.7 BMI z score: -0.12±0.97/0.27±0.86 All Subjects (Mean ±SD) Weight (kg): 59.9±15.8/6.0±7.4** BMI (kg/m2): 22.0±4.3/1.9±2.7** BMI z score: 0.22±1.31/0.59±0.87** **P<0.01 (Wilcoxon) **Change score between treatment groups:** Risperidone-Olanzapine Weight (kg): p=0.037 BMI (kg/m2): p=0.46 BMI z score: NS Risperidone-Quetiapine Weight (kg): NS BMI (kg/m2): NS BMI z score: NS Olanzapine-Quetiapine Weight (kg): p<0.001 BMI (kg/m2): p<0.001 BMI z score: p=0.001 aANCOVA Sidak post hoc adjusted for multiple comparisons. Analysis of differences in change score between treatment groups were done by means of ANCOVA, controlling for age, baseline BMI, z score, psychosis, and duration of prior total lifetime antipsychotic usage	Spanish Ministry of Health, Instituto de Salud Carlos III, RETICS, Fondo de Investigacion Sanitaria, Asociacion adrilena de Salud Mental, NARSAD 2005: Independent Investigator Award

Evidence Table 16. Observational studies in youths

Author, year Country	Efficacy/ effectiveness outcomes	Harms	Funder
Fraguas, 2008 (Cont...)		**Risk for adverse health outcome (baseline/month 6):** Risperidone (%) BMI ≥ 95th percentile: 13.6/31.8 BMI ≥ 85th percentile: 27.3/40.9 Weight gain (≥ 0.5 increasein BMI z score): --/50.0 Olanzapine (n, %) BMI ≥ 95th percentile: 10.0/50.0 BMI ≥ 85th percentile: 20.0/60.0 Weight gain (≥ 0.5 increasein BMI z score): --/75.0 Quetiapine (n, %) BMI ≥ 95th percentile: 4.2/8.3 BMI ≥ 85th percentile: 12.5/20.8 Weight gain (≥ 0.5 increasein BMI z score): --/29.2 All Subjects (n, %) BMI ≥ 95th percentile: 10.6/28.8 BMI ≥ 85th percentile: 19.7/39.4 Weight gain (≥ 0.5 increasein BMI z score): --/50.0 **Change score between treatment groups:** BMI ≥ 95th percentile: p=0.091 BMI ≥ 85th percentile: p=0.048c Weight gain (≥ 0.5 increasein BMI z score): p=0.010d cDifference between baseline and month 6 in having BMI ≥ 85th percentile post hoc (Fisher exact test when needed) comparisons: risperidone-olanzapine, p=0.035; risperidone-quetiapine, p=0.625; olanzapine-quetiapine, p=0.049 Difference in weight gain (≥ 0.5 increasein BMI z score) post hoc (Fisher exact test when needed) comparisons: risperidone-olanzapine, p=0.096; risperidone-quetiapine, p=0.148; olanzapine-quetiapine, p=0.002	

Evidence Table 16. Observational studies in youths

Author, year Country	Study design	Time period covered Data source	Sample size	Population characteristics
Khan 2009 U.S.	Retrospective chart review	Time period covered: September 1, 2003-August 25, 2005 Data source: Chart review of children and adolescents at the psychiatric unit of the Austin State Hospital	49 Olanzapine: 25, Risperidone: 24	Mean age: 13 yrs %Male: 73.5% African American: 18.4% Asian: 2% Hispanic: 14.3% Caucasian: 65.3% fasting blood glucose: 86.5mg/dL Triglyceride: 72mg/dl High density lipoprotein: 44.6mg/dL Low density lipoprotein: 93.5mg/dL Systolic blood pressure: 109.4mmHg Diastolic blood pressure: 69mmHg Risk factors at baseline Cardiovascular disease(smoing risk factor included): 0.7 Diabetes mellitus: 1.0 Metabolic syndrome: 0.75 Mean duration of treatment: 27 days

Evidence Table 16. Observational studies in youths

Author, year Country	Efficacy/ effectiveness outcomes	Harms	Funder
Khan 2009 U.S.	NR	Olanzapine vs risperidone Proportion pf patients with BMI>85%: 7 (28%)vs 4(17%) during treatment Mean(SD) change from baseline in BMI:1.7 (1.5) vs 1.3 (1.5), p<0.001 for both groups, difference between groups=NS Proportion of patients classified as "overweight" at endpoint: 7(28%) vs 4 (16.7%) Proportion of patients classified as "at risk for being overweight at endpoint: 5(20%) vs 7 (29.2%) Mean (SD)increase in weight from baseline to endnpoint: 7.4 lbs (range -7 to +28 pounds) vs 91 lbs (range -7 to +38pounds) Mean (SD) change in systlic blood pressure (mmHg) from baseline to endpoint: 5.4 (15)* vs -3.2 (14), * p<0.044 , p=NS between groups Mean (SD) change in diastolic blood pressure (mmHg) from baseline to endpoint: 1.4 (12) vs -4.2 (14), p=NS for change from baseline or between groups Risk factors at endpoint Cardiovascular disease (smoking risk factor included): Olanzapine 0.6 (0.5),z=0.00, p=1.00. Risperidone: 0.3 (0.5)z=-3.00, p=0.003 Cardiovascular disease (smoking risk factor excluded): Olanzapine 0.6 (0.5), z=-1.667, p=0.096. Risperidone: 0.3 (0.5), z=-1.414, p=0.157 Diabetes mellitus: Olanzapine: 1.2 (0.9), z=-2.653, p=0.008. Risperidone: 1.2 (1.0), z=0, p=0.782, Metabolic syndrome: Olanzapine: 1.0 (0.9), z=-2.484, p=0.013, Risperidone: 0.9 (1.0), z=0, p=1.00	

Evidence Table 17. Quality assessment of observational studies in youths

Author Year Country	Non-biased selection?	High overall loss to follow-up or differential loss to follow-up?	Outcomes pre-specified and defined?	Ascertainment techniques adequately described?
Correll 2009 (SATIETY)	Unclear; 173/505 (34%) who refused to participate or were ineligible had less autism-spectrum disorders, substance abuse comorbidity, and mixed ethnicity	18% excluded from analysis overall due to lack of post-baseline assessment 20% excluded from analysis for quetiapine and risperidone, vs 13% for aripiprazole and olanzapine	Yes	Yes
Fleischhaker 2006	Unclear; distribution across comparison groups of different diagnoses, prior experience with antipsychotic agents and use of co-medications NR; numerically lower proportion of males in olanzapine group compared to clozapine and risperidone (56% vs 69% vs 68%)	Attrition NR; all 51 participants included in analysis	Yes	Yes
Fleischhaker 2008	Yes	46% (28/61) excluded due to early discontinuation (34%), low number of weight and height measurements (8%) and anorexia nervosa (3%); attrition per treatment group NR	Yes	Yes
Fraguas 2008	Yes	Yes/Yes Overall=28%, risperidone=42%, olanzapine=20%, quetiapine=17%	Yes	Yes

Evidence Table 17. Quality assessment of observational studies in youths

Author Year Country	Non-biased and adequate ascertainment methods?	Statistical analysis of potential confounders?	Adequate duration of follow-up?	Overall quality rating
Correll 2009 (SATIETY)	Yes	Some, categorical outcomes adjusted for differences at baseline, others analyzed by stratification and other methods.	No	Fair
Fleischhaker 2006	Unclear about reliability/validity of adapted version of Dosage Record Treatment Emergent Symptom Scale (DOTES) (e.g., computerized, German language, included additional information from chart review)	Stratified by drug-naiveté and comedication use for weight gain	No; mean=7.4 weeks	Poor
Fleischhaker 2008	Yes	Yes for change in BMI standard deviation scores (SDS), unclear for others. Reported that "since the groups differed significantly in age [at baseline], several analyses were conducted to test the influence of age that is confounded with medication group. " No linear or monotone relationships found for BMI-SDS. Results for others NR.	Yes	Fair
Fraguas 2008	Yes	Yes for age, BMI z score, psychosis, duration of prior total lifetime antipsychotic usage	Yes	Fair

Evidence Table 17. Quality assessment of observational studies in youths

Author Year Country	Non-biased selection?	High overall loss to follow-up or differential loss to follow-up?	Outcomes pre-specified and defined?	Ascertainment techniques adequately described?
Khan 2009	Unclear (eligibility criteria described, but #'s and reasons for exclusion NR)	No	Yes	No
Roke, 2012 The Netherlands	Unclear. Significantly more subjects with DBD in control group	No, No. 17.6% overall withdrawal and less than 10% differential	Yes	Yes

Evidence Table 17. Quality assessment of observational studies in youths

Author Year Country	Non-biased and adequate ascertainment methods?	Statistical analysis of potential confounders?	Adequate duration of follow-up?	Overall quality rating
Khan 2009	Unclear (NR)	No (controlled for smoking but not for nutritional status also higher proportion males in risperidone group-83% vs 64%)	No, 27 days	Poor
Roke, 2012 The Netherlands	Yes	Yes, controlled for age, BMI, tanner stage, type of medication, duration of antipsychotic use, use of dosage, risperidone levels, 9-OH risperdione levels on hyperprolactinemia in patients using risperidone corrected for age and BMI Z-score.	Yes, 52 months	Fair