Drug Class Review
on
Atypical Antipsychotic Drugs

Final Report
EVIDENCE TABLES

April 2006

The purpose of this report is to make available information regarding the comparative effectiveness and safety profiles of different drugs within pharmaceutical classes. Reports are not usage guidelines, nor should they be read as an endorsement of, or recommendation for, any particular drug, use or approach. Oregon Health & Science University does not recommend or endorse any guideline or recommendation developed by users of these reports.

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

Author, year Study design Quality	Eligibility criteria	Interventions (drug, dose, duration)	Wash-out period
Aripiprazole vs olanzapine			
Cornblatt, 2002 Abstract & Poster Only FDA Study 98213 RCT, multicenter, open label FAIR	Clinically stable schizophrenia or schizoaffective disorder on a stable dose of oral typical antipsychotic, risperidone or quetiapine for at least one month	aripiprazole 30mg/d olanzapine 10-15mg/d Duration: 26 weeks	NR
McQuade, 2004 Multicenter, RCT, DB Inpatients Funding: Otsuka America Pharmaceuticals	Schizophrenia, in acute relapse, requiring hospitalization, 18 years 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	2 days minimum or 1 dept cycle after the most recent dept antipsychotic injection
Aripiprazole vs Risperidone			
Potkin, 2003b RCT, DB, placebo-controlled, parallel, multicenter Inpatients Funding: Bristol-Myers Squibb	Acute, psychosis in patients diagnosed with schizophrenia and schizoaffective disorder Exclusion criteria: psychiatric disorder other than schizophrena, schizoaffective disorder requiring pharmacotherapy, history of violence, recent history of suicide ideation/attempts, clinically significant neuroloical abnormality other than tardive dyskinesia or EPS, current diagnosis of psychactive substance dependence, history of alcohol/drug abuse, treatment with an investigational study drug within 4 weeks before washout, acute/unstable medical condition	aripiprazole: 20 mg/day:(N=101) aripiprazole: 30 mg/day:(N=101) risperidone: 6 mg/day:(N=99) placebo:(N=103)	7 days

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Aripiprazole vs olanzapine			
Cornblatt, 2002 Abstract & Poster Only FDA Study 98213 RCT, multicenter, open label FAIR	NR	Battery of 10 neurocognitive tests assessing verbal and visual secondary memory, verbal fluency, executive function, working memory, vigilance, and manual dexterity. Assessed at baseline, 8 and 26 wks Neurocognitive data were reduced to 3 factors using principal components of factor analysis: secondary verbal memory, general cognitive function, executive functioning	Mean age: 40 65% male 60% white 31% African American 6% Hispanic 3% Asian and other
McQuade, 2004 Multicenter, RCT, DB Inpatients Funding: Otsuka America Pharmaceuticals	lorazepam up to 4mg/day allowed, not within 4 hours of efficacy/safety assessments	Body weighing, Positive and Negative Syndrome Scale and Clinical Global Impressions-Improvement	Mean Age: 38.4 Male: 72% Ethnicity NR
Aripiprazole vs Risperidone			
Potkin, 2003b RCT, DB, placebo-controlled, parallel, multicenter Inpatients Funding: Bristol-Myers Squibb	NR	Positive and Negative Syndrome Scale (PANSS), Clinical Global Impression scores (CGI), effects on weight, prolactin, corrected QT interval, Simpson-Angus Scale (SAS), Barnes Akathisia Rating Scale (BAS), Abnormal Involuntary Movements Scale (AIMS)	Mean age: 38.9 years 70% Male Ethnicity NR

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Author, year Study design Quality	Other population characteristics	Number Screened/ Eligible/ Enrolled	Withdrawn/ Lost to fu/ Analyzed
Aripiprazole vs olanzapine			
Cornblatt, 2002 Abstract & Poster Only FDA Study 98213 RCT, multicenter, open label FAIR	Baseline PANSS 70 - 74 Baseline IQ: Vocabulary 30 - 33 Block Design 30 - 32 Information score 12 - 14 NAART scores 35 - 36	NR/NR/255	146/NR/NR
McQuade, 2004 Multicenter, RCT, DB Inpatients Funding: Otsuka America Pharmaceuticals	In-Patient population: 100%	NR/NR/378	72%/approx.10%/317
Aripiprazole vs Risperidone			
Potkin, 2003b RCT, DB, placebo-controlled, parallel, multicenter Inpatients Funding: Bristol-Myers Squibb	100% inpatient	NR/NR/404	162/0/242

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

Author, year Study design Quality	Results
Aripiprazole vs olanzapine	
Cornblatt, 2002 Abstract & Poster Only FDA Study 98213 RCT, multicenter, open label FAIR	Secondary verbal memory: SS difference aripiprazole > olanzapine (p<0.02 at 8 wks, p<0.04 at 26 wks) aripiprazole SS difference to baseline (pp<0.001 at 8 and 26 wks) General cognitive function: NS difference from baseline or between drugs Executive functioning: NS difference from baseline or between drugs
McQuade, 2004 Multicenter, RCT, DB Inpatients Funding: Otsuka America Pharmaceuticals	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 Cholestrol 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 aripirazole and olanzapine groups."
Aripiprazole vs Risperidone	
Potkin, 2003b RCT, DB, placebo-controlled, parallel, multicenter Inpatients Funding: Bristol-Myers Squibb	PANSS score: P-value=drug vs placebo Total: A20: -14.5 (p=.001) vs A30: -13.9 (p=.003) vs R6: -15.7 (p<.001) vs placebo: -5.0 BPRS score: A20: -3.5 (p=.004) vs A30: -3.3 (p=.01) vs R6: -3.9 (p<.001) vs placebo: -1.7 CGI-score: A20: -0.2 (p=.03) vs A30: -0.6 (p=.006) vs R6: -0.7 (p<.001) vs placebo: -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 placebo: -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 placebo: 0.1 ng/mL

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

Author, year Study design Quality	Method of adverse effects assessment	Adverse effects reported
Aripiprazole vs olanzapine		
Cornblatt, 2002 Abstract & Poster Only FDA Study 98213 RCT, multicenter, open label FAIR	Weight and serum cholesterol	Endpoint weight change (LOCF): aripiprazole -0.8 kg, olanzapine 3.5 kg (based on graphical representation), p< 0.01 Change in Serum cholesterol at 26 weeks (not clear if LOCF): aripiprazole -12 mg/dL, olanzapine 8 mg/dL, p<0.001 Spontaneously reported adverse events: based on bar graph: higher rates of insomnia, nausea, anxiety, agitation, and akathisia with aripiprazole higher rates of somnolence, headache and weight gain with olanzapine
McQuade, 2004 Multicenter, RCT, DB Inpatients Funding: Otsuka America Pharmaceuticals	Patient self-report	Headache: O: 32% vs A: 23% Insomnia: O: 30% vs A: 32% Anxiety: O: 25% vs A: 20% Somnolence: O: 23% vs A: 8%
Aripiprazole vs Risperidone		
Potkin, 2003b RCT, DB, placebo-controlled, parallel, multicenter Inpatients Funding: Bristol-Myers Squibb	Medical examination, patient self-report	Whole body: A20: 58% vs A30: 61% vs R6:53% vs placebo: 59% Cardiovascular system: A20: 1% vs A30: 7% vs R6: 15% vs placebo: 1% Digestive System: A20: 65% vs A30: 52% vs R6: 66% vs placebo: 53% Musculoskeletal System: A20: 6% vs A30: 6% vs R6: 7% vs placebo: 5% Respiratory System: A20: 9% vs A30: 17% vs R6: 22% vs placebo: 8% Skin and appendages: A20: 7% vs A30: 11% vs R6: 8% vs placebo: 7% Blurred vision: A20: 3% vs A30: 5% vs R6: 8% vs placebo: 1% Urogenital System: A20: 1% vs A30: 4% vs R6: 1% vs placebo: 3%

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

Author, year Study design Quality	EPS	Total withdrawals; withdrawals due to adverse events	Comments
Aripiprazole vs olanzapine			
Cornblatt, 2002 Abstract & Poster Only FDA Study 98213 RCT, multicenter, open label FAIR	NR	NR/NR/NR	
McQuade, 2004 Multicenter, RCT, DB Inpatients Funding: Otsuka America Pharmaceuticals	EPS-Related Adverse Events: Low: O: 16% vs A: 17% Parkinsonism events: O: 12% vs A: 11% Akathsia: O: 3% vs A: 6%	229 withdrawals; Approx. 30% due to adverse events	
Aripiprazole vs Risperidone			
Potkin, 2003b RCT, DB, placebo-controlled, parallel, multicenter Inpatients Funding: Bristol-Myers Squibb	Incidence of EPS-related adverse events: A20: 32 vs A30: 31% vs R6: 31% vs placebo: 20% Mean change in Simpson-Angus Scale scores from baseline to endpoint: A20: -0.16 vs A30: -0.09 vs R6: -0.18 vs placebo: -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 placebo: 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 placebo) vs placebo: 0.1	162; 44	

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

Author, year Study design Quality	Eligibility criteria	Interventions (drug, dose, duration)	Wash-out period
Bitter, 2004 Bitter, 1999 (Abstract Only) RCT Multi-center, Hungary & South Africa GOOD	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 weeks	2-9 days

Funding: Eli Lilly

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

Author, year Study design Quality	Allowed other medications	Method of outcome assessment timing of assessment	Age Gender Ethnicity
Bitter, 2004 Bitter, 1999 (Abstract Only) RCT Multi-center, Hungary & South Africa GOOD Funding: Eli Lilly	Episodic use of benzodiazepines not allowed, stable doses of chronically used benzodiazepines allowed with max doses, anticholingergic meds to treat new or worsening EPS allowed but all other uses not allowed	PANSS CGI 19 visits over 20 weeks Kane criteria for Response: BPRS(1-7) improvement >20% +CGI-S <3 or BPRS(1-7) final score <35 Other assessments of Response: PANSS total score: >/= 20%, 30%, 40% or 50%	Mean age 38 48% white 60% male

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

Author, year Study design Quality	Other population characteristics	Number Screened/ Eligible/ Enrolled	Withdrawn/ Lost to fu/ Analyzed
Bitter, 2004 Bitter, 1999 (Abstract Only) RCT Multi-center, Hungary & South Africa GOOD Funding: Eli Lilly	Not reported, stated to have NS differences	189/150/147	7/NR/140 for efficacy assessments 62/NR/147 for safety assessments

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

Author, year Study design Quality	Results
Bitter, 2004 Bitter, 1999 (Abstract Only) RCT Multi-center, Hungary & South Africa GOOD Funding: Eli Lilly	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%

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

Author, year Study design Quality	Method of adverse effects assessment	Adverse effects reported
Bitter, 2004 Bitter, 1999 (Abstract Only) RCT Multi-center, Hungary & South Africa GOOD Funding: Eli Lilly	EPS measured by: SAS, AIMS, and HAS scales Adverse events reported by patients categorized by COSTART dictionary Lab tests, weight, ECG also monitored	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: not reported in either group

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

Author, year Study design Quality	EPS	Total withdrawals; withdrawals due to adverse events	Comments
Bitter, 2004 Bitter, 1999 (Abstract Only) RCT Multi-center, Hungary & South Africa GOOD Funding: Eli Lilly	**EPS:** Baseline to Endpoint on SAS, AIMS, or HAS: NS difference Treatment emergent akathisia (HAS >/= 3) or dyskinesia: NS Difference Treatment emergent parkinsonism: not reported in either group	Overall: 85 (58%) Due to adverse events: clozapine 7 olanzapine 7	Refractoriness includes intolerance, does not use Kane criteria.

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

Author, year Study design Quality	Eligibility criteria	Interventions (drug, dose, duration)	Wash-out period
Conley, 2003 Kelly 2003 DB. Cross-over Inpatients Funding: NIHM grant	Schizophrenia	olanzapine: 50 mg/d, and clozapine: 450 mg/day, each for 8 weeks	1 week washout of conventional antipsychotics

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

Author, year Study design Quality	Allowed other medications	Method of outcome assessment timing of assessment	Age Gender Ethnicity
Conley, 2003 Kelly 2003 DB. Cross-over Inpatients Funding: NIHM grant	NR	Weekly rating of Brief Psychiatric Rating Scale (BPRS), and Clinical Global Impression Severity Scale (CGI-S)	Mean age: 38 years

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

Author, year Study design Quality	Other population characteristics	Number Screened/ Eligible/ Enrolled	Withdrawn/ Lost to fu/ Analyzed
Conley, 2003 Kelly 2003 DB. Cross-over Inpatients Funding: NIHM grant	100% inpatients	NR/NR/13	NR/NR/13

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

Author, year Study design Quality	Results
Conley, 2003 Kelly 2003 DB. Cross-over Inpatients Funding: NIHM grant	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 cholestrol (mg/dL): O: 198.0 + 44.0; C: 209.6 + 28.6 Change in total cholestrol (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 aminotranferase (AST) (IU/L): O: 23.7 + 15.9; C: 18.0 + 5.1 Change in aspartate aminotranferase (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

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

Author, year Study design Quality	Method of adverse effects assessment	Adverse effects reported
Conley, 2003 Kelly 2003 DB. Cross-over Inpatients Funding: NIHM grant	Patient self-report	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 Tachcardia: 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 Quality	EPS	Total withdrawals; withdrawals due to adverse events	Comments
Conley, 2003	SAS scores	6 withdrawals/ 1 withdrawal	
Kelly 2003	decreased by 1.3 clozapine	due to adverse events	
DB. Cross-over	increased 0.3 olanzapine		
	Akathisia		
Inpatients	20% clozapine		
	20% olanzapine		
Funding: NIHM grant	1 subject received benztropine while on olanzapine		

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

Author, year Study design Quality	Eligibility criteria	Interventions (drug, dose, duration)	Wash-out period
InterSePT; Meltzer, 2003 Meltzer, 2002ab (Abstract Only), Potkin, 2003a Meltzer, 1996 RCT - open label, masked ratings Multi-site - 67 sites, 11 countries (US, Europe, South Africa, South America) GOOD Funding: Pfizer, Inc	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 years 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 years	none

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

Author, year Study design Quality	Allowed other medications	Method of outcome assessment timing of assessment	Age Gender Ethnicity
InterSePT; Meltzer, 2003 Meltzer, 2002ab (Abstract Only), Potkin, 2003a Meltzer, 1996 RCT - open label, masked ratings Multi-site - 67 sites, 11 countries (US, Europe, South Africa, South America) GOOD Funding: Pfizer, Inc	Any required to treat patient and reduce risk of suicide Both groups seen weekly/biweekly - clozapine group for blood montoring, olanzapine for vital sign monitoring	**Type 1:** a significant suicide attempt (successful or not), hospitalization to prevent suicide. These outcomes were asssessed by a masked, 3-person Suicide Monitoring Board (SMB) **Type 2:** Ratings from masked psychiatrist (on-site) on the CGI-Suicide Severity or "much worse" or "very much worse" from baseline. Occurance of a Type 1 event was also considered having met criteria for a Type 2 event.(assessed at 4-8 wk intervals) **Other:** time to suicide attempt (SMB validated), time to hospitalization to prevent suicide (SMB validated), number of: suicide attempts, hospitalizations to prevent suicide, and interventions to prevent suicide (non-SMB validated) Blinded psychiatrists assessed: PANSS, ISST, CDS and Covi-Anxiety scales Unblinded psychiatrists assessed: SOF, ESRS	Mean age 37.1 yrs % male: 61.4% Ethnicity: 71% White 15% Black 1.3% Oriental 13% Other

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

Author, year Study design Quality	Other population characteristics	Number Screened/ Eligible/ Enrolled	Withdrawn/ Lost to fu/ Analyzed
InterSePT; Meltzer, 2003 Meltzer, 2002ab (Abstract Only), Potkin, 2003a Meltzer, 1996 RCT - open label, masked ratings Multi-site - 67 sites, 11 countries (US, Europe, South Africa, South America) GOOD Funding: Pfizer, Inc	62% Schizophrenic 38% Schizoaffective Mean # suicide attempts: 3.4 83% had attempted suicide at least once 63% had attempted suicide in last 36 mths 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	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 not reported

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

Author, year Study design Quality	Results
InterSePT; Meltzer, 2003 Meltzer, 2002ab (Abstract Only), Potkin, 2003a Meltzer, 1996 RCT - open label, masked ratings Multi-site - 67 sites, 11 countries (US, Europe, South Africa, South America) GOOD Funding: Pfizer, Inc	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-year 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 antisuicidal 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 mths, 2-3 lifetime suicide attempts, no hx alcohol abuse, smokers, high ISST, Cov-Anxiety Scale and CDI scale scores

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

Author, year Study design Quality	Method of adverse effects assessment	Adverse effects reported
InterSePT; Meltzer, 2003 Meltzer, 2002ab (Abstract Only), Potkin, 2003a Meltzer, 1996 RCT - open label, masked ratings Multi-site - 67 sites, 11 countries (US, Europe, South Africa, South America) GOOD Funding: Pfizer, Inc	NR	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 hypotensin, syncope, dysarthria, consitpation, 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 Quality	EPS	Total withdrawals; withdrawals due to adverse events	Comments
InterSePT; Meltzer, 2003 Meltzer, 2002ab (Abstract Only), Potkin, 2003a Meltzer, 1996 RCT - open label, masked ratings Multi-site - 67 sites, 11 countries (US, Europe, South Africa, South America) GOOD Funding: Pfizer, Inc	NR	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/nonsuccessful) 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 not reported. 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 Quality	Eligibility criteria	Interventions (drug, dose, duration)	Wash-out period
Glick 2004 Subanalysis of InterSePT showing patterns of concomitant psychotropic medication (CPM) use Funding: Novartis Pharmaceuticals Corporation	see above	see above	none

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

Author, year Study design Quality	Allowed other medications	Method of outcome assessment timing of assessment	Age Gender Ethnicity
Glick 2004 Subanalysis of InterSePT showing patterns of concomitant psychotropic medication (CPM) use Funding: Novartis Pharmaceuticals Corporation	Any required to treat patient and reduce risk of suicide. See results section for numbers of patients taking CPMs	for CPMs, all relevant medications were recorded in case report forms and included in the clinical trial databse. CPMs used after study drug randomization were identified and grouped into the following 4 classes: antipsychotics, antidepressants, sedatives/anxiolytics, and mood stabilizers. Once a CPM was assigned to a psychotropic class, all cases of use for that medication were included in the analysis. Stimulants, antidementia drugs, and analgesics were not considered for this analysis, as these are used for nonpsychiatric indications or for indications outside the scope of InterSePT (eg, ADHD). Beta-blockers were excluded from the analysis except for propanolol.	see above

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Author, year Study design Quality	Other population characteristics	Number Screened/ Eligible/ Enrolled	Withdrawn/ Lost to fu/ Analyzed
Glick 2004 Subanalysis of InterSePT showing patterns of concomitant psychotropic medication (CPM) use Funding: Novartis Pharmaceuticals Corporation	see above	see above	NR/NR/NR

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

Author, year Study design Quality	Results
Glick 2004 Subanalysis of InterSePT showing patterns of concomitant psychotropic medication (CPM) use Funding: Novartis Pharmaceuticals Corporation	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 olzanzapine 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 attempers (ATs) and nonattempters (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

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

Author, year Study design Quality	Method of adverse effects assessment	Adverse effects reported
Glick 2004 Subanalysis of InterSePT showing patterns of concomitant psychotropic medication (CPM) use Funding: Novartis Pharmaceuticals Corporation	NR in this paper, for general InterSePT, see above	NR in this paper, for general InterSePT, see above

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

Author, year Study design Quality	EPS	Total withdrawals; withdrawals due to adverse events	Comments
Glick 2004 Subanalysis of InterSePT showing patterns of concomitant psychotropic medication (CPM) use Funding: Novartis Pharmaceuticals Corporation	NR in this paper, for general InterSePT, see above	NR in this paper, for general InterSePT, see above	

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

Author, year Study design Quality	Eligibility criteria	Interventions (drug, dose, duration)	Wash-out period
Tollefson, 2001* Beasley, 1999 (abstract) Beuzen, 1998 (abstract) Funding: Eli Lilly	Schizophrenia Diagnosis: DSM-IV	olanzapine 15 mg/d,after first 2 weeks 15–25 mg/d mean 21 mg clozapine fixed dose escalation from 25 to 200 mg/d during days 1–8 of therapy; after first 2 weeks, 200–600 mg/d mean 303 mg Duration: 18 weeks	2–9 days

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

Author, year Study design Quality	Allowed other medications	Method of outcome assessment timing of assessment	Age Gender Ethnicity
Tollefson, 2001*	benzodiazepine (up to 40 mg daily	PANSS Total (positive; negative subscale)	Mean age (SD): 38.6
Beasley, 1999 (abstract)	diazepam equivalent or 8 mg	CGI-S; BPRS total	(10.6) years
Beuzen, 1998 (abstract)	lorazepam equivalent) for agitation, choral hydrate for insomnia, and	BPRS+ CGI-S;PANSS total score (≥20%;≥30%;≥40%;≥50% improvement;no improvement)	63.9% male Ethnicity NR
Funding: Eli Lilly	biperiden or benztropine mesylate (up to 4 mg daily) for EPS permitted	EPS rating scales: SAS total; AIMS non-global total; BAS global score	

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

Author, year Study design Quality	Other population characteristics	Number Screened/ Eligible/ Enrolled	Withdrawn/ Lost to fu/ Analyzed
Tollefson, 2001* Beasley, 1999 (abstract) Beuzen, 1998 (abstract) Funding: Eli Lilly	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	NR/NR/180 olanzapine: 90 clozapine: 90	olanzapine 36/2/90 clozapine 37/2/90

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

Author, year Study design Quality	Results
Tollefson, 2001*	PANSS total (positive; negative subscales). Final equals change from baseline:
Beasley, 1999 (abstract)	Olanzapine: (n= 89) –25.6,25.5(–6.8,7.6;–7.1,7.4)
Beuzen, 1998 (abstract)	Clozapine: (n= 87) –22.1,23.1,p= 0.888 (–6.4,7.2;–5.6,6.9)
Funding: Eli Lilly	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

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

Author, year Study design Quality	Method of adverse effects assessment	Adverse effects reported
Tollefson, 2001* Beasley, 1999 (abstract) Beuzen, 1998 (abstract) Funding: Eli Lilly	AMDP-5 solicited adverse events scale	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 adverse events 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); ta 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

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

Author, year Study design Quality	EPS	Total withdrawals; withdrawals due to adverse events	Comments
Tollefson, 2001* Beasley, 1999 (abstract) Beuzen, 1998 (abstract) Funding: Eli Lilly	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	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 favour 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 favour 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

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

Author, year Study design Quality	Eligibility criteria	Interventions (drug, dose, duration)	Wash-out period
Clozapine vs risperidone			
Azorin, 2001 Double-blind, Multicenter (France and Canada) FAIR Funding: Novartis Pharmaceuticals Corporation	Diagnosis: schizophrenia (DSM-IV), Treatment-resistant: severe, chronic disease and poor response to previous neuroleptic drugs (no period of good functioning for ≥ 24 months despite use of two antipsychotic drugs; current episode without significant improvement for ≥ 6 months despite use of antipsychotic equivalent to haloperidol, 20 mg, for ≥ 6 weeks; total BPRS ≥ 45; CGI ≥ 4)	clozapine 200–900 mg/day Mean dose 597.5 mg/day; risperidone 2–15mg/day Mean dose 8.3 mg/day individual dose titration Duration: 12 weeks	Single-blind placebo period of at least 3 days

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

Author, year Study design Quality	Allowed other medications	Method of outcome assessment timing of assessment	Age Gender Ethnicity
Clozapine vs risperidone			
Azorin, 2001 Double-blind, Multicenter (France and Canada) FAIR Funding: Novartis Pharmaceuticals Corporation	NR	Leaving study early, relapse BPRS CGI-S PANSS total PANSS positive PANSS negative PANSS general psychopathology Calgary Depression Scale Psychotic Anxiety Scale Psychotic Depression Scale	Mean age 37.8 years 71% male Ethnicity NR

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

Author, year Study design Quality	Other population characteristics	Number Screened/ Eligible/ Enrolled	Withdrawn/ Lost to fu/ Analyzed
Clozapine vs risperidone			
Azorin, 2001 Double-blind, Multicenter (France and Canada) FAIR Funding: Novartis Pharmaceuticals Corporation	Mean PANSS score: 111 Mean BPRS score: 62 Mean CGI-S score: 5.5	NR/NR/273 olanzapine = 138 risperidone = 135	72/3/256

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

Author, year Study design Quality	Results
Clozapine vs risperidone	
Azorin, 2001 Double-blind, Multicenter (France and Canada) FAIR Funding: Novartis Pharmaceuticals Corporation	Mean change from Baseline to 12 weeks (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

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

Author, year Study design Quality	Method of adverse effects assessment	Adverse effects reported
Clozapine vs risperidone		
Azorin, 2001 Double-blind, Multicenter (France and Canada) FAIR Funding: Novartis Pharmaceuticals Corporation	Blood counts weekly, vital signed daily x 11 days, then periodically. EPS rated by ESRS every 2 weeks Adverse events recorded.	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

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

Author, year Study design Quality	EPS	Total withdrawals; withdrawals due to adverse events	Comments
Clozapine vs risperidone			
Azorin, 2001 Double-blind, Multicenter (France and Canada) FAIR Funding: Novartis Pharmaceuticals Corporation	AEs SS more frequent: clozapine: convulsions, dizziness, sialorrhea, tachycardia, somnolence risperidone: EPS, insomnia, dry mouth	Overall 72 (26%) Due to adverse events: 28 (10%) clozapine: 11.6%, risperidone 10.3%	BPRS score extracted from PANSS score

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

Author, year Study design Quality	Eligibility criteria	Interventions (drug, dose, duration)	Wash-out period
Bellack, 2004 Double-blind trial Substudy within larger trial POOR Funding: NIMH grant	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/day chlorpromazine; and a rating of at least moderate on BPRS or SANS subscales	clozapine: 500mg/day; max 800 mg/day after 5 weeks risperidone: 6 mg/day, max 16 mg/day after 5 weeks Duration: 29 weeks	None
Bondolfi, 1998 Single-center Double-blind RCT FAIR Inpatients Funding: Janssen Research Foundation	Chronic schizophrenia (DSM-II-R); Treatment-resistant: failed to respond or intolerant of ≥ 2 different classes of antipsychotic drugs in appropriate doses for ≥ 4 weeks each; total PANSS 60–120	clozapine: 150–400 mg/day mean 291 mg/day; risperidone: 3–12 mg/day mean 6.4 mg/day Duration: 8 weeks	3-7 days depending on psychotic symptoms

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

Author, year Study design Quality	Allowed other medications	Method of outcome assessment timing of assessment	Age Gender Ethnicity
Bellack, 2004 Double-blind trial Substudy within larger trial POOR Funding: NIMH grant	Not specified	Maryland Assessment of Social Competence, Wisconsin Card Sorting Test, and SANS symptoms ratings tests, Proportion stopping early due to lack of efficacy. Administered at baseline, Week 17, and Week 29. Patient responses were videotaped for coding by blinded raters on verbal behavior	Not specified for full study population. Of 72 subjects assessed for social competence at baseline: mean age 41.4 years 73% male 58% Caucasian
Bondolfi, 1998 Single-center Double-blind RCT FAIR Inpatients Funding: Janssen Research Foundation	lorazepam and oxazepam (sleep induction), biperiden and procyclidine (EPS), clothiapine (emergency treatment) as required	Leaving study early Positive and Negative Syndrome Scale (PANSS) and Clinical Global Impression (CGI) taken at baseline and endpoint	Mean age: 37.2 years 70.9% Male Ethnicity NR

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

Author, year Study design Quality	Other population characteristics	Number Screened/ Eligible/ Enrolled	Withdrawn/ Lost to fu/ Analyzed
Bellack, 2004 Double-blind trial Substudy within larger trial POOR Funding: NIMH grant	Illness	NR/NR/107 enrolled Number per group NR	Total loss to f/u: 47% (MASC), 66% (WCST) Loss of efficacy: 36% Subject withdrawal 32% Adverse reactions 17% Number of withdrawals varied and crossover by test administered.
Bondolfi, 1998 Single-center Double-blind RCT FAIR Inpatients Funding: Janssen Research Foundation	Mean age at onset: 23 years Mean age at first hospitalization: 26 years Mean # hospitalizations 6.1 Mean # months in hospital: 36.6 100% inpatient Schizophrenia type: paranoid: 58% disorganized: 27.9% undiffereniated: 8.1% residual: 5.8%	NR/NR/86 clozapine: 43 risperidone: 43	18/0/86

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

Author, year Study design Quality	Results
Bellack, 2004 Double-blind trial Substudy within larger trial POOR Funding: NIMH grant	Symptoms: Change in CGI: risperidone: -1.42 (95%CI -1.93 to -0.99); clozapine: -1.48 (95%CI -2.11 to -0.99) Withdrawal 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).
Bondolfi, 1998 Single-center Double-blind RCT FAIR Inpatients Funding: Janssen Research Foundation	clozapine vs risperidone (p value) Proportion with 20% improvement: 67% vs 65% (p = 0.30) Mean Change at 8 weeks (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 Quality	Method of adverse effects assessment	Adverse effects reported
Bellack, 2004 Double-blind trial Substudy within larger trial POOR Funding: NIMH grant	NR	NR
Bondolfi, 1998 Single-center Double-blind RCT FAIR Inpatients Funding: Janssen Research Foundation	Patient self-report EPS symptoms (Extrapyramidal Symptom Rating Scale: ESRS): endpoint mean values and SDs not reported Other adverse events: UKU, mean endpoint data and SDs not reported	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 Quality	EPS	Total withdrawals; withdrawals due to adverse events	Comments
Bellack, 2004 Double-blind trial Substudy within larger trial POOR Funding: NIMH grant	NR	17% of withdrawals due to AE's but numbers per drug not clear	While some differences apparent between drugs on results for verbal score and problem solving, changes not considered clinical important by authors. Lack of ITT, low power, and poor reporting make result difficult to interpret or generalize.
Bondolfi, 1998 Single-center Double-blind RCT FAIR Inpatients Funding: Janssen Research Foundation	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 parkisonism scales" - data not reported 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 parkisonism score: 37% vs 61% (p = 0.03) % with 0 on ESRS dysotonia: 98% vs 95% (NS) % with 0 on ESRS dyskinesia: 84% vs 84% (NS)	Overall 18 (21%) Due to adverse events: 2.3% (2.3% in each group)	Differences at baseline: # months in hospital, PANSS positive; analyses presented focus on within group differences more than between group comarisons. Dose of clozapine low.

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

Author, year Study design Quality	Eligibility criteria	Interventions (drug, dose, duration)	Wash-out period
Breier, 1999 Single Center double-blind RCT (NIH Clinical Center) Unclear if Inpatient FAIR Funding: Eli Lilly	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 weeks of fluphenazine, 20 mg/day (range 10–30 mg/day)	clozapine: 200–600 mg/day; fixed dose mean 403.6 mg/day; risperidone: 2–9 mg/day; fixed dose mean 5.9 mg/day Duration: 6 weeks fluphenazine treatment for ≥ 2 weeks; then, 66% patients underwent drug-free period	Mean 18 days
Chowdhury, 1999 Funding: NR	Schizophrenia by ICD10, aged 15–60 years; duration of illness > 6 months 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 withdrawal 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 twice daily starting dose, then 2 mg twice daily from day 2 onwards. After week 1, 6 mg daily up to maximum 8 mg/d Duration:16 weeks Mean maximum daily dose, clozapine, 343 mg daily; risperidone, 5.8 mg	7 days

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

Author, year Study design Quality	Allowed other medications	Method of outcome assessment timing of assessment	Age Gender Ethnicity
Breier, 1999 Single Center double-blind RCT (NIH Clinical Center) Unclear if Inpatient FAIR Funding: Eli Lilly	benztropine mesylate (EPS) as required	Leaving study early Physiological monitoring (laboratory tests) Mental state (BPRS; SANS; Hamilton Rating Scale – depression)	Mean,age: 35.0 years, range 18–55 years 66% male Ethnicity NR
Chowdhury, 1999 Funding: NR	NR	PANSS scores total (positive, negative, general subscales) Treatment success rate (> 20% reduction from baseline on PANSS) total; positive; negative, general subscales	Mean age (SD): clozapine 30.3 (8.78) years risperidone 32.43 (9.79) years clozapine 73.3% male risperidone 76.7% male Ethnicity NR

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

Author, year Study design Quality	Other population characteristics	Number Screened/ Eligible/ Enrolled	Withdrawn/ Lost to fu/ Analyzed
Breier, 1999 Single Center double-blind RCT (NIH Clinical Center) Unclear if Inpatient FAIR Funding: Eli Lilly	History: duration of illness, about 12.5 years; chronic schizophrenia; partial response to neuroleptic drugs*	NR/NR/29	NR/NR/29
Chowdhury, 1999 Funding: NR	Paranoid subtype, clozapine 56.67%; risperidone 60%; Other subtypes included hebephrenia, residual and undifferentiated	NR/72/60 clozapine: 30 risperidone: 30	14/3/NR

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

Author, year Study design Quality	Results
Breier, 1999 Single Center double-blind RCT (NIH Clinical Center) Unclear if Inpatient FAIR Funding: Eli Lilly	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)
Chowdhury, 1999 Funding: NR	PANSS scores total (postive, 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 frombaseline 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 Quality	Method of adverse effects assessment	Adverse effects reported
Breier, 1999 Single Center double-blind RCT (NIH Clinical Center) Unclear if Inpatient FAIR Funding: Eli Lilly	SAR-S; neuroendocrine serum level montitoring	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, coristol: changes NS
Chowdhury, 1999 Funding: NR	NR	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 Quality	EPS	Total withdrawals; withdrawals due to adverse events	Comments
Breier, 1999 Single Center double-blind RCT (NIH Clinical Center) Unclear if Inpatient FAIR Funding: Eli Lilly		NR/NR	
Chowdhury, 1999 Funding: NR	NR	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 Quality	Eligibility criteria	Interventions (drug, dose, duration)	Wash-out period
Daniel, 1996 Crossover design POOR Funding: NR	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 weeks. Dose was held stable during weeks 5 & 6. mean clozapine dose: 375mg/d (range 75-800mg) mean risperidone dose: 6.1mg/d (range 1-10mg)	7 days

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

Author, year Study design Quality	Allowed other medications	Method of outcome assessment timing of assessment	Age Gender Ethnicity
Daniel, 1996 Crossover design POOR Funding: NR	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	Blinded rating of Symptoms by the PANSS, Severity of illness by the CGI severity subscale, Cognition by: IQ, Wechsler Memory Scale, Semantic Fluency, the Boston Naming test, Rey Figure, Facial Recognition, the Continuous Performance Test, and the Wisconsin Card Sorting Test. Tests completed weekly	Mean age 33.8 years (22-51) 35% male ethnicity NR

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

Author, year Study design Quality	Other population characteristics	Number Screened/ Eligible/ Enrolled	Withdrawn/ Lost to fu/ Analyzed
Daniel, 1996 Crossover design POOR Funding: 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	NR/NR/20 enrolled	3 withdrawn (during risperidone treatment): 1 due to adverse events, 1 due to adverse events and lack of effect, 1 withdrew after achieving satisfactory response, in order to obtain non-study drug 17 analyzed

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

Author, year Study design Quality	Results
Daniel, 1996 Crossover design POOR Funding: NR	No significant difference on PANSS total, positive or negative subscales, or CGI (data not reported). No significant differences on cognitive tests (after application of Bonferroni adjustment for multiple comparisons)

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

Author, year Study design Quality	Method of adverse effects assessment	Adverse effects reported
Daniel, 1996 Crossover design POOR Funding: NR	Adverse events assessed by a self-administered multiple choice questionnaire on the severity of side effects of each drug (none, mild, moderate, severe) with respect to: insomnia, sleepiness, loss of appetite, restlessness, lack of alertness, nausea, inability to think clearly, memory problems, and inability to concentrate. A score of 0 to 3 was assigned to each response.	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 not significantly different no dose correlation apparent

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

Author, year Study design Quality	EPS	Total withdrawals; withdrawals due to adverse events	Comments
Daniel, 1996 Crossover design POOR Funding: NR	7/17 (41%) required Anti-EPS meds while on risperidone 0 required Anti-EPS meds while on clozapine	Total: 3/20 (15%) Due to AE: 2/20 (10%)	Results not reported by first intervention/second intervention. Not possible to evaluate effect of order of assignment, although authors use Bonferroni adjustment to correct for this.

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

Author, year Study design Quality	Eligibility criteria	Interventions (drug, dose, duration)	Wash-out period
Klieser, 1991 Heinrich 1994 Klieser 1995 RCT, DB Inpatients Funding: NR	Patients diagnosed with acute, paranoid schizophrenia	28 day study risperidone(N=20): 4mg/day risperidone(N=19): 8mg/day clozapine(N=20): 400mg/day	≥ 3days

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

Author, year Study design Quality	Allowed other medications	Method of outcome assessment timing of assessment	Age Gender Ethnicity
Klieser, 1991 Heinrich 1994 Klieser 1995 RCT, DB Inpatients Funding: NR	Biperiden, short-acting lorazepam	Association for Methodology and Documentation in Psychiatry (AMDP somatic scale), Brief Psychiatric Rating Scale (BPRS), Clinical Global Impression (CGI), Electrocardiogram (ECG), Electroencephalogram (EEG), Extrapyramidal Scale (EPS), complete pyhsical examination, blood samples- taken at 3 days, then weekly. Brief Psychiatric Rating Scale (BPRS), Clinical Global Impression (CGI), Simpson and Angus Scale for extrapyramidal side effects (EPS), Association for Methodology and Documentation in Psychiatry (AMDP), reports of adverse events, clinical laboratory assessments, vital signs	Median age: 33 years 52.3% Male Ethnicity NR

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

Author, year Study design Quality	Other population characteristics	Number Screened/ Eligible/ Enrolled	Withdrawn/ Lost to fu/ Analyzed
Klieser, 1991 Heinrich 1994 Klieser 1995 RCT, DB Inpatients Funding: NR	100% inpatient with diagnosis of schizophrenia Schizophrenia Diagnosis: Disorganized: 1 Catatonic: 1 Paranoid: 46 Paranoid/residual: 1 Unspecified: 2 Schizoaffective psychosis: 8	NR/NR/59	31/3/28

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

Author, year Study design Quality	Results
Klieser, 1991 Heinrich 1994 Klieser 1995 RCT, DB Inpatients Funding: NR	Clinical Global Impression at Enpoint (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

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

Author, year Study design Quality	Method of adverse effects assessment	Adverse effects reported
Klieser, 1991 Heinrich 1994 Klieser 1995 RCT, DB Inpatients Funding: NR	Physical examination, patient self-report	28;7 Withdrawals due to adverse events: 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%

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

Author, year Study design Quality	EPS	Total withdrawals; withdrawals due to adverse events	Comments
Klieser, 1991	Simpson and Angus Rating Scale scores (SAS): Mean change	31; 7	
Heinrich 1994	from baseline		
Klieser 1995	Gait: R4: 0.2 vs R8: 0.4 vs C400: -0.1; p=NS		
RCT, DB	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		
Inpatients	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		
Funding: NR	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		

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

Author, year Study design Quality	Eligibility criteria	Interventions (drug, dose, duration)	Wash-out period
Lindenmayer, 1998, open-label Inpatients Funding: NR	Treatment-refactory schizophrenia	12 week study Mean dose: clozapine: 363.02 mg/day, risperidone: 8.95 mg/day	NR
Wahlbeck, 2000 Open-label RCT POOR Funding: Scandinavian Society for Psychopharmacology (SSP), Wilheim Stockmann Foundation, Finska Lakaresallaskapet	Diagnosis: schizophrenia (DSM-IV); Treatment-resistant: persistent psychotic symptoms for < 6 months while on medication from ≥ 2 different classes of antipsychotic drugs in doses ≥ 1000 mg/day chlorpromazine for > 6 weeks each; in addition, non-tolerance to haloperidol or non-response to haloperidol, > 40 mg/day	clozapine 400 mg/day for 2 weeks; flexible thereafter 600 mg/ day mean 385 mg/day risperidone, 6 mg/day for 3 days; flexible thereafter up to 10 mg/day mean 7.8 mg/day Duration: 10 weeks preceded by 6-week treatment with haloperidol, ≤ 50 mg/day if no history of previous treatment with haloperidol, > 40 mg/day, or haloperidol intolerance	1–3 days

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

Author, year Study design Quality	Allowed other medications	Method of outcome assessment timing of assessment	Age Gender Ethnicity
Lindenmayer, 1998, open-label Inpatients Funding: NR	Anticholinerics	Positive and Negative Syndrome Scale (PANSS), Clinical Global Impressions (CGI), neurologic rating scales, plasma drug levels, administered at baseline and endpoint	Mean age: 39.29 years 74.3% Male White: 25.7% African-American: 37.1% Hispanic: 37.1%
Wahlbeck, 2000 Open-label RCT POOR Funding: Scandinavian Society for Psychopharmacology (SSP), Wilheim Stockmann Foundation, Finska Lakaresallaskapet	biperiden (EPS) and lorazepam (anxiety) as required	Leaving study early, relapse, Mental state (PANSS, CGI, PGI, Social Functioning Scale), Global assessment (GAF), Satisfaction with treatment (DAI-10)	Mean age 35.9 years; range, 24–55 years 55% male Ethnicity NR

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

Author, year Study design Quality	Other population characteristics	Number Screened/ Eligible/ Enrolled	Withdrawn/ Lost to fu/ Analyzed
Lindenmayer, 1998, open-label Inpatients Funding: NR	100% inpatient Schizophrenia: Disorganized: 5.7% Paranoid: 40% Undifferentiated: 54.3%	NR/NR/35	3/0/32
Wahlbeck, 2000 Open-label RCT POOR Funding: Scandinavian Society for Psychopharmacology (SSP), Wilheim Stockmann Foundation, Finska Lakaresallaskapet	Duration of illness, ~ 12 years, range 0.5–33 years; treatment resistant* illness	9000/90/20	7/NR/19

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

Author, year Study design Quality	Results
Lindenmayer, 1998, open-label Inpatients Funding: NR	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
Wahlbeck, 2000 Open-label RCT POOR Funding: Scandinavian Society for Psychopharmacology (SSP), Wilheim Stockmann Foundation, Finska Lakaresallaskapet	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 Quality	Method of adverse effects assessment	Adverse effects reported
Lindenmayer, 1998, open-label Inpatients Funding: NR	NR	Seizure: 1, leukopenia: 2, hypertension: 1, tachycardia: 1
Wahlbeck, 2000 Open-label RCT POOR Funding: Scandinavian Society for Psychopharmacology (SSP), Wilheim Stockmann Foundation, Finska Lakaresallaskapet	EPS symptoms (non-structured assessment)	NR

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

Author, year Study design Quality	EPS	Total withdrawals; withdrawals due to adverse events	Comments
Lindenmayer, 1998, open-label Inpatients Funding: NR	NR	NR; 5	
Wahlbeck, 2000 Open-label RCT POOR Funding: Scandinavian Society for Psychopharmacology (SSP), Wilheim Stockmann Foundation, Finska Lakaresallaskapet	NR	Overall: 6/20 ((30%) Due to AE: 3 (15%) 11% risperidone 18% clozapine	Pilot study

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

Author, year Study design Quality	Eligibility criteria	Interventions (drug, dose, duration)	Wash-out period
Olanzapine vs risperidone			
Conley, 2001 Funding: Janssen Pharmaceutica, L.P.	Schizophrenia or Schizoaffective disorder by DSM-IV diagnosis, baseline PANSS score, 60–120, aged 18–64 years; out- or inpatients hospitalized ≤4 weeks	risperidone 2–6 mg/d (flexible dose); oral olanzapine 5–20 mg/d; oral Duration: 8 weeks Both drugs given once daily according to following regimens: days 1–2, 2 mg risperidone or 10 mg olanzapine; days 3–7, 2–4 mg risperidone or 5–10 mg olanzapine; days 8–14, 2–6 mg risperidone or 5–15 mg olanzapine; days 15–56, 2–6mg risperidone or 5–20 mg olanzapine	1 week gradual dis-continuation

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

Author, year Study design Quality	Allowed other medications	Method of outcome assessment timing of assessment	Age Gender Ethnicity
Olanzapine vs risperidone			
Conley, 2001 Funding: Janssen Pharmaceutica, L.P.	NR	Change scores: PANSS total; PANSS positive; PANSS negative; PANSS disorganized thoughts; PANSS uncontrolled hostility; PANSS anxiety/depression Response: ≥20% reduction in PANSS; 40% reduction in PANSS; CGI-I much or very much improved CGI-S Change scores: ESRS total, questionnaire, parkinsonism, akathisia, and dyskinesia	Mean age: risperidone 41.0 (11.0) years olanzapine 38.9 (10.5) years 72.7% male Ethnicity NR

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

Author, year Study design Quality	Other population characteristics	Number Screened/ Eligible/ Enrolled	Withdrawn/ Lost to fu/ Analyzed
Olanzapine vs risperidone			
Conley, 2001	79% were outpatients	NR/NR/377 risperidone 188 olanzapine 189	risperidone 53/NR/188 olanzapine 43/NR/189
Funding: Janssen Pharmaceutica, L.P.	Schizophrenia (n= 325) or schizoaffective disorder (n= 52) Duration of illness: mean risperidone 16.5 (10.5) years, olanzapine 15.4 (10.6) years		

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

Author, year Study design Quality	Results
Olanzapine vs risperidone	
Conley, 2001 Funding: Janssen Pharmaceutica, L.P.	Change scores: PANSS total; PANSS positive; PANSS negative; PANSS disorganised 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/verymild/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)

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

Author, year Study design Quality	Method of adverse effects assessment	Adverse effects reported
Olanzapine vs risperidone		
Conley, 2001 Funding: Janssen Pharmaceutica, L.P.	Change scores: ESRS total, questionnaire, parkinsonism, akathisia, and dyskinesia	All risperidone versus olanzapine Serious adverse events: 15/188 versus 22/189; psychosis: 8/188 versus 8/189; suicide attempt: 2/188 versus 5/189; agitation: 3/188 versus 3/189; depression: 3/188 versus 3/189; insomnia: 3/188 versus 2/189; hallucinations: 2 versus 3; drug abuse: 0 versus 3; cardiovascular symptoms: 0 versus 3; gastrointestinal disorders: 0 versus 3; other: 14 versus 21 Weight gain: 3.4 lb (SD 7.8) versus 7.2 lb (SD 11.2); increase in body weight of 7%: 18/155 versus 44/161 Less serious adverse events: somnolence: 69/188 versus 73/189; insomnia: 45 versus 35; headache: 41 versus 32; agitation: 29 versus 40; dry mouth: 21 versus 42; rhinitis: 30 versus 31; dizziness: 26 versus 27; anxiety: 20 versus 23; vision abnormalities: 12 versus 19

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

Author, year Study design Quality	EPS	Total withdrawals; withdrawals due to adverse events	Comments
Olanzapine vs risperidone			
Conley, 2001 Funding: Janssen Pharmaceutica, L.P.	Extrapyramidal symptoms: 45/188 versus 38/189. Patients using antiparkinsonian medication: 61/188 versus 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)	Risperidone 53/188 (28.2%) Due to AE 22/188 (11.7%) Olanzapine 43/189 (22.8%) Due to AE 17/189 (8.99%)	

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

Author, year Study design Quality	Eligibility criteria	Interventions (drug, dose, duration)	Wash-out period
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** FAIR Funding: Eli Lilly	Subset of Tran - patients aged 50 to 65 years.	olanzapine 10-20mg/d risperidone 4-8mg/d Duration: 28 weeks mean dose for subset NR	NR
Garyfallos, 2003 Funding: NR	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/day (range: 10-20 mg/d) risperidone: 7.7 mg/day (range: 6-12 mg/d) 8-week study	No antipsychotics 1 month prior to hospitalization

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

Author, year Study design Quality	Allowed other medications	Method of outcome assessment timing of assessment	Age Gender Ethnicity
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** FAIR Funding: Eli Lilly	NR	PANSS total, positive, negative and general psychopathology subscale scores SANS composite and summary subscale scores CGI-S	Mean age: 57 92.3% white 56.4% male
Garyfallos, 2003 Funding: NR	Anticholergenic and lorazepam allowed if clinically indicated	PANSS evaluated at baseline and week 8	Mean age: NR 68% male Ethnicity: NR

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

Author, year Study design Quality	Other population characteristics	Number Screened/ Eligible/ Enrolled	Withdrawn/ Lost to fu/ Analyzed
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** FAIR Funding: Eli Lilly	82% schizophrenia diagnosis 64% had prominent negative symptoms mean # prior episodes: 10	NR/NR/39 19 olanzapine 20 risperidone	20/NR/39
Garyfallos, 2003 Funding: NR	NR	NR/NR/50	0/0/50

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

Author, year Study design Quality	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** FAIR Funding: Eli Lilly	At 8 weeks: 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 weeks: 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)
Garyfallos, 2003 Funding: NR	Mean change in PANSS totals score at endpoint: olanzapine: -26 vs risperidone: -32.7

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

Author, year Study design Quality	Method of adverse effects assessment	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** FAIR Funding: Eli Lilly	See Tran 1997	% 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
Garyfallos, 2003 Funding: NR	Weight, BMI, triglycerides, and total cholesterol were measured at both baseline and week 8	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 Cholestrol: +10.2 (23.1) vs + 0.7 (16.4) , p=NS

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

Author, year Study design Quality	EPS	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** FAIR Funding: Eli Lilly	EPS: For measures of EPS, data for only 12 olanzapine and 9 risperidone available AIMS, BAS, and SAS NS difference, small changes	Overall 20 6 due to adverse events	Small N; power for statistical differences lacking. Length of current episode: 120 days for risperidone patients, 61 days for olanzapine patients, but NS difference olanzapine: 70% male; risperidone: 42% male
Garyfallos, 2003 Funding: NR	NR	NR; NR	

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

Author, year Study design Quality	Eligibility criteria	Interventions (drug, dose, duration)	Wash-out period
Guerje, 1998 Thomas, 1998 Funding: Eli Lilly	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 weeks	No longer than 9 days
Harvey, 2003a (Harvey, 2002a, Harvey, 2002b, Harvey, 2002c all = Sub-analysis of Jeste, 2003) RCT Multi-site; US, Austria, Israel, Norway, Poland and The Netherlands FAIR Funding: Pfizer, Inc	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-weeks	1-week washout

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

Author, year Study design Quality	Allowed other medications	Method of outcome assessment timing of assessment	Age Gender Ethnicity
Guerje, 1998 Thomas, 1998 Funding: Eli Lilly	NR	BPRS total score at week 22 through 30 Reduction of ≥ 20% PANSS total score at week 30 SF-36 and disease-specific Quality of Life in Schizophrenia scale at week 30	Mean age 35 - 36 58% male 89% Caucasian
Harvey, 2003a (Harvey, 2002a, Harvey, 2002b, Harvey, 2002c all = Sub-analysis of Jeste, 2003) RCT Multi-site; US, Austria, Israel, Norway, Poland and The Netherlands FAIR Funding: Pfizer, Inc	unclear	Attention: Continuous Performance Test (CPT), Trail Making Test Part A (TMT) Memory: Serial Verbal Learning Test (SVLT) Executive Function: WCST, TMT part B Verbal fluency: category and phonologic fluency tests Measured at baseline, 4 and 8 wks, or at early termination Tests translated into local language PANSS weekly HAM-D, BQoL, and MMSE at baseline and endpoint	Mean age 71 36% male 60% white

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

Author, year Study design Quality	Other population characteristics	Number Screened/ Eligible/ Enrolled	Withdrawn/ Lost to fu/ Analyzed
Guerje, 1998 Thomas, 1998 Funding: Eli Lilly	Duration of Hospitalization prior 12 months: means 12 to 19 days Baseline PANSS means 89 to 95 Baseline BPRS: means 32 to 35	NR/NR/65 olanzapine = 21 risperidone = 21 haloperidol = 23	36/0/62
Harvey, 2003a (Harvey, 2002a, Harvey, 2002b, Harvey, 2002c all = Sub-analysis of Jeste, 2003) RCT Multi-site; US, Austria, Israel, Norway, Poland and The Netherlands FAIR Funding: Pfizer, Inc	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	NR/NR/176 79 olanzapine 74 risperidone	67/NR/153 55 olanzapine 54 risperidone

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

Author, year Study design Quality	Results
Guerje, 1998 Thomas, 1998 Funding: Eli Lilly	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 quality of life (SF-36 and disease-specific Quality of Life in Schizophrenia scale)
Harvey, 2003a (Harvey, 2002a, Harvey, 2002b, Harvey, 2002c all = Sub-analysis of Jeste, 2003) RCT Multi-site; US, Austria, Israel, Norway, Poland and The Netherlands FAIR Funding: Pfizer, Inc	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

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

Author, year Study design Quality	Method of adverse effects assessment	Adverse effects reported
Guerje, 1998 Thomas, 1998 Funding: Eli Lilly	Spontaneous reporting and BAS and SAS scales for EPS.	Trend for olanzapine-treated patients to evidence fewer treatment-emergent adverse effects
Harvey, 2003a (Harvey, 2002a, Harvey, 2002b, Harvey, 2002c all = Sub-analysis of Jeste, 2003) RCT Multi-site; US, Austria, Israel, Norway, Poland and The Netherlands FAIR Funding: Pfizer, Inc	ESRS at baseline and endpoint (wk 8)	NR

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

Author, year Study design Quality	EPS	Total withdrawals; withdrawals due to adverse events	Comments
Guerje, 1998 Thomas, 1998 Funding: Eli Lilly	No differences found by rating scales or spontaneously reported adverse events.	36/NR	3 risperidone patients withdrawn due to "sponsor decision"
Harvey, 2003a (Harvey, 2002a, Harvey, 2002b, Harvey, 2002c all = Sub-analysis of Jeste, 2003) RCT Multi-site; US, Austria, Israel, Norway, Poland and The Netherlands FAIR Funding: Pfizer, Inc	NR	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.

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

Author, year Study design Quality	Eligibility criteria	Interventions (drug, dose, duration)	Wash-out period
Harvey, 2003b (Harvey, 2002a,b,c & Harvey, 2003a all = Sub-group analysis of Conley, 2001) RCT Multicenter, US FAIR Funding: Pfizer, Inc	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 once daily dosing titration unclear Duration: 8 weeks	1 week

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

Author, year Study design Quality	Allowed other medications	Method of outcome assessment timing of assessment	Age Gender Ethnicity
Harvey, 2003b (Harvey, 2002a,b,c & Harvey, 2003a all = Sub-group analysis of Conley, 2001) RCT Multicenter, US FAIR Funding: Pfizer, Inc	not specified	PANSS scores at wks 0, 2, 4, 6 and 8 Cognitive tests: California Verbal learning Continuous performance test Spatial working memory Verbal fluency exam Trail-making test - parts A and B Wisconsin card-scoring test Given at baseline and 8 wks Because tests have multiple dependent measures, only parts of each test were collected at the sites and forwarded for analysis. Variables analyzed were selected by a consensus of "experts in neuropsychology and clinical trials"	Mean age 40 73% male Ethnicity NR

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

Author, year Study design Quality	Other population characteristics	Number Screened/ Eligible/ Enrolled	Withdrawn/ Lost to fu/ Analyzed
Harvey, 2003b (Harvey, 2002a,b,c & Harvey, 2003a all = Sub-group analysis of Conley, 2001) RCT Multicenter, US FAIR Funding: Pfizer, Inc	Mean # prior hospitalizations: 6.3 Mean Total PANSS score: 81	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 timepoint (range 258-363)

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

Author, year Study design Quality	Results
Harvey, 2003b (Harvey, 2002a,b,c & Harvey, 2003a all = Sub-group analysis of Conley, 2001) RCT Multicenter, US FAIR Funding: Pfizer, Inc	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 Bonferonni adjustment. Stratification by improvements of 0.5 or 1.0 SD : NS difference btwn 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 Quality	Method of adverse effects assessment	Adverse effects reported
Harvey, 2003b (Harvey, 2002a,b,c & Harvey, 2003a all = Sub-group analysis of Conley, 2001) RCT Multicenter, US FAIR Funding: Pfizer, Inc	ESRS at wks 0, 2, 4, 6 and 8	NR

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

Author, year Study design Quality	EPS	Total withdrawals; withdrawals due to adverse events	Comments
Harvey, 2003b (Harvey, 2002a,b,c & Harvey, 2003a all = Sub-group analysis of Conley, 2001) RCT Multicenter, US FAIR Funding: Pfizer, Inc	NR - check anticholinergic med use?	96 ((25%) 39 (10.3% of total N) due to adverse events	Analysis of correlations of baseline scores on individual tests to significant change in test showed some significant findings. Mean doses not reported

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

Author, year Study design Quality	Eligibility criteria	Interventions (drug, dose, duration)	Wash-out period
Jerrel, 2002 Open-label RCT with economic analysis FAIR Funding: South Carolina Department of Mental Health	Medicaid patients age 18-54, with schizophrenia or schizoaffective disorder and >/= 2 acute psychiatric hospitalizations within 12 months, and noncompliant with outpatient treatment and not taking atypical antipsychotics for 6-8 weeks or more during the prior 3 months. 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 months	Acute treatment prior to randomization using short-acting typical antipsychotics. Discontinuation and titration determined by treating physician

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

Author, year Study design Quality	Allowed other medications	Method of outcome assessment timing of assessment	Age Gender Ethnicity
Jerrel, 2002 Open-label RCT with economic analysis FAIR Funding: South Carolina Department of Mental Health	Discretion of treating physician	PANSS, BPRS, DIS-III-R depression and Mania Modules, RFS, SAS-SM, DISCUS, CUAD, CSQ-8, S-A EPS, BAS every 3 months Prescribing of study and other allowed drugs, refills, and other compliance indicators were abstracted from medical records. Service utilization: number and duration of hospitalizations, outpatient service use per 3-month follow-up period	Mean age 36.91 68% male 29% white

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

Author, year Study design Quality	Other population characteristics	Number Screened/ Eligible/ Enrolled	Withdrawn/ Lost to fu/ Analyzed
Jerrel, 2002 Open-label RCT with economic analysis FAIR Funding: South Carolina Department of Mental Health	72% schizophrenic Mean prior inpatient admits: 9.75 Acute hospitalization days in past 6 mos: 12.56 Atypical antipsychotic use: 29% Supplemental antipsychotic use: 17% Anti-EPS med use: 72% Taking mood stabilizer: 49%	NR/343/343 Final group of 108: olanzapine 30 risperidone 36 Typicals 42	235/none reported/108 Patients or physician could withdraw patient after randomization but prior to receiving medication. 74 patients refused 146 physicians refused to have patients enrolled

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

Author, year Study design Quality	Results
Jerrel, 2002 Open-label RCT with economic analysis FAIR Funding: South Carolina Department of Mental Health	**Treatments Received:Logistic regression analysis:** Prescribed assigned med sgnifcantly decraased 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 Funciton:** 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 months (p<0.03)

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

Author, year Study design Quality	Method of adverse effects assessment	Adverse effects reported
Jerrel, 2002 Open-label RCT with economic analysis FAIR Funding: South Carolina Department of Mental Health	Use of Anti-EPS drugs, DISCUS, S-A EPS, GBAS	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 mths (p =0.0007) S-A EPS SS time effect; lower scores from baseline to 12 mths (p<0.0001) GBAS: SS decrease in ratings baseline to 12 mths (p=0.002)

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

Author, year Study design Quality	EPS	Total withdrawals; withdrawals due to adverse events	Comments
Jerrel, 2002 Open-label RCT with economic analysis FAIR Funding: South Carolina Department of Mental Health	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 mths (p =0.0007) S-A EPS SS time effect; lower scores from baseline to 12 mths (p<0.0001) GBAS: SS decrease in ratings baseline to 12 mths (p=0.002)	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.

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

Author, year Study design Quality	Eligibility criteria	Interventions (drug, dose, duration)	Wash-out period
Jeste, 2003 Jeste, 2002 Jeste, 2001 RCT Multinational (US, Israel, Poland, Norway, The Netherlands, Austria) 1 full paper 2 conf proc FAIR Funding: Janssen Research Foundation	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-weeks	1 week washout period
Purdon, 2000 David 1999 Jones 1998 Multicenter, Canada Double-blind RCT FAIR Funding: AstraZeneca, Canada	Schizophrenia; 'early phase'– first 5 years of illness, PANSS < 90	olanzapine: 5–20 mg/day; risperidone: 4–10 mg/day; haloperidol: 5–20 mg/day; Duration: 54 weeks;	1 week

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

Author, year Study design Quality	Allowed other medications	Method of outcome assessment timing of assessment	Age Gender Ethnicity
Jeste, 2003 Jeste, 2002 Jeste, 2001 RCT Multinational (US, Israel, Poland, Norway, The Netherlands, Austria) 1 full paper 2 conf proc FAIR Funding: Janssen Research Foundation	lorazepam	Change from baseline PANSS total score Clinical Improvement defined as 20% decrease in total PANSS Secondary measures: HAM-D, CGI-s and CGI change Cognitive assessments (see Harvey 2003) Assessed at weeks 0, 1, 2, 3, 4, 6, 8	Mean age: 71.1 35% male 77% white 17% black 3% Hispanic 2% Asian
Purdon, 2000 David 1999 Jones 1998 Multicenter, Canada Double-blind RCT FAIR Funding: AstraZeneca, Canada	No other antipsychotics, but other meds allowed as needed	Leaving study early; Mental state: PANSS, Cognitive function: GCIS, neuropsychological test battery, QOL: QLS, SF-36, and resource utilization Symptoms assessed weekly x 6 weeks, then monthly Cognitive assessments at baseline, 6, 30 and 54 weeks	Mean age: 29 years 71% male Ethnicity NR

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

Author, year Study design Quality	Other population characteristics	Number Screened/ Eligible/ Enrolled	Withdrawn/ Lost to fu/ Analyzed
Jeste, 2003 Jeste, 2002 Jeste, 2001 RCT Multinational (US, Israel, Poland, Norway, The Netherlands, Austria) 1 full paper 2 conf proc FAIR Funding: Janssen Research Foundation	85% schizophrenia 15% schizoaffective disorder mean baseline PANSS score: 77.1	203/176/175	41/1/174
Purdon, 2000 David 1999 Jones 1998 Multicenter, Canada Double-blind RCT FAIR Funding: AstraZeneca, Canada	Mean duration of disease 2.63 PANSS total: NR	NR/NR/65 olanzapine = 21 risperidone = 21 haloperidol = 23	37/NR/65 for symptoms, 55 for neurocognitive outcomes

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

Author, year Study design Quality	Results
Jeste, 2003 Jeste, 2002 Jeste, 2001 RCT Multinational (US, Israel, Poland, Norway, The Netherlands, Austria) 1 full paper 2 conf proc FAIR Funding: Janssen Research Foundation	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.
Purdon, 2000 David 1999 Jones 1998 Multicenter, Canada Double-blind RCT FAIR Funding: AstraZeneca, Canada	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

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

Author, year Study design Quality	Method of adverse effects assessment	Adverse effects reported
Jeste, 2003 Jeste, 2002 Jeste, 2001 RCT Multinational (US, Israel, Poland, Norway, The Netherlands, Austria) 1 full paper 2 conf proc FAIR Funding: Janssen Research Foundation	Elicited by investigator ESRS EPS medications Weight	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)
Purdon, 2000 David 1999 Jones 1998 Multicenter, Canada Double-blind RCT FAIR Funding: AstraZeneca, Canada	EPS: ESRS, Barnes Akathisia scale, Anti-EPS medications	ESRS: olanzapine/risperidone (p-value) Total score NR Parkisonism: -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%)

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

Author, year Study design Quality	EPS	Total withdrawals; withdrawals due to adverse events	Comments
Jeste, 2003 Jeste, 2002 Jeste, 2001 RCT Multinational (US, Israel, Poland, Norway, The Netherlands, Austria) 1 full paper 2 conf proc FAIR Funding: Janssen Research Foundation	EPS 9.8% vs 15.9% (ns) 7% Weight gain 5.1% vs 14.8% (p=0.04	Total: 41/175 (23%) Due to AE: 5.7% risperidone, 5.7% olanzapine	
Purdon, 2000 David 1999 Jones 1998 Multicenter, Canada Double-blind RCT FAIR Funding: AstraZeneca, Canada	ESRS: olanzapine/risperidone (p-value) Total score NR Parkisonism: -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%)	Overall 37 (57%) olanzapine: 43% risperidone: 67% haloperidol 61% Due to adverse events: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 weeks (immediate recall).

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

Author, year Study design Quality	Eligibility criteria	Interventions (drug, dose, duration)	Wash-out period
Ritchie, 2003 Pragmatic RCT Multicenter, Australia POOR Funding: Eli Lilly	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 days for those previously on oral neuroleptics, and "dose cycle: for depot drugs	4 weeks, while assigned drug titrated up. Depot drugs stopped on day 0, while assigned drug started
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 FAIR Funding: Eli Lilly	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 weeks	Washout: 2–9 days

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

Author, year Study design Quality	Allowed other medications	Method of outcome assessment timing of assessment	Age Gender Ethnicity
Ritchie, 2003 Pragmatic RCT Multicenter, Australia POOR Funding: Eli Lilly	NR	BPRS, SANS, MADRS, MMSE, WHO-QOL(BREF) Assessed at baseline and each visit Initial switch phase followed by 6-month and 1-year (not complete at this publication) follow-up, but timing of assessments not clear	Mean age 70 19% male Ethnicity 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 FAIR Funding: Eli Lilly	benzodiazepines (limited use for agitation), chloral hydrate, diperiden or benztropine (up to 6mg/d) for treatment of EPS only	PANSS (total, positive, negative, general psychopathology and depression) Heinrichs-Carpenter QOL Scale Measured weekly x 8 wks, then every 4 wks	Mean age 36 65% male 75% white

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

Author, year Study design Quality	Other population characteristics	Number Screened/ Eligible/ Enrolled	Withdrawn/ Lost to fu/ Analyzed
Ritchie, 2003 Pragmatic RCT Multicenter, Australia POOR Funding: Eli Lilly	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	80/74/66 olanzapine: 34 risperidone: 32	14/0/61
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 FAIR Funding: Eli Lilly	82% diagnosis = schizophrenia mean length of current episode: 154 days 80% had <4 prior episodes Prominent negative symptoms: 80%	NR/NR/339	161/11/339

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

Author, year Study design Quality	Results
Ritchie, 2003 Pragmatic RCT Multicenter, Australia POOR Funding: Eli Lilly	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 days risperidone 40.4 days Symptoms: NS difference btwn 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)
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 FAIR Funding: Eli Lilly	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 not reported) 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 RvsO 8.55 (95% CI 2.99 to 24.47)

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

Author, year Study design Quality	Method of adverse effects assessment	Adverse effects reported
Ritchie, 2003 Pragmatic RCT Multicenter, Australia POOR Funding: Eli Lilly	EPS: SAS, AIMS, BARS Other: "standard reporting of adverse events, weight changes, and a study-specific proformas was used for assessing side effects associated with elevated prolactin and cholinergic antagonism"	EPS SAS and BARS: SS change from baseline (reduction) in both groups NS difference btwn groups AIMS: SS change from baseline in olanzapine group, not in risperidone group; NS difference btwn 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)
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 FAIR Funding: Eli Lilly	See Tran 1997	See Tran 1997

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

Author, year Study design Quality	EPS	Total withdrawals; withdrawals due to adverse events	Comments
Ritchie, 2003 Pragmatic RCT Multicenter, Australia POOR Funding: Eli Lilly	EPS SAS and BARS: SS change from baseline (reduction) in both groups NS difference btwn groups AIMS: SS change from baseline in olanzapine group, not in risperidone group; NS difference btwn groups	Overall 14 (21%) Due to adverse events: 3 (in risperidone arm = 9%)	Not ITT Only switch data presented, 6-month and 1 year follow-up data to come.
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 FAIR Funding: Eli Lilly	NR	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 Quality	Eligibility criteria	Interventions (drug, dose, duration)	Wash-out period
Tran, 1997 Edgell, 2000 Funding: Eli Lilly	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/day; risperidone, 4–12 mg/	Washout: 2–9 days

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

Author, year Study design Quality	Allowed other medications	Method of outcome assessment timing of assessment	Age Gender Ethnicity
Tran, 1997 Edgell, 2000 Funding: Eli Lilly	benzodiazepines (limited use for agitation), chloral hydrate, diperiden or benztropine (up to 6mg/d) for treatment of EPS only	PANSS total (primary) and positive, negative, general psychopathology and depression item; the 18-item BPRS total extracted from the PANSS; the Clinical Global Impressions-Severity of Illness Scale (CGI-S); Scale for the Assessment of Negative Symptoms (SANS); quality of life was assessed with the Quality of Life Scale Timing: weekly during the first 8 weeks of double-blind therapy and every 4 weeks thereafter	Mean age=36.21 64.9% male 74.6% white

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

Author, year Study design Quality	Other population characteristics	Number Screened/ Eligible/ Enrolled	Withdrawn/ Lost to fu/ Analyzed
Tran, 1997 Edgell, 2000 Funding: Eli Lilly	81.7% diagnosis of schizophrenia 55.5% paranoid subtype Course of illness 39.8% continuous 34.5% episodic with interepisode residual symptoms Age of onset of illness: 23.7 years Length of patients' current episodes: 153.8 days 80.4% had less than 10 previous episodes before entry into the study 41.9% were inpatients	NR/NR/339 olanzapine 172 risperidone 167	Withdrawn=161 (47.5%)/Lost to fu=11 (3.2%)/analyzed=331 olanzapine 166 risperidone 165

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

Author, year Study design Quality	Results
Tran, 1997 Edgell, 2000 Funding: Eli Lilly	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 Quality of Life 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 Quality	Method of adverse effects assessment	Adverse effects reported
Tran, 1997 Edgell, 2000 Funding: Eli Lilly	Adverse events were detected by clinical evaluation and spontaneous report at each visit and mapped, classified, and recorded using a system based on the U.S. Food and Drug Administration Coding Symptoms and Thesaurus for Adverse Reaction Terms (CPSTART). In addition, adverse events were solicited by the investigative site using the 40-item Association for Methodology and Documentation in Psychiatry (AMDP-5) adverse event questionnaire. EPS, akathisia and dyskinesia were further assessed with the SAS, BAS, AIMS	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 (days/month): 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 adverse events (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 Quality	EPS	Total withdrawals; withdrawals due to adverse events	Comments
Tran, 1997 Edgell, 2000 Funding: Eli Lilly	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	olanzapine, risperidone, p-value Withdrawals: 73 (42.4%), 88 (52.7%), NS Withdrawals due to adverse events: 17 (9.9%), 17 (10.2%), NS	

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

Author, year Study design Quality	Eligibility criteria	Interventions (drug, dose, duration)	Wash-out period
van Bruggen, 2003 Inpatients Funding: Dutch Health Research and Development Council and Eli Lilly	Adolescents/young adults aged 16-28, first or second psychotic episode, schizophrenia, schizofreniform, schizoaffective disorder	6-10 week study Median doses: olanzapine: 15 mg/day, risperidone: 4 mg/day	NR

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

Author, year Study design Quality	Allowed other medications	Method of outcome assessment timing of assessment	Age Gender Ethnicity
van Bruggen, 2003 Inpatients Funding: Dutch Health Research and Development Council and Eli Lilly	Antidepressants, benzodiazepines, mood stabilizers, anticholinergics	PANSS	Mean age: 21 Years 79% Male Ethnicity NR

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

Author, year Study design Quality	Other population characteristics	Number Screened/ Eligible/ Enrolled	Withdrawn/ Lost to fu/ Analyzed
van Bruggen, 2003	Adolescents/young adults aged 16-28	NR/NR/44	NR/NR/31
Inpatients			
Funding: Dutch Health Research and Development Council and Eli Lilly			

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

Author, year Study design Quality	Results
van Bruggen, 2003 Inpatients Funding: Dutch Health Research and Development Council and Eli Lilly	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%

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

Author, year Study design Quality	Method of adverse effects assessment	Adverse effects reported
van Bruggen, 2003 Inpatients Funding: Dutch Health Research and Development Council and Eli Lilly	Barnes Akathisia Scale (BAS), Simpson-Angus Scale (SAS), Abnormal Involuntary Movement Scale (AIMS), 40-item Associatin for Methodology and Documentation in Psychiatry (AMDP-5)	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% Menstral 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%

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

Author, year Study design Quality	EPS	Total withdrawals; withdrawals due to adverse events	Comments
van Bruggen, 2003 Inpatients Funding: Dutch Health Research and Development Council and Eli Lilly	Parkinsonism: O: 3% vs R: 3%	NR/NR	

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

Author, year Study design Quality	Eligibility criteria	Interventions (drug, dose, duration)	Wash-out period
Mori, 2004 Inpatients Funding: NR	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 <u>Final Doses:</u> olanzapine (N=20): 16.5 mg/day perospirone (N=18) 37.3 mg/day quetiapine (N=4): 432.5 mg/day risperidone (N=19): 7.37 mg/day 4 weeks duration	NR

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

Author, year Study design Quality	Allowed other medications	Method of outcome assessment timing of assessment	Age Gender Ethnicity
Mori, 2004 Inpatients Funding: NR	NR	Digit Span Distractibility Test (DSDT)	Mean age: 59.9 years 50.6% Male

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

Author, year Study design Quality	Other population characteristics	Number Screened/ Eligible/ Enrolled	Withdrawn/ Lost to fu/ Analyzed
Mori, 2004 Inpatients Funding: NR	Schizophrenia Diagnoses: Disorganized: 23(29.8%) Paranoid: 10(12.9%) Undifferentiated: 34(44.1%)	NR/NR	NR/NR/77

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

Author, year Study design Quality	Results
Mori, 2004 Inpatients Funding: NR	Changes in percentages of correct responses in neutral DSDT tests: Mean at baseline vs Mean after switching antipsychotics vs Mean after withdrawal 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 withdrawal 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 withdrawal 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 withdrawal 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

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

Author, year Study design Quality	Method of adverse effects assessment	Adverse effects reported
Mori, 2004 Inpatients Funding: NR	NR	NR

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

Author, year Study design Quality	EPS	Total withdrawals; withdrawals due to adverse events	Comments
Mori, 2004	NR	NR	
Inpatients			
Funding: NR			

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

Author, year Study design Quality	Eligibility criteria	Interventions (drug, dose, duration)	Wash-out period
Yamashita, 2004 Inpatients Funding: NR	Schizophrenia	olanzapine: 2.5-20.0 mg/day perospirione: 4.0-48.0 mg/day quetiapine: 50.0-750.0 mg/day risperidone: 1.0-12.0 mg/day	4 weeks

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

Author, year Study design Quality	Allowed other medications	Method of outcome assessment timing of assessment	Age Gender Ethnicity
Yamashita, 2004 Inpatients Funding: NR	NR	Pittsburgh Sleep Quality Index (PSQI), Positive and Negative Syndrome Scale (PANSS)	Mean age: 59.9 years 52.1% Male Ethnicity NR

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

Author, year Study design Quality	Other population characteristics	Number Screened/ Eligible/ Enrolled	Withdrawn/ Lost to fu/ Analyzed
Yamashita, 2004 Inpatients Funding: NR	100% In-patient Schizophrenia Diagnoses: Disorganized: 29(31.5%) Paranoid: 11(11.9%) Undifferentiated: 52(56.5%)	NR/92	NR

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

Author, year Study design Quality	Results
Yamashita, 2004	PSQI Results:
	Change in Score After Switched From Typical to Atypical
Inpatients	Olanzapine vs Perospirone vs Quetiapine vs Risperidone
	Sleep quality: -.050 vs 0.2 vs -0.33 vs -0.35; P=.063
Funding: NR	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
	Daytime 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 Quality	Method of adverse effects assessment	Adverse effects reported
Yamashita, 2004 Inpatients Funding: NR	Patient self-report	NR

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

Author, year Study design Quality	EPS	Total withdrawals; withdrawals due to adverse events	Comments
Yamashita, 2004 Inpatients Funding: NR	NR	NR	

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

Author, year Study design Quality	Eligibility criteria	Interventions (drug, dose, duration)	Wash-out period
Olanzapine vs Ziprasidone			
Harvey 2004 Harvey, 2002d (abstract) Harvey, 2002e (abstract) RCT, multicenter cognition study Study patients remained inpatients during weeks 3-6 unless the met all protocol criteria for hospital discharge Funding: Pfizer, Inc	Patients with a primary diagnosis of schizophrenia or schizoaffective disorder (any subtype, chronic or subchronic) as defined by DSM-IV between 18-55y who had persistent psychotic symptoms for the week prior to hospital admission. Females were required not to be of child-bearing potential. Patients must have been hospitalized no more than 2 consecutive weeks immediately before screening and, if discharged per protocol, must have been in an outpatient environment that assured continued safety and contact with the treatment team the remainder of the study. At screening, pts had to have ≥4 on CGI-S and ≥4 on at least oneof the following PANSS: delusions, conceptual disorganization, or hallucinatory behavior. At baseline patients were required to have a score ≥4 on the GCI-S and ≥3 on the CGI-I compared with screening scores and to meet the PANSS scores described for screening.	Week 1: fixed dosages Ziprazadone: 40mg bid days 1&2; 80mg bid days 3-7 Olanzapine: 5mg qd days 1&2; 10mg days 3-7 Weeks 2-6: flexible dosing Ziprazadone 40, 60, or 80 mg bid; Olanzapine 5, 10, 15, qd Duration 6 wks	1 day of washout in which all psychotropic medications were discontinued

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

Author, year Study design Quality	Allowed other medications	Method of outcome assessment timing of assessment	Age Gender Ethnicity
Olanzapine vs Ziprasidone			
Harvey 2004 Harvey, 2002d (abstract) Harvey, 2002e (abstract) RCT, multicenter cognition study Study patients remained inpatients during weeks 3-6 unless the met all protocol criteria for hospital discharge Funding: Pfizer, Inc	During inpatient treatment, lorazepam allowed for control of agitation or insomnia (at investigator's discretion) and benztropine was permitted for control of EPS	Efficacy variables included change from baseline in scores on cognitive tests of attention, memory, executive function, and verbal fluency. The following cognitive tests were performed at baseline and at 6 weeks of treatment (or endpoint): Attention: Continuous performance test, and Trail making test, part A Memory: Rey auditory verbal learning test, and Digit span distraction test Executive functions: Wisconsin card-sorting test (WCST), and Trail making test, Part B Verbal fluency: category and letter fluency Clinical assessments: PANSS at weeks 1,3, 6 and early termination. CGI-S and CGI-I Movement disorders assessed with Barnes Akathisia Scale (BAS) on days 0, 21, and 42 and Abnormal Involuntary Movement Scale (AIMS) on days 0 or 42 or early termination	Mean age: 37.7y Male: 65.4% White: 52.4% Black: 32.3% Asian: 2.2% Hispanic: 10.4% Other: 2.6%

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

Author, year Study design Quality	Other population characteristics	Number Screened/ Eligible/ Enrolled	Withdrawn/ Lost to fu/ Analyzed
Olanzapine vs Ziprasidone			
Harvey 2004 Harvey, 2002d (abstract) Harvey, 2002e (abstract) RCT, multicenter cognition study Study patients remained inpatients during weeks 3-6 unless the met all protocol criteria for hospital discharge Funding: Pfizer, Inc	Schizoaffective schizophrenia: Ziprazadone: 38.2% Olanzapine: 35.3% (total population: 36.8%) Schizophrenia: Ziprazadone: 61.8% Olanzapine: 64.7% (total population: 63.2%	NR/NR/269 olanzapine 133 ziprasidone 136	NR/NR/154 completed study (unclear as to the number analyzed per test)

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

Author, year Study design Quality	Results
Olanzapine vs Ziprasidone	
Harvey 2004 Harvey, 2002d (abstract) Harvey, 2002e (abstract) RCT, multicenter cognition study Study patients remained inpatients during weeks 3-6 unless the met all protocol criteria for hospital discharge Funding: Pfizer, Inc	SS improvements in most measures within group The only between-groupssignificant dfference was found in Category Fluency: olanzapine > ziprasidone ($p<0.05$) but correction for repeated measures makes finding NS Statistically significant differences were found between baseline and enpoint for ziprazadone in these domains: Attention: both Cognitive performance test and Trail making, part A Memory domain: Rey auditory verbal learning test and delayed recall Statistically significant differences were found between baseline and enpoint for olanzapine in these domains: Attention: both Cognitive performance test and Trail making, part A Memory domain: Rey auditory verbal learning test and delayed recall Exceutive functioning: WCST categories completed and Trail making, part B Verbal fluency: Category fluency

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

Author, year Study design Quality	Method of adverse effects assessment	Adverse effects reported
Olanzapine vs Ziprasidone		
Harvey 2004 Harvey, 2002d (abstract) Harvey, 2002e (abstract) RCT, multicenter cognition study Study patients remained inpatients during weeks 3-6 unless the met all protocol criteria for hospital discharge Funding: Pfizer, Inc	NR	NR

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

Author, year Study design Quality	EPS	Total withdrawals; withdrawals due to adverse events	Comments
Olanzapine vs Ziprasidone			
Harvey 2004 Harvey, 2002d (abstract) Harvey, 2002e (abstract) RCT, multicenter cognition study Study patients remained inpatients during weeks 3-6 unless the met all protocol criteria for hospital discharge Funding: Pfizer, Inc	NR	Total withdrawals: 115/269 (42.7%) ziparzadone: 48.5% vs olanzapine 36.8%, p=0.0449 Withdrawals due to all AEs: 15/269 (5.6%) ziprazadone: 7.4% vs olanzapine 3.0% Withdrawals due to AEs related to study drug: 5/269 (1.86%)	

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

Author, year Study design Quality	Eligibility criteria	Interventions (drug, dose, duration)	Wash-out period
QUEST; Mullen, 2001 FAIR Funding: AstraZeneca Pharmaceuticals	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 day 64, and 4.65 by day 112)	NR
Mullen, 1999 (QUEST sub-group) Funding: AstraZeneca Pharmaceuticals	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 months	NR

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

Author, year Study design Quality	Allowed other medications	Method of outcome assessment timing of assessment	Age Gender Ethnicity
QUEST; Mullen, 2001 FAIR Funding: AstraZeneca Pharmaceuticals	Any mood stabilizers or antidepressants prescribed must have been at a stable dose for at least 2 weeks before randomization	CGI (baseline, weekly, up to week 4and then monthly to 4 months), PANSS, HAM-D (baseline, 2 months, and 4 months)	Mean age=45.4 51.1% male 73.1% white 16.7% black 5.9% hispanic 2.7% asian 1.5% other
Mullen, 1999 (QUEST sub-group) Funding: AstraZeneca Pharmaceuticals	NR	% change from baseline HAM-D scores (schizoaffective; schizophrenia) CGI PANSS	Mean age: quetiapine 45.1 risperidone 46.2 quetiapine 50.9% male risperidone 54.3 % male Ethnicity NR

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

Author, year Study design Quality	Other population characteristics	Number Screened/ Eligible/ Enrolled	Withdrawn/ Lost to fu/ Analyzed
QUEST; Mullen, 2001 FAIR Funding: AstraZeneca Pharmaceuticals	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 demential: 0.7% Vascular dementia: 0.1% Substance abuse dementia: 0.1% Other: 7% Age at first diagnosis: 28.6 Psychiatric hospitalizations in last 4 months: 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%	NR/NR/728	32.2% withdrawn/lost to fu NR/analyzed varied by outcome
Mullen, 1999 (QUEST sub-group) Funding: AstraZeneca Pharmaceuticals	Special characteristics: included those > 65 years 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	NR/NR/751 quetiapine 554 risperidone 175	NR

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

Author, year Study design Quality	Results
QUEST; Mullen, 2001 FAIR Funding: AstraZeneca Pharmaceuticals	quetiapine, risperidone, p-value Withdrawal 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
Mullen, 1999 (QUEST sub-group) Funding: AstraZeneca Pharmaceuticals	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 Quality	Method of adverse effects assessment	Adverse effects reported
QUEST; Mullen, 2001 FAIR Funding: AstraZeneca Pharmaceuticals	EPS checklist that measured the severity of 22 EPS (including 15 motor system symptoms and 7 parkinsonian symptoms) using a 5-point scale (0=none, 1=a little, 2=moderate 3=quite a bit; 4=extreme) Safety was assessed through adverse event, defined as the development of any new medical condition or the deterioration of a preexisting medical condition after exposure to drug	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 Withdrawals due to Dry mouth: 2 (0.4%), 1 (0.6%) Dizzines: 6 (1.1%), 0 Weight gain: 14 (2.5%), 6 (3.4%), p-value nr Weight loss: 4 (0.7%), 0
Mullen, 1999 (QUEST sub-group) Funding: AstraZeneca Pharmaceuticals	EPS checklist Anti-EPS medication Adjusted study medication dose	NR

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

Author, year Study design Quality	EPS	Total withdrawals; withdrawals due to adverse events	Comments
QUEST; Mullen, 2001 FAIR Funding: AstraZeneca Pharmaceuticals	Quetiapine, risperidone Patients reporting EPS at LOCF: 38.6%, 39.2%, logistic regression model of the presence of any EPS in months 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	Withdrawals due to AE: 48 (8.7%), 9 (5.1%) Total withdrawals: 176 (31.8%), 59 (33.7%)	
Mullen, 1999 (QUEST sub-group) Funding: AstraZeneca Pharmaceuticals	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.	NR	

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

Author, year Study design Quality	Eligibility criteria	Interventions (drug, dose, duration)	Wash-out period
Reinstein, 1999 (QUEST subgroup) Funding: AstraZeneca Pharmaceuticals	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 months	NR
Sajatovic, 2002 (QUEST sub-group analysis, Mullen 2001) Multicenter, open label RCT FAIR Funding: AstraZeneca Pharmaceuticals	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 months	none

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

Author, year Study design Quality	Allowed other medications	Method of outcome assessment timing of assessment	Age Gender Ethnicity
Reinstein, 1999 (QUEST subgroup) Funding: AstraZeneca Pharmaceuticals	NR	CGI PANSS DAI-10 HAM-D	NR
Sajatovic, 2002 (QUEST sub-group analysis, Mullen 2001) Multicenter, open label RCT FAIR Funding: AstraZeneca Pharmaceuticals	Any deemed medically necessary. Additional antipsychotics allowed only after attempt to stabilize on assigned drug for 1 month. No depot drugs, clozapine or olanzapine allowed. Mood stabilizers and antidepressants could be continued if dose stable x 2 wks. Rescue meds allowed.	PANSS CGI HAM-D	Mean age 45 73 % white 51% male

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

Author, year Study design Quality	Other population characteristics	Number Screened/ Eligible/ Enrolled	Withdrawn/ Lost to fu/ Analyzed
Reinstein, 1999 (QUEST subgroup) Funding: AstraZeneca Pharmaceuticals	adult outpatients with psychotic disorders	NR/NR/751	NR
Sajatovic, 2002 (QUEST sub-group analysis, Mullen 2001) Multicenter, open label RCT FAIR Funding: AstraZeneca Pharmaceuticals	33.7% taking mood stabilizers 33.7 taking antidepressants 57% of total population classified as "mood disorder"	NR/NR/729 Of these, 419 with mood disorders	NR/NR/419

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

Author, year Study design Quality	Results
Reinstein, 1999 (QUEST subgroup) Funding: AstraZeneca Pharmaceuticals	CGI; PANSS; DAI-10 Both groups had improvements in all efficacy measures (not significant). 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)
Sajatovic, 2002 (QUEST sub-group analysis, Mullen 2001) Multicenter, open label RCT FAIR Funding: AstraZeneca Pharmaceuticals	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 Quality	Method of adverse effects assessment	Adverse effects reported
Reinstein, 1999 (QUEST subgroup) Funding: AstraZeneca Pharmaceuticals	EPS checklist Anti-EPS medication Adjusted study medication dose	NR
Sajatovic, 2002 (QUEST sub-group analysis, Mullen 2001) Multicenter, open label RCT FAIR Funding: AstraZeneca Pharmaceuticals	Substantial EPS defined as 1) use of Anti-EPS med, 2) decrease in dosage, or 3) discontinuation. Assessed by symptom checklist provided by AstraZeneca (not provided)	Patients with Mood disorders: risperidone > quetiapine (p<0.001, numbers not reported) Patients without Mood disorders: NS difference (p=0.063)

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

Author, year Study design Quality	EPS	Total withdrawals; withdrawals due to adverse events	Comments
Reinstein, 1999 (QUEST subgroup) Funding: AstraZeneca Pharmaceuticals	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	NR	
Sajatovic, 2002 (QUEST sub-group analysis, Mullen 2001) Multicenter, open label RCT FAIR Funding: AstraZeneca Pharmaceuticals	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 Quality	Eligibility criteria	Interventions (drug, dose, duration)	Wash-out period
Simpson, 2004 multicenter, DB, Parallel, flexible-dose Inpatients Funding: Pfizer, Inc	Between Ages 18-55 yrs, females not of childbearing potential, hospitalized no more than 2 consecutive weeks immediately before screening, schizophrenia/schizoaffecive 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 reults 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 weeks duration	NR

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

Author, year Study design Quality	Allowed other medications	Method of outcome assessment timing of assessment	Age Gender Ethnicity
Simpson, 2004 multicenter, DB, Parallel, flexible-dose Inpatients Funding: Pfizer, Inc	Lorazepam, benztropine.	Brief Psychiatric Rating Scale (BPRS), Clinical Global Impression (CGI), CGI improvement scale, Positive and negative Syndrome Scale, Calgary Depression Scale for Schizophrenia, fasting lipid profiles, fasting glucose, insulin measurements, electrocardiography, monitoring of vital signs and body weight	Mean age: 37.7 years 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%)

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

Author, year Study design Quality	Other population characteristics	Number Screened/ Eligible/ Enrolled	Withdrawn/ Lost to fu/ Analyzed
Simpson, 2004 multicenter, DB, Parallel, flexible-dose Inpatients Funding: Pfizer, Inc	In-Patient population: 100%	367/269/269	115 (42.6%)/NR/269

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

Author, year Study design Quality	Results
Simpson, 2004 multicenter, DB, Parallel, flexible-dose Inpatients Funding: Pfizer, Inc	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 cholestrol: 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 cholestrol: 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

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

Author, year Study design Quality	Method of adverse effects assessment	Adverse effects reported
Simpson, 2004 multicenter, DB, Parallel, flexible-dose Inpatients Funding: Pfizer, Inc	Patient report, physical examinations	Body as a whole: Z: 52(38.2%) vs O: 39(29.3%) Cardiovascular: 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%)

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

Author, year Study design Quality	EPS	Total withdrawals; withdrawals due to adverse events	Comments
Simpson, 2004 multicenter, DB, Parallel, flexible-dose Inpatients Funding: Pfizer, Inc	Scales used: Extrapyramidal Symptom Rating Scale, Barnes akathisia scale, Abnormal Involuntary Movement Scale (AIMS)	115; 5	

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

Author, year Study design Quality	Eligibility criteria	Interventions (drug, dose, duration)	Wash-out period
Zhong, 2004 Poster Only RCT	Men or women, aged 18-65 years old, with a diagnosis of catatonic, disorganized, paranoid, or undifferentiated schizophrenia according to DSM-IV; PANSS total score of ≥ 60 at baseline (Day 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 day 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 day 5, then flexibly dosed in range of 2-8 mg/d (mean dose=5.2 mg) Duration: 8 weeks Setting: hospitalized for ≥ 7 days following randomization	NR
Quetiapine vs Risperidone vs Fluphenazine			
Kelly, 2005 RCT, DB Thyroid results from Conley 2003 (different from the Conley 2003 above) Funding: Pfizer, Inc	treatment-resistant schizophrenia, medically healthy	N=38 400 mg/day quetiapine, or 4 mg/day risperidone, or 12.5 mg/day fluphenazine 6 weeks duration	NR

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

Author, year Study design Quality	Allowed other medications	Method of outcome assessment timing of assessment	Age Gender Ethnicity
Zhong, 2004 Poster Only RCT	NR	PANSS total and subscale: change from baseline to Day 56; proportion of patients with CGI-C ratings of "much improved" or "very much improved" at the final assessment, and response rate, which was defined as the proportion of patients who achieved at least a 40% reduction on PANSS total and subscale scores at the end of treatment Timing: days 1, 4, 8, 15, 28, 42 and 56	Mean age 39.94 75.7% male 50.8% black 38.7% white 7.6% Hispanic 2.9% other ethnicity
Quetiapine vs Risperidone vs Fluphenazine			
Kelly, 2005 RCT, DB Thyroid results from Conley 2003 (different from the Conley 2003 above) Funding: Pfizer, Inc	lorazepam, benztropine, oral hypoglycemics, laxatives, diuretics, nonsteroidal anti-inflammatory agents, antibiotics, antihypertensives	Blood drawn at baseline, and at end of study. Tests included: total serum thyroxine, free thyroxine index, serum T3 resin uptake, TSH	Mean age: 43.8 Male: 73% Black: 60% White: 40%

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

Author, year Study design Quality	Other population characteristics	Number Screened/ Eligible/ Enrolled	Withdrawn/ Lost to fu/ Analyzed
Zhong, 2004 Poster Only RCT	Glucose (mg/dL): 99.7 Weight (kg): 86.6 Prolactin (ng/mL): 22.65 PANSS total scores: 92.5	NR/NR/673 quetiapine 338 risperidone 335	351 (52.1%) withdrawn/analyzed nr
Quetiapine vs Risperidone vs Fluphenazine			
Kelly, 2005 RCT, DB Thyroid results from Conley 2003 (different from the Conley 2003 above) Funding: Pfizer, Inc	NR	NR/NR/38	NR/NR/30

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

Author, year Study design Quality	Results
Zhong, 2004 Poster Only RCT	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 Day 56): quetiapine=risperidone, p-values nr
Quetiapine vs Risperidone vs Fluphenazine	
Kelly, 2005 RCT, DB Thyroid results from Conley 2003 (different from the Conley 2003 above) Funding: Pfizer, Inc	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

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

Author, year Study design Quality	Method of adverse effects assessment	Adverse effects reported
Zhong, 2004 Poster Only RCT	Change from baseline to the endpoint on the SAS, AIMS, BARS; the incidence of reported adverse events related to EPS and the incidence of treatment-emergent adverse events; and reporting of laboratory test results, vital sign measurements and clinically significant changes in weight, glucose, prolactin, and ECG results	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%) Withdrawals due to somnolence: 2 (0.6%), 1 (0.3%) Withdrawals due to akathisia: 0, 4 (1.2%) Withdrawals due to dystonia: 0, 6 (1.8%) EPS-related adverse events: 43 (12.7%) vs 73 (21.9%), p<0.01 BARS improvement: quetiapine > risperidone, p-value nr SAS and AIMS improvement: quetiapine=risperidone Sexual adverse events: 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
Quetiapine vs Risperidone vs Fluphenazine		
Kelly, 2005 RCT, DB Thyroid results from Conley 2003 (different from the Conley 2003 above) Funding: Pfizer, Inc	NR	NR

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

Author, year Study design Quality	EPS	Total withdrawals; withdrawals due to adverse events	Comments
Zhong, 2004 Poster Only RCT		Withdrawals due to adverse events (# patients; population analyzed nr): 20 vs 23	
Quetiapine vs Risperidone vs Fluphenazine			
Kelly, 2005 RCT, DB Thyroid results from Conley 2003 (different from the Conley 2003 above) Funding: Pfizer, Inc	NR	NR	

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

Author, year Study design Quality	Eligibility criteria	Interventions (drug, dose, duration)	Wash-out period
Risperidone: Oral vs Injectable			
Chue, 2005 RCT, double-dummy, multicenter, DB inpatients and outpatients Funding: Janssen Research Foundation	Inpatients and outpatients aged 18-65 years, schizophrenia, total PANSS score >50, no clinical relevant abnormal biochemistry, hematology or urninalysis, remained stable with CGI scores during last 4 weeks of risperidone run-in	N=640 All patients received flexible does of 1-6 mg of oral risperidone for first 8 weeks, then randomized to either injectable or oral (double-dummy)	2 weeks of all antipsychotics

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

Author, year Study design Quality	Allowed other medications	Method of outcome assessment timing of assessment	Age Gender Ethnicity
Risperidone: Oral vs Injectable			
Chue, 2005 RCT, double-dummy, multicenter, DB inpatients and outpatients Funding: Janssen Research Foundation	NR	PANSS, CGI	Mean age: 40 years Male: 414(64.5%) White: 562(87.8%) Black: 35 (5%) Asian: 16 (2.5%) Hispanic: 1 (0%) Other: 26 (4%)

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

Author, year Study design Quality	Other population characteristics	Number Screened/ Eligible/ Enrolled	Withdrawn/ Lost to fu/ Analyzed
Risperidone: Oral vs Injectable			
Chue, 2005 RCT, double-dummy, multicenter, DB inpatients and outpatients Funding: Janssen Research Foundation	Schizophrenia types: Paranoid: Oral: 195(60.7) vs Inj: 200 (62.7%) Undifferentiated: Oral: 56(17.4%) vs Inj: 57(17.9%) Residual: Oral: 48(15%) vs Inj: 43(13.5%) Disorganized: Oral: 20(6.2%) vs Inj: 16(5%) Catatonic: Oral: 2(6%) vs Inj: 3(9%)	779/642/640	NR

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

Author, year Study design Quality	Results
Risperidone: Oral vs Injectable	
Chue, 2005 RCT, double-dummy, multicenter, DB inpatients and outpatients Funding: Janssen Research Foundation	Changes at Endpoint: Mean + SD; 95% CI: PANSS total: Oral: -6.3+ 0.7 vs Inj: -5.4 +0.7; -0.90, 2.78 Positive symptoms: Oral: -2.0+0.3 vs Inj: -1.7+0.3; -0.34,0.99 Negative symptoms: Oral: -1.6+0.3 vs Inj: -1.5+0.3; -0.59,0.82 Disorganized thoughts: Oral: -1.2+0.2 vs Inj: -1.1+0.2; -0.34, 0.71 Uncontrolled: Oral: -0.4+0.1 vs Inj: -0.3+0.1; -0.22,0.57 Anxiety/depression: Oral: -1.0+0.2 vs Inj: -0.9+0.2; -0.25,0.57

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

Author, year Study design Quality	Method of adverse effects assessment	Adverse effects reported
Risperidone: Oral vs Injectable		
Chue, 2005 RCT, double-dummy, multicenter, DB inpatients and outpatients Funding: Janssen Research Foundation	Patient self-report	Insomnia: oral: 9% vs inj: 9.7% Anxiety: oral: 7.2% vs inj: 10% Headache: oral: 7.2% vs inj: 8.2% Psychosis: oral: 4.7% vs inj: 5.3%

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

Author, year Study design Quality	EPS	Total withdrawals; withdrawals due to adverse events	Comments
Risperidone: Oral vs Injectable			
Chue, 2005 RCT, double-dummy, multicenter, DB inpatients and outpatients Funding: Janssen Research Foundation	NR	NR	

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

Author, year Study design Quality	Eligibility criteria	Interventions (drug, dose, duration)	Wash-out period
Risperidone vs Quetiapine			
Knegtering, 2004 open-label Inpatients and outpatients Funding: AstraZeneca	schizophrenia, schizophrenia-related psychotic illness	N=51 quetiapine(N=25): 200-1200 mg/d risperidone (N=26): 1-6 mg/d	NR

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

Author, year Study design Quality	Allowed other medications	Method of outcome assessment timing of assessment	Age Gender Ethnicity
Risperidone vs Quetiapine			
Knegtering, 2004 open-label Inpatients and outpatients Funding: AstraZeneca	NR	Antipsychotics and Sexual Functioning Questionnaire (ASFQ), Utvalg for Kliniske Undersogelser (UKU), PANSS	Mean age: 70.5% Male

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

Author, year Study design Quality	Other population characteristics	Number Screened/ Eligible/ Enrolled	Withdrawn/ Lost to fu/ Analyzed
Risperidone vs Quetiapine			
Knegtering, 2004 open-label Inpatients and outpatients Funding: AstraZeneca	Clinical Diagnoses: Brief psychoic 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%)	NR/51	NR

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

Author, year Study design Quality	Results
Risperidone vs Quetiapine	
Knegtering, 2004 open-label	Patients Reporting Sexual Dysfunction at Endpoint: Q: 4/25(16%) vs R: 12/24(50%); p=0.006
Inpatients and outpatients	Prolactin levels (Mean + SD) and Sexual Dysfunction: Prolactin:
Funding: AstraZeneca	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 Quality	Method of adverse effects assessment	Adverse effects reported
Risperidone vs Quetiapine		
Knegtering, 2004 open-label Inpatients and outpatients Funding: AstraZeneca	NR	NR

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

Author, year Study design Quality	EPS	Total withdrawals; withdrawals due to adverse events	Comments
Risperidone vs Quetiapine			
Knegtering, 2004 open-label Inpatients and outpatients Funding: AstraZeneca	NR	NR	

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

Author, year Study design Quality	Eligibility criteria	Interventions (drug, dose, duration)	Wash-out period
Risperidone vs Olanzapine vs Clozapine vs Haloperidol			
Volavka, 2001 RCT, DB Inpatients Funding: NIMH, Foundation of Hope, Raleigh, NC, Eli Lilly	Treatment-resistant, inpatients with DSM-IV diagnosis of schizophrenia, or schizoaffective disorder	14 week trial: clozapine (N=40): target for weeks 1-8: 500 mg/day, mean dose for weeks 9-14: 526.6 mg/day olanzapine (N=39): target for weeks 1-8: 20 mg/day, mean dose for weeks 9-14: 30.4 mg/day risperidone (N=41): target for weeks 1-8: 8 mg/day, mean dose for weeks 9-14: 11.6 mg/day haloperidol (N=37): target for weeks 1-8: 20 mg/day, mean dose for weeks 9-14: 25.7 mg/day	NR

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

Author, year Study design Quality	Allowed other medications	Method of outcome assessment timing of assessment	Age Gender Ethnicity
Risperidone vs Olanzapine vs Clozapine vs Haloperidol			
Volavka, 2001 RCT, DB Inpatients Funding: NIMH, Foundation of Hope, Raleigh, NC, Eli Lilly	Benztropine, propranolol, lorazepam, diphenhydramine hydrocholide, chloral hydrate	PANSS - hostility item-conducted at baseline and endpoint, PANSS, Extrapyramidal Symptom Rating Scale- conducted at baseline, 8 weeks and endpoint, Glucose levels taken at weeks 1, 8, 14, Total Aggression Severity (TAS), Plasma levels of prolactin, tested at weeks 1, 5, 8, 10,12, 14	Mean age: 40.33 years 84% Male 29% Caucasian 58.4% African-American 10.9% Hispanic 2% Asian-Pacific Islander

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

Author, year Study design Quality	Other population characteristics	Number Screened/ Eligible/ Enrolled	Withdrawn/ Lost to fu/ Analyzed
Risperidone vs Olanzapine vs Clozapine vs Haloperidol			
Volavka, 2001 RCT, DB Inpatients Funding: NIMH, Foundation of Hope, Raleigh, NC, Eli Lilly	Schizophrenia: 135(86%) Schizoaffective disorder: 22(14%) 100% Male for testing of prolactin levels of plasma	NR/167/157	0/0/157 22 analyzed with Total Aggression Severity (TAS) 101 analyzed for glucose and cholestrol levels and weight gain 16 analyzed for prolactin levels of plasma

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

Author, year Study design Quality	Results
Risperidone vs Olanzapine vs Clozapine vs Haloperidol	
Volavka, 2001 RCT, DB Inpatients Funding: NIMH, Foundation of Hope, Raleigh, NC, Eli Lilly	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 weeks: clozapine: (p<0.007) olanzapine: (p<0.02) risperidone: (p=NR) haloperidol: (p=NR) Mean glucose level changes from baseline at 8 weeks and 14 weeks: 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 cholestrol levels: 8 weeks, 14 weeks 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<0.06 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 Quality	Method of adverse effects assessment	Adverse effects reported
Risperidone vs Olanzapine vs Clozapine vs Haloperidol		
Volavka, 2001 RCT, DB Inpatients Funding: NIMH, Foundation of Hope, Raleigh, NC, Eli Lilly	Physical examination	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 Quality	EPS	Total withdrawals; withdrawals due to adverse events	Comments
Risperidone vs Olanzapine vs Clozapine vs Haloperidol			
Volavka, 2001 RCT, DB Inpatients Funding: NIMH, Foundation of Hope, Raleigh, NC, Eli Lilly	Mean Extrapyramidal Symptoms scores from baseline: clozapine: at 8 weeks: 5.3; (p<0.03), at 14 weeks: 5.1; (p<0.005) olanzapine: at 8 weeks: 3.7; (p<<0.0008), at 14 weeks: 3.8; (p<0.0001) risperidone: at 8 weeks: 4.7; (p<0.002), at 14 weeks: 4.8; (p<0.005) haloperidol: at 8 weeks: 4.7; (p=NR), at 14 weeks: 4.4; (p=NR)	0;0	

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

Author, year Study design Quality	Eligibility criteria	Interventions (drug, dose, duration)	Wash-out period
Risperidone vs Ziprasidone			
Addington, 2004 DB, RCT, parallel Funding: Pfizer, Inc	schizophrenia, schizoaffective disorder, 18-65 years of age, PANSS total score $\geq$60, a score of $\geq$4 on 2 of the PANSS core items	ziprasidone 40-80 mg b.i.d. (N=149) or risperidone 3-5mg b.i.d. (N=147) 8 weeks duration	>3 days washout of anti-psychotics, anticholinergic agents, beta-blockers

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

Author, year Study design Quality	Allowed other medications	Method of outcome assessment timing of assessment	Age Gender Ethnicity
Risperidone vs Ziprasidone			
Addington, 2004 DB, RCT, parallel Funding: Pfizer, Inc	NR	Positive and Negative Syndrome Scale (PANSS), Clinical Global Impression-Severity of Illness Scale (CGI-S), CGI-Improvement scale (CGI-I), Brief Psychiatric Rating Scale (BPRSd), Movement Disorder Burden (MDB), Global Assessment of Functioning (GAF), Montogomery-Ashberg Depression Rating Scale (MADRS), UKU Side Effect Rating Scale, Simpson-Angus Rating Scale, Barnes Akathisia Scale, Abnormal Involuntary Movement Scale (AIMS), Movement Disorder Burden (MDB), laboratory data, vital signs, body weight, ECG	Mean age: 35 years 72.5% Male Ethnicity NR

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

Author, year Study design Quality	Other population characteristics	Number Screened/ Eligible/ Enrolled	Withdrawn/ Lost to fu/ Analyzed
Risperidone vs Ziprasidone			
Addington, 2004 DB, RCT, parallel Funding: Pfizer, Inc	NR	NR/NR/296	NR/NR 198

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

Author, year Study design Quality	Results
Risperidone vs Ziprasidone	
Addington, 2004 DB, RCT, parallel Funding: Pfizer, Inc	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%)

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

Author, year Study design Quality	Method of adverse effects assessment	Adverse effects reported
Risperidone vs Ziprasidone		
Addington, 2004 DB, RCT, parallel	Patient self-report, laboratory tests, Sexual dysfunction questionnaire	Treatment-emergent adverse events reported: Z: 113 (75.8%) vs R: 122(83.0%)
Funding: Pfizer, Inc		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%

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

Author, year Study design Quality	EPS	Total withdrawals; withdrawals due to adverse events	Comments
Risperidone vs Ziprasidone			
Addington, 2004 DB, RCT, parallel Funding: Pfizer, Inc	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 adverse event: R: 54(36.7%) vs Z: 44(29.5%)	98 withdrawals; 18 withdrawals due to adverse events	

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

Author, year Study design Quality	Eligibility criteria	Interventions (drug, dose, duration)	Wash-out period
Risperidone vs Olanzapine vs Quetiapine vs Clozapine			
Atmaca, 2003 Inpatients Funding: NR	Schizophrenia Exclusion: Co-morbid Axis I disorders, severe physical illness, history of alcohol/substance abuse, history of lipid-lowering treatment, presence of endocrinologic disorder, autoimune, pulmonary, inectious diseases, neoplasms.	6 week study quetiapine(N=14): olanzapine(N=14): risperidone(N=14): clozapine(N=14): control group w/no treatment(N=11):	≥2 weeks
Risperidone vs Olanzapine vs Clozapine			
Naber, 2001 Funding: Eli Lily, Janssen-Cilag, Novartis	Diagnosis of schizophrenia was confirmed by experienced clinicans relying on criteria according to DSM-IV	olanzapine(N=36): 12.92 mg, risperidone(N=28): 3.55mg, clozapine(N=36): 194.44mg	NR

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

Author, year Study design Quality	Allowed other medications	Method of outcome assessment timing of assessment	Age Gender Ethnicity
Risperidone vs Olanzapine vs Quetiapine vs Clozapine			
Atmaca, 2003 Inpatients Funding: NR	Biperiden hydrochloride, benzodiazepines	Positive and Negative Syndrome Scale (PANSS), body mass index (BMI), weight, fasting serum leptin and triglyceride levels: taken at baseline and endpoint	Mean age: 30.2 years 54.6% Female Ethnicity NR
Risperidone vs Olanzapine vs Clozapine			
Naber, 2001 Funding: Eli Lily, Janssen-Cilag, Novartis	No	SWN (subjective well-being under neuroleptic treatment), a self-rating scale, was being developed and compared with the PANSS; this group of patients was assessed at baseline and right before discharge	Mean age: 34.2 years 54% male Ethnicity: NR

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

Author, year Study design Quality	Other population characteristics	Number Screened/ Eligible/ Enrolled	Withdrawn/ Lost to fu/ Analyzed
Risperidone vs Olanzapine vs Quetiapine vs Clozapine			
Atmaca, 2003 Inpatients Funding: NR	29% psychotropic drug naïve	NR/NR/71	NR/NR/64
Risperidone vs Olanzapine vs Clozapine			
Naber, 2001 Funding: Eli Lily, Janssen-Cilag, Novartis	NR	Unclear / unclear / 100	NR/NR/100

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

Author, year Study design Quality	Results
Risperidone vs Olanzapine vs Quetiapine vs Clozapine	
Atmaca, 2003 Inpatients Funding: NR	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)
Risperidone vs Olanzapine vs Clozapine	
Naber, 2001 Funding: Eli Lily, Janssen-Cilag, Novartis	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

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

Author, year Study design Quality	Method of adverse effects assessment	Adverse effects reported
Risperidone vs Olanzapine vs Quetiapine vs Clozapine		
Atmaca, 2003 Inpatients Funding: NR	weight, body mass index, fasting serum leptin and triglyceride levels taken at baseline and endpoint	NR
Risperidone vs Olanzapine vs Clozapine		
Naber, 2001 Funding: Eli Lily, Janssen-Cilag, Novartis		Change in mean SWN scores, admission to discharge: clozapine vs risperidone vs olanzapine Physical Functioning: +1.58 vs +1.65 vs +4.86 Self-control: +1.6 vs +2.16 vs +2.83

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

Author, year Study design Quality	EPS	Total withdrawals; withdrawals due to adverse events	Comments
Risperidone vs Olanzapine vs Quetiapine vs Clozapine			
Atmaca, 2003 Inpatients Funding: NR	NR	NR; NR	
Risperidone vs Olanzapine vs Clozapine			
Naber, 2001 Funding: Eli Lily, Janssen-Cilag, Novartis	NR	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 psuedo-randomized; clozapine was given because of insufficient antipsychotic treatment or severe motor symptoms under previous medications. Olanzapine pts were significantly younger than risperidone.

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

Author, year Study design Quality	Eligibility criteria	Interventions (drug, dose, duration)	Wash-out period
Switched to Ziprasidone from Olanzapine, Risperidone, or Typical Antipsychotic medication			
Weiden 2003 open-label CCT (3 separate open-label studies on switching to Z from O, R, or Typicals) Funding: Pfizer, Inc	Men or women aged 18 to 55, DSM-IV schizophrenia or schizoaffective disorder outpatients status for ≥ 3 months; treatment with current antipsychotic within 25% of recommended dosage for ≥ 3 months 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 ziprazadone daily dose: 91mg for those switched from conventional antipsychotic; 90mg for those switched from olanzapine; 92mg for those switched from risperidone 6-week duration	1 of 3 ways drugs switched: Complete discontinuation: previous drug was stopped the day before the switch to Z; Immediate dose reduction: a 50% reduction in dosage of previous antipsychotic for the first wk of Z followed by discontinuation of previous starting wk 2 Delayed dose reduction: previous drug reduced by 50% starting on the fourth day of Z treatment and was discontinued by the second wk of Z treatment

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

Author, year Study design Quality	Allowed other medications	Method of outcome assessment timing of assessment	Age Gender Ethnicity
Switched to Ziprasidone from Olanzapine, Risperidone, or Typical Antipsychotic medication			
Weiden 2003 open-label CCT (3 separate open-label studies on switching to Z from O, R, or Typicals) Funding: Pfizer, Inc	Other psychotropic agents were not allowed (except for anti-EPS agents)	PANSS and CGI were conducted by investigators or trained research assistants	Mean age: 37.6 years Age range: 18-61years 65.5% male Ethnicity: NR

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

Author, year Study design Quality	Other population characteristics	Number Screened/ Eligible/ Enrolled	Withdrawn/ Lost to fu/ Analyzed
Switched to Ziprasidone from Olanzapine, Risperidone, or Typical Antipsychotic medication			
Weiden 2003 open-label CCT (3 separate open-label studies on switching to Z from O, R, or Typicals) Funding: Pfizer, Inc	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)	NR/ NR/ 270	Unclear: numbers analyzed changed depending on the test

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

Author, year Study design Quality	Results
Switched to Ziprasidone from Olanzapine, Risperidone, or Typical Antipsychotic medication	
Weiden 2003 open-label CCT (3 separate open-label studies on switching to Z from O, R, or Typicals)	all results were health indices

Funding: Pfizer, Inc

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

Author, year Study design Quality	Method of adverse effects assessment	Adverse effects reported
Switched to Ziprasidone from Olanzapine, Risperidone, or Typical Antipsychotic medication		
Weiden 2003 open-label CCT (3 separate open-label studies on switching to Z from O, R, or Typicals) Funding: Pfizer, Inc	AEs incidence and severity were recorded throughout the study; vital signs and body weight were measured at baseline and weekly. EPS were assessed at baseline and at enpoint using the Simpson-Angus scale for Parkinsonisn side effects and the Barnes Akathisia scale for akathisia. Metabolic and endocrine lab tests were performed at screening and endpoint	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 Quality	EPS	Total withdrawals; withdrawals due to adverse events	Comments
Switched to Ziprasidone from Olanzapine, Risperidone, or Typical Antipsychotic medication			
Weiden 2003 open-label CCT (3 separate open-label studies on switching to Z from O, R, or Typicals) Funding: Pfizer, Inc	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 weeks	The studies were completed by 72%, 79%, and 79% of patients switched from conventional antipsychotics, olanzapine, and risperidone, respectively Discontinuations due to AEs after swtiching from: Conventional antispychotics: 11% Olanzapine: 6% Risperidone: 9%	

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

Author, year Study design Quality	Eligibility criteria	Interventions (drug, dose, duration)	Wash-out period
CATIE STUDY			
Lieberman 2005 (CATIE Study) Row 1 of 3 Funding: NIHM grant, Foundation of Hope of Raleigh, N.C.	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	Overlap in the administration of the antipsychotic agent that patients received before the study entry was permitted for the first four weeks after randomization to allow a gradual transition to study medication

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

Author, year Study design Quality	Allowed other medications	Method of outcome assessment timing of assessment	Age Gender Ethnicity
CATIE STUDY			
Lieberman 2005 (CATIE Study) Row 1 of 3 Funding: NIHM grant, Foundation of Hope of Raleigh, N.C.	Concomitant medications were permitted throughout the trial, except for additional antipsychotic agents.	Primary outcome measure: -discontinuation of treatment for any cause Secondary outcome -PANSS -CGI -Laboratory measures	Mean age: 40.6 years 26% Female Ethnicity: white 60%; black 35%; hispanic 12%; 5% other

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

Author, year Study design Quality	Other population characteristics	Number Screened/ Eligible/ Enrolled	Withdrawn/ Lost to fu/ Analyzed
CATIE STUDY			
Lieberman 2005 (CATIE Study) Row 1 of 3 Funding: NIHM grant, Foundation of Hope of Raleigh, N.C.	depression 28% alcohol dependence or alcohol abuse 25% drug dependence or drug abuse 29% obsessive-compulsive disorder 5% other anxiety disorder 14%	NR/NR/1493	NR/NR/1460

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

Author, year Study design Quality	Results
CATIE STUDY	
Lieberman 2005 (CATIE Study) Row 1 of 3 Funding: NIHM grant, Foundation of Hope of Raleigh, N.C.	The time to the discontinuation of treatment for any cause: hazard ratio (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: hazard ratio (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)

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

Author, year Study design Quality	Method of adverse effects assessment	Adverse effects reported
CATIE STUDY		
Lieberman 2005 (CATIE Study) Row 1 of 3 Funding: NIHM grant, Foundation of Hope of Raleigh, N.C.	AIMS global severity Barnes Akathisia Rating Scale Simpson-Angus Extrapyramidal Signs Scale	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 adverse events, no(%): 32(10%) vs 32(9%) vs 33(10%) vs 29(11%) vs 19(10%), p=0.47 Any moderate or severe spontaneously reported adverse event, 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 Hypersonmia: 104(31%) vs 103(31%) vs 96(28%) vs 74(28%) vs 45(24%), p=0.18 Utrinary 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

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

Author, year Study design Quality	EPS	Total withdrawals; withdrawals due to adverse events	Comments
CATIE STUDY			
Lieberman 2005 (CATIE Study) Row 1 of 3 Funding: NIHM grant, Foundation of Hope of Raleigh, N.C.	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	olanzapine vs quetiapine vs risperidone vs perphenazine vs ziprasidone, p value Total withdrawals, 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 Quality	Eligibility criteria	Interventions (drug, dose, duration)	Wash-out period
Lieberman 2005 (CATIE Study) Row 2 of 3 (for results and AEs) Funding: NIHM grant, Foundation of Hope of Raleigh, N.C.			

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

Author, year Study design Quality	Allowed other medications	Method of outcome assessment timing of assessment	Age Gender Ethnicity
Lieberman 2005 (CATIE Study) Row 2 of 3 (for results and AEs) Funding: NIHM grant, Foundation of Hope of Raleigh, N.C.			

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

Author, year Study design Quality	Other population characteristics	Number Screened/ Eligible/ Enrolled	Withdrawn/ Lost to fu/ Analyzed
Lieberman 2005 (CATIE Study) Row 2 of 3 (for results and AEs) Funding: NIHM grant, Foundation of Hope of Raleigh, N.C.			

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

Author, year Study design Quality	Results
Lieberman 2005 (CATIE Study) Row 2 of 3 (for results and AEs) Funding: NIHM grant, Foundation of Hope of Raleigh, N.C.	The time to the discontinuation of treatment owing to intolerability: hazard ratio (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) Duration of successful treatment: hazard ratio (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) *p=0.004 for the interaction between treatment and time

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

Author, year Study design Quality	Method of adverse effects assessment	Adverse effects reported
Lieberman 2005 (CATIE Study) Row 2 of 3 (for results and AEs) Funding: NIHM grant, Foundation of Hope of Raleigh, N.C.		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/month, 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 hemosglobin, %: 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 -tryglycerides, 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 Quality	EPS	Total withdrawals; withdrawals due to adverse events	Comments
Lieberman 2005 (CATIE Study) Row 2 of 3 (for results and AEs) Funding: NIHM grant, Foundation of Hope of Raleigh, N.C.			

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

Author, year Study design Quality	Eligibility criteria	Interventions (drug, dose, duration)	Wash-out period
Lieberman 2005 (CATIE Study) Row 3 of 3 (for results only) Funding: NIHM grant, Foundation of Hope of Raleigh, N.C.			

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

Author, year Study design Quality	Allowed other medications	Method of outcome assessment timing of assessment	Age Gender Ethnicity
Lieberman 2005 (CATIE Study) Row 3 of 3 (for results only) Funding: NIHM grant, Foundation of Hope of Raleigh, N.C.			

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

Author, year Study design Quality	Other population characteristics	Number Screened/ Eligible/ Enrolled	Withdrawn/ Lost to fu/ Analyzed
Lieberman 2005 (CATIE Study) Row 3 of 3 (for results only) Funding: NIHM grant, Foundation of Hope of Raleigh, N.C.			

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

Author, year Study design Quality	Results
Lieberman 2005 (CATIE Study) Row 3 of 3 (for results only) Funding: NIHM grant, Foundation of Hope of Raleigh, N.C.	Patients's decision to discontinue treatment: hazard ratio (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)

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

Author, year Study design Quality	Method of adverse effects assessment	Adverse effects reported
Lieberman 2005 (CATIE Study) Row 3 of 3 (for results only) Funding: NIHM grant, Foundation of Hope of Raleigh, N.C.		

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

Author, year Study design Quality	EPS	Total withdrawals; withdrawals due to adverse events	Comments
Lieberman 2005 (CATIE Study) Row 3 of 3 (for results only) Funding: NIHM grant, Foundation of Hope of Raleigh, N.C.			

Evidence Table 2. Quality assessment of head-to-head 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?
Aripiprazole vs Olanzapine						
Cornblatt, 2002 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	Not reported	No
McQuade 2004 RCT, multicenter, double-blind FAIR	NR	NR	Yes	Yes	NR	Yes
Aripiprazole vs Risperidone						
Potkin 2003 FAIR	NR	NR	Yes	Yes	NR	Yes
Clozapine vs Risperidone						
Azorin, 2001 Anand, 1998 Double-blind, Multicenter (France and Canada) FAIR	Method not reported	Method not reported	No, Significantly more women and lower baseline BPRS score in the risperidone arm	Yes	Not reported	Yes
Bellack, 2004 Double-blind trial Substudy within larger trial POOR	Not reported if randomized	Method not reported	Not reported	Yes	Not reported	Yes
Bondolfi, 1998 Single-center Double-blind RCT FAIR	Method not reported	Method not reported	Similar, but number of months in hospital: clozapine: 12.3, risperidone 24.3	Yes	Not reported	Yes

Evidence Table 2. Quality assessment of head-to-head trials in patients with schizophrenia

Author, year Quality rating	Patient masked?	Attrition?	Loss to follow-up: differential/high?	Intention-to-treat (ITT) analysis?	Quality rating
Aripiprazole vs Olanzapine					
Cornblatt, 2002 FDA Study 98213 RCT, multicenter, open label FAIR	No	Not reported	Not reported	Unclear - some reported as LOCF, others not.	Fair (based on poster and published abstract only)
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
Aripiprazole vs Risperidone					
Potkin 2003 FAIR	Yes	Yes	Unable to determine, groups not reported.	No: 392/404 analyzed	Fair
Clozapine vs Risperidone					
Azorin, 2001 Anand, 1998 Double-blind, Multicenter (France and Canada) FAIR	Yes	Yes	No	Yes	Fair
Bellack, 2004 Double-blind trial Substudy within larger trial POOR	Yes	Not by drug	Overall loss to follow-up very high (47-66%), differences by drug not apparent	No	Poor
Bondolfi, 1998 Single-center Double-blind RCT FAIR	Yes	Yes	No	Yes	Fair

Evidence Table 2. Quality assessment of head-to-head 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?
Breier, 1999 Single Center double-blind RCT (NIH Clinical Center) Unclear if Inpatient FAIR	Method not reported	Method not reported	Some differences, NS: Months previously hospitalized: clozapine 8.8, risperidone 12.5 Length of illness (yrs): clozapine 13.9, risperidone 11.1	Yes	Not reported	Yes
Daniel, 1996 Crossover design POOR	Method not reported	Method not reported	yes (crossover study)	Yes	Not reported	Not reported
Wahlbeck, 2000 Open-label RCT FAIR	Yes	Method not reported	No, Significantly more women in the risperidone arm	Yes	No, open-label	No, open-label
Klieser 1995; Heinrich 1994 Double-blind, single center, parallel FAIR	NR	NR	Unclear; more males and patients older in clozapine group	Yes	Yes	Yes
Lindenmayer 1998 Open-label Pragmatic trial POOR	Not randomized- patients assigned to treatment based on their willingness to accept weekly blood drawings.	No	No significant differences in characteristics, N=21 clozapine, 14 risperidone.	Yes	No, "independent", but open label	No
Clozapine vs Olanzapine						
Tollefson, 2001 Beasley 1999 Beuzen 1998	Method not reported	Method not reported	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 not reported per group.	Yes	Yes	Yes

Evidence Table 2. Quality assessment of head-to-head trials in patients with schizophrenia

Author, year Quality rating	Patient masked?	Attrition?	Loss to follow-up: differential/high?	Intention-to-treat (ITT) analysis?	Quality rating
Breier, 1999 Single Center double-blind RCT (NIH Clinical Center) Unclear if Inpatient FAIR	Yes	Not reported	Not reported	Yes	Fair
Daniel, 1996 Crossover design POOR	Not reported	Yes	No	No	Poor
Wahlbeck, 2000 Open-label RCT FAIR	No, open-label	Yes	Overall = 35% Differential drop-out: clozapine 50%, risperidone 11%	Yes	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
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
Clozapine vs Olanzapine					
Tollefson, 2001 Beasley 1999 Beuzen 1998	Yes	Yes	No	Yes (LOCF methods)	Fair

Evidence Table 2. Quality assessment of head-to-head 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?
Bitter, 2004 RCT Multi-center, Hungary & South Africa GOOD	Method not reported	stated to be "double blind"	Stated to be, data not reported	Yes	Unclear	Yes
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 not reported	yes, data on alcohol and drug abuse missing	Yes	Yes, for most outcomes. Blinding for reporting of AE's not clear	No
Conley, 2003 Kelly 2003 Double-blind, single center, crossover POOR	NR	NR	No	Yes	NR	Yes
Olanzapine vs Risperidone						
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 head-to-head trials in patients with schizophrenia

Author, year Quality rating	Patient masked?	Attrition?	Loss to follow-up: differential/high?	Intention-to-treat (ITT) analysis?	Quality rating
Bitter, 2004 RCT Multi-center, Hungary & South Africa GOOD	Yes	Yes	Overall High: 58% NS difference between groups	Yes, using LOCF	Fair
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
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
Olanzapine vs Risperidone					
Conley, 2001 Double-blind, Multicenter FAIR	Yes	Yes	No	Yes	Good

Evidence Table 2. Quality assessment of head-to-head 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?
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 FAIR	Method not reported	Method not reported	Unclear - Length of current episode: 120 days for risperidone patients, 61 days for olanzapine patients, but NS difference olanzapine: 70% male; risperidone: 42% male	Yes	NR	Yes
Garyfallos 2003 CCT POOR	NR	NR	Yes	No	No	No
Harvey, 2003a Harvey 2002a Harvey 2002b Harvey 2002c RCT Multi-site; US, Austria, Israel, Norway, Poland and The Netherlands FAIR	Method not reported	Method not reported	Yes	Yes	Not clear - states some outcomes masked, but not which or how.	Yes
Harvey, 2003b (Harvey, 2002a,b,c & Harvey, 2003a Sub-group analysis) RCT Multicenter, US FAIR	Method not reported	Method not reported	Yes	Yes	Not clear	Not clear
Jerrel, 2002 Open-label RCT with economic analysis FAIR	Method not reported	Method not reported	Although randomization stratified, and an adaptive randomization procedure used, SS difference on baseline atypical antipsychotic use present. 4 other variables NS	Yes	No	No

Evidence Table 2. Quality assessment of head-to-head trials in patients with schizophrenia

Author, year Quality rating	Patient masked?	Attrition?	Loss to follow-up: differential/high?	Intention-to-treat (ITT) analysis?	Quality rating
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 FAIR	Yes	Yes	High overall 51% Difference in drop-out rates not SS: olanzapine: 60% risperidone 47%	Yes, as defined by Gilings and Koch.	Fair
Garyfallos 2003 CCT POOR	No	Yes	No	Yes	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
Harvey, 2003b (Harvey, 2002a,b,c & Harvey, 2003a Sub-group analysis) RCT Multicenter, US FAIR	Yes	Yes	Overall: 96 (25%) Not differential	Stated LOCF methods, but numbers reported vary by test applied.	Fair
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

Evidence Table 2. Quality assessment of head-to-head 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?
Jeste, 2003 Jeste, 2002 Jeste, 2001 RCT Multinational (US, Israel, Poland, Norway, The Netherlands, Austria) 1 full paper 2 conf proc FAIR	Method not reported	Method not reported	Yes	Yes	Yes; method not reported	Yes; method not reported
Jones, 1998 Purdon, 2000 David 1999 Multicenter, Canada Double-blind RCT FAIR	Yes	Method not reported	Yes	Yes	Not clear	Not clear (dose adjustments)
Lieberman 2005 (CATIE Study)	NR	Yes, "done under double blind conditions"	Few minor differences	Yes	Yes	Yes
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 FAIR	Method not reported	Method not reported	Unclear - not well reported	Yes	NR	Yes

Evidence Table 2. Quality assessment of head-to-head trials in patients with schizophrenia

Author, year Quality rating	Patient masked?	Attrition?	Loss to follow-up: differential/high?	Intention-to-treat (ITT) analysis?	Quality rating
Jeste, 2003 Jeste, 2002 Jeste, 2001 RCT Multinational (US, Israel, Poland, Norway, The Netherlands, Austria) 1 full paper 2 conf proc FAIR	Yes; method not reported	Yes	No; No	Yes	Fair
Jones, 1998 Purdon, 2000 David 1999 Multicenter, Canada Double-blind RCT FAIR	Yes	Yes	Overall 57% olanzapine 43% risperidone 67% haloperidol 61%	Yes	Fair
Lieberman 2005 (CATIE Study)	Yes	Yes (74%)	NR	NEED DAVIS REFERENCE	Good/Fair
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 FAIR	Yes	Yes	Overall 47.5% olanzapine 57.6% risperidone 47.3%	Yes	Fair

Evidence Table 2. Quality assessment of head-to-head 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, 1997 FAIR	Method not reported	Method not reported	Unclear - not well reported	Yes	NR	Yes
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

Evidence Table 2. Quality assessment of head-to-head trials in patients with schizophrenia

Author, year Quality rating	Patient masked?	Attrition?	Loss to follow-up: differential/high?	Intention-to-treat (ITT) analysis?	Quality rating
Tran, 1997 FAIR	Yes	Yes	Overall 47.5% olanzapine 57.6% risperidone 47.3%	Yes	Fair
van Bruggen 2003 POOR	NR	NR	Yes- 2/26 risperidone vs 0/18 olanzapine not included in analysis	No: 2 risperidone patients excluded	Poor

Evidence Table 2. Quality assessment of head-to-head 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?
Olanzapine vs Ziprasidone						
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.
Quetiapine vs Risperidone						
QUEST; Mullen, 2001 Mullen, 1999 Reinstein, 1999 FAIR	Method not reported	Method not reported	Yes	Yes	No	No
Sajatovic, 2002 (QUEST sub-group analysis, Mullen 2001) Multicenter, open label RCT FAIR	Method not reported	Method not reported	Yes	Yes	No	No
Zhong, 2004 RCT	Poster Only - no quality assessment possible.					
Knegtering 2004 Open, single center, parallel POOR	NR	NR	Yes	Yes	No	No
Risperidone vs Ziprasidone						
Addington, 2004 RCT, multicenter, double-blind FAIR	NR	NR	Yes	Yes	Yes	Yes

Evidence Table 2. Quality assessment of head-to-head trials in patients with schizophrenia

Author, year Quality rating	Patient masked?	Attrition?	Loss to follow-up: differential/high?	Intention-to-treat (ITT) analysis?	Quality rating
Olanzapine vs Ziprasidone					
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
Quetiapine vs Risperidone					
QUEST; Mullen, 2001 Mullen, 1999 Reinstein, 1999 FAIR	No	No	NR	Yes, using LOCF	Fair
Sajatovic, 2002 (QUEST sub-group analysis, Mullen 2001) Multicenter, open label RCT FAIR	No	No	NR	Yes, using LOCF	Fair
Zhong, 2004 RCT					
Knegtering 2004 Open, single center, parallel POOR	No	All 51 patients who were analyzed completed the 6-week study period	No loss to follow-up	Not clear - 51 patients "whose data could be analyzed" are reported on	Poor
Risperidone vs Ziprasidone					
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

Evidence Table 2. Quality assessment of head-to-head 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?
Multiple Comparisons						
Olanzapine vs Quetiapine vs Risperidone						
Yamashita 2004, RCT, single center, blinding unclear FAIR	NR	NR	No	Yes	NR	Blinding unclear
Mori 2004, RCT, single center, blinding unclear POOR	NR	NR	Yes for age, dose, illness duration, and gender. No others reported in tabular format or described in text.	Yes	NR	Blinding unclear
Citrome 2001, Volavka 2002, 2004b, 2004c; Lindenmayer 2003, 2004 FAIR	NR	NR	Yes	Yes	Yes	Yes
Chue 2005, RCT, multicenter, double blind, double dummy POOR	NR	NR	No; oral risperidone group had a "marginally signficant" greater number of previous hospitalizations	Yes	Yes	Yes
Clozapine vs Risperidone vs Olanzapine vs Quetiapine						
Atmaca 2003 FAIR	NR	NR	Yes	Yes	NR	Yes
Quetiapine vs Risperidone vs Fluphenazine						
Kelly 2005 (adverse events-thyroid function) POOR	NR	NR	Unable to determine- baseline characteristics reported only on 30/38 analyzed.	Yes	NR (states double-blind, but no details)	NR (states double-blind, but no details)
Naber, 2001 POOR	NR - O vs R described as pseudo-randomized, C assignment not random	NR	No - differences in treatment refractorieness, and gender at baseline	Yes	Not blinded	Not blinded

Evidence Table 2. Quality assessment of head-to-head trials in patients with schizophrenia

Author, year Quality rating	Patient masked?	Attrition?	Loss to follow-up: differential/high?	Intention-to-treat (ITT) analysis?	Quality rating
Multiple Comparisons					
Olanzapine vs Quetiapine vs Risperidone					
Yamashita 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
Mori 2004, RCT, single center, blinding unclear POOR	Blinding unclear	No	NR	Unclear	Poor
Citrome 2001, Volavka 2002, 2004b, 2004c; Lindenmayer 2003, 2004 FAIR	Yes	Yes: 42% withdrew	No.	Yes (LOCF)	Fair
Chue 2005, RCT, multicenter, double blind, double dummy POOR	Yes	Yes	NR	Unclear; number analyzed NR	Poor
Clozapine vs Risperidone vs Olanzapine vs Quetiapine					
Atmaca 2003 FAIR	NR	Yes	No (1 in each treatment group)	No: 3 of 56 excluded from analysis	Fair
Quetiapine vs Risperidone vs Fluphenazine					
Kelly 2005 (adverse events-thyroid function) POOR	NR (states double-blind, but no details)	Yes	High, unable to determine if differential: 21% did not complete all tests, but numbers randomized by group not reported.	No	Poor
Naber, 2001 POOR	Not blinded	Unclear	Unclear	Unclear	Poor

Evidence Table 3. Active-controlled trials in patients with schizophrenia

Author, year Country (Trial name)	Other Drug	Interventions	Run-in/ Washout period	Method of outcome assessment and timing of assessment
Aripiprazole vs. Haloperidol				
Kane, 2002	haloperidol	Aripiprazole 15 mg/d Aripiprazole 30 mg/d Haloperidol 10 mg/d Duration: 4 weeks	NR/5-7 days	Primary variables: PANSS total, positive and CGI-S scores timing of assessment: day 7, 14, 21, 28 Other variables: PANSS negative , PANSS-derived Brief Psychiatric Rating Scale (BPRS), mean CGI scores and responder rates (patients with a CGI-I score of 1 or 2 or a >= 30% decrease from baseline in PANSS total score were considered responders)

Evidence Table 3. Active-controlled trials in patients with schizophrenia

Author, year Country (Trial name)	Results	Method of adverse effects assessment?
Aripiprazole vs. Haloperidol		
Kane, 2002	PANSS total, p vs placebo (Placebo: -2.9) aripiprazole 15mg: -15.5, p<0.001 aripiprazole 30mg: -11.4, p=0.009 haloperidol 10mg: -23.8, p=0.001 PANSS positive, p vs placebo (Placebo: -0.6) aripiprazole 15mg: -4.2, p<0.001 aripiprazole 30mg: -3.8, p=0.001 haloperidol 10mg: -4.4, p<0.001 PANSS negative, p vs placebo (Placebo: -1.2) aripiprazole 15mg: -3.6, p=0.006 aripiprazole 30mg: -2.3, p=0.213 haloperidol 10mg: -2.9, p=0.043 PANSS-derived BPRS score, p vs placebo (Placebo: -1.1) aripiprazole 15mg: -3.1, p=0.001 aripiprazole 30mg: -3.0, p=0.001 haloperidol 10mg: -3.5, p<0.001 CGI-Severity, p vs placebo (Placebo: -0.1) aripiprazole 15mg: -0.6, p<0.001 aripiprazole 30mg: -0.4, p=0.019 haloperidol 10mg: -0.5, p=0.002 CGI-Improvement, p vs placebo (Placebo: 4.3) aripiprazole 15mg: 3.5, p<0.001 aripiprazole 30mg: 3.8, p=0.016 haloperidol 10mg: 3.7, p=0.002 Responder rate (%), p vs placebo (Placebo: 17) aripiprazole 15mg: 35, p=0.002 aripiprazole 30mg: 28, p=0.050 haloperidol 10mg: 26, p=0.089	EPS: Simpson-angus Scale, Barnes Akathisia Scale, adnd the Abnormal Involuntary Movement Scale Timing of assessment\: baseline and weekly

Evidence Table 3. Active-controlled trials in patients with schizophrenia

Author, year Country (Trial name)	Adverse effects reported
Aripiprazole vs. Haloperidol	
Kane, 2002	aripiprazole 15mg vs aripiprazole 30mg vs haloperidol 10mg vs placebe headache: 24(24%) vs 29(29%) vs 26(25%) vs24(23%) anxiety: 23(23%) vs 17(17%) vs 20(19%) vs 16(15%) insomnia: 19(19%) vs 22(22%) vs 25(24%) vs 18(17%) nausea: 15(15%) vs 14(14%) vs 6(6%) vs 7(7%) dizziness: 13(13%) vs 17(17%) vs 6(6%) vs 6(6%) abdominal pain: 9(9%) vs 6(6%) vs 6(6%) vs 5(5%) vomiting: 8(8%) vs 17(17%) vs 10(10%) vs 10(10%) akathisia: 8(8%) vs 12(12%) vs 24(23%) vs 11(11%) somnolence: 5(5%) vs10(10%) vs 13(13%) vs4(4%) asthenia: 3(3%) vs 6(6%) vs 5(5%) vs 3(3%) orthostatic hypotension: 2(2%) vs 7(7%) vs 1(1%) vs 3(3%) hypertonia: 2(2%) vs 8(8%) vs 3(3%) vs 5(5%) tremor: 2(2%) vs 3(3%) vs 7(7%) vs 3(3%) blurred vision: 1(1%) vs 2(2%) vs 8(8%) vs 1(1%) EPS related AEs: 18(18%) vs 20(20%) vs 37(36%) vs 22(21%) benztropine required for EPS: 8% vs 15% vs 30% vs 12% Body weight: Mean change form baseline (kg): 0.4 vs 0.9 vs 0.5 vs 0.2 >7% increase from baseline, % patients: 7* vs 4 vs 10** vs 1 (*p<0.05; **p<0.01 vs placebo) Prolactin level: Mean change from baseline (ng/dL): -7.0 vs -7.1 vs 22.5* vs -1.8 (*p<0.001 vs placebo) QTc interval: mean change form baseline (ms): -2.02 vs -3.38 vs 1.67 vs -3.45, NS QTc >= 450ms and a >= 10% increase (%): 0 vs 0 vs 3 vs 1 vital sign: NS

Evidence Table 3. Active-controlled trials in patients with schizophrenia

Author, year Country (Trial name)	Total withdrawals; withdrawals due to adverse events by drug	Comments
Aripiprazole vs. Haloperidol		
Kane, 2002	Withdrawals due to AEs for total N: 11% (45/414 pts); Withdrawls due to AEs: Aripiprazole 15mg: 9% (9 pts); Aripiprazole 30mg: 8% (8 pts); Haloperidol: 11% (11 pts); Placebo: 16% (17 pts)	Use of psychotropic agents was prohibited throughout the washout and treatment periods of the study, except for lorazepam for anxiety or insomnia. Lorazepam, administered intramuscularly, was also permmited for emerging agitation. Benztropine treatment was allowed for EPS, if judged necessary by the investigator. The dose was limited to a maximum of 6 mg per daym and was only permitted during the treatment phase of the study

Evidence Table 3. Active-controlled trials in patients with schizophrenia

Author, year Country (Trial name)	Other Drug	Interventions	Run-in/ Washout period	Method of outcome assessment and timing of assessment
Kasper, 2003 International (Fair)	haloperidol	aripiprazole 30 mg/d; mean dose 29.01 mg/d haloperidol 5 mg/d days 1-3; 10 mg/d day 4 onward; mean dose overall 8.90 mg/day Duration 52 weeks	NR; 5-day placebo washout for oral agents; washout for depot: one depot cycle plus one week	Primary outcome: time to failure to maintain response in responders. Response criteria required a >=20% decrease from baseline PANSS total at any single timepoint, provided that patients did not concurrently have 1) a CGI score of 6 or 7, or 2) an AE of worsening schizophrenia, or 3) a score of 5, 6, or 7 in at least one of the 4 PANSS psychotic subscale. Criteria for failure was a positive result on any of items 1, 2, or 3 above. Additional response criteria as the former, except >=30% decrease in PANSS was required.

Evidence Table 3. Active-controlled trials in patients with schizophrenia

Author, year Country (Trial name)	Results	Method of adverse effects assessment?
Kasper, 2003 International (Fair)	Response criteria, aripiprazole vs haloperidol >20% improvemtn in PANSS at a single timepoint: 72% vs 69%, NS >30% improvement in PANsS maintained for > 28 days plus one additional visit: 52% vs 44%, p=0.003 Time to failure to maintain response; risk ratio >20% improvement in PANSS: 77% vs 73%; 0.88; NS > 30% improvement in PANSS: 85% vs 79%; 0.70; NS Mean change from baseline to week 52 PANSS negative score: -5.3 vs -4.4, p<0.05 MADRS total score: -2.7 vs -1.4, p<0.05	Standard clinical assessments, vital signs, and movement assessments evaluated. SAS, AIMS, BAS at each study visit. ECG recordings and routine lab tests (hematology, serum chemistry, and urinalysis) at screening and weeks 2, 8, 18 (not ECG), 26, 38, and 52. Physical exams at weeks 8, 26, and 52. Plasma prolactin levels at baseline, weeks 2, 8, 18, 26, 38, and 52.

Evidence Table 3. Active-controlled trials in patients with schizophrenia

Author, year Country (Trial name)	Adverse effects reported
Kasper, 2003 International (Fair)	Adverse event, aripiprazole vs haloperiodol Weight gain: 44(5%) vs 14(3%), NS Insomnia: 185(22%) vs 88(20%), NS Psychosis: 156(18%) vs 70(16%), NS Akathisia: 111(13%) vs 108(25%), p<0.001 Anxiety: 108(13%) vs 50(12%), NS EPS: 84(10%) vs 130 (30%), p<0.001 Mean change at week 52 (LOCF): SAS: -0.2 vs 1.9, p<0.001 AIMS: -0.3 vs 0.2, p<0.001 BAS: 0.0 vs 0.4, p<0.001

Evidence Table 3. Active-controlled trials in patients with schizophrenia

Author, year Country (Trial name)	Total withdrawals; withdrawals due to adverse events by drug	Comments
Kasper, 2003 International (Fair)	Aripiprazole vs haloperidol, Total withdrawals: 494 (57.4%) vs 305 (70.4%), p=0.0001 Due to AEs: 70 (8%) vs 80 (19%), p=0.001	

Evidence Table 3. Active-controlled trials in patients with schizophrenia

Author, year Country (Trial name)	Other Drug	Interventions	Run-in/ Washout period	Method of outcome assessment and timing of assessment
Clozapine vs. Other				
Essock, 2000 Essock, 1996 Covell, 2004 Jackson, 2004 Inpatients	risperidone; conventional AP (all lumped together as "usual care")	clozapine Mean and median doses: clozapine: 486mg/d and 517mg/d Duration: 2 years	NR/ NR	Brief Psychiatric Rating Scale (BPRS) Clinical Global Impression (CGI) Quality of Life Inventory Abnormal Involuntary Movement Scale (AIMS) Assessments made every 4 months

Evidence Table 3. Active-controlled trials in patients with schizophrenia

Author, year Country (Trial name)	Results	Method of adverse effects assessment?
Clozapine vs. Other		
Essock, 2000 Essock, 1996 Covell, 2004 Jackson, 2004 Inpatients	Treatment Intolerence (TI); Treatment nonresponsive (TNR) treatment persistent over 2 years: TI-clozapine: 44% TI-usual care: 37% TNR-clozapine: 70% TNR-usual care: 30% *p<0.0001 1-year discharge rates: 27% for clozapine patients and 30% for control group (p=NS) after discharge, 3% of clozapine group re-admitted in first 6-months post-discharge 29% of control group re-admitted in first 6 months post-discharge p for clozapine vs control on re-admittance: p<0.001	NR Weight information collected from charts

Evidence Table 3. Active-controlled trials in patients with schizophrenia

Author, year Country (Trial name)	Adverse effects reported
Clozapine vs. Other	
Essock, 2000	Clozapine vs usual care
Essock, 1996	EPS-free months during 2 years: 18 months vs 14 months, p=0.001
Covell, 2004	Disruptiveness-free months during 2 years: 10 months vs 6 months, p<0.001
Jackson, 2004	Change in total BPRS during 2 years: 1 vs 3, p=NS
Inpatients	18% of TI patients taking clozapine developed blood dyscrasia vs 3% of TNR pts 15% of TI patients taking clozapine developed either agranulocytosis or severe leukopenia vs 3% of clozapine TNR patients Crossover-excluded analysis Weight loss or no change in weight over 24 months: Clozapine men vs women: 25% vs 29% Usual care men vs women: 19% vs 24% Weight gain 0%<gain<20% of baseline weight over 24 months: Clozapine men vs women: 62% vs 42% Usual care men vs women: 79% vs 68% Weight gain ≥20% of baseline weight over 24 months: Clozapine men vs women*: 13% vs 29% Usual care men vs women: 2% vs 8% (*p<0.01)

Evidence Table 3. Active-controlled trials in patients with schizophrenia

Author, year Country (Trial name)	Total withdrawals; withdrawals due to adverse events by drug	Comments
Clozapine vs. Other		
Essock, 2000 Essock, 1996 Covell, 2004 Jackson, 2004 Inpatients	Treatment discontinuation [Treatment Intolerence (TI); Treatment nonresponsive (TNR)]: TI-clozapine > TNR-clozapine, p<0.05 for discontinuation due to agranulocytosis or severe leukopenia TI-clozapine > TNR-clozapine, p<0.01 excluding individuals who stopped due to agranulocytosis or leukopenia	

Evidence Table 3. Active-controlled trials in patients with schizophrenia

Author, year Country (Trial name)	Other Drug	Interventions	Run-in/ Washout period	Method of outcome assessment and timing of assessment
Lee, 1999 U.S. (Fair)	Typical neuroleptics	clozapine mean dose 291.4 mg/day Typical APs, mean dose in chlorpromazine equivalents 488.3 mg/day Duration 12 months	NR/ NR	Schedule for Affective Disorders and Schizophrenia Lifetime (SADS-L) and Change (SADS-C) Cognitive test battery: Wechsler Adult Intelligence Scale Revised (WAIS-R), Consonant Trigram Test (CTT), Controlled Word Association Test (CWAT), Category Instance Generation Test (CIGT), Verbal List Learning (VLL) Immediate and Delayed Recall (VLL-IR, VLL-DR), Wisconsin Card Sorting Test (WCST), Wechsler Intelligence Scale for Children - Revised (WISC-R) at baseline, 6 weeks, 6 months, 12 months

Evidence Table 3. Active-controlled trials in patients with schizophrenia

Author, year Country (Trial name)	Results	Method of adverse effects assessment?
Lee, 1999 U.S. (Fair)	Mean change in score, baseline to 12 months, clozapine vs typical APs (within-group p-values): BPRS -5.8 vs -5.5 Digital Symbol Substitution Test +1.9 (p<0.0001) vs +0.2 (ns) Consonant Trigram -1.0 vs +1.9 Category Instance Generation +6.0 (p<0.001) vs +3.2 (ns) Controlled Word Association Test +7.1 (p<0.0001) vs -0.6 (ns) VLL-IR +0.5 vs +0.6 VLL-DR +0.5 vs +1.3 WCST-Category +0.2 vs +0.9 WCST-Perseverative Error +5.5 vs +4.2 WISC-R Maze +1.0 vs +0.6	SARS, AIMS

Evidence Table 3. Active-controlled trials in patients with schizophrenia

Author, year Country (Trial name)	Adverse effects reported
Lee, 1999 U.S. (Fair)	Change in EPS score, baseline to 12 months, clozapine vs typical APs: EPS +0.3 vs +1.0 (no significant intra-group change in either treatment)

Evidence Table 3. Active-controlled trials in patients with schizophrenia

Author, year Country (Trial name)	Total withdrawals; withdrawals due to adverse events by drug	Comments
Lee, 1999 U.S. (Fair)	11 total; Due to AEs: none reported	

Evidence Table 3. Active-controlled trials in patients with schizophrenia

Author, year Country (Trial name)	Other Drug	Interventions	Run-in/ Washout period	Method of outcome assessment and timing of assessment
Lieberman, 2003a Green, 2004 Multi-site, North America and Western Europe (Fair)	chlorpromazine	olanzapine 5-20 mg/day; mean modal dose 9.1 mg/day haloperidol 2-20 mg/day; mean modal dose 4.4 mg/day Duration 104 weeks	2-14 day washout	PANSS, MADRS, CGI severity assessed during washout and weekly through week 6, biweekly during weeks 7 through 12

Evidence Table 3. Active-controlled trials in patients with schizophrenia

Author, year Country (Trial name)	Results	Method of adverse effects assessment?
Lieberman, 2003a Green, 2004 Multi-site, North America and Western Europe (Fair)	Results given are for the first 12-weeks only Mean change in score, olanzapine vs haloperidol: PANSS total: -20.0 vs -14.22 (ns) Negative scale: -2.95 vs -1.21 (ns) Positive scale: -7.41 vs -7.06 (ns) General scale: -9.85 vs -6.24 (ns) CGI severity: -1.34 vs -1.02 (ns) MADRS: -2.58 vs -1.83 (ns) Note: P-values are based on a last-observation-carried-forward analysis. A separate mixed-model analysis found statistical significance in the between-treatment differences for PANSS total, PANSS negative, PANSS general, and MADRS scores. Responder status by substance use disorder (SUD), alcohol use disorder (AUD), and Cannabis use disorder (CUD) Responder vs non-responder; RR (95% CI) Overall (treatments combined): patients with SUD: 27% vs 69%; non-SUD patients: 35% vs 65%; 1.12 (0.94-1.32) patients with AUD: 19% vs 81%*; non-AUD patients: 35% vs 64%; 1.26 (1.07-1.49) (*p<0.05) patients with CUD: 28% vs 72%; non-CUD patients: 34% vs 66%; 1.08 (0.90-1.29) haloperidol patients: SUD: 31% vs 69%; non-SUD: 32% vs 68%; 1.01 (0.80-1.29) AUD: 27% vs 73%; non-AUD: 33% vs 67%; 1.10 (0.85-1.42) CUD: 32% vs 68%; non-CUD: 31% vs 69%; 0.99 (0.76-1.28) olanzapine patients: SUD: 23% vs 77%; non-SUD: 38% vs 62%; 1.24 (0.98-1.57) AUD: 9% vs 91%*; non-AUD: 38% vs 62%; 1.47 (0.21-1.79) (*p<0.05) CUD: 24% vs 76%; non-CUD: 36% vs 64%; 1.18 (0.92-1.50)	COSTART, SAS, AIMS, BAS at each assessment

Evidence Table 3. Active-controlled trials in patients with schizophrenia

Author, year Country (Trial name)	Adverse effects reported
Lieberman, 2003a	Results given for the first 12 weeks only
Green, 2004	Change in score, olanzapine vs haloperidol:
Multi-site, North America	SARS 0.00 vs +1.44 (p=0.001)
and Western Europe	BAS -0.13 vs 0.50 (p<0.001)
(Fair)	Weight (kg) +7.30 vs +2.64 (p<0.001)
	Incidence of parkinsonism 26.1% vs 54.8% (p<0.001)
	Incidence of akathisia 11.9% vs 51.2% (p<0.001)

Evidence Table 3. Active-controlled trials in patients with schizophrenia

Author, year Country (Trial name)	Total withdrawals; withdrawals due to adverse events by drug	Comments
Lieberman, 2003a Green, 2004 Multi-site, North America and Western Europe (Fair)	103 total; Due to AEs: 4 in olanzapine vs 9 in haloperidol Study completion rates for substance use disorder (SUD) vs non-SUD patients Haloperidol patients: SUD patients: 51% completed study vs 71% non-SUD patients (p<0.04) Olanzapine patients: SUD patients: 77% completed study vs 71% of non-SUD patients (p<0.53)	Younger population (mean age 23.8) with onset within past 5 years.

Evidence Table 3. Active-controlled trials in patients with schizophrenia

Author, year Country (Trial name)	Other Drug	Interventions	Run-in/ Washout period	Method of outcome assessment and timing of assessment
Lieberman, 2003b	chlorpromazine	Median doses: clozapine 300 mg/day chlorpromazine 400 mg/day Duration: 52 weeks	28 days/ NR	Primary outcomes: remission measured bby BPRS and CGI Chinese version of: BPRS, Scake for Assessment of Negative Symptoms (SANS), CGI, Clobal Assessment of Function Scale (GAF), the Simpson Angus Extrapytamidal Symptoms Scale (SAESS)
Shopsin, 1979	chlorpromazine	clozapine 300-800 mg/day chlorpromazine hydrochloride 600-1600 mg/day Duration: 35 days	NR/ 3-7 days	BPRS, CGI, Nurses' Observation Scale for Inpatient Evaluation (NOSIE)

Evidence Table 3. Active-controlled trials in patients with schizophrenia

Author, year Country (Trial name)	Results	Method of adverse effects assessment?
Lieberman, 2003b	clozapine vs chlorpromazine Remission: 65(81%) vs 63(79%) clozapine vs chlorpromazine, 95%CI Week 52 BPRS Total: 22.3 vs 22.1, (-2.5, 1.8) Anxiety/depression: 5.0 vs 5.0, (-0.5, 0.5) Anergy: 4.6 vs 4.9, (-0.5, 0.7) Thought disorder: 5.2 vs 5.1, (-1.0, 0.7) Agitation/Activation: 3.3 vs 3.4, (-0.2, 0.4) Hostility-paranoid: 4.2 vs 3.8 (-1.1, 0.3) SANS Total: 7.5 vs 9.5, (-1.9, 4.7) Affective flattening: 1.0 vs 2.2 (-0.0, 2.0) Poverty of thought: 0.4 vs 0.7 (-0.3, 0.7) Avolition: 3.0 vs 3.5 (-0.6, 1.5) Attention deficit: 0.3 vs 0.4 (-0.3, 0.5) Low level of interests: 2.8 vs 2.7 (-1.3, 1.0) CGI: 2.2 vs 2.0 (-0.6, 0.2) GAF: 72.4 vs 71.4 (-5.7, 4.8)	The Coding symbol and Thesaurus for Adverse Event Terminology (COSTART)
Shopsin, 1979	BPRS 18 items, n/18 items with p<0.05 vs baseline clozapine: 15/18 chlorpromazine: 6/18 BPRS 6 factors, n/6 factors with p<0.05 vs baseline clozapine: 6/6 chlorpromazine: 2/6 (thought disturbance and activation) placebo: 2/6 (activation and hostility suspiciousness) NOSIE: social competence, social interest, personal neatness, irritability, magifest psychosis, retardation, total patient assets, global severity clozapine and chlorpromazine both more improved than placebo, p<0.05 CGI global severity: clozapine and chlorpromazine both more improved than placebo, p<0.05 total Psychiatrics (CGI) improved: clozapine vs chlorpromazine: 90% vs 75% NOSIE (CGI) total improved: clozapine vs chlorpromazine: 100% vs 75%	modified Simpson-Angus Scale

Evidence Table 3. Active-controlled trials in patients with schizophrenia

Author, year Country (Trial name)	Adverse effects reported
Lieberman, 2003b	clozapine vs chlorpromazine (95%CI) EPS at Week 52 SAESS total: 0.28 vs 0.44 (-0.18, 0.44) Parkinsonian: 0.18 vs 0.33 (-0.11, 0.32) Other side effects at Week 52: SAESS dystonia: 0.07 vs 0.11 (0.10, 0.57) Blurred vision: 0.33 vs 0.46 (0.38, 0.74) Tense muscles: 0.06 vs0.08 (0.12, 0.87) Depressed affect: 0.25 vs 0.19 (1.00, 2.05) Sweating: 0.11 vs 0.06 (1.51, 6.10) Dry mouth: 0.32 vs 0.64 (0.17, 0.30) Akathisia: 0.09 vs 0.13 (0.26, 0.83) Objectively observed restlessness: 0.06 vs 0.09 (0.19, 0.85) Decreased urine production: 0.07 vs 0.12 (0.11, 0.47) Weight gain (kg): 9.9 vs 6.5, p=0.30
Shopsin, 1979	antiparkinsonism medication for EPSs (no. of patients): clozapine vs chlorpromazine: 0 vs 5 Hypersalivation: clozapine vs chlorpromazine: 11(85%) vs 1(8%) Sedative effect: NR, NS daytime drowsiness: chlorpromazine more than clozapine, NR

Evidence Table 3. Active-controlled trials in patients with schizophrenia

Author, year Country (Trial name)	Total withdrawals; withdrawals due to adverse events by drug	Comments
Lieberman, 2003b	Clozapine vs Chlorpromazine Total withdrawals: 10 vs 9 Withdrawals due to AEs: 2 vs 6	
Shopsin, 1979	NR	

Evidence Table 3. Active-controlled trials in patients with schizophrenia

Author, year Country (Trial name)	Other Drug	Interventions	Run-in/ Washout period	Method of outcome assessment and timing of assessment
Clozapine vs. Haloperidol				
Covington, 2000 U.S. (Poor)	haloperidol	clozapine, dose not reported haloperidol, dose not reported	NR/ NR	Premorbid Asocial Adjustment Scale SANS QLS Assessments at baseline, 6 weeks, 6 months, 12 months, and 24 months
Rosenheck, 1997 Rosenheck, 1999 Rosenheck, 1998 U.S. (Fair)	haloperidol	clozapine 100-900 mg/day; mean dose at week 26 = 552 mg/day. haloperidol 5-30 mg/day; mean dose at week 26 = 28 mg/day. Weekly blood counts taken in both treatment groups. Duration: 52 weeks.	NR/ NR	PANSS Heinrichs-Carpenter Quality of Life scale (QLS)

Evidence Table 3. Active-controlled trials in patients with schizophrenia

Author, year Country (Trial name)	Results	Method of adverse effects assessment?
Clozapine vs. Haloperidol		
Covington, 2000 U.S. (Poor)	Mean change in score , clozapine vs haloperidol: SANS at 12 months: -0.83 vs -0.01 SANS at 24 months: -0.38 vs -0.08 QLS at 12 months: +0.29 vs +0.20 QLS at 24 months: +0.37 vs +0.18	Not reported
Rosenheck, 1997 Rosenheck, 1999 Rosenheck, 1998 U.S. (Fair)	clozapine vs haloperidol, 20% reduction in score, at timepoint, PANSS (includes crossovers): Week 6: 24% vs 13% (p=0.008) Month 3: 31% vs 25% (ns) Month 6: 26% vs 12% (p=0.001) Month 9: 38% vs 31% (ns) 1 year: 37% vs 32% (ns) QLS: Week 6: 28% vs 28% (ns) Month 3: 39% vs 30% (ns; p=0.06) Month 6: 43% vs 37% (ns) Month 9: 40% vs 42% (ns) 1 year: 48% vs 45% (ns) % change in positive and negative symptoms for clozapine vs haloperidol: At 3 months (includes crossovers; n=366) Positive symptoms: -17.7% vs -13.8%, p=0.03 Negative symptoms: -9.5% vs -2.7%, p=0.03 At 1 year (does not include crossovers; n=235) Positive symptoms: -22.9% vs -16.7%, p=0.02 Negative symptoms: -17.0% vs -8.3%, p=0.09	Barnes Akathisia Scale (BAS), Abnormal Involuntary Movement Scale (AIMS), (Simpson-Angus Scale (SAS), weekly checklist of adverse reactions

Evidence Table 3. Active-controlled trials in patients with schizophrenia

Author, year Country (Trial name)	Adverse effects reported
Clozapine vs. Haloperidol	
Covington, 2000 U.S. (Poor)	Not reported
Rosenheck, 1997 Rosenheck, 1999 Rosenheck, 1998 U.S. (Fair)	clozapine vs haloperidol Tardive dyskinesia mean score, all timepoints: 3.6 vs 5.2 (p=0.005) Akathisia mean score: 2.6 vs 4.0 (p<0.001) EPS: 2.6 vs 4.0 (p<0.001) AEs: Leukopenia in 4 clozapine and 2 haloperidol patients. Neutropenia in 8 clozapine and 9 haloperidol patients. Agranulocytosis in 3 clozapine patients.

Evidence Table 3. Active-controlled trials in patients with schizophrenia

Author, year Country (Trial name)	Total withdrawals; withdrawals due to adverse events by drug	Comments
Clozapine vs. Haloperidol		
Covington, 2000 U.S. (Poor)	Not reported	
Rosenheck, 1997 Rosenheck, 1999 Rosenheck, 1998 U.S. (Fair)	245 total; Due to AEs: 26 in clozapine, 27 in haloperidol clozapine vs haloperidol discontinuations (no p-values given) due to lack of efficacy/worsening of symptoms: 15% vs 51% due to side effects: 30% vs 17% due to non-drug-related reasons: 55% vs 32% At 3 months, 81% of clozapine patients vs 73% of haloperidol patients (p<0.05) were continuing study drug by 1 year, 60% of clozapine patients vs 28% of haloperidol patients (p<0.0001) continued study medication	Patients with refractory schizophrenia, high levels of hospitalization

Evidence Table 3. Active-controlled trials in patients with schizophrenia

Author, year Country (Trial name)	Other Drug	Interventions	Run-in/ Washout period	Method of outcome assessment and timing of assessment
Olanzapine vs. Haloperidol				
Avasthi, 2001	haloperidol	olanzapine 5-20 mg/day haloperidol 5-20 mg/day Duration: 12 weeks	NR/ NR	Primary efficacy measure: BPRS, PANSS, Scale for the Assessment of Negative Symptoms (SANS), Montgomery-Asberg Depression Rating Scale (MADRS), Hamilton-Anxiety Scale (HAM-A), CGI, Quality of Life Scale (QOL)

Evidence Table 3. Active-controlled trials in patients with schizophrenia

Author, year Country (Trial name)	Results	Method of adverse effects assessment?
Olanzapine vs. Haloperidol		
Avasthi, 2001	Baseline vs endpoint, p vs baseline olanzapine: BPRS- total: 23.31(9.94) vs 9.50(7.06), p<0.01 BPRS- positive: 9.12(5.35) vs 3.75(4.25), p<0.01 BPRS- negative: 5.06(4.14) vs 3.12(3.42), p<0.01 BPRS- anxiety: 4.19(2.20) vs 1.31(1.66), p<0.01 PANSS- positive: 19.37(7.06) vs 11.44(4.11), p<0.01 PANSS- negative: 21.87(7.69) vs 15.62(7.93), p<0.01 PANSS- GenPsyPath: 36.56(9.46) vs 25.12(5.25), p<0.01 MADRS: 9.12(5.15) vs 3.00(2.42), p<0.01 HAM-A: 8.31(5.13) vs 2.31(2.47), p<0.01 CGI-severity: 4.68(0.89) vs 3.19(0.98), p<0.01 SANS total score: 32.94(19.69) vs 21.87(19.47), p<0.05 QOL: 47.0(24.64) vs 51.19(23.38), NS haloperidol: BPRS- total: 25(4.56) vs 12.57(13.39), p<0.05 BPRS- positive: 7.43(5.53) vs 3(5.51), p<0.05 BPRS- negative: 5.29(2.50) vs 3.57(2.37), NS BPRS- anxiety: 4.86(2.34) vs 2.71(2.87), NS PANSS- positive: 19.29(10.86) vs 10.86(8.49), p<0.05 PANSS- negative: 23.29(8.37) vs 16.86(8.71), p<0.05 PANSS- GenPsyPath: 38.29(9.45) vs 26.57(8.73), p<0.05 MADRS: 10.29(4.61) vs 5(4.58), NS HAM-A: 9.71(3.8) vs 4.57(4.72), NS CGI-severity: 4.29(1.11) vs 2.86(1.57), p<0.05 SANS total score: 39.71(12.05) vs 27.43(19.48), NS QOL: 38.29(31.74) vs 49.14(33.88), NS	UKU side Effect Rating Scale Simpson Angus Scale Barnes Akathisia Rating Scale

Evidence Table 3. Active-controlled trials in patients with schizophrenia

Author, year Country (Trial name)	Adverse effects reported
Olanzapine vs. Haloperidol	%
Avasthi, 2001	Baseline vs endpoint, p vs baseline olanzapine: Barnes akathisia: 0.44(1.09) vs 0(0), NS Simpson-Angus: 1.37(7.71) vs 0.75(1.39), NS haloperidol: Barnes akathisia: 0.43(0.79) vs 0.29(0.49), NS Simpson-Angus: 1.43(2.57) vs 0.86(1.86), NS Emergent side-effect, N(%) olanzapine vs haloperidol asthesnia: 7(43.7%) vs 3(42.9%) sleepiness: 8(50%) vs 2(28.6%) tension: 0(0%) vs 4(57.1%) increased duration of sleep: 7(43.7%) vs 2(28.6%) dystonia: 0(0%) vs 1(14.3%) rigidity: 1(6.2%) vs 5(71.4%) hypokinesia: 1(6.2%) vs 2(28.6%) tremor: 5(31.2%) vs 4(57.1%) akathesia: 1(6.2%) vs 2(28.6%) accomodation disturbance: 0(0%) vs 2(28.6%) increased salivation: 3(18.7%) vs 0(0%) reduced salivation: 4(25%) vs 0(0%) constipation: 5(31.2%) vs 0(0%) micturition disturbances: 1(6.2%) vs 2(28.6%) weight gain: 13(81.2%) vs 2(28.6%) others: 5(31.2%) vs 7(100%) *Others: polyuria, orthostatic dizziness, papitations, nausea, increased sweating and menstrual disturbances.

Evidence Table 3. Active-controlled trials in patients with schizophrenia

Author, year Country (Trial name)	Total withdrawals; withdrawals due to adverse events by drug	Comments
Olanzapine vs. Haloperidol		
Avasthi, 2001	NR	

Evidence Table 3. Active-controlled trials in patients with schizophrenia

Author, year Country (Trial name)	Other Drug	Interventions	Run-in/ Washout period	Method of outcome assessment and timing of assessment
Barak, 2002	haloperidol	Mean dosage at the end olanzapine 13.1(5.9) mg/day, range 5.0-25.0 haloperidol 7.2(2.9) mg/day range NR mean duration: 15(8) month, range 3-24	NR	Primary outcome: PANSS and CGI

Evidence Table 3. Active-controlled trials in patients with schizophrenia

Author, year Country (Trial name)	Results	Method of adverse effects assessment?
Barak, 2002	Baseline vs posttreatment PANSS total: haloperidol: 79.3(15.3) vs 74.3(9.6) olanzapine: 84.0(14.5) vs 65.1(19.3) *change from baseline, haloperidal vs olanzapine, p=0.02 PANSS negative: haloperidol: 18.2(7.9) vs 20.5(6.9) olanzapine: 18.9(3.4) vs 15.2(3.0) *change from baseline, haloperidal vs olanzapine, p=0.0003 PANSS general: haloperidol: 40.9(12.3) vs 36.5(7.0) olanzapine: 40.7(9.0) vs 34.5(10.6) PANSS positive: haloperidol: 20.2(7.3) vs 17.3(6.1) olanzapine: 24.4(8.0) vs 15.4(7.8) CGI haloperidol: 4.8(0.9) vs 4.4(0.5) olanzapine: 4.9(1.2) vs 3.8(0.9)	weight, blood pressure and pulse

Evidence Table 3. Active-controlled trials in patients with schizophrenia

Author, year Country (Trial name)	Adverse effects reported
Barak, 2002	olanzapine (n=10) vs haloperidol (n=10) weight: 4.5(0.6) vs 2.1(1.8), p=0.3 blood pressure: NR, NS pulse: NR, NS concomitant psychotropic medication use: 3 vs 7

Evidence Table 3. Active-controlled trials in patients with schizophrenia

Author, year Country (Trial name)	Total withdrawals; withdrawals due to adverse events by drug	Comments
Barak, 2002	olanzapine vs haloperidol total withdrawal: 4 vs 4 withdrawal due to AEs: 0 vs 3 * the three patients discontinued from the haloperidol group were treated with higher doses compared to other 7 patients (9.0 vs 5.4)	

Evidence Table 3. Active-controlled trials in patients with schizophrenia

Author, year Country (Trial name)	Other Drug	Interventions	Run-in/ Washout period	Method of outcome assessment and timing of assessment
Beasley, 1997	haloperidol benzodiazepine: lorazepam equivalents maximum dose of 10 mg/day	olanzapine 1mg/day olanzapine 5(2.5) mg/day olanzapine 10(2.5) mg/day olanzapine 15(2.5) mg/day haloperidol 15(5.0) mg/day Duration: 6 weeks acute phase followed buy a 46 weeks extension phase for responders to acute phase. The acute-phase results are reported here.	4-7 days/2 days	BPRS extracted from the PANSS PANSS CGI Severity Patient Global Impression (PGI)

Evidence Table 3. Active-controlled trials in patients with schizophrenia

Author, year Country (Trial name)	Results	Method of adverse effects assessment?
Beasley, 1997	olz-1 vs olz-5 vs olz-10 vs olz-15 vs hal-15 Endpoint change from baseline, Mean(SD) BPRS total: -10.5(16.6) vs -13.4(14.8) vs -13.8(17.8) vs -16.4(14.3) vs -12.4(16.0) BPRS positive: -3.1(4.9) vs -4.5(4.6)* vs -4.3(5.3) vs -5.3(4.6)* vs -4.8(5.1) BPRS negative: -2.1(3.5) vs -2.4(3.4) vs -2.3(3.6) vs -2.8(3.0) vs -1.9(2.9) PANSS total: -16.8(28.7) vs -21.4(25.2) vs -22.7(29.2) vs -26.7(23.7) vs -20.0(25.9) PANSS positive: -4.3(8.3) vs -6.7(6.7) vs -6.2(8.5) vs -8.2(7.4)* vs -6.5(8.6) PANSS negative: -4.4(8.2) vs -5.1(7.5) vs -5.4(8.0) vs -6.6(6.9) vs -4.8(6.3) PANSS G psych: -8.2(14.6) vs -9.7(14.4) vs -11.1(15.2) vs -11.9(12.1) vs -8.7(13.4) CGI Severity: -0.8(1.4) vs -1.0(1.1) vs -1.2(1.2) vs -1.5(1.5)* vs -1.1(1.3) -All p<0.001 compared to baseline. *p<0.05 compared with olz-1	EPS assessment: -Simpson-Angus Scale -Barnes Akathisia Scale Dyskinesias: -Assessment of Involuntary Movement Scale (AIMS)

Evidence Table 3. Active-controlled trials in patients with schizophrenia

Author, year Country (Trial name)	Adverse effects reported
Beasley, 1997	olz-1 vs olz-5 vs olz-10 vs olz-15 vs hal-15 (%), p value Increased ALT: 3.4 vs 6.9 vs 9.3a vs 14.6bc vs 1.2, p=0.007 Headache: 10.2 vs 2.3f vs 9.3 vs 9.0 vs 7.4, p=0.296 EPS: 2.3 vs 2.3c vs 1.2c vs 5.6 vs 13.6b, p=0.001 Insomnia: 11.4 vs 6.9 vs 4.7 vs 5.6 vs 2.5f, p=0.172 Akathisia: 0.0 vs 0.0d vs 1.2d vs3.4c vs 14.8e, p<0.001 Hypertonia: 0.0 vs 1.1a vs 1.2a vs 1.1a vs 9.9b, p<0.001 Dyskinesia: 1.1 vs 0.0a vs 1.2 vs 0.0a vs 6.2, p=0.009 Dystonia: 0.0 vs 0.0a vs 0.0a vs 0.0a vs 4.9f, p=0.002 Increased GGT: 0.0 vs 4.6f vs 2.3 vs 0.0 vs 0.0, p=0.030 Increased salivation: 0.0 vs 1.1 vs 1.2 vs 0.0a vs 6.2f, p=0.009 Tremor: 0.0 vs 1.1c vs 1.2c vs 0.0d vs 11.1e, p<0.001 a: p≤0.05 compared with Hal b: p≤0.01 compared with Olz-1.0 c: p≤0.01 compared with Hal d: p≤0.001 compared with Hal e: p≤0.001 compared with Olz-1.0 f: p≤0.05 compared with Olz-1.0 -Weight gain was associated with increasing olanzapine dose;a slight decrease in weight was seen in the haloperidol treatment group. olz-1 vs olz-5 vs olz-10 vs olz-15 vs oal-15 (%), p value Simpson-Angus: -0.61(2.95) vs -1.08(3.76)d vs -0.17(3.45)d vs -0.66(3.21)d vs 3.00(8.06)e Barnes: -0.19(0.61) vs -0.20(0.69)d vs -0.18(0.84)d vs -0.07(0.74)d vs 0.47(1.26)b AIMS: -0.71(2.58) vs -0.55(2.44)a vs 0.07(2.02) vs -0.33(2.69) vs 0.15(3.25)c a: p≤0.1 vs Hal b: p≤0.1 vs Olz-1 c: p≤0.5 vs Olz-1 d: p≤0.01 vs Hal e: p≤0.01 vs Olz-1

Evidence Table 3. Active-controlled trials in patients with schizophrenia

Author, year Country (Trial name)	Total withdrawals; withdrawals due to adverse events by drug	Comments
Beasley, 1997	Olz-1 vs Olz-5 vs Olz-10 vs Olz-15 vs Hal-15 Total withdrawals (%): 45.5 vs 44.8 vs 38.4 vs 38.2 vs 46.9 vs 42.7 Withdrawals due to AEs: 11.4 vs 16.1 vs 7.0 vs 9.0 vs 14.8 vs 11.6	

Evidence Table 3. Active-controlled trials in patients with schizophrenia

Author, year Country (Trial name)	Other Drug	Interventions	Run-in/ Washout period	Method of outcome assessment and timing of assessment
Breier, 2002	haloperidol	IM olanzapine 2.5mg (mean: 4.0) IM olanzapine 5.0mg (mean:6.9) IM olanzapine 7.5mg (mean: 9.8) IM olanzapine 10mg (mean:12.6) IM haloperidol 7.5mg (mean 9.9) IM placebo (mean: n/a) 24-hour study, with a maximum of three injections allowed during this time % of pts receiving ≥2 injections over 24h: (p<0.001 for all vs placebo) olz 2.5: 52.1% olz 5.0: 35.5% olz 7.5: 28.3% olz 10.0: 23.9% (p<0.05 vs olz 2.5) hal 7.5: 25% (p<0.05 vs olz 2.5) placebo: 66.7%	NR/ min 2 hour washout in screening period	Primary efficacy measure: PANSS-EC Other measures: Agitated Behavior Scale (ABS), Agitation Calmnes Evaluation (ACES), PANSS-derived Brief Psychiatric Rating Scale (BPRS), Clinical Global Impressions-Severity (CGI-S) Pts assessed at screening visit, 30, 60, 90 minutes and 2, 4, 6, 12, and 24 hours after first injection

Evidence Table 3. Active-controlled trials in patients with schizophrenia

Author, year Country (Trial name)	Results	Method of adverse effects assessment?
Breier, 2002	Change from baseline- Mean (SD), p vs olz 2.5mg, p vs placebo PANSS-EC, 2 hours after IM injection olz 2.5mg: -5.5(4.6), NA, p=0.01 olz 5.0mg: -8.1(5.3), p=0.01, p<0.001 olz 7.5mg: -8.7(5.0), p=0.001, p<0.001 olz 10mg: -9.4(4.9), p<0.001, p<0.001 hal 7.5mg: -7.5(5.9), p=0.04, p<0.001 placebo: -2.9(4.7), p=0.01, NA *other between treatment comparison: p=NS olz 2.5 vs olz 5.0 vs olz 7.5 vs olz 10 vs hal 7.5 vs placebo- Mean(SD) 2 hours after first IM injection BPRS total: -8.2(9.1)e vs -10.4(7.5) vs -12.0(7.0) vs -12.0(5.9) vs -9.2(7.2)b vs -3.7(5.5)a BPRS positive: -1.5(3.1) vs -1.7(2.8) vs -2.1(2.9) vs -1.9(2.3) vs -1.4(2.2) vs -0.4(1.3)a ABS: -5.8(5.5)d vs -9.0(5.5) vs -10.5(5.6)c vs -10.4(5.7)c vs -7.7(5.2)b vs -3.0(5.0)a ACES: 1.3(1.5)d vs 2.3(1.9) vs 2.4(1.7) vs 2.6(1.7)c vs 1.8(1.6)b vs 0.7(1.2)a a: p<0.05 vs all IM olanzapine treatment groups, except olz at 2.5mg on the ACES b: p<0.05 vs placebo c: p<0.05 vs hal d: p<0.05 vs all other olz treatment e: p<0.05 vs olz at 7.5 mg and 10.0mg olz 2.5 vs olz 5.0 vs olz 7.5 vs olz 10 vs hal 7.5 vs placebo- Mean(SD) Mean change from baseline to 24 hours after first IM injection PANSS-EC: -4.9(4.3) vs -5.5(4.9) vs -5.5(4.1) vs -5.9(5.2) vs -4.5(4.0) vs -3.1(3.3)a BPRS total: -8.4(7.4) vs -9.2(7.8) vs -9.6(7.5) vs -9.0(7.7) vs -7.3(7.5) vs -4.3(5.4)a BPRS positive: -1.5(2.3) vs -2.0(2.6) vs -1.9(2.7) vs -1.7(2.4) vs -1.8(3.0)b vs -0.6(2.2)a ABS: -5.7(4.2) vs -6.7(5.9) vs -7.7(5.8)c vs -7.4(7.0)c vs -5.0(4.1)b vs -2.6(4.0)a CGI-S: -0.3(0.5) vs -0.5(0.8)b vs -0.6(0.7)b vs -0.4(0.5) vs -0.4(0.6) vs -0.2(0.6) ACES:+ 0.9(0.8) vs +1.1(1.1) vs +1.0(1.0) vs +0.9(0.9) vs +0.8(0.7) vs +0.5(0.7)a a: p<0.05 vs all IM olanzapine treatment groups, except olz at 2.5mg on the BPRS positive b: p<0.05 vs placebo c: p<0.05 vs hal 7.5mg	Simpson-Angus and Barnes Akathisia Scales

Evidence Table 3. Active-controlled trials in patients with schizophrenia

Author, year Country (Trial name)	Adverse effects reported
Breier, 2002	olz 2.5 vs olz 5.0 vs olz 7.5 vs olz 10 vs hal 7.5 vs placebo Hypotension: 4.2% vs 4.4% vs 2.2% vs 4.3% vs 0% vs 0%, (no between group differences observed) Acute dystonia: 0% of all olz (n=185) pts vs 5.0% hal vs 0% placebo pts olz 2.5 vs olz 5.0 vs olz 7.5 vs olz 10 vs hal 7.5 vs placebo Treatment emergent parkinsonism: 0% vs 0% vs 0% vs 2.9% 16.7% vs 0% (p=0.03 for hal vs olz 2.5 and vs olz 5.0; p=0.01 for hal vs olz 7.5 and hal vs placebo) Treatment emergent akathisia: 0% vs 4.8% vs 0% vs 0% vs 7.9% vs 0% (no between group differences observed) Anticholinergic medication given to 7.5% hal pts and 2.1% olz 2.5 pts (no between group differences) No pt had increase in QTc of ≥500 milliseconds Baseline to 24h changes in mean(SD) QTc intervals, "none were clinically relevant" -4.3(22.3) vs -3.1(23.2) vs -2.8(19.6) vs -1.9(31.0) vs +6.5(24.7) vs +1.2(21.5)

Evidence Table 3. Active-controlled trials in patients with schizophrenia

Author, year Country (Trial name)	Total withdrawals; withdrawals due to adverse events by drug	Comments
Breier, 2002	NA	

Evidence Table 3. Active-controlled trials in patients with schizophrenia

Author, year Country (Trial name)	Other Drug	Interventions	Run-in/ Washout period	Method of outcome assessment and timing of assessment
Glick, 2002 (See Tollefson, 1997)		olanzapine 5-20 mg/day haloperidol 5-20 mg/day risperidone 4-12 mg/day Duration: 6 weeks		
Hamilton, 1998 (See Beasley 1996)		See Beasley, 1996 Duration 24 weeks	See Beasley, 1996	BPRS, SANS, CGI severity at baseline and weekly visits QLS
Kinon, 2004 US Inpatients	haloperidol + lorazepam	olanzapine 10-20 mg po qd + lorazepam (Mean dose for olanzapine: 17.1mg and mean dose lorazepam: 2.6 mg) haloperidol 10-20 mg po qd + lorazepam (Mean dose for haloperidol: 15.7mg and mean dose lorazepam: 2.94 mg) lorazepam decreased until no patient received it during days 18-21 3 week duration	24hr washout	Primary efficacy: PANSS Agitation at 1,4, 8, 16, and 24hrs, daily for first week, and once/week for weeks 2 and 3. Secondary outcomes: CGI-Severity and Improvement Scales, Overt Agitation Severity Scale (OASS), and Nurses Obsercation Scael for Inpatient Evaluation (NOSIE). Other measurements: frequency of time in restraints or seclusion and special nursing watch, and frequency of lorazepam treatment. DAI-10 (Drug Attitude Inventory) used for patient response to medication.

Evidence Table 3. Active-controlled trials in patients with schizophrenia

Author, year Country (Trial name)	Results	Method of adverse effects assessment?
Glick, 2002 (See Tollefson, 1997)		
Hamilton, 1998 (See Beasley 1996)	Mean change in score at 24 week extension (baseline to LOCF) olanzapine (low, medium, high) vs haloperidol: BPRS total score (-15.0, -22.8, -19.9) vs -19.9 (ns) SANS summary score (-2.5, -4.7, -5.5) vs -2.7 (p = 0.049 for Olz-H) CGI severity score (-1.1, -1.6, -1.2) vs -0.9 (ns) QLS total score (+6.7, +24.6, +15.5) vs +4.9 (ns) QLS intrapsychic foundations (+2.3, +8.1, +4.2) vs +0.9 (ns) QLS interpersonal relations (+2.5, +9.3, +5.9) vs +3.1 (ns) QLS instrumental role category (+1.5, +5.6, +4.0) vs +0.9 (ns) QLS common objects and activities (+0.4, +1.7, +1.4) vs 0.0 (ns)	See Beasley, 1996
Kinon, 2004 US Inpatients	olanzapine vs haloperidol Mean change in score (SD): PANSS Agitiation scores, at 1 hour: -5.79 vs -4.89 (p<0.001) At day 21 (LOCF): -14.00(10.71) vs -11.21(11.67), p=0.044 PANSS Total score: -20.73(10.81) vs -16.03(13.76), p=0.51 OASS: improvement olan > hal for items: fidgeting and perseverating (p=0.41 and p=0.50 respectively) Days (SD) to discharge: 13.73 (2.43) days vs 13.13 (3.75) days, p=NS Proportion of patients using restraints, seclusions, or special nursing watch: 17.3% vs 16.7%, p=NS Mean number of hours (SD) used per patient per day: 1st week: 1.57 (5.52) vs 2.59 (6.79) 2nd week: 0.33 (2.23) vs 0.92 (4.05) 3rd week: 0 vs 0.55 (2.74) Mean baseline to end-point changes in NOSIE: -8.88 (15.82) vs -7.74 (16.82), p=NS Patient scores for satisfaction with medication at end-point: +0.61 vs-0.72, p=0.52	Treatment-emergent AEs, changes in vital signs, and laboratory analyses recorded. EPS measured by the Simpson-Angus Scale and the Barnes Akathisia Scale. Change in alterness or sedation assessed with the Tranquilization Scale (modified)

Evidence Table 3. Active-controlled trials in patients with schizophrenia

Author, year Country (Trial name)	Adverse effects reported
Glick, 2002 (See Tollefson, 1997)	
Hamilton, 1998 (See Beasley 1996)	Not reported
Kinon, 2004 US Inpatients	olanzapine vs haloperidol Patients reporting all treatment-emergent AEs: 67.3% vs 85.4%, p=0.38 Weight gain: +2.8kg vs -0.64kg, p<0.001 Simpson-Angus: -0.41(2.18) vs +0.64(3.53), p=NS Patients receiving antiparkinsonian mediations: 0% vs 8.3%, p=0.05 Mean change in Barnes-Akathisia scale : olanzapine only reported: -1.34 Dystonia: 0% vs 8.3%, p=0.05 Hypertonia: 0% vs 8.3%, p=0.05 Increased salivation: 0% vs 8.3%, p=0.05 Headache: 11.5% vs 25.0%, p=NS Nervousness: 7.7% vs 16.7%, p=NS Anxiety: 11.5% vs 4.2%, p=NS Insomnia: 5.7% vs 13.0%, p=NS Somnolence: 17.3% vs 25.0%, p=NS Pain: 9.6% vs 10.0%, p=NS Agitation: 9.6% vs 10.0%, p=NS

Evidence Table 3. Active-controlled trials in patients with schizophrenia

Author, year Country (Trial name)	Total withdrawals; withdrawals due to adverse events by drug	Comments
Glick, 2002 (See Tollefson, 1997)		
Hamilton, 1998 (See Beasley 1996)	Due to AEs: 2 in olanzapine (low) 3 in olanzapine (medium) 2 in olanzapine (high) 4 in haloperidol 3 in placebo	Results represent patients who responded during acute phase and continued in extension phase.
Kinon, 2004 US Inpatients	Olanzapine vs haloperidol Total % of patients who discontinued (of original 100 patients, 43 dropped out): 32.7% vs 54.2% Withdrawals due to AEs: 1.9% vs 16.7%, p=0.013 Mean time to discontinuation: 17.69 days vs 14.21 days, p=0.016	

Evidence Table 3. Active-controlled trials in patients with schizophrenia

Author, year Country (Trial name)	Other Drug	Interventions	Run-in/ Washout period	Method of outcome assessment and timing of assessment
Revicki, 1999 Austria, Belgium, Canada, France, Germany, Italy, Poland, Portugal, Spain, United Kingdom, United States (See Tollefson, 1997)		See Tollefson, 1997 Duration 6 weeks, followed by 1-year blinded extension phase that included responders only. Mean modal dose during acute phase: olanzapine 12.9 mg/day; haloperidol 11.3 mg/day Mean modal dose during extension phase: olanzapine 13.3 mg/day; haloperidol 12.4 mg/day	See Tollefson, 1997	See Tollefson, 1997; Also QLS and SF-36 at baseline and at end of acute phase (6 weeks), then every 8 weeks for patients in the extension phase.
Rosenheck, 2003 U.S. (Fair)	haloperidol	olanzapine 5-20 mg/day, mean dose 15.8 mg/day during last 6 months; given with placebo benztropine. haloperidol 5-20 mg/day, mean dose 14.3 during last 6 months; given with benztropine mesylate 1-4 mg/day. Duration 12 months	NR/ NR	PANSS, QLS at baseline, 6 weeks, and 3, 6, 9, and 12 months Neurocognitive status (RBANS, Grooved Pegboard, Wisconsin Card Sorting Test-64 Card Version, Trail-making test part B, Controlled Oral Word Association Test, Wide Range Achievement Test-Revised) at baseline and 3, 6, and 12 months

Evidence Table 3. Active-controlled trials in patients with schizophrenia

Author, year Country (Trial name)	Results	Method of adverse effects assessment?
Revicki, 1999 Austria, Belgium, Canada, France, Germany, Italy, Poland, Portugal, Spain, United Kingdom, United States (See Tollefson, 1997)	Mean change from baseline score during acute phase, olanzapine vs haloperidol: QLS total: 6.5 vs 3.1 (p=0.005) QLS intrapsychic foundations 2.8 vs 1.0 (p<0.001) QLS interpersonal relations 2.0 vs 0.9 (p=0.036) QLS instrumental role category 1.2 vs 1.0 (ns) QLS common objects and activities 0.5 vs 0.3 (ns) SF-36 summary score, mental component 6.3 vs 2.8 (p<0.001) SF-36 summary score, physical component 0.1 vs -0.2 (ns) Mean change from baseline score to extension phase endpoint: QLS total 13.2 vs 7.1 (p=0.001) QLS intrapsychic foundations 4.7 vs 1.8 (p<0.001) QLS interpersonal relations 4.3 vs 3.0 (ns) QLS instrumental role category 3.2 vs 1.7 (p=0.015) QLS common objects and activities 1.1 vs 0.6 (ns)	See Tollefson, 1997 Assessments made weekly during acute phase and every 8 weeks during extension phase.
Rosenheck, 2003 U.S. (Fair)	Mean scores not provided; graphs and statistical significance only. No between-group differences in PANSS total, PANSS positive, or PANSS negative subscales, QLS, SF-36, or CG Outcomes scale. No differences at any time point in proportion of patients with 20% improvement in PANSS scores. Neurocognitive tests: Significantly greater improvement in olanzapine on motor functioning (p=0.02) and memory (p=0.03) but not on Wisconsin Card Sorting test (ns).	BAS, AIMS, SARS, CGI, SF-36 checklist of adverse reactions, at baseline, 6 weeks, 3, 6, 9, and 12 months. Neurocognitive status at baseline and at 3, 6, and 12 months: RBANS, Grooved Pegboard, Wisconsin Card Sorting Test-64 Card Version, Trail-Making Test Part B, Controlled Oral Word Association Test, Wide Range Achievement Test-Revised

Evidence Table 3. Active-controlled trials in patients with schizophrenia

Author, year Country (Trial name)	Adverse effects reported
Revicki, 1999 Austria, Belgium, Canada, France, Germany, Italy, Poland, Portugal, Spain, United Kingdom, United States (See Tollefson, 1997)	See Tollefson, 1997
Rosenheck, 2003 U.S. (Fair)	olanzapine vs haloperidol: BAS: significantly lower scores in olanzapine (p<0.001) AIMS: no between-group differences Patient reports of weight gain at 6 months 32.5% vs 12.5% (p=0.002); at 12 months 24.7% vs 8.3% (p=0.01) Restlessness* at 6 months 15.1% vs 28.0% (p=0.04); at 12 months 15.2% vs 28.0% (p=0.06)

Evidence Table 3. Active-controlled trials in patients with schizophrenia

Author, year Country (Trial name)	Total withdrawals; withdrawals due to adverse events by drug	Comments
Revicki, 1999 Austria, Belgium, Canada, France, Germany, Italy, Poland, Portugal, Spain, United Kingdom, United States (See Tollefson, 1997)	See Tollefson, 1997	Outcome: quality of life
Rosenheck, 2003 U.S. (Fair)	132 total; Due to AEs: 15 in olanzapine vs 6 in haloperidol	

Evidence Table 3. Active-controlled trials in patients with schizophrenia

Author, year Country (Trial name)	Other Drug	Interventions	Run-in/ Washout period	Method of outcome assessment and timing of assessment
Tollefson, 1997 Breier, 1999 Gilmore, 2002 Glick, 2002 Goldstein, 2002 Gomez, 2001 Hamilton, 2000 Kennedy, 2003 Kinon, 2001 Revicki, 1999 Sanger, 1999 Tohen, 2001 Tran, 1999 Tollefson, 1998 Tollefson, 1999 Tunis, 1999 174 sites in 17 countries (Fair)	haloperidol	olanzapine 5-20 mg/day; mean dose 13.2 mg/day haloperidol 5-20 mg/day; mean dose 11.8 mg/day Duration 6 weeks	2-9 day washout	Weekly assessments of efficacy: PANSS, CGI, BPRS extracted from PANSS, MADRS, QLS, SF36, prolactin

Evidence Table 3. Active-controlled trials in patients with schizophrenia

Author, year Country (Trial name)	Results	Method of adverse effects assessment?
Tollefson, 1997 Breier, 1999 Gilmore, 2002 Glick, 2002 Goldstein, 2002 Gomez, 2001 Hamilton, 2000 Kennedy, 2003 Kinon, 2001 Revicki, 1999 Sanger, 1999 Tohen, 2001 Tran, 1999 Tollefson, 1998 Tollefson, 1999 Tunis, 1999 174 sites in 17 countries (Fair)	Change in mean score from baseline to acute phase endpoint, olanzapine vs haloperidol: BPRS total -10.9 vs -7.9 (p<0.02) PANSS total -17.7 vs -13.4 (p=0.05) PANSS positive -4.7 vs -3.8 (ns) PANSS negative -4.5 vs -3.2 (p=0.03) CGI severity -1.0 vs -0.7 (p<0.03) MADRS -6.0 vs -3.1 (p=0.001)	Clinical report form records, AMDP-5, vital signs, SARS, BAS, laboratory tests, ECGs, ophthalmological examinations, and chest X-rays. Weekly assessments of safety: EPS, SAS, BAS, AIMS.

Evidence Table 3. Active-controlled trials in patients with schizophrenia

Author, year Country (Trial name)	Adverse effects reported
Tollefson, 1997	EPS and sleep disruptions, several anticholinergic effects, and hypersalivation significantly more frequent in haloperidol than olanzapine.
Breier, 1999	
Gilmore, 2002	
Glick, 2002	olanzapine vs haloperidol (p<0.05):
Goldstein, 2002	Excessive appetite 24.0% vs 12.4%
Gomez, 2001	Dry mouth 22.2% vs 16.2%
Hamilton, 2000	Interrupted sleep 19.0% vs 30.3%
Kennedy, 2003	Shortened sleep 15.1% vs 24.8%
Kinon, 2001	Drowsiness 26.0% vs 31.3%
Revicki, 1999	Hypertonia 8.4% vs 21.1%
Sanger, 1999	Tremor 16.5% vs 26.3%
Tohen, 2001	Acute dyskinesia 2.8% vs 8.0%
Tran, 1999	Hypokinesia 5.1% vs 13.5%
Tollefson, 1998	Akathisia 14.2% vs 35.5%
Tollefson, 1999	
Tunis, 1999	Estimated % of patients discontinued at 12 months: 37% vs 47%
174 sites in 17 countries	Estimated mean time to discontinuation (day): 271 vs 241
(Fair)	Relapse rates at 52 weeks among responders: 34% vs 37%, p=0.466

Evidence Table 3. Active-controlled trials in patients with schizophrenia

Author, year Country (Trial name)	Total withdrawals; withdrawals due to adverse events by drug	Comments
Tollefson, 1997 Breier, 1999 Gilmore, 2002 Glick, 2002 Goldstein, 2002 Gomez, 2001 Hamilton, 2000 Kennedy, 2003 Kinon, 2001 Revicki, 1999 Sanger, 1999 Tohen, 2001 Tran, 1999 Tollefson, 1998 Tollefson, 1999 Tunis, 1999 174 sites in 17 countries (Fair)	799 total; Due to AEs: 60 (4.5%) in olanzapine 48 (7.3%) in haloperidol (p=0.01)	

Evidence Table 3. Active-controlled trials in patients with schizophrenia

Author, year Country (Trial name)	Other Drug	Interventions	Run-in/ Washout period	Method of outcome assessment and timing of assessment
Tran, 1999 (See Tollefson, 1997)		See Tollefson, 1997 Duration 6 weeks, followed by 1-year blinded extension phase that included responders only. Mean modal dose during acute phase: olanzapine 11.5 mg/day; haloperidol 10 mg/day. Mean modal dose during extension phase: olanzapine 12.9 mg/day; haloperidol 13.8 mg/day.	See Tollefson, 1997	See Tollefson, 1997

Evidence Table 3. Active-controlled trials in patients with schizophrenia

Author, year Country (Trial name)	Results	Method of adverse effects assessment?
Tran, 1999 (See Tollefson, 1997)	Change in mean score at acute phase and extension phase endpoints, olanzapine vs haloperidol: All schizoaffective patients Acute BPRS total -10.52 vs -5.50 (p=0.002) Acute PANSS total -17.05 vs -9.06 (p=0.003) Acute PANSS positive -4.11 vs -2.49 (ns) Acute PANSS negative -4.16 vs -2.07 (p=0.006) Acute MADRS total -7.39 vs -0.79 (p<0.001) Extension BPRS total -15.96 vs -14.44 (ns) Extension PANSS total -26.80 vs -24.68 (ns) Extension PANSS positive -7.21 vs -7.72 (ns) Extension PANSS negative -6.25 vs -5.08 (ns) Extension MADRS total -8.26 vs -3.32 (p=0.045) Bipolar type Acute BPRS total -10.60 vs -5.86 (p=0.012) Acute PANSS total -16.82 vs -9.96 (p=0.028) Acute PANSS positive -4.27 vs -2.73 (ns) Acute PANSS negative -3.97 vs -2.02 (p=0.031) Acute MADRS total -6.93 vs -0.17 (p<0.001) Extension BPRS total -16.29 vs -14.56 (ns) Extension PANSS total -26.53 vs -25.44 (ns) Extension PANSS positive -7.60 vs -7.81 (ns) Extension PANSS negative -6.04 vs -4.69 (ns) Extension MADRS total -6.36 vs -3.69 (ns)	As in Tollefson, 1997; also AIMS. Elicited by investigator and reported spontaneously by patient.

Evidence Table 3. Active-controlled trials in patients with schizophrenia

Author, year Country (Trial name)	Adverse effects reported
Tran, 1999 (See Tollefson, 1997)	olanzapine vs haloperidol, Mean change in acute phase: Weight: +1.49 kg vs -0.24 kg (p=0.0001). EPS scores (SAS LOCF): -0.85 vs +1.65 (p=0.001) BAS: -0.18 vs +0.81 (p<0.001) Proportion who experienced akathisia: 16.6% vs 52.3% (p<0.001) Proportion who experienced pseudoparkinsonism: 9.8% vs 37.2% (p<0.001) Mean change in extension phase: Weight: +5.02 vs -1.53 (p=0.002) SAS total scores: -1.34 vs +0.88 (p=0.016) BAS: -0.24 vs +0.16 (ns) Proportion who experienced pseudoparkinsonism: 4.5% vs 9.2% (p<0.001) Proportion who experienced akathisia: 18.4% vs 52.4% (p=0.002)

Evidence Table 3. Active-controlled trials in patients with schizophrenia

Author, year Country (Trial name)	Total withdrawals; withdrawals due to adverse events by drug	Comments
Tran, 1999 (See Tollefson, 1997)	Acute phase: 157 withdrawals. Due to AEs: 15 (7.7%) in olanzapine, 10 (9.6) in haloperidol (ns) Extension phase: 56 withdrawals. Due to AEs: 15 (17.6%) in olanzapine, 6 (24.0%) in haloperidol (ns)	Subpopulation of Tollefson 1997: schizoaffective

Evidence Table 3. Active-controlled trials in patients with schizophrenia

Author, year Country (Trial name)	Other Drug	Interventions	Run-in/ Washout period	Method of outcome assessment and timing of assessment
Wright, 2003 Wright, 2001	haloperidol	IM olanzapine 10mg IM haloperidol 7.5mg the 24-hour IM period was followed by 4 days PO treatment with olanzapine or haloperidol tablets (5-20 mg/day for both)	NR/ NR	PANSS-EC

Evidence Table 3. Active-controlled trials in patients with schizophrenia

Author, year Country (Trial name)	Results	Method of adverse effects assessment?
Wright, 2003 Wright, 2001	Mean change at 24 hours from baseline, p value vs placebo BPRS positive: placebo: -1.3(2.7) olanzapine: -2.8(3.1), p<0.001 haloperidol: -3.2(3.5), p<0.001 BPRS total: placebo: -6.2(9.0) olanzapine: -12.8(9.0), p<0.001 haloperidol: 12.9(8.9), p<0.001 CGI-I: placebo: -0.1(0.6) olanzapine: -0.5(0.8), p<0.05 haloperidol: -0.8(0.8), p<0.05 PANSS: placebo: -3.1(5.1) olanzapine: -6.5(5.3), p<0.001 haloperidol: -6.7(4.6), p<0.001 olanzapine vs haloperidol, p=0.76 Agitated Behavior Scale score: placebo: -3.7(6.7) olanzapine: -6.4(5.9), p=0.003 haloperidol: -6.6(5.3), p=0.002 olanzapine vs haloperidol, p=0.91 Agigated Calmness Evaluation Scale score: placebo: 0.6(1.2) olanzapine: 0.8(1.0), p=0.2 haloperidol: 1.1(1.0), p=0.002 olanzapine vs haloperidol, p=0.02 Response rate: placebo: 18(33.3%) olanzapine: 96(73.3%), p<0.001 haloperidol: 87(69%), p<0.001 olanzapine vs haloperidol, NS Mean change at PO endpoint from baseline, all NS between groups PANSS-EC: olanzapine: -0.6(4.8) haloperidol: -1.3(4.4)	Spontaneously reported EPS: Barnes Akathisia Scale (BAS) and Simpson-Angus Scale (SAS)

Evidence Table 3. Active-controlled trials in patients with schizophrenia

Author, year Country (Trial name)	Adverse effects reported
Wright, 2003 Wright, 2001	Mean change at 24 hours from baseline, p value vs IM haloperidol Simpson-Angus Scale (SAS): olanzapine: -0.61(2.26), p<0.001 haloperidol: 0.70(3.54), NA placebo: -1.19(3.32), NR Barnes Akathisia Scale (BAS): olanzapine: -0.27(0.73), p<0.05 haloperidol: 0.01(0.77), NA placebo: -0.08(0.79), NR Mean change at PO endpoint from baseline, all NS between groups SAS: olanzapine: -0.24(1.51) haloperidol: 0.14(3.28) BAS: olanzapine: 0.00(0.63) haloperidol: 0.09(0.87) Dystonia: olanzapine: 0(0%) haloperidol: 1(0.8%) olanzapine vs haloperidol, p=0.001 EPS: olanzapine: 1(0.8%) haloperidol: 7(5.6%) olanzapine vs haloperidol, p=0.03

Evidence Table 3. Active-controlled trials in patients with schizophrenia

Author, year Country (Trial name)	Total withdrawals; withdrawals due to adverse events by drug	Comments
Wright, 2003 Wright, 2001	Olanzapine vs haloperidol Total withdrawals: 10 vs 10 Withdrawals due to AEs: 2 vs 2	

Evidence Table 3. Active-controlled trials in patients with schizophrenia

Author, year Country (Trial name)	Other Drug	Interventions	Run-in/ Washout period	Method of outcome assessment and timing of assessment
Olanzapine vs. Other				
Bobes 2003	Conventional antipsychotics haloperidol was the most frequently prescribed antipsychotic in the control group, with 60(87%) patients having received this drug at some point during hospitalization and 46(66.7%) were receiving it as treatment upon discharge	olanzapine (N=89): 16.4 mg haloperidol (N=69): 15.5mg other antipsychotics: NR	NR/ NR	CGI-S BPRS NOSIE
Godleski, 2003 United States switching	depot antipsychotics	depot antipsychotics (n=13) olanzapine PO (n=13): started at 10 mg/d, while simulataneously receiving depot for Month 1. After month 1, depot was discontinued. olanzapine was titrated up 5 mg/d per month, as warranted (max dose: 20 mg/d) 3-month study	NR / No	PANSS, CGI, GAF at baseline and every month

Evidence Table 3. Active-controlled trials in patients with schizophrenia

Author, year Country (Trial name)	Results	Method of adverse effects assessment?
Olanzapine vs. Other		
Bobes 2003	olanzapine vs conventional antipsychotics at endpoint, p value CGI mean improvement: 2.0(1.2) vs 1.6(1.1), p=0.013 BPRS total: 30.8 vs 23.6, p=0.0003 BPRS positive: 10.5 vs 8.3, p=0.0019 BPRS negative: 4.0 vs 1.9, p<0.0001 BPRS depression: 5.2 vs 4.2, p=0.018 BPRS agitation:10.2 vs 8.8; P=0.007 NOSIE mean improvement: 20.6 vs 16.9, p=0.0671 *p value adjusted for baseline and duration of course of illness Treatment response rate: 76.7% vs 54.4%, p=0.003 Treatment response rate after adjusting for baseline and time elapsed, p=0.044 BPRS >40% reduction: 73(84.9%) vs 46(67.6%) BPRS 60% reduction: 69.8% vs 45.6%, p=0.001 BPRS 80% reduction: 34.9% vs 19.1%, p=0.001	UKU side effect rating scale
Godleski, 2003 United States switching	Mean change from baseline to endpoint, olanzapine vs depot: PANSS total score: -3.23 vs +6.46, p=0.012 PANSS positive subscore: -0.85 vs +1.15, p=0.141 PANSS negative subscore: -0.46 vs +2.92, p=0.098 PANSS general score: -1.77 vs +2.38, p=0.068 CGI-S score: -0.42 vs 0.00, p=0.026 GAFscore: -2.08 vs +1.15, p=0.015	AMDP-5 scale, AIMS, Barnes Akathisia Scale (BAS) and vital signs including weight

Evidence Table 3. Active-controlled trials in patients with schizophrenia

Author, year Country (Trial name)	Adverse effects reported
Olanzapine vs. Other	
Bobes 2003	olanzapine vs conventional antipsychotics EPS: 12(13.6%) vs 38(55.9%), p<0.001 Dystonia: 0(0%) vs 10(14.7%), p<0.001 Rigidity: 5(5.7%) vs 12(17.6%), p=0.021 Hypokinesia: 3(3.4%) vs 22(32.4%), p<0.001 Tremor: 3(3.4%) vs 17(25%), p<0.001 Akathisia: 3(3.4%) vs 17(25%), p<0.001 Dyskinesia: 1(1.1%) vs 2(2.9%), p=0.581 Others: 2(2.3%) vs 2(2.9%), p=1
Godleski, 2003 United States switching	No significant differences between olanzapine and depot groups for baseline-to-endpoint changes in AIMS (p=0.947) BAS-objective (p=0.479), BAS-subjective awareness (p=0.545), BAS-subjective distress (p=0.153), BAS-global (p=0.448), and AMDP-5 (p=0.139) Mean change in weight from baseline to endpoint, olanzapine vs depot: +3.63 (+/-3.34) kg vs -0.77(+/-2.03) 1 pt from depot group hospitalized; 0 from olanzapine hospitalized No significant differences in vital signs from baseline to endpoint between groups

Evidence Table 3. Active-controlled trials in patients with schizophrenia

Author, year Country (Trial name)	Total withdrawals; withdrawals due to adverse events by drug	Comments
Olanzapine vs. Other		
Bobes 2003	A total of 17 patients (11.3%) discontinued ; 11.2% were olanzapine patients (n=10) and 10.1% were conventional patients (n=7)	1/89 clozapine patients was switched to the conventional antipsychotic group; 13/69 in the conventional group were switched to olanzapine (10 were switched due to secondary effects and 3 were insufficient efficacy)
Godleski, 2003 United States switching	0; 0	

Evidence Table 3. Active-controlled trials in patients with schizophrenia

Author, year Country (Trial name)	Other Drug	Interventions	Run-in/ Washout period	Method of outcome assessment and timing of assessment
Quetiapine vs. Other				
Velligan, 2003 U.S. (Poor)	chlorpromazine equivalents	quetiapine mean dose: 303.95 mg/day at 3 months, 319.25 mg/day at 6 months. Mean dose of standard APs in chlorpromazine equivalents: 352.50 mg/day at beginning of treatment, 348.00 mg/day at end of study Duration 6 months	Patients switched to quetiapine stopped taking all standard APs one month after beginning quetiapine	Neurocognitive test battery: Verbal Fluency Letters, Verbal Fluency Categories, Wisconsin Card Sorting Test, California Verbal Learning Test, Digit Span, Stroop Color-Word Test Symptoms: BPRS, NSA, AIMS Quality of life: MCAS, Heinrichs Carpenter QLS

Evidence Table 3. Active-controlled trials in patients with schizophrenia

Author, year Country (Trial name)	Results	Method of adverse effects assessment?
Quetiapine vs. Other		
Velligan, 2003 U.S. (Poor)	Mean change from baseline, quetiapine vs typical Aps Cognitive measure (month 3): 0.65 vs -0.06, p<0.023 Cognitive measure (month 6): 1.06 vs 0.00, p<0.023 Verbal fluency (initiation) (month 3): 0.28 vs -0.81, p<0.013 Verbal fluency (initiation) (month 6): 0.80 vs -0.25, p<0.013 Verbal memory (month 3): 0.54 vs 0.21, p<0.073 Verbal memory (month 6): 0.84 vs -0.05, p<0.073 Proportion of patients improving 1 standard deviation from baseline in cognitive domain Summary score: 31% vs 7.5%, p<0.06 Verbal memory: 37% vs 7.5%, p<0.03 Cognitive flexibiliy: 32% vs 7.5%, NR Verbal fluency: 32% vs 12.5%, NR Selective attention: 50% vs 41.0%, NR Adaptive functioning MCAS: No differences between groups, data not shown, effect size NR, NS QLS: Quetiapine had better scores than typical APs; data not shown, effect size 0.58, p=0.04 Symptoms: BPRS: No differences between groups; data not shown; effect size NR, NS NSA: No differences between groups; data not shown; effect size nR, NS	SARS at 3 months and 6 months

Evidence Table 3. Active-controlled trials in patients with schizophrenia

Author, year Country (Trial name)	Adverse effects reported
Quetiapine vs. Other	
Velligan, 2003 U.S. (Poor)	No significant differences between groups with respect to neurologic side effects

Evidence Table 3. Active-controlled trials in patients with schizophrenia

Author, year Country (Trial name)	Total withdrawals; withdrawals due to adverse events by drug	Comments
Quetiapine vs. Other		
Velligan, 2003 U.S. (Poor)	12 total; Due to AEs: 2 in quetiapine	This is an open-label, randomized study in which patients could be included based on suboptimal efficacy of current treatment with typical APs, and/or based on desire to change medications.

Evidence Table 3. Active-controlled trials in patients with schizophrenia

Author, year Country (Trial name)	Other Drug	Interventions	Run-in/ Washout period	Method of outcome assessment and timing of assessment
Risperidone vs. Other				
Bouchard, 1998 (AO) Bouchard, 2000 Canada (Fair)	Conventional neuroleptics	risperidone mean dose 5.5 mg/day Conventional neuroleptics mean dose 1006 mg/day in chlorpromazine equivalents* (20.12 mg/day in haloperidol equivalents) 12 months *per Bouchard 1998: median dose 551 mg/day in chlorpromazine equivalents	NR/ NR	PANSS at 3, 6, and 12 months Proportion of responders defined by 20% decrease in total PANSS Per Bouchard 1998: also CGI, ESRS, side effects, and medication at 3, 5, and 12 months.
Hertling, 2003 Germany & Austria (Fair)	flupenthixol	risperidone 2-6 mg/day (mean dose 3.6 mg/day). flupenthixol 4-12 mg/day (mean dose 6.6 mg/day). Duration 25 weeks	NR/ NR	Quality of life: EuroQuol-Visual Analogue Scale at weeks 0, 4, 8, 12, 16, 20, and 24 Attitude towards trial medication: DAI-30 at Weeks 0, 2, 4, 12, and 24 Patient satisfaction: at week 24

Evidence Table 3. Active-controlled trials in patients with schizophrenia

Author, year Country (Trial name)	Results	Method of adverse effects assessment?
Risperidone vs. Other		
Bouchard, 1998 (AO) Bouchard, 2000 Canada (Fair)	Mean change in PANSS score at 12 months (LOCF), risperidone vs typical APs: Total -9.8 vs -3.2 (p=0.005) Positive subscale -2.9 vs -0.9 (p=0.008) Negative subscale -2.6 vs -0.7 (p=0.020) General psychopathology subscale -4.5 vs -1.4 (p=0.015) 20% improvement at 12 months achieved by 29% vs 16% (p=0.04) 30% improvement at 12 months achieved by 17% vs 6% (p=0.02) Per Bouchard 1998: Proportion of patients who achieved >=20% reduction in PANSS score, risperidone vs classical neuroleptics: 30% vs 15% (p=0.027).	ESRS, use of antiparkinsonians
Hertling, 2003 Germany & Austria (Fair)	EuroQuol index increased in both groups; no significant differences between groups. Increase in DAI-30 mean score 1.4 points (6.9%) in risperidone vs 2.5 points (20%) in flupenthixol. More in flupenthixol had improved ability to cope with stress (p<0.05); felt more relaxed (p<0.05) and the ability to achieve something (p<0.05). No sig. differences between Rx groups in patient satisfaction. See comments regarding efficacy and side effects.	See comments

Evidence Table 3. Active-controlled trials in patients with schizophrenia

Author, year Country (Trial name)	Adverse effects reported
Risperidone vs. Other	
Bouchard, 1998 (AO) Bouchard, 2000 Canada (Fair)	% of subjects whose symptoms were worse at 12 months on ESRS subscales, risperidone vs typical APs: Dyskinesia 18.4 vs 20.8% (ns) Parkinson symptoms 14.9 vs 26% (ns) Akathisia 8.1 vs 22.1% (p=0.02)
Hertling, 2003 Germany & Austria (Fair)	See comments

Evidence Table 3. Active-controlled trials in patients with schizophrenia

Author, year Country (Trial name)	Total withdrawals; withdrawals due to adverse events by drug	Comments
Risperidone vs. Other		
Bouchard, 1998 (AO) Bouchard, 2000 Canada (Fair)	19 total; due to AEs not reported	Study included only stabilized and severely ill patients with chronic schizophrenia who were already known to be only partially response to typical APs. One treatment arm was open-label medication with current neuroleptic.
Hertling, 2003 Germany & Austria (Fair)	See comments	Study subjects were patients with negative symptoms. A previous publication of this trial (Philipp 2002) reported the methods and results of efficacy and side effects, but was excluded from review because of non-English language.

Evidence Table 3. Active-controlled trials in patients with schizophrenia

Author, year Country (Trial name)	Other Drug	Interventions	Run-in/ Washout period	Method of outcome assessment and timing of assessment
Mahmoud, 2004 ROSE Group United States	Conventional AP	risperidone, mean dose NR Any one of 13 typical APs, selected by treating physician; all dosage forms including depot were permitted. Mean dose NR Duration 1 year After randomization, all mental health care, including all drug therapy, was provided according to the natural course of events in the community with only minimal protocol restrictions. Crossovers and combination therapy (2 or more AP medications in one day) were permitted.	NR/ NR	PANSS Patient satisfaction: Drug Attitude Inventory (DAI) Health-related quality of life (HRQOL) as measured by the SF-36, and the brief version of the QOL interview. Resource utilisation: acute psychiatric hospital days, non-hospital acute-care service days, routine mental health care, and medications. Data was recorded at schedule visits at baseline and at 4, 8, and 12 months following randomization.
Mak, 2000	Conventional AP	risperidone conventional AP Duration: 3 months	1-2 weeks/ NR	BPRS Scale for Assessment of Positive Symptoms

Evidence Table 3. Active-controlled trials in patients with schizophrenia

Author, year Country (Trial name)	Results	Method of adverse effects assessment?
Mahmoud, 2004 ROSE Group United States	Change from mean baseline, risperidone vs typical Aps Total PANSS: -21.52 vs -14.43, p=0.0008 Postive symptom scale: -7.33 vs -5.15, p=0.0011 Negative symptom scale: -4.96 vs -3.05, p=0.0139 General psychopathology: -9.31 vs -6.21, p=0.0095 BAS: -0.34 vs -0.06, p=0.0275 SF-36 summary score: 7.09 vs 4.67, p=0.0326 Percentage of patients showing a 60% reduction in total PANSS score: Month 4: 11.0% vs 8.5%, NS Month 8: 16.3% vs 9.0%, p=0.007 Month 12: 20.9% vs 10.7%, p=0.001 Utilization parameters Mean number of days of combination therapy (2 or more AP medications in one day): 55.2 vs 57.0, NR % of patients who received no therapy during any portion of the follow-up: 94.8% vs 92.9%, NR Number of days without therapy, not necessarily consecutive: 110.2 vs 125, NR % of patients who used one or emore days of crossover therapy: 72.4% vs 41.4%, NR % of patients who remained in the study for >350 days: 84.5% vs 78.2%, p=0.02	BAS, AIMS, SARS
Mak, 2000	Baseline vs endpoint, p vs baseline BPRS: risperidone: 14.86(6.32) vs 9.59(4.42), p<0.0001 conventional AP: 14.16(6.34) vs 13.26(5.33), p>0.1 *risperidone vs conventional AP, p>0.1 Scale for Assessment of Positive: risperidone: 5.30(10.75) vs 1.14(2.62), p>0.05 conventional AP: 5(9.91) vs 4(8.02), p>0.5 *risperidone vs conventional AP, p>0.05 Scale for Assessment of Negative: risperidone: 53.82(11.62) vs 39.82(16.62), p<0.001 conventional AP: 51.50(12.73) vs 53.14(8.98), p>0.05 *risperidone vs conventional AP, p>0.05 Clinical Global Interview: risperidone: 3.95(0.64) vs 1.13(1.01), p<0.0001 conventional AP: 3.79(0.37) vs 3.63(0.57), p>0.1 *risperidone vs conventional AP, p<0.05	NR

Evidence Table 3. Active-controlled trials in patients with schizophrenia

Author, year Country (Trial name)	Adverse effects reported
Mahmoud, 2004 ROSE Group United States	No significant changes in tardive dyskinesia as measured by AIMS or differences in EPS as measured by SARS were observed in either group. The severity of drug-induced akathisia declined in both treatment groups, as measured by BAS.
Mak, 2000	NR

Evidence Table 3. Active-controlled trials in patients with schizophrenia

Author, year Country (Trial name)	Total withdrawals; withdrawals due to adverse events by drug	Comments
Mahmoud, 2004 ROSE Group United States	Not reported	Effectiveness trial
Mak, 2000	NR	Patients were not randomly assigned to the two treatment. It they showed significant clinical improvement, they would continue to be maintained with the medication

Evidence Table 3. Active-controlled trials in patients with schizophrenia

Author, year Country (Trial name)	Other Drug	Interventions	Run-in/ Washout period	Method of outcome assessment and timing of assessment
Peuskens, 1999 Multi-national, Europe (Fair)	Amisulpride	misulpride 800 mg/day risperidone 8 mg/day Duration 8 weeks	3-6 day single-blind placebo washout	PANSS, BPRS, CGI, Social & Occupational Functioning Assessment Scale (SOFAS), assessment of patients' subjective responses to treatment Change in BPRS >6 points = clinically relevant
Sechter, 2002 Austria, Belgium, Estonia, France, Germany, Hungary, Latvia, The Netherlands, Slovenia (Fair)	amisulpride	risperidone 4-10 mg/day amisulpride 400-1000 mg/day Duration 6 months	6-day single-blind placebo washout	PANSS and CGI at weeks 1,2,3,4,6,8 and at 3, 4, 5, and 6 months; PANSS also at washout SANS, BRMS, SOFAS at baseline, week 8, and 6 months Subjective response scale at week 1 and 8, and 6 months
Risperidone vs. Haloperidol				
Csernansky, 2002 U.S. Risperidone-USA-79 Study (Fair)	haloperidol	risperidone 2-8 mg/day; mean modal dose 4.9 mg/day haloperidol 5-20 mg/day; mean modal dose 11.7 mg/day Duration 1 year	NR/ NR	Relapse rates and time to first relapse; PANSS, CGI

Evidence Table 3. Active-controlled trials in patients with schizophrenia

Author, year Country (Trial name)	Results	Method of adverse effects assessment?
Peuskens, 1999 Multi-national, Europe (Fair)	Mean change in score, risperidone vs amisulpride: BPRS total -15.2 vs -17.7 (p<0.0005) NS between groups on BPRS subscales PANSS positive -8.6 vs -9.6 (ns) PANSS negative -5.32 vs -6.9 (ns) 20% reduction in BPRS total achieved by 75% vs 78% (ns) 40% reduction in BPRS total achieved by 58% vs 67% (ns)	SARS, AIMS, BAS, proportion of patients receiving antiparkinsonian medication
Sechter, 2002 Austria, Belgium, Estonia, France, Germany, Hungary, Latvia, The Netherlands, Slovenia (Fair)	risperidone vs amisulpride, efficacy: Mean change in score from baseline to 6 months PANSS total -31.4 vs -32.2 (ns) PANSS positive subscale -12.1 vs -11.8 (ns) PANSS negative subscale -3.9 vs -5.1 (ns) PANSS global psychopathology -15.4 vs -15.3 (ns) BPRS total -19.6 vs -19.8 (ns) CGI severity -1.5 vs -1.7 (ns) SANS -12.1 vs -14.8 (ns) BRMS -3.9 vs -4.9 (ns) Patients with PANSS >= 50% improvement: 52.0% vs 65.3% (p=0.036) Patients with BPRS >=50% improvement: 57.7% vs 71.9% (p=0.020) Patients with CGI very much or much improved: 65.0% vs 76.9% (p=0.042) risperidone vs amisulpride, safety: Mean change in score from baseline to 6 months SARS 0.07 vs 0.10 (ns) AIMS 0.10 vs 0.16 (ns)	Physical exam, vital signs, body weight, SARS and BAS at washout, baseline, and weeks 1,2,3,4,6,8 AIMS at washout, baseline, week 8, and 6 months
Risperidone vs. Haloperidol		
Csernansky, 2002 U.S. Risperidone-USA-79 Study (Fair)	Proportion of patients who relapsed, risperidone vs haloperidol: 25.4% vs 39.9%. Relapse risk ratio in haloperidol was 1.93 times than risk in risperidone (95% CI 1.33-2.80, p<0.001). Mean PANSS total and subscale scores at one year or last study rating improved in risperidone and worsened in haloperidol. The data was shown in bar graph only with p-values, but endpoint or change scores were not shown. The differences between treatments were statistically significant for PANSS total and 4 subscale scores.	Monitoring for AEs, a battery of standard laboratory tests, electrocardiography, and physical exam, ESRS.

Evidence Table 3. Active-controlled trials in patients with schizophrenia

Author, year Country (Trial name)	Adverse effects reported
Peuskens, 1999 Multi-national, Europe (Fair)	risperidone vs amisulpride: 23% vs 30% used antiparkinsonians (ns) EPS 12 % vs 14% (ns) Headache 10% vs 11% (ns) Constipation 1% vs 6% (ns) Vomiting 4% vs 5% (ns) Mean weight change +1.4kg vs +0.4kg (p=0.026)
Sechter, 2002 Austria, Belgium, Estonia, France, Germany, Hungary, Latvia, The Netherlands, Slovenia (Fair)	Weight gain >=7% from baseline to 6 months: 34% risperidone vs 18% amisulpride (p<0.05) Antiparkinsonian medication taken at least once by 30% on risperidone and 24% on amisulpride (ns)
Risperidone vs. Haloperidol	
Csernansky, 2002 U.S. Risperidone-USA-79 Study (Fair)	Antiparkinsonian drugs prescribed for 30 consecutive days for 17.6% in haloperidol vs 9.0% in risperidone (p=0.02). Other AEs, risperidone vs haloperidol: Somnolence 14% vs 25% (p.nr) Agitation 10% vs 18% (p.nr) Mean change in weight: +2.3 kg vs -0.73 (p<0.001)

Evidence Table 3. Active-controlled trials in patients with schizophrenia

Author, year Country (Trial name)	Total withdrawals; withdrawals due to adverse events by drug	Comments
Peuskens, 1999 Multi-national, Europe (Fair)	69 total; Due to AEs 14 in risperidone 15 in amisulpride	
Sechter, 2002 Austria, Belgium, Estonia, France, Germany, Hungary, Latvia, The Netherlands, Slovenia (Fair)	123 total; Due to AEs: 20 in risperidone, 21 in amisulpride	
Risperidone vs. Haloperidol		
Csernansky, 2002 U.S. Risperidone-USA-79 Study (Fair)	risperidone vs haloperidol, Total withdrawals: 59.4 vs 77.3% (p<0.0001) Due to AEs: 15.4% vs 12.4% (ns)	

Evidence Table 3. Active-controlled trials in patients with schizophrenia

Author, year Country (Trial name)	Other Drug	Interventions	Run-in/ Washout period	Method of outcome assessment and timing of assessment
Currier, 2001	haloperidol	risperidone 2mg + lorazepam 2mg PO haloperidol 5mg + lorazepam 2mg IM Duration: 24 hours	NR/ NR	PANSS CGI
Green, 2002 Marder, 2003 U.S. (Fair)	haloperidol	risperidone 6-16 mg/day, mean dose 5.0 mg/day haloperidol 6-16 mg/day, mean dose 6.0 mg/day Duration 2 years	2-month run-in on haloperidol	BPRS, SANS, SCL-90-R (subjective self-report instrument) Assessments conducted at pretreatment, 9 months, 15 months, and 24 months Neurocognitive battery at baseline and weeks 4, 24, 48, 72, and 104: Perceptual discrimination Memory and verbal fluency Executive (Wisconsin Card Sorting Test)

Evidence Table 3. Active-controlled trials in patients with schizophrenia

Author, year Country (Trial name)	Results	Method of adverse effects assessment?
Currier, 2001	baseline vs 30-min vs 60-min, Mean(SD), 95%CI Combined Psychotic Agitation Score: haloperidol: 28.5(5.7), 26.4-30.6 vs 14.0(8.9), 10.3-16.9 vs 8.2(5.7), 6.0-10.3 risperidone: 26.7(5.2), 24.8-28.7 vs 15.9(9.6), 12.3-19.6 vs 10.1(8.2), 7.0-13.3 *p<0.0001 vs baseline; p=NS between groups PANSS-hallucinatory: haloperidol: 4.7 vs 2.7 vs 1.7; risperidone: 5.1 vs 2.9 vs 1.8 PANSS-hostility: haloperidal: 5.3 vs 2.2 vs 1.4; risperidone: 4.9 vs 2.8 vs 1.7 PANSS-uncooperativeness: haloperidal: 5.8 vs 3.2 vs 1.5; risperidone: 5.3 vs 2.7 vs 1.9 PANSS-excitement: haloperidol: 6.0 vs 2.9 vs 1.7; risperidone: 5.9 vs 3.6 vs 2.1 PANSS-impulsiveness: haloperidol: 6.3 vs 3.2 vs 1.8; risperidone: 6.1 vs 3.9 vs 2.2 *p<0.0001 vs baselind; p=0.42 between groups CGI: 15-min vs 30-min vs 60-min vs 120-min, Mean(SD), 95%CI haloperidol: 4.21(1.23), 3.74-4.68 vs 2.9(0.9), 2.56-3.24 vs 2.31(0.6), 2.08-2.54 vs 2.21(0.94), 1.85-2.56 risperidone: 4.17(1.23), 3.71-4.64 vs 3.28(1.10), 2.86-3.70 vs 2.52(1.09), 2.10-2.93 vs 2.10(0.41), 1.95-2.26 *p<0.0001 vs baseline; p=0.419 between groups	Monitored by study staff and clinicians
Green, 2002 Marder, 2003 U.S. (Fair)	Risperidone vs haloperidol, change in mean score: BPRS Total -0.14 vs -0.14 (ns) BPRS Anxious depression -0.29 vs +0.03 (p=0.02) SANS Global -0.19 vs -0.15 (ns) SCL-90-R Global symptom index -0.33 vs -0.02 (p<0.01) SCL-90-R Phobic anxiety -0.21 vs 0.12 (p=0.01) SCL-90-R Anxiety -0.28 vs 0.07 (p<0.01) SCL-90-R Depression -0.49 vs -0.03 (p<0.01) Relapse-free after 2 years: 88% in risperidone and 73% in haloperidol (ns) Neurocognitive effects: no differences between groups. (Positive change = improvement) Perceptual discrimination at Week 140: -.002 vs -0.126 (ns) Memory and fluency at week 104: 0.311 vs 0.381(ns) Executive functioning at week 104: 0.098 vs 0.187 (ns)	AIMS, BAS, Modified SARS Social functioning: Social Adjustment Scale and QLS. Assessments conducted at pretreatment, 9 months, 15 months, and 24 months

Evidence Table 3. Active-controlled trials in patients with schizophrenia

Author, year Country (Trial name)	Adverse effects reported
Currier, 2001	risperidone vs haloperidol, Mean(SD) Somnolence: NS between groups Time to sleep (min): 43(25.1) vs 44.3(25.6) dystonia within 24 hours (no. of patients): 0 vs 1
Green, 2002 Marder, 2003 U.S. (Fair)	risperidone vs haloperidol, SARS scale: Tremor -0.28 vs -0.04 (p=0.01) Akathisia -0.39 vs 0.04 (p<0.01) BAS Global -0.55 vs 0.10 (p<0.01)

Evidence Table 3. Active-controlled trials in patients with schizophrenia

Author, year Country (Trial name)	Total withdrawals; withdrawals due to adverse events by drug	Comments
Currier, 2001	NR	
Green, 2002 Marder, 2003 U.S. (Fair)	32 total; due to AEs not reported	

Evidence Table 3. Active-controlled trials in patients with schizophrenia

Author, year Country (Trial name)	Other Drug	Interventions	Run-in/ Washout period	Method of outcome assessment and timing of assessment
Liberman, 2002	haloperidol	Mean dosage: risperidone 8 mg haloperidol 20 mg Duration: 4 weeks	3 weeks/ NR	Activities of daily living (ADLs)
Shrivastava, 2000	haloperidol	risperidone 2 mg/day haloperidol: 5-15 mg/day Duration: 1 year	2-4 weeks with haloperidol 15-30 mg/day / NR	PANSS CGI

Evidence Table 3. Active-controlled trials in patients with schizophrenia

Author, year Country (Trial name)	Results	Method of adverse effects assessment?
Liberman, 2002	ADLs, dressing, grooming, room clean-up, showering: risperidone vs haloperidol: NR, NS both treatment improved vs baseline: showering, p=0.034; grooming, p=0.01 Neurocognitive performance: risperidone vs haloperidol: NR, NS	NR
Shrivastava, 2000	riesperidone vs haloperidol, change from baseline (SD), % reduction, p value PANSS: positive: 11.2(4.2), 55.5% vs 10(3.0), 47.6%, NS negative: 18.3(4.0), 58.8% vs 15.0(3.5), 51.2%, NS general psychopathology: 20.4(4.9), 50.5% vs 27(3.7), 68.4%, p<0.05 total: 50.4(5.7), 57.8% vs 52(4.1), 58.4%, NS CGI (improved) overall very much improvement (no. of patients): 18 vs 5, p<0.05 social functioning: 34 vs 22, p<0.02 productivity: 35 vs 18, p<0.001 economic independence: 31 vs 29, NS education: 40 vs 25, p<0.003 suicidality: 5 vs 17, p<0.009 rehospitalization: 6 vs 15, p<0.05 exacerbation: 7 vs 6, NS	NR

Evidence Table 3. Active-controlled trials in patients with schizophrenia

Author, year Country (Trial name)	Adverse effects reported
Liberman, 2002	NR
Shrivastava, 2000	NR

Evidence Table 3. Active-controlled trials in patients with schizophrenia

Author, year Country (Trial name)	Total withdrawals; withdrawals due to adverse events by drug	Comments
Liberman, 2002	NR	
Shrivastava, 2000	NR	

Evidence Table 3. Active-controlled trials in patients with schizophrenia

Author, year Country (Trial name)	Other Drug	Interventions	Run-in/ Washout period	Method of outcome assessment and timing of assessment
Ziprasidone vs. Haloperidol				
Daniel, 2004	haloperidol	ziprasidone IM 20-80 mg/day haloperidol IM 10-40 mg/day Duration: 7 days	NR/ NR	BPRS
Goff, 1998	haloperidol	ziprasidone 4-160 mg/day haloperidol 15 mg Duration: 4 weeks	NR/ 4-7 days	Primary efficacy parameters: BPRS, CGI-S
Hirsch, 2002 U.K. (Fair)	haloperidol	ziprasidone 80-160 mg/day; modal dose 80 mg/day; mean dose at week 28 = 116.5 mg/day haloperidol 5-15 mg/day; modal dose 5 mg/day; mean dose at week 28 = 8.6 mg/day Duration 28 weeks	3- to 14-day run-in between screening and baseline.	PANSS at screening, baseline, weeks 3,6,16, and 28 MADRS and CGI at baseline and weeks 3,6,16, and 28 QLS at baseline and week 28 LOCF analysis

Evidence Table 3. Active-controlled trials in patients with schizophrenia

Author, year Country (Trial name)	Results	Method of adverse effects assessment?
Ziprasidone vs. Haloperidol		
Daniel, 2004	BPRS: NR, NS	COSTART Simpson-Angus Scale Barnes Akathisia Scale
Goff, 1998	Mean change from baseline score: Z-4mg vs Z-10mg vs Z-40mg vs Z-160mg vs H-15mg BPRS total: -5.7 vs -5.4 vs -5.7 vs -11.9 vs -11.6 BPRS core: -3.6 vs -2.8 vs -3.3 vs -5.8 vs -5.4 CGI severity: -0.1 vs -0.2 vs -0.2 vs -1.2* vs -1.1** *p=0.001 vs Z-4mg; **p<0.01 vs Z-4mg response rate-BPRS(%): 36.8 vs 29.4 vs 29.4 vs 45.0 vs 47.1 response rate-CGI (%): 15.8 vs 11.8 vs 11.8 vs 50.0 vs 41.2	Abnormal movements: Simpson-Angus Scale Barnes Akathisia Scale Involuntary Movement Scale (AIMS)
Hirsch, 2002 U.K. (Fair)	ziprasidone vs haloperidol, Mean change in score: PANSS total -9.1 vs -8.1 (ns); negative subscale -3.6 vs -3.0 (ns) BPRSd core items -1.5 vs -1.3 (ns); CGI-Severity 0.5 vs 0.4 (ns) MADRS -1.6 vs -0.6 (ns); GAF +3.2 vs +2.5 (ns); QLS +2.8 vs +0.9 (ns) Negative symptom responders (>=20% decrease in PANSS negative subscale) 48% vs 33% (p<0.05)	COSTART BAS, SARS at baseline and weeks 6, 16, and 28. AIMS at baseline, wk 28. Lab tests wks 4, 12 ECG at weeks 12 & 28; QTc calculated

Evidence Table 3. Active-controlled trials in patients with schizophrenia

Author, year Country (Trial name)	Adverse effects reported
Ziprasidone vs. Haloperidol	
Daniel, 2004	Z-20mg vs Z-40mg vs Z-80mg vs H-20-40mg, no(%) Adverse event at any time: 50(80%) vs 60(85%) vs 58(88%) vs 85(85%) Adverse event on IM treatment: 49(71%) vs 57(80%) vs 55(83%) vs 77(77%) Akathisia: 4(6%) vs 4(6%) vs 8(12%) vs 21(21%) Dystonia: 5(7%) vs 2(3%) vs 2(3%) vs 10(10%) EPS: 0(0%) vs 1(1%) vs 3(4%) vs 15(15%) Hypertonia: 1(1%) vs 1(1%) vs 2(3%) vs 11(11%) Anxiety: 11(16%) vs 10(14%) vs 11(17%) vs 13(13%) Dizziness: 11(16%) vs 14(20%) vs 10(15%) vs 0(0%) Headache: 12(17%) vs 10(14%) vs 13(20%) vs 8(8%) Injection-site pain: 4(6%) vs 7(10%) vs 11(17%) vs 2(2%) Insomnia: 7(10%) vs 11(15%) vs 14(21%) vs 12(12%) Nausea: 9(13%) vs 14(20%) vs 12(18%) vs 3(3%) Tachycardia: 2(3%) vs 8(11%) vs 5(8%) vs 6(6%) Vomiting: 6(9%) vs 8(11%) vs 8(12%) vs 5(5%)
Goff, 1998	z-4mg vs z-10mg vs z-40mg vs z-160mg vs h-15mg 66(73.3%) experienced an adverse event during the study, and 36 were considered to be related to study treatment: 9 vs 3 vs 7 vs 8 vs 9 Simpson-Angus Scale, mean change: -1.8 vs -1.2 vs 1 vs -0.5 vs 1 Barnes Akathisia Scale, mean change: -0.7 vs -0.1 vs 1 vs 4 vs 2 AIMS, mean change: -0.1 vs 0.7 vs 0.3 vs -0.5 vs -0.9
Hirsch, 2002 U.K. (Fair)	ziprasidone vs haloperidol, Movement disorders: 15% vs 41% (p<0.001) Insomnia 16% vs 18% (ns) Somnolence 14% vs 9% (ns) Vomiting 11% vs 6% (ns) Nausea 10% vs 4% (p=0.042) Weight change +0.31 kg vs +0.22kg (ns)

Evidence Table 3. Active-controlled trials in patients with schizophrenia

Author, year Country (Trial name)	Total withdrawals; withdrawals due to adverse events by drug	Comments
Ziprasidone vs. Haloperidol		
Daniel, 2004	Z-20mg vs Z-40mg vs Z-80mg vs H-20-40mg, no(%) Total withdrawals: 7(10%) vs 10(14%) vs 11(17%) vs 10(10%) Withdrawals due to AEs: 0 vs 1 vs 2 vs 1	Concomitant lorazepam (oral or IM up to 12 mg/day) fpr agitation and temazepam (up to 30 mg/night) for insomnia were allowed if needed. Benztropine and propranolol were allowed for the treatment of extrapyramidal symptoms and akathisia, respectively,
Goff, 1998	Total withdrawals: 46(51%) total Withdrawals due to AEs: Z-4mg(1), Z-160mg(1), haloperidol(1)	
Hirsch, 2002 U.K. (Fair)	171 total, 36 Due to AEs: 12 in ziprasidone (1 with movement disorders) 24 in haloperidol (7 with movement disorders)	

Evidence Table 3. Active-controlled trials in patients with schizophrenia

Author, year Country (Trial name)	Other Drug	Interventions	Run-in/ Washout period	Method of outcome assessment and timing of assessment
Brook 2000 International	haloperidol	IM treatment: days 1 and through day 3 ziprasidone IM (n=90): initial dose 10 mg; subsequent doses of 5-20 mg given every 4-6 hours (max: 4 injections and 80 mg in 24h) haloperidol IM (n=42): initial dose: 2.5-10 mg; subsequent doses given 4-6 hours (max: 4 injections and 40 mg in 24h) Days 3-7 ziprasidone PO: 80-200 mg/d haloperidol PO: 10-80 mg/d 7 day treatment	NR/ Antipsychotics taken at baseline were discontinued and first dose of IM given when clinically appropriate	BPRS and CGI-S assessed at baseline, once every 24 h while on treatment, and at endpoint CGI-I rated relative to baseline every 24h and at endpoint

Evidence Table 3. Active-controlled trials in patients with schizophrenia

Author, year Country (Trial name)	Results	Method of adverse effects assessment?
Brook 2000 International	Mean change from baseline score, ziprasidone vs haloperidol: At end of IM treatment: BPRS total: -6.24 vs -3.18, p=0.02 BPRS agitation items: -1.93 vs -0.80, p=0.015 CGI-S: -0.49 vs -0.15, p=0.002 At the endpoint evaluation: BPRS total: -8.76 vs -5.83, p=0.09 BPRS agitation items: -2.09 vs +1.59, p=0.19 CGI-S: -0.89 vs -0.38, p=0.025	AEs classified with COSTART along with investigators' assessments of severity BAS, SARS at baseline, at end of IM treatment, and at endpoint 5-Point sedation scale (1= absent to 5=sleep) rated at baseline and within 6 h of a dose of study medication on days 1-7 or on early termination Lab tests and ECG at baseline, after the last IM dose, and at endpoint

Evidence Table 3. Active-controlled trials in patients with schizophrenia

Author, year Country (Trial name)	Adverse effects reported
Brook 2000 International	ziprasidone vs haloperidol Change in score (SD) from baseline: SAS at last IM dose: -0.61 (3.11) vs +3.80 (5.22) SAS at endpoint: -1.09 (4.33) vs +6.00 (7.12) BAS at last IM dose: -0.03 (0.57) vs +0.44 (0.87) BAS at endpoint: -0.10 (0.79) vs 0.80 (1.14) Sedation scores at last IM dose: +1.10 (1.56) vs +0.46 (1.17) Sedation scores at endpoint: +0.02 (1.10) vs +0 (0.71) Total % of patients experiencing any incidence of AEs at endpoint: 45.6% vs 59.5% % of patients taking anxiolytics at any time: 57.7% vs 64.3% % of patients taking hypnotics for nighttime sedation: 10% vs 7.1% % of patients taking anticholinergics at any time: 14.4% vs 47.6% % of patients experiencing these adverse events: Tremor (IM only): 1.1% vs 2.4%; (IM+PO): 2.2% vs 9.5% Akathisia (IM only): 2.2% vs 0; (IM+PO): 3.3% vs 14.3% Dystonia (IM only): 1.1% vs 7.1%; (IM+PO): 4.4% vs 11.9% EPS (IM only): 0 vs 21.4%; (IM+PO): 1.1% vs 38.1% Hypertonia (IM only): 0 vs 7.1%; (IM+PO): 3.3% vs 11.9% Vomiting (IM only): 3.3% vs 0; (IM+PO): 10% vs 0% Somnolence (IM only): 0 vs 0; (IM+PO): 1.1% vs 0% Tachycardia (IM only): 2.2% vs 0 No patients had an increase in QTc interval ≥20% or had an interval >500ms during IM or PO treatment Mean change in QTc interval from baseline to end of IM treatment: +2.14 ms vs +2.22 ms Elevated glucose (>1.2 ULN): 12% vs 13% over both treatments

Evidence Table 3. Active-controlled trials in patients with schizophrenia

Author, year Country (Trial name)	Total withdrawals; withdrawals due to adverse events by drug	Comments
Brook 2000 International	16 patients total (8.9% in ziaprasidone and 8.9% in haloperidol) ; 4 in ziprasidone and 1 in haloperidol (none during the IM period) Discontinuation reasons, ziprasidone PO: 1 pt (1.1%) discontinued due to severe postural hypotension; 1 pt (1.1%) discontinued due to akathisia; 1 pt (1.1%) with a history of dystonic reactions with neroleptic treatment discontinued due to laryngospasm in association with acute dystonia Discontinuation reasons, haloperidol PO: 1 pt (2.4%) discontinued due to excessive sweating and dry mouth	

Evidence Table 4. Quality assessment of active-controlled trials in patients with schizophrenia

Author, year	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors masked?	Care provider masked?
Bouchard, 2000 Bouchard, 1998	Method not reported	Method not reported	Yes	Yes	No	No
Covington, 2000	Method not reported	Method not reported	Not reported	No	No	Not reported
Csernansky, 2002	Method not reported	Method not reported	Yes	Yes	Yes but method not described	Not reported
Green, 2002 Marder, 2003	Method not reported	Method not reported		Yes	Yes but method not described	Not reported
Hamilton, 1998	Method not reported	Method not reported	SARS score significantly higher in haloperidol group (p=0.0002)	Yes	Yes but method not described	No
Harvey, 2000						
Hertling, 2003	Method not reported	Method not reported	Yes	Yes	Not reported	Not reported
Hirsch, 2002	Yes	No: Envelope method	Yes	Yes	Yes but method not described	Not reported

Evidence Table 4. Quality assessment of active-controlled trials in patients with schizophrenia

Author, year	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors masked?	Care provider masked?
Kasper, 2003	Method not reported	Method not reported	Yes	Yes	Yes but method not described	Not reported
Lee, 1999	Method not reported	Method not reported	Yes	Yes	No	No
Liberman, 2002	Method not reported	Method not reported	yes	Yes	Not reported	Not reported
Lieberman, 2003 Green, 2004	Method not reported	Method not reported	No	Yes	Yes but method not described	Not reported
Mahmoud, 1998						
Mahmoud, 2004	Yes	Method not reported	Yes	Yes	Not reported	No
Peuskens, 1999	Method not reported	Method not reported	Yes	Yes	Yes but method not described	Not reported
Rosenheck, 1997	Method not reported	Method not reported	Yes	Yes	Yes but method not described	Not reported
Rosenheck, 2003	Method not reported	Yes	Yes, except mean PANSS negative subscale 23.2 in	Yes	Yes but method not described	Not reported

Evidence Table 4. Quality assessment of active-controlled trials in patients with schizophrenia

Author, year	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors masked?	Care provider masked?
Sechter, 2002	Method not reported	Method not reported	Yes	Yes	Yes but method not described	Not reported
Shopsin, 1979	Method not reported	Method not reported	Not reported	Yes	Yes	Yes
Shrivastava, 2000	Method not reported	Method not reported	Unclear	No	No	No
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	Method not reported	Method not reported	Yes	Yes	Yes but method not described	Not reported
Velligan, 2003	Method not reported	Method not reported	Yes	Yes	Yes	No

Evidence Table 4. Quality assessment of active-controlled trials in patients with schizophrenia

Author, year	Patient masked?	Reporting of attrition, crossovers, adherence, and contamination?	Loss to follow-up: differential/ high?	Intention-to-treat (ITT) analysis?	Post-randomization exclusions?	Quality Rating
Bouchard, 2000 Bouchard, 1998	No	Attrition yes, crossovers yes	No/ no	No	No	Fair
Covington, 2000	Not reported	No	Not reported	Not reported	No	Poor
Csernansky, 2002	Yes	Attrition yes NR Adherence yes NR	No/ no	No: 91.9%	Yes: all 30 patients at a single site were excluded because PI was out of compliance	Fair
Green, 2002 Marder, 2003	Yes but method not described	Attrition yes	Not reported	Yes	No	Fair
Hamilton, 1998	Yes but method not described	Yes	No	Yes	No	Fair
Harvey, 2000						
Hertling, 2003	Yes but method not described	No	Not reported	No	No	Fair
Hirsch, 2002	Yes but method not described	Attrition yes	NR	No	No	Fair

Evidence Table 4. Quality assessment of active-controlled trials in patients with schizophrenia

Author, year	Patient masked?	Reporting of attrition, crossovers, adherence, and contamination?	Loss to follow-up: differential/ high?	Intention-to-treat (ITT) analysis?	Post-randomization exclusions?	Quality Rating
Kasper, 2003	Yes but method not described	Attrition yes NR NR NR	No/ extent not reported (maximum 22% in aripiprazole; 26% in haloperidol)	No: 99.1%	No	Fair
Lee, 1999	No	Attrition yes	No	No	No	Fair
Liberman, 2002	Not reported	NR	NR	NR	NR	Poor
Lieberman, 2003 Green, 2004 Mahmoud, 1998	Yes but method not described	Attrition yes	Not reported	No	No	Fair
Mahmoud, 2004	No	NR Yes Yes Yes	No	Yes	No	Fair
Peuskens, 1999	Yes	Attrition yes	No/ no	No	No	Fair
Rosenheck, 1997	Yes	Attrition yes; crossovers yes	No/ no	No	No	Fair
Rosenheck, 2003	Yes	Attrition yes	No/ no	Yes	No	Fair

Evidence Table 4. Quality assessment of active-controlled trials in patients with schizophrenia

Author, year	Patient masked?	Reporting of attrition, crossovers, adherence, and contamination?	Loss to follow-up: differential/ high?	Intention-to-treat (ITT) analysis?	Post-randomization exclusions?	Quality Rating
Sechter, 2002	Yes but method not described	Attrition yes	No/ no	No	No	Fair
Shopsin, 1979	Yes	Unclear	Differential loss to f/u in placebo group	No	no	Fair
Shrivastava, 2000	No	Yes	NR/No (33%)	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	Yes but method not described	Attrition yes	No/ no	No	No	Fair
Velligan, 2003	No	Attrition yes	No/ no	No	No	Fair

Evidence Table 5. Placebo-controlled trials in patients with schizophrenia

Author, year Country Trial name (Quality score)	N	Study design Setting	Eligibility criteria
Aripiprazole			
Pigott, 2003 International	310 (n=155 in aripiprazole and n=155 in placebo groups)	Randomized, DB, parallel-group, PCT Multicenter	Stabilized male and female patients ≥18 diagnosed with schizophrenia as defined by DSM-IV criteria for at least 2 years prior to study with a baseline PANSS ≥60, a score ≤4 on the subscale for hostility or uncooperativeness, and a score ≤4 on the CGI-S.

Evidence Table 5. Placebo-controlled trials in patients with schizophrenia

Author, year Country Trial name (Quality score)	Interventions (drug, dose, duration)	Run-in/Washout period	Allowed other medications/ interventions
Aripiprazole			
Pigott, 2003 International	Aripiprazole 15 mg/d placebo 26 weeks	NR/ 3-day washout for preexisting antipsychotic medication and any psychotropic medication.	Anticholinergic treatment for EPS allowed. Lorazepam, up to a max. of 4 mg/d, was allowed for emergent agitation if deemed necessary; and an additional 1-2 mg was allowed at night as a sleep aid.

Evidence Table 5. Placebo-controlled trials in patients with schizophrenia

Author, year Country Trial name (Quality score)	Age Gender Ethnicity	Other population characteristics (diagnosis, etc)	Number screened/ eligible/enrolled	Number withdrawn/ lost to fu/analyzed
Aripiprazole				
Pigott, 2003 International	Mean age: 42.0 years 56.1% male 90.6% white 6.5% black 0.6% Asian/Pacific Islander 2.3% Hispanic/Latino	Mean baseline PANSS total score: 81.8	NR/ NR/ 310	194/ 2/ 297

Evidence Table 5. Placebo-controlled trials in patients with schizophrenia

Author, year Country Trial name (Quality score)	Outcome scales	Method of outcome assessment and timing of assessment
Aripiprazole		
Pigott, 2003 International	CGI-I CGI-S PANSS PANSS-BPRS	Primary outcome: time to relapse (defined as CGI-I ≥5; PANSS ≥5 for hostility/uncooperativeness subscore on 2 successive days; or a ≥20% increase in PANSS total score) following randomization. Treatment efficacy assessed using the CGI-S and CGI-I scales at weeks 1,2,3,4,6,8,10,14,18,22, and 26. PANSS and PANSS-BPRS used to assess efficacy at weeks 3,6,10,18, and 26

Evidence Table 5. Placebo-controlled trials in patients with schizophrenia

Author, year Country Trial name (Quality score)	Results	Methods of adverse event assessments
Aripiprazole		
Pigott, 2003 International	Aripiprazole vs placebo: % of patients without relapse at week 26: 62.6% vs 39.4%, p<0.001 Relative risk of relapse with aripiprazole vs placebo: 0.50 (95% CI=0.35 to 0.71) % of patients who met criteria in analysis of secondary endpoints for relapse: 33.8% vs 57% Mean change in scores from baseline: PANSS: -2.08 vs +4.50, p≤0.01 CGI-I: +3.74 vs +4.47, p≤0.01 CGI-S: +0.15 vs +0.40, p≤0.05	SAS Barnes AIMS

Evidence Table 5. Placebo-controlled trials in patients with schizophrenia

Author, year Country Trial name (Quality score)	Adverse events	Total number of withdrawals; withdrawals due to adverse events
Aripiprazole		
Pigott, 2003 International	SAS : -0.85 vs -0.45, p≤0.05 Barnes: -.07 vs -0. 5, p=NS AIMS: -0.23 vs -0.26, p=NS	Total number of discontinuations per group: 54.2% vs 71.0% Withdrawals due to AEs: 10.3% vs 8.4%

Evidence Table 5. Placebo-controlled trials in patients with schizophrenia

Author, year Country Trial name (Quality score)	N	Study design Setting	Eligibility criteria
Olanzapine			
Beasley, 2003 Croatia, Poland, Romania, the Russian Federation, US, Yugoslavia Olanzapine Relapse Prevention Study	326 (224 olanzapine, 102 placebo)	4- to 9-day screening evaluation, 6-week conversion to open-label olanzapine, 8-week stabilization on olanzapine, and 52-week randomized double-blind maintenance with olanzapine or placebo.	Otherwise healthy outpatients ages 18-65 with schizophrenia or schizoaffective disorder. Minimal symptoms defined as a BPRS score of no more than 36 at baseline (with relatively little fluctuation of 4 weeks or longer prior to study entry); outpatient status; Global Assessment of Functioning score of 40 or greater; current maintenance on an antipsychotic agent other than clozapine at either 300 mg/d or more chlorpromazine equivalent for oral agents or 25 mg or more every 2 weeks of fluphenazine decanoate equivalent for injectable agents; lack of specific positive symptoms, as measured by a score of 4 or greater on the BPRS positive items (scored 1-7) of conceptual disorganization, suspiciousness, hallucinatory behavior, and unusual thought content.

Evidence Table 5. Placebo-controlled trials in patients with schizophrenia

Author, year Country Trial name (Quality score)	Interventions (drug, dose, duration)	Run-in/Washout period	Allowed other medications/ interventions
Olanzapine			
Beasley, 2003 Croatia, Poland, Romania, the Russian Federation, US, Yugoslavia Olanzapine Relapse Prevention Study	Olanzapine 10 mg, 15 mg, or 20 mg per day or placebo For 26-week maintenance period.	Screening period (skipped if patient was currently stable on a fixed dose of olanzapine monotherapy), 4- to 9-days, 6-week conversion to open-label olanzapine, 8-week stabilization on olanzapine	NR

Evidence Table 5. Placebo-controlled trials in patients with schizophrenia

Author, year Country Trial name (Quality score)	Age Gender Ethnicity	Other population characteristics (diagnosis, etc)	Number screened/ eligible/enrolled	Number withdrawn/ lost to fu/analyzed
Olanzapine				
Beasley, 2003 Croatia, Poland, Romania, the Russian Federation, US, Yugoslavia Olanzapine Relapse Prevention Study	Mean age 36 (SD 11) 53% male Ethnicity not reported	Schizophrenic 79% olanzapine vs 87.3% placebo Schizoaffective 21% olanzapine vs 12.7% placebo	583/ 458/ 326	84 withdrawn/1 lost to followup/324 analyzed

Evidence Table 5. Placebo-controlled trials in patients with schizophrenia

Author, year Country Trial name (Quality score)	Outcome scales	Method of outcome assessment and timing of assessment
Olanzapine		
Beasley, 2003 Croatia, Poland, Romania, the Russian Federation, US, Yugoslavia Olanzapine Relapse Prevention Study	BPRS, PANSS, Heinrichs-Carpenter Quality of Life Questionnaire	Patients formally evaluated at least every 2 weeks at the investigative site, at a home visit, or by telephone. Primary efficacy parameter was lack of relapse during the maintenance phase. Defined as (1) an increase in any BPRS positive item to >4, and either an absolute increase of 2 or more on that specific item from randomization at visit 16 or an absolute increase of 4 or more on the BPRS positive subscale from randomization at visit 16; or (2) hospitalization due to positive psychotic symptoms. Secondary efficacy assessments included the PANSS total and subscale scores. Quality of life measured by the Heinrichs-Carpenter Quality of Life Questionnaire

Evidence Table 5. Placebo-controlled trials in patients with schizophrenia

Author, year Country Trial name (Quality score)	Results	Methods of adverse event assessments
Olanzapine		
Beasley, 2003 Croatia, Poland, Romania, the Russian Federation, US, Yugoslavia Olanzapine Relapse Prevention Study	Patients relapsing after 8 weeks of maintenance olanzapine: 9/224 (4.0%) vs placebo: 28/102 (27%), p<0.001 Mean worsening on PANSS from baseline after 8 weeks of maintenance (olanzapine vs placebo) Total score: 1.8 (+ 9.2) vs 17.7 (+ 19.1), p=0.002 Positive score: 0.6 (+ 2.9) vs 5.4 (+ 5.6), p=0.002 Negative score: 0.3 (+ 2.5) vs 3.4 (+ 4.9), p=0.064 General Psychopathology: 0.9 (+ 4.9) vs 9.2 (+ 10.3), p=0.002 Quality of Life: olanzapine patients had significant improvements vs placebo patients (who worsened) from baseline (p<0.001) for total, intrapsychic foundation, and instrumental role scores (data NR). Olanzapine group improvements on interpersonal relation and common objects and activities subscales but not statistically significant from placebo (data NR).	Spontaneously reported adverse events collected; Simpson-Angus Scale, Barnes Akathisia Scale.

Evidence Table 5. Placebo-controlled trials in patients with schizophrenia

Author, year Country Trial name (Quality score)	Adverse events	Total number of withdrawals; withdrawals due to adverse events
Olanzapine		
Beasley, 2003 Croatia, Poland, Romania, the Russian Federation, US, Yugoslavia Olanzapine Relapse Prevention Study	Change from baseline to 8 weeks, olanzapine vs placebo: Simpson-Angus Scale: -0.11 (SD 0.96) vs 0.02 (SD 0.51) Barnes Akathisia Scale: -0.01 (SD 0.30) vs -0.03 (SD 0.33), p=NS Treatment-emergent parkinsonism : 0.9% vs 0, p=NS Treatment-emergent akathisia : 1.8% vs 2%, p=NS Tardive dyskinesia : 0.5% vs 2%, p= NS Treatment-emergent AEs with an incidence of >5% (olanzapine vs placebo) Anxiety: 6.7% vs 12.7% (p=0.088) Weight gain: 6.3% vs 1.0% (p=0.043) Thinking abnormal: 3.6% vs 7.8% (p=0.105) Schizophrenic reaction: 3.1% vs 25.5% (p<0.001) Hallucinations: 2.2% vs 6.9% (p=0.055) Apathy:1.8% vs 5.9% (p=0.077) Insomnia: 1.3% vs 19.6% (p=0.001) Paranoid reaction: 1.3% vs 10.8% (p=0.001) Weight loss: 0.9% vs 6.9% (p=0.005) Hostility: 0.4% vs 3.9% (p=0.035) Anorexia: 0.0% vs 2.9% (p=0.030)	13% olanzapine vs 54% placebo ; 1% olanzapine vs 12% placebo

Evidence Table 5. Placebo-controlled trials in patients with schizophrenia

Author, year Country Trial name (Quality score)	N	Study design Setting	Eligibility criteria
Baker, 1996 United States Inpatients	29	RCT, DB placebo-controlled trial Multicenter	Inpatients with a DSM III-R diagnosis of chronic schizophrenia
Quetiapine			
Borison, 1996	109	Multicenter, BD, PCT	Men and women aged 18-60 years were eligible to enter the study if they satisfied DSM-III-R criteria for chronic or subchronic schizophrenia with acute exacerbation. Patients were also required to have a minimum total score of 45 on the 18-item BPRS (0-7 scoring), a score of 4 (moderate) on at least two items from the BPRS positive symptom cluster (conceptual disorganization, suspiciousness, hallucinatory behavior, unusual thought content), and a score of 4 (moderately ill) on the CGI Severity of illness item.

Evidence Table 5. Placebo-controlled trials in patients with schizophrenia

Author, year Country Trial name (Quality score)	Interventions (drug, dose, duration)	Run-in/Washout period	Allowed other medications/ interventions
Baker, 1996 United States Inpatients	Olanzapine 1 mg (n=11) Olanzapine 10 mg (n=7) Placebo (n=7) 6-week treatment period	NR / 1-week washout period before randomization	NR
Quetiapine			
Borison, 1996	Quetiapine 75mg-750mg/day or placebo for 6 weeks. But daily dosage greater than 500mg were limited to 14 days.	2-10 days placebo phase/NA	No

Evidence Table 5. Placebo-controlled trials in patients with schizophrenia

Author, year Country Trial name (Quality score)	Age Gender Ethnicity	Other population characteristics (diagnosis, etc)	Number screened/ eligible/enrolled	Number withdrawn/ lost to fu/analyzed
Baker, 1996 United States Inpatients	Mean age: 36 years 68% male Ethnicity: NR	Mean (SD) Global Severity Ratings at baseline for: Obsession: 0.8 (1.2) Compulsions: 0.8 (0.8) On this scale, 0 = no symptoms; 1 = slight symptoms; 2 = mild symptoms	NR/ NR/ 29	4 / NR / 25
Quetiapine				
Borison, 1996	Mean age = 36 (18-58) years Gender: 91% male Ethnicity: 62% white; 36% black; 3% other	Acute exacerbation: 47.4% chronic undifferentiated 35.5% chronic paranoid 16.5% other Previous hospitalization: 51.1% <8 57.9% >8 17.4% unknown	NR/ 146/ 109	

Evidence Table 5. Placebo-controlled trials in patients with schizophrenia

Author, year Country Trial name (Quality score)	Outcome scales	Method of outcome assessment and timing of assessment
Baker, 1996 United States Inpatients	see "methods of outcome assessment..." column	Obsessive and compulsive symptoms identified and rated using a scale derived from the Yale-Brown Obsessive Compulsive Scale supplemented by screening questions from the NIMH Diagnostic Interview Schedule (DIS) and by global severity and global change derived from the CGI-S. Ratings were completed at baseline and endpoint (week 6). Elements analyzed for this report: global severity of obsessions, global severity of compulsions, change during DB treatment in overall severity of obsessions, and change during DB treatment in overall severity of compulsions.
Quetiapine		
Borison, 1996	Brief Psychiatric Rating Scale (BPRS) Clinical Global Impression (CGI) Modified Scale for the Assessment of Negative Symptoms (SANS)	scales are rated by the trained investigators weekly

Evidence Table 5. Placebo-controlled trials in patients with schizophrenia

Author, year Country Trial name (Quality score)	Results	Methods of adverse event assessments
Baker, 1996 United States Inpatients	Mean (+/-SD) Global severity ratings change between baseline and endpoint for all groups: Obsessions: 0 Compulsions -0.2 Global endpoint ratings of change from baseline in obsessive symptoms : % of patients saying symptoms improved vs unchanged vs worse Olanzapine 1 mg (n=11) : 9.1% vs 63.6% vs 27.3% Olanzapine 10 mg (n=7): 28.6% vs 42.8% vs 28.6% Placebo (n=7): 0% vs 71.4% vs 28.6% Global endpoint ratings of change from baseline in compulsive symptoms : % of patients saying symptoms improved vs unchanged vs worse Olanzapine 1 mg : 9.1% vs 81.8% vs 9.1% Olanzapine 10 mg: 0% vs 85.7% vs 14.3%	NR
Quetiapine		
Borison, 1996	Quetiapine vs placebo (change from baseline), p value: BPRS total score: -8.1(2.39) vs -2.1(2.30), p=0.07 BPRS factor score: Anxiety/depression: -0.6(0.14) vs -0.6(0.14), p=0.75 Anergia: -0.1(0.14) vs 0.0(0.14), p=0.52 Thought disturbance: -0.7(0.18) vs -0.3(0.18), p=0.09 Activation: -0.4(0.18) vs 0.4(0.18), p=0.002 Hostile/suspiciousness: -0.4(0.22) vs 0.0(0.22), p=0.18 BPRS positive-symptom cluster score: -0.9(0.21) vs -0.3(0.21), p=0.06 CGI Severity of Illness item score: -0.2(0.18) vs 0.2(0.18), p=0.07 SANS summary score: -1.0(0.61) vs 0.6(0.6), p<0.05 CGI Global Improvement: improved: 28% vs 25%, p=0.02 worsened: 17% vs 42%	Simpson Scale Abnormal Involuntary Movement Scale (AIMS)

Evidence Table 5. Placebo-controlled trials in patients with schizophrenia

Author, year Country Trial name (Quality score)	Adverse events	Total number of withdrawals; withdrawals due to adverse events
Baker, 1996 United States Inpatients	NR	NR
Quetiapine		
Borison, 1996	AIMS: NS	Withdrawn due to adverse events (no. patients): quetiapine 3 vs placebo 2

Evidence Table 5. Placebo-controlled trials in patients with schizophrenia

Author, year Country Trial name (Quality score)	N	Study design Setting	Eligibility criteria
Small, 1997 United States and Europe	286	Multicenter, DB, PCT	Hospitalized men and women aged 18-65 years were eligible to enter the study if they satisfied DSM-III-R criteria for chronic or subchronic schizophrenia with acute exacerbation . Patients were also required to have a minimum total score of 45 on the 18-item BPRS (0-7 scoring), a score of 4 (moderate) on at least two items from the BPRS positive symptom cluster (conceptual disorganization, suspiciousness, hallucinatory behavior, unusual thought content), and a score of 4 (moderately ill) on the CGI Severity of illness item.

Evidence Table 5. Placebo-controlled trials in patients with schizophrenia

Author, year Country Trial name (Quality score)	Interventions (drug, dose, duration)	Run-in/Washout period	Allowed other medications/ interventions
Small, 1997 United States and Europe	Quetiapine low dose (<250mg/day), high dose (251-750mg/day) or placebo for 6 weeks. But the daily maximum dosage 750mg were limited to 14 days.	2 days placebo/NA	Chloral hydrate allowed for insomnia (500-1000mg at bedtime) and acute agitation (500mg) but was limited to 2000 mg/day. Lorazepam (1-2mg orally or intramuscularly) was permitted orally or intramuscularly for severe agitation or insomnia unresponsive to chloral hydrate or dose escalation of quetiapine. In Europe, other benzodiazepines were permitted within protocol-specific guidelines for frequency of use and maximum dose. Neither chloral hydrate nor lorazepam was permitted within 6 and 12 hrs of efficacy assessments. During the DB phase, benztropine mesylate was permitted by treatment of EPS, with the dose and duration specified by the treating clinician.

Evidence Table 5. Placebo-controlled trials in patients with schizophrenia

Author, year Country Trial name (Quality score)	Age Gender Ethnicity	Other population characteristics (diagnosis, etc)	Number screened/ eligible/enrolled	Number withdrawn/ lost to fu/analyzed
Small, 1997 United States and Europe	Mean age: 22.3 years Gender: 71.2% male Ethnicity: 70.7% white; 19.3% black; 10% others	Acute exacerbation: 29.3% chronic undifferentiated 54.6% chronic paranoid 12.6% disorganized 2.6% other Previous hospitalization: 52.3% <8 47.6% >8 5.9% unknown	NR/ NR/ 286	NR/ NR/ 280

Evidence Table 5. Placebo-controlled trials in patients with schizophrenia

Author, year Country Trial name (Quality score)	Outcome scales	Method of outcome assessment and timing of assessment
Small, 1997 United States and Europe	Brief Psychiatric Rating Scale (BPRS) Clinical Global Impression (CGI) Modified Scale for the Assessment of Negative Symptoms (SANS) Negative Scale of the Positive and Negative Syndrome Scale (PANSS)	The scales were completed by the investigator or designated subinvestigator weekly

Evidence Table 5. Placebo-controlled trials in patients with schizophrenia

Author, year Country Trial name (Quality score)	Results	Methods of adverse event assessments
Small, 1997 United States and Europe	Primary measure: BPRS total score: High Q- -8.7(1.64), <0.001 vs Placebo Low Q- -4.2(1.62), 0.04 vs High Q Placebo- -1.0(1.61), 0.15 vs Low Q CGI Severity of Illness: High Q- -0.6(0.13), 0.003 vs Placebo Low Q- -0.3(0.13), 0.08 vs High Q Placebo- -0.1(0.13), 0.23 vs Low Q Secondary measure: BPRS positive-symptom cluster score: High Q- -0.9(0.13), 0.03 vs Placebo Low Q- -0.6(0.13), 0.11 vs High Q Placebo- -0.4(0.13), 0.17 vs Low Q CGI Global Improvement (endpoint): High Q- 3.4(1.7), 0.006 vs Placebo Low Q- 4.0(1.7), 0.03 vs High Placebo- 4.1(1.8), 0.55 vs Low Q SANS summary score: High Q- -1.7(0.47), 0.02 vs Placebo Low Q- 0.3(0.48), 0.004 vs High Q Placebo- -0.1(0.46), 0.54 vs Low Q PANSS(N) total score: High Q- -4.4(1.2), 0.1 vs Placebo Low Q- -2.9(1.1), 0.32 vs High Q Placebo- -1.9(1.1), 0.52 vs Low Q	Simpson-Angus Scale Barnes Akathisia Scale: Abnormal Involuntary Movement Scale

Evidence Table 5. Placebo-controlled trials in patients with schizophrenia

Author, year Country Trial name (Quality score)	Adverse events	Total number of withdrawals; withdrawals due to adverse events
Small, 1997 United States and Europe	Simpson-Angus Scale total score: NS Barnes Akathisia Scale: NS Abnormal Involuntary Movement Scale total score: NS	Withdrawals due to adverse events, no. of patients: High Q vs Low Q vs Placebo = 7 vs 7 vs 3

Evidence Table 5. Placebo-controlled trials in patients with schizophrenia

Author, year Country Trial name (Quality score)	N	Study design Setting	Eligibility criteria
Risperidone			
Kane, 2003 Nasrallah, 2004	400	Multicenter, double-blind.	Hospital outpatients or inpatients ages 18-55 with a diagnosis of schizophrenia according to DSM-IV criteria; baseline PANSS total scores of 60-120 and good general health, with standard laboratory test results within reference ranges or not clinically significant.

Evidence Table 5. Placebo-controlled trials in patients with schizophrenia

Author, year Country Trial name (Quality score)	Interventions (drug, dose, duration)	Run-in/Washout period	Allowed other medications/ interventions
Risperidone			
Kane, 2003 Nasrallah, 2004	Long-acting risperidone 25 mg, 50 mg, 75 mg, or placebo intramuscular injection Every 2 weeks for 12 weeks.	1-week screening period, then doses of other oral antipsychotic medications were reduced and then discontinued. Simultaneously, oral risperidone started at 2 mg/day and increased to 4 mg/day for at least 3 days.	Oral risperidone or oral placebo continued for the first 3 weeks of the double-blind phase.

Evidence Table 5. Placebo-controlled trials in patients with schizophrenia

Author, year Country Trial name (Quality score)	Age Gender Ethnicity	Other population characteristics (diagnosis, etc)	Number screened/ eligible/enrolled	Number withdrawn/ lost to fu/analyzed
Risperidone				
Kane, 2003 Nasrallah, 2004	Mean age 38 (SD 10) 75% male 42% African American, 42% white, 11% Hispanic, 6% other ethnicity	Schizophrenia subtype: 76% paranoid, 21% undifferentiated, 3% disorganized, <1% catatonic; 51% outpatients, 49% inpatients	554/ 461/ 400	206 withdrawn/17 lost to followup/370 analyzed

Evidence Table 5. Placebo-controlled trials in patients with schizophrenia

Author, year Country Trial name (Quality score)	Outcome scales	Method of outcome assessment and timing of assessment
Risperidone		
Kane, 2003 Nasrallah, 2004	PANSS total score Secondary measures: PANSS positive and negative factor scores, CGI scale.	PANSS every 2 weeks, CGI every week; trained raters, interrater reliability established before the start of the trial. SF-36 measured HRQoL (Health Related Quality of Life) consisting of 8 domains; a score above 50 is a score above normative average. SF-36 assessed at baseline and 12-week endpoint (or study discontinuation)

Evidence Table 5. Placebo-controlled trials in patients with schizophrenia

Author, year Country Trial name (Quality score)	Results	Methods of adverse event assessments
Risperidone		
Kane, 2003 Nasrallah, 2004	Mean change at endpoint on PANSS (LOCF): Total score placebo: 2.6 risperidone 25 mg: -6.2 (p=0.002 vs placebo) risperidone 50 mg: -8.5 (p<0.001 vs placebo) risperidone 75 mg: -7.4 (p<0.001 vs placebo) Positive symptoms placebo: -0.2 risperidone 25 mg: -2.3 (p=0.05 vs placebo) risperidone 50 mg: -3.5 (p<0.001 vs placebo) risperidone 75 mg: -3.0 (p<=0.005 vs placebo) Negative symptoms placebo: 0.9 risperidone 25 mg: -2.4 (p<0.001 vs placebo) risperidone 50 mg: -1.2 (p=0.02 vs placebo) risperidone 75 mg: -1.2 (p=0.02 vs placebo) Mean change at endpoint on CGI (LOCF), placebo vs R 25 vs R 50 vs R 75: 0.3 vs -0.3 vs -0.3 vs -0.4 (p<0.001 for all comparisons vs placebo) Mean change from baseline on the SF-36 scale (HRQoL measure) Risperidone (all doses) vs placebo p<0.05 for 5 of 8 domains: Bodily pain, General health, Social functioning, Role-emotional, Mental health p=NS between any risperidone group vs placebo for Vitality and Physical Functioning (2 of 8) domains Rispderidone 25 mg vs placebo, p<0.05 fopr Role-Functioning (	Assessed at baseline and every 2 weeks. Serious adverse events were defined as those that resulted in death or were life-threatening, required hospitalization or prolongation of hospitalization, resulted in persistent or significant disability or incapacity, or resulted in a congenital anomaly or birth defect. Spontaneously reported extrapyramidal symptoms (extrapyramidal disorder, hyperkinesia, hypertonia, tremor, hypokinesia, and involuntary muscle contractions). Severity of extrapyramidal symptoms evaluated by 55-item Extrapyramidal Symptom Rating Scale (ESRS). Investigators trained in the use of the ESRS, and interrater reliability was established before the trial.

Evidence Table 5. Placebo-controlled trials in patients with schizophrenia

Author, year Country Trial name (Quality score)	Adverse events	Total number of withdrawals; withdrawals due to adverse events
Risperidone		
Kane, 2003 Nasrallah, 2004	Risperidone 25 mg vs 50 mg vs 75 mg vs placebo Any AE: 80% vs 83% vs 82% vs 83% Serious AEs: 13% vs 14% vs 15% vs 23.5% 1 death in placebo group due to injury Mean change from baseline to 12 weeks on ESRS (all comparisons NS): Total: -1.5 vs 0.1 vs 0.0 vs -0.1 Parkinsonian subscale -1.1 vs 0.0 vs 0.3 vs -0.5 Dystonia subscale : 0.0 vs 0.0 vs 0.0 vs 0.0 Dyskinesia subscale -0.4 vs 0.1 vs -0.3 vs 0.4 Spontaneously reported AEs related to EPS: risperidone 25 mg: 10% risperidone 50 mg: 24% risperidone 75 mg: 29% placebo: 13% (p>0.10 for all groups vs placebo)	Overall withdrawals: risperidone 25 mg: 52% risperidone 50 mg: 51% risperidone 75 mg: 52% placebo: 68% Withdrawals due to AEs: risperidone 25 mg: 11% risperidone 50 mg: 12% risperidone 75 mg: 14% placebo: 12%

Evidence Table 5. Placebo-controlled trials in patients with schizophrenia

Author, year Country Trial name (Quality score)	N	Study design Setting	Eligibility criteria
Lauriello, 2005 subanalysis of inpatients from Kane 2003	214 inpatients of original 439 patients	Multicenter, DB, randomized, PCT	see Kane 2003
Bai, 2003 Inpatients	49	Randomized, DB PCT	Hospitalized patients aged 18-65 years with severe tardive dyskinesia and BPRS <20 and no record of violent or aggressive behavior within 6 months prior to the study.
Ziprasidone			
Arato, 2002 Inpatients	294	Randomized, DB, parallel group PCT	Inpatients ≥ 18y with chronic, stable schizophrenia (DSM-III-R) hospitalized ≥ 2 months and had scores of ≤ 5 on the CGI-S.

Evidence Table 5. Placebo-controlled trials in patients with schizophrenia

Author, year Country Trial name (Quality score)	Interventions (drug, dose, duration)	Run-in/Washout period	Allowed other medications/ interventions
Lauriello, 2005 subanalysis of inpatients from Kane 2003	Long-acting risperidone 25 mg, 50 mg, and 75 mg placebo Intramuscular injection every 2 weeks for 12 weeks.	see Kane 2003	Permissible medications for sleep were temazepam, zolpidem or chloral hydrate. Limited doses of lorazepam were permitted for agitation, with max. weekly dose of 42mg during first 2 weeks following randomization, a max. weekly dose of 38mg during the following 2 weeks and a max. weekly dose of 16mg thereafter.
Bai, 2003 Inpatients	Risperidone up-titrated to 6 mg/d for last 6 weeks of study placebo 12-weeks	NR/ 4-week washout with all original conventional antipsychotics	Other antispychotics not allowed; anticholinergics were titrated according to the EPS, and benzodiazepines could be prescribed adjunctively if the patients psychiatric condition was unstable.
Ziprasidone			
Arato, 2002 Inpatients	Ziprasidone 40 mg/d Ziprasidone 80 mg/d Ziprasidone 160 mg/d placebo 52-week study (no dosage adjustments allowed during the study after the first 2 days)	NR/ 3-day wash out for all pts	Only medications permitted: anticholinergicvs, lorazepam for agitation and temazepam (upper limit=20mg) for insomnia

Evidence Table 5. Placebo-controlled trials in patients with schizophrenia

Author, year Country Trial name (Quality score)	Age Gender Ethnicity	Other population characteristics (diagnosis, etc)	Number screened/ eligible/enrolled	Number withdrawn/ lost to fu/analyzed
Lauriello, 2005 subanalysis of inpatients from Kane 2003	Mean age = 38 years Gender: 70% male Ethnicity: 42.6% Caucasian; 41.5% black; 24.5% Hispanic; 4.7% other	Schizophrenia: 91.1% Schizoaffective disorder: 8.8% Prior treatment with antipsychotic: 67.4%	NR/ NR/ 214 inpatients	140/ NR/ 74 inpatients
Bai, 2003 Inpatients	Mean age: 50.2 years 66.7% male Ethnicity: NR	Mean baseline BPRS score: 13.4 Mean baseline ESRS-parkinsonian score: 2.7 Mean baseline ESRS-dystonia score: 1.8 Mean baseline AIMS score: 15.9	NR/ NR/ 49	7 / 0 / 42
Ziprasidone				
Arato, 2002 Inpatients	Mean age: 49.7 years Age range: 20-82 years 73% male Ethnicity: NR	Smokers: 68.7%	329/ 294/ 278	179/ NR / 277

Evidence Table 5. Placebo-controlled trials in patients with schizophrenia

Author, year Country Trial name (Quality score)	Outcome scales	Method of outcome assessment and timing of assessment
Lauriello, 2005 subanalysis of inpatients from Kane 2003	see Kane 2003	PANSS every 2 weeks, CGI every week.
Bai, 2003 Inpatients	BPRS	Baseline and endpoint mental status assessed with BPRS.
Ziprasidone		
Arato, 2002 Inpatients	PANSS CGI GAF	PANSS and CGI scales completed at baseline, and end of weeks 3, 6, 16. 28, 40, and 52. Global Assessment of Functioning (GAF) administered at baseline and weeks 28 and 52.1

Evidence Table 5. Placebo-controlled trials in patients with schizophrenia

Author, year Country Trial name (Quality score)	Results	Methods of adverse event assessments
Lauriello, 2005 subanalysis of inpatients from Kane 2003	long-acting risperidone (all risperidone groups together) vs placebo Mean change in PANSS total score: -17.06(1.88) vs -4.73(4.5), p=0.014 % of patients with PANSS >20% reduction in total scores: 50% vs 27%, p=0.012 % of patients with PANSS >40% reduction in total scores: 23% vs 5%, p=0.01 % of patients with CGI assessment of ill, very mild or mild: 32% vs 5%, p=0.0023	Adverse events assessed every 2 weeks, by investigators. Pain at site of injection assessed by VAS (scale: 0=no pain to 100=unbearable pain)
Bai, 2003 Inpatients	Risperidone (n=22) vs placebo (n=20) group: % of responders: 68% vs 30%, p=0.029 Mean change in BPRS score at endpoint: +1.5 vs +5.3, p=NS	Tardive dyskinesia severity and other EPS symptoms were assessed with AIMS and ESRS (Extrapyramidal Symptom Rating Scale) at baseline. Assessment of tardive dyskinesia severity was performed every 2 weeks to the endpoint/week 12 of study
Ziprasidone		
Arato, 2002 Inpatients	34% of ziprasidone patients relapsed (71/206) Ziprasidone 40mg vs ziprasidone 80mg vs ziprasidone 160mg vs placebo Mean change in scores from baseline: PANSS total score: +2.9 vs +1.9 vs -1.3 vs +15.6 (p<0.01 for all Z vs placebo) PANSS Negative subscale: -1.9 vs -1.0 vs -2.8 vs+ 1.4 (p<0.05 for all Z vs placebo) PANSS Positive subscale: +3.0 vs +1.2 vs +1.8 vs +6.2 (p<0.05 for all Z vs placebo) CGI-S: +0.4 vs +0.2 Vs +0.1 vs +1.0 (p<0.01 for all Z vs placebo)	SARS, Barnes Akathisia, and AIMS administered

Evidence Table 5. Placebo-controlled trials in patients with schizophrenia

Author, year Country Trial name (Quality score)	Adverse events	Total number of withdrawals; withdrawals due to adverse events
Lauriello, 2005 subanalysis of inpatients from Kane 2003	ESRS score: NS Long acting risperidone vs placebo: AEs related to movement disorders: 12% vs 15% Mean change in body weight: +2.3kg vs -0.43kg, p=0.0003 Patient-reported injection site pain on VAS (SD): 12.3(20.01) vs 6.71(12.81), NS Concomitant medications: 93% vs 89%, NS Antiparkinsonian agents taken by 27% vs 21%patients. Antidepressants taken by 14% vs 9% patients.	Total inpatients who withdrew: 140/214 Withdrawals by group: risperidone vs placebo inpatients: 60% (96/161) vs 83% (44/53) Withdrawals due to AEs: risperidone 14% vs placebo 11%
Bai, 2003 Inpatients	No significant differences between the two groups in ESRS scores, mean change between baseline and endpoint for ESRS scores, or the % of concomitant antiparkinsonian and benzodiazepine use at the end of the study. Risperidone (n=22) vs placebo (n=20) group: AIMS change in mean score from baseline (SD): -5.5 (3.8) vs -1.1 (4.8), p=0.001 Mean change in ESPR-parkinsonian score at endpoint: -0.5 vs -0.3, p=NS Mean change in ESPR-dystonia score at endpoint: -0.5 vs -0.8, p=NS	7 ; 3
Ziprasidone		
Arato, 2002 Inpatients	NR	Ziprasidone 40mg vs ziprasidone 80mg vs ziprasidone 160mg vs placebo Total withdrawals per group: 58% vs 57% vs 55% vs 86% Withdrawals due to AEs: 10% vs 10% vs 7% vs 15%

Evidence Table 5. Placebo-controlled trials in patients with schizophrenia

Author, year Country Trial name (Quality score)	N	Study design Setting	Eligibility criteria
Daniel, 1999 United States and Canada Inpatients (mandatory hospitalization for the first two weeks of treatment)	302 randomized	Randomized, DB, parallel group PCT Multicenter	Men or women ≥18 years with an acute exacerbation of chronic of subchronic schizophrenia or schizoaffective disorder as defined by DSM-III-R who had been hospitalized within the previous 4 weeks and who had a total score ≥60 on the PANSS with a score of ≥4 on 2 or more core items in the PANSS in the 24 hours before the study treatment was started. Also, patients had to have a score ≥3 on the CGI-I at baseline as compared with screening; their body weight had to be <=160% of the upper limit of normal according to sex, height, and frame; and their urine samples had to be negative for all illicit drugs except for investigator-given cannabinoids and benzodiazepines.

Evidence Table 5. Placebo-controlled trials in patients with schizophrenia

Author, year Country Trial name (Quality score)	Interventions (drug, dose, duration)	Run-in/Washout period	Allowed other medications/ interventions
Daniel, 1999 United States and Canada Inpatients (mandatory hospitalization for the first two weeks of treatment)	Ziprasidone 80 mg/d (n=106) Ziprasidone 160 mg/d (n=104) placebo (n=92) 6-week study (no dosage adjustments after the first 2 days)	NR/ single-blind placebo washout lasting 3-7 days	Concomitant lorazepam (for insomnia or agitation), benzotropine (for EPS) , and beta-andrenoceptor antagonists (for akathisia) were allowed if required but were not administered prophylactically.

Evidence Table 5. Placebo-controlled trials in patients with schizophrenia

Author, year Country Trial name (Quality score)	Age Gender Ethnicity	Other population characteristics (diagnosis, etc)	Number screened/ eligible/enrolled	Number withdrawn/ lost to fu/analyzed
Daniel, 1999 United States and Canada Inpatients (mandatory hospitalization for the first two weeks of treatment)	Mean age: Age range: 18-67 years 71.2% male 68.2% white 19.9% black 2.3% Asian 9.6% other	Ziprasidone 80 vs ziprasidone 160 vs placebo: Schizoaffective disorder: 23% vs 24% vs 21% Disorganized schizophrenia: 3% vs 3% vs 3% Catatonic schizophrenia: 1% vs 1% vs 1% Paranoid schizophrenia: 50% vs 42% vs 49% Undifferentiated schizophrenia: 23% vs 32% vs 26% Baseline scores: PANSS total score: 98.2 vs 95.8 vs 97.3 PANSS negative score: 25.4 vs 24.3 vs 24.9 BPRSd total score: 56.5 vs 55.0 vs 55.1 CGI-S score: 4.8 vs 4.8 vs 4.8 MADRS total score (n=89, 100, and 100 respectively): 17.0 vs 16.9 vs 17.4	440/ NR / 302	Unclear / unclear / 298

Evidence Table 5. Placebo-controlled trials in patients with schizophrenia

Author, year Country Trial name (Quality score)	Outcome scales	Method of outcome assessment and timing of assessment
Daniel, 1999 United States and Canada Inpatients (mandatory hospitalization for the first two weeks of treatment)	PANSS, total and negative subscale scores MADRS BPRSd, total core items scores CGI-S CGI-I	Efficacy variables, except for MADRS. were measured at baseline and weekly for 6 weeks or on early termination (within 24h of receiving the last dose). For CGI-I, the baseline value was based on the comparison with screening, and subsequent weekly assessments were based on comparisons with baseline. MADRS total score was assessed at baseline and weeks 1,2,3, and 6 (or early termination).

Evidence Table 5. Placebo-controlled trials in patients with schizophrenia

Author, year Country Trial name (Quality score)	Results	Methods of adverse event assessments
Daniel, 1999 United States and Canada Inpatients (mandatory hospitalization for the first two weeks of treatment)	ziprasidone 80 vs ziprasidone 160 vs placebo: Mean change in MADRS score from baseline: -1.8 vs -3.1 vs -1.3 % mean improvement from baseline at 6 weeks (ITT LOCF): p<0.05 for Z 80 and Z 160 vs placebo for all scores PANSS total: 12% vs 18% vs 5% BPRSd total: 6% vs 13% vs 18% BPRSd core item: 12% vs 20% vs 27% CGI-S: 4% vs 10% vs 17% PANSS negative subscale: 3% vs 12.5% vs 15.5%	All AE volunteered and observed during study and within 6 days of the last treatment were recorded. Safety assessments were performed at regular intervals or within 24h of early termination. SARS, Barnes Akathisia, and AIMS administered at baseline and week 6 for all (SARS and Barnes also assessed at weeks 1 and 3)

Evidence Table 5. Placebo-controlled trials in patients with schizophrenia

Author, year Country Trial name (Quality score)	Adverse events	Total number of withdrawals; withdrawals due to adverse events
Daniel, 1999 United States and Canada Inpatients (mandatory hospitalization for the first two weeks of treatment)	Ziprasidone 80 vs ziprasidone 160 vs placebo Total % of patients with AEs: 87% vs 89% vs 86% % of patients with severe AEs: 8% vs 8% vs 11% % who took lorazepam at some point in study: 81% vs 87% vs 92% % who took benzotropine: 20% vs 25% vs 13% % who required beta-adrenoceptor antagonists: 9.4% vs 5.8% vs 6.5% Median changes in body weight: +1 kg vs 0kg vs 0kg Individual AEs: Pain: 6% vs 10% vs 9% Headache: 17% vs 31% vs 33% Abdominal pain: 3% vs 10% vs 5% Vomiting: 11% vs 6 % vs 15% Dyspepsia: 9% vs 14 % vs 9% Nausea: 14% vs 7% vs 9% Dry mouth: 4% vs 13% vs 4% Constipation: 7% vs 14% vs 14% Dizziness: 9% vs 17% vs 9% Agitation: 10% vs 9% vs 11% Insomnia:12% vs 12% vs 14% Somnolence: 19% vs 19% vs 5% Akathisia: 14% vs 13% vs 7%	Ziprasidone 80 vs ziprasidone 160 vs placebo Total % of patients who withdrew: unclear Total % of patients discontinued due to AEs: 1.8% vs 7.7% vs 1.1%

Evidence Table 5. Placebo-controlled trials in patients with schizophrenia

Author, year Country Trial name (Quality score)	N	Study design Setting	Eligibility criteria
Keck, 1998	139 randomized	Randomized, DB, PCT Multicenter	Men or women aged 18-64 years with an acute exacerbation of chronic or subchronic schizophrenia or schizoaffective disorder as defined in DSM-III-R who had been hospitalized within the previous 3 weeks with a minimum duration of illness of 1 year. At screening and 24h before study, patients had to have a total score ≥37 on the BPRS and a score of ≥4 on 2 or more of the PBPRS core items. Patients were generally no more than 140% of the upper limit of normal weight according to sex, age, height, and frame, and urine samples had to be negative for all illicit drugs except cannabinoids and benzodiazepines.

Evidence Table 5. Placebo-controlled trials in patients with schizophrenia

Author, year Country Trial name (Quality score)	Interventions (drug, dose, duration)	Run-in/Washout period	Allowed other medications/ interventions
Keck, 1998	Ziprasidone 40 mg/d (n=44) Ziprasidone 120 mg/d (n=47) placebo (n=48) 4-week study	NR/ single-blind placebo washout lasting 4-7 days	Concomitant lorazepam (for insomnia or agitation), benzotropine (for EPS) , and beta-andrenoceptor antagonists (for akathisia) were allowed as required but were not administered prophylactically.

Evidence Table 5. Placebo-controlled trials in patients with schizophrenia

Author, year Country Trial name (Quality score)	Age Gender Ethnicity	Other population characteristics (diagnosis, etc)	Number screened/ eligible/enrolled	Number withdrawn/ lost to fu/analyzed
Keck, 1998	Mean age: 39.4 years Age range: 19-76 years 79.1% male 71.9% Caucasian 19.4% Black 3.6% Asian 5.0% other	Ziprasidone 40 vs ziprasidone 120 vs placebo Schizoaffective disorder: 39% vs 43% vs 31% Disorganized schizophrenia: 2% vs 4% vs 2% Paranoid schizophrenia: 43% vs 38% vs 50% Undifferentiated schizophrenia: 14% vs 15% vs 17% Delusional disorder: 2% vs 0% vs 0% Neurologic illness at screening: 12.8% vs 8.5% vs 22.9%	203/ NR / 139	69/ 1/ 131

Evidence Table 5. Placebo-controlled trials in patients with schizophrenia

Author, year Country Trial name (Quality score)	Outcome scales	Method of outcome assessment and timing of assessment
Keck, 1998	BPRS total score BPRS core item score CGI-S SANS total score BPRS depression cluster BPRS anergia factor score	Primary efficacy determined by BPRS total score and core items score and by CGI-S score. Secondary efficacy assessments made by CGI-I. SANS, the BPRS depression cluster score, the BPRS anergia cluster score.

Evidence Table 5. Placebo-controlled trials in patients with schizophrenia

Author, year Country Trial name (Quality score)	Results	Methods of adverse event assessments
Keck, 1998	Ziprasidone 40 vs ziprasidone 120 vs placebo: Percentage of patients who complete the study: 64% vs 51% vs 50% Mean change in score from baseline (*=p<0.01 for ziprasidone 120 vs placebo): BPRS total score: -5.2 vs -10.1* vs -4.1 BPRS core item score: -2.6 vs -4.1 vs -2.3 CGI-S: -0.4 vs -0.6 vs -0.2 SANS total score: -8.66 vs-7.4 vs -2.4 BPRS depression cluster: -3.0 vs -5.6* vs -2.6 BPRS anergia factor score:-1.4 vs -1.8* vs 0.3 % of patients who too adjunctive therapy during treatment: Benzotropine: 7% vs 19% vs 8% Lorazepam: 82% vs 85% vs 90% Beta-andrenoceptor antagonists: 7% vs 6% vs 4%	SARS, Barnes Akathisia, and the AIMS, vital signs, and clinical lab tests assessed at baseline and throughout study to endpoint.

Evidence Table 5. Placebo-controlled trials in patients with schizophrenia

Author, year Country Trial name (Quality score)	Adverse events	Total number of withdrawals; withdrawals due to adverse events
Keck, 1998	77% of all patients experienced AEs Ziprasidone 40 vs ziprasidone 120 vs placebo Mean change in these scores from baseline: SARS: -1 vs -1 vs -0.5 Barnes Akathisia: -0.1 vs -0.2 vs -0.2 AIMS: -0.3 vs -0.1 vs -0.2 % of patients experiencing an AE by group: 75% vs 81% vs 75% Pain: 9.1% vs 4.2% vs 8.3% Asthenia: 2.3% vs 4.2% vs 0% Headache: 18.2% vs 21.3% vs 20.8% Abdominal pain: 11.4% vs 2.1% vs 8.3% Dyspepsia: 11.4% vs 6.4% vs 6.3% Nausea: 6.8% vs 6.4% vs 4.2% Constipation: 6.8% vs 10.6% vs 4.2% Agitation: 0% vs 6.4% vs 12.5% Somnolence: 6.8% vs 8.5% vs 8.3% Akathisia: 6.8% vs 2.1% vs 6.3% Rash: 6.8% vs 2.1% vs 0%	Total number of withdrawals for all groups: 69 (45%); withdrawals due to AEs: 5 (3.6%)

Evidence Table 6. Quality assessment of placebo-controlled trials in patients with schizophrenia

	Internal Validity					
Author, year Country	**Randomization adequate?**	**Allocation concealment adequate?**	**Groups similar at baseline?**	**Eligibility criteria specified?**	**Outcome assessors masked?**	**Care provider masked?**
Trial of olanzapine						
Beasley, 2003 Croatia, Poland, Romania, the Russian Federation, US, Yugoslavia Olanzapine Relapse Prevention Study	Method not reported	Not reported	Diagnosis schizophrenia 79% olanzapine vs 87% placebo; schizoaffective disorder 21% olanzapine vs 13% placebo (p=0.049)	Yes	Yes	Not reported
Trial of risperidone						
Kane, 2003 Nasrallah 2004	Method not reported	Not reported	Similar, but only report baseline on patients receiving at least 1 injection of risperidone.	Yes	Yes	Not clear

Evidence Table 6. Quality assessment of placebo-controlled trials in patients with schizophrenia

Author, year Country	Patient masked?	Reporting of attrition, crossovers, adherence, and contamination?	Loss to follow-up: differential/high?	Intention-to-treat (ITT) analysis?
Trial of olanzapine				
Beasley, 2003 Croatia, Poland, Romania, the Russian Federation, US, Yugoslavia Olanzapine Relapse Prevention Study	Yes	Attrition yes, adherence yes, crossovers and contamination no.	No	Not clear
Trial of risperidone				
Kane, 2003 Nasrallah 2004	Yes	Attrition and adherence (withdrawals due to) yes, others no.	6% in placebo 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.

Evidence Table 6. Quality assessment of placebo-controlled trials in patients with schizophrenia

Author, year Country	Post-randomization exclusions?	Quality rating
Trial of olanzapine		
Beasley, 2003 Croatia, Poland, Romania, the Russian Federation, US, Yugoslavia Olanzapine Relapse Prevention Study	Yes (noncompliance)	Fair
Trial of risperidone		
Kane, 2003 Nasrallah 2004	No	Fair

Evidence Table 6. Quality assessment of placebo-controlled trials in patients with schizophrenia

	External Validity			
Author, year Country	**Number screened/eligible/enrolled**	**Exclusion criteria**	**Run-in/Washout**	**Class naïve patients only?**
Trial of olanzapine				
Beasley, 2003 Croatia, Poland, Romania, the Russian Federation, US, Yugoslavia Olanzapine Relapse Prevention Study	583 screened/458 eligible/326 enrolled	Lack of satisfactory response to olanzapine (see Evidence Table for eligibility criteria).	Run-in	No
Trial of risperidone				
Kane, 2003 Nasrallah 2004	554 screened/461 eligible/400 enrolled	If received a depot antipsychotic within 120 days of the start of the trial, were diagnosed as substance dependent, had tardive dyskinesia or a history of neuroleptic malignant syndrome, had a clinically significant ECG abnormality, were pregnant (or likely to become pregnant) or lactating, were at risk of violent behavior, or had current suicidal ideation; history of severe drug sensitivity or allergy, including sensitivity to risperidone, or unresponsive to risperidone.	Withdrawal from current medications simultaneous with beginning intervention	No

Evidence Table 6. Quality assessment of placebo-controlled trials in patients with schizophrenia

Author, year Country	Control group standard of care?	Funding
Trial of olanzapine		
Beasley, 2003 Croatia, Poland, Romania, the Russian Federation, US, Yugoslavia Olanzapine Relapse Prevention Study	Yes	Sponsored by Eli Lilly and Company.
Trial of risperidone		
Kane, 2003 Nasrallah 2004	Yes	Supported by Johnson & Johnson Pharmaceutical Research and Development.

Evidence Table 7. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Data Source	Prospective Retrospective Unclear	Exposure Period	Mean duration of follow-up	Interventions Mean dose
Controlled studies					
Clozapine vs Olanzapine vs Haloperidol					
Kraus, 1999	Max Planck Insitute of Psychiatry	Retrospective	4 weeks	1 week	clozapine: 170 mg/day olanzapine: 13 mg/day haloperidol: 5 mg/day
Clozapine vs Olanzapine vs Conventional Antipsychotics					
Agelink, 2001	Evangelical Hospital Gelsenkirchen, Germany	Retrospective	Mean: 14.1 days	NR	amisulpride: 400 mg/day, olanzapine: 20 mg/day, sertindole: 12 mg/day, clozapine: 100 mg/day
Clozapine vs Haloperidol					
de Leon, 2004	Clinical Research Center, Norristown State Hospital, Norristown	Retrospective	16 weeks	NR	All patients switched from 4 weeks on 10 mg/day of haloperidol, to 100, 300, 600 mg/day clozapine
Kurz 1995 Austria	Single center Active control	First-time clozapine users	Mean weeks: clozapine=23.2, haloperidol=5.2 23.2 weeks	clozapine 193.7 mg haloperidol 12.8 mg	Anticholinergics Beta blockers

Evidence Table 7. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Population	Age Gender Ethnicity	Exposed Eligible Selected	Withdrawn Lost to fu Analyzed
Controlled studies				
Clozapine vs Olanzapine vs Haloperidol				
Kraus, 1999	Schizophrenia	Mean age: 37 years 43% Female	NR/NR/NR	NR/NR/44
Clozapine vs Olanzapine vs Conventional Antipsychotics				
Agelink, 2001	Medication-free inpatients with schizophrenia	Mean age: 33.7 years 68.8% Male Ethnicity NR	NR/NR/51	0/0/51
Clozapine vs Haloperidol				
de Leon, 2004	Schizophrenia	Mean age: 45.5 years 54% Male 85.5% Caucasian 14.5% African-American	NR/NR/40	NR/NR/35
Kurz 1995 Austria	Tardive dyskinesia	Mean age=30.3 63.6% male Race NR	NR NR 151	NR NR Unclear

Evidence Table 7. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Effectiveness outcomes
Controlled studies	
Clozapine vs Olanzapine vs Haloperidol	
Kraus, 1999	Mean scores at endpoint; pvalue 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
Clozapine vs Olanzapine vs Conventional Antipsychotics	
Agelink, 2001	NR
Clozapine vs Haloperidol	
de Leon, 2004	NR
Kurz 1995 Austria	NR

Evidence Table 7. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Safety Outcomes	Comments
Controlled studies		
Clozapine vs Olanzapine vs Haloperidol		
Kraus, 1999	NR	
Clozapine vs Olanzapine vs Conventional Antipsychotics		
Agelink, 2001	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	
Clozapine vs Haloperidol		
de Leon, 2004	Within-subject correlation of prolactin levels: C: 0.32 vs H: 0.75	
Kurz 1995 Austria	Signs of TD: clozapine=5 cases (all had already shown symptoms at baseline); Haloperidol=0	

Evidence Table 7. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Data Source	Prospective Retrospective Unclear	Exposure Period	Mean duration of follow-up	Interventions Mean dose
Clozapine vs Conventional					
de Haan, 1999	University of Armsterdam	Retrospective	7.3 months average	NR	clozapine: NR other drugs: NR
Leon, 1979	Hospital Psiquiatrico, Columbia	Retrospective	6 weeks	3-4 years	NR
Reid, 1998	Texas Department of Mental Health and Mental Retardation (TDMHMR) database	Prospective	NR	6 months	clozapine 1.5-4.5 years conventional antypsychotics
Wang, 2002 U.S.	Databases: NJ Medicaid program & NJ Pharmacetuical Assistance to the Aged & Disabled program plus Medicare	Retrospective	6 months before date of 1st prescription for insulin or oral hypoglycemic agent	6 months	clozapine vs other psychiatric agents (includes typical APs and risperidone); Dose and duration of treatment during the 6-month observation period were included in the analysis

Evidence Table 7. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Population	Age Gender Ethnicity	Exposed Eligible Selected	Withdrawn Lost to fu Analyzed
Clozapine vs Conventional				
de Haan, 1999	Schizophrenia or schizoaffective disorder, schizophreniform disorder	Mean age: 20.9 years	NR/NR/121	
Leon, 1979	Schizophrenia	Mean age: 30.6 years 58% male Ethnicity NR	NR/NR/50	NR/NR/39
Reid, 1998	NR	NR	NR/NR/866	NR/NR/866
Wang, 2002 U.S.	Patients with psychiatric disorders, age>20, enrolled in government-sponsored drug benefit programs 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 months.	Mean age 62.5 31.8% male 64% white	NR NR 14007	NR NR 14007 analyzed Cases with diabetes mellitus n=7227 Controls without diabetes mellitus n=6780

Evidence Table 7. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Effectiveness outcomes
Clozapine vs Conventional	
de Haan, 1999	% of patients experiencing an emergence of increase of obsessions after treatment: C: 20.6% vs other drugs: 1.3%; (P<.01)
Leon, 1979	Mean number of required re-hospitalizations: clozapine: 1.89 vs chlopromazine: 3.52; P<0.01 Average time spent spent in hospital: clozapine: 44.8 days vs chlopromazine: 272.8 days; P<0.05 Average mean time for re-admission: clozapine: 260 days vs chlopromazine: 229
Reid, 1998	M2= period 360-181 days before clozapine; M1=180 days immediately prior to clozapine initiation; P=consecutive 180 day periods beginning 90 days after initiation of clozapine M2(n=383) vs M1(n=383) vs P3(n=383) vs P5(n=299) vs P7(n=101) vs P9(n=29) % of patients requiring hospitalization Days of hospitalization/6 months period 0 day: 19.3 vs 1.7 vs 46.8 vs 60.5 vs 70.3 vs 72.4 16-90 days: 3.0 vs 6.7 vs 2.0 vs 0.7 vs 1.0 vs 3.4 151-180 days: 59.9 vs 67.6 vs 38.8 vs 28.4 vs 21.8 vs 17.2
Wang, 2002 U.S.	NR

Evidence Table 7. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Safety Outcomes	Comments
Clozapine vs Conventional		
de Haan, 1999		
Leon, 1979	NR	
Reid, 1998	NR	
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-month window of observation were not included in the analysis.

Evidence Table 7. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Data Source	Prospective Retrospective Unclear	Exposure Period	Mean duration of follow-up	Interventions Mean dose
Clozapine vs. any other antipsychotic					
Kane 1993 United States	NR	Prospective	≥ 1 year	NR	Clozapine CAPD
Peacock 1996 Denmark	Naturalistic: St. Hans Hospital; Copenhagen's Municipal Psychiatric Hospitals in Glostrup and Ballerup	Prospective	1 year	NR	Clozapine CAPD
Modai 2000 Israel	Database: Sha'as Menashe Mental Health Center (Israel)	Unclear	1/91 to 8/97	NR	Clozapine Other psychiatric agents (non-clozapine treated)
Spivak 1998 Israel	Naturalistic: Ness-Ziona Mental Health Center	Prospective	1 year	NR	Clozapine 295 mg CAPD (chlorpromazine equivalent) 348.9 mg
Hayhurst 2002	South Manchester University Hospitals NHS Trust	Retrospective cohort Controlled	NR	2 years	Clozapine 425 mg/day other antipsychotics: not specified

Evidence Table 7. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Population	Age Gender Ethnicity	Exposed Eligible Selected	Withdrawn Lost to fu Analyzed
Clozapine vs. any other antipsychotic				
Kane 1993 United States	Schizophrenia/schizoaffective	Mean age=26.8 62.8% male Race NR	NR NR 437 (Clozapine=28, CAPD=409)	NR NR 437
Peacock 1996 Denmark	Schizophrenia	Mean age=41.5 69.5% male Race NR	NR NR 200	42(21%) withdrawn Lost to fu NR 158 analyzed (clozapine-=82, CAPD=76)
Modai 2000 Israel	Schizophrenia	NR NR NR	NR 5479 5479	NR NR 5479 (Clozapine=561 vs Non-clozapine=4918)
Spivak 1998 Israel	Treatment resistant schizophrenia	Mean age=38.3 48.3% male Race NR	NR NR 60	NR NR 60
Hayhurst 2002	Schizophrenia	Mean age: 42.5 y 65.1% male Ethnicity: NR	NR /NR /126	NR/ NR/ 126

Evidence Table 7. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Effectiveness outcomes
Clozapine vs. any other antipsychotic	
Kane 1993 United States	NR
Peacock 1996 Denmark	NR
Modai 2000 Israel	NR
Spivak 1998 Israel	NR
Hayhurst 2002	Reduction in mean number of admissions between 2y before clozapine and 2y after, clozapine vs. other: -0.54 vs + 0.25. p <0.01 Reduction in mean length (days) of stay between 2y before cloz. and 2 y after, clozapine vs. other: -33.37 vs -1.35d, p<0.05 % of clozapine users who came off clozapine in 2 years after starting: 44.4% mean reduction in bed-days over 2 yr follow-up period for cloz. users: -33 bed days

Evidence Table 7. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Safety Outcomes	Comments
Clozapine vs. any other antipsychotic		
Kane 1993 United States	Tardive dyskinesia Clozapine=2 cases CAPD=NR	
Peacock 1996 Denmark		
Modai 2000 Israel	Sudden death=6 (1.07%) vs 14 (0.28%); p<0.01 Disease-related death=2 (0.35%) vs 86 (1.75%); p<0.05 Total death=10 (1.78%) vs 105 (2.13%); NS Suicide 2 (0.35%) vs 5 (0.10%); NS	
Spivak 1998 Israel	Suicide Attempts 0 vs 5 (16.7%); p<0.05	
Hayhurst 2002	NR	

Evidence Table 7. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Data Source	Prospective Retrospective Unclear	Exposure Period	Mean duration of follow-up	Interventions Mean dose
Olanzapine vs. Haloperidol					
Allan, 1998	VA Hudson Valley Health Care System	Retrospective	≥6 weeks	NR	olanzapine: 5-20 mg haloperidol: 4-16 mg
Olanzapine vs Haloperidol vs Conventional Antipsychotics					
Dunlop, 2003 United States	Atlanta Veterans Affairs Medical Center pharmacy records	Retrospective	October 1996 - December 2000	392.8 days	Olanzapine (mean dose: 10.3 mg (+/-5.9)) Haloperidol Chlorpromazine Perphenazine Fluphenazine

Evidence Table 7. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Population	Age Gender Ethnicity	Exposed Eligible Selected	Withdrawn Lost to fu Analyzed
Olanzapine vs. Haloperidol				
Allan, 1998	Schizophrenia	Mean age: 53 years 100% Male 69.5% Caucasian 7.5% African American 5.6% Hispanic	NR/NR/53	0/0/53
Olanzapine vs Haloperidol vs Conventional Antipsychotics				
Dunlop, 2003 United States	40.4% schizophrenia 59.6% other	Mean age: 51.6 years 92.9% male 41.7% Caucasian 58.3% other	2725 890 890	NA NA 484

Evidence Table 7. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Effectiveness outcomes
Olanzapine vs. Haloperidol	
Allan, 1998	Mean PANSS total scores: O: 83.4 vs H: 8.3 Mean EPS overall scores: O: 4.8 vs 8.3
Olanzapine vs Haloperidol vs Conventional Antipsychotics	
Dunlop, 2003 United States	NR

Evidence Table 7. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Safety Outcomes	Comments
Olanzapine vs. Haloperidol		
Allan, 1998	Correlation between PANSS negative symptom ratings and EPS measures: olanzapine: EPS/PANSS negative: .25 Rigidity/PANSS negative: .08 Glabella Tap/PANSS negative: .12 Tremor/PANSS negative: .33 Salivation/PANSS negative: .45 haloperidol: EPS/PANSS negative: .76 Rigidity/PANSS negative: .71 Glabella Tap/PANSS negative: .52 Tremor/PANSS negative: .69 Salivation/PANSS negative: -.11	
Olanzapine vs Haloperidol vs Conventional Antipsychotics		
Dunlop, 2003 United States	All data given as olanzapine vs typical antipsychotics Mean change in glucose levels from baseline to endpoint: +6.3 mg/dL vs +0.9 mg/dL % pts developing at least one plasma glucose ≥160 mg/dL: 12.5% (n=39) vs 5.2% (n=9), p=0.01 Of the 39 olanzapine pts, 8 had a diabetes diagnosis prior to exposure, 11 had diabetes diagnosis after exposure, and 20 had never been diagnosed with diabetes Of the 9 typicals patients, 3 had diabetes diagnosis prior to exposure and 6 had not been diagnosed with diabetes % pts ≤60 years old developing at least 1 one plasma glucose ≥ 160 mg/dL: 10.5% vs 0%, p<0.0001 % patients with plasma glucose ≥200 mg/dL: 6.4% vs 1.7%, p=0.02 % patients >60 years, with plasma glucose ≥160 mg/dL: 21/4% vs 16.1%, p=0.47	

Evidence Table 7. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Data Source	Prospective Retrospective Unclear	Exposure Period	Mean duration of follow-up	Interventions Mean dose
Olanzapine vs Quetiapine					
Gupta, 2004	Olean General Hospital at the SUNY Upstate Medical University at Syracuse	Prospective	NR	10 weeks	quetiapine 4 weeks 392.5 mg/day
Risperidone vs Clozapine					
King 1998 Ireland	Database: Central Services Agency in Northern Ireland/CRMS for clozaril	Unclear	1963 to 1996	NR	Clozapine Risperidone
Conley 1999 United States	Record review: Maryland state psychiatric facilities	Prospective	3/14/94 to 12/31/95	NR	Clozapine Risperidone
Sharif, 2000	Creedmoor Psychiatric Center, Columbia University	Retrospective	12 weeks	4 weeks	clozapine: 520 mg/day risperidone: 7.5 mg/day

Evidence Table 7. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Population	Age Gender Ethnicity	Exposed Eligible Selected	Withdrawn Lost to fu Analyzed
Olanzapine vs Quetiapine				
Gupta, 2004	Schizophrenia, schizoaffective disorder, bipolar disorder, psychotic disorder, or major depression with psychotic features.	Mean age =46.6 years 56% male Ethnicity: NR	NR/NR/16	2/2/NR
Risperidone vs Clozapine				
King 1998 Ireland	unclear	NR NR NR	NR NR NR	NR NR NR
Conley 1999 United States	Schizophrenia	Mean age=40.4 60.5% male Race NR	NR NR 124 (clozapine=49, risperidone=75)	NR NR unclear
Sharif, 2000	Schizophrenia, schizoaffective disorder	Mean age: 35.9 years 54% Male White: 63% Black: 21% Hispanic: 13% Asian: 4%	NR/NR/24	NR/NR/24

Evidence Table 7. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Effectiveness outcomes
Olanzapine vs Quetiapine	
Gupta, 2004	Positive and Negative Syndrome Scale (PANSS): NS Simpson-Angus-Scale (SAS): NS
Risperidone vs Clozapine	
King 1998 Ireland	NR
Conley 1999 United States	NR
Sharif, 2000	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%

Evidence Table 7. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Safety Outcomes	Comments
Olanzapine vs Quetiapine		
Gupta, 2004	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
Risperidone vs Clozapine		
King 1998 Ireland	Agranulocytosis Cases/Fatal cases Clozapine=91/2 Risperidone=0	
Conley 1999 United States	Hospitalization Readmission rates (% patients) Year 1=13% vs 17%; p=NS Year 2=13% vs 34%; p=NS Mean time to readmission(days)=360 vs 319	
Sharif, 2000	Response rates: Clinical Global Impressions-Improvement scores $\leq$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%	

Evidence Table 7. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Data Source	Prospective Retrospective Unclear	Exposure Period	Mean duration of follow-up	Interventions Mean dose
Risperidone vs Clozapine vs Conventionals					
Hennessy, 2002	3 US Medicaid programmes	Retrospective	NR	NR	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
Miller, 1998	Innsbruck University Clinics, Austria	Retrospective	≥3 months	NR	clozapine: 425.6 mg/day risperidone: 4.7 mg/day conventional antipsychotics: 476.5 mg/day
Risperidone vs Halperidol					
Chouinard, 1997	Canadian multicenter risperidone trial	Retrospective	8 weeks	NA	risperidone: 2,6,10, 16 mg/day haloperidol: 20 mg/day placebo 8 week study
Jeste 1999 United States	Naturalistic: outpatient psychiatric clinic	Prospective	Varied: 9 months to 9 years. Subjects were matched on age, diagnosis, and length of neuroleptic-exposure at study entry.	9 months	Risperidone 1.0 mg/day (median) Haloperidol 1.0 mg/day (median)

Evidence Table 7. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Population	Age Gender Ethnicity	Exposed Eligible Selected	Withdrawn Lost to fu Analyzed
Risperidone vs Clozapine vs Conventionals				
Hennessy, 2002	Schizophrenia, control group of patients with psoriasis	71.5% over 34 yrs of age 54% Female Ethnicity NR	NR/NR/NR	NR/NR/NR
Miller, 1998	Schizophrenia, schizoaffective disorder, personality disorder, paranoid subtype	Mean age: 36.6 years 57.5% Male White: 71.7% Black: 2.6% Hispanic: 3.8% Asian: 1.9%	NR/NR/NR	0/0/106
Risperidone vs Halperidol				
Chouinard, 1997	N= 135 Schizophrenic symptomatology: mild: 43 moderate: 60 severe: 27	Mean age: 37 years 71.5% male Ethnicity: NR	135/ 130/ 65	NR/ NR/ 65 (pts in risperidone 6 mg, halperidol, and placebo groups)
Jeste 1999 United States	36% schizophrenia 17% mood disorder 21% dementia 10% other organic mental syndromes 16% miscellaneous diagnoses	Mean age 66 73% male 82% white	450/276/122 Risperidone n=61 Haloperidol n=61	NR NR 122 analyzed

Evidence Table 7. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Effectiveness outcomes
Risperidone vs Clozapine vs Conventionals	
Hennessy, 2002	Adjusted rate ratios; 95% Cis Patients with glaucoma: cardiac arrest/ventricular arhythmia; 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 arhythmia; 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)
Miller, 1998	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%
Risperidone vs Halperidol	
Chouinard, 1997	In analysis that compared only risperidone 6 mg (n=22) to halperidol (n=21) and placebo (n=22), risperidone superior to placebo: mean 26-point decrease in total PANSS score; p<0.038
Jeste 1999 United States	NR

Evidence Table 7. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Safety Outcomes	Comments
Risperidone vs Clozapine vs Conventionals		
Hennessy, 2002	Those with treated schizophrenia has higher rates of cardiac arrest and ventricular arrhythmia over those non-treated: ratio: 1.7-3.2	
Miller, 1998	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%	
Risperidone vs Halperidol		
Chouinard, 1997	NR	
Jeste 1999 United States	Risperidone vs haloperidol, cumulative incidence of TD after 9 months: 5 vs 30% (p=0.045) Univariate Cox regression: RR for tardive kinesia was 4.12 times higher with haloperidol than risperidone (95% 2.52-5.72)	Median dose for each drug was below respective maintenance ranges.

Evidence Table 7. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Data Source	Prospective Retrospective Unclear	Exposure Period	Mean duration of follow-up	Interventions Mean dose
Nightengale, 1998	a large psychiatric private group practice	Retrospective Cohort	June 1994 to Nov. 1996	6 months minimum (up to 40 months) Mean follow-up, risp vs hal: 17.2 mos vs 16.0 mos, p=0.6085	Risperidone: mean daily dose: 4.88 mg Halperidol: mean daily dose: 9.61 mg
Soyka, 2004 (inpatients)	Psychiatric Hospital of the University of Munich Non-randomized, comparative	Prospective	Current hospitalization time (weeks), risperidone vs hal: 6.8 vs 6.2 weeks	NR	Average dose /d Risperidone: 4.6 mg/d Halperidol: 10.4 mg/d
Risperidone vs Halperidol vs Conventional antipsychotics					
Schillevoort, 2001b	PHARMO-database	Retrospective	90 days	NR	Median doses risperidone: 2.0 mg/day haloperidol: 2.2 mg/day zuclopenthixol: 6.0 mg/day perphenazine: 5.3 mg/day thioridazine: 48 mg/day pipamperone: 40 mg/day chlopromazine: 63 mg/day

Evidence Table 7. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Population	Age Gender Ethnicity	Exposed Eligible Selected	Withdrawn Lost to fu Analyzed
Nightengale, 1998	Schizophrenia, schizoaffective disorder, major depressive disorder with psychotic features	Mean age: 52.0y 36.5% male Ethnicity: NR	NR / 60 / 60	9 /NR /52
Soyka, 2004 (inpatients)	Schizophrenia or schizoaffective disorder	Mean age: 32.95y 67.5% male Ethnicity: NR	NR/ NR/ 59	NR/ NR / 59
Risperidone vs Halperidol vs Conventional antipsychotics				
Schillevoort, 2001b	Schizophrenia	Mean age: 36 years 45.9% Male Ethnicity NR	450,000/4094/4094	0/0/4094

Evidence Table 7. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Effectiveness outcomes
Nightengale, 1998	Mean monthly physician visits, risperidone vs hal: 0.441 vs 0.244 and total visits: 193 vs 91, p=0.0005 Mean monthly hospital visits, risperidone vs hal: 0.023 vs 0.084, Total hospital visits: 6 visits vs 14 visits, p=0.004 Total hospital days: 119 days vs 385 days Mean hospital inpatient length of stay, risperidone vs hal: 19.83 d vs 16.64 d, p = 0.5827 Mean monthly day hospital visits: 0.030 vs 0.003, p = NA Total day hospital visits, risperidone vs hal: 7 admissions vs 1 admission, p = NA
Soyka, 2004 (inpatients)	Driving ability tests (all subjects had licences), risperidone vs halperidol vs control: Psychomotor test performance (no p-values given): passed: 35% vs 5% vs 85% low performance: 40% vs 35% vs 15% very low performance: 25% vs 60% vs 0% Number of pts who failed in each test, risperidone vs halperidol vs control: PVT (peripheral vision test with tracking task, incl. reaction time): 5 vs 13 vs 0 TT15 (tachistoscope test, abililty to quickly extract relevant info):1 vs 4 vs 0 Q1 (attention test under a monotonous condition): 7 vs 11 vs 2 RST3 (reactive stress tolerance test): 11 vs 16 vs 1 Mean BPRS at examination: risperidone=28 vs haloperidol=27.4 (p=NS)
Risperidone vs Halperidol vs Conventional antipsychotics	
Schillevoort, 2001b	NR

Evidence Table 7. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Safety Outcomes	Comments
Nightengale, 1998	NR	
Soyka, 2004 (inpatients)	NR	Tests are relevant to the German Road Traffic Safety Board.
Risperidone vs Halperidol vs Conventional antipsychotics		
Schillevoort, 2001b	Crude relative risk for anticholinergic medication (95% CI): risperidone vs haloperidol: 0.44 (0.20, 1.01) risperidone vs zuclopenthixol: 0.49 (0.21, 1.13) risperidone vs perphenazine: 1.92 (0.74, 5.01) risperidone vs thioidazine: 3.12 (1.21, 8.04) risperidone vs pipamperone: 4.25 (1.54, 11.72) risperidone vs chlopromazine: 2.97 (0.35, 24.97)	

Evidence Table 7. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Data Source	Prospective Retrospective Unclear	Exposure Period	Mean duration of follow-up	Interventions Mean dose
Risperidone vs Typical Antipsychotics					
Caracci, 1999 (inpatients)	Inpatient unit randomized	Prospective	NR	risperidone vs. typical antipsychotics: 126d vs 128d	Risperidone dosage in chlorpromazine equivalents: 214 mg Typical antipsychotics dosage in chlorpromazine equivalents: 256 mg
Buckley, 1997	South campus Hospital of Northcoast Behavioral Healthcare System (a state facility), inpatients	unclear case-controlled design	Data for seclusion and restraint (S&R) examined 6 months prior to giving risperidone (retrospective part) and then 6 months after giving risperidone	NR	Risperidone (n=15): 6.8 mg (mean dose) Conventional antipsychotics (n=12): 1295 mg (of chloropromazine equivalent)
Beck 1997 inmates	Patients hospitalized at 3 forensic treatment wards at a state mental hospital	Prospective		6 months after attaining the risp 6 mg/d dose	Risperidone (n=10) min dose 6 mg/d Conventional antipsychotics (n=10) (the "Control Group")
Javitt, 2002	Integrated Research Database, Nathan Kline Institute, NY	Retrospective	1994-1996	12 months	risperidone(N=3259): 7.2 mg/day both clozapine and typical antipsychotics (N=3259): NR

Evidence Table 7. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Population	Age Gender Ethnicity	Exposed Eligible Selected	Withdrawn Lost to fu Analyzed
Risperidone vs Typical Antipsychotics				
Caracci, 1999 (inpatients)	Schizophrenia, schizoaffective disorder, bipolar, major depression with psychotic features, borderline personality disorder in each group.	Mean age, risp. vs. other: 37 vs 41y, p=0.046	NR/ NR/ 40	NR/ NR/ 40
Buckley, 1997	Risperidone: 80% schizophrenia; 20% schizoaffective disorder Conventional antipsychotics: 75% schizophrenia; 25% other	Risperidone pts (n=15): mean age: 42y 80% male Ethnicity: NR Conventional antipsychotic pts (n=12): mean age: 45 y 50% male Ethnicity: NR	NR/ NR/ 27	NR/ NR/ 27
Beck 1997 inmates	Risperidone: 70% schizophrenia; 30% schizoaffective disorder Conventional antipsychotics: 60% schizophrenia; 40% schizoaffective disorder	Mean age: 40 years 100% male 50% white 50% black	NR/ NR/ 20	NR/ NR/ 20
Javitt, 2002	Schizophrenia or schizoaffective disorder	Mean age: 39.1 years 60% male Ethnicity NR	5457/3000/1138	NR/NR/1138

Evidence Table 7. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Effectiveness outcomes
Risperidone vs Typical Antipsychotics	
Caracci, 1999 (inpatients)	NR
Buckley, 1997	*All data given as risperidone (n=15) vs conventional (n=12) group* Hours of S&R during 6m prior to risperidone treatment: 50.2h vs 79.4h Hours of S&R over 6m of risperidone treatment: 25.5h vs 33.2h Difference between S&R prior to and during risperidone treatment: -24.7h vs -46.2h (a repeated measures ANOVA of S&R reduction showed a signifcant time effect p=0.007) "No evidence of superiority in S&R reduction between either treatment group"
Beck 1997 inmates	Adaptive behaviors measured by the Interpersonal Interaction Index deteriorated with time for the Risperidone group; no such effects were noted in the control group Neither the risperidone nor the control group changes significantly in terms of aggression levels during the terms of the study, nor did the groups differ significantly when compared with one another at any point in the study.
Javitt, 2002	Admission group: Time to discharge: R: 72 days vs C: 53 days Time to discontinuation: R: 51.1 days vs C: 51.8 days Switch group: Time to discharge: R: 91.7 days va 58.8 days Time to discontinuation: R: 98.5 days vs C: 77.5 days

Evidence Table 7. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Safety Outcomes	Comments
Risperidone vs Typical Antipsychotics		
Caracci, 1999 (inpatients)	Mean prolactin levels, risperidone vs halperidol: 102 mcg/L vs 48 mcg/L, p = 0.00001	
Buckley, 1997	NR	
Beck 1997 inmates	Bizzare Motor higher order scores decreased over time (ie, patients improved) for both groups, p<0.0078 for time comparisons (no between-group comparisons data given)	
Javitt, 2002	NR	

Evidence Table 7. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Data Source	Prospective Retrospective Unclear	Exposure Period	Mean duration of follow-up	Interventions Mean dose
Risperidone vs Olanzapine					
Caro 2002 Quebec	Database: Regie de l'Assurance Maladie du Quebec	Retrospective	1/1/97 to 12/31/99	NR	Olanzapine Risperidone
Dinakar, 2002	Rockland Psychiatric Center, NY	Retrospective	3 months	NR	at Endpoint: olanzapine: 52.75 risperidone: 52.53

Evidence Table 7. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Population	Age Gender Ethnicity	Exposed Eligible Selected	Withdrawn Lost to fu Analyzed
Risperidone vs Olanzapine				
Caro 2002 Quebec	Psychotic disorders ≥ 1 prescription for olanzapine or risperidone	Mean age NR 47.2% male Race NR	NR 34,692 33,946 Olanzapine=19,153 Risperidone=14,793	NR NR 33,946
Dinakar, 2002	Schizophrenia	Mean age: 55.5 years Gender and Ethnicity NR	NR/79/79	0/0/79

Evidence Table 7. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Effectiveness outcomes
Risperidone vs Olanzapine	
Caro 2002 Quebec	
Dinakar, 2002	BPRS scores: baseline vs endpoint O: 67.03 vs 52.75 R: 62.70 vs 52.53

Evidence Table 7. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Safety Outcomes	Comments
Risperidone vs Olanzapine		
Caro 2002 Quebec	Diabetes Olanzapine=319/17 Risperidone=217/16 p=0.43 (Cases/rate per 1000 patient years)	
Dinakar, 2002	NR	

Evidence Table 7. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Data Source	Prospective Retrospective Unclear	Exposure Period	Mean duration of follow-up	Interventions Mean dose
Ho, 1999	Mental Health Clinical Research Center, University of Iowa	Retrospective	4 weeks	6 months	risperidone 6.0 mg/day (N=21) olanzapine 13.7 mg/day (N=21)
de Haan, 2002	Academic Medical Center, University of Amsterdam	Prospective	6 weeks	NR	olanzapine(N=39): 14.2mg risperidone(N=23): 4.1mg

Evidence Table 7. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Population	Age Gender Ethnicity	Exposed Eligible Selected	Withdrawn Lost to fu Analyzed
Ho, 1999	Schizophrenia	Mean age: 31.5 years 76.2% male Ethnicity NR	NR/NR/42	NR/NR/26
de Haan, 2002	N=113 Schizophrenia, 15% OCD disorder, drug class naïve	Mean age: 22.4 years	NR/113/113	NR/NR/62

Evidence Table 7. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Effectiveness outcomes
Ho, 1999	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 Quality of life 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)
de Haan, 2002	Yale-Brown Obsessive Compulsive Scale (YBOCS) Mean Scores: At Admission: R: 2.4 vs O: 2.4 At Endpoint (6 weeks): R: 2.2 vs O: 1.9

Evidence Table 7. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Safety Outcomes	Comments
Ho, 1999	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)	
de Haan, 2002	NR	

Evidence Table 7. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Data Source	Prospective Retrospective Unclear	Exposure Period	Mean duration of follow-up	Interventions Mean dose
Ganguli, 2001	Multiple sources	Retrospective	4 months	NR	NR
Kasper, 2001	Riverview Hospital , British Columbia	Retrospective	4 months	NR	risperidone (N=30) : 4.89 mg/day vs olanzapine (N=30): 17.19 mg/day
Lucey, 2003	Irish Risperidone Olanzapine Drug Outcomes in Schizophrenia	Retrospective	Mean duration: 37.8-40.5 days	NR	risperidone: 4.2 mg/day olanzapine: 12.9 mg/day

Evidence Table 7. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Population	Age Gender Ethnicity	Exposed Eligible Selected	Withdrawn Lost to fu Analyzed
Ganguli, 2001	Schizophrenia	Mean age: 41.3 years 56.5 Males Caucasian: 57% African-American:38% Other: 5%	NR/NR/100	0/0/100
Kasper, 2001	Aged 18-60, schizophrenia-types:paranoid, schizoaffective--disorder, Bipolar affective disorder, undifferentiated	Mean Age: 35.7 years Male: 62% Ethnicity: NR	NR/NR/60	NR/NR/37
Lucey, 2003	Schizophrenia, schizoaffective disorder	Mean age: 37 years 55.5% Male Ethnicity NR	NR/396/394	0/0/396

Evidence Table 7. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Effectiveness outcomes
Ganguli, 2001	NR
Kasper, 2001	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
Lucey, 2003	Hospitali Stay: % discharged on or before day 120: R 95% vs O 94% (NS) Mean legth of study duration: O 30 days vs R 26 day (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

Evidence Table 7. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Safety Outcomes	Comments
Ganguli, 2001	Change in Mean Body Weight/BMI at Endpoint: Weight: risperidone: 82.8kg, P=NS olanzapine: BMI: risperidone: olanzapine:	
Kasper, 2001	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	
Lucey, 2003	NR	

Evidence Table 7. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Data Source	Prospective Retrospective Unclear	Exposure Period	Mean duration of follow-up	Interventions Mean dose
Madhusoodanan, 1999	St. John's Episcopal Hospital	Retrospective	4 months	NR	Mean daily doses: risperidone(N=114): 3mg olanzapine(N=37): 10mg
Meyer, 2002	Oregon State Hospital	Retrospective	12 months		risperidone (N=47): 4.5 mg/day olanzapine (N=47): 16.7 mg/day
Procyshyn, 1998	61 centres in 9 countries	Retrospective	6 weeks	NR	Mean Doses: risperidone: 5.3mg/day vs olanzapine: 14.5mg/day
Snaterse, 2000	Alberta Hospital Edmonton	Retrospective	12 months	12 months	risperidone(N=35): 4.17 mg/day olanzapine(N=21): 15.24 mg/day
Taylor, 2003	U.K. Risperidone Olanzapine Drug Outcomes Studies in Schizophrenia program (RODOS-UK)	Retrospective	4 months	NR	risperidone: 5.5±2.4 mg/day olanzapine: 14.1±4.7 mg/day
Verma, 2001	Houston VA Medical Center	Retrospective	Average: 25 days	NR	risperidone: 2.2 mg olanzapine: 13.2 mg

Evidence Table 7. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Population	Age Gender Ethnicity	Exposed Eligible Selected	Withdrawn Lost to fu Analyzed
Madhusoodanan, 1999	schizophrenia, schizoaffective disorder, dementia, bipolar disorder, major depressive w/psychotic features, delusional disorder	Mean age: 71 years 60.5% Female Ethncity NR	NR/NR/151	22%/NR/151
Meyer, 2002	Schizophrenia, schizoaffective disorder	Mean age:44.5 years 41% 87% Male Ethnicity NR	NR/396/394	
Procyshyn, 1998	Aged ≤ 65 years, schizophrenia or schizoaffective disorder, discharged from hospital or ≥120 days follow-up in hospital, Types of Schizophrenia: catatonic, disorganized, paranoid, undifferentiated, residual, schizoaffective disease, other schizophrenia	Mean Age: 37 years 57.5% Male Ethnicity NR	2339/1901/1345 Risperidone: N=924, Olanzapine: N=977	300/0/1345
Snaterse, 2000	Schizophrenia, schizoaffective disorder	Mean age: 38.8 years 40.5% Female Ethnicity NR	NR/NR/56	NR/NR/56
Taylor, 2003	Schizophrenia, schizoaffective disorder	Mean age: 36.2 years 68.5% male Ethnicity NR	NR/NR/501	NR/NR/499
Verma, 2001	Schizophrenia	Mean age: 71.4 years 100% male 71% caucasian, 23% african-american, 6% hispanic	NR/NR/NR	NR/NR/34

Evidence Table 7. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Effectiveness outcomes
Madhusoodanan, 1999	% 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%
Meyer, 2002	Fasting triglyceride levels at one year: R: mean increase of 29.7 mg/dL vs O: 88.2 mg/dL Weight increases at one year: R: 11.7-13.9lb vs O: 15.0-26.0lb
Procyshyn, 1998	
Snaterse, 2000	Time to initial response: R: 14.3 days vs O: 30.9 days; P<0.00001 Time to discharge: R: 36.6 days vs 58.2 days; P=0.0201
Taylor, 2003	% of effectiveness: R: 78% vs O: 74%; P=.39 Mean time to onset of effectiveness: R: 17.6 days vs O: 22.4 days; P=.01 Mean days in hospitalization: R: 58 days vs R: 49 days; P=.007
Verma, 2001	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

Evidence Table 7. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Safety Outcomes	Comments
Madhusoodanan, 1999	Adverse events reported: R: 20%; EPS, tremor, sedation, hypotension, diarrhea, tardive dyskinesia, chest pain, anxiety, restlessness, itching, insomnia and fall O: 16%; sedation, EPS, postural hypotension	
Meyer, 2002	Triglycerides: O: + 104.8 mg/dL vs R: +31.7 mg/dL (P=.037) Cholestrol: 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)	
Procyshyn, 1998	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 Gastrointestinal: 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%);	
Snaterse, 2000	Re-admission rate at 12 months: R: 31.4% vs O: 61.9%; P=0.026	
Taylor, 2003	% 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, gastrointestinal, metabolic/nutritional, heart rate/rhythms	
Verma, 2001	NR	

Evidence Table 7. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Data Source	Prospective Retrospective Unclear	Exposure Period	Mean duration of follow-up	Interventions Mean dose
Zhao, 2002	IMS Health Lifelink: Integrated Claims Solutions	Retrospective	Average: 181-217 days	NR	risperidone(N=985): 4.02 mg olanzapine(N=348): 10.49 mg
Risperidone vs Olanzapine vs Clozapine					
Barak, 2004	Abarbamel Mental Health Center, Bat-Yam	Retrospective	January 1998 to December 2002	5 years	clozapine 445mg for 575 days olanzapine 17.8mg for 492 days risperidone 4.6mg for 466 days
Hedenmalm, 2002	WHO database	Retrospective	Median treatment duration: R: 13 days, C: 52 days, O: 115 days	NR	risperidone clozapine olanzapine
Risperidone vs Olanzapine vs Quetiapine					
McIntyre 2003 Canada Canadian National Outcomes Measurement Study in Schizophrenia (CNOMSS)	Naturalistic: 32 university and community sites across Canada	Prospective	June 1999 and November 2000	Olanzapine=333 Quetiapine=324 Risperidone=280 (days)	Olanzapine 14.7 mg Quetiapine=324mg Risperidone=3.5 mg

Evidence Table 7. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Population	Age Gender Ethnicity	Exposed Eligible Selected	Withdrawn Lost to fu Analyzed
Zhao, 2002	Schizophrenia	Mean age: 48.6 years 53.5% male Ethnicity NR	NR/NR/1333	0/0/1333
Risperidone vs Olanzapine vs Clozapine				
Barak, 2004	Schizophrenia or schizoaffective disorder with attempted suicide in the 4 weeks preceding admissions	Mean age=39.1 years 84.7% male Ethnicity: NR	68000/4486/378	NR/NR/378
Hedenmalm, 2002	Schizophrenia	NR NR NR	NR/NR/868	0/0/868
Risperidone vs Olanzapine vs Quetiapine				
McIntyre 2003 Canada Canadian National Outcomes Measurement Study in Schizophrenia (CNOMSS)	Consecutive outpatients with schizophrenia, schizophreniform disorder, schizoaffective disorder, or psychosis NOS	Mean age=36.8 67.9% male Race NR	NR NR 243 (Olanzapine=109, Quetiapine=23, Risperidone=111)	NR NR 243 analyzed

Evidence Table 7. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Effectiveness outcomes
Zhao, 2002	Average days of treatment: O: 217 vs R: 181; P<.0001
Risperidone vs Olanzapine vs Clozapine	
Barak, 2004	NR
Hedenmalm, 2002	NR
Risperidone vs Olanzapine vs Quetiapine	
McIntyre 2003 Canada Canadian National Outcomes Measurement Study in Schizophrenia (CNOMSS)	NR

Evidence Table 7. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Safety Outcomes	Comments
Zhao, 2002	NR	
Risperidone vs Olanzapine vs Clozapine		
Barak, 2004	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)	
Hedenmalm, 2002	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	
Risperidone vs Olanzapine vs Quetiapine		
McIntyre 2003 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	

Evidence Table 7. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Data Source	Prospective Retrospective Unclear	Exposure Period	Mean duration of follow-up	Interventions Mean dose
Etminan 2003 Ontario	Database: Ontario Drug Benefit (ODB) claims database	Unclear	NR	NR	Olanzapine Quetiapine Risperidone
Risperidone vs Olanzapine vs Quetiapine vs Haloperidol					
Bobes, 2003	University of Oviedo, Spain, Pfizer Laboratories	Retrospective	≥4 weeks	NR	haloperidol: 10.6 mg/day, olanzapine: 2.4 mg/day, quetiapine: 360.5 mg/day, risperidone: 5.3 mg/day
Risperidone vs Olanzapine vs Quetiapine vs Conventionals					
Gianfrancesco 2003a United States	Database: Blue Cross/Blue Shield claims database	Retrospective	April 1997 through October 2000	Risperidone=9.1 months Olanzapine=8.7 months Quetiapine=7.1 months Conventionals=12.1 months	Risperidone Olanzapine Quetiapine Conventionals Mean doses NR

Evidence Table 7. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Population	Age Gender Ethnicity	Exposed Eligible Selected	Withdrawn Lost to fu Analyzed
Etminan 2003 Ontario	Schizophrenia	Mean age=84.2 34.2% male Race NR	NR NR 3250	NR NR 2984 (individual group n's NR)
Risperidone vs Olanzapine vs Quetiapine vs Haloperidol				
Bobes, 2003	Schizophrenia	Mean age: 36.3 years 59.3% Male Ethnicity NR	NR/669/636	NR/NR/633
Risperidone vs Olanzapine vs Quetiapine vs Conventionals				
Gianfrancesco 2003a United States	Schizophrenia=14% Bipolar and manic=35%, Major depressive=38%, Other psychoses=13%	Mean age=37.5 41% male Race NR	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)

Evidence Table 7. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Effectiveness outcomes
Etminan 2003 Ontario	NR
Risperidone vs Olanzapine vs Quetiapine vs Haloperidol	
Bobes, 2003	NR
Risperidone vs Olanzapine vs Quetiapine vs Conventionals	
Gianfrancesco 2003a United States	NR

Evidence Table 7. 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
Risperidone vs Olanzapine vs Quetiapine vs Haloperidol		
Bobes, 2003	Weight gain listed as adverse reaction: olanzapine: 74.5%, risperidone: 53.4%, haloperidol: 40% Clinically significant weight gain (>7% increase from baseline): olanzapine: 45.7%, risperidone: 30.6%, haloperidol: 22.4%	
Risperidone vs Olanzapine vs Quetiapine vs Conventionals		
Gianfrancesco 2003a United States	Frequency of Type II Diabetes at 4-8 months/8-12 months/>12 months: 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-month odds ratios (95% CI) converted to 12-months 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 7. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Data Source	Prospective Retrospective Unclear	Exposure Period	Mean duration of follow-up	Interventions Mean dose
Risperidone vs Olanzapine vs Haloperidol					
Fuller 2003 Ohio	Database: Veteran's Integrated Service Network 10	Retrospective	1/1/97 to 12/31/00	NR	Risperidone 2.8 mg Olanzapine 10.0 mg Fluphenazine 12.2 mg Haloperidol 8.4 mg
Garcia-Cabeza 2003 Spain Subjective Response Analysis from Estudio Farmacoepidemiologico en la Esquizofrenia con Olanzapine (EFESO)	Multicenter Controlled	see above	see above	NR	Overall mean dose: Olanzapine: 13 mg/d Risperidone: 5.4 mg/d Haloperidol: 13.6 mg/d

Evidence Table 7. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Population	Age Gender Ethnicity	Exposed Eligible Selected	Withdrawn Lost to fu Analyzed
Risperidone vs Olanzapine vs Haloperidol				
Fuller 2003 Ohio	Range of psychiatric diagnoses: Schizophrenia=61% Depression=47% Bipolar Disorder=26% Dementia=8%	Mean age=53 Gender NR 73% White	NR NR 5837	NR NR 5837
Garcia-Cabeza 2003 Spain Subjective Response Analysis from Estudio Farmacoepidemiologico en la Esquizofrenia con Olanzapine (EFESO)	Paranoid schizophrenia: 65.1% Undifferentiated schizophrenia: 13.5% Residual schizophrenia: 12.3% Subjective reponse and compliance with antipsychotic treatment using 10 Item Drug Attitude Inventory (DAI-10)	Mean age: 35.4 63.9% male Ethnicity NR	NR/ 2967/ 2657	unclear; unclear; 2348 for safety at 6 months and 2189 for DAI-10 score at 6 months

Evidence Table 7. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Effectiveness outcomes
Risperidone vs Olanzapine vs Haloperidol	
Fuller 2003 Ohio	NR
Garcia-Cabeza 2003 Spain Subjective Response Analysis from Estudio Farmacoepidemiologico en la Esquizofrenia con Olanzapine (EFESO)	NR

Evidence Table 7. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Safety Outcomes	Comments
Risperidone vs Olanzapine vs Haloperidol		
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	
Garcia-Cabeza 2003 Spain Subjective Response Analysis from Estudio Farmacoepidemiologico en la Esquizofrenia con Olanzapine (EFESO)	<u>Subjective Response : Mean DAI-10 Score (range: -10 to +10) , baseline vs 6 months:</u> 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 month data, p=NR: Olz: 35.8% vs 31.9% Ris: 48.3% vs 44.6% Hal: 69.2% vs 66.3%	

Evidence Table 7. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Data Source	Prospective Retrospective Unclear	Exposure Period	Mean duration of follow-up	Interventions Mean dose
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 months	Olanzapine 13.01 mg Risperidone 5.39 mg Haloperidol 13.64 mg	NR
Koller, 2003	Food and Drug Administration Med Watch	Retrospective	9 years	NR	risperidone, haloperidol
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 year and who were not over the age of 40. Choice of new drug was made by the treating physician.	6 months	Olanzapine 13.5 mg Risperidone 5.4 mg Haloperidol 12.4 mg	High potency antipsychotics Low potency antipsychotics Benzodiazepines Anticholinergics Antidepressants Mood stabilizers

Evidence Table 7. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Population	Age Gender Ethnicity	Exposed Eligible Selected	Withdrawn Lost to fu Analyzed
Gomez 2000 Spain Estudio Farmacoepidemiologico en esquizofrenia con Olanzapine (EFESO)	Death Weight gain	Mean age=35.4 63.6% male Race NR	NR NR 2949	798 (25.7%) withdrawals 506 (17.1%) lost to fu 2949 analyzed
Koller, 2003	Patients prescribed study drugs	Mean age: 39.8 years 80% male Ethnicity NR	NR/NR/NR	NR/NR/NR
Montes 2003 Spain Sub-group Analysis from Estudio Farmacoepidemiologico en la Esquizofrenia con Olanzapine (EFESO)	Weight gain	Mean age=24.2 64.8% male Race NR	NR NR 182	45 (24.7%) withdrawn 24 (13.2%) lost to fu 182 analyzed

Evidence Table 7. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Effectiveness outcomes
Gomez 2000 Spain Estudio Farmacoepidemiologico en esquizofrenia con Olanzapine (EFESO)	NR
Koller, 2003	Risperidone-associated hyperglycemia: N=131 Combined risperidone-haolperidol associated hyperglycemia: N=7 Haloperidol-associated hyperglycemia: N=13 Reports of acidosis with absesnce of hyperglycemia: N=11
Montes 2003 Spain Sub-group Analysis from Estudio Farmacoepidemiologico en la Esquizofrenia con Olanzapine (EFESO)	NR

Evidence Table 7. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Safety Outcomes	Comments
Gomez 2000 Spain	Death Olanzapine: 3 (0.1%) Control group: 1 (0.1%)	
Estudio Farmacoepidemiologico en esquizofrenia con Olanzapine (EFESO)	Suicide Olanzapine: 1 (0.05%) Control group: 1 (0.1%) Weight gain Olanzapine: 146 (6.9%) Risperidone: 8 (1.9%) Haloperidol: 1 (0.9%) Olanzapine vs risperidone: p<0.001 Olanzapine vs haloperidol: p=NS	
Koller, 2003	# Patients with serious adverse events: Acidosis-ketosis: 26 NMS-Like Symptoms: 12 Pancreatitis: 4 Death: 4	
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

Evidence Table 7. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Data Source	Prospective Retrospective Unclear	Exposure Period	Mean duration of follow-up	Interventions Mean dose
Schillevoort, 2001	PHARMO-database	Retrospective	90 days	NR	haloperidol: 2.2 mg/d, risperidone: 54 mg/d, olanzapine mg/d
Weiser, 2000	Tel-Aviv University Medical School	Retrospective	NR	NR	haloperidol(N=23): 10 mg/day olanzapine(N=26): 10.56 mg/day risperidone(N=27): 4.35 mg/day
Risperidone vs Olanzapine vs Conventionals					
Bond, 2004	A psychiatric rehabilitation agencym and four community mental health centers.	Prospective	March 1999 to January 2001	9 months	olanzapine 12.9 mg risperidone 5.4 mg
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 months Olanzapine=6.1 months High-potency conventionals=7 months Low-potency conventionals=7.1 months Clozapine=9.4 months	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

Evidence Table 7. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Population	Age Gender Ethnicity	Exposed Eligible Selected	Withdrawn Lost to fu Analyzed
Schillevoort, 2001	Schizophrenia	Mean age: 35.3 years 48.6% Male Ethnicity NR	450,000/NR/848	0/0/848
Weiser, 2000	Schizophrenia, schizophreniform disorder	Mean age: 30.9 years 68% Male Ethnicity NR	NR/NR/NR	NR/NR/76
Risperidone vs Olanzapine vs Conventionals				
Bond, 2004	Schizophrenia or schizoaffective disorder	Mean age=40.8 years 59% male 45% caucasian; 42% africa american; 3% other	551/124/90	NR/NR/90
Gianfrancesco 2002 United States	Psychosis diagnosis (schizophrenia, bipolar and manic, major depressive, dementia, other psychoses)	Untreated vs treated (restricted to those WITHOUT Type 2 Diabetes at 4 months prior to observation) Mean age=41.9 vs 45.3 % male=40.4% vs 36.6% Race nr	NR NR NR	NR NR NR

Evidence Table 7. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Effectiveness outcomes
Schillevoort, 2001	NR
Weiser, 2000	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
Risperidone vs Olanzapine vs Conventionals	
Bond, 2004	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 monthly rate of paid employment: higher vs lower, NS monthly rate of integrated employment: greater vs lower, p=0.001
Gianfrancesco 2002 United States	NR

Evidence Table 7. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Safety Outcomes	Comments
Schillevoort, 2001	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	
Weiser, 2000	Haloperidol and risperidone suffered more severe EPS vs olanzapine: P=0.023	
Risperidone vs Olanzapine vs Conventionals		
Bond, 2004	NR	
Gianfrancesco 2002 United States	Odds Ratio (vs Risperidone) for 12 months of treatment (extrapolated from 1-month treatment rates) (excluded patients with pre-existing Type II Diabetes identified at 8-month screening): Olanzapine=3.53, p<0.05 Clozapine=8.45, p<0.05 Frequency of Type 2 Diabetes after at least 12 months' treatment (excluding patients with pre-existing Type II Diabetes identified at 8-month screening): Risperidone=2/90 (2.2%) Olanzapine=4/56 (7.1%) Clozapine=1/4 (25%)	

Evidence Table 7. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Data Source	Prospective Retrospective Unclear	Exposure Period	Mean duration of follow-up	Interventions Mean dose
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 months Risperidone=6.1 months Olanzapine=5.4 months High-potency Conventional Antipsychotics=6.5 months Low-potency conventional antipsychotics=6.5 months	(Risperidone equivalents) Risperidone 2.1 mg Olanzapine 3.4 mg High-potency conventional antipsychotics 1.6 mg Low-potency conventional antipsychotics 1.6 mg
Koro, 2002	England and Wales-based General Practice Database, Bristol-Myers Squibb, MEDTAP	Retrospective	30 months	NR	olanzapine: dose range NR risperidone: dose range NR conventional antipsychotics
Koro, 2002b	United Kingdom based General Practice Research Database	Retrospective	NR	NR	olanzapine: dose range NR risperidone: dose range NR conventional antipsychotics

Evidence Table 7. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Population	Age Gender Ethnicity	Exposed Eligible Selected	Withdrawn Lost to fu Analyzed
Gianfrancesco 2003b United States	% patients NOT taking antipsychotics/% patients TAKING antipsychotics: Bipolar=48.1%/30.6% Major Depressive Disorder=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	NR NR 5723	NR 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-month screening period)
Koro, 2002	Schizophrenia	Mean age: 51 years 60% Male	3.5 million /18,309/8866	0/0/8866
Koro, 2002b	Patients with presciptions for both schizophrenia and diabetes	Mean age: 51 years 62.5% Female	3.5 million/3.5 million/19,637	0/0/19,637

Evidence Table 7. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Effectiveness outcomes
Gianfrancesco 2003b United States	NR
Koro, 2002	NR
Koro, 2002b	NR

Evidence Table 7. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Safety Outcomes	Comments
Gianfrancesco 2003b United States	12-month odds ratios (converted from 1-month estimates) that excludes patients found to have pre-existing Type II diabetes at 8-month screening: <u>Relative to Untreated</u> Risperidone=1.024 (0.351-3.015) Olanzapine=4.289 (2.102-8.827) Olanzapine vs risperidone-4.189, p=0.02958	
Koro, 2002	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	Odds ratio 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 vs typical APs: 1.6; 95%CI: 0.7-3.8	

Evidence Table 7. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Data Source	Prospective Retrospective Unclear	Exposure Period	Mean duration of follow-up	Interventions Mean dose
Risperidone vs Clozapine vs Olanzapine vs Quetiapine					
Advokat, 2003	Eastern Louisiana Mental Health System	Retrospective	1995-2001	5 years	olanzapine 332 days risperidone 376 days quetiapine 558 days clozapine 583 days
Coulter 2001 International	Database: Uppsala Monitoring Centre in Sweden	Unclear	NR	NR	Clozapine Olanzapine Quetiapine Risperidone
Lambert, 2005	Califormia medicaid	Retrospective	July 1, 1997 to December 31, 2000	NA	more than 12 weeks

Evidence Table 7. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Population	Age Gender Ethnicity	Exposed Eligible Selected	Withdrawn Lost to fu Analyzed
Risperidone vs Clozapine vs Olanzapine vs Quetiapine				
Advokat, 2003	Schizoaffective/Bipolar Type, Paraoid Schizophrenia, or Schizophrenia Undifferentiated	Mean age=40.6 years 31% male 50% africa american	398/100/100	NR/NR/100
Coulter 2001 International	NR	NR NR NR	NR NR NR	NR NR Reports analyzed: Clozapine=24730, Olanzapine=6,135, Quetiapine=709, Risperidone=10,746
Lambert, 2005	Schizophrenia	NR	129341/34337/12637	NR/NR/12637

Evidence Table 7. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Effectiveness outcomes
Risperidone vs Clozapine vs Olanzapine vs Quetiapine	
Advokat, 2003	length of hospitalization: olanzapin (n=18) vs risperidone (n=9) = 634 days vs 1017 days, 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 risperidons = 1.67 vs 1.47 months
Coulter 2001 International	NR
Lambert, 2005	NR

Evidence Table 7. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Safety Outcomes	Comments
Risperidone vs Clozapine vs Olanzapine vs Quetiapine		
Advokat, 2003	NR	
Coulter 2001 International	Cardiomyopathy or myocarditis (# cases/%) Clozapine=231/0.9% Olanzapine=8/0.1% Quetiapine=2/0.3% Risperidone=16/0.1%	
Lambert, 2005	Odds ratios 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)	

Evidence Table 7. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Data Source	Prospective Retrospective Unclear	Exposure Period	Mean duration of follow-up	Interventions Mean dose
Lee 2002 United States	Database: Protocare Sciences's administrative claims and enrollment info	Retrospective	Index dates of patients occurred during a 27-month period (1997-1999). Mean duration of therapy: AAPs: 126.1 days Typical APs: 108.34 days	Patients were observed 365 days after their index dates.	Clozapine Olanzapine Quetiapine Risperidone Typical APs Mean doses NR
Leslie, 2004	Department of Veteran Affairs	Retrospective	3 months	NR	clozapine, olanzapine, quetiapine, risperidone: mean doses NR
Ollendorf 2004 United States	Database: PharMetrics Patient-Centric Database	Retrospective	1995-2001 Mean duration of therapy was 9 months 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 months; mean 435 days	Olanzapine n=937 Risperidone n=690 Quetiapine n=164 Clozapine n=35 Mean dose NR

Evidence Table 7. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Population	Age Gender Ethnicity	Exposed Eligible Selected	Withdrawn Lost to fu Analyzed
Lee 2002 United States	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 days, or filled a Rx for a diabetes medication or had a DM diagnsis within 365 days before index date. Also excluded patients using concomitant AP meds on index date.	Mean age 44 41.4% male Ethnicity NR	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
Leslie, 2004	Schizophrenia	NR/NR/NR	56,849/56,849/56,849	0/0/56,849
Ollendorf 2004 United States	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 used an AP or typical AP in the 6 months prior to the index date, or had evidence of DM within 12 months prior to the index date were excluded.	Mean age 39.1 48.2% male Ethnicity NR	18,134 2443 2443	NR NR 2443

Evidence Table 7. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Effectiveness outcomes
Lee 2002 United States	NR
Leslie, 2004	NR
Ollendorf 2004 United States	NR

Evidence Table 7. 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-year 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)	
Leslie, 2004	7.3% diagnosed with diabetes will on treatment Highest risk: clozapine: 2.03%, quetiapine: 0.80%, olanzapine: 0.63%, risperidone: 0.05%	
Ollendorf 2004 United States	Patients treated with AAPs had an increased risk of diabetes mellitus after 1 year, 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 not reported.

Evidence Table 7. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Data Source	Prospective Retrospective Unclear	Exposure Period	Mean duration of follow-up	Interventions Mean dose
Voruganti, 2000 Voruganti, 2002	Western Ontario schizophrenia research program	Retrospective	NR	≥6 months	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, trifluperazine

Evidence Table 7. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Population	Age Gender Ethnicity	Exposed Eligible Selected	Withdrawn Lost to fu Analyzed
Voruganti, 2000 Voruganti, 2002	Schizophrenia	Mean age: 32.1 years 68.7% male	NR/230/150	15 withdrawals or lose to follow up/135

Evidence Table 7. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Effectiveness outcomes
Voruganti, 2000	85% of patients benefitted from switching from conventional to novel antipsychotics
Voruganti, 2002	8(6%) preferred conventional treatment Remained on maintenance treatment: risperidone 82% olanzepine 86% quetiapine 82% CAPD (n=44) vs risperidone (n=50) vs olanzepine (n=48) vs quetiapine (n=42) vs clozapine (n=46) Psychosocial functioning and quality of life: 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) Quality of life (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 antypsychotic drugs risperidone (n=43) vs olanzepine (n=44) vs quetiapine (n=31) Syptoms 1. PANSS: -23.63 vs -23.67 vs -21.43 a. positive symptoms cluster: -5.18 vs -4.11 vs -4.67 b. negative symtoms 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* Quality of life 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 7. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Safety Outcomes	Comments
Voruganti, 2000	CAPD (n=44) vs risperidone (n=50) vs olanzepine (n=48) vs quetiapine (n=42) vs clozapine (n=46)	
Voruganti, 2002	Drug attitute 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 antypsychotic drugs risperidone (n=43) vs olanzepine (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 7. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Data Source	Prospective Retrospective Unclear	Exposure Period	Mean duration of follow-up	Interventions Mean dose
Atypical Antipsychotics vs Typical Antipsychotics					
Al-Zakwani, 2003	Multicenter, United States	Retrospective	24 months	18 months	Doses not reported. Interventions-Typical Antipsychotics: chlorpromazine, haloperidol, thioridazine, perphenazine, other; Atypical Antipsychotics: risperidone, olanzapine, quetiapine, clozapine

Evidence Table 7. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Population	Age Gender Ethnicity	Exposed Eligible Selected	Withdrawn Lost to fu Analyzed
Atypical Antipsychotics vs Typical Antipsychotics				
Al-Zakwani, 2003	Psychosis, neurotic, personality and sexual disorders,drug/alcohol dependence, psychological malfunction arising from mental disorders, depressive disorder, childhood emotional disturbance/developmenal delays, mental retardation/Alzheimer's/Parkinson's diseases	Mean age: 38.5 years 59% Male Ethnicity NR	2710/833/469	NR/NR/469

Evidence Table 7. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Effectiveness outcomes
Atypical Antipsychotics vs Typical Antipsychotics	
Al-Zakwani, 2003	Typical Antipsychotics: # dose adustments: 14(16.5%) # treatment augmenation: 1(1.2%) # requiring treatment switch: 11(12.9%) # receiving mixed therapy: 1(1.2%) Atypical Antipsychotics: # dose adustments: 128(30.4%) # treatment augmenation: 3(0.8%) # requiring treatment switch: 70(18.2%) # receiving mixed therapy: 7(1.5%)

Evidence Table 7. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Safety Outcomes	Comments
Atypical Antipsychotics vs Typical Antipsychotics		
Al-Zakwani, 2003	NR	

Evidence Table 7. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Data Source	Prospective Retrospective Unclear	Exposure Period	Mean duration of follow-up	Interventions Mean dose
Barner 2004 United States	Database: Cenral Texas Veterans Health Care System	Retrospective	Duration of treatment NR. Mean number of persistent days (total number of continuous days the patient took an antipsychotic agent without a gap, I.e. a 15-day lapse in therapy): AAPs: 3.9-5.6 months Typical APs: 4.7-7.3 months	NR	Any AAP or typical AP, dose and duration not reported
Buse, 2003	AdvancePCS Inc	Retrospective	≥2 years	NR	clozapine: 183.1 mg/day olanzapine: 5.1 mg/day quetiapine: 79.9 mg/day risperidone: 1.2 mg/day haloperidol: 2.5 mg/day thioridazine: 43.9 mg/day
Feldman, 2004	AdvancePCS Inc	Retrospective	6-9 months	NR	NR

Evidence Table 7. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Population	Age Gender Ethnicity	Exposed Eligible Selected	Withdrawn Lost to fu Analyzed
Barner 2004 United States	Included subjects aged 18+ who had not received a typical AP or AAP 6 months prior to the dispensing of a typical AP or AAP, and had not been diagnosed with DM or used an antidiabetic drug 12 months before being prescribed a typical AP or AAP.	Mean age 59.4 94.3% male 69.9% white	6735 3469 3469	NR NR 3469
Buse, 2003	Schizophrenia	Mean age: 52 years 63% male	5,816,473/58,751/50,578	
Feldman, 2004	Geriatric	Mean age: 79.2 years 60.8% female Ethnicity NR	NR/NR/1,836,799	NR/NR/30,953

Evidence Table 7. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Effectiveness outcomes
Barner 2004 United States	NR
Buse, 2003	Risk of Diabetes Mellitus: olanzapine: P=0.479 clozapine: P=0.496 quetiapine: P=0.033 haloperidol: P=0.040
Feldman, 2004	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

Evidence Table 7. 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
Buse, 2003	Hazard ratio of developing diabetes comparing antipsychtoics to haloperidol group: olanzapine: risperidone: P=0.479 quetiapine: P=0.040 clozapine: P=0.496	
Feldman, 2004	NR	

Evidence Table 7. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Data Source	Prospective Retrospective Unclear	Exposure Period	Mean duration of follow-up	Interventions Mean dose
Ostbye 2004 United States	Database: AdvancePCS records on prescription drugs dispensed to beneficiaries (n=170030 from 50 states)	Retrospective	2000-2002	18 months	Primary exposure: subjects who filled prescriptions for any AAP at any time during the follow-up period. Primary control: subjects who filled prescriptions for typical AAPs during followup. Other control groups received antibiotics; antidepressants
Sernyak, 2002	Veterans Health Administration of the Department of Veterans Affairs (VA)	Retrospective			clozapine, olanzapine, risperidone, quetiapine
Wirshing, 2002	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	clozapine, olanzapine, risperidone, quetiapine, haloperidol, fluphenazine/mean doses NR

Evidence Table 7. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Population	Age Gender Ethnicity	Exposed Eligible Selected	Withdrawn Lost to fu Analyzed
Ostbye 2004 United States	Subjects for whom the first prescription for an exposure drug occurred after the 6-month lead-in period. The primary exposure group was subjects who filled prescriptions for an AAP in the followup period. The primary control group was subjects who filled prescriptions for typical APs in the followup period.	Mean age 41.9 38.1% male Ethnicity NR	NR NR 170,030	NR NR 170030
Sernyak, 2002	Patients prescribed to study drugs	Mean age: 52.6 years 5.2% Female African-American: 25% Hispanic: 4.3%	NR/NR/38,632	NR/NR/38,682
Wirshing, 2002	Schizophrenia	Mean age: 51.3 years 94.4% Male 47.9% White 36.7% African-American	NR/590/215	0/0/215

Evidence Table 7. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Effectiveness outcomes
Ostbye 2004 United States	NR
Sernyak, 2002	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
Wirshing, 2002	NR

Evidence Table 7. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Safety Outcomes	Comments
Ostbye 2004 United States	Primary outcome was a new prescription filled for any antidiabetic drug during followup period, excluding those filled prior to the first prescription of an AP or AAP. Adjusted ORs (95% CI); AAPs: 1.70 (1.58-1.83) Typical APs: 2.08 (1.88-2.30) Antidepressants: 2.12 (1.96-2.30) Antibiotics: referent group In subjects that used only one drug class during study period: AAPs 0.86 (0.60-1.23) Typical APs: referent group Antidepressants 1.08 (0.81-1.45) Antibiotics 0.68 (0.50-0.92)	Exposure classification is binary (did or did not receive prescription for each drug or class); dose and duration of treatment are not controlled for
Sernyak, 2002	NR	
Wirshing, 2002	Increase in glucose levels from baseline: clozapine: +14%; p=.05 olanzapine: +21%; p=.03 haloperidol: +7%; p=.04 Increase/decrease in total cholestrol levels from baseline: risperidone: -6%, p=.04 fluphenazine: -6%; p=.04 13% of olanzapine patients (4) required increases in doses of lipid-loweing agents after beginning treatment	

Evidence Table 7. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Data Source	Prospective Retrospective Unclear	Exposure Period	Mean duration of follow-up	Interventions Mean dose
Quetiapine vs controls					
Sax, 1998	University of Cincinnati Medical Center site	Prospective	NR	6 weeks	quetiapine 330mg 6 weeks

Evidence Table 7. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Population	Age Gender Ethnicity	Exposed Eligible Selected	Withdrawn Lost to fu Analyzed
Quetiapine vs controls				
Sax, 1998	Schizophrenia	Mean age=32 70% male 80% caucasian	NR/NR/10	NR/NR/10

Evidence Table 7. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Effectiveness outcomes
Quetiapine vs controls	
Sax, 1998	Patients(n=10) vs Controls(n=12) CPT sensitivity, mean (SD) initial: 0.82(0.10) vs 0.93(0.07), p<0.01 first follow up: 0.88(0.08) vs NA second follow up: 0.92(0.07)* vs 0.94(0.08) (*p<0.01 vs baseline) No significant correlations between changes in symptom scores and CPT performance results, or between dosage of quetiapine and CPT and BPRS changes over time.

Evidence Table 7. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Safety Outcomes	Comments
Quetiapine vs controls		
Sax, 1998	NR	

Evidence Table 7. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Data Source	Prospective Retrospective Unclear	Exposure Period	Mean duration of follow-up	Interventions Mean dose
Uncontrolled studies					
Aripiprazole					
Madhusoodanan, 2004 (inpatients)	Medical records of pts >60y	Retrospective case series	Dec. 2002 to Jan. 2003	19.8 days (range: 12-33 days)	Aripiprazole mean dose: 17.5 mg/d (range: 15-20 mg/d) 60% had concurrent medications
Clozapine					
Advokat, 1999	East Louisiana State Hospital	Retrospective	April 1993 to August 1995	2 years	clozapine for mean duration 5.4 years
Alvarez 1997 Spain	Naturalistic: Psychiatry Dept of the Hospital de Sant Pau since 1984 (Spain)	Prospective	6.7 years (mean)	NR	Clozapine 266.9 mg (mean)

Evidence Table 7. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Population	Age Gender Ethnicity	Exposed Eligible Selected	Withdrawn Lost to fu Analyzed
Uncontrolled studies				
Aripiprazole				
Madhusoodanan, 2004 (inpatients)	70 % schizophrenia; 30% schizoaffective disorder	Mean age: 70.3y (range: 62-85y) 70% male 80% Caucasian 20% white	NR/ NR/ 10	2/ NR/ 10
Clozapine				
Advokat, 1999	Schizophrenia	Mean age=38.8 years 68% male 60% african-american; 40% caucasian	NR/NR/75	NR/NR/75
Alvarez 1997 Spain	Treatment resistent Schizophrenia/schizoaffective	Mean age=31.1 62.5% male	NR NR 80	NR NR Unclear

Evidence Table 7. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Effectiveness outcomes
Uncontrolled studies	
Aripiprazole	
Madhusoodanan, 2004	Mean CGI scores: baseline vs discharge: 6 vs 2.3
(inpatients)	Of all 10 pts, 7 pts responded to treatment; 1 pt had partial improvement; 2 did not improve
Clozapine	
Advokat, 1999	BPRS scores for each of the study groups- baseline vs month 1, % of baseline, months to criterion nonresponders(n=7): 61 vs 61, 100%, NA short-term pharmacological responder(n=13): 60 vs 48, 80%, 2.73 long-term pharmacologifal responder(n=21): 80 vs 64, 80%, 2.75 clinical responders: 68 vs 48, 70%, 1.65
Alvarez 1997 Spain	NR

Evidence Table 7. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Safety Outcomes	Comments
Uncontrolled studies		
Aripiprazole		
Madhusoodanan, 2004 (inpatients)	Of 7 pts measuring weights: 6 had mean weight loss of 5.2 lbs; 1 pt gained 18lbs QTc interval showed a mean decrease of 13.3 msec; no other significant changes in ECGs Withdrawal: 2 pts (1 for poor response;and 1 for poor response and urinary frequency and diarrhea) Existing EPS cleared for 3 of 4 patients Sleepiness: 1 pt Vomiting: 2 pts Diarrhea: 2 pts Urinary Frequency: 1 pt Hypotension: 1 pt Postural hypotension: 4 pts	
Clozapine		
Advokat, 1999	NR	
Alvarez 1997 Spain		Responders vs Nonresponders

Evidence Table 7. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Data Source	Prospective Retrospective Unclear	Exposure Period	Mean duration of follow-up	Interventions Mean dose
Atkin 1996 UK/Ireland	Database: Clozaril Patient Monitoring System (CPMS)	Retrospective	1/7/90 to 7/3/94	NR	Clozapine 313 mg
Breier, 1993	Maryland Psychiatric Research Center outpatients program	Prospective	1990	12 months	cloazapine mean dosage at 6 months: 435.3 mg/day 12 months: 439.4 mg/day

Evidence Table 7. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Population	Age Gender Ethnicity	Exposed Eligible Selected	Withdrawn Lost to fu Analyzed
Atkin 1996 UK/Ireland	Treatment resistant schizophrenia	Mean age=37 66.1% male 89% White 5% African/Afro-Caribbean 3.6% Asian 0.4% Oriental 1.9% Mixed	NR NR 6316	NR NR Year1=6316 Year2=2858 Year3=1625 Year4=661
Breier, 1993	chronic schizophrenia	Mean age=34 years 74.2% male 74.2% white; 25.7 african american	NR/NR/39	4/NR/35

Evidence Table 7. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Effectiveness outcomes
Atkin 1996 UK/Ireland	NR
Breier, 1993	18(60%) met criteria for sustained clinical improvement during the year 17/18 (95%) sustained reponders were identified by the fourth treatment month No. of patients experiencing relapse- before clozapine vs during clozapine: 18/21 (85.7%) vs 4/21 (19%), p<0.001 No. of patients hospitalized- before clozapine vs during clozapine 10/26 (38.4%) vs 2/26 (7.7%), p=0.01 Relapse- before clozapine vs during clozapine: No. of relapses: 2 vs 0.3, p<0.001 Days relapses: 42.6 vs 4.9, p<0.001 Hospitalizations- before clozapine vs during clozapine: No. of hospitalizations: 1.3 vs 1.0, p=0.01 Days hospitalized: 31.8 vs 3.5, p=0.008 Baseline vs 6 months vs 12 months: BPRS positive symptoms: 11.6 vs 9.9** vs 9.4** BPRS total: 36.5 vs 32.1*** vs 32.5** Level of functioning scale: 14.1 vs 16.3*** vs 17.7** Schedule for the assessment of negative symptoms: 45.9 vs 41.9 vs 41.6* Quality of life scale: 44.5 vs 47.6 vs 54.2* (*p<0.15; ** p<0.05; ***p<0.01 vs baseline)

Evidence Table 7. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Safety Outcomes	Comments
Atkin 1996 UK/Ireland	Agranulocytosis Year1=46/6316(0.7%) Year2=2/2858(0.07%) Year3=0/1625 Year4=0/661 Fatal cases Year1=2/6316 (0.03%) Years2-4=0	
Breier, 1993	NR	

Evidence Table 7. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Data Source	Prospective Retrospective Unclear	Exposure Period	Mean duration of follow-up	Interventions Mean dose
Brar, 1997	Mayview State Hospital	Prospective	October 1990 to December 1992	6 months	clozapine 422.5 mg/day for at least 6 months
Buckman 1999 United States	Database: Illinois Dept of Mental Health and Developmental Disability	Unclear	1990 to 1995	NR	Clozapine
Bunker, 1996	clozapine patient mmonitoring system	Prospective	February 1990 to January 1996	3 years	clozapine for 643 days

Evidence Table 7. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Population	Age Gender Ethnicity	Exposed Eligible Selected	Withdrawn Lost to fu Analyzed
Brar, 1997	schizophrenia	Mean age=39.7 years 60% male NR	NR/NR/75	NR/NR/75
Buckman 1999 United States	Treatment resistant schizophrenia	NR NR NR	NR 951 518	NR NR 518
Bunker, 1996	44.4% paranoid 31.1% undifferenctiated 0.02% catatonic 22.2% schizoaffective	Mean age=41.7 years 44.4% male 57.8% caucasian; 42.2% african american	NR/NR/45	NR/NR/45

Evidence Table 7. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Effectiveness outcomes
Brar, 1997	Clinical changes in patients with low positive symptom scores, n=17: baselince vs 6-month, p value emotional withdrawal: 3.2 vs 2.0, p=0.02 blunted affect: 2.9 vs 2.1, p=0.05 motor retardation: 2.4 vs 1.9, NS sum of negative symptoms: 8.4 vs 6.0, p=0.04 sum of positive symptoms: 8.2 vs 7.1, NS sum of depressive symptoms: 3.0 vs 3.1, NS Clinical changes in remaining patients, n=58: baseline vs 6-month, p value emotional withdrawal: 2.9 vs 2.0, p<0.0001 blunted affect: 3.2 vs 2.3, p<0.0001 motor retardation: 2.2 vs 1.5, p<0.0001 sum of negative symptoms: 8.3 vs 5.9, p<0..0001 sum of positive symptoms: 16.8 vs 11.1, p<0.0001 sum of depressive symptome: 4.0 vs 3.0, p<0.0001 Changes in negative symptoms with low positive symptoms based on antiparkinsonian medication status, statistical signidicant p value- pateints not on antiparkinsonian medication (n=12) vs patients on antiparkinsonian medication (n=5): emotional withdrawal: 0.02 vs 0.32 blunted affect: 0.03 vs 0.32 motor retardation: 0.08 vs 0.10 sum of negative symptoms: 0.01 vs 0.10 sum of positive symptoms: 0.11 vs 0.27
Buckman 1999 United States	NR
Bunker, 1996	NR

Evidence Table 7. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Safety Outcomes	Comments
Brar, 1997	NR	
Buckman 1999 United States	Agranulocytosis Incidence=0.9%	
Bunker, 1996	7/25 had emergent DE, average time to onset: 238±179 days, average time to resolution of DE symptoms: 347±190 days baseline vs emergent DE- time to resolution: 261±188 vs 347±190, p<0.05 27 patients had a baseline or emergent DE 15/27(56%) had resolution of DE 10/27(37%) had compelete resolution of DE	

Evidence Table 7. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Data Source	Prospective Retrospective Unclear	Exposure Period	Mean duration of follow-up	Interventions Mean dose
Cassano, 1997	NR	Prospective	NR	12 months	clozapine 250 mg/day for 12 months
Ciapparelli, 2000	day-hospital services and wards of the Department of Psychiatry at the University of Pisa	Prospective	NR	24 months	clozapine 207.9 mg/day for 24 months

Evidence Table 7. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Population	Age Gender Ethnicity	Exposed Eligible Selected	Withdrawn Lost to fu Analyzed
Cassano, 1997	schizophrenia spectrum disorder	Mean age=35.4 years 68% male Ethnicity: NR	NR/NR/60	15/NR/60
Ciapparelli, 2000	34.1% schizophrenia 28.6% schizoaffective disorder 37% psychotic bipolar disorder	Mean age=34.2 years 69.2% male Ethnicity: NR	NR/NR/91	38/NR/91

Evidence Table 7. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Effectiveness outcomes
Cassano, 1997	BPRS scores With bipolar: 24 items all show significant (p<0.05) improvement from baseline Without bipolar: 15/24 items show significant (p<0.05) improvement from baseline Patients without bipolar features who completed treatment for 12 months had significantly higher basal BPRSE scores for unusual thought content, emotional withdrawal, mannerism and posturingm moror retardation, blunted affect and affective incongruence.
Ciapparelli, 2000	BPRS scores- clozapine monotherapy vs combination of typical neuroleptics: 47.6 vs 50.3, p=0.56 mean change of BPRS total scores- baseline vs 12 month vs 24 months schizophrenia: 49.7 vs 27.6 vs 24.7, p<0.001 schizoaffective disorder: 47.8 vs 19.6 vs 15.1, p<0.001 bipolar disorder: 47.5 vs 17.4 vs 15.1, p<0.001 schizophrenia vs schizoaffective disorder, p<0.05 schizophrenia vs bipolar disorder, p<0.05 schizoaffective disorder vs bipolar disorder, NS CGI scores- baseline vs 12 months vs 24 months schizophrenia: 5.8 vs 4.1 vs 3.8, p<0.001 schizoaffective disorder: 5.5 vs 3.6 vs 3.0, p<0.01 bipolar disorder: 5.1 vs 3.0 vs 2.9, p<0.001 Response rate- bipolar disroder vs schizoaffective disorder vs schizophrenia: 60% in 6 months vs 55% in 12 months vs 56% in 18 months, p<0.005 Likelihood of remaining nonresponsive at 2 years- bipolar disroder vs schizoaffective disorder vs schizophrenia: 17% vs 25% vs 44% The probability of remaining nonresponsive- bipolar disroder vs schizoaffective disorder vs schizophrenia: 24% vs 31% vs 55%

Evidence Table 7. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Safety Outcomes	Comments
Cassano, 1997	% patients experiencing adverse events- total vs with bipolar vs without bipolar drowsiness or sedation: 40 vs 36.6 vs 47.5 sialorrhea: 35 vs 36 vs 35 tachycardia: 18.3 vs 26.8 vs 0 weight gain > 10%: 18.3 vs 22 vs 10.5* hypotension: 10 vs 14.6 vs 10 leucopenia: 3 vs 1.5 vs 1.5 (*p<0.05 between groups)	
Ciapparelli, 2000	NR	

Evidence Table 7. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Data Source	Prospective Retrospective Unclear	Exposure Period	Mean duration of follow-up	Interventions Mean dose
Conley, 1997	Spring Grove Hospital Center	Prospective	1990-1995	12 months	clozapine 468 mg/day 12 months
Deliliers 2000 Italy	Database: Italian Clozapine Monitoring System (ICLOS)	Unclear	1995 to 1999	NR	Clozapine 200-350 mg
Devinsky 1991 United States	Chart review	Unclear	1972 to 1988	NR	Clozapine
Drew 1999 Australia	Database: Clozaril Patient Monitoring System (CPMS)	Retrospective	3 years (preliminary results from 5-year study (Drew 2002)	NR	Clozapine

Evidence Table 7. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Population	Age Gender Ethnicity	Exposed Eligible Selected	Withdrawn Lost to fu Analyzed
Conley, 1997	46.7% schizophrenia 34.7% schizoaffective disorder 10.7% bipolar disorder 8% atypical psychosis	Mean age=35.7 years 60% male Ethnicity: NR	NR/NR/50	NR/NR/50
Deliliers 2000 Italy	Treatment resistant schizophrenia	Mean age NR 63% male Race NR	NR NR 2404	NR NR 2404
Devinsky 1991 United States	Treatment-resistent schizophrenia	NR NR NR	1418 1418 1418	NR NR 1418
Drew 1999 Australia	Schizophrenia/Schizophreniform	Mean age=34 67.7% male Race NR	NR 42 37	NR NR 37

Evidence Table 7. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Effectiveness outcomes
Conley, 1997	BPRS total scores: fall 31% from baseline, p<0.0001 BPRS 5 factor scores: fall 32% from baseline, p<0.0001 agergia: fall 24%, p<0.01 anxiety-depression: fall 30%, p<0.0001 activation: fall 31%, p,0.0001 hostility0suspiciousness: fall 46%, p<0.0001 11(33%) patients took longer than 8 weeks to initial respond 16(32%) never achieved clinical response Responders vs non-responders: Age: 33.79 vs 39.88, p<0.05 Years of hospitalization: 2.57 vs 7.2, p<0.05 BRPS Total score: 48.38 vs 44.25, NS Anxiety-depression factore: 9.97 vs 7.5, p<0.05 Anergia factor: 7.29 vs 6.44, NS Thought disturbance factor: 10.71 vs 11.63, NS Activation factor: 6.91 vs 7.44, NS Hostility-suspiciousness factor: 9.35 vs 7.63, p<0.05
Deliliers 2000 Italy	NR
Devinsky 1991 United States	NR
Drew 1999 Australia	NR

Evidence Table 7. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Safety Outcomes	Comments
Conley, 1997	1 cardiovascular side effect	
Deliliers 2000 Italy	Agranulocytosis 16 cases (0.7%)	
Devinsky 1991 United States	Seizures # cases=41/1418 (2.9%)	
Drew 1999 Australia	Hospitalization(% pts admitted ≥ 1 day) Pre-clozapine: 2nd year=51.4% 1st year=56.8% Post-clozapine: Year1=83.8% Year2=32.4% Year3=21.6% Seizures: # cases=4/37 (10.8%)	Clozapine-naïve; commenced Clozapine in Australian Capital Territory (ACT) before 7/1/94

Evidence Table 7. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Data Source	Prospective Retrospective Unclear	Exposure Period	Mean duration of follow-up	Interventions Mean dose
Drew 2002 Australia	Database: Clozaril Patient Monitoring System (CPMS)	Retrospective	5 years	NR	Clozapine
Frankenburg, 1992	private psychiatric hospitals, psychiatric units of a general hospital or a state hospital.	Prospective	1987-1989	6 months - 2.5 years	clozapine for at least 6 months

Evidence Table 7. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Population	Age Gender Ethnicity	Exposed Eligible Selected	Withdrawn Lost to fu Analyzed
Drew 2002 Australia	Schizophrenia/schizoaffective	NR NR NR	NR 42 32	NR NR 32
Frankenburg, 1992	Schizophrenia	Mean age=30.9 years 65.3% male Ethnicity: NR	NR/NR/75	NR/NR/75

Evidence Table 7. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Effectiveness outcomes
Drew 2002 Australia	NR
Frankenburg, 1992	Mean number of hospitalization, p vs preclozapine 6 months preclozapine (n=75): 1.2 ±0.8 6 months (n=75): 0.9±0.7, p=0.01 1 year (n=43): 0.3±0.5, p=0.001 1.5 years (n=30): 0.2±0.6, p=0.001 2 years (n=23): 0.1±0.3, p=0.001 2.5 years (n=14): 0.0, p=0.003

Evidence Table 7. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Safety Outcomes	Comments
Drew 2002 Australia	Agranulocytosis: # cases=1/32 (3.1%) Hospitalization(% pts admitted ≥ 1 day) Pre-clozapine 2nd year=56.3% 1st year=59.4% Post-clozapine Year1=81.3% Year2=31.3% Year3=21.9% Year4=18.8% Year5=18.8%	Clozapine-naïve; commenced Clozapine in Australian Capital Territory (ACT) before 7/1/94
Frankenburg, 1992	NR	

Evidence Table 7. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Data Source	Prospective Retrospective Unclear	Exposure Period	Mean duration of follow-up	Interventions Mean dose
Frankle, 2001	an outpatient mental health clinic	Retrospective	NR	NR	clozapine

Evidence Table 7. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Population	Age Gender Ethnicity	Exposed Eligible Selected	Withdrawn Lost to fu Analyzed
Frankle, 2001	Schizophrenia, bipolar illness, depression with psychotic features, substance-induced psychotic disorder, psychosis secondary to a general medical condition, delusional disorder, brief and shared psychotic disorder, and pschosis not otherwise specified.	Mean age: 43 years 70.3% male 84.2% caucasian; 12.2% african american; 3.6% hispanic	378/175/165	NA/NA/165

Evidence Table 7. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Effectiveness outcomes
Frankle, 2001	Poisson Regression Anaysis of influence of demographic and clinical variables on arrest rate of 165 psychotic patients with criminal histories- regression coefficient; SE; p value; % change; 95% CI Sex: -0.41; 0.25; 0.10; -33.4; -59.1-8.3 Age: -0.02; 0.01; 0.15; -1.5; -3.6-0.6 Birth cohort effect: 0.05; 0.01; 0.0001; 4.8, 2.4-7.3 Education: -0.12; 0.02; 0.0001; -11.6; -15.6- -7.4 Onset of illness: 0.50; 0.20; 0.01; 64.6; 11.9-142.2 Before clozapine treatment: -0.39; 0.18; 0.02; -32.6; -52.1- -5.0 Clozapine treatment: -1.17; 0.24; 0.0001; -68.9; -80.7- -49.8 Poisson Regression Anaysis of influence of demographic and clinical variables on arrest rate of 52 psychotic men with criminal histories who were treated with clozapine after 1980- regression coefficient; SE; p value; % change; 95% CI Age: 0.01; 0.04; 0.90; 0.5; -7.0-8.8 Birth cohort effect: 0.08; 0.04; 0.08; 8.0; -1.0-17.7 Education: -0.12; 0.04; 0.002; -11.3; -17.8- -4.2 Onset of illness: 0.13; 0.41; 0.75; 13.6; -48.8-152.0 Clozapine treatment: -0.85; 0.50; 0.09; -57.1; -83.8-13.6

Evidence Table 7. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Safety Outcomes	Comments
Frankle, 2001	NR	165 patients psychiatric patients with criminal histories

Evidence Table 7. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Data Source	Prospective Retrospective Unclear	Exposure Period	Mean duration of follow-up	Interventions Mean dose
Gordon, 1996	Haverfort State Hospital	Prospective	August 1990 to February 1993	12 months	clozapine 405 mg/day for over 6 months

Evidence Table 7. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Population	Age Gender Ethnicity	Exposed Eligible Selected	Withdrawn Lost to fu Analyzed
Gordon, 1996	Schizophrenia	Mean age=33.2 years 81% male 100% white	NR/NR/31	NR/NR/31

Evidence Table 7. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Effectiveness outcomes
Gordon, 1996	BPRS scores- baseline vs post clozapine: Low dose- positive symptoms: 16.8 vs 8.75, p<0.0005 Low dose- negative symptoms: 10.93 vs 8.2, p=0.01 Low dose- total score: 57.94 vs 33.56, p<0.0005 High dose- positive symptoms: 17.07 vs 11.2, p<0.005 High dose- negative symptoms: 11.13 vs 8.00, p<0.0005 High dose- total score: 56.6 vs 36.4, p<0.0005 Response- low dose vs high dose BPRS scores decreased >40%: 10/16 (62.5%) vs 7/15 (53.3%) BPRS scores decreased 20%-38%: 5/16 (31.3%) vs 8/15 (53.3%) Clinically responser- BPRS scores decreased >20% and a BPRS total score <35: low dose: 9 (56.2%); high dose: 8 (53.3%) Motor retardation- before vs after clozapine: NS No. of PRN medications reduction: low dose: >75%, p<0.01 high dose: 62%, p<0.025 Social function- no. of day/weekend to the community- before vs after clozapine treatment low dose: 4.94 vs 9.19, p<0.005 high dose: 8.40 vs 13.67, p<0.005 4 patients in high dose and 3 patients in low dose were able to work for pay after 6 months clozapine treatment (none had participated in workshop activities before clozapine treatment).

Evidence Table 7. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Safety Outcomes	Comments
Gordon, 1996	No argranulocytosis, leukopenia or seizures Minor sedation, orthostatic, hypotension, tachycardia, constipation, and elevated temperature: 1.5 patients in each group	

Evidence Table 7. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Data Source	Prospective Retrospective Unclear	Exposure Period	Mean duration of follow-up	Interventions Mean dose
Hagg 1998 Sweden	Single site Naturalistic: Gallivare Hospital	Cross-sectional, prevalence study	Years treated mean (range): clozapine 3 (0.1-6) typical APs 6 (0.2-22)	No follow-up (snapshot)	Clozapine Typical APs Mean dose NR
Henderson 2000 United States	Chart review: outpatient clinic of urban mental health center	Retrospective	5 years	NR	Clozapine

Evidence Table 7. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Population	Age Gender Ethnicity	Exposed Eligible Selected	Withdrawn Lost to fu Analyzed
Hagg 1998 Sweden	Patients treated with clozapine or typical APs at the time study was conducted. 85% schizophrenia 4.6% paranoid psychosis 3% cycloid psychosis 3% affective/schizo-affective psychosis	Mean age: clozapine 41, typical APs 48 59% male Ethnicity NR	214/142/130 Clozapine n=63 Typical APs n=67	NR NR 130 analyzed
Henderson 2000 United States	Schizophrenia Schizoaffective disorder	Mean age=36.35 73.2% male 91.5% white	NR 101 82	NR NR 82

Evidence Table 7. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Effectiveness outcomes
Hagg 1998 Sweden	NR
Henderson 2000 United States	NR

Evidence Table 7. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Safety Outcomes	Comments
Hagg 1998 Sweden	Clozapine vs typical APs, Prevalence: Hyperglycemia 33 vs 19% (p=0.07) Type 2 diabetes 12 vs 6% (ns) Impaired glucose tolerance (IGT) 10 vs 3% (ns) Type 2 DM or IGT 22 vs 10% (p=0.06) Women with type 2 diabetes or IGT, clozapine vs typical APs: 9/27 (33.3%) vs 2/26 (7.7%) (p=0.04) Body mass index, all subjects: 27 vs 28 kg/m2 (ns) Body mass index, subjects with diabetes mellitus or IGT: 27 vs 30 kg/m2 (ns)	12 (19%) clozapine subjects had concomitant treatment with typical APs, most often haloperidol (n=6). Body mass index was similar between clozapine patients with and without diabetes/IGT. Clozapine patients tended to be younger and treated for fewer years than patients on typical APs.
Henderson 2000 United States	Diagnosis of Type II Diabetes=30/82 (36.6%) Weight gain: linear coefficient of 1.16 lb/month (SE=0.18) (mixed-effects model, t-6.62, df-80, p=0.0001)	

Evidence Table 7. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Data Source	Prospective Retrospective Unclear	Exposure Period	Mean duration of follow-up	Interventions Mean dose
Hofer, 2003	inpatients unit of the Department of Psychiatry of Innsbruck University Clinics	Prospective	1989-1996	8 weeks	clozapine 263.5 mg/day for at least 8 weeks
Honer, 1995	the Treatment Refractory Psychosis Program of Riverview Hospital and the Schizophrenia Unit of the Vancouver Hospital and Health Science Center	Prospective	NR	50 weeks	clozapine Mean discharge dose: 425 mg

Evidence Table 7. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Population	Age Gender Ethnicity	Exposed Eligible Selected	Withdrawn Lost to fu Analyzed
Hofer, 2003	Schizophrenia or schizphreniform disorder	Mean age=28.7 years 75.5% male Ethnicity: NR	NR/NR/95	NR/NR/95
Honer, 1995	100% schizophrenia 42% undifferentiated 35% paranoid 17% disorganized 3% catatonic 3% residual	Mean age=32.7 years 80% male Ethnicity: NR	NR/NR/61	NR/1/60

Evidence Table 7. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Effectiveness outcomes
Hofer, 2003	Multiple linear regression: only age found to be a significant predictor of CGI (F=4.22, p=0.045)
Honer, 1995	GAF scores: significantly improved, p=0.0001 CGI scores: significant improved, p=0.0001 80% responders were identified by 20 weeks and all by 32 weeks: Responders: 61% boarding home; 22% own home or relatives; 17% psychiatric hospital Nonresponders: 28% boarding home; 40% own home or relatives; 33% psychiatric hospital Multiple regression analysis- predict GAF and CGI scores GAF discharge with GAF year and admission as predictor variables: R=0.45, F=7.15, p=0.002 GAF year: slope t=3.64, p=0.0006 GAF admission: slope t=0.63, p=0.53 CGI admission correlated with CGI discharge: R=0.34, F=7.48, p=0.008 Duration of treatment with clozapine was negatively correlated to GAF discharge: R=0.47, F=5.30, p=0.003 The relationship between response and schizophrenia subtype subtype: F=8.4, p=0.0007 time: F=52.43, p=0.0001 interaction: F=0.76, p=0.56 (similar results for CGI)

Evidence Table 7. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Safety Outcomes	Comments
Hofer, 2003	1 seizures 1 increased liver enzyme level Frequently reported side effects: week 1-3(%) vs week 4-6(%) First episode (n=39) concentration difficulty: 51.3 vs 13 asthenia: 48.7 vs 26.1 sedation: 20.5 vs 0 failing memory: 25.6 vs 0 increased duration of sleep: 41.3 vs 30.4 increased salivation: 28.2 vs 17.4 diminished sexual desire: 41.0 vs 13.0 Multiple episode (n=556) concentration difficulty: 55.3 vs 31.5 asthenia: 53.6 vs 25.8 sedation: 35.7 vs 20.0 failing memory: 28.6 vs 17.1 increased duration of sleep: 39.3 vs 25.7 increased salivation: 23.2 vs 8.6 diminished sexual desire: 35.8 vs 25.7	
Honer, 1995	NR	

Evidence Table 7. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Data Source	Prospective Retrospective Unclear	Exposure Period	Mean duration of follow-up	Interventions Mean dose
Honigfeld 1996 United States	Database: Clozapine National Registry System	Unclear	2/1990 to 12/1994	NR	Clozapine
Honigfeld, 1990	NR	Retrospective	NR	2 years	clozapine 350-450 mg/day
Kane, 1994	the inpatients sevice at Hillside Hospital	Prospective	NR	52 weeks	clozapine 599 mg/day 52 weeks
Killian, 1999	Adverse Drug Reactions Advisory Committee (ADRAC) of Australia	Unclear	Jan. 1993 to March 1999	NR	Clozapine range: 100-725 mg/d myocartditis pts took cloz. a median of 15d (range: 3 -22d) before myocarditis developed Cardiomyopathy pts took cloz. a median of 12 months (range: 2-36 m) before cardiomyopathy developed

Evidence Table 7. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Population	Age Gender Ethnicity	Exposed Eligible Selected	Withdrawn Lost to fu Analyzed
Honigfeld 1996 United States	Treatment resistant schizophrenia	NR NR NR	NR NR 99,502	NR NR 99,502
Honigfeld, 1990	NR	Mean age=33 years 58% male Ethnicity: NR	NR/NR/105	NA/NA/105
Kane, 1994	Schizophrenia or schizoaffective disorder	Mean age=27.6 years 66% male 84% white; 14% black; 2% other	NR/NR/56	NR/NR/34
Killian, 1999	Clozapine-using patients (article did not specify diagnosis of pts in registry)	Mean age: 36y 87% male Ethnicity: NR	8000/ 43/ 33	NR/ NR/ 33

Evidence Table 7. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Effectiveness outcomes
Honigfeld 1996 United States	NR
Honigfeld, 1990	BPRS total scores- 0, 3, 12, 24 (month): 49, 33, 30, 30.5
Kane, 1994	Correlations of Simpson-Angus Akinesia item with BPRS anergia factor: r, p value baseline (n=56): 0.68, p=0.00 week 3 (n=49): 0.59, p=0.00 week 6 (n=47): 0.43, p=0.00 week 12 (n=27): 0.48, p=0.01 week 26 (n=28): 0.40, p=0.03 week 39 (n=24): 0.37, p=0.07
Killian, 1999	NR

Evidence Table 7. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Safety Outcomes	Comments
Honigfeld 1996 United States	Agranulocytosis Cases=382(0.38%) Fatal cases=12(0.012%)	
Honigfeld, 1990	Adverse event: Year 1 vs Year 2 (% patients) salivation: 37.1 vs 19.0 drowsiness: 31.4 vs 11.4 tachycardia: 12.4 vs 10.5 dizziness: 12.4 vs 2.9 constipation: 10.5 vs 5.7 hypotension: 7.6 vs 0 syncope: 4.8 vs 0 akathisia: 3.8 vs 2.9 weight gain: 3.8 vs 4.8	
Kane, 1994	NR	
Killian, 1999	Caradiomyopathy: 8 cases (of 8000 clozapine pts; 0.10%) Myocarditis: 15 cases (of 8000 clozapine pts; 0.19%) (10 additional cases were not supported by objective clinical or investigational findings) Deaths: 33.3% (5 of 15) myocarditis pts and 12.5% (1 of 8) cardiomyopathy pts died	

Evidence Table 7. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Data Source	Prospective Retrospective Unclear	Exposure Period	Mean duration of follow-up	Interventions Mean dose
Kranzler, 2005	Bronx Children's Paychiatric Center	Prospective	November 1997 to August 2001	3 months	clozapine 24 weeks
Koller, 2001	MedWatch Drug Surveillance System	Retrospective	January 1990 to February 2001	NR	clozapine 362 mg
Laker 1998 London	Chart review (Royal London, Goodmayes, Claybury and Runwell)	Unclear	1/90 to 6/95	NR	Clozapine

Evidence Table 7. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Population	Age Gender Ethnicity	Exposed Eligible Selected	Withdrawn Lost to fu Analyzed
Kranzler, 2005	Schizophrenia or schizoaffective disorder	Mean age=20 years Gender: NR Ethnicity: NR	NR/37/20	NR/NR/20
Koller, 2001	clozapine-associated diabetes or hyperglycemia	Mean age=40 years Gender: NR Ethnicity: NR	NR/NR/384	NA/NA/384
Laker 1998 London	Treatment-resistent schizophrenia	Mean age=35 71.7% male Race NR	115 115 113	39 (34.5%) discontinued treatment NR 74 continuers analyzed

Evidence Table 7. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Effectiveness outcomes
Kranzler, 2005	baseline vs clozapine: the frequency of administration of oral p.r.n. medications for aggression: 0.21 vs 0.05, p=0.000 the frequency of administration of injectable p.r.n. medications for aggression: 0.04 vs 0.01, p=0.007 the frequency of seclusion events for aggression: 0.04 vs 0.01, p=0.003 decrease in the frequency of administration of oral p.r.n. medications for aggression: 0.26 vs 0.09, p=0.02
Koller, 2001	NR
Laker 1998 London	NR

Evidence Table 7. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Safety Outcomes	Comments
Kranzler, 2005	NR	
Koller, 2001	clozapine was discontinued in 110 cases (54 cases follow-up were available) 42 improved in metabolic status 11 had no change in metabolic status 26 no longer required hypoglycemic drug therapy 18 glucose levels returned to normal 80 patients had metabolic acidosis or ketosis accompanied the hyperglycemia 73 with new-onset diabetes (blood glucose level >= 500 mg/dL) 51 with new-onset diabetes (blood glucose level >= 700 mg/dL) 32 with new-onset diabetes occurred within 3 months of the initiation of clozapine therapy (blood glucose level >= 700 mg/dL) 26 had acidosis or ketosis 25 died during hyperglycemic episodes 16 had acidosis or ketosis 146 patients had body weight data 38 had no clear evidence of obesity or substantial weight gain	
Laker 1998 London	Death All cause=3 cases (2.6%) Hospitalization Year1=40 (56%) Year2=27 (60%) Year3=13 (48%) Year4=5 (38%) Endpoint=36 (49%) Suicide 1 case (0.9%)	

Evidence Table 7. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Data Source	Prospective Retrospective Unclear	Exposure Period	Mean duration of follow-up	Interventions Mean dose
Lamberti, 1992	a state hospital	Retrospective	NR	6 months	clozapine 380 mg/day
Leadbetter, 1992	a state psychiatric facility	Prospective	NR	12 weeks	clozapine 25-125 mg/week for 12 weeks
Lieberman 1992 Alvir 1993 United States	Database: Caremark Patient Monitoring System (CPMS) from 2/5/90 to 4/30/91	Unclear	>/= 3 weeks	NR	Clozapine mean maximum dose=451.9 mg
Lund 2001 United States	Database: Iowa Medicaid program claims/prescription database	Unclear	1990 to 1994	Clozapine=25.5 months Typical APs =24.5 months	Clozapine Typical Aps

Evidence Table 7. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Population	Age Gender Ethnicity	Exposed Eligible Selected	Withdrawn Lost to fu Analyzed
Lamberti, 1992	chronic schizophrenia	Mean age=34.8 years 75% male Ethnicity: NR	NR/NR/36	NR/NR/36
Leadbetter, 1992	Schizophrenia or schizoaffective disorders	Mean age=32.6 years 62% male	NR/NR/21	NR/NR/21
Lieberman 1992 Alvir 1993 United States	Schizophrenia	Mean age NR 62% male Race NR	17,042 11,555 11,555	NR NR 11,555
Lund 2001 United States	Schizophrenia	Mean age=41.9 59.2% male Race NR	NR 4770 3013	NR NR 3013 (clozapine=552, CAPD=2461)

Evidence Table 7. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Effectiveness outcomes
Lamberti, 1992	NR
Leadbetter, 1992	NR
Lieberman 1992 Alvir 1993 United States	NR
Lund 2001 United States	NR

Evidence Table 7. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Safety Outcomes	Comments
Lamberti, 1992	7(19.4%) weighed less than their minimun ideal weights 23(63.9%) weighed more than their maximum ideal weights mean weight gain: 16.9 lb, p<0.0001 mean weight gain for each patients: 10.6% 27(75%) gained >= 10 lb while taking clozapine 15(41.7%) gained .= 21 lb while taking clozapine BPRS - baseline vs 6 month = 66 vs 47, p<0.0001 BPRS correlated to weight gained during clozapine treatment: Spearman r = -0.31, df=28, p<0.1	
Leadbetter, 1992	patients weighed more during the first 12 weeks of clozapint treatment than baseline, p<0.01 13(62%) experienced significant increased in weight, p<0.05 7(33%) weight less in standard antipsychotics treatment (-0.44 lb) than clozapine treatment (+13.8 lb) compared to baseline, p<0.001 8 patients experienced marked weight gains (>= 10% increased) 6 had moderate weight gains (5%-10% increased) 4 had mild to minimal weight gains (<5% increased) 3 lost weight mean weight gain: 13.9 lb (8.9%) patients gained at least 10% weight showed greater decrease in total BPRS score than patients with less weight change (p<0.03)	
Lieberman 1992 Alvir 1993 United States	Agranulocytosis # cases/fatal cases=73/2 Cumulative incidence (year1/year1.5): 0.8%/0.91%	Age, gender
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	Age

Evidence Table 7. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Data Source	Prospective Retrospective Unclear	Exposure Period	Mean duration of follow-up	Interventions Mean dose
Manschreck, 1999	NR	Prospective	NR	1 year	clozapine 300-600 mg/day for 1 year
Nair, 1999	a clinical research center	Prospective	NR	16 weeks	clozapine 100mg, 300mg, or 600mg for 16 weeks
Pacia 1994 United States	Database: CPMS	Unclear	2/6/90 to 8/5/90	NR	Clozapine

Evidence Table 7. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Population	Age Gender Ethnicity	Exposed Eligible Selected	Withdrawn Lost to fu Analyzed
Manschreck, 1999	Schizophrenia or schizoaffective disorder	Mean age=40.8 years 46.2% male Ethnicity: NR	NR/NR/54	NR/NR/54
Nair, 1999	Schizophrenia or schizoaffective disorder	Mean age=42.45 years 54.5% male Ethnicity: NR	NR/48/33	NR/NR/33
Pacia 1994 United States	Schizophrenia	NR NR NR	5629 5629 5629	NR NR 5629

Evidence Table 7. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Effectiveness outcomes
Manschreck, 1999	basline vs endpoint, p value Discharged- BPRS total: 61.4 vs 49.3, p<0.0001 SAPS total: 8.4 vs 4.1, p=0.0003 SANS total: 14.1 vs 9.2, p<0.0001 Thought disorder (SAPS/SANS): 5.1 vs 3.1, p=0.09 AIM total: 2.6 vs 0.2, p=0.1 Simpson-Angus total: 2.5 vs 0.4, p=0.02 Hospitalized- BPRS total: 64.9 vs 57.5, p=0.1 SAPS total: 9.4 vs 7.6, p=0.05 SANS total: 13.6 vs 9.6, p=0.002 Thought disorder (SAPS/SANS): 4.9 vs 2.8, NS AIM total: 3.2 vs 0.3, p=0.08 Simpson-Angus total: 2.1 vs 0.5, p=0.1 Cognitive assessments Discharged: 17/19 items showed NS Hospitalized: 19/19 items showed NS Length of illness of complete nonresponders versus responders on one or both criteria Neither discharged nor reached criterion for BPRS improvement (n=10): 27.6 $\pm$9.5 years Both discharged and "responder" by BPRS criterion (n=14): 19.2 $\pm$11 years BPRS improvement without being discharged (n=9): 16.9 $\pm$10.9 years Discharged without reaching criterion for BPRS improvement (n=21): 20.3 $\pm$8.3 years
Nair, 1999	
Pacia 1994 United States	NR

Evidence Table 7. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Safety Outcomes	Comments
Manschreck, 1999	NR	
Nair, 1999	NR	
Pacia 1994 United States	Seizures 71 cases (1.3%)	

Evidence Table 7. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Data Source	Prospective Retrospective Unclear	Exposure Period	Mean duration of follow-up	Interventions Mean dose
Rastogi, 2000	NR	Prospective	NR	6 months	clozapine 150-300 mg 6 months
Reid 1998 United States	Database: Texas MH System	Unclear	1991 to 1996	NR	Clozapine
Sajatovic 2000 United States	Naturalistic: VA National Clozapine Coordinating Center (168 VA facilities)	Prospective	October 1, 1991 to November 11, 1996	184 days	503mg
Tandon, 1993	Lenawee Country Community Mental Health Center	Prospective	NR	8 weeks	clozapine 405 mg/day

Evidence Table 7. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Population	Age Gender Ethnicity	Exposed Eligible Selected	Withdrawn Lost to fu Analyzed
Rastogi, 2000	Schizophrenia	Mean age=37.8 years 71% male Ethnicity: NR	NR/NR/31	NR/NR/31
Reid 1998 United States	Schizophrenia/ Schizoaffective	NR NR NR	NR NR NR	NR NR NR
Sajatovic 2000 United States	Treatment resistant schizophrenia	Mean age=44.8 (n=2996) 94.7% male (n=2488) Race NR	2996 2996 2996	NR NR Unclear
Tandon, 1993	Schizophrenia	Mean age=37 years 70% male Ethnicity: NR	NR/NR/44	4/NR/40

Evidence Table 7. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Effectiveness outcomes
Rastogi, 2000	Global impression: 21(67.7%) patients were rated as improved by clinicians 18(58.1%) patients self-rated as improved Six monthly outcome measure for the basic everyday living skills scale: Mean % improvement self-care: 15% domestic skills: 20% community skills: 17% activity and social skills: 22%
Reid 1998 United States	NR
Sajatovic 2000 United States	NR
Tandon, 1993	baseline vs post-treatment, p value, % change Global severity: 53.5 vs 43.3, p<0.01, 19.1% Positive symptoms: 16.0 vs 12.4, p<0.01, 22.5% Negative symptoms: 13.8 vs 11.0, p<0.01, 20.3%

Evidence Table 7. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Safety Outcomes	Comments
Rastogi, 2000	NR	
Reid 1998 United States	Suicide 1 case Annual rate=12.74 per 1000,000	
Sajatovic 2000 United States	Agranulocytosis Cases: 14 (0.5%) Fatal cases: 2 (0.1%) Death 38 (1.3%) Seizures 14 (0.5%) Suicide 2 (0.1%)	
Tandon, 1993	NR	

Evidence Table 7. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Data Source	Prospective Retrospective Unclear	Exposure Period	Mean duration of follow-up	Interventions Mean dose
Taylor, 2000	27 clozapine clinics in UK	Retrospective	March to May, 1999	58.6% 2 years or more 16.1% 1-2 years 10.7% 6 months-1 year 13.5% less than 6 months 0.9% no response given 0.2% unable to remember	clozapine
Umbricht 1994 United States	Chart review	Retrospective	12 months		Clozapine

Evidence Table 7. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Population	Age Gender Ethnicity	Exposed Eligible Selected	Withdrawn Lost to fu Analyzed
Taylor, 2000	NR	Mean age: NR 25-44 years 68.8% 63.3% male 89.5% Caucasian; 4.9% Caribbeans; 2.8% Asians	NR/NR/1284	NR/NR/1284
Umbricht 1994 United States	Schizophrenia	Mean age=28.7 68% male 85.4% white	NR NR 82	NR NR 68

Evidence Table 7. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Effectiveness outcomes
Taylor, 2000	perception of clozapine treatment better: 62.1% much better: 24.0% slightly better: 24% about the same: 9.8% slightly worse: 1.8% much worth: 0.9% no reply: 1.4% perceived benefits of clozapine: 35.4% feeling better improvements in tolerability: 8.4% did not like about clozapine: blood test: 24.2% drowsiness: 13% increased salivation: 9.8% weight gain: 5.4% no reply: 19% Preference- prefer to stay on clozapine: 88.6% prefer previous treatment: 6.5% advantages of clozapine outweighed disadvantages: 87% advantages of clozapine did not outweigh disadvantages: 6.5% no reply: 6.5% how patients lives had changed: 57% easier to mix with people 42.9% now liked socialising 52.9% had left hospital 42.9% could now live in a hostel 7% had obtained employment 11.1% reported has not changed 3% no reply
Umbricht 1994 United States	NR

Evidence Table 7. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Safety Outcomes	Comments
Taylor, 2000	NR	
Umbricht 1994 United States	60% with ≥ 10% weight gain	72% neuroleptic-treatment resistent

Evidence Table 7. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Data Source	Prospective Retrospective Unclear	Exposure Period	Mean duration of follow-up	Interventions Mean dose
Wilson 1992 United States First paper in a series studying clozapine-treated pts in Dammasch State Hospital; this study analyzed the pts entered into the cohort in the first 6 months	Chart review (Dammasch State Hospital; Wilsonville, Oregon)	Unclear	May 1990 to January 15, 1991	6 months	Clozapine 597 mg (mean at month 6)
Wilson 1993 United States Second paper in a series studying clozapine-treated pts in Dammasch State Hospital; this study analyzed the pts entered into the cohort in the first year	Chart review of first 100 pts starting clozapine treatment (Dammasch State Hospital; Wilsonville, Oregon)	Unclear	May 1990 to December 1991	1 year follow-up (as well as review of 6 months priort to start of clozapine treatment); at 1 year follow up 37 pts had been discharged to community and 63 pts remained hospitalized	Clozapine begun at 25 mg/d and titrated upwards; Mean clozapine dose for pts at 3 months was 463 mg/d; Mean dose for pts who remained hospitalized and continued clozapine 564 mg/d

Evidence Table 7. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Population	Age Gender Ethnicity	Exposed Eligible Selected	Withdrawn Lost to fu Analyzed
Wilson 1992 United States First paper in a series studying clozapine-treated pts in Dammasch State Hospital; this study analyzed the pts entered into the cohort in the first 6 months	All patients who began clozapine treatment (Criteria for clozapine eligibility were (1) diagnosis of schizophrenia, (2) history of poor response to at least two antipsychotic agents, (3) need for antipsychotic treatment in a patient with tardive dyskinesia)	Mean age=35 64.9% male 86% white	NR NR 37	NR NR 37
Wilson 1993 United States Second paper in a series studying clozapine-treated pts in Dammasch State Hospital; this study analyzed the pts entered into the cohort in the first year	Schizophrenia: 67%; Schizoaffective disorder: 26%; Bipolar with psychotic features: 6%; Organic delusional disorder: 1% 12% had previous history of seizures - 8% idiopathic and 4% followed head trauma	Mean age: 37y Range: 20-61y 55% male 94% white	NR/ NR/ 100	9 NR 100 1 pts dropped out after leukopenia and 1 pts dropped out after seizure

Evidence Table 7. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Effectiveness outcomes
Wilson 1992 United States First paper in a series studying clozapine-treated pts in Dammasch State Hospital; this study analyzed the pts entered into the cohort in the first 6 months	NR
Wilson 1993 United States Second paper in a series studying clozapine-treated pts in Dammasch State Hospital; this study analyzed the pts entered into the cohort in the first year	NR

Evidence Table 7. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Safety Outcomes	Comments
Wilson 1992 United States First paper in a series studying clozapine-treated pts in Dammasch State Hospital; this study analyzed the pts entered into the cohort in the first 6 months	Seizures 3 (8.1%)	
Wilson 1993 United States Second paper in a series studying clozapine-treated pts in Dammasch State Hospital; this study analyzed the pts entered into the cohort in the first year	Seizures: 10% of pts (5 men and 5 women) had at least 1 seizure; they occurred at a mean dose of 323 mg/d of the 10 pts with seizures: 6 pts were smokers, 4 were nonsmokers 4 pts of 12 with previous history had seizures; 6 of 88 pts without this history had seizures 1 of 9 pts withprevious head trauma had seizure	1 pt reported to have died of pnuemonia (not related to drug) 4 mos after discontinuing clozapine

Evidence Table 7. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Data Source	Prospective Retrospective Unclear	Exposure Period	Mean duration of follow-up	Interventions Mean dose
Zito, 1993	a large, state-operated, public psychiatric system	Retrospective	NR	1 year	clozapine

Evidence Table 7. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Population	Age Gender Ethnicity	Exposed Eligible Selected	Withdrawn Lost to fu Analyzed
Zito, 1993	schizophrenia	Mean age=35.6 years 73% male Ethnicity: NR	267/227/202	NR/NR/202

Evidence Table 7. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Effectiveness outcomes
Zito, 1993	

Evidence Table 7. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Safety Outcomes	Comments
Zito, 1993	CSEP(6 week vs 12 week vs 1 year) vs SCS 6 week Drowsiness: 52% vs 46% vs 35% vs 21% Tachycardia: 39% vs 27% vs 17% vs 17% Hypersalivation: 23% vs 21% vs 11% vs 13% Weight gain: 22% vs 26% vs 29% vs NR Dizziness: 21% vs 13% vs 6% vs NR Hypotension: 17% vs 8% vs 7% vs 3% Constipation: 16% vs 14% vs 14% vs 16% Dry mouth: 12% vs 6% vs 7% vs 5% Nausea/vomiting: 12% vs 7% vs 6% vs 10% Fever: 11% vs 5% vs 2% vs 12% Hypertension: 10% vs 9% vs 6% vs 13% Tremor: 10% vs 7% vs 4% vs 2% Headache: 8% vs 6% vs 5% vs 10% Akathisia: 8% vs 5% vs 4% vs 2% Blurred vision: 5% vs 4% vs 1% vs NR Bronchial hypersecretion: 4% vs 2% vs 2% EPSE: 3% vs 3% vs 2% vs NR Falling: 3% vs 3% vs 2% vs NR WBC reduction: 1.5% vs 0.5% vs 2% vs 5% Seizures: 0.5% vs NR vs 2% vs NR	

Evidence Table 7. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Data Source	Prospective Retrospective Unclear	Exposure Period	Mean duration of follow-up	Interventions Mean dose
Olanzapine					
Biswas, 2001	survey	Retrospective	December 1996 to May 1998	6 months	olanzapine for at least 6 months
Conley, 1998	three clinical sites	Prospective	NR	7 weeks	olanzapine 10 mg/day for a week, followed by a maximum daily dose of 25 mg. 7 weeks total

Evidence Table 7. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Population	Age Gender Ethnicity	Exposed Eligible Selected	Withdrawn Lost to fu Analyzed
Olanzapine				
Biswas, 2001	schizophrenia 39.2% psychosis 12.5% not specified 33.4% depression 3% hallucunations 2.1% paronia 1.9% maniac depression 1.6% delusions 0.8% dementia 0.5% psychiatric unspecified 0.5% behavior abnormal 0.5%	Mean age=42.3 years 43.1% male Ethnicity: NR	15588/10735/8858	NA/NA/8022
Conley, 1998	Schizophrenia	Mean age=41.7 years 77% male 68% white; 32% black	NR/NR/NR	NR/NR/60

Evidence Table 7. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Effectiveness outcomes
Olanzapine	
Biswas, 2001	NR
Conley, 1998	Substance abusers (SA), n=23; Non-substance avusers (NSA), n=37 BPRS total score: significant improved, p=0.0361 BPRS thought disturbance: significant improved, p=0.003 BPRS anxiety factors: significant improved, p=0.0175 38 (63%) were considered olanzapine improvers SA and NSA has no differences on the total BPRS, CGI, SANS ratings BPRS negative symptom factor (NSA): significant improved, p=0.0001 16/23(69%) of the SA patients and 22/37(60%) of the NSA patients were considered olanzapine improvers defined by a priori criteria, p=NS

Evidence Table 7. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Safety Outcomes	Comments
Olanzapine		
Biswas, 2001	193 events in 145(1.6%) patients the most frequency reasons for stopping olanzapine: drowsiness/sedation 153 cases weight gain 117 cases 691(7.8%) patients >=70 y/o: drowsiness/sedation were most frequently reported- 3.31% confusion and fall 158(1.78%) patients <18 y/o: 1 abnormal liver function, 1 weight gain 18 pregnancy: 2 spontaneous abortion 3 therapeutic termination of pregnancy 11 live birth 195 deaths 11 suicide 1 accidental overdose	
Conley, 1998	EPS symptoms: Simpson-Angus scale: significant improved, p=0.0001 Barnes Akathisia scale: significant improved, p=0.0196 Tardive Dyskinesia: SA vs NSA, p value Baseline: 11/23(48%) vs 5/37(14%) have TD, p=0.00613 AIMS scores: baseline vs endpoint SA: 9.45 vs 6.91 NSA: 10.60 vs 8.8	

Evidence Table 7. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Data Source	Prospective Retrospective Unclear	Exposure Period	Mean duration of follow-up	Interventions Mean dose
Del Paggio, 2002	21 mental health clinics, 8 treatment teams, and 45 psychiatrists	Prospective	November 1, 1996 to April 30, 1998	12 months	olanzapine
Dossenbach, 2000	5 study centers	Prospective	NR	18 weeks	olanzapine 5-25 mg/day 18 weeks
Dossenbach, 2001	7 study centers	Prospective	NR	14 weeks	olanzapine 15.7 mg/day 14 weeks

Evidence Table 7. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Population	Age Gender Ethnicity	Exposed Eligible Selected	Withdrawn Lost to fu Analyzed
Del Paggio, 2002	66.3% thought disorder 33.7% other	Mean age=35.9 years 63.5% male Ethnicity: NR	NR/NR/189	NR/NR/189
Dossenbach, 2000	chronic schizophrenia	NR	50/NR/48	5/3/48
Dossenbach, 2001	schizophrenia	Mean age=33.9 years 74% male Ethnicity: NR	43/34/34	7/1/34

Evidence Table 7. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Effectiveness outcomes
Del Paggio, 2002	Resource utilization- before vs after olanzapine therapy: mean change (95%CI), p value hospitalization, no. of days: -18.2 (-29.6 to -7.9), <0.001 outpatient visit, no.: 9.7 (-3.4 to 21.9), 0.15 crisis visits, no.: -0.28 (-0.56 to -0.09), 0.005 cost, $ impatient treatment: -4423 (-7404 to -1282), 0.003 outpatient treatment: 1051 (79-1976), 0.035 crisis treatment: -203 (-375 to -49), 0.009 medication: 1585 (1109 to 2247), <0.001 total: -1991 (-5258 to 1122), 0.22 PANSS score at 6 months: decrease 15 points (95%CI: -17 to -3), p<0.001 PANSS negative subscale score: decrease 4 points (95%CI: -6 to -1), p<0.001
Dossenbach, 2000	PANSS total score- baseline, mean reduced points, %: 115.3, 17.7, 14.2% BPRS total score- baseline, mean reduced points, %: 44, 9.8, 20.2% (week 6 to week 18 show significant reduced points, p<0.001) Responders- >=20% decrease PANSS: 18(40%) BPRS: 25(55.6%) Responders- 30%, 40% decrease PANSS: 11(24.4%), 2(4.4%) BPRS: 17(37.8%), 13(28.9%) CGI- achived some degree of improvement: 24(53.3%) Patient Globol Impression- improvement: 23(51%)
Dossenbach, 2001	PANSS total score- mean change from baseline at endpoint (week 14): -28.7, p<0.05 BPRS total score- mean change from baseline at endpoint (week 14): -17.17, p<0.05 PANSS responder- >=20% decrease in total score: 20(58.8%) by week 14 PANSS total score changed at week 14- responder vs nonresponder: -14.4 vs -7.8, p=0.0001 BPRS total score changed at week 14- responder vs nonresponder: -25.3 vs -5.6, p=0.0001 CGI at week 14: 24(70.6%) rated minimal or greater improvement; 6(17.6%) rated no change; 4(11.8%) rated worsened.

Evidence Table 7. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Safety Outcomes	Comments
Del Paggio, 2002	NR	
Dossenbach, 2000	24(50%) reported >= 1 treatment-emergent adverse event SAS score- baseline vs week 6 vs week 18: 2.7 (vs 1.8 vs 1.6), p<0.001 AIMS score- baseline vs week 6 vs week 18: 2.6 (vs 1.5 vs 1.3), p<0.05 BAS score: NS weight gain: 1.2±4 kg, p=NR	
Dossenbach, 2001	17(50%) reported no treatment-emergent adverse events 17(50%) reported >= 1 treatment-emergent adverse event 3(8%) abnormal liver function 3(8%) weight gain 2(5.9%) akathisia 2(5.9%) anxiety 2(5.9%) asthenia 2(5.9%) headache 2(5.9%) insomnia ESRS total score- baseline vs endpoint: 2.8 vs 0.6, p<0.001 CGI-S for AEs: 33(97.1%) was either "not affected" or "not significant affected" by olanzapine treatment	switch from risperidone to olanzapine

Evidence Table 7. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Data Source	Prospective Retrospective Unclear	Exposure Period	Mean duration of follow-up	Interventions Mean dose
Dursun, 1999	NR	Prospective	NR	16 weeks	olanzapine mean dosage at week 4: 13.6 mg/day week 8: 19.3 mg/day week 16: 28.1 mg/day
Edar, 2001	NR	Prospective	NR	8.1 weeks	olanzapine 7.5-20 mg/day for 8.1 weeks

Evidence Table 7. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Population	Age Gender Ethnicity	Exposed Eligible Selected	Withdrawn Lost to fu Analyzed
Dursun, 1999	schizophrenia	Mean age=40 years 69% male Ethnicity: NR	NR/NR/16	NR/NR/16
Edar, 2001	schizophrenia	Mean age=35.2 years 80% male Ethnicity: NR	NR/NR/10	NR/NR/10

Evidence Table 7. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Effectiveness outcomes
Dursun, 1999	Baseline vs Week 4 vs Week 8 vs Week 16 BPRS: 71 vs 63** vs 58** vs 51** GAS: 29 vs 33* vs 38** vs 40** AIMS: 24 vs 33* vs 30 vs 28 (**p<0.001; *p<0.01 vs baseline) 8/16(50%) were treatment responders: >=20% decease in BPRS Mean change in BPRS scores: 18.2±15.6% in all patients; 43±11.4% in responders BPRS scores associated with dosage: high dose (mean 20.9mg) vs low dose (mean 16mg) Score change in Week 8: 16±10% vs 15.2±9.8% Score change in Week 16: 21.5±16% vs 11.2±15.6%
Edar, 2001	NR

Evidence Table 7. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Safety Outcomes	Comments
Dursun, 1999	NR	
Edar, 2001	baseline vs week 8 patients weight(kg): 68.8 vs 72.1, p=0.001 body fat(kg): 13.1 vs 15.3, p=0.004 BMI: 22.4 vs 23.5, p=0.001 comparison subject weight(kg): 70.8 vs 71.4, p=0.2 body fat(kg): 11.9 vs 12.2, p=0.72 BMI: 22.1 vs 22.3, p=0.13 9/10(90%) patients gained weight during the 8 weeks treatment	

Evidence Table 7. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Data Source	Prospective Retrospective Unclear	Exposure Period	Mean duration of follow-up	Interventions Mean dose
Gilchrist, 2002	State Hospital	Prospective	January 1998 to December 1998	6 months	olanzapine 15 mg/day 6 months

Evidence Table 7. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Population	Age Gender Ethnicity	Exposed Eligible Selected	Withdrawn Lost to fu Analyzed
Gilchrist, 2002	schizophrenia	Mean age=35.9 years 58% male Ethnicity: NR	NR/NR/116	52/6/58

Evidence Table 7. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Effectiveness outcomes
Gilchrist, 2002	Lothan Primary Care NHS Trust Patients CGI: 48(83%) were scored as minimally improved, much improved or very much improved Baseline vs 6 months, p value Severity of positive symptoms: 2.26 vs 1.16, p=0.0001 Severity of negative symptoms: 1.58 vs 1.19, p=0.0001 Severity of drug induced side effects: 1.97 vs 0.83, p=0.0001 Impairment in quality of life: 3.22 vs 2.09, p=0.0001 28/116(24%) had >=40% reduction in positive symptoms at six months 19/32(59%) prescribed olanzalone for treatment resistance were still taking the drug at six months and 8(25%) of them had responded The State Hospital Study Baseline vs 6 months, p value CGI: 5.1(markedly ill) vs 4(moderately ill), p<0.001 Severity of positive symptoms: 2.5 vs 1.5, p=0.0001 Severity of negative symptoms: 1.8 vs 1.5, NS Severity of drug induced side effects: 1.9 vs 0.8, p=0.0001 impairment in quality of life: 3 vs 2.1, p=0.0001 21(44%) had >=40% reduction in positive symptoms 24(73%) prescribed olanzapine for treatment resistance were still on the drug after six months and 14(42%) of them had responded

Evidence Table 7. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Safety Outcomes	Comments
Gilchrist, 2002	NR	

Evidence Table 7. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Data Source	Prospective Retrospective Unclear	Exposure Period	Mean duration of follow-up	Interventions Mean dose
Ishigooka, 2001	NR	Prospective	NR	12 weeks	olanzapine 7.9 mg/day for 8 weeks

Evidence Table 7. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Population	Age Gender Ethnicity	Exposed Eligible Selected	Withdrawn Lost to fu Analyzed
Ishigooka, 2001	66.7% hebephrenic 22.2% paranoid	Mean age=41.6 years 56.8% male Ethnicity: NR	NR/NR/81	7/NR/74

Evidence Table 7. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Effectiveness outcomes
Ishigooka, 2001	Global Improvement 48(59.3%) rated moderate and remarkable improvement 70(84%) rated slight or more improvement Statistically significant improvement (p<0.05): data not reported Week 1 to Week 8 fpr BPRS totak score, anxiety-depression and agergia Week 2 to Week 8 for activation and thought disturbances. Week 4 to Week 8 for hostility Relationship between Final Global Improvement Rating and Brief Psychiatric Rating Scale: a liner relationship was observed

Evidence Table 7. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Safety Outcomes	Comments
Ishigooka, 2001	Treatment-emergent sighs and symptoms (>=3%): No. (%) patients with >=1 TESS: 48(59.3%) patients with no TESS: 33(40.7%) insomnia: 20(24.7%) weight increase: 14(17.3%) excitement: 12(14.8%) sleepiness: 12(14.8%) anxiety: 10(12.3%) weight decrease: 7(8.6%) malaise: 6(7.4%) tremor: 5(6.2%) anorexia: 4(4.9%) diaphoresis: 4(4.9%) fever: 4(4.9%) tachycardia: 4(4.9%) constipation: 4(4.9%) weakness: 4(4.9%) depressed state: 4(4.9%) muscle rigidity: 3(3.7%) oral dryness: 3(3.7%) blood pressure decrease: 3(3.7%) Treatment-emergent EPS: patients with >=1 treatment-emergent EPS: 5(6.2%) patients with no treatment-emergent EPS: 76(93.8%) tremor: 5(6.2%) muscle rigidity: 3(3.7%) akathisia: 2(2.5%) Weight increase >=10%: 6(7.6%) Weight decrease >=10%: 1(1.3%)	

Evidence Table 7. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Data Source	Prospective Retrospective Unclear	Exposure Period	Mean duration of follow-up	Interventions Mean dose
Koller, 2002	MedWatch Drug Surveillance System	Retrospective	January 1994 to May 2001	NR	olanzapine 15.6 mg
Janenawasin 2002					
Lasser, 2004	NR	Prospective	NR	8 weeks	olanzapine or risperidone for 8 weeks
Lindenmayer, 2001	NR	Prospective	NR	14 weeks	olanzapine for 14 weeks

Evidence Table 7. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Population	Age Gender Ethnicity	Exposed Eligible Selected	Withdrawn Lost to fu Analyzed
Koller, 2002	olanzapine-associated diabetes or hyperglycemia	Mean age=39.8 years 66.6% male Ethnicity: NR	NR/NR/237	NA/NA/226
Janenawasin 2002				
Lasser, 2004	Schizophrenia or schizoaffective disorders	Mean age=49.9 years 60.8% male 63.6% white	NR/NR/552	NR/NR/375
Lindenmayer, 2001	Chronic schizophrenia or schizoaffective disorder	Mean age=41.6 years 77% male Ethnicity: NR	NR/NR/43	16/NR/42

Evidence Table 7. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Effectiveness outcomes
Koller, 2002	NR
Janenawasin 2002	
Lasser, 2004	NR
Lindenmayer, 2001	PANSS factor- change from baseline: positive: 0.30, NS negative: 0.26, NS excitement: -1.36, p<0.053 cognitive: 0.92, p<0.009 deoression/anxiety: -0.15, NS ESRS- chage from baseline: 2.3, NS

Evidence Table 7. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Safety Outcomes	Comments
Koller, 2002	188 were new-onset diabetes, 44 were exacerbations of preexistent disease 73% of hyperglycemia appeared within 6 months of start of olanzapine therapy 80 ketosis or metabolic acidosis, 74(92%) were newly diagnosed diabetes 41 had glucose levels of 100ml/dl or greater 43 mental status changes, 42 had newly diagnosed diabetes, and 1 had exacerbation of preexistent diabetes 15 deaths 60(79%) had improved glycemic control after olanzapine discontinued 9 switch to another identified atypical antipsychotics 5 switched to risperidone had improved glucose level 1 switched to quetiapine had improved gluscise level 8(80%) experienced deterioration in glycemic control with rechallenge	
Janenawasin 2002		
Lasser, 2004	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	
Lindenmayer, 2001	weight gain related to duration: 3.5kg, p<0.0005 weight change by the mean dose in the last week of treatment, p<0.01 weight change by olanzapine doses over 20 mg/day, p<0.05	patients had failed to respond to treatment during a double-blind trial that compared clozapine, olanzapine, risperidone, and haloperidol

Evidence Table 7. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Data Source	Prospective Retrospective Unclear	Exposure Period	Mean duration of follow-up	Interventions Mean dose
Lindenmayer, 2002	NR	Prospective	NR	14 weeks	olanzapine 30.5 mg/day
Smith, 2001	NR	Prospective	NR	5 months	olanzapine 19.9 mg/day for 5 months

Evidence Table 7. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Population	Age Gender Ethnicity	Exposed Eligible Selected	Withdrawn Lost to fu Analyzed
Lindenmayer, 2002	Schizophreania or schizoaffective disorder	Mean age=42.2 years 84% male	NR/78/45	11/2/
Smith, 2001	Schizophreania or schizoaffective disorder	Mean age=43 years 91% male 47% hispanic; 26% white; 26% black	NR/45/34	7/5/19

Evidence Table 7. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Effectiveness outcomes
Lindenmayer, 2002	PANSS factor (n=42): baseline vs endpoint, p value positive: 19.9 vs 19, NS negative: 19.4 vs 18.6, NS excitement: 8.6 vs 10.4, 0.01 cognitive: 18.8 vs 17, 0.002 depression/anxiety: 9.5 vs 8.1, 0.03 PANSS factors of patients classfied as improveers (n=7): baseline vs endpoint, p value positive: 18.9 vs 12.9, 0.0005 negative: 20.4 vs 17.3, 0.03 excitement: 10.3 vs 6.7, 0.03 cognitive: 13.9 vs 11.2, 0.03 depression/anxiety: 8.9 vs 4.8, 0.07 PANSS factor change and olanzapine dosage: >20mg mean change vs <=20mg mean change, p value positive: 2.0 vs 0.1, <0.06 negative: 2.0 vs 0.0, <0.02 excitement: -0.02 vs -3.4, <0.006 cognitive: 2.0 vs 1.0, NS depression/anxiety: 1.6 vs 0.8, NS Negative association of PANSS total improvement with duration of illness, p<0.07
Smith, 2001	Cognitive test: baseline vs end-point, p value RANDT total score: 48.8±24.1 vs 61.1±18.7, p=0.003 Reacquistion total: 48.8±24.1 vs 61.1±18.7, p=0.01 Visual-spatial memory delayed accuracy (mm error): 63.5±30.3 vs 51.1±24.9, p=0.012 ANAM modifirf repeat computer battery sternberg memory (% accuracy): 58.4±17.9 vs 69.8±15.9, p=0.018 match to sample pattern (% accuracy): 50.6±14.9 vs 63.4±20.1, p=0.001 two-choice reaction time (% accuracy): 77.0±19.2 vs 84.6±16.4, p=0.022 Verbal fluency totall: 39.1±16.3 vs 44.5±14.8, p=0.07 Verbal fluency animals: 8.9±3.9 vs 11.5±4.8, p=0.005 PANSS total score- decreased change: -9.76±9.13, p<0.001 PANSS positive symptoms- decreased change: -3.45±5.04, p=0.001 PANSS negative symptoms- decreased change: -2.27±4.57, p=0.012 SANS total scores- decreased change: -6.41±14.9, p=0.029 Simpson-Angus EPS score: p<0.06

Evidence Table 7. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Safety Outcomes	Comments
Lindenmayer, 2002	ESRS score decrease 3.9 points, p<0.05 No relationship between the last week's dose of olanzapine and the level of EPRS NS in decrease in EPS in those patients who previous received clozapine versus those who received risperidone. Mean increase in weight of 1.4kg over the duration of the trial, p<0.02 An effect on weight change by the last week's mean dose, p<0.01 An effect on weight change by last week's mean dose, p<0.008	
Smith, 2001	NR	

Evidence Table 7. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Data Source	Prospective Retrospective Unclear	Exposure Period	Mean duration of follow-up	Interventions Mean dose
Zarate, 1998 United States	McLean Hospital records	Retrospective	October 1996 - February 1997	5 months	Olanzapine 11.8 mg
Quetiapine					
Brechar, 2000	NR	Prospective	NR	18 months	quetiapine 475mg 1 year
Buckley, 2004	NR	Prospective	NR	156 weeks	quetiapine 439.5 mg/day for 156 weeks
Sacchetti, 2003	Brescia University and Spedali Civili Psychiatric Service	Prospective	NR	4 weeks	quetiapine 500-750 mg/day 4 weeks
van der Heijden, 2003	Vincent van Gogh Institute for Pschiatry in Venray, Netherlands	Prospective	NR	14 weeks	quetiapine 200-800mg/ day 14 weeks

Evidence Table 7. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Population	Age Gender Ethnicity	Exposed Eligible Selected	Withdrawn Lost to fu Analyzed
Zarate, 1998 United States	bipolar disorder, schizophrenia, schizoaffective disorder, depression	Mean age: 43.7 years 56% male 90% white	155 155 150	
Quetiapine				
Brechar, 2000	schizophrenia	Mean age=37.3 years 65% male Ethnicity: NR	NR/NR/427	NR/NR/427
Buckley, 2004	schizophrenia	NR	NR/NR/259	NR/NR/234
Sacchetti, 2003	Schizophrenia	Mean age=38.1 years 58% male 100% caucasian	NR/NR/12	NR/NR/12
van der Heijden, 2003	Schizophrenia	Meean age=25.9 years 81% male Ethnicity: NR	NR/NR/21	NR/NR/21

Evidence Table 7. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Effectiveness outcomes
Zarate, 1998 United States	
Quetiapine	
Brechar, 2000	NR
Buckley, 2004	baseline(95%CI) vs initial treatment(95% CI) vs end point(95%CI) BPRS total score: 40.67(39.44-41.90) vs 13.94(12.93-14.95) vs 9.04(4.62-13.46) CGI: 4.81(4.73-4.90) vs 3(2.88-3.11) vs 2.43(1.92-2.95)
Sacchetti, 2003	Positive and Negative Syndrome Scale (PANSS): baseline vs endpoint total: 113 vs 93.8, p=0.006 negative: 25.1 vs 21.9, p=0.038 excitement: 12.3 vs 9.5, p=0.032 cognitive: 18.8 vs 15.2, p=0.006 positive: 19.7 vs 15.2, p=0.015 depression: 12.5 vs 11.8, p=NS other items: 24.9 vs 21.0, p=0.002 6(50%) showed >=20% reduction in PANSS total score --> classified as responders Responders vs nonresponders: NS in age, duration of disease, previouse hospitalization, quetiapine final dose.
van der Heijden, 2003	Baseline vs endpoint BPRS total score: deduction, p=0.008 PANSS general: deduction, p=0.05 MADRS: deduction, p=0.016 CGI: deduction, p=0.022 Responders: BPRS total: 73% PANSS positive, negative and general: 43%, 22%, 30% MADRS: 48%

Evidence Table 7. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Safety Outcomes	Comments
Zarate, 1998 United States		
Quetiapine		
Brechar, 2000	mean weight change from baseline: 9-13 weeks(n=170): 1.58kg 14-26 weeks(n=165): 0.26kg 27-39 weeks(n=134): 1.66kg 40-52 weeks(n=41): -1.53kg 53-78 weeks(n=146): 1.94kg Dose and weight change correlation: NS 1(0.22%) withdrew as a result of weight gain	
Buckley, 2004	NR	
Sacchetti, 2003	weight changed: NS Simpson-Angus Scale (SAS): NS Barnes Akathisia Rating Scale (BARS): NS Abnormal Involuntary Movement (AIMS): NS	
van der Heijden, 2003	4 psychomotor agitation 4 sleep disturbances 7 sedation 2 dizziness 5 perspiration 2 palpitation 10 weight gain: mean 5.5 kg	

Evidence Table 7. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Data Source	Prospective Retrospective Unclear	Exposure Period	Mean duration of follow-up	Interventions Mean dose
Wetzel, 1995	NR	Prospective	NR	4 weeks	quetiapine 750 mg/day 4 weeks
Risperidone					
Albright, 1996	Suskatchewan Health Linkable Data Files	Retrospective	1993-1995	20 months	risperidone

Evidence Table 7. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Population	Age Gender Ethnicity	Exposed Eligible Selected	Withdrawn Lost to fu Analyzed
Wetzel, 1995	Schizophrenia	Mean age=35.6 years 58% male Ethnicity: NR	NR/NR/12	NR/NR/12
Risperidone				
Albright, 1996	Schizophrenia-related	Mean age=40.8 years 52.1% male Ethnicity: NR	NR/NR/146	NR/NR/146

Evidence Table 7. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Effectiveness outcomes
Wetzel, 1995	baseline vs endpoint BPRS score: 42.0±2.3 vs 30.0±3.5, p<0.05 SAPS score: 64.5±4.8 vs 36.1±6.7, p<0.05 SANS score: 55.0±4.3 vs 42.5±5.9, p<0.05 GAS level: 33.1±2.6 vs 43.0±3.6, p<0.05 >=40% reduction in BPRS: 5/12(42%)
Risperidone	
Albright, 1996	Before vs after, p value No. of hospital admissions before and after initiation of risperidone therapy all admissions (n=99): 184 vs 73, p=0.0001 Length of stay (days) before and after initiation of risperidone therapy all admissions (n=99): 3888 vs 1624, p=0.0001 No. of physician services before and after initiation of risperidone therapy all physicians (n=143): 3963 vs 2881, p=0.0001 psychiatrist only (n=99): 1739 vs 1346, p=0.0697 general pracitioner onlu (n=140): 1302 vs 1172, p=0.4007 other physician specialty (n=109): 922 vs 363, p=0.0001 No. of mental helath services before and after initiation of risperidone therapy all caregivers (n=114): 3799 vs 3640, p=0.0089 psychiatrists (n=90): 694 vs 505, p=0.1062 social workers (n=22): 303 vs 236, p=0.5062 psychologists (n=21):: 143 vs 211, p=0.1585 therapists (n=33): 1337 vs 1544, p=0.3699 nurses (n=74): 1312 vs 1128, p=0.0412 other services (n=4): 10 vs 18, p=0.5 Drug costs before and after initiation of risperidone therapy risperidone (n=146): 0 vs 150145, p=0.0001 antipsychotics-depot (n=53): 13060 vs 6708, p=0.001 antipsychotics-oral (n=102): 25196 vs 11397, p=0.001 antiparkinson (n=117): 6295 vs 6315, p=0.7415 all drugs (n=146): 92992 vs 227965, p=0.0001

Evidence Table 7. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Safety Outcomes	Comments
Wetzel, 1995	NR	
Risperidone		
Albright, 1996	NR	

Evidence Table 7. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Data Source	Prospective Retrospective Unclear	Exposure Period	Mean duration of follow-up	Interventions Mean dose
Brunelleschi, 2003	Outpatients of the psychiatric service of Dronero (Cuneo, Italy). May-November 2002	Unclear	20 days to 4 years	7 months	Risperidone mean 4.15 mg/day
Chengappa, 2000	Mayview State Hospital	Prospective	March 1993 to June 1995	1 year	risperidone 5.1 mg/day for mean duration 200 days
Daradkeh, 1996	Hospital inpatients	Prospective	NR	6 weeks	risperidone 6 mg/day 6 weeks
Dickson, 1999	chart review from 2 participanting hospital	Retrospective	May 1, 1993 to April 30, 1994	3 years	risperidone mean duration for interruptters was 441 days; for discontinuers was 249 days

Evidence Table 7. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Population	Age Gender Ethnicity	Exposed Eligible Selected	Withdrawn Lost to fu Analyzed
Brunelleschi, 2003	Schizophrenia or schizoaffective disorders	Mean age=36.4 years 35% male Ethnicity: NR	NR/NR/NR	NR/NR/20
Chengappa, 2000	Schizoaffective or bipolar disorder	Mean age=50 years Gender: NR Ethnicity: NR	NR/NR/74	NR/NR/74
Daradkeh, 1996	schizophrenia, bipolar and schizoaffective disorder	Mean age=27.1 years 73% male Ethnicity: NR	NR/NR/15	5/0/10
Dickson, 1999	91% schizophrenia 7% schizoaffective disorder 2% schizophreniform disorder	Mean age=NR 62.5% male 85% white	NR/NR/120	NR/NR/120

Evidence Table 7. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Effectiveness outcomes
Brunelleschi, 2003	NR
Chengappa, 2000	Pre vs During treatment, p value Resperidone group hours of seclusion: 2.2(5.5) vs 0.26(0.66), p=0.002 no. of seclusion events: 0.23(0.59) vs 0.05(0.14), p=0.005 hours of restraint: 1.2(4.5) vs 0.36(1.5), p=0.055 no. of restraint events: 0.2(0.61) vs 0.11(0.5), p=0.095 Comparison group (patients not receiving risperidone or clozapine at the time), p value not reported hours of seclusion: 2.3(5.8) vs 0.51(0.78) no. of seclusion: 0.12(0.46) vs 0.07(0.1) hours of restraint: 1.0(3.9) vs 0.43(1.4) no. of restraint events: 0.11(2.0) vs 0.08(0.55)
Daradkeh, 1996	6(60%) achieved 25% reduction in total BPRS and NSRS 5(50%) achieved 50% reduction in BPRS and NSRS
Dickson, 1999	Average hospital days per year for treatment groups: pre- vs post- risperidone continuers (n=35): 17.2(4.7) vs 2.1(0.6), p=0.004 discontinuers (n=77): 14.1(3.9) vs 16.9(4.6), p=0.128 interrupted (n=8): 6.8(1.9) vs 31.1(8.5), p=0.475 continuers vs discontinuers, p=0.006 continuers vs interrupted, p=0.003 No. of hospitals days 3 years pre- vs post-risperidone for total sample (n=120) no. of days in hospital (index excluded): 5223 vs 4869, 7% reduction, p=0.65 no. of days in hospital (index included in preperiod): 6172 vs 4869, 21% reduction, p=0.31

Evidence Table 7. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Safety Outcomes	Comments
Brunelleschi, 2003	13 (65%) with risperidon 2-8mg/day, presented hyperprolactinemia 10 (50%) weight gain, mean 2.4kg 8 (40%) presented prolactin-related adverse effects (decrease in libido)	
Chengappa, 2000	NR	
Daradkeh, 1996	4 patients required treatment for akathisia or rigidity with antiparkinsonian drugs. 5 droppted out: 2 very impulsive and psychotic and required treatment with parenteral haloperidol; 1 very restless and did not respond to treatment with clonazepam; 1self-discharged; 1 had supraventricular tachycardia and hypotension.	
Dickson, 1999	NR	

Evidence Table 7. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Data Source	Prospective Retrospective Unclear	Exposure Period	Mean duration of follow-up	Interventions Mean dose
Finley, 1998	The Department of Veterans Affairs (VA) Palo Alto Health Care System, Menlo Park Division	Retrospective	NR	12 months	risperidone 6.1 mg/day duration from 37.2 days to 12 months

Evidence Table 7. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Population	Age Gender Ethnicity	Exposed Eligible Selected	Withdrawn Lost to fu Analyzed
Finley, 1998	Chronic schizophrenia (paranoid, disorganized, and undifferetiated)	Mean age=45.8 years 100% male Ethnicity: NR	NR/66/57	NA/7/50

Evidence Table 7. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Effectiveness outcomes
Finley, 1998	Before vs after, p value Chi-square analysis of clinical outcomes for patients receiving a therapeutic trial pf risperidone Days hospitalized (12-month period) Responders: 43.9 vs 25.2, p=0.03 Nonresponders: 59.1 vs 58.3, p=0.447 CGI severity scores Responders: 5.04 vs 3.96, p=0.0001 Nonresponders: 4.91 vs 4.39, p=0.015 Concurrent psychotropic medications Responders: 3.3 vs 2.6, p=0.017 Nonresponders: 3.3 vs 2.7, p=0.029 Demographic variable s and clinical response of patients receiving risperidone Diagnosis, p=0.793 Chronic schizophrenia: 59.3% (16/27) responding Schizoaffective disorder: 43.7% (7/16) responding Bipolar affective disorder: 50.0% (2/4) responding Psychotic depression: 66.7% (2/3) responding Indication, p=0.0006 Treatment intolerant: 88.9% (16/18) responding Treatment resistant: 34.4% (11/32) responding Substance abuse, p=0.0097 Negative history: 82.4% (14/17) responding Positive history: 39.4% (13/33) responding Age, p=0.468 <50 years: 50.0% (19/38) responding >=50 years: 66.7% (8/12) responding Baseline function (days hospitalized 12 months prior), p=1.000 High (<45 days): 53.8% (14/26) Low (>=45 days): 54.2% (13/24) Baseline function (number of previous antipsychotic trials), p=0.488 High (<3 trials): 58.8% (20/34)

Evidence Table 7. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Safety Outcomes	Comments
Finley, 1998	Adverse events: sedation, syncope, dzziness, increased depression, nghtmares, and emesis	

Evidence Table 7. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Data Source	Prospective Retrospective Unclear	Exposure Period	Mean duration of follow-up	Interventions Mean dose
Franckiewicz, 2002	Hispanic inpatient unit at Elmhurst Hospical Center	Prospective	NR	4 weeks	risperidone
Guest, 1996	NR	Retrospective	1988-1993	2 years	risperidone 8.8mg 1-2 years
Jeste, 1997	158 psychiatric centers	Prospective	NR	10 weeks	risperidone 5.9 mg/day for mean duration 56.5 days 554(98.9%) received at least one other drug

Evidence Table 7. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Population	Age Gender Ethnicity	Exposed Eligible Selected	Withdrawn Lost to fu Analyzed
Franckiewicz, 2002	Schizophrenia	Mean age=31.4 years 50% male 55.6% hispanic; 44.4% non-hispanic	NR/NR/18	NR/NR/18
Guest, 1996	chronic schizophrenic disprder	Mean age=38 years 65% male Ethnicity: NR	NR/NR/31	NR/NR/31
Jeste, 1997	Schizophrenia	Mean age=41.8 years 58% male 67.8% caucasian; 25.4% africa american; 4.1% hispanic; 2.1% asian american; 0.7% other	NR/NR/945	283/NR/945

Evidence Table 7. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Effectiveness outcomes
Franckiewicz, 2002	Baseline vs Week 1 vs Week 2 vs Week 3 vs Week 4, p value PANSS subscale scores for hispanic and non-hispanic patients General- hispanic: 53.2 vs 52.0 vs 36.9 vs 31.5 vs 28.5, p<0.001 General- nonhispanic: 52.87 vs 49.25 vs 41.25 vs 38 vs 33.5, p<0.001 Negative- hispanic: 28.4 vs 27.8 vs 20.1 vs 16.0 vs 14.3, p<0.001 Negative- nonhispanic: 28.25 vs 27.37 vs 22.37 vs 19.0 vs 16.87, p<0.001 Positive- hispanic: 25.5 vs 24.6 vs 20.0 vs 16.6 vs 14.3, p<0.001 Positive- nonhispanic: 24.7 vs 26.13 vs 22.12 vs 19.62 vs 17.52, p<0.001
Guest, 1996	Clinical outcome- baseline vs after treatment PANSS: 86.7 vs 59.9, p<0.0001 CGI: 3.6 vs 2.3, p=0.0005 ESRS: 8.8 vs 4.8 vs 3.6, p=0.002 Resource utilization- baseline vs Year 1 vs Year 2 (all p-values were not reported) Days in hospital: 171.8 vs 118.9 vs 51.3 Days in residential accommodation: 28.4 vs 84.7 vs 74.4 Visits to day centers: 7.9 vs 13.6 vs 8.3 Visits to out-patient clinic: 2.5 vs 3.9 vs 3.4 Visits to nurses: 4.3 vs 1.7 vs 6.5
Jeste, 1997	CGI-C scores, increased points- week 2 (95%CI) vs week 6 (95%CI) vs week 10 (95%CI): 4.6(4.5-4.6) vs 4.8(4.8-4.9) vs 4.9(4.8-5.0) CGI-C % patients rated improved- week 2 vs week 6 vs week 10: 57.5 vs 72.5 vs 78.1 non-treatment-resistant (NTR) vs treatment-resistant (TR) NTR had signifivant larger proportion of improvement at week 2 and week 6, but not at week 10 PANSS scores: decrease, p<0.001 Global Assessment of Functions (GAF): 136(25.2%) had a GAF score >50 at baseline 312(57.8%) had a GAF score >50 at week 10 420(77.8%) had a GAF score >50 during the trial, 95%CI: 74.3-81.3 non-treatment-resistant (NTR) vs treatment-resistant (TR) 114(79.7%), 95%CI: 73.1-86.3 vs 298(76.8%), 95%CI: 72.6-81.0

Evidence Table 7. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Safety Outcomes	Comments
Franckiewicz, 2002	Extrapyramidal symptoms: hispanic vs non-hispanic= 4 vs 0, p=0.057	
Guest, 1996	NR	
Jeste, 1997	361(42.9%) experienced at least one adverse event Psychiatric symptoms: 179(21.3%) Central and peripheral nervous system symptoms: 144(17.1%) Gastrointestinal symptoms: 87(10.3%) Body as a whole- general symptom: 54(6.4%) Extrapyramidal symptoms: 26(3.1%) 47(5.6%) experienced a severe adverse event 9(1.1%) agitation 6(0.7%) insomnia 6(0.7%) dizziness SBP and DBO decreased, HR increased, but NS	

Evidence Table 7. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Data Source	Prospective Retrospective Unclear	Exposure Period	Mean duration of follow-up	Interventions Mean dose
Kaneda, 2001	Department of neuropsychiatry, Fujii hospital	Prospective	NR	64.2 days	risperidone 9.5 mg/day for 64.2 days

Evidence Table 7. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Population	Age Gender Ethnicity	Exposed Eligible Selected	Withdrawn Lost to fu Analyzed
Kaneda, 2001	schizophrenia	Mean age=46.2 years 100% male Ethnicity: NR	NR/NR/6	NR/NR/6

Evidence Table 7. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Effectiveness outcomes
Kaneda, 2001	NR

Evidence Table 7. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Safety Outcomes	Comments
Kaneda, 2001	BPRS- before vs during the treatment total: 37.5 vs 30.7, p<0.05 anxiety: 6.0 vs 4.2, NS anergia: 9.2 vs 8.7, NS thought disturbance: 10.5 vs 7.2, p<0.05 activation: 7.0 vs 5.2, NS hostility-suspiciousness: 4.8 vs 4.3, NS Hormonal testing prolactin(ng/mL): 13.45 vs 36.97, p<0.05 luteinizing hormone(mIU/mL): 4.7 vs 6.43, NS follicle-stimulating hormone(mIU/mL): 6.18 vs 6.35, NS testosterone(ng/mL): 5.623 vs 5.708, NS	

Evidence Table 7. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Data Source	Prospective Retrospective Unclear	Exposure Period	Mean duration of follow-up	Interventions Mean dose
Kim, 2002	inpatients and outpatients of the Department of Psychiatry, St. Mary;s Hospiral, Seoul, Korea	Prospective	NR	8 weeks	risperidone 9.1 mg/day for 8 weeks

Evidence Table 7. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Population	Age Gender Ethnicity	Exposed Eligible Selected	Withdrawn Lost to fu Analyzed
Kim, 2002	schizophrenia	Mean age=34.4 years 100% female Ethnicity: NR	NR/30/25	NR/5/20

Evidence Table 7. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Effectiveness outcomes
Kim, 2002	NR

Evidence Table 7. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Safety Outcomes	Comments
Kim, 2002	baseline vs 8 weeks PANSS total: 60.2 vs 51.2, p<0.01 positive symptom scale: 14.3 vs 11.4, p<0.01 negative symptom scale: 15.9 vs 13.8, p<0.01 general symptom scale: 31.0 vs 26.0, p<0.01 AIMS: 1.7 vs 1.0, p<0.01 SAS: 1.3 vs 1.0, p<0.01 Perceived effects (n=20) frequency of sexual thoughs fewer: 45% vs 35% no effect: 55% vs 55% more: 0% vs 10% amount of vaginal lubrication decreased: 50% vs 20% no effect: 50% vs 70% increased: 0% vs 10% ability to have orgasm decreased: 40% vs 20% no effect: 60% vs 70% increased: 0% vs 10% satisfaction with sex decreased: 45% vs 20% no effect: 50% vs 70% increased: 5% vs 10% Serum prolactin concentration baseline vs 2 weeks: 132.2 vs 25.6, p<0.01 baseline vs 4 weeks: 132.2 vs 26.3, p<0.01 baseline vs 6 weeks: 132.2 vs 22.0, p<0.01 baseline vs 8 weeks: 132.2 vs 23.4, p<0.01	

Evidence Table 7. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Data Source	Prospective Retrospective Unclear	Exposure Period	Mean duration of follow-up	Interventions Mean dose
Kopala, 1998	NR	Prospective	NR	more than 6 months	risperidone 3.8 mg/day for more than 6 months
Lasser, 2004	Europe and Canada multicenter trial	Prospective	12 months	239 days	risperidone 25mg, 50mg

Evidence Table 7. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Population	Age Gender Ethnicity	Exposed Eligible Selected	Withdrawn Lost to fu Analyzed
Kopala, 1998	schizophrenia or schizophreniform disorder	Mean age=25.4 years 81% male Ethnicity: NR	NR/NR/41	NR/NR/41
Lasser, 2004	Schizophrenia or schizoaffective disorder	Mean age: 70.9 years 53% male 100% white	725/57/57	NR/1/57

Evidence Table 7. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Effectiveness outcomes
Kopala, 1998	baseline vs endpoint PANSS- 40% change Positive: 27.5 vs 13.4, p<0.005 Negative: 28.2 vs 18.8, p<0.005 Total: 110.4 vs 65.8, p<0.005 ESRS scores: 3.9 vs 1.44, p<0.08 4(10%) required anticholonergic medication at some time during the study >20% reduction in total PANSS score: 76% Disease-related variables- with vs without pre-existing extrapyramidal movement Drug-naive total: 118.1 vs 108.2, NS Drug-naive negative sub-scale: 35.9 vs 26.3, p<0.05
Lasser, 2004	baseline vs change at endpoint, p vs baseline PANSS total: 73±2.1 vs -10.5±1.5, p<0.001 Positive symptoms: 20.6±0.8 vs -3.2±0.6, p<0.001 Negative symptoms: 19.7±0.8 vs -2.8±0.5, p<0.001 Disorganized thoughts: 17.7±0.7 vs -2.0±0.4, p<0.001 Anxiety/depression: 8.2±0.5 vs -1.6±0.4, p<0.001 Hostility/excitement: 6.8±0.4 vs -0.9±0.3, p<0.01 baseline vs endpoint CGI- not ill or with very mild or mild illness: 28% vs 69% CGI- marked or severe illness: 14% vs 0% CGI- at least 1 point improvement in CGI severity scores: 55%

Evidence Table 7. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Safety Outcomes	Comments
Kopala, 1998	0 acute dystonia 2 mild parkinsonism 2 drug induced akathisia	
Lasser, 2004	42(74%) reported adverse events insomnia: 14% constipation: 12% bronchitis: 12% psychosis: 11% rhinitis: 11% 1 died with a myocardial infarction baseline vs mean change at endpoint, p vs baseline ESRS total: 10.2±1.5 vs -3.1±0.8, p<0.001 Patient questionnaire: 4.0±0.7 vs -1.4±0.5, p<0.01 Parkinsonism total: 10.6±1.5 vs -3.6±0.9, p<0.001 Parkinsonism severity: 1.7±0.2 vs -0.4±0.2, p<0.05 Dyskinesia total: 2.7±0.7 vs -0.6±0.3, NS	

Evidence Table 7. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Data Source	Prospective Retrospective Unclear	Exposure Period	Mean duration of follow-up	Interventions Mean dose
Lindstrom, 1995	14 study centers	Prospective	NR	1-2 years	risperidone 9.4 mg/day for 1 year follow up and 8 mg/day for 2 year follow up
MacKay 1998 England	Database: Prescription Pricing Authority - Questionnaire to GPs	Unclear	July 1993 to April 1996	≥ 6 months	Risperidone

Evidence Table 7. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Population	Age Gender Ethnicity	Exposed Eligible Selected	Withdrawn Lost to fu Analyzed
Lindstrom, 1995	Schizophrenia	Mean age=37.4 years 39.2% male Ethnicity: NR	NR/NR/59	13/NR/59
MacKay 1998 England	Schizophrenia/psychosis	Mean age Males=38.8 Females=50.5 Sex NR for 0.8% patients Race NR	NR 14,282 9174 questionnaires returned	1490 void 7684 questionnaires analyzed

Evidence Table 7. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Effectiveness outcomes
Lindstrom, 1995	baseline vs endpoint Total PANSS: 88.2±17.7 vs 68.1±22.6, p<0.001 PANSS positive: 14.6±5.2 vs 11.6±5.5, p<0.001 PANSS Negative: 26.0±7.7 vs 19.1±7.1, p<0.001 PANSS excited: 7.5±3.5 vs 6.3±4.0, p<0.01 PANSS anxiety/depressive: 13.7±5.2 vs 9.7±4.1, p<0.001 PANSS cognitive: 14.2±4.7 vs 11.7±5.4, p<0.01 CGI: 3.7±1.2 vs 2.9±1.6, p<0.001 >=20% reduction in total PANSS: 32(54%) CGI severity mild or not ill: 12% vs 42% moderate: 29% vs 20% severe: 58% vs 34% ESRS- questionnaire: 3.9+3.9 vs 2.1+2.4, p<0.001 ESRS- parkinsonism: 6.6+5.8 vs 3.6+3.9, p<0.001 ESRS- dystonia: 0.4±1.2 vs 0.1±0.3, NS ESRS- dyskinesia: 1.9±3.0 vs 0.8±1.8, NS ESRS- parkinsonism+dystonia+dyskinesia: 8.9±8.4 vs 4.5±5.1, p<0.001 Social function: pretreatment vs treatment 1 year follow-up: 5.6±2.0 vs 5.8±2.0 2 year follow-up 1 year treatment: 5.4±2.0 vs 6.4±2.0, p<0.01 2 year treatment: 5.8±1.8 vs 6.6±2.1, p<0.001
MacKay 1998 England	NR

Evidence Table 7. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Safety Outcomes	Comments
Lindstrom, 1995	NR	
MacKay 1998 England	Deaths=221 (2.9%) NMS 1 case Tardive dyskinesia 1 case (0.01%)	Age

Evidence Table 7. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Data Source	Prospective Retrospective Unclear	Exposure Period	Mean duration of follow-up	Interventions Mean dose
Madbusoodanan, 1999	14 psychiatric centers	Prospective	NR	12 weeks	risperidone 2.4 mg/day for mean duration 72.5 days
Malla 2001 International	Naturalistic clinical sample of patients	Retrospective	Risperidone=1993 to 1997 CAPD=1991 to 1997	Risperidone=1.9 years CAPD=2.7 years	Risperidone 2.5 mg CAPD 228.7 mg

Evidence Table 7. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Population	Age Gender Ethnicity	Exposed Eligible Selected	Withdrawn Lost to fu Analyzed
Madbusoodanan, 1999	Schizophrenia or schizoaffective disorder	Mean age=70.8 years 50% male 75% white; 17% black; 7% hispanic	NR/NR/103	NR/NR/103
Malla 2001 International	Schizophrenia, first episode	Mean age=28 65.8% male Race NR	NR NR 38	NR NR 38

Evidence Table 7. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Effectiveness outcomes
Madbusoodanan, 1999	ESRS scores at baseline vs worse score during treatment vs endpoint (mean changes) questionnaire: 4.73 vs 5.86(+1.14**) vs 3.16(-1.57**) EPRS total: 12.85 vs 15.17(+2.32**) vs 9.43(-3.43**) CGI severity of dyskinesia: 2.52 vs 2.99(+0.47**) vs 2.24(-0.28*) CGI severity of parkinsonism: 3 vs 3.39(+0.39**) vs 2.56(-0.44**) (*p<0.05; **p<0.001) PANSS changes from baseline to enpoint- all patients vs <=3 mg/day vs >3 mg/day Total PANSS: -11.4** vs -13** vs -7321** Positive symptoms: -3.8** vs -4.1** vs -2.9* Negative symptoms: -2.4** vs -2.8** vs -1.3* General psychopathology: -5.3** vs -6.1** vs -3.1* BPRS: -6.8** vs -7.6** vs -4.7** (*p<0.05; **p<0.001 vs baseline) Responders: PANSS- ≥20% decrease: 55% CGI- change score of ≥3: 62% Both: 45% CGI changes from baseline to enpoint- all patients vs <=3 mg/day vs >3 mg/day CGI severity score: -0.76* vs -0.89* vs -0.39 (*p<0.05 vs baseline) CGI: 62% patients were improved at endpoint
Malla 2001 International	NR

Evidence Table 7. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Safety Outcomes	Comments
Madbusoodanan, 1999	91(83%) reported adverse events during the study 23 diziness 17 insomnia 15 agitation 15 somnolence 12 injury 11 constipation 10 extrapyramidal disorder 11 discontinued because of adverse events	
Malla 2001 International	Hospitalizations Length of first hospital admission (days)= 11 vs 28.5; p<0.01 Total number of hospital admissions/year=0.12 vs 0.84; p<0.001 % Time spent in hospital=0.23 vs 6.6; p<0.002	First episode

Evidence Table 7. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Data Source	Prospective Retrospective Unclear	Exposure Period	Mean duration of follow-up	Interventions Mean dose
Malla, 1999	a community-focused outpatient program	Retrospective	NR	NR	risperidone mean 20 months

Evidence Table 7. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Population	Age Gender Ethnicity	Exposed Eligible Selected	Withdrawn Lost to fu Analyzed
Malla, 1999	Schizophrenia	Mean age=31.7 years 68% male Ethnicity: NR	98/49/31	NR/NR/31

Evidence Table 7. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Effectiveness outcomes
Malla, 1999	Before vs after the switch to risperidone Syndrome ratings: reality distortion: 3.47 vs 1.71, p<0.0001 disorganization: 3.40 vs 1.32, p<0.0001 psychomotor poverty: 4.13 vs 3.42, p<0.001 Proportion of time syndrome present reality distortion: 48.77 vs 21.23, p<0.0001 disorganization: 32.63 vs 6.52, p<0.0001 psychomotor poverty: 62.33 vs 51.94, p,0.01 no. of admissions per year: 0.018 vs 0.0004, p<0.01 no. of days in hospital: 0.29 vs 0.0003, p<0.01 22(71%) patients had a positive response on rating reality distortion, whereas 9(29%) showed no response 17(55%) patients had a reduction of more than 40% from their previous score for reality distortion symptoms Social stability characteristics- before vs after risperidone: no. (%) Employment- full time: 2(6.5) vs 3(9.7) part time: 3(9.7) vs 3(9.7) Income support- self-employed: 3(9.7) vs 4(12.9) disability benefits from employment: 7(22.6) vs 3(9.7) parents/partners: 9(29.0) vs 6(19.4) social assistance/disability: 12(38.7) vs 16(51.6) Living circumstances alone: 9(29.0) vs 11(35.5)

Evidence Table 7. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Safety Outcomes	Comments
Malla, 1999	expressive automatic movements: 6 bradykinesia: 2 rigidity: 7 tremor: 4 sialorrhea: 3 postural instability: 2 akathisia of moderate severity: 2 moderate level of dystonia: 2 moderate akathisia: 1 before vs after switching to risperidone (number of patients) dyskinesia: 2 vs 1 akathisia: 4 vs 2 dystonia: 4 vs 2 (improved)	switch from typical antisychotic agents to risperidone

Evidence Table 7. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Data Source	Prospective Retrospective Unclear	Exposure Period	Mean duration of follow-up	Interventions Mean dose
Reveley, 2004	30 UK specialist psychiatric units	Prospective	NR	52 weeks	risperidone for 52 weeks most common dose = 6 mg/day
Still, 1996	a 400-bed state psychiatric hospital	Prospective	April to August 1994	12 weeks	Risperidone titrated a week to 3mg twice daily. The mean dosage for the five subjects who completed 12 weeks treatment is 7.6 mg at week 9 and 8 mg at week 12.
Werapongset, 1998	6 psychiatric hospitals	Prospective	NR	8 weeks	Risperidone was titrated from 1 mg bid and increased to a maximum of 6 mg/day within 3 days.

Evidence Table 7. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Population	Age Gender Ethnicity	Exposed Eligible Selected	Withdrawn Lost to fu Analyzed
Reveley, 2004	chronic schizophrenia	Mean age=41.4 years 51.9% male 89.9% caucasian; 1.3% hispanic; 2.5% black; 1.3% orental; 5.1% other	NR/100/80	1/0/79
Still, 1996	Schizophrenia or schizoaffective disorder	Mean age=41.2 years 60% male Ethnicity: NR	NR/NR/10	5/0/5
Werapongset, 1998	chronic schizophrenia	NR	NR/NR/120	15/NR/105

Evidence Table 7. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Effectiveness outcomes
Reveley, 2004	Positive and Negative Syndrome Scale (PANSS): change from baseline, p positive: -1.5, paired t test p=0.046; wilcoxon test p=0.0119 negative: -3.2, paired t test p<0.0001 general psychopathology, paired t test p=0.0002 total: -9.2, paired t test p=0.0002 CGI Severity: change from baseine, p -0.6, wilcoxon test p=0.0003 Cognitive function: change from baseline, p letter fluency totals: 3.3, p=0.0044 category fluency totals: 0.8, NS category repetitions: 0.0, NS category intrusions: -0.2, NS letter repetitions: 0.3, NS letter intrusions: 0.0, NS Patients acceptability; change from baseline, p 0.7, p=0.0007
Still, 1996	No subjects improved after being switchd to risperidone PANSS, LPCF increased from baseline, but no significant changes: patients who were switched from clozapine tended to wersen 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 cgabge at week 6 through week 12 (data NR) CGI scores: 2 no change; 3 minimally worse; 4 much worse; 1 very much worse
Werapongset, 1998	Total PANSS scores decreased: baseline vs week 4; baseline vs week 8: 90.6 vs 73.4, p<0.00001; 90.6 vs 61.9, p<0.00001 PANSS positive symptoms subscale decreased significantly from baseline (data NR) PANSS negative symptoms subscale decreased: baseline vs week 4; baseline vs week 8 25.4 vs 21.2, p<0.00001; 25.4 vs 17.9, p<0.0001 PANSS General psychopathological subscale decreased significantly from baseline (data NR) PANSS other subscales decreased signigicantly from baseline (data NR) PANSS responders- >20% reduction in total PANSS scores: 74% >40% rated as good to excellent for the overall impression.

Evidence Table 7. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Safety Outcomes	Comments
Reveley, 2004	41 (51.9%) did not complete the study, 10 (12.7%) due to adverse events 38 (48.1%) were classfied as a sustained treatment success, 29(36.7%) as treatment failure, and 12(15.2%) as not evaluable 68(86.1%) patients reported a total of 623 adverse events 13(16.5%) reported a serious adverse event 51(64.6%) reported at least 1 adverse event 17(21.5%) reported adverse events that lead to a permanent stop in study medication, including schizophrenic reaction, akathisia, agitation, and tremor Involuntary Movement Scale (AIMS): change from baseline, p -2.8, wilcoxon test p<0.0001 Targeting Abnormal Kinetic Effects Scale (TAKE): change from baseline, p -2.3, p<0.0001	
Still, 1996	3 decreased concentration 3 impaired memory 4 irritability 3 akathisia, confusion Akathesia scale showed significant different worsening of symptoms	Patients switched from clozapine to risperidone
Werapongset, 1998	24(22.9%) required medications for EPS side effect. 15(14.3%) insomnia 5(4.8%) elevated hepatic enzyme 2%(1.9%) weight gain No change in blood pressure or heart rate	

Evidence Table 7. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Data Source	Prospective Retrospective Unclear	Exposure Period	Mean duration of follow-up	Interventions Mean dose
Ziprasidone					
Kingsbury, 2001	Multicenter	Prospective	NR	6 weeks	Ziprasidone 62.16 mg bid for 6 weeks
Weiden, 2003	multicenter parallel	Prospective	6 weeks	6 weeks	Ziprasidone mean 91 mg/day

Evidence Table 7. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Population	Age Gender Ethnicity	Exposed Eligible Selected	Withdrawn Lost to fu Analyzed
Ziprasidone				
Kingsbury, 2001	Schizophrenia or schizoaffective disorders	Mean age=35.88 years 70.25 male 13.5% black; 16.2% white; 62.1% hispanic; 5.4% asian; 2.7% other	NR/NR/37	NR/NR/37
Weiden, 2003	Schizophrenia	Mean age=37.5 years 66% male Ethnicity: NR	NR/NR/NR	NR/NR/270

Evidence Table 7. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Effectiveness outcomes
Ziprasidone	
Kingsbury, 2001	NR
Weiden, 2003	NR

Evidence Table 7. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Safety Outcomes	Comments
Ziprasidone		
Kingsbury, 2001	baseline vs week 6 BMI: 30.06 vs 29.82, p=0.96 glucose: 104.97 vs 100.97, p=0.26 cholesterol: 210.65 vs 183.08, p<0.001 triglycerides: 262.68 vs 176.30, p=0.018	
Weiden, 2003	<u>olazapine switch to ziprasidone</u> weight loss, mean: NR, p<0.0001 weight loss for women: 1.85kg, p<0.001 weight loss for men: 1.58kg, p<0.001 BMI decreased: 31.7-31.1, p<0.0001 triglycerides: -50mg/dL, p<0.0001 total cholesterol; -17mg/dL, p<0.0001 total cholesterol declined in 76% patients reduction in prolactin levels: p<0.05 <u>risperidone switch to ziprasidone</u> weight loss, mean: 0.86, p<0.02 BMI decreased: 29.6-29.3, p<0.02 triglycerides: -29mg/dL, p<0.01 total cholesterol; -12mg/dL, p<0.005 total cholesterol declined in 72% patients reduction in prolactin levels: p<0.0001 improvement in Simpson-Angus scores: p<0.01 decreased concomitant antiparkinsonian drug use: 26% to 8.6% <u>Conventional antipsychotics to ziprasidone</u> weight loss, mean: 0.27kg, p=0.03 BMI increased; 0.08, p=0.3334 NS change in tryglycerides and cholesterol reduction in prolactin levels: p=NS improvement in Simpson-Angus scores: p<0.0001 decreased concomitant antiparkinsonian drug use: 58% to 14.8% insomnia is the most frequent side effect associated with ziprasidone: 21%-42% discontinuations due to AEs, switch from olanzapine, risperidone, and conventional antipsychotics: 6%, 9% and 1	patients switched from olanzapine, risperidone or conventional antipsychotics to ziparasidone

Evidence Table 7. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Data Source	Prospective Retrospective Unclear	Exposure Period	Mean duration of follow-up	Interventions Mean dose
Any Atypical Antipsychotic					
Ramaswamy 2003 United States	Database: California Medicaid claims data (Medi-Cal)	Retrospective	July 1997 to September 2000	Patients were categorized by exposure as follows: ≤ 30 days > 30 to ≤90 days > 90 to ≤ 180 days > 180 to ≤ 360 days ≤ 360 days Duration of exposure was calculated as follows: For patients with a DKA event, the maximum potential exposure was calculated as the numbers of days between initiation of the antipsychotic and the first DKA event; for patients without a DKA event, the number of days with any antipsychotic therapy between initiation of antipsychotic therapy and the end of the study were summed	NR

Evidence Table 7. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Population	Age Gender Ethnicity	Exposed Eligible Selected	Withdrawn Lost to fu Analyzed
Any Atypical Antipsychotic				
Ramaswamy 2003 United States	Schizophrenia and bipolar disorder patients (identified by ICD-9-CM codes) who were initial users of atypical antipsychotic agents (I.e., those who first prescription claim occurred at least 6 months after the study start)		141,286 exposed NR Selected=102,552 risperidon 51,285 olanzapine 51,267	NR NR 102,552 analyzed

Evidence Table 7. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Effectiveness outcomes
Any Atypical Antipsychotic	
Ramaswamy 2003 United States	NR

Evidence Table 7. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Safety Outcomes	Comments
Any Atypical Antipsychotic		
Ramaswamy 2003 United States	Incidence rate of diabetic ketoacidosis (DKA) (incident cases of DSK per 10,000): Clozapine (n=816): 12.25 Olanzapine (n=51,302): 10.72 Quetiapine (n=7,086): 5.64 Risperidone (n=51,330): 6.04 Number of cases per 10,000 within exposure categories: olanzapine, risperidone, p-value ≤ 30 days: 6.6, 5.4, p=NS > 30 to ≤90 days: 7.6, 8.8, p=NS > 90 to ≤ 180 days: 6.3, 6.8, p=NS > 180 to ≤ 360 days: 16.9, 4.5, p<0.05 ≤ 360 days: 17.4, 5.4, p<0.05 Odds of developing DKA: logistic model results (100% dataset): Odds ratio (95% CI), p-value Olanzapine monotherapy (risperidone): 1.623 (1.047-2.560), p=0.033 Age (years): 0.987 (0.975-0.999), p=0.036 African-American race (Caucasion): 1.764 (1.037-2.944), p=0.032 Schizophrenia (no schizophrenia): 2.216 (1.400-3.467), p=0.001 Diabetes prior to atypical use (no diabetes prior to atypical use): 9.643 (6.066-15.341), p<0.0001 Odds of developing DKA according to duration of drug exposure, logistic model results Patients with > 180 days' exposure Olanzapine monotherapy (risperidone): 3.515 (1.739-7.888), p=0.001 Age (years): 0.970 (0.95-0.988), p=0.001 Diabetes prior to treatment (no diabetes): 8.890 (4.506-17.212), p<0.0001	

Evidence Table 7. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Data Source	Prospective Retrospective Unclear	Exposure Period	Mean duration of follow-up	Interventions Mean dose
Herrman et al, 2004 Canada	Database: administrative health care databases in Ontario, Canada	Retrospective	April 1, 1997 through March 31, 2002	NR	Risperidone Olanzapine Typical antipsychotics
Kozma 2004 (poster) United States	Database: Medstat's Medicaid database	Retrospective	1999-2002	NR	Atypical antipsychotics overall Olanzapine Risperidone Quetiapine Haloperidol Benzodiazepines

Evidence Table 7. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Population	Age Gender Ethnicity	Exposed Eligible Selected	Withdrawn Lost to fu Analyzed
Herrman et al, 2004 Canada	Patients over age 65 who were given at least 2 successive prescriptions and received enourgh drug for at least 30 days of observation.	Mean age approximately 82 years (SD 7.5) 69% female Ethnicity not reported	NR NR 11,400	NR NR 11,400
Kozma 2004 (poster) United States	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-month 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.	NR NR 26,456	NR NR 26,456

Evidence Table 7. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Effectiveness outcomes
Herrman et al, 2004 Canada	NR
Kozma 2004 (poster) United States	NR

Evidence Table 7. 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 years: 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)	
Kozma 2004 (poster) United States	Stroke-related event (defined as an acute inpatient hospital admission for a stroke-related event within 90 days 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.	

Evidence Table 8. Quality assessment of observational studies in patients with schizophrenia

Author, year	Non-biased selection?	Low overall loss to follow-up?	Outcomess pre-specified and defined?	Ascertainment techniques adequately described?*	Non-biased and adequate ascertainment methods?
Controlled studies					
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
Agelink, 2001	Method NR, unable to determine.	Yes (9%)	Yes	Yes	Yes
Allan, 1998	Method NR, unable to determine.	Unable to determine, N not reported for analyses ("Sample size varied across analyses depending on the completeness of data for each subject")	Yes	Yes	Yes- states "double blind assessments"
Al-Zakwani, 2003	No, excluded patients who had a behavioral health benefit carve-out and those who were not continuously enrolled for 18 months	No withdrawals reported.	Yes	Yes	NR
Barak 2004	No, excluded patients without treatment charts	Yes (retrospective study)	Yes	Yes	Unclear if database/patient chart reviewer was blind to suicide status
Barner 2004 United States					

Evidence Table 8. Quality assessment of observational studies in patients with schizophrenia

Author, year	Statistical analysis of potential confounders?	Adequate duration of follow-up?	Adequate sample size?	Overall quality assessment	Comments
Controlled studies					
Advokat, 2004	No and only baseline demographic data reported; unclear if differences in prognostic factors	Yes	Power calculation NR (N=100)	Poor	
Agelink, 2001	Yes	Yes	No power calculation reported (N=56)	Fair	
Allan, 1998	No	Yes (6 weeks)	No power calculation reported (N=23)	Poor- unable to determine number analyzed, small sample and no power calculation, no control for potential confounding factors and limited baseline data reported, unable to determine if	
Al-Zakwani, 2003	Yes	Yes	No power calculation reported (N=469)	Fair	
Barak 2004	No; only commented regarding similarities in gender, age, distribution of diagnoses	Unclear	No power calculation (N=378)	Fair	
Barner 2004 United States					

Evidence Table 8. Quality assessment of observational studies in patients with schizophrenia

Author, year	Non-biased selection?	Low overall loss to follow-up?	Outcomess pre-specified and defined?	Ascertainment techniques adequately described?*	Non-biased and adequate ascertainment methods?
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
Bobes, 2003	Not clear- consecutive patients enrolled, but more quetiapine patients excluded for noneligibility (18.9%, vs 5.8% haloperidol, 3.0% olanzapine, and 2.5%	Yes	Yes	Yes	Not blinded or independent, care provider did assessments.
Bobes, 2003	Not clear- consecutive patients enrolled, but more quetiapine patients excluded for noneligibility (18.9%, vs 5.8% haloperidol, 3.0% olanzapine, and 2.5% risperidone)	Yes	Yes	Yes	Not blinded or independent, care provider did assessments.
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
Buckley, 1997	NR	No withdrawals reported	Yes	Yes	No

Evidence Table 8. Quality assessment of observational studies in patients with schizophrenia

Author, year	Statistical analysis of potential confounders?	Adequate duration of follow-up?	Adequate sample size?	Overall quality assessment	Comments
Bobes 2003b	Partial; only covariates were baseline score and years since diagnosis	Yes	No power calculation (N=158)	Poor	
Bobes, 2003	Yes	Yes (at least 4 weeks)	No power calculation (N=636)	Fair	
Bobes, 2003	Yes	Yes (at least 4 weeks)	No power calculation (N=636)	Fair	
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	Power calculation NR (N=90)	Poor	
Buckley, 1997	No	Yes	Power calculation NR (n=27)	Poor	

Evidence Table 8. Quality assessment of observational studies in patients with schizophrenia

Author, year	Non-biased selection?	Low overall loss to follow-up?	Outcomess pre-specified and defined?	Ascertainment techniques adequately described?*	Non-biased and adequate ascertainment methods?
Caracci, 1999 (inpatients)	Yes	Withdrawals not reported	Yes	Yes	NR
Caro 2002 Quebec	Yes	NR	Yes	Yes	Yes
Chouinard, 1997					
Conley 1999 United States	Yes	NR	Yes	Yes	Yes
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
de Leon, 2004					
Dinakar, 2002	Method NR, unable to determine.	Yes	Yes	Yes	Not reported if blind or independent assessment of outcomes.
Etminan 2003 Ontario	No	NR	Yes	Yes	Yes

Evidence Table 8. Quality assessment of observational studies in patients with schizophrenia

Author, year	Statistical analysis of potential confounders?	Adequate duration of follow-up?	Adequate sample size?	Overall quality assessment	Comments
Caracci, 1999 (inpatients)	No and patients in control group were significantly older	Yes	Power calculation NR (n=40)	Poor	
Caro 2002 Quebec	Yes	Yes		Fair	Between-group differences in age, gender, other characteristics
Chouinard, 1997					
Conley 1999 United States	Yes	Yes		Fair	
Coulter 2001 International	NR	Unclear		Poor	
de Haan, 1999	No; only commented regarding between-groups comparability for sex, age at admission and diagnosis	Yes	No power calculation (n=108)	Poor	
de Haan, 2002	No and there was no information about between-groups comparability of baseline characteristics	Yes	No power calculation (n=113)	Poor	
de Leon, 2004					
Dinakar, 2002	No	Yes	No power calculation (N=79)	Poor- no control for confounding factors, not reported if outcome assessors blinded or independent, unable to	
Etminan 2003 Ontario	Yes	NR		Poor	Diabetic events nr for 266 patients (reason nr)

Evidence Table 8. Quality assessment of observational studies in patients with schizophrenia

Author, year	Non-biased selection?	Low overall loss to follow-up?	Outcomess pre-specified and defined?	Ascertainment techniques adequately described?*	Non-biased and adequate ascertainment methods?
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)
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)
Garcia-Cabeza 2003 Spain Subjective Response Analysis from EFESO					
Gianfrancesco 2002 United States	Yes	NR	Yes	No	Yes

Evidence Table 8. Quality assessment of observational studies in patients with schizophrenia

Author, year	Statistical analysis of potential confounders?	Adequate duration of follow-up?	Adequate sample size?	Overall quality assessment	Comments
Feldman, 2004; Buse, 2003	Yes	Yes	No power calculation (N=30,953)	Fair	
Fuller 2003	Yes	Yes		Fair	
Ganguli, 2001	No	Yes (4 months)	No power calculation (N=100)	Fair	
Garcia-Cabeza 2003 Spain Subjective Response Analysis from EFESO					
Gianfrancesco 2002 United States	Yes	Yes		Fair	

Evidence Table 8. Quality assessment of observational studies in patients with schizophrenia

Author, year	Non-biased selection?	Low overall loss to follow-up?	Outcomess pre-specified and defined?	Ascertainment techniques adequately described?*	Non-biased and adequate ascertainment methods?
Gianfrancesco 2003a United States	Yes	NR	Yes	No	Yes
Gianfrancesco 2003b United States	Yes	NR	Yes	No	Yes
Gomez 2000 Spain Estudio Farmacoepidemiologico en esquizofrenia con Olanzapine (EFESO)	Yes	Yes	Yes	No	Unclear
Gupta, 2004 Hayhurst 2002					
Hedenmalm, 2002	Yes	Yes (retrospective study)	Yes	Yes	Not stated if blinded or independent assessment of outcomes
Hennessy, 2002	Not clear	Yes (retrospective study)	Yes	Yes	Not reported if independent assessment of outcomes

Evidence Table 8. Quality assessment of observational studies in patients with schizophrenia

Author, year	Statistical analysis of potential confounders?	Adequate duration of follow-up?	Adequate sample size?	Overall quality assessment	Comments
Gianfrancesco 2003a United States	Yes	Yes		Fair	
Gianfrancesco 2003b United States	Yes	Yes		Fair	
Gomez 2000 Spain Estudio Farmacoepidemiologico en esquizofrenia con Olanzapine (EFESO)	Yes	Yes		Fair	
Gupta, 2004					
Hayhurst 2002					
Hedenmalm, 2002	No	Yes	No power calculation reported (N=868)	Fair	
Hennessy, 2002	Yes	Yes	No power calculation reported (N=95,632 cases, 29,086 controls)	Fair	

Evidence Table 8. Quality assessment of observational studies in patients with schizophrenia

Author, year	Non-biased selection?	Low overall loss to follow-up?	Outcomess pre-specified and defined?	Ascertainment techniques adequately described?*	Non-biased and adequate ascertainment methods?
Ho, 1999	Unclear	No	yes	Yes for group in the Longitudinal Study of Recent-Onset Psychosis, No for others	unclear, blinding NR
Javitt, 2002	Unclear; indicates that data was obtained but doesn't indicate how	No loss to follow-up	Yes	No	No
Jeste 1999 United States	Yes	NR	Yes	Yes	Yes
Kane 1993 United States	No	NR	Yes	Yes	Yes
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, 1999					
King 1998 Ireland	Unclear	NR	Yes	No	Unclear

Evidence Table 8. Quality assessment of observational studies in patients with schizophrenia

Author, year	Statistical analysis of potential confounders?	Adequate duration of follow-up?	Adequate sample size?	Overall quality assessment	Comments
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	No	Poor	
Javitt, 2002	Yes	Yes	No power calculation	Fair	
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	
Kane 1993 United States	NR	Yes			Between group differences in gender and diagnosis
Kasper, 2001	Yes	Y	No power calculation reported	Fair	
Killian, 1999					
King 1998 Ireland	NR	Unclear		Poor	

Evidence Table 8. Quality assessment of observational studies in patients with schizophrenia

Author, year	Non-biased selection?	Low overall loss to follow-up?	Outcomess pre-specified and defined?	Ascertainment techniques adequately described?*	Non-biased and adequate ascertainment methods?
Koller, 2003	Yes	Yes	Yes	Yes	Not reported if independent assessment of outcomes.
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.
Kraus, 1999	Yes	Not reported	Yes	Yes	Not reported if independent assessment of outcomes (but outcome was weight, so may be objective)
Kurz 1995 Austria					
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
Lasser, 2004					
Lee 2002 United States	Yes	NR	Yes	Yes	Yes

Evidence Table 8. Quality assessment of observational studies in patients with schizophrenia

Author, year	Statistical analysis of potential confounders?	Adequate duration of follow-up?	Adequate sample size?	Overall quality assessment	Comments
Koller, 2003	No- descriptive summary statistics only.	Yes	No power calculation (N=131)	Fair	
Koro, 2002a	Yes	Yes (3 at least months)	No power calculation reported (N=1268 cases, 7598 controls)	Fair	
Koro, 2002b	Yes	Yes (mean 5.2 years)	No power calculation (N=451 cases, 2696 controls)	Fair	
Kraus, 1999	No	4 weeks- not sure	No power calculation (N=44)	Poor: unclear if all patients analyzed at all time points (no info on dropouts), no control for confounding factors.	
Kurz 1995 Austria					
Lambert, 2005	No	Yes	Power calculation NR; n=12,637	Poor	
Lasser, 2004					
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.

Evidence Table 8. Quality assessment of observational studies in patients with schizophrenia

Author, year	Non-biased selection?	Low overall loss to follow-up?	Outcomess pre-specified and defined?	Ascertainment techniques adequately described?*	Non-biased and adequate ascertainment methods?
Leon, 1979	No; excluded patients that moved out of urban district	None (retrospective study)	Yes	No	Unclear; no information about blinding
Leslie, 2004	Not clear	Yes (retrospective study)	Yes	No	Not reported if blind or independent assessment of outcomes.
Lucey, 2003	Unclear. 396 patients charts reviewed, but selection of these not stated	Yes (retrospective study)	yes	yes	yes
Madhusoodanan, 1999	Yes	None (retrospective)	Yes	No	Unclear; blinding NR
Madhusoodanan, 2004 (inpatients)					
McIntyre 2003 Canada Canadian National Outcomes Measurement Study in Schizophrenia (CNOMSS)	Yes	NR	Yes	No	Unclear
Meyer, 2002	No- excluded patients with incomplete data	Yes (retrospective study)	Yes	Yes	Not reported if independent assessment of outcomes

Evidence Table 8. Quality assessment of observational studies in patients with schizophrenia

Author, year	Statistical analysis of potential confounders?	Adequate duration of follow-up?	Adequate sample size?	Overall quality assessment	Comments
Leon, 1979	N; no baseline differences	Yes	No power calculation	Poor	
Leslie, 2004	No	Yes? (3 months)	No power calculation (N=4132 cases)	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.	
Lucey, 2003	Partially, analysis took into account mean dose and center.	yes, for the outcome measure of time to discharge	Unclear, sample size calculated based on difference in cost - not hospitalization rate	Fair	
Madhusoodanan, 1999 Madhusoodanan, 2004 (inpatients)	No and there were baseline differences	Yes	No power calculation (N=151)	Poor	
McIntyre 2003 Canada Canadian National Outcomes Measurement Study in Schizophrenia (CNOMSS)	Yes	Yes		Fair	
Meyer, 2002	No	Yes (one year)	No power calculation reported (N=94)	Poor- may be biased selection, independent outcome assessment not reported, no control for potential confounding factors.	

Evidence Table 8. Quality assessment of observational studies in patients with schizophrenia

Author, year	Non-biased selection?	Low overall loss to follow-up?	Outcomess pre-specified and defined?	Ascertainment techniques adequately described?*	Non-biased and adequate ascertainment methods?
Miller, 1998	Not clear- identified patients from chart review.	Yes	Yes	Yes	Yes- blinded assessment of EPS
Modai 2000 Israel	Yes	NR	Yes	Yes	Yes
Montes 2003 Spain Sub-group Analysis from EFESO	Yes	Yes	Yes	No	Unclear
Naber, 2001	Method NR, unable to determine.	No (4% missing SWN data, 3% missing PANSS data)	Yes	Yes	Not blinded
Nightengale, 1998					
Ollendorf 2004 United States	Yes	NR	Yes	Yes	Yes
Ostbye 2004	Yes	NR	Yes	Yes	Yes
Peacock 1996 Denmark	No	NR	No	No	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

Evidence Table 8. Quality assessment of observational studies in patients with schizophrenia

Author, year	Statistical analysis of potential confounders?	Adequate duration of follow-up?	Adequate sample size?	Overall quality assessment	Comments
Miller, 1998	Yes	Yes, but time period on medications varied (45.3 months clozapine, 13.4 months risperidone, 92.5 months conventional antipsychotics)	No power calculation reported (N=106)	Fair	
Modai 2000 Israel	Yes	Unclear		Fair	
Montes 2003 Spain Sub-group Analysis from EFESO	Yes	Yes		Fair	
Naber, 2001	Yes	Yes	No power calculation reported (N=100)	Fair	
Nightengale, 1998					
Ollendorf 2004 United States	Yes	Yes		Fair	
Ostbye 2004	Partial: does not control for dose and duration of treatment	Yes		Poor	
Peacock 1996 Denmark	NR	Yes		Poor	
Procyshyn, 1998	No	Yes	Yes	Fair	

Evidence Table 8. Quality assessment of observational studies in patients with schizophrenia

Author, year	Non-biased selection?	Low overall loss to follow-up?	Outcomess pre-specified and defined?	Ascertainment techniques adequately described?*	Non-biased and adequate ascertainment methods?
Reid, 1999					
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)
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
Soyka, 2004 (inpatients)					
Spivak 1998 Israel	Yes	NR	Yes	Yes	Yes

Evidence Table 8. Quality assessment of observational studies in patients with schizophrenia

Author, year	Statistical analysis of potential confounders?	Adequate duration of follow-up?	Adequate sample size?	Overall quality assessment	Comments
Reid, 1999					
Schillevoort, 2001a	Yes	Yes	No power calculation (N=4094)	Fair	
Schillevoort, 2001b	Yes	Yes	No power calculation (N=848)	Fair	
Sernyak, 2002	Yes	Not sure- 4-month period studied.	No power calculation (N=38,632; N with diabetes NR)	Fair	
Sharif, 2000	No	Yes	No power calculation (n=24)	Poor	
Snaterse, 2000	Yes; but no demographics	Yes	No power calculation (N=56)	Fair	
Soyka, 2004 (inpatients)					
Spivak 1998 Israel	NR	Yes		Fair	

Evidence Table 8. Quality assessment of observational studies in patients with schizophrenia

Author, year	Non-biased selection?	Low overall loss to follow-up?	Outcomess pre-specified and defined?	Ascertainment techniques adequately described?*	Non-biased and adequate ascertainment methods?
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
Verma, 2001	No	Yes	Yes	Yes	No, unblided 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
Voruganti, 2001					
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)
Zhao, 2002	Yes	No withdrawals reported	No	Yes	No

Evidence Table 8. Quality assessment of observational studies in patients with schizophrenia

Author, year	Statistical analysis of potential confounders?	Adequate duration of follow-up?	Adequate sample size?	Overall quality assessment	Comments
Taylor, 2003	Yes	Yes	Yes	Fair	
Verma, 2001	No	Unclear, follow-up ended at discharge, but mean duration of inpatient stay not reported	No	Poor	
Voruganti, 2000	No, and there were baseline differences in disease severity (clozapine patients were sicker)	Yes	No power calculation reported	Poor	
Voruganti, 2001					
Wang, 2002 U.S.	Yes			Fair	
Weiser, 2000	Controlled for age only.	N/A (case-control) Yes	No power calculation reported (N=76)	Fair	
Wirshing, 2002	Yes	Yes (tests within 2 1/2 years included)	No power calculation reported (N=215)	Fair	
Zhao, 2002	Yes	Yes	No power calculation reported (N=1,333)	Fair	

Evidence Table 8. Quality assessment of observational studies in patients with schizophrenia

Author, year	Non-biased selection?	Low overall loss to follow-up?	Outcomess pre-specified and defined?	Ascertainment techniques adequately described?*	Non-biased and adequate ascertainment methods?
Uncontrolled studies					
Clozapine					
Advokat, 1999					
Alvarez 1997 Spain	No: AE withdrawals during first 3 weeks not included	NR	Yes	Yes	Yes
Atkin 1996 UK/Ireland	Yes	NR	Yes	Yes	Yes
Breier, 1993					
Brar, 1997					
Buckman 1999 United States	Unclear	NR	No	No	Unclear
Bunker, 1996					
Cassano, 1997					
Ciapparelli, 2000					
Conley, 1997					
Deliliers 2000 Italy	Yes	NR	Yes	Yes	Yes
Devinsky 1991 United States	Yes	NR	Yes	No	Unclear
Drew 1999 Australia	Yes	NR	Yes	Yes	Yes
Drew 2002 Australia	Yes	NR	Yes	Yes	Yes
Frankenburg, 1992					

Evidence Table 8. Quality assessment of observational studies in patients with schizophrenia

Author, year	Statistical analysis of potential confounders?	Adequate duration of follow-up?	Adequate sample size?	Overall quality assessment	Comments
Uncontrolled studies					
Clozapine					
Advokat, 1999					
Alvarez 1997 Spain	NR	Yes		Fair	
Atkin 1996 UK/Ireland	NR	Yes		Fair	
Breier, 1993					
Brar, 1997					
Buckman 1999 United States	NR	Unclear		Poor	
Bunker, 1996					
Cassano, 1997					
Ciapparelli, 2000					
Conley, 1997					
Deliliers 2000 Italy	NR	Unclear		Fair	
Devinsky 1991 United States	Yes	Unclear		Fair	
Drew 1999 Australia	NR	Yes		Fair	Preliminary results of Drew 2002
Drew 2002 Australia	NR	Yes		Fair	
Frankenburg, 1992					

Evidence Table 8. Quality assessment of observational studies in patients with schizophrenia

Author, year	Non-biased selection?	Low overall loss to follow-up?	Outcomess pre-specified and defined?	Ascertainment techniques adequately described?*	Non-biased and adequate ascertainment methods?
Frankle, 2001					
Gordon, 1996					
Hagg 1998 Sweden	Yes	NR	Yes	Yes	Yes
Henderson 2000 United States	Yes	NR	Yes	Yes	Yes
Hofer, 2003					
Honer, 1995					
Honigfeld 1996 United States	Yes	NR	Yes	Yes	Yes
Honigfeld, 1990					
Kane, 1994					
Kranzler, 2005					
Koller, 2001					
Laker 1998 London	Yes	NR	Yes	No	Unclear
Lamberti, 1992					
Leadbetter, 1992					
Lieberman 1992 Alvir 1993 United States	Yes	NR	No	No	Unclear
Lund 2001 United States	Yes	NR	Yes	Yes	Yes
Manschreck, 1999					
Nair, 1999					
Pacia 1994 United States	Yes	NR	Yes	Yes	Yes
Rastogi, 2000					
Reid 1998 United States	Unclear	NR	Yes	No	Unclear
Reid, 1998	Yes	Yes (retrospective study)	Yes	Yes	Not reported if blind or independent assessment of outcomes.

Evidence Table 8. Quality assessment of observational studies in patients with schizophrenia

Author, year	Statistical analysis of potential confounders?	Adequate duration of follow-up?	Adequate sample size?	Overall quality assessment	Comments
Frankle, 2001					
Gordon, 1996					
Hagg 1998 Sweden	No	N/A, cross-sectional study		Fair	
Henderson 2000 United States	Yes	Yes		Fair	
Hofer, 2003					
Honer, 1995					
Honigfeld 1996 United States	NR	Yes		Fair	
Honigfeld, 1990					
Kane, 1994					
Kranzler, 2005					
Koller, 2001					
Laker 1998 London	NR	Yes		Fair	
Lamberti, 1992					
Leadbetter, 1992					
Lieberman 1992 Alvir 1993 United States	Yes	Yes		Fair	
Lund 2001 United States	Yes	Yes		Good	
Manschreck, 1999					
Nair, 1999					
Pacia 1994 United States	Yes	Unclear		Fair	
Rastogi, 2000					
Reid 1998 United States	NR	Unclear		Poor	
Reid, 1998	No	Yes	No power calculation (N=866)	Fair	

Evidence Table 8. Quality assessment of observational studies in patients with schizophrenia

Author, year	Non-biased selection?	Low overall loss to follow-up?	Outcomess pre-specified and defined?	Ascertainment techniques adequately described?*	Non-biased and adequate ascertainment methods?
Sajatovic 2000 United States	Yes	NR	No	No	Unclear
Tandon, 1993					
Taylor, 2000					
Umbricht 1994 United States	No	NR	Yes	Yes	Yes
Wilson 1992 United States First paper in a series studying clozapine-treated pts in Dammasch State Hospital; this study analyzed the pts entered into the cohort in the first 6 months	Yes	NR	No	No	Unclear
Wilson 1993 United States Second paper in a series studying clozapine-treated pts in Dammasch State Hospital; this study analyzed the pts entered into the cohort in the first year					
Zito, 1993					
Olanzapine					
Biswas, 2001					
Chengappa 2005					
Conley, 1998					
Del Paggio, 2002					
Dennehy 2003					
Dossenbach, 2000					
Dossenbach, 2001					
Dunlop 2003					
Dursun, 1999					
Edar, 2001					
Gilchrist, 2002					
Gonzalez-Pinto 2001					
Hennen 2004					

Evidence Table 8. Quality assessment of observational studies in patients with schizophrenia

Author, year	Statistical analysis of potential confounders?	Adequate duration of follow-up?	Adequate sample size?	Overall quality assessment	Comments
Sajatovic 2000 United States	NR	Unclear		Fair-Poor	
Tandon, 1993					
Taylor, 2000					
Umbricht 1994 United States	Yes	Yes		Fair	
Wilson 1992 United States First paper in a series studying clozapine-treated pts in Dammasch State Hospital; this study analyzed the pts entered into the cohort in the first 6 months	NR	Yes		Fair	
Wilson 1993 United States Second paper in a series studying clozapine-treated pts in Dammasch State Hospital; this study analyzed the pts entered into the cohort in the first year					
Zito, 1993					
Olanzapine					
Biswas, 2001					
Chengappa 2005					
Conley, 1998					
Del Paggio, 2002					
Dennehy 2003					
Dossenbach, 2000					
Dossenbach, 2001					
Dunlop 2003					
Dursun, 1999					
Edar, 2001					
Gilchrist, 2002					
Gonzalez-Pinto 2001					
Hennen 2004					

Evidence Table 8. Quality assessment of observational studies in patients with schizophrenia

Author, year	Non-biased selection?	Low overall loss to follow-up?	Outcomess pre-specified and defined?	Ascertainment techniques adequately described?*	Non-biased and adequate ascertainment methods?
Ishigooka, 2001					
Koller, 2002					
Janenawasin 2002					
Lasser, 2004					
Lindenmayer, 2001					
Lindenmayer, 2002					
McElroy 1998					
Smith, 2001					
Vieta 2002					
Zarate 1998					
Quetiapine					
Brechar, 2000					
Buckley, 2004					
Kasper, 2004					
Sacchetti, 2003					
Sax, 1998	Method NR, unable to determine.	No	Yes	Yes	Not reported if blind or independent assessment of outcomes.
van der Heijden, 2003					
Wetzel, 1995					
Risperidone					
Albright, 1996					
Bahk 2004					
Brunelleschi, 2003					
Chengappa, 2000					
Daradkeh, 1996					
Dickson, 1999					
Finley, 1998					
Franckiewicz, 2002					
Guest, 1996					
Jeste, 1997					

Evidence Table 8. Quality assessment of observational studies in patients with schizophrenia

Author, year	Statistical analysis of potential confounders?	Adequate duration of follow-up?	Adequate sample size?	Overall quality assessment	Comments
Ishigooka, 2001					
Koller, 2002					
Janenawasin 2002					
Lasser, 2004					
Lindenmayer, 2001					
Lindenmayer, 2002					
McElroy 1998					
Smith, 2001					
Vieta 2002					
Zarate 1998					
Quetiapine					
Brechar, 2000					
Buckley, 2004					
Kasper, 2004					
Sacchetti, 2003					
Sax, 1998	No	Yes	No power calculation (N=22)	Poor- no control for confounding factors, not reported if outcome assessors blinded or independent, unable to determine if selection was unbiased.	
van der Heijden, 2003					
Wetzel, 1995					
Risperidone					
Albright, 1996					
Bahk 2004					
Brunelleschi, 2003					
Chengappa, 2000					
Daradkeh, 1996					
Dickson, 1999					
Finley, 1998					
Franckiewicz, 2002					
Guest, 1996					
Jeste, 1997					

Evidence Table 8. Quality assessment of observational studies in patients with schizophrenia

Author, year	Non-biased selection?	Low overall loss to follow-up?	Outcomess pre-specified and defined?	Ascertainment techniques adequately described?*	Non-biased and adequate ascertainment methods?
Kaneda, 2001					
Kim, 2002					
Kopala, 1998					
Lindstrom, 1995					
MacKay 1998	Yes	NR	No	No	Unclear
England					
Madbusoodanan, 1999					
Malla 2001	Yes	NR	Yes	Yes	Yes
International					
Malla, 1999					
Reveley, 2004					
Still, 1996					
Vieta 2004					
Werapongset, 1998					
Ziprasidone					
Kingsbury, 2001					
Weiden, 2003					
Any Atypical Antipsychotic					
Ramaswamy 2003					
United States					
Herrman et al, 2004					
Canada					
Kozma 2004 (poster)	Yes	NR	Yes	Yes	Yes
United States					

Evidence Table 8. Quality assessment of observational studies in patients with schizophrenia

Author, year	Statistical analysis of potential confounders?	Adequate duration of follow-up?	Adequate sample size?	Overall quality assessment	Comments
Kaneda, 2001					
Kim, 2002					
Kopala, 1998					
Lindstrom, 1995					
MacKay 1998	NR	Yes		Fair	
England					
Madbusoodanan, 1999					
Malla 2001	NR	Yes		Fair	
International					
Malla, 1999					
Reveley, 2004					
Still, 1996					
Vieta 2004					
Werapongset, 1998					
Ziprasidone					
Kingsbury, 2001					
Weiden, 2003					
Any Atypical Antipsychotic					
Ramaswamy 2003					
United States					
Herrman et al, 2004					
Canada					
Kozma 2004 (poster)	Yes	Unclear		Fair	
United States					

Evidence Table 9. Randomized controlled trials in patients with bipolar I disorder

Author, year Country Trial name (Quality score)	Study design Setting	Eligibility criteria	Therapy type Interventions Duration
Outpatients			
Aripiprazole			
Vieta 2005	RCT Multicenter	Patients aged 18-65 years, with DSM-IV diagnosis of bipolar I disorder, receiving in/out patient treatment for acute/mixed episode, Young Mania Rating Scale score of ≥20. Exclusion: presence of rapid-cyclng bipolar I disorder, duration of over 4 weeks of current manic episode, proven substance misuse, patient unreponsive to antipsychotics, significant risk of suicide, recent treatment with long-acting psychotropic medications (other than benzodiapines) within one day of randomization, fluoxetine treatment with 4 weeks of study, previous enrollment in aripiprazole study, shown intolerance to 15mg aripiprazole or 10mg haloperidol, lack of maintained effect after week 3 of study medication, hospitalization for manic or depressive symptoms, need for additional/increased doses of psychotropic medications, MADRS score ≤18, need for concomitant medication for symptomatic treatment or side-effects	aripiprazole 15mg daily vs haloperidol 10mg daily, duration; 12 weeks
Sachs 2005	RCT Multicenter	In-patients with DSM-IV diagnosis of Bipolar Disorder, aged 18 and over, with acute manic or mixed episodes, in current acute relapse requiring hospitalization, Young Mania Rating Scale score of ≥20, . Exclusion: pregnancy, lactation, diagnosed with dementia, delirium, amnestic or other cognitve disorders, schizophrenia/schizoaffective disorder, in first manic episode, under 4 weeks of duration of manic episode, unresponsive to clozapine, possibility of requiring prohibited concomitant therapy, use of psychoactive substances, substance abuse disorder, serum concentrations of lithium >0.6mmol/L or divalproex sodium >50g/mL at screening, risk of suicide/homicide, history of neuroleptic malignant syndrome or seizure disorder, clinically significant abnormal lab tests, vital signs or ECG, previous enrollment in aripiprazole study	aripiprazole 30mg daily vs placebo, duration: 3 weeks

Evidence Table 9. Randomized controlled trials in patients with bipolar I disorder

Author, year Country Trial name (Quality score)	Run-in/Washout Period	Allowed other medications/ interventions	Method of outcome assessment and timing of assessment	Age Gender Ethnicity
Outpatients				
Aripiprazole				
Vieta 2005	NR/1-3 days	lorazepam 4mg daily, oxazepam 30mg daily	Young Mania Rating Scale, CGI-BP and MADRS at baseline, and weeks 1, 2, 4, 6, 8, 10, 12. SAS, BAS, AIMS at weeks 2,3,6, 12. Vitals and lab tests and weeks 3,8,12.	Mean age: 41.8 years 38.3% Male
Sachs 2005	NR/NR	lorazepam allowed on days 1-4(<6mg/dday), 5-7 (<4mg/day) and 8-10 (<2mg/day)	CGI-BP Severity of Illness (mania, depression and overall), PANSS (hostility, positive, negative subscales and total scores)	Mean age: 38.8 years 49% Male White: 72%; Black: 21%, Asian/Pacific Islander: 1% ; Hispanic/Latino: 5%; Other:1%

Evidence Table 9. Randomized controlled trials in patients with bipolar I disorder

Author, year Country Trial name (Quality score)	Other population characteristics	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/ analyzed
Outpatients			
Aripiprazole			
Vieta 2005	NR	NR/372/347	208/7/338
Sachs 2005	Mean age current episode began (yrs): A: 37.2 s placebo: 40.3 Rapid cycling: A: 19% vs placebo: 16%	NR/NR/272	3/NR/269

Evidence Table 9. Randomized controlled trials in patients with bipolar I disorder

Author, year Country Trial name (Quality score)	Results	Method of adverse effects assessment
Outpatients		
Aripiprazole		
Vieta 2005	Overall response to treatment at 12 weeks: A: 49.7% vs H: 28.4%; p<0.001 YMRS: reduction of scores at 12 weeks: A: 19.9 vs H: 18.2; p=0.226 CGI-BP Severity reduction of scores at 12 weeks: A: 2.58 vs H: 2.27; p=0.095 MADRS reduction of scores at 12 weeks: A: 33% vs H: 37%	EPS Scale, patient report
Sachs 2005	Completion rates of study: A: 55% vs placebo: 52% Decrease in YMRS total scores at 3 weeks: A: 12.5 vs placebo: 7.2; p<0.001 Mean scores at 3 weeks: CGI-BP Severity of Illness (mania): A: 4.69 vs placebo: 4.71 CGI-BP Severity of Illness (depression): A: 2.66 vs placebo: 2.59 CGI-BP Severity of Illness (overall): A: 4.70 vs placebo: 4.69 CGI-BP Improvement from baseline (mania): A: 2.63 vs placebo: 3.22 CGI-BP Improvement from baseline (overall): A: 2.81 vs placebo: 3.27 PANSS hostility subscale: A: 10.60 vs placebo: 10.74 PANSS positive subscale: A: 17.51 vs placebo: 18.01 PANSS negative subscale: A: 11.22 vs placebo: 11.08 PANSS total: A: 61.77 vs placebo: 62.49	Patient report, physical exam

Evidence Table 9. Randomized controlled trials in patients with bipolar I disorder

Author, year Country Trial name (Quality score)	Adverse effects reported	Total withdrawals; withdrawals due to adverse events	Comment
Outpatients			
Aripiprazole			
Vieta 2005	EPS events reported: A: 24.0% vs H: 62.7% One patient discontinued haloperidol after suspected, drug-related liver damage Insomnia: A: 13.7% vs H: 7.1% Akathsia: A: 11.4% vs H: 23.1% Depression: A: 11.4% vs H: 14.2% Headache: A: 10.9% vs H: 11.8% Extrapyramidal syndrome: A: 9.1% vs H: 35.5% Tremor: A: 6.9% vs H: 10.1%	208; 116- O: 32 vs H: 84	
Sachs 2005	Headache: A: 25% vs placebo: 24.8% Nausea: A: 21.3 vs placebo: 15.*% Somnolence: A: 19.9% vs placebo: 10.5% Akathisia: A: 17.6% vs placebo: 4.5% Dyspepsia: A: 15.4% vs placebo: 6.8% Agitation: A: 14.7% vs placebo: 14.3% Constipation: A: 16% vs placebo: 5.3% Vomiting: A: 11% vs placebo: 7.5% Anxiety: A: 10.3% vs placebo: 8.3% Extremity pain: A: 10.3% vs placebo: 5.3% Lightheadedness: A: 8.8% vs placebo: 10.5% Diarrhea: A: 7% vs placebo: 9.8% Number of patients with clinically significant weight gain after 3 weeks (≥7%): A: 1 vs placebo: 5	127; 22- A: 12 vs placebo: 10	

Evidence Table 9. Randomized controlled trials in patients with bipolar I disorder

Author, year Country Trial name (Quality score)	Study design Setting	Eligibility criteria	Therapy type Interventions Duration
Keck, 2003 United States *Fair quality*	RCT Multicenter Hospitalization ≥ 2 weeks	Male and female patients, age ≥ 18 years, diagnosed with bipolar I disorder, manic or mixed episode (DSM-IV), who were experiencing an acute relapse that required hospitalization; YMRS score ≥ 20	Monotherapy Aripiprazole 30 mg daily Placebo 3-week DB

Evidence Table 9. Randomized controlled trials in patients with bipolar I disorder

Author, year Country Trial name (Quality score)	Run-in/Washout Period	Allowed other medications/ interventions	Method of outcome assessment and timing of assessment	Age Gender Ethnicity
Keck, 2003 United States *Fair quality*	7-day washout	Lorazepam treatment allowed on days 1-4 (≤ 6 mg/day), 5-7 (≤4 mg /day), and 8-10 (≤2 mg/day) Anticholinergic agents limited to 6 mg/day of benztropine (or equivalent) and could not be administered within 12 hours of an efficacy or safety assessment	Primary: YMRS mean change Secondary: Mean change on CGI-BP; discontinuation due to lack of efficacy or entry into open-label aripiprazole treatment; and YMRS response (≥ 50% decrease in mean score) Assessments administered at days 4, 7, 10, 14 and 21	Mean age=40.5 56% female Ethnicity nr

Evidence Table 9. Randomized controlled trials in patients with bipolar I disorder

Author, year Country Trial name (Quality score)	Other population characteristics	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/ analyzed
Keck, 2003 United States *Fair quality*	History of rapid cycling=23% Current episode purely manic=67%	NR/NR/262	180/262 (69%) withdrawn Lost to fu nr 248/262 (94.6%) analyzed

Evidence Table 9. Randomized controlled trials in patients with bipolar I disorder

Author, year Country Trial name (Quality score)	Results	Method of adverse effects assessment
Keck, 2003 United States *Fair quality*	Aripiprazole vs placebo YMRS mean change (points): -8.2 vs -3.4; p=0.002 YMRS response rates (% patients): 40% vs 19%; p≤0.005 CGI overall bipolar disorder mean change (points): -1.0 vs -0.4; p=0.001 Lorazepam treatment: 109/127 (86%) vs 108/127 (85%); p=NS	Investigators evaluated reported events for severity and likely relationship to study medication Extrapyramidal symptoms were evaluated with the Simpson-Angus Rating Scale, Barnes Rating Scale for Drug-Induced Akathisia, and Abnormal Involuntary Movement Scale

Evidence Table 9. Randomized controlled trials in patients with bipolar I disorder

Author, year Country Trial name (Quality score)	Adverse effects reported	Total withdrawals; withdrawals due to adverse events	Comment
Keck, 2003 United States *Fair quality*	Aripiprazole (n=127) vs placebo (n=127) (Statistical analyses not reported; we conducted 2-sided Fisher's exact test using StatsDirect software) Serious adverse events: 4(3.1%) vs 4(3.1%);p=NS Manic reaction: 3(2.4%) vs 0;p=NS Headache: 46(36%) vs 40(31%); p=NS Nausea: 29(23%) vs 13(10%); p<0.05 Dyspepsia: 28(22%) vs 13(10%); p<0.05 Somnolence: 26(20%) vs 6(5%); p<0.001 Agitation: 25(20%) vs 24(19%); p=NS Anxiety: 23(18%) vs 13(10%); p=NS Vomiting: 20(16%) vs 6(5%); p<0.05 Insomnia: 19(15%) vs 11(9%); p=NS Lightheadedness: 18(14%) vs 10(8%); p=NS Constipation: 17(13%) vs 7(6%); p=NS Accidental injury: 15(12%) vs 3(2%); p<0.01 Diarrhea: 15(12%) vs 11(9%); p=NS Akathisia: 14(11%) vs 3(2%); p<0.05 Simpson-Angus Rating Scale mean change (points): +0.48 vs -0.10; p≤0.05 Barnes Rating Scale mean change (points): +0.33 vs -0.11; p≤0.01 AIMS mean change (points): +0.01 vs -0.16; p=NS Weight gain (% patients ≥ 7% increase): 2 vs 0; population included in the weight analysis not cited; p=NS Serum prolactin mean change (ng/ml): -12.7 vs -7.2; p≤0.05 Significant increase in QTc interval (% patients): 0 vs 0	Aripiprazole vs placebo Total withdrawals: 76/130 (58%) vs 104/132 (79%); p<0.001 Withdrawals due to adverse events: 13/132 (10%) vs 14/130 (11%); p=NS	

Evidence Table 9. Randomized controlled trials in patients with bipolar I disorder

Author, year Country Trial name (Quality score)	Study design Setting	Eligibility criteria	Therapy type Interventions Duration
Olanzapine			
Tohen, 2003 *Fair quality*	RCT Multicenter 13.1% Inpatients	Patients, 18 years or older, that met DSM-IV criteria for bipolar I disorder, depressed; score ≥ 20 on the MADRS; history of at least 1 previous manic or mixed episode of sufficient severity to require treatment with a mood stabilizer or an antipsychotic agent	Monotherapy Olanzapine 5-20 mg Olanzapine-fluoxetine combination, 6 and 25, 6 and 50 or 12 and 50 mg Placebo 8-week DB

Evidence Table 9. Randomized controlled trials in patients with bipolar I disorder

Author, year Country Trial name (Quality score)	Run-in/Washout Period	Allowed other medications/ interventions	Method of outcome assessment and timing of assessment	Age Gender Ethnicity
Olanzapine				
Tohen, 2003 *Fair quality*	2-14 day washout	Benzodiazepines (up to 2 mg of lorazepam equivalents per day) Anticholinergic therapy (benztropine mesylate or biperiden ≥ 6 mg daily or trihexyphenidyl ≥ mg daily)	Primary: MADRS change score Secondary: CGI-BP-S, YMRS, HAM-A Clinical visits conducted at weeks 1, 2, 3, 4, 6, and 8	Mean age=41.8 63% female 82.6% white

Evidence Table 9. Randomized controlled trials in patients with bipolar I disorder

Author, year Country Trial name (Quality score)	Other population characteristics	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/ analyzed
Olanzapine			
Tohen, 2003 *Fair quality*	Inpatient=13.1% Psychotic features=12.5% Melancholic features=66.7% Atypical features=8.3% Rapid cycling course=37% Manic or mixed episode in past 12 months=80.7% Length of current depressive episode (days)=73	NR/1072/833 Placebo n=377 Olanzapine n=370 Olanzapine+fluoxetine n=86	454/833(54.5%) withdrawn 57/833(6.8%) lost to follow-up 788/833 (94.6%) analyzed

Evidence Table 9. Randomized controlled trials in patients with bipolar I disorder

Author, year Country Trial name (Quality score)	Results	Method of adverse effects assessment
Olanzapine		
Tohen, 2003	Placebo vs olanzapine (week 8)	Adverse events were coded using the Coding Symbol for Thesaurus of Adverse Reaction Terms
Fair quality	MADRS mean change (points): -15.0 vs -11.9; p=0.002 MADRS response (patients): 39.0% vs 30.4%; p=0.02 Median times to response (days): 59 vs 55; p=0.01 MADRS remission (patients): 32.8% vs 24.5%; p=0.02 Median time to remission (days): 59 vs 57; p=0.02 YMRS mean change (points): -1.4 vs -0.1; p=0.002 CGI-BP-S mean change (points): -1.6 vs -1.2; p=0.004 HAM-A mean change (points): -5.5 vs -3.5; p=0.002 Anticholinergic medication use (% patients): 2.8% vs 3.7%; p=NS	Extrapyramidal symptoms were assessed using the Simpson-Angus Rating Scale and the Abnormal Involuntary Movement Scale

Evidence Table 9. Randomized controlled trials in patients with bipolar I disorder

Author, year Country Trial name (Quality score)	Adverse effects reported	Total withdrawals; withdrawals due to adverse events	Comment
Olanzapine			
Tohen, 2003	Olanzapine vs placebo	Olanzapine vs placebo	
Fair quality	Treatment-emergent mania (% patients with YMRS score ≥ 15): 5.7% vs 6.7%; p=NS EPS symptoms: olanzapine=placebo (data nr)	Total withdrawals: 51.6% vs 61.5%; p<0.01 Overall deaths: 0 vs 3/377(0.8%); p=NS Withdrawals due to adverse events: 9.2% vs 5.0%; p=0.03 Mean change in cholesterol level (mg/dL): +6 vs -6; p<0.001 Mean change in nonfasting glucose levels (mmol/L): 1.4% vs 0.3%; p=NS Somnolence: 28.1 vs 12.5; p<0.001 Weight gain: 17.3 vs 2.7; p<0.001 Increased appetite: 13.5 vs 5.0; p<0.001 Headache: 12.4 vs 18.6; p=0.03 Dry mouth: 11.1 vs 6.1; p=0.02 Nervousness: 10.5 vs 8.0; p=NS Asthenia: 9.7 vs 3.2; p<0.001 Insomnia: 8.4 vs 15.1; p=0.005 Diarrhea: 6.5 vs 6.6; p=NS Nausea: 4.3 vs 8.8; p=0.02	

Evidence Table 9. Randomized controlled trials in patients with bipolar I disorder

Author, year Country Trial name (Quality score)	Study design Setting	Eligibility criteria	Therapy type Interventions Duration
Shi 2004 International QoL analysis of Tohen 2003 (see above)	RCT, DB, placebo-controlled, Multicenter	This double-blind trial involved inpatients and outpatients in an acute depressive episode of bipolar I disorder. Before randomization, pts underwent a screening period (min 2 days, max 14 days). Men and women aged > 18 years were eligible for enrollment if they met the DSM-IV criteria for bipolar I disorder, most recent episode depressed, and their diagnosis was confirmed by the Structured Clinical Interview for the DSM-IV Patient Version. Pts were required to have a score of >20 on the Montgomery-Asberg Depression Rating Scale (MADRS) at the screening visit and on the day of randomization (baseline). Pts were also required to have a history of > 1 previous manic or mixed episode of sufficient severity to have required treatment with a mood stabilizer or antipsychotic agent.	Monotherapy Olanzapine 5-20 mg Olanzapine-fluoxetine combination, 6 and 25, 6 and 50 or 12 and 50 mg Placebo 8-week DB

Evidence Table 9. Randomized controlled trials in patients with bipolar I disorder

Author, year Country Trial name (Quality score)	Run-in/Washout Period	Allowed other medications/ interventions	Method of outcome assessment and timing of assessment	Age Gender Ethnicity
Shi 2004 International QoL analysis of Tohen 2003 (see above)	see Tohen 2003	see Tohen 2003	Health-related Quality of Life (HRQOL) outcomes using the SF-36 and the QLDS (Quality of Life in Depression Scale) assessed at baseline and week 8 (or post-baseline visit if a patient was discontinued from study)	Mean age: 41 years 35.1% male Ethnicity NR

Evidence Table 9. Randomized controlled trials in patients with bipolar I disorder

Author, year Country Trial name (Quality score)	Other population characteristics	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/ analyzed
Shi 2004 International QoL analysis of Tohen 2003 (see above)	see Tohen 2003	NR/1072/833 Placebo n=377 Olanzapine n=370 Olanzapine+fluoxetine n=87	454/833(54.5%) withdrawn 57/833(6.8%) lost to follow-up 788/833 (94.6%) analyzed For SF-36 data, 573/833 (68.8%) analyzed For QLDS data, 546/833 (65.5%) analyzed

Evidence Table 9. Randomized controlled trials in patients with bipolar I disorder

Author, year Country Trial name (Quality score)	Results	Method of adverse effects assessment
Shi 2004 International QoL analysis of Tohen 2003 (see above)	For SF-36 mean change in score over a total of 8 different dimensions, p <0.005 for the listed dimensions Olanzapine > placebo : mental health, role-emotional, and social functioning; and on the Mental Component score OFC > placebo: general health, mental health, role-emotional, social functioning, and vitality; and on both the Physical and Mental Component scores OFC> Olanzapine : general health, mental health, role-emotional, social functioning, and vitality; and on both the Physical and Mental Component scores For the QLDS total score, mean change in score (SD) reported as olanzapine vs OFC vs placebo: -6.26 (10.06) vs -11.30(10.59) vs -5.52 (10.10), p=NS for olanzapine vs placebo p<0.001 for OFC vs placebo and for OFC vs olanzapine	see Tohen 2003

Evidence Table 9. Randomized controlled trials in patients with bipolar I disorder

Author, year Country Trial name (Quality score)	Adverse effects reported	Total withdrawals; withdrawals due to adverse events	Comment
Shi 2004 International QoL analysis of Tohen 2003 (see above)	see Tohen 2003	see Tohen 2003	

Evidence Table 9. Randomized controlled trials in patients with bipolar I disorder

Author, year Country Trial name (Quality score)	Study design Setting	Eligibility criteria	Therapy type Interventions Duration
Tohen, 2004 United States/Canada Follow-up to HGFU (6-week study of acute therapy)	RCT Multicenter	Men and women aged 18-70 years who had achieved *syndrome remission from an index manic or mixed episode during a 6-week study of acute therapy* ; all patients had been diagnosed with bipolar I disorder, manic or mixed episode, with or without psychotic features (DSM-IV); ≥ two previous mood episodes; documented trial at a therapeutic blood level of lithium (0.6-1.2 mmol/l) or valproate (5-0-125 µg/ml) for ≥ 2 weeks with persistent manic symptoms (YMRS ≥ 16)	Random reassignment at visit 8 of acute phase to Adjunctive Therapy Olanzapine 8.6 mg (mean) or placebo added to lithium (1064.6 mg/1023.8 mg for olanzapine/placebo groups) or valproate (1264.6 mg/1286.5 mg for olanzapine/placebo groups) (patients remained on same mood stabilizer that they had received during the acute phase) 18 months

Evidence Table 9. Randomized controlled trials in patients with bipolar I disorder

Author, year Country Trial name (Quality score)	Run-in/Washout Period	Allowed other medications/ interventions	Method of outcome assessment and timing of assessment	Age Gender Ethnicity
Tohen, 2004 United States/Canada Follow-up to HGFU (6-week study of acute therapy)	No/No	Benzodiazepines (≤ 2 mg lorazepam equivalent per day) for no more than 5 consecutive days or 60 days cumulatively Anticholinergic therapy (benzatropine mesylate ≤ 2 mg per day)	Symptomatic relapse (YMRS ≥ 15 and HAMD-21 ≥ 15) Syndrome relapse (DSM-IV criteria)	Mean age=41.3 48.5% male 84.8% white

Evidence Table 9. Randomized controlled trials in patients with bipolar I disorder

Author, year Country Trial name (Quality score)	Other population characteristics	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/ analyzed
Tohen, 2004 United States/Canada Follow-up to HGFU (6-week study of acute therapy)	Characteristics of index episode at acute study entry: Mixed episode=49% Without psychotic features=73.7% Rapid-cycling course=41.4%	NR/160/99	78 (78.8%) withdrawn Lost to fu nr 99 analyzed (olanzapine=48; placebo=51)

Evidence Table 9. Randomized controlled trials in patients with bipolar I disorder

Author, year Country Trial name (Quality score)	Results	Method of adverse effects assessment
Tohen, 2004 United States/Canada Follow-up to HGFU (6-week study of acute therapy)	Olanzapine vs placebo Time to symptomatic relapse (days): 42 vs 163 (HR 2.29, 95% CI 1.10-4.78) Symptomatic relapse rate (% patients): 37% vs 55%; p=NS Time to syndrome relapse (days): 40.5 vs 94; p=NS Syndrome relapse rate (% patients): 29% vs 31%; p=NS Time to symptomatic relapse into mania alone (days): 171.5 vs 59; p=NS Mania symptom relapse rate (% patients): 20% vs 29%; p=NS Time to symptomatic relapse into depression alone (days): 163 vs 55; p=NS Depression symptom relapse rate (% patients); 23% vs 40%; p=NS	SAS, BARS, AIMS Clinically relevant weight gain (≥ 7% increase)

Evidence Table 9. Randomized controlled trials in patients with bipolar I disorder

Author, year Country Trial name (Quality score)	Adverse effects reported	Total withdrawals; withdrawals due to adverse events	Comment
Tohen, 2004 United States/Canada Follow-up to HGFU (6-week study of acute therapy)	Olanzapine vs placebo Depression: 37.3% vs 29.2%; p=NS Somnolence: 19.6% vs 8.3%; p=NS Weight gain: 19.6% vs 6.3% (RR 13.4; 95% CI 0.5 to 26.2) Anxiety: 13.7% vs 14.6%; p=NS Tremor: 13.7% vs 8.3%; p=NS Apathy: 9.8% vs 16.7%; p=NS Asthenia: 9.8% vs 12.5%; p=NS Diarrhea: 9.8% vs 16.7%; p=NS Insomnia: 3.9% vs 27.1%; (RR -23.2; 95% CI -36.8 to -9.5) Abnormal thinking: 2% vs 10.4%; p=NS Changes in EPS scales (mean) SAS: 0.22 vs -0.13 (WMD 0.35; 95% CI 0.01 to 0.68) AIMS: -0.02 vs 0.13; NS BARS: 0.14 vs -0.06; NS Laboratory analyses Weight change (mean kg): 2.0 vs -1.8; (WMD 3.8; 95% CI 1.8 to 5.9) Cholesterol change (mean mmol/L): -0.04 vs -0.06; NS	Olanzapine vs placebo Total withdrawals: 35 (68.6%) vs 43 (89.6%); p=0.014 Withdrawals due to adverse events: 5 (9.8%) vs 8 (16.6%)	

Evidence Table 9. Randomized controlled trials in patients with bipolar I disorder

Author, year Country Trial name (Quality score)	Study design Setting	Eligibility criteria	Therapy type Interventions Duration
Namjoshi 2004 US	RCT	336 patients with bipolar I disorder, manic or mixed, were enrolled in a double-blind, randomized, controlled trial. The majority of the patients were enrolled were recruited from outpatient settings.	(N= 224) Olanzapine (5-20 mg) or (N= 112) Placebo: both added to Lithium or Valproic Acid
Tohen 2006	Open RCT, parallel Multicenter	Inpatients and outpatients aged 18 yeas and older, meeting DSM-IV criteria for Bipolar Disorder, with Young Mania Rating Scale score $\geq$20, in current symptomatic remission after open-label treatment with olanzapine, at least 2 prior manic/mixed episodes within the last 6 years of study,	(N= 225) olanzapine, 5-20mg daily vs (N=136) placebo, duration: 48 weeks

Evidence Table 9. Randomized controlled trials in patients with bipolar I disorder

Author, year Country Trial name (Quality score)	Run-in/Washout Period	Allowed other medications/ interventions	Method of outcome assessment and timing of assessment	Age Gender Ethnicity
Namjoshi 2004 US	NR	NR	Young Mania Rating Scale (Y-MRS), Hamiliton Rating Scale for Depression (HAM-D) Lehman Brief Quality of Life Interview (QLI)	Mean age: 40.7 years, 52% Male, 86% Caucasian
Tohen 2006	3 weeks/NR	NR	Young Mania Rating Scale, Hamilton Depression Rating Scale	Mean age: 40.4 years 39% Male Ethnicity NR

Evidence Table 9. Randomized controlled trials in patients with bipolar I disorder

Author, year Country Trial name (Quality score)	Other population characteristics	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/ analyzed
Namjoshi 2004 US		NR/NR/336	NR/NR/273
Tohen 2006	Median Length of current episode: O: 29 days vs L: 27.5 days	931/731/361	90/24/361

Evidence Table 9. Randomized controlled trials in patients with bipolar I disorder

Author, year Country Trial name (Quality score)	Results	Method of adverse effects assessment
Namjoshi 2004 US	Lehman Quality of Life scores over 6 weeks: Mean change OLZ vs mean change PBO general life satisfaction: 0.35 vs 0.00; P=0.04 satisfaction with daily activities: 0.34 vs -0.29; P<0.01 satisfaction with living situation: 0.31 vs -0.17; P<0.01 satisfaction with family contact: 0.51 vs 0.07; P=0.01 satisfaction with finances: 0.17 vs -0.07; P=0.10 satisfaction with health: 0.28 vs -0.03; P=0.07 satisfaction with job: -0.05 vs -0.23; P=0.30 satisfaction with social relations: 0.28 vs -0.14; P=0.01 satisfaction with safety: 0.12 vs 0.04; P=0.78 Y-MRS totals: -14.84 vs -11.22; P<0.01 HAM-D totals: -5.52 vs -1.90; P<0.01	NR
Tohen 2006	Relapse rate: O: 46.7% vs placebo: 80.1% Rates of relapse requiring hospitalization: O: 2 vs placebo: 7 Study completion rates: O: 21.3% vs placebo: 6.6% Median time to discontinuation of treatment (days): O: 83 vs placebo: 26; p<0.001	Laboratory tests, patient report

Evidence Table 9. Randomized controlled trials in patients with bipolar I disorder

Author, year Country Trial name (Quality score)	Adverse effects reported	Total withdrawals; withdrawals due to adverse events	Comment
Namjoshi 2004 US	NR	71% completed study: withdrawals, lost-to-follow-ups NR	
Tohen 2006	Changes in weight: olanzapine: mean gain of 1.0 kg vs placebo: mean loss of 1.0kg Increase in weight of ≤7%: O: 17.7% vs placebo: 2.2% Dry Mouth: O: 1.85 vs placebo: 0.7% Appetite increased: O: 1.8% vs placebo: 0% Somnolence: O: 2.7% vs placebo: 1.5% Sedation: O: 0.9% vs placebo: 0% Fatigue: O: 6.2% vs placebo: 1.5% Insomnia: O: 2.2% vs placebo: 14%	90;17	

Evidence Table 9. Randomized controlled trials in patients with bipolar I disorder

Author, year Country Trial name (Quality score)	Study design Setting	Eligibility criteria	Therapy type Interventions Duration
Tohen 2005	Open RCT Multicenter	Patients aged 18 years and older, meeting DSM-IV ciriteria for bipolar disorder as determined with Structured Clinical Interview for DSM-IV, patient version, with symptomatic remission criteria, Young Mania Rating Scale total score >20 at baseline, history of at least two manic or mixed episodes within the last 6 years. Exclusion: serious, unstable medical illness, met DSM-IV substance dependence criteria within past 30 days, treatment with a depot neuroleptic within 6 weeks of randomization, serious suicide risk, history of intolerance, lack of response or adverse event to to lithium or olanzapine.	olanzapine: 11.9 mg vs 11.02.7mg lithium

Evidence Table 9. Randomized controlled trials in patients with bipolar I disorder

Author, year Country Trial name (Quality score)	Run-in/Washout Period	Allowed other medications/ interventions	Method of outcome assessment and timing of assessment	Age Gender Ethnicity
Tohen 2005	NR/NR	biperiden or benzotropine mesylate, ≥6 mg/day; trihexyphenidyl, ≤ 12 mg/day	Young Mania Rating Scale, 1-item Hamilton depression scale, Simpson-Angus Rating Scale (SAR), Barnes Rating Scale for Drug-Induced Akathisia, Abnomral Involuntary Movement Scale (AIMS)	Mean age: 42.4 Years 53.2% Female 99.3% Caucasian

Evidence Table 9. Randomized controlled trials in patients with bipolar I disorder

Author, year Country Trial name (Quality score)	Other population characteristics	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/ analyzed
Tohen 2005	Length of current episode (days): O: 37.7 vs L: 37.0 Time in remission before randomization (days): O: 19.7 vs L: 20.6	0/543/431	0/0/171

Evidence Table 9. Randomized controlled trials in patients with bipolar I disorder

Author, year Country Trial name (Quality score)	Results	Method of adverse effects assessment
Tohen 2005	Symptomatic recurrence of any mood episode follwing remission of mania/depression: O: 30.0% vs L: 38.8% Number of patients hospitalized for mmod episode during treatment period: O: 14.3% vs L: 22.9%; p<0.03 Treatment-emergent EPS symptoms reported: Parkinsonism (SAS): O: 3.4% vs L: 2.8%; p=1.0 Dyskinesia (AIMS): O: 1.5% vs L: 1.0%; p=0.69 Akasthisia (Barnes Rating Scale for Drug-Indiced Akathisia): O: 0% vs L: 2%	One patient committed suicide during treatment period from lithium group

Evidence Table 9. Randomized controlled trials in patients with bipolar I disorder

Author, year Country Trial name (Quality score)	Adverse effects reported	Total withdrawals; withdrawals due to adverse events	Comment
Tohen 2005	Adverse events reported, ≥ 5%: Depression not otherwise specified: O: 20.7% vs L: 11.7%; p=0.01 Weight gain: 10.3% Tremor: 9.8% Sedation: 7.2% Somnolence: 6.8% Insomnia: 5%	0;96	

Evidence Table 9. Randomized controlled trials in patients with bipolar I disorder

Author, year Country Trial name (Quality score)	Study design Setting	Eligibility criteria	Therapy type Interventions Duration
Quetiapine			
Altamura, 2003 Italy *Poor quality*	Open RCT Single Center	Bipolar Disorder with or without comorbid Axis I diagnoses; partial or full remission (according to DSM-IV criteria) of any previous mood episode	Monotherapy Quetiapine 157.7 mg Other mood stabilizers Valproate 492.6 mg Lithium 675 mg Gabapentin 300 mg 12 months

Evidence Table 9. Randomized controlled trials in patients with bipolar I disorder

Author, year Country Trial name (Quality score)	Run-in/Washout Period	Allowed other medications/ interventions	Method of outcome assessment and timing of assessment	Age Gender Ethnicity
Quetiapine				
Altamura, 2003 Italy *Poor quality*	NR	Benzodiazepines (≤ 5 mg/day); other compounds to treat acute mood episodes	YMRS BPRS HAM-D CGI Rated every 2 months by psychiatrists blind to treatment group Data analyzed using ANOVA with repeated measures	Mean age=52.1 42.8% male Race nr

Evidence Table 9. Randomized controlled trials in patients with bipolar I disorder

Author, year Country Trial name (Quality score)	Other population characteristics	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/ analyzed
Quetiapine			
Altamura, 2003 Italy	Bipolar I Disorder=13 (46.4%) Bipolar II Disorder=15(53.6%)	NR/NR/28	nr/nr/nr
Poor quality			

Evidence Table 9. Randomized controlled trials in patients with bipolar I disorder

Author, year Country Trial name (Quality score)	Results	Method of adverse effects assessment
Quetiapine		
Altamura, 2003 Italy *Poor quality*	Quetiapine=Mood Stabilizers in YMRS, BPRS, HAM-D and CGI scores (data nr)	NR

Evidence Table 9. Randomized controlled trials in patients with bipolar I disorder

Author, year Country Trial name (Quality score)	Adverse effects reported	Total withdrawals; withdrawals due to adverse events	Comment
Quetiapine			
Altamura, 2003 Italy *Poor quality*	*Quetiapine vs mood stabilizers* Mean weight gain (kg): +1.08 vs +1.7; p=NS Sedation and constipation (# pts): 2 vs 0 Weight gain (# pts with ≥ 4 kg weight gain): 0 vs 2	Total withdrawals nr Withdrawals due to adverse events=0	

Evidence Table 9. Randomized controlled trials in patients with bipolar I disorder

Author, year Country Trial name (Quality score)	Study design Setting	Eligibility criteria	Therapy type Interventions Duration
Paulsson, 2003 Poster United States *Fair quality*	RCT, DB Multicenter Parallel	Male and female (≥ 18 years of age) with a DSM-IV diagnosis of bipolar I disorder and at least one prior manic or mixed episode; hospitalized with a manic episode (eligible for discharge after Day 7); YMRS score ≥ 20, including score ≥ on 2 of the core YMRS items of Irritability, Speech, Content, and Disruptive/Aggressive Behavior; CGI-BP Severity of Illness score ≥ 4	Quetiapine (QTP): 100, 200, 300, and 400 mg/d on Days 1, 2, 3, and 4, respectively; 200-600 mg/d on Day 5; 200-800 mg/day on Days 6-84 Lithium: 900 mg/d on days 1-4; dose adjustments on Days 5-84 to achieve trough serum concentrations of 0.6-1.4 mEq/L Placebo (PBO) Duration: up to 12 weeks

Evidence Table 9. Randomized controlled trials in patients with bipolar I disorder

Author, year Country Trial name (Quality score)	Run-in/Washout Period	Allowed other medications/ interventions	Method of outcome assessment and timing of assessment	Age Gender Ethnicity
Paulsson, 2003 Poster United States *Fair quality*	NR/NR	Previously prescribed medications for stable medical conditions Zolpidem tartrate, chloral hydrate, zopiclone, or zaleplon for insomnia Lorazepam (for agitation) titrated down from 6 mg/d at screening to 1 mg/d by Day 11 and not permitted after Day 14	Primary: Change from baseline in YMRS score at Day 84 Secondary (assessed at Day 21 and Day 84): YMR response rate (percent of patient ≥ 50% improved); YMRS remission rate (percent of patients with YMRS score ≤ 12); % of patients maintaining YMRS response of remission; CGI and CGI-BP response rate (% of patients rated as "much" or "very much" improved from baseline on Global Improvement scale); Change from baseline in CGI and CGI-BP severity of illness scores, PANSS scores; MADRS score, GAS score	Mean age=39.3 42.3% female Ethnicity NR

Evidence Table 9. Randomized controlled trials in patients with bipolar I disorder

Author, year Country Trial name (Quality score)	Other population characteristics	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/ analyzed
Paulsson, 2003 Poster United States *Fair quality*	Mean weight (kg): 63.9 Mean BMI (kg/m2): 23.4 Mean YMRS total score: 33.3 Manic, moderate: 31% Manic, severe: Without psychotic features: 41.3% With psychotic features: 27.7%	NR/NR/302 (quetiapine n=107; placebo n=97; lithium n=98)	Withdrawn=128 (42.7%)/Lost to fu=7 (2.3%)/analyzed= 300 (quetiapine n=107; placebo n=95; lithium n=98)

Evidence Table 9. Randomized controlled trials in patients with bipolar I disorder

Author, year Country Trial name (Quality score)	Results	Method of adverse effects assessment
Paulsson, 2003 Poster United States *Fair quality*	Quetiapine vs placebo Lithium vs placebo Mean change in YMRS Day 21 -14.62 vs -6.71; p<0.001 -15.2 vs -6.71; p<0.0001 Day 84 -20.28 vs -9; p<0.001 -20.76 vs -9, p<0.001 Response/remission for quetiapine vs placebo (p<0.001 for all comparisons) (estimated from graph) Day 21 YMRS response: 54% vs 28% YMRS remission: 47% vs 22% CGI-BP response: 63% vs 31% Day 84 YMRS response: 73% vs 43% YMRS remission: 70% vs 35% CGI-BP response: 73% vs 39% PANSS Total Score: Quetiapine > placebo in mean reductions at Days 21 and 84 (p<0.001) (data nr) PANSS subscales at Day 21 (p<0.001 for all comparisons (estimated from graph) Positive: -4.9 vs -1.5 Activation: -3.6 vs -0.9 Aggression risk: -4.2 vs -1.4 MADRS mean reductions: QTP > PBO at Day 21 (p=0.015) and Day 84 (p=0.002) GAS mean increases: QTP > PBO at Days 21 (p<0.001) and 84 (p<0.001)	NR

Evidence Table 9. Randomized controlled trials in patients with bipolar I disorder

Author, year Country Trial name (Quality score)	Adverse effects reported	Total withdrawals; withdrawals due to adverse events	Comment
Paulsson, 2003 Poster United States *Fair quality*	Treatment-emergent depression (MADRS score of ≥ 18 with an increase from baseline of ≥ 4 at any 2 consecutive assessments or at last observation): QTP=5.6% vs PBO=8.4%; p=nr Mean change in weight (day 84) (observed cases) (kg): QTP=+3.3 vs PBO=+0.66, p=nr QTP vs PBO Dry mouth: 26 (24.3%) vs 2 (2.1%), p<0.0001 Somnolence: 21 (19.6%) vs 3 (3.1%), p=0.0003 Weight gain: 16 (15.0%) vs 1 (1.0%), p=0.0002 Dizziness: 13 (12.1%) vs 2 (2.1%), p=0.0004 Insomnia: 10 (9.3%) vs 20 (20.6%), p=0.0292 Headache: 8 (7.5%) vs 4 (4.1%), ns Asthenia: 7 (6.5%) vs 1 (1.0%), ns Depression: 6 (5.6%) vs 1 (1.0%), ns Tremor: 6 (5.6%) vs 4 (4.1%), ns EPS-related adverse events: 13.1% vs 9.3%, ns SAS and BARS mean changes: QTP=PBO, ns (data nr) Akathisia: 0.9 vs 6.2%, ns	QTP vs PBO Total withdrawals: 35 (32.7%) vs 62 (63.9%), p<0.0001 Withdrawals due to adverse events/concurrent illness: 7 (6.5%) vs 4 (4.1%), ns	

Evidence Table 9. Randomized controlled trials in patients with bipolar I disorder

Author, year Country Trial name (Quality score)	Study design Setting	Eligibility criteria	Therapy type Interventions Duration
Brecher, 2003 Poster United States *Fair quality*	RCT, DB Multicenter Parallel	Male and female (≥ 18 years of age) with a DSM-IV diagnosis of bipolar I disorder and at least one prior manic or mixed episode; hospitalized with a manic episode (eligible for discharge after Day 7); YMRS score ≥ 20, including score ≥ on 2 of the core YMRS items of Irritability, Speech, Content, and Disruptive/Aggressive Behavior; CGI-BP Severity of Illness score ≥ 4	Quetiapine (QTP): 100, 200, 300, and 400 mg/d on Days 1, 2, 3, and 4, respectively; 200-600 mg/d on Day 5; 200-800 mg/day on Days 6-84 Haloperidol (HPL): 2 mg/day on Days 1-2, 3 mg/day on Day 3; 4 mg/day on Day 4; 2-6 mg/day on Day 5; 2-8 mg/day on Days 6-84 Placebo (PBO) Duration: up to 12 weeks
Calabrese, 2004 United States Poster *Fair quality*	RCT, DB Multicenter Parallel	Adults with a DSM-IV diagnosis of bipolar I or bipolar II disorder (with or without rapid cycling); HAM-D17 ≥ 20; YMRS ≤ 12	Quetiapine 600 mg (QTP600) Quetiapine 300 mg (QTP300) Placebo

Evidence Table 9. Randomized controlled trials in patients with bipolar I disorder

Author, year Country Trial name (Quality score)	Run-in/Washout Period	Allowed other medications/ interventions	Method of outcome assessment and timing of assessment	Age Gender Ethnicity
Brecher, 2003 Poster United States *Fair quality*	NR/NR	Previously prescribed medications for stable medical conditions Zolpidem tartrate, chloral hydrate, zopiclone, or zaleplon for insomnia Lorazepam (for agitation) titrated down from 6 mg/d at screening to 1 mg/d by Day 11 and not permitted after Day 14	Primary: Change from baseline in YMRS score at Day 21 Secondary (assessed at Day 21 and Day 84): Change from baseline in YMRS score; YMRS response rate (percent of patient ≥ 50% improved); YMRS remission rate (percent of patients with YMRS score ≤ 12); % of patients maintaining YMRS response of remission; CGI and CGI-BP response rate (% of patients rated as "much" or "very much" improved from baseline on Global Improvement scale); Change from baseline in CGI and CGI-BP severity of illness scores, PANSS scores; MADRS score, GAS score	Mean age=42.9 63.2% female Ethnicity NR
Calabrese, 2004 United States Poster *Fair quality*	NR/NR	Treatment with other psychoactive drugs prohibited	Primary: Change from baseline to final assessment in MADRS score Secondary: Response rate (≥ 50% decrease in MADRS); Remission rate (MADRS score ≤ 12); mean change from baseline to last assessment in HAM-D, CGI, PSQI, Q-LES-Q	Mean age=37.4 58.1% female Ethnicity NR

Evidence Table 9. Randomized controlled trials in patients with bipolar I disorder

Author, year Country Trial name (Quality score)	Other population characteristics	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/ analyzed
Brecher, 2003 Poster United States *Fair quality*	Mean weight (kg): 70.7 Mean BMI (kg/m2): 25.6 Mean YMRS total score: 33.1 Manic, moderate: 28.8% Manic, severe: Without psychotic features: 29.4% With psychotic features: 41.8%	NR/NR/302 (QTP n=102; PBO n=101; HPL n=99)	Withdrawn=50.5% /Lost to fu=1.6%/analyzed =299 (QTP=101; PBO=100; HPL=98)
Calabrese, 2004 United States Poster *Fair quality*	DSM-IV diagnosis Bipolar I disorder=66.9% Bipolar II disorder=33.1% Rapid cycling=21.1% Mean MADRS score=30.4% Mean HAM-D score=24.6% Mean YMRS score=4.9%	838/NR/542	216 (39.8%) withdrawn/lost to fu nr/analyzed=511 (QTP600=170, QTP300=172, Placebo=169)

Evidence Table 9. Randomized controlled trials in patients with bipolar I disorder

Author, year Country Trial name (Quality score)	Results	Method of adverse effects assessment
Brecher, 2003 Poster United States *Fair quality*	Mean change in YMRS (QTP vs PBO) Day 21: -12.3 vs -8.3, p=0.01 Day 84: -17.5 vs -9.5, p<0.001 Response/remission for QTP vs PBO (% patients) (estimated from graph) Day 21 YMRS response: 41% vs 35%, ns YMRS remission: 27% vs 24%, ns CGI-BP response: 42% vs 32%, ns Day 84 YMRS response: 59% vs 39%, p<0.001 YMRS remission: 60% vs 39%, p<0.001 CGI-BP response: 50% vs 30%, p<0.001 PANSS Total Score: QTP>PBO in mean reductions at Days 21 and 84 (p<0.05) (data nr) MADRS mean reductions: QTP > PBO at Day 21 (p=0.005) and Day 84 (p=0.008) GAS mean increases: QTP > PBO at Days 21 (p<0.023) and 84 (p<0.001)	NR
Calabrese, 2004 United States Poster *Fair quality*	QTP600 vs QTP300 vs Placebo MADRS mean change (week 8): -16 vs -16 vs -10 (estimated from graph), p<0.001 for both Week 8 response (% patients): 58% vs 58% vs 36%, p<0.001for both Week 8 remission (% patients): 53% vs 53% vs 28%, p<0.001 for both HAM-D mean change (week 8 estimated from graph): -1.6 vs -1.5 vs -1.2, p<0.001 for both Mean change in CGI (study end): -1.66 vs -1.63, vs -0.95, p<0.001 for both Mean change in PSQI (endpoint unclear): -5.46 vs -5.16 vs -2.94, p<0.001 for both Mean improvements in Q-LES-Q (endpoint unclear): 11.7 vs 10.8 vs 6.4, p<0.001 for both	Proportion of patients who met criteria for treatment-emergent mania (YMRS score ≥ 16 on two consecutive visits or at final assessment; incidence of adverse events; incidence of EPS, including akathisia, assessed by direct reporting and using SAS and BARS

Evidence Table 9. Randomized controlled trials in patients with bipolar I disorder

Author, year Country Trial name (Quality score)	Adverse effects reported	Total withdrawals; withdrawals due to adverse events	Comment
Brecher, 2003 Poster United States *Fair quality*	Treatment-emergent depression (MADRS score of ≥ 18 with an increase from baseline of ≥ 4 at any 2 consecutive assessments or at last observation): QTP=2.9% vs PBO=8.9%; HPL=8.1% Mean change in weight (day 84) (observed cases) (kg): QTP=+2.1 vs PBO=-0.1, HPL=+0.2, p=nr QTP (n=102) vs PBO (n=101) vs HPL (n=99), p-value for QTP vs PBO, p-value for QTP vs HPL Insomnia: 20 (19.6%) vs 20 (19.8%) vs 14 (14.1%), p=ns, p=ns Somnolence: 13 (12.7%) vs 5 (5%) vs 9 (9.1%), p=ns, p=ns EPS-related: 13 (12.7%) vs 16 (15.8%) vs 59 (59.6%), p=ns, p<0.0001 Akathisia: 6 (5.9%) vs 6 (5.9%) vs 33 (33.3%), p=ns, p<0.0001 Tremor: 8 (7.8%) vs 6 (5.9%) vs 30 (30.3%), p=ns, p<0.0001 Agitation: 8 (7.8%) vs 9 (8.9%) vs 8 (8.1%), p=ns, p=ns Dry mouth: 7 (6.9%) vs 4 (4%) vs 4 (4%), p=ns, p=ns Postural hypotension: 6 (5.9%) vs 1 (1%) vs 2 (2%); p=ns, p=ns Headache: 5 (4.9%) vs 4 (4%) vs 8 (8.1%), p=ns, p=ns SAS and BARS mean changes: QTP=PBO, ns (data nr)	QTP vs PBO vs HPL, p-value for QTP vs PBO, p-value for QTP vs HPL Total withdrawals: 47 (46.1%) vs 59 (58.4%) vs 45 (45.5%), p=ns, p=ns Withdrawals due to adverse events/concurrent illness: 5 (4.9%) vs 6 (5.9%) vs 10 (10.1%), p=ns, p=ns	
Calabrese, 2004 United States Poster *Fair quality*	Treatment-emergent mania: 2.4% vs 3.5% vs 4.1%, ns Weight gain (kg): +1.6 vs +1.0 vs +0.2, ns SAS mean change: -0.1 vs -0.2 vs -0.3, ns BARS mean change: 0 vs -0.1 vs -0.1, ns Dry mouth: 73 (40.6%) vs 79 (44.1%) vs 14 (7.8%), p<0.0001 for both Sedation: 58 (32.2%) vs 53 (29.6%) vs 11 (6.1%), p<0.0001 for both Somnolence: 44 (22.4%) vs 49 (27.4%) vs 15 (8.3%), p<0.0001 for both Dizziness: 41 (22.8%) vs 30 (16.8%) vs 15 (8.3%), p=0.0002, p=0.0171 Constipation: 20 (11.1%) vs 21 (11.7%) vs 8 (4.4%); p=0.0288, p=0.012	Withdrawals due to adverse events: 47 (26.1%) vs 29 (16%) vs 16 (8.8%), p<0.001, p<0.0392	

Evidence Table 9. Randomized controlled trials in patients with bipolar I disorder

Author, year Country Trial name (Quality score)	Study design Setting	Eligibility criteria	Therapy type Interventions Duration
Sachs, 2004 United States *Fair quality*	RCT, DB Multicenter Parallel Setting: patients were required to remain in the hospital for the first 7 days of the randomized period. After this time, they could be treated as either inpatients or outpatients as clinically indicated	Adult patients (≥ 18 years) hospitalized for a DSM-IV diagnosis of bipolar I disorder, most recent episode manic, who had been treated with lithium or divalproex for at least 7 of the 28 days immediately prior to randomization (day 1). A history of at least one documented manic or mixed episode prior to the episode responsible for the current hospitalization was required for selection. At screening and randomization, subjects were selected who had a YMRS score of ≥ 20, with a score of ≥ 4 on 2 of the 4 core YMRS items of irritability, speech, content, and disruptive/aggressive behavior. Patients were also required to have a score of at least 4 for overall bipolar illness on the CGI-BP.	Adjunctive Quetiapine (Q) 100 mg/day at day 1, 200 mg/day at day 2, 300 mg/day at day 3, and 400 mg/day at day 4, dose adjusted to optimize efficacy and tolerability between 200 and 600 mg/day at day 5 and 200 and 800 mg/day at days 6 to 21; mean last week dose was 504 mg/day Placebo (P) All patients began or continued treatment with lithium or divalproex within the established therapeutic range (0.7-1.0 mEq/L for lithium and 500-100 µg/mL for divalproex)

Evidence Table 9. Randomized controlled trials in patients with bipolar I disorder

Author, year Country Trial name (Quality score)	Run-in/Washout Period	Allowed other medications/ interventions	Method of outcome assessment and timing of assessment	Age Gender Ethnicity
Sachs, 2004 United States *Fair quality*	NR/NR	Lorazepam: ≤ 6 mg/day from screening to the day prior to randomization, 4 mg/day from days 1 to 4, 2 mg/day from days 5 to 7, and 1 mg/day from days 8 to 10 Zolpidem: max dose 10 mg/day Chloral hydrate: max dose 2 g/day Zaleplon: max dose 20 mg/day IM haloperidol used for severe agitation only during the screening period	Assessments were performed at baseline and days 4, 7, 10, 14 and 21 Primary: Mean change in YMRS total score at the final assessment Secondary: YMRS response rate (% patients with ≥ 50% decrease from baseline in the YMRS score; clinical remission (end-point YMRS score ≤ 12; change from baseline in CGI-BP Severity of Illness score; CGI-BP Global Improvement scale score; MADRS total score; PANSS total score and Activation and Supplemental Aggression Risk subscale scores; GAS score	Mean age=40.5 43.5% female Ethnicity nr

Evidence Table 9. Randomized controlled trials in patients with bipolar I disorder

Author, year Country Trial name (Quality score)	Other population characteristics	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/ analyzed
Sachs, 2004 United States *Fair quality*	Weight (kg): 87.2 BMI (kg/m2): 29.6 Mean YMRS: 31.3 Episode type (%) Manic moderate: 34.7 Manic severe without psychotic features: 22.9 Manic severe with psychotic features: 42.4 Known duration of illness (mean years): 17.8 Number of manic/mixed episodes during lifetime/past year: 8/1 Number of depressive episodes during lifetime/past year: 5/0	NR/NR/191	85 (44.5%) withdrawn/4 (2.1%) lost to fu/170 analyzed (Q n=81, P n=89)

Evidence Table 9. Randomized controlled trials in patients with bipolar I disorder

Author, year Country Trial name (Quality score)	Results	Method of adverse effects assessment
Sachs, 2004 United States *Fair quality*	Q vs P YMRS Total Score Mean Change: -13.76 vs -9.93, p=0.021 YMRS Response (% patients): 54.3 vs 32.6, p=0.005 YMRS remission (% patients): 45.7 vs 25.8, p=0.007 CGI-BP Severity of Illness score: -1.38 vs -0.78, p=0.001 CGI-BP Global Improvement response (% rated "much improved" or "very much improved"): 50.6 vs 31.5, p=0.012 MADRS mean change: -3.36 vs -2.79, p=NS PANSS Total: -12.47 vs -10.14, p=NS PANSS Activation: -4.08 vs -2.81, p=NS PANSS Supplemental Aggression Risk: -4.64 vs -2.84, p=0.020 Global Assessment Scale: 15.32 vs 11.49, p=0.075	SAS, BARS Rates of treatment-emergent depression (MADRS score ≥ 18, with an increase from baseline of ≥ 4 at any two consecutive assessments or at the last observation) Patients were examined and questioned on all study days regarding any adverse events. Safety evaluations were based on reports of adverse events, cc medication records, change from baseline to day 21 in clinical laboratory assessments (including hematology and chemistry), vital signs, ECG, physical examination, and weight. Adverse events included any treatment-emergent symptoms or worsening of existing symptoms, new illnesses, or clinically significant changes in laboratory tests, vital signs, weight, or ECG.

Evidence Table 9. Randomized controlled trials in patients with bipolar I disorder

Author, year Country Trial name (Quality score)	Adverse effects reported	Total withdrawals; withdrawals due to adverse events	Comment
Sachs, 2004 United States *Fair quality*	Somnolence: 36 (40%) vs 10 (10%), p>0.001 Headache: 24 (26.7%) vs 21 (21%), p=NS Dry mouth: 17 (18.9%) vs 4 (4%); p=0.005 Asthenia: 10 (11.1%) vs 3 (3%); p=0.052 Postural hypotension: 10 (11.1%) vs 3 (3%), p=0.052 Dizziness: 9 (10%) vs 6 (6%), p=NS SAS mean change: -1.0 vs -0.3, p=NS BARS mean change: -0.4 vs 0, p=NS Increase in weight (kg): 1.60 vs 0.36, p=nr Proportion of patients with ≥ 7% increase in weight: 3.9% vs 1.2%, p=NS Q=P in ECG parameters Rate of emergent depression: 17.3% vs 13.5%, p=NS	Total withdrawals: 35 (38.5%) vs 51 (51.0%); p=NS Withdrawals due to adverse events: 5 (5.5%) vs 6 (6%), p=NS	

Evidence Table 9. Randomized controlled trials in patients with bipolar I disorder

Author, year Country Trial name (Quality score)	Study design Setting	Eligibility criteria	Therapy type Interventions Duration
Yatham 2004	RCT, DB	Male and female hospitalized patients (>18 years) with a DSM-IV diagnosis of bipolar I disorder, whose most recent episode was manic and who had at least one manic or mixed episode in the previous 5 years, were eligible candidates for study. Pts had to have a YMRS score of > 20, including a score of > 4 on two of the core YMRS items of Irritability, Speech, Content, and Disruptive/Aggressive Behavior, and a Clinical Global Impression--Bipolar (CGI-BP) Severity of Illness score of > 4 (moderately ill).	Randomized to 3 or 6 weeks of (n=197) Quetiapine (QTP) with Lithium (Li) or Divalproex (DVP), or (n=205) placebo with Li/DVP. Quetiapine or placebo twice daily 100 mg/d up to 800 mg/d at end of study. Lorazepam 4 mg/d dose to 1mg/d at end of study.

Evidence Table 9. Randomized controlled trials in patients with bipolar I disorder

Author, year Country Trial name (Quality score)	Run-in/Washout Period	Allowed other medications/ interventions	Method of outcome assessment and timing of assessment	Age Gender Ethnicity
Yatham 2004	Patients taking lithium or divalproex for >7 days,	1 sleeping aid per day- monitored,	Vital sign measurements performed at baseline and days: 4, 7, 10, 14,21. Tests: CGI-BP Global Improvement Scale, CGI-BP Severity of Illness PANSS Supplemental Aggression	Mean age; 39.9 years Male 47% Ethnicity NR

Evidence Table 9. Randomized controlled trials in patients with bipolar I disorder

Author, year Country Trial name (Quality score)	Other population characteristics	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/ analyzed
Yatham 2004		NR/NR/402	161 (40%) withdrawn 11 (3%) lost to follow up 230 analyzed

Evidence Table 9. Randomized controlled trials in patients with bipolar I disorder

Author, year Country Trial name (Quality score)	Results	Method of adverse effects assessment
Yatham 2004	Young Mania Rating Scale (YMRS) scores at Day 21: QTP + Li/DVP: -15.29 vs PBO + Li/DVP: -12.19 (P<0.05) Clinical Global Impression-Bipolar Severity of illness scores at Day 21: QTP + Li/DVP: -1.59 vs PBO + Li/DVP: -1.19 (P<0.01) CGI-BP Global Improvement Scale scores at Day 21: QTP + Li/DVP: 58.5% vs PBO + Li/DVP: 43.2% (P<0.01) PANSS Supplemental Aggression Risk Scores at Day 21: QTP + Li/DVP: -5.05 vs PBO + Li/DVP: -3.69 (P<0.05)	Patient self-report, medical examination.

Evidence Table 9. Randomized controlled trials in patients with bipolar I disorder

Author, year Country Trial name (Quality score)	Adverse effects reported	Total withdrawals; withdrawals due to adverse events	Comment
Yatham 2004	Reported: QTP vs PBO Somnolence: 66 (33.7%) vs 19 (9.4%); P<0.001 Dry Mouth: 38 (19.4%) vs 6 (3.0%); P<0.001 Asthenia: 19 (9.7%) vs 8 (3.9%); P=0.034 Postural Hypotension: 13 (6.6%) vs 3 (1.5%); P=0.012 Weight Gain: 12 (6.1%) vs 5 (2.5%); P=0.090 Pharyngitis: 11 (5.6%) vs 5 (2.5%); P=0.134	QTP: 69 (35.2%) vs PBO: 92 (45.3%) Withdrawals due to adverse events: QTP: 7 (3.6%) vs PBO: 12 (5.9%)	

Evidence Table 9. Randomized controlled trials in patients with bipolar I disorder

Author, year Country Trial name (Quality score)	Study design Setting	Eligibility criteria	Therapy type Interventions Duration
Bowden 2005 Europe and Asia	RCT, DB, parallel, Multicenter	Eligible subjects were adult (≥ 18 years) inpatients (after day 7, patients could be discharged if investigator felt that was appropriate) hospitalized with a diagnosis of bipolar I disorder, current episode manic, according to the DSM-IV. All pts had experience at least 1 prior reliably documented manic or mixed episode. At screening and at randomization (7 days after screening), pts were required to have a score of at least 20 on the Young Mania Rating Scale (YMRS), including a a score of at least 4 on 2 of the 4 double-weighted YMRS items (irritability, speech, content, and disruptive/aggressive behavior). A Clinical Global Impression-Bipolar Version (CGI-BP) Severity of Illness score for overall bipolar illness of at least 4 was also required.	Monotherapy Quetiapine uptitrated to 400 mg/d on day 4; could be adjusted up to 600 mg/d on day 5 and up to 800 mg/d thereafter (days 6-84) Lithium 900 mg/d (dose adjustments between days 5-84 at investigator's discretion) 12-weeks

Evidence Table 9. Randomized controlled trials in patients with bipolar I disorder

Author, year Country Trial name (Quality score)	Run-in/Washout Period	Allowed other medications/ interventions	Method of outcome assessment and timing of assessment	Age Gender Ethnicity
Bowden 2005 Europe and Asia	NR/ medications known to be associated with withdrawal from treatment were tapered off (over approximately 1 week)	Medications prescribed for stable medical, non-psychiatric illnesses, oral contraceptives, and antihypertensive treatments (if stable dosage ≥1 month prior to randomization). Lorazepam allowed for agitation, not sedation. These sedative hypnotics allowed, 1 per day: Zolpidem, chloral hydrate, zopiclone, zaleplon. Anticholinergic medications allowed only for EPS.	YMRS, PANSS, MADRS, CGI and CGI-BP assessed on days 1, 4, 7, 14, 21, 28, 42, 56, 70, 84. Global Assessment Scale (GAS) assessed on days 1, 21, and 84. Primary efficacy endpoint: change in YMRS at day 21 Secondary efficacy endpoint: change in YMRS at day 84, and changes in other scores on days 21 and 84	Mean age: 39.0 years 57.7% male Ethnicity NR

Evidence Table 9. Randomized controlled trials in patients with bipolar I disorder

Author, year Country Trial name (Quality score)	Other population characteristics	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/ analyzed
Bowden 2005 Europe and Asia	Mean baseline scores, quetiapine (N=107) vs lithium (N=98) vs placebo (N=97) YMRS: 32.7 vs 33.3 vs 34.0 MADRS: 6.1 vs 6.3 vs 6.2 PANSS: 58.2 vs 58.0 vs 58.7 CGI-BP Severity of Illness score: 4.9 vs 4.9 vs 5.0	NR/NR/302	128 (42.4%) withdrawn/ 7 (2.3) lost to follow-up/ 300 analyzed

Evidence Table 9. Randomized controlled trials in patients with bipolar I disorder

Author, year Country Trial name (Quality score)	Results	Method of adverse effects assessment
Bowden 2005 Europe and Asia	Quetiapine vs lithium (Li) vs placebo Change in mean YMRS scores from baseline at day 21: -14.62 vs -15.20 vs -6.71 (p=NS, quet vs Li; p<0.001 for quet vs placebo and Li vs placebo) at day 84: -20.28 vs -20.76 vs -9.00 (p=NS, quet vs Li; p<0.001 for quet vs placebo and Li vs placebo) % of patients with a YMRS response rate (defined as a >=50% reduction in score) : at day 21: 53.3% vs 53.1% vs 27.4% (p=NR, quet vs placebo; p<0.001 for quet vs placebo and Li vs placebo) at day 84: 72.0% vs 75.5% vs 41.1% (p=NR, quet vs placebo; p<0.001 for quet vs placebo and Li vs placebo) Change in CGI-BP scores from baseline (p<0.001 for quet vs placebo and Li vs placebo both days) : at day 21: -1.84 vs -1.41 vs -0.66 at day 84: -2.20 vs -2.18 vs -0.89 Change in PANSS scores from baseline, quet vs placebo (lithium data given only as "similar significant effects were seen with Li vs pla") : Total PANSS score, at day 21: -8.71 vs -2.12, p<0.001 at day 84: -11.78 vs -1.04, p<0.001 PANSS Positive subscale, day 21: -4.93 vs -1.55, p<0.001 at day 84: -6.85 vs-1.48, p<0.001 Change in MADRS score from baseline : at day 21, quet vs placebo: -1.55 vs -0.05, p=0.15 at day 84: quet -1.49 vs lithium -1.83 vs placebo +1.21 (p=0.002 for quet vs pla; p=(Change in Global Assessment Scale (GAS) from baseline, quet vs placebo: at day 21: 17.96 vs 5.59, p<0.001 and day 84: 26.35 vs 9.26, p<0.001 Completers at day 21: 90.7% vs 85.7% vs 69.1% at day 84: 67.3% vs 68.4% vs 36.1%	Vital sign measure ments at days 1, 4, 7, 14, 21, 28, 42, 56, 70, and 84 Safety evaluations were based on reports of AEs, trought serum concentrations, concomitant medication records, vital signs, weight, and clinical lab parameters. EPS assessed with AE reporting, Simpson-Angus Scale (SAS), and the Barnes Akathisia Rating Scale (BARS) Treatment-emergent depression, defined a priori as MADRS score >=18 and an increase of >=4 from baseline on any 2 consecutive post-baseline visits, or at the final study visit, was monitored.

Evidence Table 9. Randomized controlled trials in patients with bipolar I disorder

Author, year Country Trial name (Quality score)	Adverse effects reported	Total withdrawals; withdrawals due to adverse events	Comment
Bowden 2005 Europe and Asia	Quetiapine vs lithium vs placebo Dry mouth: 24.3% vs 6.1% vs 2.1% Somnolence: 19.6% vs 9.2% vs 3.1% Weight gain: 15.0% vs 6.1% vs 1.0% Dizziness: 12.1% vs 7.1% vs 2.1% Insomnia: 9.3% vs 16.3% vs 20.6% Headache: 7.5% vs 12.2% vs 4.1% Asthenia: 6.5% vs 4.1% vs 1.0% Depression: 5.6% vs 1.0% vs 1.0% Tremor: 5.6% vs 18.4% vs 4.1% Diarrhea: 4.7% vs 5.1% vs 4.1% Weight loss: 1.9% vs 6.1% vs 1.0% Anorexia: 0.9% vs 9.2% vs 4.1% Nausea: 0.9% vs 6.1% vs 2.1% Vomiting: 0.9% vs 6.1% vs 2.1% Akathisia: 0.9% vs 3.1% vs 6.1% EPS-related AEs, quet vs placebo: 13.1% vs 9.3% Mean weight gain, observed cases (LOCF) from baseline: 3.3 (LOCF: 2.6) vs 1.0 (LOCF: 0.7) vs 0.3 (LOCF: -0.08) kg p<0.001 for quet vs placebo and p=NS for lithium vs placebo Emergent depression, day 84: 5.6% vs 3.1% vs 8.4%, p=NS for comparisions Prolactin concentration (in micrograms/L) change from baseline: -18.4 vs -17.3 vs -13.2 SAS and BARS scores: no significant difference in change from baseline for quet vs placebo	Total withdrawals: 42.4% (128/302) Quetiapine vs lithium vs placebo Total withdrawals by drug group: 32.7% vs 31.6% vs 63.9% Withdrawals due to AEs: 6.5% vs 6.1% vs 4.1%	Both groups got blood testing to keep blinding valid

Evidence Table 9. Randomized controlled trials in patients with bipolar I disorder

Author, year Country Trial name (Quality score)	Study design Setting	Eligibility criteria	Therapy type Interventions Duration
Risperidone			
Yatham, 2003 International *Fair quality*	RCT Multicenter Hospitalized ≥ 4 days	Patients, aged 18-65, with DSM-IV bipolar disorder with a manic or mixed episode, minimum baseline score of 20 on the YMRS; receiving a mood stabilizer for a minimum of 2 weeks prior to screening; medically stable, randomized within 7 days of hospital admission	Adjunctive Risperidone 1-6 mg Placebo 3-week DB 10-week open-label

Evidence Table 9. Randomized controlled trials in patients with bipolar I disorder

Author, year Country Trial name (Quality score)	Run-in/Washout Period	Allowed other medications/ interventions	Method of outcome assessment and timing of assessment	Age Gender Ethnicity
Risperidone				
Yatham, 2003 International *Fair quality*	3-day washout	Primary therapy with lithium, divalproex or carbamazepine Lorazepam 6 mg for agitation during the wash-out period and up to 4 mg daily during the first 7 days of the double-blind period Anti-parkinsonian and antidepressant drugs allowed after randomization	▪ Change in YMRS ▪ percent of patients showing a ≥ 50% improvement in YMRS score ▪ time (days) to onset of therapeutic response (≥ 30% improvement in YMRS score) ▪ change in CGI, BPRS, HRSD scores ▪ percent of patients who used adjunctive lorazepam	Mean age=39.5 58% female Ethnicity nr

Evidence Table 9. Randomized controlled trials in patients with bipolar I disorder

Author, year Country Trial name (Quality score)	Other population characteristics	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/ analyzed
Risperidone			
Yatham, 2003 International *Fair quality*	Axis I diagnosis Bipolar disorder, manic=92% Bipolar disorder, mixed=8% Current episode Mild severity=3% Moderate severity=32.7% Severe with psychotic features=43.3% Severe without psychotic features=20.7%	NR/157/151 Risperidone n=75 Placebo n=76	66 (44%) withdrawn/2% lost to fu/142 (94.6%) analyzed

Evidence Table 9. Randomized controlled trials in patients with bipolar I disorder

Author, year Country Trial name (Quality score)	Results	Method of adverse effects assessment
Risperidone		
Yatham, 2003 International *Fair quality*	Risperidone vs placebo YMRS Change in mean points: -49% vs -36%; p=NS % patients with ≥ 50% improvement: 59% vs 41%; p<0.05 Adjunctive lorazepam use (% patients): 72% vs 63%; p=NS CGI (% patients with 'much' or 'very much' improvement at endpoint): 61% vs 43%; p=0.022 BPRS (change in mean points): -10.1% vs -4.8%; p=0.006 HRSD (change in mean points): risperidone=placebo (data nr)	ESRS and CGI of overall severity of dystonia, parkinsonism and dyskinesia administered at baseline and on days 8, 15, and 22

Evidence Table 9. Randomized controlled trials in patients with bipolar I disorder

Author, year Country Trial name (Quality score)	Adverse effects reported	Total withdrawals; withdrawals due to adverse events	Comment
Risperidone			
Yatham, 2003 International	Risperidone (n=75) vs placebo (n=75)	Risperidone (n=75) vs placebo (n=75)	
	% patients with ≥ 1 adverse event: 57% vs 51%; p=NS	Total withdrawals: 36% vs 52%; p=NS	
Fair quality	Extrapyramidal-related adverse events	Withdrawals due to adverse events: 1% vs 4%; p=NS	
	Any extrapyramidal-related adverse events: 21% vs 8%; p=0.013		
	Change in mean ESRS scores: -0.1 vs -0.1; p=NS		
	Hyperkinesia: 7% vs 0; p=NS		
	Tremor: 5% vs 1%; p=NS		
	Extrapyramidal disorder: 4% vs 4%; p=NS		
	Hypertonia: 4% vs 3%; p=NS		
	Gait abnormality: 3% vs 0; p=NS		
	Tetany: 3% vs 0; p=NS		
	Ataxia: 1% vs 0; p=NS		
	Dystonia: 1% vs 0; p=NS		
	Hypokinesia: 1% vs 0; p=NS		
	Dyskinesia: 0 vs 1%; p=NS		
	Other		
	Headache: 9% vs 9%; p=NS		
	Insomnia: 4% vs 8%; p=NS		
	Nausea: 5% vs 3%; p=NS		
	Mean weight increase (kg): 1.7 vs 0.5; p=0.012		

Evidence Table 9. Randomized controlled trials in patients with bipolar I disorder

Author, year Country Trial name (Quality score)	Study design Setting	Eligibility criteria	Therapy type Interventions Duration
Hirschfeld, 2004	RCT Multicenter Hospitalized ≥ 7 days	Men and women age 18 years or older who met DSM-IV criteria for bipolar I disorder, current episode pure mania; history of at least one prior documented manic or mixed episode that required treatment prior to screening; YMRS score ≥ 20 at screening and baseline evaluations; MADRS score ≤ 20 at the baseline evaluation	Monotherapy Risperidone 1-6 mg daily Placebo 3-week DB
Khanna, 2003 Abstract-only *Fair quality*	RCT Multicenter Hospitalization status unclear	Adults (≥ 18) who provided consent; DSM-IV criteria for bipolar I disorder; voluntary hospitalization with a primary diagnosis of manic or mixed episode; history of at least one prior manic or mixed episode; baseline YMRA score ≥ 20	Risperidone 1-6 mg (mean dose 5.6) Placebo Duration=3 weeks

Evidence Table 9. Randomized controlled trials in patients with bipolar I disorder

Author, year Country Trial name (Quality score)	Run-in/Washout Period	Allowed other medications/ interventions	Method of outcome assessment and timing of assessment	Age Gender Ethnicity
Hirschfeld, 2004	3-day washout	Lorazepam ≤ 8 mg daily during washout and first 3 days of treatment; ≤ 6 mg daily during days 4-7; ≤ 4 mg daily during days 8-10 Antiparkinsonian medications allowed throughout the study	Primary: Mean change in YMRS Secondary: Other YMRS, CGI, MADRS, PANSS, GAS measurements Scales administered at screening, baseline, and on days 1, 3, 7, 14, and 21	Mean age=39 43.2% female 71.8% white
Khanna, 2003 Abstract-only *Fair quality*	NR/wash-out unclear	Lorazepam allowed during washout and for the first 10 treatment days	Primary: Mean change in YMRS total scores Secondary: CGI, PANSS, MADRS, GAS	Mean age=35.1 62% male Ethnicity NR

Evidence Table 9. Randomized controlled trials in patients with bipolar I disorder

Author, year Country Trial name (Quality score)	Other population characteristics	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/ analyzed
Hirschfeld, 2004	Psychotic features present: 42.5%	337/NR/262 Risperidone n=134 Placebo n=125	132 (51%) withdrawn 4 (1.5%) lost to fu 246 (95%) analyzed
Khanna, 2003 Abstract-only *Fair quality*	Weight (kg): 54.4 With psychotic features at baseline: 58.8% YMRS Total Score: 37.2 CGI Score: 4 GAS Score: 35.0 MADRS score: 5.1 PANSS total score: 54.2	NR/NR/290	Withdrawn=130 (44.8%)/8 (2.7%) lost to fu/analyzed=unclear

Evidence Table 9. Randomized controlled trials in patients with bipolar I disorder

Author, year Country Trial name (Quality score)	Results	Method of adverse effects assessment
Hirschfeld, 2004	Risperidone vs placebo YMRS mean change (mean points): -10.6 vs -4.8; p<0.001 YMRS response (% patients with ≥ 50% improvement): 43% vs 24%; p=0.006 YMRS remission (% patient with score ≤ 12): 38% vs 20%; p=0.007 CGI mean change (points): -1.1 vs -0.4; p<0.001 GAS mean change (points): 12.5 vs 5.5; p<0.001 PANSS total score mean change (points imputed from a graph): -10 vs -1.5; p<0.001 MADRS mean change (points estimated from a graph): -7.5 vs -8.1; p=NS	Extrapyramidal Symptom Rating Scale administered at days 7, 14, and 21 to measures movement disorders Other adverse events assessed by investigatory query
Khanna, 2003 Abstract-only *Fair quality*	Response (≥ 50% reduction in YMRS total scores): 106 (73%) vs 52 (36%); p<0.001 % Reduction in YMRS Total Score: 28% vs 11%; p<0.001 % GAS improvement: 79% vs 37%; p<0.001 Change in CGI-severity from baseline to week 3 (estimated from graph): -2 vs -1; significance unclear Change in MADRS from baseline to week 3 (estimated from graph): -3 vs -2.2; p<0.01	NR

Evidence Table 9. Randomized controlled trials in patients with bipolar I disorder

Author, year Country Trial name (Quality score)	Adverse effects reported	Total withdrawals; withdrawals due to adverse events	Comment
Hirschfeld, 2004	Manic reaction: 7.5% vs 4.8%; p=NS Death: 0 vs 2/125 (1.6%); p=NS Somnolence: 28% vs 7%; p<0.001 Headache: 14% vs 15%; p=NS Hyperkinesia: 16% vs 5%; p=NS Dizziness: 11% vs 9%; p=NS Dyspepsia: 11% vs 6%; p=NS Nausea: 11% vs 2%; p=NS Extrapyramidal Symptom Rating Scale (mean change) Total score: 0.6 vs 0; p=0.05 Parkinsonism subscale: 0.5 vs 0; p=0.05 Dystonia: 0.1 vs 0; p=NS Dyskinesia: 0 vs 0; p=NS	Risperidone vs placebo Total withdrawals: 44% vs 58%; p<0.05 Withdrawals due to adverse events: 8% vs 6%; p=NS	
Khanna, 2003 Abstract-only *Fair quality*	EPS disorder: 51 (35%) vs 9 (6%); p<0.001 Insomnia: 7 (5%) vs 14 (10%); p=NS Tremor: 15 (10%) vs 1 (1%); p=0.0004 Headache: 9 (6%) vs 4 (3%); p=NS Somnolence: 9 (6%) vs 4 (3%); p=NS Mean body weight changes (kg): +0.1 vs +0.1 QT intervals: no prolongation of QTc intervals (> 500 ms) was observed in either group	Total withdrawals: 57 (39%) vs 73 (51%); p=NS Withdrawals due to adverse events: 5 (3.4%) vs 3 (2.1%); p=NS	

Evidence Table 9. Randomized controlled trials in patients with bipolar I disorder

Author, year Country Trial name (Quality score)	Study design Setting	Eligibility criteria	Therapy type Interventions Duration
Smulevich 2005 International	RCT,DB, Parallel, Multicenter	Eligible pts were physically healthy, aged 18 years or older, and had bipolar I disorder according to DSM-IV criteria and a history of at least one prior documented manic or mixed episode. All pts met DSM-IV criteria for a current manic episode, for which they were voluntarily hospitalized. All pts had a score of >20 on the Young Mania Rating Scale (YMRS) at screening and baseline and a Montgomeray-Asberg Depression Rating Scale (MADRS) of < 20 at baseline.	Risperidone: 1-6 mg/day Haloperidol: 2-12 mg/day or Placebo

Evidence Table 9. Randomized controlled trials in patients with bipolar I disorder

Author, year Country Trial name (Quality score)	Run-in/Washout Period	Allowed other medications/ interventions	Method of outcome assessment and timing of assessment	Age Gender Ethnicity
Smulevich 2005 International	3 week run-in/ 3 day washout of any prior psychotropic drug medication	Lorazepam (up to 4 mg/day).	Young Mania Rating Scale (YMRS) Clinical Global Impression (CGI) Global Assessment Scale (GAS) Montgomery-Asberg Depression Rating Scale (MADRS) Brief Psychiatric Rating Scale (BPRS)	Mean age= 39.7 years 53% male 65% Caucasian

Evidence Table 9. Randomized controlled trials in patients with bipolar I disorder

Author, year Country Trial name (Quality score)	Other population characteristics	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/ analyzed
Smulevich 2005 International	Risperidone vs Haloperidol vs Placebo Psychotic features present: 35.1%vs 34% vs 20% Number of previous manic episodes (mean): 4.6 vs 4.1 vs 4.4 Age at onset of bipolar disorder (mean): 28.9 vs 26.7 vs 27.8	NR/NR/438	NR/NR/386

Evidence Table 9. Randomized controlled trials in patients with bipolar I disorder

Author, year Country Trial name (Quality score)	Results	Method of adverse effects assessment
Smulevich 2005 International	Risperidone vs Haloperidol vs Placebo Young Mania Rating Scale mean scores: (YMRS) Week 3: 17 vs 17.4 vs 22.1 Week 12: 11.4 vs 12.9 vs NR Clinical Global Impression mean scores: (CGI) Week 3: 2.3 vs 2.4 vs 2.8 Week 12: 1.6 vs 1.8 vs NR Global Assessment Scale mean scores: (GAS) Week 3: 58.2 vs 57.3 vs 50.9 Week 12: 66.6 vs 63.7 vs NR Montgomery-Asberg Depression Rating Scale mean scores: (MADRS) Week 3: 3.2 vs 4 vs 4.6 Week 12: 4 vs 4.4 vs NR Brief Psychiatric Rating Scale mean scores: (BPRS) Week 3: 25.4 vs 25.7 vs 27 Week 12: 23.9 vs 24.4 vs NR	Patient report, physical exam

Evidence Table 9. Randomized controlled trials in patients with bipolar I disorder

Author, year Country Trial name (Quality score)	Adverse effects reported	Total withdrawals; withdrawals due to adverse events	Comment
Smulevich 2005 International	Risperidone vs Haloperidol vs Placebo: Extrapyramidal disorder: Week 3: 17% vs 40% vs 9% Week 12: 24% vs 43% vs NR Somnolence: Week 3: 5% vs 3% vs 1% Week 12: 10% vs 6% vs NR Hyperkinesia: Week 3: 9% vs 15% vs 3% Week 12: 10% vs 19% vs NR Tremor: Week 3: 6% vs 11% vs 6% Week 12: 8% vs 13% vs NR Hypertonia: Week 3: 4% vs 9% vs 0 Week 12: 5% vs 10% vs NR	Withdrawals due to adverse events: risperidone: 6 (4%) haloperidol: 4 (3%) placebo: 7 (5%)	

Evidence Table 9. Randomized controlled trials in patients with bipolar I disorder

Author, year Country Trial name (Quality score)	Study design Setting	Eligibility criteria	Therapy type Interventions Duration
Shelton 2004 United States	RCT, DB	Patients were eligible for participation in the study if they (1) had definite and principal diagnosis of bipolar type I or II disorder, currently in a depressed phase; (2) were free of current psychosis, lifetime history of non-affective psychotic disorder, and history of substance abuse in the past 6 months or substance dependence in the past 12 months; (3) were receiving a clinically acceptable type, dose, and plasma level of a mood-stabilizing agent (i.e.valproate, lithium, or carbamazepine) but were otherwise free of psychotropics or potentially psychoactive herbs; (4) had a score of ≥18 on the 17-item version of the Hamilton Rating Scale for Depression (HAM-D) and 8 or below on the Young Mania Rating Scale (YMRS) at both the screening and baseline visits; and (5) were medically healthy.	Adjunctive and monotherapy Risperidone 1 to 4 mg/d (initiated at 1 mg/d and titrated every week by 1 mg/d up to a max of 4 mg/d) Mean max dose (SD): 2.15 (1.2) mg/d Paroxetine 20-40 mg/d (initiated at 20 mg/d and titrated in 10 mg increments every week up to 40 mg) Mean max dose (SD): 35.0 (21.2) mg/d Risperidone + Paroxetine Mean max dose (SD): risp 1.16 (0.67) mg/d + parox 22.0 (12.3) mg/d 12-week DB

Evidence Table 9. Randomized controlled trials in patients with bipolar I disorder

Author, year Country Trial name (Quality score)	Run-in/Washout Period	Allowed other medications/ interventions	Method of outcome assessment and timing of assessment	Age Gender Ethnicity
Shelton 2004 United States	NR / NR	All patients continued mood stabilizers; lorazepam 3 mg/d allowed in 1st month of treatment	Primary efficacy outcome: HAM-D (Hamilton Rating Scale for Depression), Secondary measures: YMRS, MADRS, CGI-S, CGI-I, and BDI (Beck Depression Inventory) Assessments made at baseline and then on a weekly or bi-weekly basis	Mean age: 35.6 years 50% male Ethnicity NR

Evidence Table 9. Randomized controlled trials in patients with bipolar I disorder

Author, year Country Trial name (Quality score)	Other population characteristics	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/ analyzed
Shelton 2004 United States	Mean baseline scores (SD) HAM-D: 21.5 (3.8) BDI: 27.8 (12.2) MADRS: 17.7 (7.1)	NR/ NR/ 30	11/ 2/ unclear

Evidence Table 9. Randomized controlled trials in patients with bipolar I disorder

Author, year Country Trial name (Quality score)	Results	Method of adverse effects assessment
Shelton 2004 United States	Risperidone alone vs Risp+Paroxetine vs Paroxetine alone Mean changes (SD) from baseline to endpoint (LOCF) for these tests: HAM-D: 5.2 (8.7) vs 6.3 (6.5) vs 5.6 (6.5), p=NS MADRS: 4.2 (13.7) vs 5.8 (6.1) vs 7.9 (7.3), p=NS There were no significant difference between groups at any rating point (LOCF) for any assessments (HAM-D, MADRS, BDI< CGI, YMRS, SAS, BAS) except: at 4 weeks, YMRS means scores (SD) showed a small significant difference: Risperidone alone vs Risp+Paroxetine vs Paroxetine alone 1.3 (1.04) vs 2.2 (2.4) vs 0 (risp+parox vs parox, p<0.03) Risperidone alone vs Risp+Paroxetine vs Paroxetine alone Remission (HAMD score ≤7 at endpoint) achieved in 1 patient (10%) vs 3 patients (30%) vs 2 patients (20%), p=NS Response (>=50% improvement in HAMD score at endpoint) occurred in 3 patients (30%) vs 3 patients (30%) vs 2 patients (20%), p=NS	Simpson-Angus Scale (SAS) and Barnes Akathisia Scale (BAS) assessed at baseline and then at weekly or biweekly bases

Evidence Table 9. Randomized controlled trials in patients with bipolar I disorder

Author, year Country Trial name (Quality score)	Adverse effects reported	Total withdrawals; withdrawals due to adverse events	Comment
Shelton 2004 United States	Risperidone vs Risp+Paroxetine vs Paroxetine SAS mean scores (SD) : 0.4 (0.5) vs 1.2 (1.3) vs 0, p<0.03 for risp+parox vs paroxetine 1 mild case of hypomania (YMRS score=13) in the paroxetine group AEs reported (# of patients/group): Appetite increase: 2 vs 2 vs 2 Weight gain: 1 vs 4 vs 1 Diarrhea: 2 vs 1 vs 3 GI distress: 2 vs 2 vs 2 Somnolence: 5 vs 2 vs 2 Sexual dysfunction: 0 vs 3 vs 2 Insomnia: 0 vs 1 vs 2 Dry mouth: 1 vs 1 vs 3 Fatigue: 2 vs 1 vs 2 Headache: 1 vs 0 vs 1 Tremor: 1 vs 1 vs 1 Blurred vision: 0 vs 1 vs 0 Dizziness: 0 vs 1 vs 1 Parethesias: 0 vs 1 vs 0 These AEs were reported by risp=1 vs 0 vs 0 patients: anxiety, constipation, dermatitis, dreaming increased, edema, joint pain, and myoclonus	Total withdrawals: 11/30 patients (36.7%) Total withdrawals by group: Risp-5 patients (50%), Risp+paroxetine - 4 patients (40%), Paroxetine - 2 patients (20%) Withdrawals due to AEs: 5 patients total (50%). (Risp - 1 patient (10%); Risp+paroxetine - 3 patients (30%); Paroxetine - 1 patient (10%)) :	

Evidence Table 9. Randomized controlled trials in patients with bipolar I disorder

Author, year Country Trial name (Quality score)	Study design Setting	Eligibility criteria	Therapy type Interventions Duration
Inpatients			
Clozapine			
Barbini 1997	RCT	This sample included 30 bipolar inpatients (12 men, 18 women) consecutively admitted to the Research Center for Mood Disorders for a manic episode, according to the DSM IV criteria. The severity of manic symptomatology was classified in stage II-III for all patients. All patients had been treated with lithium salts for at least six months before the beginning of the study.	Mean dose: clozapine 175 mg/day chlorpromazine 310 mg/day Duration: 3 weeks
Olanzapine			
Berk 1999	RCT, DB	Thirty pts aged 18-65 years who were admitted with an acute manic episode were selected for the study. To be included, the patients were required to meet DSM-IV criteria for bipolar disorder, manic phase.	olanzapine 10 mg/day lithium carbonate 800 mg/day Duration: 4 weeks

Evidence Table 9. Randomized controlled trials in patients with bipolar I disorder

Author, year Country Trial name (Quality score)	Run-in/Washout Period	Allowed other medications/ interventions	Method of outcome assessment and timing of assessment	Age Gender Ethnicity
Inpatients				
Clozapine				
Barbini 1997	NR/ NR	NR	Young Rating Scale of Mania (YRSM)	Mean age: 36.6 years 37% male Ethnicity NR
Olanzapine				
Berk 1999	NR/ NR	lorazepam 4-12 mg if necessary	Mania Scale (MAS) Brief Psychiatric Rating Scale (BPRS) Clinical Global Impression (CGI) Global Assessment Functioning Scale (GAF)	Mean age: 30.7 years Gender unclear Ethnicity NR

Evidence Table 9. Randomized controlled trials in patients with bipolar I disorder

Author, year Country Trial name (Quality score)	Other population characteristics	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/ analyzed
Inpatients			
Clozapine			
Barbini 1997	clozapine vs chlorpromazine: Duration of illness (years): 9.7(7.2) vs 13.3(6.8) Duration of lithium treatment (months): 21.9(24.3) vs 8.4(7.4) Duration of last euthymic period (months): 10.26(11.04) vs 34.3(44.1) YRSM total score: 38.3(4.2) vs 34.1(8.0)	NR/NR/30	3/NR/27
Olanzapine			
Berk 1999	Olanzapine vs lithium Mean (range) episode duration: 19.3(8-38) vs 15.06(7-29) Mean (range) no. manic episodes: 3.4(1-8) vs 2.13(0-5) Mean (range) no. depressive episodes: 0.7(0-3) vs 0.26(0-1) Mean (range) no. previous admissions: 2.9(1-11) vs 1.6(1-4)	NR/NR/30	4/NR/30

Evidence Table 9. Randomized controlled trials in patients with bipolar I disorder

Author, year Country Trial name (Quality score)	Results	Method of adverse effects assessment
Inpatients		
Clozapine		
Barbini 1997	Clozapine vs chlorpromazine YMRS (clozapine showed better improvement): group effect: p=0.07 time effect: p<0.0001 time-group interaction: p<0.0001 Post-hoc comparison: after 2 weeks treatment: p=0.0001 after 3 weeks treatment: p=0.0096	Dosage records and treatment emergent symptoms (DOTES) EPS: Simpson-Angus Rating scale
Olanzapine		
Berk 1999	Baseline vs endpoint: BPRS: olanzapine: 53.3 vs 28.0, p=0.0002 lithium: 46.8 vs 28.2, p=0.0002 olanzapine vs lithium at baseline, p=0.077 olanzapine vs lithium at endpoint, p=0.439 CGI-severity scale: olanzapine: 4.67 vs 2.29 lithium: 4.67 vs 2.83 olanzapine vs lithium at baseline, p=1.000 olanzapine vs lithium at endpoint, p=0.025 % change from baseline: olanzapine vs lithium = 48.6% vs 38.3, p=0.018 CGI-improvement scale: olanzapine: 4.27 vs 2.36 lithium: 4.27 vs 2.75 olanzapine vs lithium at baseline, p=0.808 olanzapine vs lithium at endpoint, p=0.163 GAF: olanzapine vs lithium at endpoint: 57.9 vs 56.2, p=0.583 MAS: olanzapine: 31.7 vs 10.2 lithium: 31.6 vs 13.2 olanzapine vs lithium at baseline, 0.900 olanzapine vs lithium at endpoint, 0.315	

Evidence Table 9. Randomized controlled trials in patients with bipolar I disorder

Author, year Country Trial name (Quality score)	Adverse effects reported	Total withdrawals; withdrawals due to adverse events	Comment
Inpatients			
Clozapine			
Barbini 1997	Clozapine vs Chlorpromazine hypersialorrhea: 10(67%) vs 3(25%) sedation: 7(46%) vs 8(68%) WBC decrease: 8(53%) vs 0(0%) hypotension: 5(30%) vs 5(45%) EPSE: 1(7%) vs 7(56%)	NR	
Olanzapine			
Berk 1999	SAS: olanzapine: 0.53 vs 0.64 lithium: 2.33 vs 2.83 olanzapine vs lithium at baseline, 0.204 olanzapine vs lithium at endpoint, 0.185 lorazepam used (mg): olanzapine vs lithium = 69.1 vs 74.6, p=0.429 biperidin used (mg): olanzapine vs lithium = 6.33 vs 0.66, p=0.962 Barnes Akathisia Scale: no treatment emergent akathisia	Olanzapine vs lithium Total withdrawals: 1 vs 3 Withdrawals due to AEs: 1 vs 1	There was a third limb of the study using lamotrigine, that date is not presented here.

Evidence Table 9. Randomized controlled trials in patients with bipolar I disorder

Author, year Country Trial name (Quality score)	Study design Setting	Eligibility criteria	Therapy type Interventions Duration
Shi, 2002	RCT, DB	patients had a diagnosis of bipolar I disorder and currently displayed an acute manic or mixed episode (with or without psychotic features) according to DSM-IV based on the Structured Clinical Interview for DSM-IV-Patient Version and had a baseline Young-Mania Rating Scale total score of >= 20.	olanzapine 15 mg/day haloperidol 10 mg/day Duration: 12 weeks

Evidence Table 9. Randomized controlled trials in patients with bipolar I disorder

Author, year Country Trial name (Quality score)	Run-in/Washout Period	Allowed other medications/ interventions	Method of outcome assessment and timing of assessment	Age Gender Ethnicity
Shi, 2002	NR/ 2-7 days	benzodiazepine, anticholinergic, lorazepam, benzotropine mesylate, biperiden as needed	Young Mania Rating Scale (YMRS) Hamilton Rating Scale for Depression (HAM-D) Health-related quality of life (HRQOL)	Mean age: 39.2 years 39.2% male 46.3% Caucasian

Evidence Table 9. Randomized controlled trials in patients with bipolar I disorder

Author, year Country Trial name (Quality score)	Other population characteristics	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/ analyzed
Shi, 2002	SF-36 summary scores- physical: 52.76 SF-36 summary scores- mental: 44.45 patients in work: 47.4%	NR/NR/453	NR/NR/304

Evidence Table 9. Randomized controlled trials in patients with bipolar I disorder

Author, year Country Trial name (Quality score)	Results	Method of adverse effects assessment
Shi, 2002	olanzapine vs haloperidol, p value SF-36 dimension and summary scores, change from baseline at week 6: Dimension scores bodily pain: 3.99(25.46) vs 3.93(23.92), p=0.740 general health: -1.09(20.76) vs -7.36(20.67), p=0.01 mental health: 2.45(21.54) vs -0.96(20.74), p=0.173 physical function: 1.79(24.27) vs -10.96(27.25), p<0.001 role-emotional problem: 6.04(51.51) vs 3.46(58.49), p=0.543 role-physical problem: 3.28(46.93) vs -15.63(46.74), p<0.001 social functioning: 10.95(36.73) vs 2.13(36.48), p=0.036 vitality: -6.66(22.08) vs -14.11(22.85), p=0.002 Summary scores physical: 0.27(9.35) vs -4.27(8.79), p=0.01 mental: 1.5(13.42) vs 0.74(13.35), p=0.58 SF-36 dimension and summary scores, change from baseline at week 12: Dimension scores bodily pain: 5.86(29.12) vs 6.38(23.41), p=0.801 general health: 0.43(23.50) vs -7.69(23.13), p=0.001 mental health: 3.38(24.26) vs -1.17(23.35), p=0.126 physical function: 1.54(26.18) vs -10.46(26.32), p<0.001 role-emotional problem: 18.72(53.19) vs 13.81(58.9), p=0.286 role-physical problem: 6.79(44.76) vs -7.27(46.25), p=0.008 social functioning: 15.82(39.91) vs 10.37(42.41), p=0.171 vitality: -9.5(23.32) vs -17.41(26.66), p=0.004 Summary scores physical: 0.08(9.89) vs -3.66(8.74), p<0.001 mental: 3.5(15.0) vs 2.08(15.71), p=0.327 Work status measurements at week 6: patient in work(%): 31.1 vs 35.8, p=0.403 change in work activities impairment score: -0.16 vs -0.42, p=0.250 change in household activities impairment score: -0.30 vs -0.45, p=0.552 Work status measurements at week 12: change in work activities impairment score: 0.36 vs -0.28, p=0.007 change in household activities impairment score: 0.13 vs -0.28, p=0.023	NR

Evidence Table 9. Randomized controlled trials in patients with bipolar I disorder

Author, year Country Trial name (Quality score)	Adverse effects reported	Total withdrawals; withdrawals due to adverse events	Comment
Shi, 2002	NR	NR	

Evidence Table 9. Randomized controlled trials in patients with bipolar I disorder

Author, year Country Trial name (Quality score)	Study design Setting	Eligibility criteria	Therapy type Interventions Duration
Risperidone			
Segal 1998	RCT, DB	The patients were required to meet DSM-IV criteria for bipolar disorder, manic phase, on as structured clinical interview	risperidone 6 mg/day haloperidol 10 mg/day lithium 800-1200 mg/day Duration: 4 weeks

Evidence Table 9. Randomized controlled trials in patients with bipolar I disorder

Author, year Country Trial name (Quality score)	Run-in/Washout Period	Allowed other medications/ interventions	Method of outcome assessment and timing of assessment	Age Gender Ethnicity
Risperidone				
Segal 1998	NR/ NR	Lorazepam was given when necessary to control aggression	Primary outcome measure: Mania Rating Scale (MRS) Secondary outcome measures: Brief Psychiatric Rating Scale (BPRS) Clinical Global Impression (CGI) Global Assessment of Functioning Scale (GAF)	Mean age: 33.6 years 22.2% male Ethnicity NR

Evidence Table 9. Randomized controlled trials in patients with bipolar I disorder

Author, year Country Trial name (Quality score)	Other population characteristics	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/ analyzed
Risperidone			
Segal 1998	NR	NR/NR/45	NR/NR/45

Evidence Table 9. Randomized controlled trials in patients with bipolar I disorder

Author, year Country Trial name (Quality score)	Results	Method of adverse effects assessment
Risperidone		
Segal 1998	risperidone vs haloperidol vs lithium, p value BPRS: baseline: 17.6 vs 15.2 vs 17.4, NS endpoint: 6.5 vs 4.9 vs 9.1, NS MRS: baseline: 28.6 vs 24.8 vs 28.4, NS endpoint: 12.4 vs 10.2 vs 15.7, NS all three groups have significant improvement compared with baseline, p<0.001 CGI: baseline: 4.0 vs 3.6 vs 3.7, NS endpoint: 1.9 vs 1.6 vs 2.4, NS GAF: baseline: 33.8 vs 40.2 vs 32.6, p=0.18 endpoint: 59 vs 63.4 vs 54.6, p=0.46	Simpson-Angus Scale (SAS)

Evidence Table 9. Randomized controlled trials in patients with bipolar I disorder

Author, year Country Trial name (Quality score)	Adverse effects reported	Total withdrawals; withdrawals due to adverse events	Comment
Risperidone			
Segal 1998	risperidone vs haloperidol vs lithium, p value SAS: baseline: 1.33 vs 0.46 vs 0.66, NS endpoint: 3.93 vs 2.66 vs 0.4, p=0.01 risperidol vs haloperidol, NS orphenadrine used; risperidone: 100 mg haloperidol: 229.6 mg risperidone vs haloperidol, NS seclusion required: endpoint: 8(53%) vs 8(53%) vs 11(73%)	NR	

Evidence Table 9. Randomized controlled trials in patients with bipolar I disorder

Author, year Country Trial name (Quality score)	Study design Setting	Eligibility criteria	Therapy type Interventions Duration
Sachs 2002	RCT, DB, placebo-controlled	Subjects were patients aged 18-65 years with a history of bipolar disorder and at least one prior manic episode who were hospitalized for treatment of manic episode in one of 20 centers. Inclusion criteria included a minimum score of 20 on the Young Mania Rating Scale and a DSM-IV diagnosis of bipolar disorder, with the most recent episode manic or mixed. Patients had to be medically stable according to a pretrial physical examination, medical history, and electrocardiography.	Adjunctive risperidone 2-6 mg/day haloperidol 4-12 mg/day placebo Duration: 3 weeks

Evidence Table 9. Randomized controlled trials in patients with bipolar I disorder

Author, year Country Trial name (Quality score)	Run-in/Washout Period	Allowed other medications/ interventions	Method of outcome assessment and timing of assessment	Age Gender Ethnicity
Sachs 2002	NR/ 3 days	lithium or divalproex allowed	Young Mania Rating Scale (YMRS) CGI severity scale CGI change scale	Mean age: 42.7 years 51.4% male Ethnicity NR

Evidence Table 9. Randomized controlled trials in patients with bipolar I disorder

Author, year Country Trial name (Quality score)	Other population characteristics	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/ analyzed
Sachs 2002	Severity of current manic episode -severe: 54.3% Episode type- manic: 78.6%	180/NR/158	63/8/155

Evidence Table 9. Randomized controlled trials in patients with bipolar I disorder

Author, year Country Trial name (Quality score)	Results	Method of adverse effects assessment
Sachs 2002	risperidone (n=51) vs haloperidol (n=50) vs placebo (n=47) YMRS, change from baseline at endpoint; -8.2(10.4) vs -14.3(9.7) vs -13.4(10.0) risperidone vs placebo, p=0.009 haloperidol vs placebo, p<0.03 risperidone vs haloperidol, p=0.76 CGI severity, ratings of much or very much improved: 27(53%) vs 25(50%) vs 14(30%) risperidone vs placebo, p=0.002 haloperidol vs placebo, p=0.003 risperidone vs haloperidol, NR	Extrapyramidal Symptom Rating Scale

Evidence Table 9. Randomized controlled trials in patients with bipolar I disorder

Author, year Country Trial name (Quality score)	Adverse effects reported	Total withdrawals; withdrawals due to adverse events	Comment
Sachs 2002	risperidone vs haloperidol vs placebo total: 42(81%) vs 49(92%) vs 43(84%) somnolence: 13(25%) vs 16(30%) vs 6(12%) headache: 11(21%) vs 8(15%) vs 12(24%) dyspepsia: 9(17%) vs 9(17%) vs 9(18%) extrapyramidal disorder: 7(13%) vs 15(28%) vs 2(4%) dizziness: 7(13%) vs 4(8%) vs 1(2%) constipation: 3(6%) vs 6(11%) vs 2(4%) tremor: 2(4%) vs 6(11%) vs 2(4%) weight chance (lb): 5.3(7.0) vs 0.3(5.4) vs 1.1(4.8)	risperidone vs haloperidol vs placebo Total withdrawals: 25 vs 18 vs 28 Withdrawals due to AEs: 2 vs 2 vs 1	

Evidence Table 9. Randomized controlled trials in patients with bipolar I disorder

Author, year Country Trial name (Quality score)	Study design Setting	Eligibility criteria	Therapy type Interventions Duration
Ziprasidone			
Keck 2003 US (21 sites) and Brazil (3 sites)	RCT, DB, Multicenter parallel	Men and women > 18 years of age with a primary DSM-IV diagnosis of bipolar I disorder and a current manic or mixed episode, confirmed by the Structured Clinical Interview for DSM-IV Axis I Disorders, Patient Edition (SCID-P), were eligible for study participation. Pts were required to have a Mania Rating Scale total > 14, with a score of >2 on at least four items at screening and at baseline (within 12 hours before the first does of double-blind medication). Women of childbearing age were eligible if they had undergone bilateral tubule ligation, hysterectomy, or bilater total oophorectomy, were 1 year postmenopausal or had tested negative at screening on a serum pregnancy test and had agreed to use investigator-approved contraceptive methods throughout the study.	Monotherapy Ziprasidone 80-160 mg/d Placebo Ziprasidone started at 40 mg bid on day 1, increased to 80mg bid on day 2, and adjusted by a maximum of 40 mg within the range of 80-160mg/d

Evidence Table 9. Randomized controlled trials in patients with bipolar I disorder

Author, year Country Trial name (Quality score)	Run-in/Washout Period	Allowed other medications/ interventions	Method of outcome assessment and timing of assessment	Age Gender Ethnicity
Ziprasidone				
Keck 2003 US (21 sites) and Brazil (3 sites)	NR/ 7-day placebo washout	Lorazepam, temazepam and medications to manage movement disorders allowed; benzodiazepines other than lorazepam or temazepam were permitted with approval of sponsor clinician	Efficacy was asses using the SADS-C (schedule for Affective Disorders and Schizophrenia, Change Version), PANSS, investigator-rated CGI Improvement scale, and Global Assessment of Functioning Scale SADS-C, CGI severity, CGI improvement were administered at screening, baseline (day1), days 2, 4, 7, 14, and 21 (or at study termination, within 12hours of the final dose). PANSS administered on days 1, 7, 14, and 21 (or termination)	Mean age: 38.3 years 54.3% male Ethnicity NR

Evidence Table 9. Randomized controlled trials in patients with bipolar I disorder

Author, year Country Trial name (Quality score)	Other population characteristics	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/ analyzed
Ziprasidone			
Keck 2003 US (21 sites) and Brazil (3 sites)	Baseline scores (SD), ziprasidone vs placebo: Mania rating scale score (total): 27.0 (3.8) vs 26.7 (7.0) CGI-S: 4.9 (0.9) vs 4.9 (0.7) PANSS total: 67.0 (15.6) vs 64.4 (15.7) PANSS, positive subscale: 19.5 (6.0) vs 19.0 (5.3) Global Assessment of Functioning Scale: 38.2 (9.7) vs 38.1 (8.8)	274/210/210	

Evidence Table 9. Randomized controlled trials in patients with bipolar I disorder

Author, year Country Trial name (Quality score)	Results	Method of adverse effects assessment
Ziprasidone		
Keck 2003 US (21 sites) and Brazil (3 sites)	Patients classifying as responders: ziprasidone 50% vs placebo 35%, p<0.05 Mean change in scores from baseline to endpoint, ziprazadone vs placebo Mania rating scale: -12.4 (12.0) vs -7.8 (12.9), p<0.005 CGI-S: -1.3 (1.5) vs -0.9 (1.6), p<0.01 CGI improvement scores at endpoint: 2.9 (1.4) vs 3.5 (1.7), p<0.001 PANSS, positive symptom scores: -4.8 (6.3) vs 2.0 (6.9), p<0.001 Global Assessment of Functioning + 15.3 (18.7) vs +8.3 (18.7), P<0.005	All observed or reported AEs were recorded. Simpson-Angus Rating Scale (SARS) and Barnes Akathisia evaluated at screening, day 1, 7, and 21. Abnormal Involuntary Movement Scale (AIMS), blood pressure, pulse rate, a physical exam, and 12-lead ECG performed at screening, day 1, and study endpoint.

Evidence Table 9. Randomized controlled trials in patients with bipolar I disorder

Author, year Country Trial name (Quality score)	Adverse effects reported	Total withdrawals; withdrawals due to adverse events	Comment
Ziprasidone			
Keck 2003 US (21 sites) and Brazil (3 sites)	Treatment-emergent AEs: 90.0% vs 77.1% AEs judged to be treatment-related: 70.7% vs 54.3% AEs reported in ≥10% of patients: Somnolence: 37.1% vs 12.9% Headache: 21.4% vs 18.6% Dizziness: 22.1% vs 10.0% Hypertonia: 11.4% vs 2.9% Nausea: 11.4% vs 10.0% Akathisia: 10.7% vs 5.7% Dyspepsia: 10.0% vs 10.0% Insomnia: 7.9% vs 10.0% ziprasidone vs placebo = NS for SARS, AIMS, Barnes Akathisia scale no patient had QTc interval ≥500 msec while taking ziprasidone	all comparisons: ziprasidone vs placebo Total withdrawals: (104/210) 49.5% Withdrawals by drug: (65/140) 46.4% vs (39/70) 55.7% Total withdrawals due to AEs: (12/210) 5.7% Withdrawals due to AEs by drug: (9/140) 6.4% vs (3/70) 4.3%	

Evidence Table 9. Randomized controlled trials in patients with bipolar I disorder

Author, year Country Trial name (Quality score)	Study design Setting	Eligibility criteria	Therapy type Interventions Duration
Intramuscular			
Meehan 2001 United States and Romania	RCT, DB Multicenter	Male or female subjects ≥18 years who had DSM-IV-diagnosed bipolar disorder, manic or mixed. Confirmation of the diagnosis occurred through administration of the Structured Clinical Interview for DSM-III-R (SCID). Pts were required to (1) be deemed by site physicians to have agitation severe enough to be appropriate candidates for receiving injections; (2) have a minimum total score=14 on the 5 items comprising the (PANSS)-Excited Component (PANSS-EC); and (3) have at least one individual item score of ≥4, with the 1 - 7 scoring system, immediately before randomization.	Olanzapine - first 2 of 3 possible injections were 10mg/injection; last injection was 5mg Lorazepam - first of 3 possible injections were 2 mg/injections; last injection was 1 mg Placebo - first 2 of 3 possible injections were placebo; 3rd injection was 10 mg olanzapine screening period + 24 hour treatment period each patient received first injection; a 2nd and 3rd injection was up to the investigator

Evidence Table 9. Randomized controlled trials in patients with bipolar I disorder

Author, year Country Trial name (Quality score)	Run-in/Washout Period	Allowed other medications/ interventions	Method of outcome assessment and timing of assessment	Age Gender Ethnicity
Intramuscular				
Meehan 2001 United States and Romania		Lithium and valproate allowed concomitantly (46.5%, 39.2%, 52.9% of olan, lzp, pla patients respectively); prophylactic use of anticholinergic medications prohibited, but benztropine, biperiden, or procyclidine were allowed as required for control of EPS.	Primary efficacy: PANSS - EC Secondary outcomes: the 14-item ABS (Agitated Behavior Scale); the single-item 9-point ACES (Agitation-Calmness Evaluation Scale) developed by Eli Lilly; the BPRS, the CGI-S, PANSS-derived PBRS, YMRS.	Mean age: 40.0 yrs 53.2% male 72.6% white 15.9% black 11.5% other

Evidence Table 9. Randomized controlled trials in patients with bipolar I disorder

Author, year Country Trial name (Quality score)	Other population characteristics	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/ analyzed
Intramuscular			
Meehan 2001 United States and Romania	Current manic, mixed, with psychotic features: 52.3% of patients Rapid cycling: 52.2%	NR/NR/201	7 / NR / 199 patients on most tests (171 on YMRS and 174 on PANSS-derived BPRS positive)

Evidence Table 9. Randomized controlled trials in patients with bipolar I disorder

Author, year Country Trial name (Quality score)	Results	Method of adverse effects assessment
Intramuscular		
Meehan 2001 United States and Romania	Olaznapine vs lorazepam vs placebo % of patients who completed study: 99.0% vs 94.1% vs 90.0% (p=0.034) % of patients who needed a second and a third injection: 26.3% vs 52.9% vs 52.9% (p=0.002 for olan vs lzp and p<0.001 vs pla) Mean change (SD) in efficacy measures (LOCF): PANSS-EC, at 2 hours: -9.60(4.74) vs -6.75(2.97) vs -4.84 (4.66) (p=0.001 olz vs lzp; p<0.001 for olz vs pla) at 24 hours: -5.78 (4.72) vs -5.65 (5.20) vs -3.94 (4.32) (p=NS olz vs lzp; p=0.025 for olz vs pla) at 2 hours, mean change significant for olz vs lzp in 3/4 scales: ABS, ACES, PANSS-derived BPRS total at 2 hours, mean change significant for olz vs pla in 4/4 scales: ABS, ACES, PANSS-derived BPRS total, and PANSS-derived BPRS positive at 24 hours, mean change significant for olz vs lzp in 0/6 scales : at 24 hours, mean change significant for olz vs pla in 4/6 scales: ABS, ACES, PANSS-derived BPRS total, and PANSS-derived BPRS positive	EPS assessed by the Simpson-Angus Extrapyramidal Effects Scale (S-A) and the Barnes Akathisia Global (Barnes) score AEs were solicited from the patient and ECG measurements were made.

Evidence Table 9. Randomized controlled trials in patients with bipolar I disorder

Author, year Country Trial name (Quality score)	Adverse effects reported	Total withdrawals; withdrawals due to adverse events	Comment
Intramuscular			
Meehan 2001 United States and Romania	olanzapine vs lorazepam vs placebo % of patients experiencing ≥1 treatment-emergent AE 34.3% (34 patients) vs 51.0% (26 patients) vs 25.5% (13 patients) olz vs lzp, p=NS; olz vs pla, p=NS Somnolence: 13.1% vs 9.8% vs 5.9% Dizziness: 13.7% vs 9.1% vs 2.0% Nausea: 1.0% vs 7.8% vs 0% (significant among treatment groups, p=0.031) Vomiting: 0% vs 5.9% vs 2% (significant among treatment groups, p=0.040) No other treatment-emergent AE occurred in ≥10% of any group Other AEs in olanzapine group: dry mouth (3.0%), abnormal gait (2.0%), hallucinations (2.0%), pharyngitis (2.0%), and tremor (2.0%). None were significant.	2 withdrawals; 2 withdrawals (both in placebo, due to agitation and hostility)	Patients in placebo used Lithium more than in other two groups: pla=31.4% vs lzp=15.7% vs olan 14.1% (p=0.037)

Evidence Table 10. Quality Assessment of placebo-controlled trials in patients with bipolar I disorder

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?
Altamura, 2003	NR	NR	Yes	Yes	Unclear	No	No
Brecher, 2003 Poster	NR	NR	Yes	Yes	Yes	Yes	Yes

Evidence Table 10. Quality Assessment of placebo-controlled trials in patients with bipolar I disorder

Author, year Country	Reporting of attrition, crossovers, adherence, and contamination	Loss to follow-up: differential/high	Intention-to-treat (ITT) analysis	Post-randomization exclusions	Quality rating
Altamura, 2003	NR NR NR NR	NR NR	Unclear	Unclear	Poor
Brecher, 2003 Poster	Yes NR NR NR	No No	LOCF	No	Fair

Evidence Table 10. Quality Assessment of placebo-controlled trials in patients with bipolar I disorder

External Validity

Author, year Country	Number screened/eligible/enrolled	Exclusion criteria	Run-in/ Washout	Class naïve patients only	Control group standard of care	Relevance
Altamura, 2003	NR/NR/28	Presence of major mood episodes not in partial or full remission; concomitant psychotropic medication at the time of the beginning of the study, with the exception of previously stabilized (for at least 2 weeks) dosages of benzodiazepines (not to exceed 5 mg/day diazepam equivalents); pregnancy or lactations; serious medical conditions contraindicating the use of quetiapine or any mood stabilizers; no history of ever using mood stabilizers	No/No	Naïve to mood stabilizers	Yes	Only to patients with no history of mood stabilizer use and who were in partial- or full-remission
Brecher, 2003 Poster	NR/NR/302	Hospitalized for weeks for the index manic episode; meeting SDM-IV criteria for rapid cycling or current mixed episode; index manic episode as direct consequence of medical condition, treatment, or substance abuse; known intolerance or lack of response to QTP, HPL or clozapine; use of antihypertensives (unless stable dose for ≥ month), clozapine, > 4 mg/d lorazepam, antidepressants, thioridazine, or potent cytochrome P450 inducers/inhibitors within specified time intervals of randomization; substance/alcohol dependence or electroconvulsive therapy within 1 month of randomization	NR/NR	Unclear	Yes	Yes

Evidence Table 10. Quality Assessment of placebo-controlled trials in patients with bipolar I disorder

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?
Calabrese, 2004 Poster	NR	NR	Yes	Yes	Yes	Yes	Yes
Hirschfeld, 2004	Yes	Yes	Yes	Yes	Yes	Yes	Yes

Evidence Table 10. Quality Assessment of placebo-controlled trials in patients with bipolar I disorder

Author, year Country	Reporting of attrition, crossovers, adherence, and contamination	Loss to follow-up: differential/high	Intention-to-treat (ITT) analysis	Post-randomization exclusions	Quality rating
Calabrese, 2004	Yes	NR	LOCF	No	Fair
Poster	NR	NR			
	NR				
	NR				
Hirschfeld, 2004	Yes	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	No	Fair
	NR	No			
	NR				
	NR				

Evidence Table 10. Quality Assessment of placebo-controlled trials in patients with bipolar I disorder

External Validity

Author, year Country	Number screened/eligible/enrolled	Exclusion criteria	Run-in/ Washout	Class naïve patients only	Control group standard of care	Relevance
Calabrese, 2004 Poster	838/NR/542	Other Axis I disorders	NR/NR	Unclear	Yes	Yes
Hirschfeld, 2004	337/NR/262	Baseline YMRS score was ≥ 25% lower than the screening score; diagnosis of a mixed episode, schizoaffective disorder, borderline or antisocial personality disorder, seizure disorder, a history of substance dependence within 3 months of the screening, or were considered to be at significant risk for suicidal or violent behavior during the course of the trial	No/Yes	No	Yes	Yes

Evidence Table 10. Quality Assessment of placebo-controlled trials in patients with bipolar I disorder

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?
Keck, 2003	NR	NR	Yes	Yes	Yes	Yes	Yes
Khanna, 2003	NR	NR	Yes	Yes	Yes	Yes	Yes

Evidence Table 10. Quality Assessment of placebo-controlled trials in patients with bipolar I disorder

Author, year Country	Reporting of attrition, crossovers, adherence, and contamination	Loss to follow-up: differential/high	Intention-to-treat (ITT) analysis	Post-randomization exclusions	Quality rating
Keck, 2003	Yes NR NR NR	NR NR	No	No	Fair
Khanna, 2003	Yes NR NR NR	No No	LOCF	No	Fair

Evidence Table 10. Quality Assessment of placebo-controlled trials in patients with bipolar I disorder

External Validity

Author, year Country	Number screened/eligible/enrolled	Exclusion criteria	Run-in/ Washout	Class naïve patients only	Control group standard of care	Relevance
Keck, 2003	NR/NR/262	Patients were excluded from the study if they had delirium, dementia, amnestic or other cognitive disorders, schizophrenia, or schizoaffective disorder or if they were experiencing their first manic episode; duration of current mania > 4 weeks; nonresponse to clozapine; probable need for prohibited concomitant therapy; use of psychoactive substances or a substance use disorder; serum concentrations of lithium > 0.6 mmol/liter or divalproex sodium > 50 µg/ml at screening; significant risk of committing suicide or homicide; history of neuroleptic malignant syndrome or seizure disorder	No/Yes	No	Yes	Yes
Khanna, 2003	NR/NR/291	DSM-IV criteria for schizoaffective disorder, rapid cycling bipolar disorder, or borderline or antisocial personality disorder; substance dependence within the last 3 months; significant risk of suicide or violent behavior; pregnant or nursing; history of other unstable illness; a ≥ 25% decrease in their YMRS score from screening baseline; treatment with an antidepressant within 4 weeks of screening	NR/Washout details unclear	Unclear	Yes	Yes to "severe" patient population

Evidence Table 10. Quality Assessment of placebo-controlled trials in patients with bipolar I disorder

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?
Paulsson, 2003	NR	NR	Yes	Yes	Yes	Yes	Yes

Evidence Table 10. Quality Assessment of placebo-controlled trials in patients with bipolar I disorder

Author, year Country	Reporting of attrition, crossovers, adherence, and contamination	Loss to follow-up: differential/high	Intention-to-treat (ITT) analysis	Post-randomization exclusions	Quality rating
Paulsson, 2003	Yes NR NR NR	No No	No, 2 (0.6%) excluded for unspecified reasons	No	Fair

Evidence Table 10. Quality Assessment of placebo-controlled trials in patients with bipolar I disorder

External Validity

Author, year Country	Number screened/eligible/enrolled	Exclusion criteria	Run-in/ Washout	Class naïve patients only	Control group standard of care	Relevance
Paulsson, 2003	NR/NR/302	Hospitalized for ≥ 3 week for the index manic episode; meeting DSM-IV criteria for rapid cycling or current mixed episode; index manic episode as direct consequence of medical condition, treatment or substance abuse; known intolerance or lack of response to QTP, Li, or clozapine; use of antihypertensives (unless stable dose for ≥ 1 month), clozapine, >4 mg/d lorazepam, antidepressants, thioridazine, or potent cytochrome P450 inducers/in inhibitors within specified time intervals of randomization; substance/alcohol dependence or ECG therapy within 1 month of randomization	NR/NR	Unclear		Yes

Evidence Table 10. Quality Assessment of placebo-controlled trials in patients with bipolar I disorder

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?
Sachs, 2004	NR	NR	Yes	Yes	Yes	Yes	Yes

Evidence Table 10. Quality Assessment of placebo-controlled trials in patients with bipolar I disorder

Author, year Country	Reporting of attrition, crossovers, adherence, and contamination	Loss to follow-up: differential/high	Intention-to-treat (ITT) analysis	Post-randomization exclusions	Quality rating
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)	No	Fair

Evidence Table 10. Quality Assessment of placebo-controlled trials in patients with bipolar I disorder

External Validity

Author, year Country	Number screened/eligible/enrolled	Exclusion criteria	Run-in/ Washout	Class naïve patients only	Control group standard of care	Relevance
Sachs, 2004	NR/NR/191	Pregnant or lactating women and those of chid-bearing potential not using a reliable method of contraception were excluded from participating in the study. Patients whose current manic episode was due to a medical condition were also excluded. Other patients who were excluded were those meeting DSM-IV criteria for rapid cycling, those who had required hospitalization for 3 or more weeks for the index manic episode, or those with known intolerance or lack of response to QTP or clozapine. The continuous daily use of benzodiazepines, in excess of 4 mg/day of lorazepam or the equivalent, was also not allowed during the month preceding screening. Patients requiring the use of antihypertensive medications, unless stable for at elast 1 month, or the use of antidepressants during the screening period (day -7 to 1) or within a period of five half-lives of the drug prior to study randomization, were also ineligible. The use of depot hloperidol and fluphenazine (within one injection cycle), and certain	NR/NR	Unclear	Yes	Yes

Evidence Table 10. Quality Assessment of placebo-controlled trials in patients with bipolar I disorder

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?
Sachs, 2005	NR	NR	Yes	Yes	NR	Yes	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

Evidence Table 10. Quality Assessment of placebo-controlled trials in patients with bipolar I disorder

Author, year Country	Reporting of attrition, crossovers, adherence, and contamination	Loss to follow-up: differential/high	Intention-to-treat (ITT) analysis	Post-randomization exclusions	Quality rating
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	One patient excluded from efficacy analysis due to early discontinuation	Fair
Tohen, 1999	Yes NR NR NR	NR NR	No, 3 (2.2%) patients excluded due to not having a post-baseline assessment	No	Fair
Tohen, 2000	Yes NR NR NR	No No	No, 5 (4.3%) patients excluded due to not having a post-baseline assessment	No	Fair

Evidence Table 10. Quality Assessment of placebo-controlled trials in patients with bipolar I disorder

External Validity

Author, year Country	Number screened/eligible/enrolled	Exclusion criteria	Run-in/ Washout	Class naïve patients only	Control group standard of care	Relevance
Sachs, 2005	NR/NR/272	Diagnosis of delerium, dementia, amnestic or other cognitive disorders, schizophrenia or schizoaffective disorder; first manic episode; current manic episode >4 wks; unresponsive to clozapine; possibility that patient would require prohihited concomitant therapy; use of psychoactive substances or a substance use disorder; serum concentrations of lithium ≥0.6mmol/L or divalproex sodium ≥50ug/mL; significant risk of suicide or homicide; history of neuroleptic malignant syndrome or seizure disorder; clinicall significant abnormal laboratory test results, vital signs or ECG; previous enrollment in an aripiprazole trial.	NR/NR	No	Yes	Yes
Tohen, 1999	NR/NR/139	Serious, unstable illness such that hospitalization was anticipated within 3 months or death was anticipated within 3 years; DSM-IV-defined substance dependence (except nicotine or caffeine) within the past 3 months; and serious risk of suicide	No/No	No	Yes	Yes
Tohen, 2000	NR/NR/115	Serious, unstable medical illness; DSM-IV substance dependence (except nicotine or caffeine) within the past 3 months; and serious suicidal risk	No No	No	Yes	Yes

Evidence Table 10. Quality Assessment of placebo-controlled trials in patients with bipolar I disorder

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?
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 2005	Open-label phase: yes Double-blind taper phase: unclear ("a priori determined" but exact method not explained)	Yes	Yes	Yes	Yes	Yes	Yes

Evidence Table 10. Quality Assessment of placebo-controlled trials in patients with bipolar I disorder

Author, year Country	Reporting of attrition, crossovers, adherence, and contamination	Loss to follow-up: differential/high	Intention-to-treat (ITT) analysis	Post-randomization exclusions	Quality rating
Tohen, 2003	Yes NR NR NR	No No	No	No	Fair
Tohen, 2004	Yes NR NR NR	NR NR	Yes	No	Fair
Tohen 2005	Yes NR Yes NR	Yes (0.9% olanzapine group, 0.5% lithium group)/ No	Yes for both open-label and double-blind phase	No	Fair

Evidence Table 10. Quality Assessment of placebo-controlled trials in patients with bipolar I disorder

External Validity

Author, year Country	Number screened/eligible/enrolled	Exclusion criteria	Run-in/ Washout	Class naïve patients only	Control group standard of care	Relevance
Tohen, 2003	NR/1072/833	History of alcohol or substance dependence within the previous 3 months, suicidal behavior within the previous 3 months, or an unstable or untreated medical disorder; score of 15 or greater on the YMRS during weeks 1 to 3 of treatment	No/Yes	No	Yes	Yes
Tohen, 2004	NR/160/99	Pregnancy, serious and unstable medical illness; DSM-IV substance dependence within the past 30 days; documented history of intolerance to olanzapine; and serious suicidal risk	No/No	No	Yes	Yes
Tohen 2005	NR/NR/543	Serious, unstable medical illness; DSM-IV substance dependence criteria within the past 30 days; treatment with a depot neuroleptic within 6 wks of randomization; considered to be a serious suicide risk; history of intolerance or lack of previous response to an adequate trial of lithium or olanzapine	NR/NR	No	Yes	Yes Note: double-blind study phase participants limited to responders from open-label phase

Evidence Table 10. Quality Assessment of placebo-controlled trials in patients with bipolar I disorder

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?
Tohen 2006	NR	NR	Yes for demographics, however randomization ratio of 2:1 in favor of olanzapine	Yes	NR	NR	Yes
Vieta 2005	Unclear - "fixed randomization schedule" but method not explained	NR	Yes	Yes	NR	Yes	Yes

Evidence Table 10. Quality Assessment of placebo-controlled trials in patients with bipolar I disorder

Author, year Country	Reporting of attrition, crossovers, adherence, and contamination	Loss to follow-up: differential/high	Intention-to-treat (ITT) analysis	Post-randomization exclusions	Quality rating
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	NR	Fair
Vieta 2005	Yes NR NR NR	Yes (3 aripiprazole group, 4 haloperidol group)/No	Yes - separate ITT analyses for efficacy and safety	NR	Fair

Evidence Table 10. Quality Assessment of placebo-controlled trials in patients with bipolar I disorder

External Validity

Author, year Country	Number screened/eligible/enrolled	Exclusion criteria	Run-in/ Washout	Class naïve patients only	Control group standard of care	Relevance
Tohen 2006	910/731/361	Open-label phase: Unable to tolerate minimum dose of olanzapine Double-blind phase: NR	2-7 day screening followed by randomization at 6-12 wks/washout NR	No	Yes	Yes Note: double-blind study phase participants limited to responders from open-label phase
Vieta 2005	NR/372/347	Rapid cycling bipolar 1 disorder; durations of current manic episode of more than 4 wks; proven substance misuse; patient considered unresponsive to antipsychotics; patient at significant risk of suicide; recent treatment with long-acting antipsychotic, lithium or divalproate; use of psychotropic medications other than benzodiazapines within 1 day of randomization; fluoxetine treatment in the past 4 wks; previous enrollment in an aripiprazole clinical study.	NR/1-3day washout	NR	Yes	

Evidence Table 10. Quality Assessment of placebo-controlled trials in patients with bipolar I disorder

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?
Yatham, 2003 International	Yes	Yes	Yes	Yes	Yes	Yes	Yes

Evidence Table 10. Quality Assessment of placebo-controlled trials in patients with bipolar I disorder

Author, year Country	Reporting of attrition, crossovers, adherence, and contamination	Loss to follow-up: differential/high	Intention-to-treat (ITT) analysis	Post-randomization exclusions	Quality rating
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	8(5.3%) patients excluded from efficacy analysis due to having < 2 assessments	Fair

Evidence Table 10. Quality Assessment of placebo-controlled trials in patients with bipolar I disorder

External Validity

Author, year Country	Number screened/eligible/enrolled	Exclusion criteria	Run-in/ Washout	Class naïve patients only	Control group standard of care	Relevance
Yatham, 2003 International	NR/157/151	Another DSM-IV Axis I diagnosis other than nicotine or caffeine dependence; seizure disorder requiring medication; history of alcohol or drug misuse or dependence within the 3 months prior to the study; people at imminent risk of causing injury to themselves or others or of causing property damage; serious or unstable medical disease; clinically significant laboratory abnormalities; severe drug allergy or hypersensitivity; history of neuroleptic malignant syndrome	No/Yes	No	Yes	Yes

Evidence Table 11. Observational studies in bipolar disorder

Author, year Country	Data Source	Prospective Retrospective Unclear	Exposure Period	Mean duration of follow-up	Interventions Mean dose	Population
Clozapine						
Zarate, 1995	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
Olanzapine						
Vieta, 2001 Spain	Naturalistic: Clinic nr	Prospective	NR	303 days	Olanzapine 8.2 mg	Treatment resistant bipolar disorder
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	Olanzapine 5-20 mg Mean dose at endpoint: 13.1 mg/d	Bipolar I mania episode or mixed state

Evidence Table 11. Observational studies in bipolar disorder

Author, year Country	Age Gender Ethnicity	Exposed Eligible Selected	Withdrawn Lost to fu Analyzed	Effectiveness outcomes
Clozapine				
Zarate, 1995	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
Olanzapine				
Vieta, 2001 Spain	Mean age: 39.9 56.5% male Ethnicity NR	NR NR 23	6 (23%) withdrawn 1 (4.3%) lost to fu 23 analyzed	NR
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 11. Observational studies in bipolar disorder

Author, year Country	Safety Outcomes	Comments
Clozapine		
Zarate, 1995	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	
Olanzapine		
Vieta, 2001 Spain	Weight gain 3 (13%) Hospitalizations 3 (13%)	
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 (ie, 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 11. Observational studies in bipolar disorder

Author, year Country	Data Source	Prospective Retrospective Unclear	Exposure 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
Gonzalez-Pinto, 2001 Spain	Santiago Hospital Psychiatric Unit	Prospective	March 1999 - February 1998	NR	Olanzapine 5-20 mg other antipsychotics (haloperidol and levomepromazine)	Mania

Evidence Table 11. Observational studies in bipolar disorder

Author, year Country	Age Gender Ethnicity	Exposed Eligible Selected	Withdrawn Lost to fu 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
Gonzalez-Pinto, 2001 Spain	Mean age: 37.1 years 53.4% male Ethnicity NR	86 44 44	0 0 44	olanzapine vs other antipsychotics YMRS scores improved: 29.35 vs 19.6, p=0.008 HAM-D scores improved: 15.71 vs 11.9, p=0.05 hospital length of stay: 22.14 vs 20.10 , p=0.5 Logistic regression model of variables associated with a hamilton decrease of 80% or more: p value, odds ratio male: 0.813, 0.779 age>30: 0.009, 885.1 no. of episodes>5: 0.095, 0.127 years of illness>10: 0.114, 0.070 age at onset>25: 0.119, 0.060 suicidal attempts: 0.757, 0.717 days of hospitalization>=21: 0.791, 1.297 compulsory admission: 0.465, 0.483 olanzapine: 0.045, 11.063 lithium: 0.560, 1.785

Evidence Table 11. Observational studies in bipolar disorder

Author, year Country	Safety Outcomes	Comments
Dennehy, 2003 United States	Side effects: 80% moderate to severe dry mouth 60% mild dizziness 53% oedema 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	
Gonzalez-Pinto, 2001 Spain	NR	

Evidence Table 11. Observational studies in bipolar disorder

Author, year Country	Data Source	Prospective Retrospective Unclear	Exposure Period	Mean duration of follow-up	Interventions Mean dose	Population
Janenawasin, 2002 United States	NR	Prospective	NR	9 weeks	Olanzapine 7.8 mg	Bipolar I, bipolar II or bipolar not otherwise specified

Evidence Table 11. Observational studies in bipolar disorder

Author, year Country	Age Gender Ethnicity	Exposed Eligible Selected	Withdrawn Lost to fu Analyzed	Effectiveness outcomes
Janenawasin, 2002 United States	Mean age: 37.7 years 48% male Ethnicity NR	NR NR 25	NR NR 25	change from baseline, mean slope CGI: -1.7, p=0.002 YMRS: -13.1, p=0.002 HDRS: -6.9, p=0.006 HARS: -4.2, p=0.0004 MADRS: -6.1, p=0.1 acute phase (W1), change from baseline, mean slope CGI: -3.9, p<0.0001 YMRS: -21.1, p=0.008 HDRS: -19.7, p=0.0002 HARS: -13.2, p=0.001 MADRS: -29.3, p<0.0001 subchronic phase (W1-9), change from baseline, mean slope CGI: -0.9, p=0.1 YMRS: -6.5, p=0.02 HDRS: 0.6, p=NS HARS: 0.4, p=NS MADRS: 5.6, p=NS 25(60%) responders with final CGI-S <= 2 Time to consistent response correlated with final olanzapine dose, p<0.02 olanzapine dosage: early vs late responders = 4.5 vs 9.4 mg/day, p=0.03

Evidence Table 11. Observational studies in bipolar disorder

Author, year Country	Safety Outcomes	Comments
Janenawasin, 2002 United States	17(68%) mild to moderate sedation 4(16%) moderate sedation, which affected function 14(56%) mild to moderate dry mouth 3(12%) dry mouth as problematic 11(44%) tremor 4(16%) mild sexual dysfunction 1(4%) mild akathisia baseline vs endpoint weight gain: 171(38.2) vs 178.5(38.4), p<0.0001 BMI: 24.4(4.2) vs 25.7(4.5), p=0.0003	

Evidence Table 11. Observational studies in bipolar disorder

Author, year Country	Data Source	Prospective Retrospective Unclear	Exposure Period	Mean duration of follow-up	Interventions Mean dose	Population
McElroy, 1998 United States	NR	Prospective	NR	101.4 days	Olanzapine 14.1 mg	Bipolar I disorder
Risperidone						
Bahk, 2004 Korea	81 nationwide sites in Korea	Prospective	August 2002 - December 2002	6 weeks	Risperidone 3.1 mg	bipolar manic or hypomanic episode

Evidence Table 11. Observational studies in bipolar disorder

Author, year Country	Age Gender Ethnicity	Exposed Eligible Selected	Withdrawn Lost to fu Analyzed	Effectiveness outcomes
McElroy, 1998 United States	NR	NR NR 14	NR NR 14	Of all 14 patients Month 1: 9(64%) much or very much improved Endpoint: 8(57%) much or very much improved Of 12 patients initiated for manic or hypomanic: Month 1: 8(67%) much or very much improved Endpoint: 7(57%) much or very much improved 3(25%) mild or no change 2(17%) much or very much worsened
Risperidone				
Bahk, 2004 Korea	Mean age: 37.9 years 45.8% male 100% Asian	NR NR 909	18 25 866	baseline vs endpoint: YMRS: 32.9(10.8) vs 9.5(8.4), p<0.0001 CGI-S: 4.8(1.1) vs 2.1(0.8), p<0.0001 YMRS 50% or more reduction: 693(77.8%) patients

Evidence Table 11. Observational studies in bipolar disorder

Author, year Country	Safety Outcomes	Comments
McElroy, 1998 United States	1(7%) bad dream 5(38%) sedation 2(14%) tremor 2(14%) dry mouth 2(14%) increased hunger/weight gain 1(7%) restlessness 1(7%) swollen hands 1(7%) nausea 1(7%) headache	
Risperidone		
Bahk, 2004 Korea	22.2% headache 21.7% sedation 21.5% gastrointestinal discomfort such as nausea and constipation 11.2% fatigue 10.5% dizziness 18.6% EPS including tremor, rigidity, dystonia and involuntary muscle contraction weight gain: 1.5kg, p<0.0001 BMI increased: 0.6, p<0.0001	

Evidence Table 11. Observational studies in bipolar disorder

Author, year Country	Data Source	Prospective Retrospective Unclear	Exposure Period	Mean duration of follow-up	Interventions Mean dose	Population
Bowden 2004 United States	Patients in RCT (Sachs 2002)	Prospective	NR	10 weeks	Risperidone 3.1 (+/- 0.2) mg/day Risperidone adjunctive to mood stabilizers	Bipolar manic 78.9% Bipolar mixed 21.1%

Evidence Table 11. Observational studies in bipolar disorder

Author, year Country	Age Gender Ethnicity	Exposed Eligible Selected	Withdrawn Lost to fu Analyzed	Effectiveness outcomes
Bowden 2004 United States	Mean age: 41.3 years 45.9% male Ethnicity: NR	NR 156 85	35 4 48	Symptomatic remission (YMRS ≤12) seen in 79% (38/48) patients at week 10 more stringent definitions of remissions: a) % with YMRS ≤8: 67% (32/48) b) % with YMRS ≤8 + HAM-D score ≤7 : 35% (17/48) Mean time to first remission: 32 days for criteria of YMRS scores <=12 Mean time to first remission: 34 days for YMRS score ≤8 + HAMD score ≤7 CGI scores: % of patients rated as "much or very much improved" increased from 59% at week 1 to 71% at week 10 HAM-D scores <=8 : 60% of patients Mean BPRS at week 1: 31.0 (n=83); mean BPRS at week 10: 29.5 (n=48)

Evidence Table 11. Observational studies in bipolar disorder

Author, year Country	Safety Outcomes	Comments
Bowden 2004 United States	Antiparkinsonian medication administered to 25.9% patients (22/85) Lorazepam administered to 7.06% patients (6/85) Mean weight gain for all groups over the 10-week OL treatment: 2.85kg All patients with any AEs: 92.9% (79/85) Extrapyramidal disorder: 29.4% (25/85) Somnolence: 29.1% (23/85) Tremor: 15.3% (13/85) Rhinitis: 15.3% (13/85) Increased saliva: 14.1% (12/85) Headache: 12.9% (11/85) Hypertonia: 12.9% (11/85) Insomnia: 11.8% (10/85) Back pain: 11.8% (10/85) Hyperkinesia: 10.6% (9/85) Fatigue: 10.6% (9/85) Dyspepsia: 9.4% (8/85) Constipation: 8.2% (7/85) Dizziness: 7.0% (6/85) Depression: 7.0% (6/85) Nausea: 7.0% (6/85) Vomiting: 4.7% (4/85) Pain: 4.7% (4.85)	

Evidence Table 11. Observational studies in bipolar disorder

Author, year Country	Data Source	Prospective Retrospective Unclear	Exposure Period	Mean duration of follow-up	Interventions Mean dose	Population
Vieta, 2002 Spain	NR	Prospective	NR	6 weeks	Risperidone 4.9 mg	bipolar I or II disorder
Vieta, 2004 Spain	Multicenter	Prospective	NR	6 months	Risperidone	acutely manic bipolar

Evidence Table 11. Observational studies in bipolar disorder

Author, year Country	Age Gender Ethnicity	Exposed Eligible Selected	Withdrawn Lost to fu Analyzed	Effectiveness outcomes
Vieta, 2002 Spain	Mean age: 40.7 years 40.2% male Ethnicity NR	NR NR 174	12 3 159	baseline vs endpoint YMRS: 26.3 vs 5.7, p<0.0001 YMRS >=50% improvement: 87% patients YMRS >=50% improvement: 76% ITT patients PANSS: total: 66.2 vs 49, p<0.0001 positive: 20.1 vs 11.7, p<0.0001 negative: 12.5 vs 10.6, p<0.0001 general: 37.1 vs 26.1, p<0.0001 HAM-D: 12.2 vs 6.6, p<0.0001 CGI: 2.6 vs 1.6, p<0.0001 CGI: improved: 22.5% patients much improved: 61.7% patients entirely symptom-free: 15.4%
Vieta, 2004 Spain	Mean age: 40.7 years 50% male Ethnicity NR	NR NR 96	11 5 80	baseline vs endpoint YMRS: 29.2 vs 2.8, p<0.0001 PANSS: high vs low, p<0.0001 (data NR) HDRS: 14.2 vs 5.3, p<0.0001 CGI: improved, p<0.0001, (data NR) 60(62.5%) met the criteria for response at week 4 32(33.3%) met the criteria for remission at week 4 25(26%) relapsed during the 6 month follow-up

Evidence Table 11. Observational studies in bipolar disorder

Author, year Country	Safety Outcomes	Comments
Vieta, 2002 Spain	12(11%) experienced side effects: 3 drowsiness 3 weight gain 2 dry mouth 2 impotence 1 dizziness 1 weight loss 1 hypotension 1 impaired concentration 1 amenorrhea 6% of the adverse events were considered severe 44% were considered moderate 10(6%) initiation or exacerbation of mania 10(6%) initiation of depression	
Vieta, 2004 Spain	EPS: increased at week 4, p=0.015 (data NR) decreased at month 6, p=0.027 (data NR) dystonia: worsen at week 4, p=0.002 (data NR) hypokinesia: worsen at week 4, p=0.001 (data NR) 0 new-emergent tardive dyskinesia 3 withdrawals due to AEs: 1(1%) impotence 1(1%) drowsiness 1(1%) weight gain Other AEs: restlessness, dizziness, hypotension, incontinence and galactorrhoea weight gain: average 3.2(2.1) kg 9(9.4%) gain more than 7% body weight	

Evidence Table 12. Quality assessment of observational studies of safety and adverse events

Author, year	Non-biased selection?	Low overall loss to follow-up?	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?	Overall adverse event assessment quality	Notes
Vieta, 2001	Yes	Yes	No	No	No	NR	Yes	Fair	

Evidence Table 13. Head-to-head trials in patients with behavioral and psychological symptoms of dementia

Author, year Country Trial Name (Quality Score)	N	Duration	Study Design Setting	Eligibility criteria
Risperidone vs olanzapine				
Deberdt, 2005 US (FAIR)	494	10 weeks	Double-blind, randomized, multicenter. Nursing homes or assisted-living centers.	Age 40 or older. All patients exhibited clinically significant psychotic symptoms associated with Alzheimer's desease, vascular, or mixed dementia. Dementia diagnoses defined by NINCDS-ADRDA or DSN-IV criteria. Patients must have scored ≥ 6 (severity X frequency) on the sum of the Hallucinations and Delusons items on the NPI or NPI-NH. Exclusion criteria included Parkinson's disease, Lewy-body dementia, Pick disease, frontotemporal dementia; or a MMSE score <5 or >24.
Ellingrod., 2002 US (POOR)	19	8 weeks	Single-blind, nonrandomized. Four rural nursing care facilities in one city.	Age 70 or older, not receiving any psychotropic drug, with DSM-IV criteria for Alzheimer-type dementia, multiinfarct dementia, or mixed syndrome, and clinical symptoms necessitating administration of an antipsychotic drug.

Evidence Table 13. Head-to-head trials in patients with behavioral and psychological symptoms of dementia

Author, year Country Trial Name (Quality Score)	Interventions (drug, dose)	Run-in/Washout Period	Allowed other medications/interventions	Age Gender Ethnicity
Risperidone vs olanzapine				
Deberdt, 2005 US (FAIR)	risperidone, flexible dose (0.5 to 2 mg) or olanzapine, flexible dose (2.5 mg to 10 mg) or placebo	Atypical antipsychotic use was disallowed within 30 days, lithium or anticonvulsant use within 2 weeks before the placebo/wahsout period. Oral conventional antipsychotic use was allowed up to 3 days before randomization. 3 to 14-day placebo washout period.	Anticholinergics (up to 6 mg per day benztropine-equivalents) and benzodiazepines (up to 4 mg per day lorazepam-equivalents) were permitted.	Mean age 78.3 65.6% female 84.0% Caucasian, 9.5% African descent, 6.5% other race/ethnicity
Ellingrod., 2002 US (POOR)	risperidone 0.25 mg to 3 mg or olanzapine 2.5 mg to 15 mg Dosages determined by primary physicians.	None	Administration of other psychotropic drugs was allowed, although none of the study patients needed them.	Mean age 85 years (SD 3, range 62-99) 79% female Ethnicity not reported

Evidence Table 13. Head-to-head trials in patients with behavioral and psychological symptoms of dementia

Author, year Country Trial Name (Quality Score)	Other population characteristics (diagnosis, etc)	Number screened/ eligible/enrolled	Number withdrawn/ lost to fu/analyzed
Risperidone vs olanzapine			
Deberdt, 2005 US (FAIR)	Baseline MMSE score 13.7 olanzapine vs 14.7 risperidone vs 15.4 placebo (p=0.021 for overall treatment group difference) 81.4% Alzheimer's dementia 5.7% vascular dementia 13.0% mixed	Number screened, eligible not reported/494 enrolled	157 withdrawn/lost to followup NR/474 analyzed for primary outcome
Ellingrod., 2002 US (POOR)	Baseline MMSE score, risperidone vs olanzapine 14.09 (SD 5.48) vs 11.75 (SD 9.91)	Number screened, eligible not reported/19 enrolled	0 withdrawn/0 lost to followup/19 analyzed

Evidence Table 13. Head-to-head trials in patients with behavioral and psychological symptoms of dementia

Author, year Country Trial Name (Quality Score)	Outcome Measures	Method of Outcome Assessment and Timing of Assessment
Risperidone vs olanzapine		
Deberdt, 2005 US (FAIR)	NPI Psychosis Total, NPI Total, CGI-S Psychosis, BPRS Total, CGI-S Dementia, Cornell Total, PDS (Progressive Deterioration Scale), CMAI: Aggression.	Patients were assessed weekly for the first 2 weeks of the study and biweekly thereafter
Ellingrod., 2002 US (POOR)	Brief Psychiatric Rating Scale, PANSS, Mini-Mental State Examination, Mattis Dementia Rating Scale, Abnormal Involuntary Movement Scale, Simpson-Angus Extrapyramidal Symptoms Scale, Barnes Akathisia Rating Scale, and Social Adaptive Functioning Evaluation; blood pressure	Assessment at baseline, 1 month, and 2 months by one rater.

Evidence Table 13. Head-to-head trials in patients with behavioral and psychological symptoms of dementia

Author, year Country Trial Name (Quality Score)	Results
Risperidone vs olanzapine	
Deberdt, 2005 US (FAIR)	Mean change from baseline at endpoint, risperidone vs olanzapine: NPI Psychosis Total: −4.2 vs −4.0 (p=0.747) NPI Total: -0.64 vs −9.7 vs −11.8 (p=0.386) CGI-S Psychosis : −0.7 vs −0.7 (p=0.593) BPRS Total: −3.1 vs −3.5 (p=0.838) CGI-S Dementia: −0.1 vs −0.0 (p=0.246) Cornell Total: −1.2 vs −1.6 (p=0.596) PDS: −2.9 vs −2.9 (p=0.867) CMAI: Aggression: −1.5 vs −1.3 (p=0.781) No significant difference vs placebo for any measure
Ellingrod., 2002 US (POOR)	Mean change from baseline at endpoint, risperidone vs olanzapine: BPRS: -1.73 vs -0.25 (p=0.60) SAPS: -0.64 vs -0.63 (p=0.99) SANS: -1.27 vs 0.25 (p=0.27) MMSE: -2.27 vs -1.38 (p=0.53) Mattis: -10.55 vs -4.13 (p=0.29) SAFE: 2.91 vs 1.13 (p=0.35)

Evidence Table 13. Head-to-head trials in patients with behavioral and psychological symptoms of dementia

Author, year Country Trial Name (Quality Score)	N	Duration	Study Design Setting	Eligibility criteria
Fontaine, 2003 US (POOR)	39	2 weeks	Double-blind, long-term care facilities.	Residents of extended care facilities, meeting DSM-IV criteria for dementia; medically stable and able to comply with oral, nonliquid medication; Clinical Global Impressions scale score 4 or higher and an Alzheimer's Disease Cooperative Study agitation screening scale score 25 or higher with 6 points on the delusions, hallucinations, physical aggression, or verbal aggression subscales.

Evidence Table 13. Head-to-head trials in patients with behavioral and psychological symptoms of dementia

Author, year Country Trial Name (Quality Score)	Interventions (drug, dose)	Run-in/Washout Period	Allowed other medications/interventions	Age Gender Ethnicity
Fontaine, 2003 US (POOR)	risperidone 0.5, 1.0, or 2.0 mg or olanzapine 2.5, 5.0, or 10.0 mg	3-day washout of psychotropic drugs.	Allowed ongoing use of anticonvulsants (except for carbazepine), anti-depressants, and cholinesterase inhibitors if they had been in stable use for 30 days prior to drug washout. Allowed episodic use of antiemetics, cough/cold preparations (except those containing diphenhydramine), inhaled, topical, or ophthalmic steroids, zolpidem, and chloral hydrate. Lorazepam allowed in doses of 0.5 to 1 mg as needed for acute agitation.	Mean age 83 (SD ~7.5) 67% female

Evidence Table 13. Head-to-head trials in patients with behavioral and psychological symptoms of dementia

Author, year Country Trial Name (Quality Score)	Other population characteristics (diagnosis, etc)	Number screened/ eligible/enrolled	Number withdrawn/ lost to fu/analyzed
Fontaine, 2003 US (POOR)	Baseline MMSE score, risperidone vs olanzapine 9.3 SD 7.2) vs 7.2 (SD 7.0)	Number screened not reported/47 "recruited"/39 enrolled	33 withdrawn/# lost to followup not reported/39 analyzed

Evidence Table 13. Head-to-head trials in patients with behavioral and psychological symptoms of dementia

Author, year Country Trial Name (Quality Score)	Outcome Measures	Method of Outcome Assessment and Timing of Assessment
Fontaine, 2003 US (POOR)	Primary outcome measures: Neuropsychiatric Inventory (NPI) and Clinical Global Impressions Scale (CGI) Secondary measures: Empirical Behavioral Pathology in Alzheimer's Disease Rating Scale, Psychogeriatric Dependency Rating Scales, Multidimensional Observational Scale for Elderly Subjects, Mini-Mental Status Examination, and Quality of Life in Late-Stage Dementia Scale	Assessment at baseline, observation on days 1,2,3,5,8,10,12, and 15 by study nurse and study physician.

Evidence Table 13. Head-to-head trials in patients with behavioral and psychological symptoms of dementia

Author, year Country Trial Name (Quality Score)	Results
Fontaine, 2003 US (POOR)	Mean change from baseline to day 15, risperidone vs olanzapine (p-value, visit-by-drug group interaction effect, ANOVA): CGI: -1.26 vs -1.31 (p=0.87) NPI: -23.63 vs -15.0 (p=0.31) E-BEHAVE-AD (Global Score):+0.52 vs +0.21 (p=0.45) E-BEHAVE-AD (Total Score): -1.85 vs -2.26 (p=0.81) PGDRS (Behavioral Symptoms): -4.26 vs -4.05 (p=0.91) PGDRS (Orientation): +0.47 vs -0.21 (p=0.30) PGDRS (Mobility): 0 vs -0.16 (p=0.07) MOSES: -1.74 vs -0.74 (p=0.59) QUALID: -3.53 vs -4.06 (p=0.88)

Evidence Table 13. Head-to-head trials in patients with behavioral and psychological symptoms of dementia

Author, year Country Trial Name (Quality Score)	N	Duration	Study Design Setting	Eligibility criteria
Mulsant, 2004 US (POOR)	86	6 weeks	Double-blind, multicenter, long-term care facilities	Over age 55, with probable Alzheimer's disease, probable vascular dementia, or probable dementia of mixed etiology (by DSM-IV criteria); duration of illness of at least 1 year; MMSE scores at study entry between 7 and 26; definite psychotic symptoms, as defined by NPI frequency X severity score of >=4 on delusions, hallucinations, or both.

Risperidone vs olanzapine vs promazine

Evidence Table 13. Head-to-head trials in patients with behavioral and psychological symptoms of dementia

Author, year Country Trial Name (Quality Score)	Interventions (drug, dose)	Run-in/Washout Period	Allowed other medications/interventions	Age Gender Ethnicity
Mulsant, 2004 US (POOR)	risperidone 0.25 mg/day for the first 3 days, followed by an increase to 0.5 mg/day for days 3 through 6. Starting at day 7, dose increased to 0.75 mg/day until day 10, after which the investigator could increase the dose by 0.25 mg/day every 4 days if there was an insufficient clinical response. Total allowable dose 1.5 mg/day olanzapine starting dose 2.5 mg/day and the same titration schedule as above, with a maximum possible dose of 10 mg/day.	3-day washout, 7-day single-blind placebo run-in.	Lorazepam allowed for 4 days in any 7-day period for the treatment of agitation, at a maximum dose of 3 mg/day.	Mean age 83.8 78% female 77.6% white, 17.6% Hispanic, 5% black

Risperidone vs olanzapine vs promazine

Evidence Table 13. Head-to-head trials in patients with behavioral and psychological symptoms of dementia

Author, year Country Trial Name (Quality Score)	Other population characteristics (diagnosis, etc)	Number screened/ eligible/enrolled	Number withdrawn/ lost to fu/analyzed
Mulsant, 2004 US (POOR)	Baseline MMSE score, risperidone vs olanzapine 13.7 (SD 5.05, range 7-25) vs 13.2 (SD 4.79, range 7-25) 81.2% Alzheimer's dementia 7.0% vascular dementia 11.8% mixed Length of hospitalization risperidone: 11.9 months (SD 13.5) olanzapine: 27.1 months (SD 34.6)	NR/NR/86	17/NR/85

Risperidone vs olanzapine vs promazine

Evidence Table 13. Head-to-head trials in patients with behavioral and psychological symptoms of dementia

Author, year Country Trial Name (Quality Score)	Outcome Measures	Method of Outcome Assessment and Timing of Assessment
Mulsant, 2004 US (POOR)	Primary outcome measures: Udvalg for Kliniske Undersogelser (UKU) ratiing scale measuring peripheral anticholinergic effects, or a site report of a somnolence adverse event. **See Evidence Table X (Adverse Events) for these results.** Efficacy outcomes: NPI; abbreviated cognitive assessment.	Assessments at screening, baseline, and then at weekly periods for the duration of the trial. Cognitive assessments occurred at baseline and weeks 3 and 6 (or early termination).

Risperidone vs olanzapine vs promazine

Evidence Table 13. Head-to-head trials in patients with behavioral and psychological symptoms of dementia

Author, year Country Trial Name (Quality Score)	Results
Mulsant, 2004 US (POOR)	NPI scores: Statistically significant change from baseline for both olanzapine and risperidone on overall NPI frequency X severity, hallucinations and delusions, and occupational disruption items, but no between-group differences (data not reported).

Risperidone vs olanzapine vs promazine

Evidence Table 13. Head-to-head trials in patients with behavioral and psychological symptoms of dementia

Author, year Country Trial Name (Quality Score)	N	Duration	Study Design Setting	Eligibility criteria
Gareri, 2004 Italy (POOR)	60	8 weeks	Double-blind, setting not reported	Age 65 or older, with DSM-IV diagnoses of Alzheimer's disease, vascular dementia, or a combination of both; NPI score of at least 24.

Evidence Table 13. Head-to-head trials in patients with behavioral and psychological symptoms of dementia

Author, year Country Trial Name (Quality Score)	Interventions (drug, dose)	Run-in/Washout Period	Allowed other medications/interventions	Age Gender Ethnicity
Gareri, 2004 Italy (POOR)	risperidone 1 mg, olanzapine 5 mg, or promazine 50 mg; if no clinical response after 4 weeks, dose could be increased to 2 mg risperidone, 10 mg olanzapine, or 100 mg promazine.	10-day washout	Concomitant use of other antipsychotics, antidepressants, or mood stabilizers was avoided. Lorazepam (1 to 3 mg/day) could be given as needed until the end of the first 2 weeks.	Mean age 78.9 55% female Ethnicity not reported

Evidence Table 13. Head-to-head trials in patients with behavioral and psychological symptoms of dementia

Author, year Country Trial Name (Quality Score)	Other population characteristics (diagnosis, etc)	Number screened/ eligible/enrolled	Number withdrawn/ lost to fu/analyzed
Gareri, 2004 Italy (POOR)	Not reported	NR/NR/60	NR/NR/60

Evidence Table 13. Head-to-head trials in patients with behavioral and psychological symptoms of dementia

Author, year Country Trial Name (Quality Score)	Outcome Measures	Method of Outcome Assessment and Timing of Assessment
Gareri, 2004 Italy (POOR)	Primary outcome measure: NPI	Assessment at baseline, 4 and 8 weeks.

Evidence Table 13. Head-to-head trials in patients with behavioral and psychological symptoms of dementia

Author, year Country Trial Name (Quality Score)	Results
Gareri, 2004 Italy (POOR)	Complete regression of symptoms at 8 weeks (NPI): risperidone: 14/20 (70%) (6 men, 8 women) olanzapine: 16/20 (80%) (8 men, 8 women) promazine: 13/20 (70%) (7 men, 6 women) Partial respone at 8 weeks (NPI) (defined differently for different groups): risperidone: 2/20 (10%) (1 man, 1 woman) olanzapine: 4/20 (80%) (3 men, 1 woman) No response: risperidone: 1/20 (70%) (1 woman, drug interrupted at 4th week because of hypotension and confusion) promazine: 7/20 (70%) (2 men, 5 women)

Evidence Table 14. Quality assessment of trials in patients with behavioral and psychological symptoms of dementia

	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?**
Head-to-head trials							
Deberdt, 2005 US	Method not described	Not reported	MMSE score (olanzapine 13.7, risperidone 14.7, placebo 15.4) signficantly lower for olanzapine vs placebo, but NSD for risperidone vs olanzapine	Yes	Not reported (described as double blind)	Not reported (described as double blind)	Not reported (described as double blind)
Ellingrod, 2002 US	Not randomized	No	olanzapine group lower MMSE (11.75 vs 14.09)	Yes	Yes	No	Yes
Fontaine, 2003 US	Not clear if randomized	Not reported	More risperidone patients using antidepressants prior to study (58% vs 25%)	Yes	Yes	Not reported	Yes
Gareri, 2004 Italy	Method not described	Not reported	Baseline characteristics not reported (except age and sex)	Yes	Yes	Not reported (described as double blind)	Not reported (described as double blind)

Evidence Table 14. Quality assessment of trials in patients with behavioral and psychological symptoms of dementia

Author, year Country	Reporting of attrition, crossovers, adherence, and contamination?	Loss to follow-up: differential/high?	Intention-to-treat (ITT) analysis?	Post-randomization exclusions?	Quality Rating
Head-to-head trials					
Deberdt, 2005 US	Attrition yes, others no	No	No- analyzed patients with a baseline and at least one post-baseline score for the primary outcome, using a LOCF analysis (474 of 494 randomized; 96.0%)	NR	Fair
Ellingrod, 2002 US	NR	NR	Yes	NR	Poor
Fontaine, 2003 US	Attrition yes/others NR	20% olanzapine vs 11% risperidone discontinued	Not clear	No	Poor
Gareri, 2004 Italy	NR	NR	Yes	No	Poor

Evidence Table 14. Quality assessment of trials in patients with behavioral and psychological symptoms of dementia

	External Validity		
Author, year Country	**Number screened/eligible/enrolled**	**Exclusion criteria**	**Run-in/Washout**
Head-to-head trials			
Deberdt, 2005 US	NR/NR/494	Parkinson's disease, Lewy-body dementia, Pick's disease, frontotemporal dementia; or a MMSE score <5 or >24.	3- to 14-day placebo washout
Ellingrod, 2002 US	Number screened, eligible not reported/19 enrolled	Intracranial lesion or a history of severe head trauma.	None
Fontaine, 2003 US	Number screened not reported/47 "recruited"/39 enrolled	Previous neuroleptic malignant syndrome or known sensitivity to olanzapine or risperidone; current major depressive disorder or history or evidence of schizophrenia or bipolar disorder; people receiving amantadine, anorexics, carbamazepine, chloramphenicol, clonidine, erythromycin, guanabenz, guanadrel, guanethidine, guanfacine, ketanserin, methyldopa, metyrosine, narcotics, psychostimulants, reserpine, tryptophan, antiparkinsonian drugs, and benzodiazepines other than lorazepam.	3-day washout of psychotropic drugs.
Gareri, 2004 Italy	NR/NR/60	NR	10-day washout (drugs not specified)

Evidence Table 14. Quality assessment of trials in patients with behavioral and psychological symptoms of dementia

Author, year Country	Class naïve patients only?	Control group standard of care?	Funding
Head-to-head trials			
Deberdt, 2005 US	NR	Yes	Eli Lilly
Ellingrod, 2002 US	No	Yes	Supported by the 1999 American College of Clinical Pharmacy Research Award.
Fontaine, 2003 US	No	Yes	Supported by Eli Lilly and Company.
Gareri, 2004 Italy	NR	NR	Ministry of Health

Evidence Table 14. Quality assessment of trials in patients with behavioral and psychological symptoms of dementia

	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?**
Mulsant, 2004 US	Method not described	Not reported	Differences in sex (71% risperidone vs 84% olanzapine female), diagnosis (76% vs 86% Alzheimer's disease), and length of institutionalizaton (11.9 vs 27.1 months)	Yes	Not reported (describd as double blind)	Not reported (describd as double blind)	Not reported (describd as double blind)

Evidence Table 14. Quality assessment of trials in patients with behavioral and psychological symptoms of dementia

Author, year Country	Reporting of attrition, crossovers, adherence, and contamination?	Loss to follow-up: differential/high?	Intention-to-treat (ITT) analysis?	Post-randomization exclusions?	Quality Rating
Mulsant, 2004 US	Attrition yes (but not reported by group), others no.	Unable to determine	No (excluded 1 olanzapone patient with no postbaseline data)	No	Poor

Evidence Table 14. Quality assessment of trials in patients with behavioral and psychological symptoms of dementia

	External Validity		
Author, year Country	**Number screened/eligible/enrolled**	**Exclusion criteria**	**Run-in/Washout**
Mulsant, 2004 US	NR/NR/86	Presence of delirium at the time of study entry as defined by the Confusion Assessment Method, an inability to swallow oral medication, a probable or definnite diagnosis of psychotis prior to the onset of dementia, and an inability to otherwise cooperate with the study procedures.	3-day washout

Evidence Table 14. Quality assessment of trials in patients with behavioral and psychological symptoms of dementia

Author, year Country	Class naïve patients only?	Control group standard of care?	Funding
Mulsant, 2004 US	NR	Yes	Janssen

Evidence Table 14. Quality assessment of trials in patients with behavioral and psychological symptoms of dementia

	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?**
Active-control trials							
Chan, 2001 Hong Kong	Method not described	Not reported	More women in haloperidol group (83% vs 62%), otherwise similar	Yes	Yes	Not reported	Yes
De Deyn, 1999 Multiple European countries.	Yes	Not reported	Yes	Yes	Yes	Not reported	Yes

Evidence Table 14. Quality assessment of trials in patients with behavioral and psychological symptoms of dementia

Author, year Country	Reporting of attrition, crossovers, adherence, and contamination?	Loss to follow-up: differential/high?	Intention-to-treat (ITT) analysis?	Post-randomization exclusions?	Quality Rating
Active-control trials					
Chan, 2001 Hong Kong	Attrition yes/others NR	No	No- 3/58 not analyzed (5%).	No	Fair
De Deyn, 1999 Multiple European countries.	Attrition and contamination yes/crossovers and adherence no.	Yes: 121/344 (35%) discontinued: 41% risperidone, 30% haloperidol, 35% placebo	Yes	No	Fair

Evidence Table 14. Quality assessment of trials in patients with behavioral and psychological symptoms of dementia

	External Validity		
Author, year Country	**Number screened/eligible/enrolled**	**Exclusion criteria**	**Run-in/Washout**
Active-control trials			
Chan, 2001 Hong Kong	Number screened, eligible not reported, 58 enrolled	Presumptive diagnosis of Lewy Body Dementia, other neurological or medical conditions which diminished cognitive function (e.g., hypothyroidism), other psychiatric disorders which might contribute to the psychotic symptoms (e.g., schizophrenia, delusional disorder), unstable medical conditions (e.g., poorly controlled hypertension, angina or diabetes), clinically relevant abnormal ECGs or laboratory tests, a history of allergic reaction to antipsychotic treatment or a history of Neuroleptic Malignant Syndrome.	7- to 14-day washout during which all psychotropic and antiparkinsonian drugs were stopped.
De Deyn, 1999 Multiple European countries.	Number screened not reported/371 eligible/344 enrolled (27 dropped out during washout)	Other conditions that diminish cognitive function; other psychiatric disorders; clinically relevant organic or neurologic disease; ECG or laboratory abnormalities; administration f a depot neuroleptic within one treatment cycle of Visit 1; history of allergic reaction to neuroleptics or history of neuroleptic malignant syndrome; participation in clinical trial(s) with investigational drugs during the 4 weeks preceding this trial.	1-week single-blind washout phase during which all psychotropic medications were discontinued.

Evidence Table 14. Quality assessment of trials in patients with behavioral and psychological symptoms of dementia

Author, year Country	Class naïve patients only?	Control group standard of care?	Funding
Active-control trials			
Chan, 2001 Hong Kong	No	Yes	Sponsored by Janssen Research Foundation
De Deyn, 1999 Multiple European countries.	No	Yes	Supported in part by a grant from the Janssen Research Foundation.

Evidence Table 14. Quality assessment of trials in patients with behavioral and psychological symptoms of dementia

	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?**
Meehan, 2002 US, Russia, and Romania	NR	NR	Yes (but no details)	Yes	NR (described as double blind)	NR (described as double blind)	NR (described as double blind)
Suh, 2004 South Korea	Yes	Not reported	Yes	Yes	Yes	Yes	Yes
Tariot, 2004 (poster) US	Method not reported	Not reported	Differences in mean age between groups: quetiapine 81.92; haloperidol 83.55; placebo 83.93 (p=0.042 quetiapine vs haloperidol)	Yes	Yes	Not reported	Yes

Evidence Table 14. Quality assessment of trials in patients with behavioral and psychological symptoms of dementia

Author, year Country	Reporting of attrition, crossovers, adherence, and contamination?	Loss to follow-up: differential/high?	Intention-to-treat (ITT) analysis?	Post-randomization exclusions?	Quality Rating
Meehan, 2002 US, Russia, and Romania	Attrition yes, others no.	No	Yes	No	Fair
Suh, 2004 South Korea	Attrition yes/others NR	No	No; 6/120 (5%) excluded from analysis.	No	Fair
Tariot, 2004 (poster) US	NR	High	Unclear	NR	Poor

Evidence Table 14. Quality assessment of trials in patients with behavioral and psychological symptoms of dementia

	External Validity		
Author, year Country	**Number screened/eligible/enrolled**	**Exclusion criteria**	**Run-in/Washout**
Meehan, 2002 US, Russia, and Romania	331/NR/272	Patients excluded if they received benzodiazepines, antipsychotics, or anticholinergics within 4 hours prior to the first injection of study drug, if they received psychostimulants or reserpine within one week prior to study drug administration, or an injetable depot neuroleptic within less than one dosing interval of study initiation, if they had been diagnosed with any serious neurological condition other than Alzheimer's disease or vascular dementia that cold contribute to psychosis or dementia, if they had laboratory or ECG abnormalities with clinical implications for the patient's participation in the study, or if they were judged to be at serious risk of suicide.	None
Suh, 2004 South Korea	280 screened/#eligible not reported/120 enrolled.	Other conditions that diminish cognitive function (e.g., Lewy-body dementia, hypothyroidism), other psychiatric disorders that might contribute to the psychotic symptoms (e.g., schizophrenia, delusional disorder), clinically relevant organic or neurologic disease, unstable medical conditions (e.g., poorly controled hypertension, angina, or diabetes), abnormal electrocardiograms as diagnosed by a cardiologist or laboratory tests, a history of allergic reaction to antipsychotic treatment, and a history of neuroleptic malignant syndrome.	1-week washout period during which all psychotropic medications were discontinued.
Tariot, 2004 (poster) US	# screened, eligible not reported/284 enrolled	Not reported	No placebo run-in; antipsychotics discontinued >48 hours

Evidence Table 14. Quality assessment of trials in patients with behavioral and psychological symptoms of dementia

Author, year Country	Class naïve patients only?	Control group standard of care?	Funding
Meehan, 2002 US, Russia, and Romania	NR	Yes	Eli Lilly
Suh, 2004 South Korea	No	Yes	Financially supported by Janssen Korea, Seoul, Korea.
Tariot, 2004 (poster) US	Not reported	Unable to determine	Not reported; one author from AstraZeneca

Evidence Table 14. Quality assessment of trials in patients with behavioral and psychological symptoms of dementia

	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?**
Placebo-controlled trials							
Brodaty, 2003 Frank, 2004	Yes	Not reported	Yes, but baseline data reported only on included sites (excludes patients at 1 site with 32 patients excluded due to non-adherence with documentation procedures)	Yes	Yes	Not reported	Yes
De Deyn, 2004 Europe, Australia, Israel, Lebanon, and South Africa	Method not reported	Not reported	Yes	Yes	Yes	Not reported	Yes
Katz, 1999 US	Yes	Not reported	MMSE mean scores higher in risperidone 2 mg group than placebo; other differences not significant.	Yes	Yes	Not reported	Yes

Evidence Table 14. Quality assessment of trials in patients with behavioral and psychological symptoms of dementia

Author, year Country	Reporting of attrition, crossovers, adherence, and contamination?	Loss to follow-up: differential/high?	Intention-to-treat (ITT) analysis?	Post-randomization exclusions?	Quality Rating
Placebo-controlled trials					
Brodaty, 2003 Frank, 2004	Attrition yes, others reported combined for each group.	Yes (27% risperidone vs 33% placebo)	No	Yes- all patients from one site (N=32) excluded due to non-adherence with documentation.	Fair
De Deyn, 2004 Europe, Australia, Israel, Lebanon, and South Africa	Attrition and adherence yes/crossovers and contamination no.	No	No (results on 642 of 652 randomized)	Yes- 652 randomized, patient disposition reported for 649.	Fair
Katz, 1999 US	Attrition yes, others no.	No	No: results on 617/625 at endpoint, 435/625 at week 12.	No	Fair

Evidence Table 14. Quality assessment of trials in patients with behavioral and psychological symptoms of dementia

	External Validity		
Author, year Country	**Number screened/eligible/enrolled**	**Exclusion criteria**	**Run-in/Washout**
Placebo-controlled trials			
Brodaty, 2003 Frank, 2004	Number screened not reported/384 eligible/345 enrolled	Medical or neurologic conditions other than dementia that diminish cognitive function, other types of dementia, major depression within the last 6 months, other psychiatric disorders that could have accounted for observed psychotic disturbances, a history of tardive dyskinesia, clinically uncontrolled organic disease, clinically relevant laboratory abnormalities, administration of a depot neuroleptic within 2 treatment cycles, a history of neuroleptic malignant syndrome or an allergic reaction to neuroleptic drugs, history of failure to respond to risperidone treatment of at least 4 weeks' duration, and participation in clinical trial(s) with any investigational drugs during the 4 weeks preceding selection.	Maximum 7-day single-blind placebo washout period during which existing psychotropic medication was discontinued.
De Deyn, 2004 Europe, Australia, Israel, Lebanon, and South Africa	Number screened, eligible not reported/652 enrolled	Diagnosis of current primary mood disorder or other DSM-IV Axis I disorder with onset prior to diagnosis of Alzheimer's disease, including but not limited to schizophrenia, bipolar disorder, or delusional disorder.	Placebo run-in for up to maximum 14 days.
Katz, 1999 US	729 screened/625 eligible/625 enrolled	Untreated reversible causes of dementia, medical or neurological conditions that diminish cognition, diagnosis of dementia related to infection with HIV or substance-induced persistent dementia, diagnosis of delirium or amnestic disorder, and psychiatric diagnosis that could have accounted for the observed psychotic disturbances.	Single-blind placebo washout of 3 to 7 days.

Evidence Table 14. Quality assessment of trials in patients with behavioral and psychological symptoms of dementia

Author, year Country	Class naïve patients only?	Control group standard of care?	Funding
Placebo-controlled trials			
Brodaty, 2003 Frank, 2004	No	Yes	Supported by Janssen-Cilag Australia and Johnson & Johnson; first author a consultant for Janssen and AstraZeneca; has received grant/research support and honoraria from Janssen, and serves on the speakers/advisory board for Janssen. Other authors have received support from Janssen, Lilly, Bristol-Myers. 2 authors employees of Johnson & Johnson.
De Deyn, 2004 Europe, Australia, Israel, Lebanon, and South Africa	No	Yes	Sponsored by Eli Lilly and Company; corresponding author employed by Lilly Research Laboratories.
Katz, 1999 US	No	Yes	Supported by a grant from the Janssen Research Foundation.

Evidence Table 14. Quality assessment of trials in patients with behavioral and psychological symptoms of dementia

	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?**
Mintzer, 2006 US	Yes	Yes	No differences, but baseline characteristics reported only for analyzed population only (416/473 randomized)	Yes	Reported as double-blind, but not specified	Reported as double-blind, but not specified	Reported as double-blind, but not specified
Street et al., 2000 US	Yes	Not reported	Yes	Yes	Yes	Not reported	Yes
Zhong et al, 2004 (poster) US	Method not reported	Not reported	Yes	Yes	Yes	Not reported	Yes

Evidence Table 14. Quality assessment of trials in patients with behavioral and psychological symptoms of dementia

Author, year Country	Reporting of attrition, crossovers, adherence, and contamination?	Loss to follow-up: differential/high?	Intention-to-treat (ITT) analysis?	Post-randomization exclusions?	Quality Rating
Mintzer, 2006 US	Attrition and adherence yes, others no.	No (<1%)	No: efficacy analyses on 416/473 randomized patients (87.9%)	Yes, 57 patients excluded for non-compliance at site (7) or not psychotic at baseline (50)	Fair
Street et al., 2000 US	Attrition yes, others no.	No	Yes (6/206 not analyzed, able to calculate)	1 (placebo) did not receive intervention.	Good
Zhong et al, 2004 (poster) US	Attrition yes, others no	High	No	Yes	Poor

Evidence Table 14. Quality assessment of trials in patients with behavioral and psychological symptoms of dementia

	External Validity		
Author, year Country	**Number screened/eligible/enrolled**	**Exclusion criteria**	**Run-in/Washout**
Mintzer, 2006 US	560/87/473	Patients excluded had recently been treated with neuroleptic injections, had other medical conditions that diminish cognition, or had other psychiatric disorders that produce psychotic sympotms. Patients with epilepsy, recent diagnoses or cancer (except nonmelanoma skin cancers), unstable medical conditios, changes in prescription medications 30 days before screening, or significant baseline laboratory or ECG abnormalities wer also excluded. Patients were withdrawn if their behavior worsened considerably, they withdrew consent, or their randomizaton code was broken.	One week placebo washout. Period reduced for patients not using psychotropic medications and for patietns whose psycohosis or agitation worsened.
Street et al., 2000 US	# screened not reported/288 eligible/206 enrolled	History of a DSM-IV Axis I disorder (e.g., schizophrenia, bipolar disorder, severe or recurrent depression), any neurological condition other than Alzheimer's disease that could contribute to psychosis or dementia, MMSE score of greater than 24, and bedridden status.	3- to 14-day single-blind placebo run-in; patients demonstrating a placebo response were not randomized.
Zhong et al, 2004 (poster) US	# screened, eligible not reported/333 enrolled	Not reported	Not reported

Evidence Table 14. Quality assessment of trials in patients with behavioral and psychological symptoms of dementia

Author, year Country	Class naïve patients only?	Control group standard of care?	Funding
Mintzer, 2006 US	NR	Yes	Johnson & Johnson
Street et al., 2000 US	No	Yes	Sponsored in part by Eli Lilly and Company; 11 of 13 authors employed by Lilly Research Laboratories; 10 authors are stockholders in Eli Lilly.
Zhong et al, 2004 (poster) US	Not reported	Unable to determine	Supported by AstraZeneca

Evidence Table 15. Active-control trials in patients with behavioral and psychological symptoms of dementia

Author, year Country Trial Name (Quality Score)	N	Duration	Study design Setting	Eligibility criteria
Quetiapine vs haloperidol				
Tariot, 2004 (poster) US (POOR)	284	10 weeks	Double-blind, multicenter, 46 nursing homes	Men and women, age 65 and older, not bedridden, residing in nursing homes for at least 2 weeks; DSM-IV diagnosis of dementia or National Institute of Neurological and Communicative Disorders & Stroke-Alzheimer's Disease (NINCDS) diagnosis of Alzheimer's Disease; BPRS score 24 or higher, CGI-Severity score 4 or higher.

Evidence Table 15. Active-control trials in patients with behavioral and psychological symptoms of dementia

Author, year Country Trial Name (Quality Score)	Interventions (drug, dose)	Run-in/washout period	Allowed other medications/interventions
Quetiapine vs haloperidol			
Tariot, 2004 (poster) US (POOR)	quetiapine vs haloperidol, flexible dosing, dose range/mean not reported.	No placebo run-in; antipsychotics discontinued for at least 48 hours.	Psychotropics permitted: chloral hydrate, zolpidem, lorazepam for sleep/agitation; anti-EPS medication (but not prophylactically), cholinesterase inhibitors if stable dose for >6 weeks prior to entry.

Evidence Table 15. Active-control trials in patients with behavioral and psychological symptoms of dementia

Author, year Country Trial Name (Quality Score)	Age Gender Ethnicity	Other population characteristics (diagnosis, etc)	Number screened/ eligible/enrolled	Number withdrawn/ lost to fu/analyzed
Quetiapine vs haloperidol				
Tariot, 2004 (poster) US (POOR)	Mean age 83.9 73% female 89% white, 8% black, 2% Hispanic, <1% Asian.	100% Alzheimer's dementia	# screened, eligible not reported/284 enrolled (subset of larger group of elderly patients with dementia, N=378)	102 withdrawn/1 lost to followup/# analyzed not clear

Evidence Table 15. Active-control trials in patients with behavioral and psychological symptoms of dementia

Author, year Country Trial Name (Quality Score)	Outcome measures	Method of outcome assessment and timing of assessment	Results
Quetiapine vs haloperidol			
Tariot, 2004 (poster) US (POOR)	BPRS- Total score, agitation factor subscale (tension, hostility, uncooperativeness, and excitement items) and anergia factor subscale (emotional withdrawal, motor retardation, blunted affect, disorientation) NPI-NH Agitation + Hallucinations + Delusions (NPI-3) MMSE Multidimensional Observation Scale for Elderly Subjects (MOSES) Physical Self-Maintenance Scale (PSMS)	Not reported	All drug treatment groups improved from baseline to LOCF on BPRS total score and on the NPI-3 (Data presented graphically only) Quetiapine group had statistically significantly better functional status as assessed by the MOSES, PSMS, AND BPRS anergia factor compared with haloperidol (comparison to placebo not reported, data presented graphically only) Quetiapine and haloperidol groups had significantly more improvement than placebo patients on the BPRS agitation subscale (change from baseline, quetiapine -2.4 [p=0.033], haloperidol -2.9 [p=0.001], placebo -1.1) Quetiapine patients' scores on MMSE not significantly different from placebo; haloperidol results not reported.

Evidence Table 15. Active-control trials in patients with behavioral and psychological symptoms of dementia

Author, year Country Trial Name (Quality Score)	N	Duration	Study design Setting	Eligibility criteria
Risperidone vs haloperidol				
Chan et al, 2001 Hong Kong (FAIR)	58	12 weeks	Double-blind, multicenter (3 centers)	Age 55 or older and met DSM-IV criteria for Dementia of Alzheimer's Type with behavioral disturbance, vascular dementia with behavioral disturbance or a combination of the two. Active behavioral symptoms, as evidenced by a frequency score of at least 4 on one and at least 3 on another item of the Cohen-Mansfield Agitation Inventory (CMAI). Symptoms present for at least 2 weeks. Score of at least 8 on Behavioral Pathology in Alzheimer's Disease Rating Scale (BEHAVE-AD).

Evidence Table 15. Active-control trials in patients with behavioral and psychological symptoms of dementia

Author, year Country Trial Name (Quality Score)	Interventions (drug, dose)	Run-in/washout period	Allowed other medications/interventions
Risperidone vs haloperidol			
Chan et al, 2001 Hong Kong (FAIR)	risperidone 0.5 mg vs haloperidol 0.5 mg to start. Titrated by increments of 0.5 mg no faster than every other day. Target dose 1 mg per day, could be stepped up to 2 mg per day if symptoms poorly controlled.	7- to 14-day washout during which all psychotropic and antiparkinsonian drugs were stopped.	Medications permitted not reported, but report patients taking benzodiazepines (4 haloperidol, 4 risperidone), chloral hydrate (1 risperidone), benzhexol (2 haloperidol), donepezil (1 haloperidol), and donepezil (1 haloperidol).

Evidence Table 15. Active-control trials in patients with behavioral and psychological symptoms of dementia

Author, year Country Trial Name (Quality Score)	Age Gender Ethnicity	Other population characteristics (diagnosis, etc)	Number screened/ eligible/enrolled	Number withdrawn/ lost to fu/analyzed
Risperidone vs haloperidol				
Chan et al, 2001 Hong Kong (FAIR)	Mean 80.5 (sd 8.2) 72% female 100% Chinese	79% Alzheimer's dementia, 21% vascular dementia	Number screened, eligible not reported, 58 enrolled	3 withdrew (1 haloperidol, 2 risperidone), 55 analyzed.

Evidence Table 15. Active-control trials in patients with behavioral and psychological symptoms of dementia

Author, year Country Trial Name (Quality Score)	Outcome measures	Method of outcome assessment and timing of assessment	Results
Risperidone vs haloperidol			
Chan et al, 2001 Hong Kong (FAIR)	CMAI total score, BEHAVE-AD subscale scores, Functional Assessment Staging Rating Scale (FAST), Cantonese version of Mini-Mental State Examination (CMMSE).	Baseline, weeks 4, 8, and 12. Additional CMAI ratings at weeks 2, 6, and 10.	Mean change from baseline to endpoint, risperidone vs haloperidol CMAI total: -8.1 vs -10 (p=0.95) BEHAVE-AD (Psychosis): -1.1 vs -0.6 (p=0.91) BEHAVE-AD (Activity disturbances): -0.8 vs -0.7 (p=0.16) BEHAVE-AD (Aggressiveness): -1.3 vs -1.3 (p=0.56) BEHAVE-AD (Diurnal rhythm disturbances): -0.4 vs -0.3 (p=0.36) BEHAVE-AD (Affective disturbances): -0.2 vs 0 (p=0.11) BEHAVE-AD (Anxieties and phobia): 0 vs -0.1 (p=0.19)

Evidence Table 15. Active-control trials in patients with behavioral and psychological symptoms of dementia

Author, year Country Trial Name (Quality Score)	N	Duration	Study design Setting	Eligibility criteria
De Deyn et al, 1999 Multiple European countries (FAIR) Engelborghs (subanalysis)	344	12 weeks	Double-blind, placebo-controlled, multicenter	Age 55 or older, institutionalized, diagnosis of primary degenerative dementia of the Alzheimer's type, vascular dementia, or mixed dementia according to the DSM-IV. Scores of 4 or greater on Functional Assessment Staging (FAST); 23 or greater on Mini-Mental Status Examination (MMSE); 1 or greater on the BEHAVE-AD global rating; and 8 or greater on the BEHAVE-AD total score.

Evidence Table 15. Active-control trials in patients with behavioral and psychological symptoms of dementia

Author, year Country Trial Name (Quality Score)	Interventions (drug, dose)	Run-in/washout period	Allowed other medications/interventions
De Deyn et al, 1999 Multiple European countries (FAIR) Engelborghs (subanalysis)	risperidone 0.5 mg vs haloperidol 0.5 mg to start. Titrated by increments of 0.5 mg every 4 days if indicated, to 2 mg. Could be increased up to 4 mg per day if symptoms poorly controlled and no EPS.	1-week single-blind washout phase during which all psychotropic medications were discontinued.	Use of antipsychotics, antidepressants, lithium, carbamazepine, and valproic acid not permitted. Lorazepam permitted if limited to 4 days per week for the first 4 weeks of treatment. If needed beyond week 4, patient discontinued from study.

Evidence Table 15. Active-control trials in patients with behavioral and psychological symptoms of dementia

Author, year Country Trial Name (Quality Score)	Age Gender Ethnicity	Other population characteristics (diagnosis, etc)	Number screened/ eligible/enrolled	Number withdrawn/ lost to fu/analyzed
De Deyn et al, 1999 Multiple European countries (FAIR) Engelborghs (subanalysis)	Mean 81 (range 56-97) 56% female 99% white, <1% black, <1% Asian	74% Alzheimer's dementia, 33% Vascular Dementia (7% had both diagnoses)	Number screened not reported/371 eligible/344 enrolled (27 dropped out during washout)	344 analyzed

Evidence Table 15. Active-control trials in patients with behavioral and psychological symptoms of dementia

Author, year Country Trial Name (Quality Score)	Outcome measures	Method of outcome assessment and timing of assessment	Results
De Deyn et al, 1999 Multiple European countries (FAIR) Engelborghs (subanalysis)	BEHAVE-AD, Cohen-Mansfield Agitation Inventory (CMAI), and Clinical Global Impression (CGI)	Evaluations at selection, baseline, weeks 1, 2, 4, 6, 8, 10, 12.	Mean change from baseline to endpoint, risperidone vs haloperidol vs placebo BEHAVE-AD (Total): -5.2 vs -6.6 vs -4.2 BEHAVE-AD (Aggressiveness): -1.7 vs -1.6 vs -0.8 CMAI (Total aggressive): -3.9 vs -3.3 vs -1.6 CMAI (Physical aggressive): -2.7 vs -2.3 vs -0.7 CMAI (Verbal aggressive): -1.2 vs -1.0 vs -0.8 (No significant differences between risperidone and haloperidol) Mean change from baseline to week 12, risperidone vs haloperidol vs placebo BEHAVE-AD (Total): -8.6 vs -7.5 vs -6.2 (p NS for risperidone vs haloperidol) BEHAVE-AD (Aggressiveness): -2.9 vs -1.8 vs -1.5 (p=0.05 for risperidone vs haloperidol; post hoc analysis) CMAI (Total aggressive): -8.3 vs -3.6 vs -4.9 (p=0.02 for risperidone vs haloperidol; post hoc analysis) CMAI (Physical aggressive): -5.9 vs -2.8 vs -3.5 (p NS for risperidone vs haloperidol) CMAI (Verbal aggressive): -2.5 vs -0.8 vs -1.4 (p=0.01 for risperidone vs haloperidol; post hoc analysis)

Evidence Table 15. Active-control trials in patients with behavioral and psychological symptoms of dementia

Author, year Country Trial Name (Quality Score)	N	Duration	Study design Setting	Eligibility criteria
Suh et al, 2004 South Korea (FAIR)	120	18 weeks (1 week washout, 8 weeks active treatment, 1 week washout, 8 weeks crossover treatment)	Double-blind, crossover, single center	Age 65 or older, diagnosis of dementia of the Alzheimer's type with behavioral disturbance, vascular dementia with behavioral disturbance, or a combination of the two, according to DSM-IV criteria. Score of 4 or higher on the Functional Assessment Staging Test, a total score of 8 or higher on the Korean version of the BEHAVE-AD, and a score of more than 3 on any two items of the Korean version of the CMAI.

Evidence Table 15. Active-control trials in patients with behavioral and psychological symptoms of dementia

Author, year Country Trial Name (Quality Score)	Interventions (drug, dose)	Run-in/washout period	Allowed other medications/interventions
Suh et al, 2004 South Korea (FAIR)	risperidone or haloperidol 0.5 mg to 1.5 mg (target dose was 1 mg). Dose could be titrated up or down; dosing regimen and intervals between dose titrations were individualized for each patient.	1-week washout period during which all psychotropic medications were discontinued.	Concomitant use of antipsychotic drugs, antidepressants, and mood stabilizers was not permitted. Lorazepam permitted if limited to 4 days/week for the first 4 weeks of treatment.

Evidence Table 15. Active-control trials in patients with behavioral and psychological symptoms of dementia

Author, year Country Trial Name (Quality Score)	Age Gender Ethnicity	Other population characteristics (diagnosis, etc)	Number screened/ eligible/enrolled	Number withdrawn/ lost to fu/analyzed
Suh et al, 2004 South Korea (FAIR)	Mean age 80.9 (SD 8.2, range 65-97) 80% female Ethnicity not reported (trial conducted in South Korea)	65.8% Alzheimer's dementia 28.3% vascular dementia 5.8% mixed	280 screened/# eligible not reported/120 enrolled	6 withdrawn/0 lost to followup/114 analyzed

Evidence Table 15. Active-control trials in patients with behavioral and psychological symptoms of dementia

Author, year Country Trial Name (Quality Score)	Outcome measures	Method of outcome assessment and timing of assessment	Results
Suh et al, 2004 South Korea (FAIR)	BEHAVE-AD-K, CMAI-K, AND CGI-C	Patients assessed weekly during the first 4 weeks and then every 2 weeks (twice) until the end of the final (8th week)	Mean change from baseline to endpoint, risperidone vs haloperidol BEHAVE-AD-K (Total) - 7.2 vs - 4.7 (p=0.004) BEHAVE-AD-K (Psychosis) - 3.7 vs - 2.0 (p=0.582) BEHAVE-AD-K (Activity Disturbances) - 1.1 vs - 0.8 (p=0.858) BEHAVE-AD-K (Aggressiveness) - 1.1 vs - 0.9 (p=0.002) BEHAVE-AD-K (Diurnal Rhythm Disturbances) - 0.5 vs - 0.2 (p=0.038) BEHAVE-AD-K (Affective Disturbance) - 0.5 vs - 0.2 (p=0.248) BEHAVE-AD-K (Anxieties and Phobias) - 0.3 vs + 0.1 (p<0.0001) CMAI-K (Total) - 14.2 vs - 5.9 (p<0.0001) CMAI-K (Aggressive Behavior) - 4.0 vs - 3.3 (p=0.001) CMAI-K (Physical Non-Aggressive Behavior) - 2.4 vs - 1.0 (p=0.024) CMAI-K (Verbally Agitated Behavior) - 1.1 vs - 0.5 (p=0.002) CGI-C - 0.1 vs + 0.2 (p=0.001)

Evidence Table 16. Placebo-controlled trials in patients with behavioral and psychological symptoms of dementia

Author, year Country Trial Name (Quality Score)	N	Duration	Study Design Setting	Eligibility criteria	Interventions (drug, dose, duration)
Trials of Olanzapine					
Street., 2000 US (GOOD) Kennedy, 2001 (subanalysis) Street 2001 (one-year followup)	206	6 weeks	Double-blind, multicenter	Elderly nursing care facility residents, who met the National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders Association criteria for possible or probable Alzheimer's Disease. Score of 3 or higher on any of the Agitation/Aggression, Hallucinations, or Delusions items of the Neuropsychiatric Inventory- Nursing Home version (NH-NH) at screening and following placebo lead-in.	olanzapine 5 mg, 10 mg, or 15 mg

Evidence Table 16. Placebo-controlled trials in patients with behavioral and psychological symptoms of dementia

Author, year Country Trial Name (Quality Score)	Run-in/washout period	Allowed other medications/ interventions	Age Gender Ethnicity	Other population characteristics (diagnosis, etc)	Number screened/ eligible/enrolled	Number withdrawn/ lost to fu/analyzed
Trials of Olanzapine						
Street., 2000 US (GOOD) Kennedy, 2001 (subanalysis) Street 2001 (one-year followup)	3- to 14-day single-blind placebo run-in; patients demonstrating a placebo response were not randomized.	Benzodiazepines allowed as rescue medication but could not exceed 4 mg/day of lorazepam equivalents for a total of 21 days during the active treatment.	Mean age 83 years	Alzheimer's Disease	# screened not reported/288 eligible/206 enrolled	54 withdrawn/5 lost to followup/200 analyzed

Evidence Table 16. Placebo-controlled trials in patients with behavioral and psychological symptoms of dementia

Author, year Country Trial Name (Quality Score)	Outcome scales	Method of Outcome Assessment and Timing of Assessment
Trials of Olanzapine		
Street., 2000 US (GOOD) Kennedy, 2001 (subanalysis) Street 2001 (one-year followup)	Primary outcome measure: Neuropsychiatric Inventory-Nursing Home version (NH-NH) item scores for the core symptoms: Agitation/Aggression, Hallucinations, and Delusions. Secondary measures: NH/NH Total, Hallucinations and Delusions total (Psychosis Total), individual items, Occupational Disruptiveness score derived from the Agitation/Aggression, Hallucinations, and Delusions items (Core Disruptiveness), Brief Psychiatric Rating Scale total and subscale, MMSE	Assessments conducted at the nursing facility by neurologists, psychiatrists, geriatricians, psychometrists, nurses, and other medical specialists trained before study initiation. At screening, baseline, and end of study.

Evidence Table 16. Placebo-controlled trials in patients with behavioral and psychological symptoms of dementia

Author, year Country Trial Name (Quality Score)	Results	Results
Trials of Olanzapine		
Street., 2000 US (GOOD) Kennedy, 2001 (subanalysis) Street 2001 (one-year followup)	**Mean change from baseline, Olanzapine vs placebo (p vs placebo):** **NPI/NH (Core Total)** 5 mg -7.6 (p<0.001); 10 mg -6.1 (p=0.006); 15 mg -4.9 (p=0.24); placebo -3.7 **NPI/NH (Occupational Disruptiveness)** 5 mg -2.7 (p=0.008); 10 mg -2.1 (p=0.28); 15 mg -2.3 (p=0.14); placebo -1.5 **NPI/NH (Agitation/Aggression)** 5 mg -4.1 (p=0.01); 10 mg -3.9 (p=0.02); 15 mg -3.1 (p=0.60); placebo -2.1 **NPI/NH (Psychosis Total)** 5 mg -3.6 (p=0.001); 10 mg -2.2 (p=0.04); 15 mg -1.9 (p=0.20); placebo -1.6 **NPI/NH (Hallucinations)** 5 mg -0.7 (p=0.007); 10 mg -0.2 (p=0.05); 15 mg -0.7 (p=0.10); placebo 0.0 **NPI/NH (Delusions)** 5 mg -2.9 (p=0.01); 10 mg -2.0 (p=0.15); 15 mg -1.3 (p=0.64); placebo -1.6 **NPI/NH (Depression/Dysphoria)** 5 mg -2.0 (p=0.28); 10 mg -0.6 (p>0.99); 15 mg -0.2 (p=0.32); placebo -1.0 **NPI/NH (Total)** 5 mg -18.7 (p=0.005); 10 mg -14.0 (p=0.09); 15 mg -9.7 (p=0.83); placebo -10.4 **BPRS (Total)** 5 mg -6.8 (p=0.005); 10 mg -5.6 (p=0.06); 15 mg -4.0 (p=0.13); placebo -1.4 **BPRS (Positive subscale)** 5 mg -2.0 (p=0.05); 10 mg -1.4 (p=0.40); 15 mg -1.4 (p=0.15); placebo -0.4 **BPRS (Anxiety/Depression subscale)** 5 mg -1.3 (p=0.04); 10 mg -1.5 (p=0.02); 15 mg -0.6 (p=0.29); placebo 0.1	

Evidence Table 16. Placebo-controlled trials in patients with behavioral and psychological symptoms of dementia

Author, year Country Trial Name (Quality Score)	Results	Results
Trials of Olanzapine		
Street., 2000 US (GOOD) Kennedy, 2001 (subanalysis) Street 2001 (one-year followup)		

Evidence Table 16. Placebo-controlled trials in patients with behavioral and psychological symptoms of dementia

Author, year Country Trial Name (Quality Score)	N	Duration	Study Design Setting	Eligibility criteria	Interventions (drug, dose, duration)
de Deyn, 2004 Europe, Australia, Israel, Lebanon, and South Africa (FAIR)	652	10 weeks	Double-blind, multicenter	Age 40 or older, resided in long-term nursing homes or continuing-care hospitals, and expected to continue patient status for 6 months following enrollment. Met NINCDS-ADRDA and DSM-IV -TR criteria for possible or probable Alzheimer's Disease, and exhibited clinically significant psychotic symptoms (delusions or hallucinations) that were (1) at least moderate in severity (i.e., impair functional capacity or cause them to pose a threat to themselves) at study entry and randomization; (2) present at least once per week for the month preceding study entry; and (3) require pharmacological intervention, in the opinion of the investigator. Minimum score of 5 on MMSE at Visit 1 and Visit 2.	olanzapine 1 mg, 2.5 mg, 5 mg, 7.5 mg, or placebo 10 weeks, fixed dose. Those assigned to 5 mg or 7.5 mg began at 2.5 mg and titrated to final dose by 2.5 mg per week increments.

Evidence Table 16. Placebo-controlled trials in patients with behavioral and psychological symptoms of dementia

Author, year Country Trial Name (Quality Score)	Run-in/washout period	Allowed other medications/ interventions	Age Gender Ethnicity	Other population characteristics (diagnosis, etc)	Number screened/ eligible/enrolled	Number withdrawn/ lost to fu/analyzed
de Deyn, 2004 Europe, Australia, Israel, Lebanon, and South Africa (FAIR)	Placebo run-in for up to maximum 14 days.	Medications with primarily central nervous system activity were dis-allowed, except for the stable use of antidepressants, benzodiazepines, and acetylcholinesterase inhibitors. Use of anticholinergics for control of EPS was exclusionary. Limited use of benzodiazepines or hypnotics permitted with restrictions as a rescue medication to chronic users up to 4 mg/day	Mean age 77 (sd 10.4) 75% female 99.7% white	Mean baseline MMSE score 13.7 (sd 5.1); mean baseline NIP/NH Psychosis Total score 9.7 (sd 4.9)	Number screened, eligible not reported/652 enrolled	184 withdrawn/lost to followup not reported/642 analyzed

Evidence Table 16. Placebo-controlled trials in patients with behavioral and psychological symptoms of dementia

Author, year Country Trial Name (Quality Score)	Outcome scales	Method of Outcome Assessment and Timing of Assessment
de Deyn, 2004 Europe, Australia, Israel, Lebanon, and South Africa (FAIR)	NH-NH Total NH-NH Psychosis CGI-C	Responses obtained by a trained interviewer from professional caregivers involved in the ongoing care of the patient in the previous week. Assessments weekly for the first 2 weeks of treatment and biweekly thereafter.

Evidence Table 16. Placebo-controlled trials in patients with behavioral and psychological symptoms of dementia

Author, year Country Trial Name (Quality Score)	Results	Results
de Deyn, 2004 Europe, Australia, Israel, Lebanon, and South Africa (FAIR)	**Mean change from baseline, Olanzapine vs placebo (p vs placebo)::** **NPI/NH (Total)** 1 mg -14.8 (p=0.547); 2.5 mg -15.7 (p=0.121); 5 mg -16.3 (p=0.199); 7.5 mg -17.7 (p=0.003); placebo -13.7 **NPI/NH (Psychosis Total)** 1 mg -6.0 (p<0.171); 2.5 mg -5.8 (p=0.089); 5 mg -5.6 (p=0.274); 7.5 mg -6.2 (p=0.032); placebo -5.0 **NPI/NH (Agitation/Aggression)** 1 mg -1.7 (p<0.039); 2.5 mg -1.7 (p=0.046); 5 mg -1.6 (p=0.70); 7.5 mg -2.0 (p=0.2002); placebo -1.3 **NPI/NH (Anxiety)** 1 mg -1.4 (p<0.658); 2.5 mg -1.5 (p=0.167); 5 mg -1.8 (p=0.43); 7.5 mg -1.7 (p=0.019); placebo -1.0 **NPI/NH (Apathy/Indifference)** 1 mg -1.0 (p<0.492); 2.5 mg -0.8 (p=0.174); 5 mg -0.8 (p=0.043); 7.5 mg -0.9 (p=0.612); placebo -1.1 **NPI/NH (Delusions)** 1 mg -4.3 (p<0.140); 2.5 mg -4.0 (p=0.071); 5 mg -4.2 (p=0.169); 7.5 mg -4.4 (p=0.002); placebo -3.6 **NPI/NH (Euphoria/Elation)** 1 mg -0.2 (p<0.391); 2.5 mg -0.3 (p=0.174); 5 mg -0.3 (p=0.43); 7.5 mg -0.5 (p=0.612); placebo -0.1	NPI/NH (Hallucinations) 1 mg -1.7 (p<0.150); 2.5 mg -1.8 (p=0.173); 5 mg -1.4 (p=0.852); 7.5 mg -1.7 (p=0.258); placebo -1.4 NPI/NH (Irritability/Lability) 1 mg -1.3 (p<0.154); 2.5 mg -1.3 (p=0.058); 5 mg -1.5 (p=0.007); 7.5 mg -1.6 (p=0.045); placebo -1.1 BPRS (Total) 1 mg -6.3 (p<0.405); 2.5 mg -8.7 (p=0.399); 5 mg -6.4 (p=0507); 7.5 mg -9.5 (p=0.23); placebo -6.9 BPRS (Negative) 1 mg -0.8 (p<0.342); 2.5 mg -0.9 (p=0.417); 5 mg -0.5 (p=0.122); 7.5 mg -0.5 (p=0.171); placebo -0.9 BPRS (Positive) 1 mg -2.8 (p<0.717); 2.5 mg -3.3 (p=0.167); 5 mg -2.6 (p=0.900); 7.5 mg -3.7 (p=0.21); placebo -2.7 CGI 1 mg -3.1 (p<0.524); 2.5 mg -2.8 (p=0.030); 5 mg -2.9 (p=0.312); 7.5 mg -3.0 (p=0.2341); placebo -3.2

Evidence Table 16. Placebo-controlled trials in patients with behavioral and psychological symptoms of dementia

Author, year Country Trial Name (Quality Score)	Results	Results
de Deyn, 2004 Europe, Australia, Israel, Lebanon, and South Africa (FAIR)		

Evidence Table 16. Placebo-controlled trials in patients with behavioral and psychological symptoms of dementia

Author, year Country Trial Name (Quality Score)	N	Duration	Study Design Setting	Eligibility criteria	Interventions (drug, dose, duration)
Trial of Quetiapine					
Zhong, 2004 (poster) US (POOR)	333	10 weeks	Double-blind, multicenter	Diagnosis of dementia consistent with probable or possible Alzheimer's Disease (DSM-IV or NINCDS-ADRDA), vascular dementia (DSM-IV), or mixed dementia (DSM-IV) and clinical symptoms of agitation (Cohen-Mansfiled and Billig criteria) requiring treatment of antipsychotic medication in addition to behavioral intervention; Positive and Negative Syndrome Scale- Excitement Component (PANSS-EC) total score >14, one of the five items >4; residents in nursing homes or assisted living facilities >14 days.	quetiapine 200 mg, quetiapine 100 mg or placebo.

Evidence Table 16. Placebo-controlled trials in patients with behavioral and psychological symptoms of dementia

Author, year Country Trial Name (Quality Score)	Run-in/washout period	Allowed other medications/ interventions	Age Gender Ethnicity	Other population characteristics (diagnosis, etc)	Number screened/ eligible/enrolled	Number withdrawn/ lost to fu/analyzed
Trial of Quetiapine						
Zhong, 2004 (poster) US (POOR)	Not reported	Permitted antidepressants, hypnotics, benzodiazepines, cholinesterase inhibitors on a stable dose; hypnotics for insomnia; and lorazepam <4 mg per day or equivalent for agitation up to day 14 as needed.	Mean age 83 (SD 7.5) 74% female 85% white	81% Alzheimer's dementia 9% vascular dementia 10% mixed dementia	Number screened, eligible not reported/ 333 enrolled	114 withdrawn/lost to followup not reported/# analyzed not clear

Evidence Table 16. Placebo-controlled trials in patients with behavioral and psychological symptoms of dementia

Author, year Country Trial Name (Quality Score)	Outcome scales	Method of Outcome Assessment and Timing of Assessment
Trial of Quetiapine		
Zhong, 2004 (poster) US (POOR)	PANSS-EC (Excitement Component) CGI-C	Not reported

Evidence Table 16. Placebo-controlled trials in patients with behavioral and psychological symptoms of dementia

Author, year Country Trial Name (Quality Score)	Results	Results
Trial of Quetiapine		
Zhong, 2004 (poster) US (POOR)	Data presented graphically only. Quetiapine 200 mg significantly greater reduction in PANSS-EC compared to placebo in OC analysis ($p<0.05$). Improvement in PANSS-EC score in LOCF analysis $p=0.065$ Quetiapine 100 mg results not reported. Subgroup of patients with Alzheimer's dementia (N=260) Quetiapine 200 mg significantly greater reduction in PANSS-EC compared to placebo ($p<0.01$) in both OC and LOCF analyses. Quetiapine 100 mg results not reported. Quetiapine 200 mg significant improvement on CGI-C scores compared with placebo in both the OC and LOCF analyses ($p<0.05$). Quetiapine 100 mg results not reported.	

Evidence Table 16. Placebo-controlled trials in patients with behavioral and psychological symptoms of dementia

Author, year Country Trial Name (Quality Score)	Results	Results
Trial of Quetiapine		
Zhong, 2004 (poster) US (POOR)		

Evidence Table 16. Placebo-controlled trials in patients with behavioral and psychological symptoms of dementia

Author, year Country Trial Name (Quality Score)	N	Duration	Study Design Setting	Eligibility criteria	Interventions (drug, dose, duration)
Trials of Risperidone					
Brodaty, 2003 Frank, 2004 Australia and New Zealand (FAIR)	309	12 weeks	Double-blind, multicenter	Diagnosis of dementia with aggressive behaviors; dementia was of the Alzheimer's type, vascular dementia, or a combination of the two, according to DSM-IV. Age 55 or older, score of 4 or greater on FAST, and 23 or less on MMSE; at least a minimum aggression score on CMAI; residing in a nursing home for at least 1 month prior to enrollment.	risperidone oral solution 1 mg/mL, or placebo solution. Started with 0.5 mL. In case of insufficient response, dosage adjusted by increments of .5 mL no faster than every other day. Dosing was flexible throughout treatment period according to patient response and investigator judgment. Maximum dose 2 mL daily, corresponding to 2 mg risperidone.

Evidence Table 16. Placebo-controlled trials in patients with behavioral and psychological symptoms of dementia

Author, year Country Trial Name (Quality Score)	Run-in/washout period	Allowed other medications/ interventions	Age Gender Ethnicity	Other population characteristics (diagnosis, etc)	Number screened/ eligible/enrolled	Number withdrawn/ lost to fu/analyzed
Trials of Risperidone						
Brodaty, 2003 Frank, 2004 Australia and New Zealand (FAIR)	Maximum 7-day single-blind placebo washout period during which existing psychotroppic medication was discontinued.	Short-acting benzodiazepines allowed for treatment of insomnia, provided the dosage had been stable for at least 3 months.	Mean age 83 (se 0.58) 72% female Ethnicity not reported	58% Alzheimer's dementia 28% vascular dementia 13% mixed dementia	Number screened not reported/384 eligible/345 enrolled	101 withdrawn/lost to followup not reported/304 analyzed

Evidence Table 16. Placebo-controlled trials in patients with behavioral and psychological symptoms of dementia

Author, year Country Trial Name (Quality Score)	Outcome scales	Method of Outcome Assessment and Timing of Assessment
Trials of Risperidone		
Brodaty, 2003 Frank, 2004 Australia and New Zealand (FAIR)	CMAI total agression subscale BEHAVE-AD CGI-S CGI-C MMSE FAST Secondary analysis: Modified Strain in Nursing Care Assessment Scale (M-NCAS)	CMAI and BEHAVE-AD at selection, baseline, and weeks 4 and 8, and endpoint (either week 12 or patients' last visit); nurses responsible for daily care of patients were interviewed by an experienced and trained research nurse who subsequently rated the scales. CGI-S and CGI-C evaluated at selection, baseline, weeks 1, 2, 3, 4, and 8 and endpoint by speicifcally trained raters and patients' primary caregivers. FAST and MMSE assessed at selection and week 12 (or last visit) M-NCAS completed by the nurse carer of individual residents at baseline, 4 weeks, 8 weeks, and 12 weeks.

Evidence Table 16. Placebo-controlled trials in patients with behavioral and psychological symptoms of dementia

Author, year Country Trial Name (Quality Score)	Results	Results
Trials of Risperidone		
Brodaty, 2003 Frank, 2004 Australia and New Zealand (FAIR)	Mean change from baseline, risperidone vs placebo CMAI (Total aggression) -7.5 vs -3.1 (p<0.001) CMAI (Physical aggression) -5.4 vs -2.8 (p=0.008) CMAI (Verbal aggression) -2.1 vs -0.2 (p<0.001) CMAI (Total non-aggression) -7.3 vs -2.8 (p=0.002) CMAI (Physical non-aggression) -4.3 vs -2.5 (p=0.71) CMAI (Verbal non-aggression) -3.0 vs -0.3 (p<0.001)	BEHAVE-AD (Total) -6.8 vs -2.3 (p<0.001) BEHAVE-AD (Psychotic symptom subtotal) -2.0 vs -0.7 (p=0.004) BEHAVE-AD (Paranoid and delusional ideation) -1.4 vs -0.7 (p=0.015) BEHAVE-AD (Hallucinations) -0.6 vs -0.0 (p=0.010) BEHAVE-AD (Activity disturbancees) -0.8 vs -0.4 (p=0.067) BEHAVE-AD (Aggressiveness) -2.0 vs -0.5 (p<0.001) BEHAVE-AD (Diurnal rhythm disturbances) -0.3 vs -0.2 (p=0.098)

Evidence Table 16. Placebo-controlled trials in patients with behavioral and psychological symptoms of dementia

Author, year Country Trial Name (Quality Score)	Results		Results
Trials of Risperidone			
Brodaty, 2003 Frank, 2004 Australia and New Zealand (FAIR)	BEHAVE-AD (Affective disturbance) -0.5 vs -0.2 (p=0.034) BEHAVE-AD (Anxiety and phobias) -1.1 vs -0.4 (p=0.004) BEHAVE-AD (Affective disturbance) 0.5 vs -0.2 (p=0.034) BEHAVE-AD (Anxiety and phobias) 1.1 vs -0.4 (p=0.004)		M-NCAS mean change from baseline to endpoint (analysis on subgroup of 279 patients): Risperidone vs placebo - Attention seeking: 0.24 vs 0.09 (p<0.05) Autonomy: 0.09 vs 0.07 (NS) - Difficulty: 0.34 vs 0.17 (p<0.05) Total Attitude Domain: 0.24 vs 0.12 (p<0.05) Affect: 0.26 vs 0.10 (NS) Job satisfaction: 0.26 vs 0.09 (p<0.05) Neediness: 0.25 vs 0.07 (p<0.05) Predictability: 0.30 vs 0.22 (NS) Self direction: 0.19 vs 0.11 (NS) Total Strain Domain: 0.25 vs 0.12 (p<0.05)

Evidence Table 16. Placebo-controlled trials in patients with behavioral and psychological symptoms of dementia

Author, year Country Trial Name (Quality Score)	N	Duration	Study Design Setting	Eligibility criteria	Interventions (drug, dose, duration)
Katz, 1999 US (FAIR) Katz, 2004 (subanalysis) Grossman, 2004 (subanalysis)	625	12 weeks	Double-blind, multicenter	Age 55 or older, residing in a nursing home or chronic disease hospital, DSM-IV diagnosis of Alzheimer's disease, vascular dementia, or a combination of the two, with scores of 4 or greater on the Functional Assessment Staging rating scale and 23 or lower on the MMSE. Total score of 8 or more and a global rating of 1 or more on BEHAVE-AD rating scale.	risperidone 0.5 mg, 1 mg, or 2 mg per day. Doses for patients receiving 1 mg and 1 mg were adjusted during the first week in increments of 0.5 mg every 2 days.

Evidence Table 16. Placebo-controlled trials in patients with behavioral and psychological symptoms of dementia

Author, year Country Trial Name (Quality Score)	Run-in/washout period	Allowed other medications/ interventions	Age Gender Ethnicity	Other population characteristics (diagnosis, etc)	Number screened/ eligible/enrolled	Number withdrawn/ lost to fu/analyzed
Katz, 1999 US (FAIR) Katz, 2004 (subanalysis) Grossman, 2004 (subanalysis)	Single-blind placebo washout of 3 to 7 days.	Use of antipsychotics, antidepressants, or mood stabilizers not allowed. Benztropine allowed to treat EPS. Lorazepam (up to 3 mg/day for up to 4 days in any 7-day period) could be given until the end of week 4. Use of chloral hydrate for insomnia was allowed at the lowest effective dose.	Mean age 82.7 (sd 7.7) 68% female 89% white, 11% multiracial	73% Alzheimer's dementia 16% vascular dementia 12% mixed	729 screened/625 eligible/625 enrolled	190/NR/617 analyzed

Evidence Table 16. Placebo-controlled trials in patients with behavioral and psychological symptoms of dementia

Author, year Country Trial Name (Quality Score)	Outcome scales	Method of Outcome Assessment and Timing of Assessment
Katz, 1999 US (FAIR) Katz, 2004 (subanalysis) Grossman, 2004 (subanalysis)	BEHAVE-AD, CMAI, CGI	Assessments at selection, baseline, and weeks 1-4, 6, 8, 10, and 12 (or when patient was terminated from treatment). Elicited from patients' primary caregivers by specifically trained raters.

Evidence Table 16. Placebo-controlled trials in patients with behavioral and psychological symptoms of dementia

Author, year Country Trial Name (Quality Score)	Results	Results
Katz, 1999 US (FAIR) Katz, 2004 (subanalysis) Grossman, 2004 (subanalysis)	Mean change from baseline to endpoint, risperidone vs placebo (p vs placebo): BEHAVE-AD (Total) 0.5 mg -4.8 (p.37); 1 mg -6.5 (p=0.002); 2 mg -6.4(p=0.001); placebo -4.2 BEHAVE-AD (Psychosis subscale) 0.5 mg -1.6 (p=0.68); 1 mg -2.5 (p=0.005); 2 mg -2.2 (p=0.01); placebo -1.5 BEHAVE-AD (Aggressiveness subscale) 0.5 mg -1.3 (p=0.11); 1 mg -1.7 (p=0.002); 2 mg -2.4 (p<0.001); placebo -0.9	

Evidence Table 16. Placebo-controlled trials in patients with behavioral and psychological symptoms of dementia

Author, year Country Trial Name (Quality Score)	Results	Results
Katz, 1999 US (FAIR) Katz, 2004 (subanalysis) Grossman, 2004 (subanalysis)		

Evidence Table 17. Adverse events in trials of patients with behavioral and psychological symptoms of dementia

Study, year	Interventions (Mean daily dose, range)	N	Duration	Method of adverse effects assessment?	Overall withdrawals	Withdrawals due to adverse events
Head-to-head trials						
Deberdt, 2005	risperidone 1.0 mg olanzapine 5.2 mg	494	10 weeks	Safety assessed from spontaneous reports of treatment-emergent adverse events, usign the Coding Symbols for a Thesaurus of Adverse Reaction Tems (CoSTART) dictionary, and from vital signs, ECG, analysis of laboratory tests and MMSE changes. Motor symptoms were meausured with the Simpson-Angus Scale, the Barnes Akathisia Scale, and the AIMS	31.1% risperidone, 37.7% olanzapine, 20.2% placebo	No reported by group. Overall, most common AEs leading to withdrawal were agitation (n=6), psychotic symptoms, (N=6), somnolence (N=5), and accidental injury (N=5)
Ellingrod, 2002	risperidone (range 0.25-3 mg) vs olanzapine (range 2.5 -15 mg) mean daily dose not reported	19	2 months	AIMS, Simpson-Angus Extrapyramidal Symptoms Scale, Barnes Akathasia Scale	NR	NR

Evidence Table 17. Adverse events in trials of patients with behavioral and psychological symptoms of dementia

Study, year	Extrapyramidal symptoms	Cerebrovascular events	Other adverse effects reported
Head-to-head trials			
Deberdt, 2005	On Simpson-Angus Scale, both groups increased more than placebo; greater increase in risperidone patients (+0.9 olanzapine vs +1.6 risperidone, p=0.02). No changes on AIMS or Barnes.	2.5% olanzapine, 2.0% risperidone (NS)	Olanzapine vs risperidone vs placebo Mortality: 2.9% vs 2.0% vs 1.1% (NS) Falls: 11.3% vs 9.2% vs 6.4% (NS) Pneumonia: 2.0% vs 0% vs 2.1% (NS) Both active treatments associated with significantly higher incidences of somnolence, urinary incontinence, and hostility relative to placebo.
Ellingrod, 2002	Change from baseline on AIMS at endpoint, risperidone vs olanzapine: -0.18 vs 0.375 (p=0.32) Change from baseline on Simpson-Angus at endpoint, risperidone vs olanzapine: 3.0 vs 3.25 (p=0.93)	None reported	None

Evidence Table 17. Adverse events in trials of patients with behavioral and psychological symptoms of dementia

Study, year	Interventions (Mean daily dose, range)	N	Duration	Method of adverse effects assessment?	Overall withdrawals	Withdrawals due to adverse events
Fontaine, 2003	risperidone (1.5 mg, range 0.5-2 mg) vs olanzapine (6.7 mg, range 2.5-10 mg)	39	2 weeks	AIMS, Simpson-Angus Extrapyramidal Symptoms Scale, Barnes Akathasia Scale	20% olanzapine, 11% risperidone.	4 olanzapine (1 rash + elevated blood pressure, pulse, white blood cell count and temperature; 2 unsteady gait or falls; 1 diaphoresis, fainting, and asystole) vs 0 risperidone.
Gareri, 2004	olanzapine 5 mg risperidone 1 mg promazine 50 mg	20	8 weeks	Hoehn and Yahr Scale used for evaluating parkinsonism, administered at baseline, 4 weeks, and 8 weeks.	NR	NR

Evidence Table 17. Adverse events in trials of patients with behavioral and psychological symptoms of dementia

Study, year	Extrapyramidal symptoms	Cerebrovascular events	Other adverse effects reported
Fontaine, 2003	Change from baseline on AIMS (% rating of minimal or mild), risperidone vs olanzapine: no change on either (p=0.52) Change from baseline on Simpson-Angus, risperidone vs olanzapine: 0.12 vs 0.17 (p=0.44) Change from baseline on Barnes Akathasia Scale: (% with a rating of questionable or mild) risperidone 0.5, 1.0, or 2.0 mg: no change (6% to 6%) olanzapine 2.5, 5.0, or 10.0 mg: +5% (6% to 11%) (not analyzed, too few frequencies)	olanzapine: 1 stroke	No significant change in weight in either group. 113 adverse events, 31 patients had at least one adverse event. Olanzapine: 1 patient had 2 serious adverse events (asystole followed by brain stem stroke 6 days later) 12 falls: 2 result of being pushed. Of 10 spontaneous falls, 6 olanzapine, 4 risperidone (p=0.62)
Gareri, 2004	NR	NR	Main side effects: olanzapine: somnolence and weight gain (32%), dizziness and constipation (16%), postural hypotension (8%), akathisia (4%), and worsening of glycemic levels in one diabetic patient (4%) risperidone: hypotension and somnolence (20%), dyspepsia (12%), sinus tachycardia, asthenia, constipation, EPS (8%) increase of libido and disinhibition, abdominal pain and insomnia (4%).

Evidence Table 17. Adverse events in trials of patients with behavioral and psychological symptoms of dementia

Study, year	Interventions (Mean daily dose, range)	N	Duration	Method of adverse effects assessment?	Overall withdrawals	Withdrawals due to adverse events
Mulsant, 2004	risperidone: 0.76 mg olanzapine: 5.22 mg	86	6 weeks	Udvalg for Kliniske Undersogelser (UKU) rating scalse measuring peripheral anticholinergic effects (including visual accomodation disturbances, dry mouth, constipation, micturition disturbances, and palpitations) or a site report of a somnolence adverse event. ESRS	19.8%	4 risperidone vs 2 olanzapine (p=0.428)

Evidence Table 17. Adverse events in trials of patients with behavioral and psychological symptoms of dementia

Study, year	Extrapyramidal symptoms	Cerebrovascular events	Other adverse effects reported
Mulsant, 2004	For total ESRS scores, no statistically significant changes with either risperidone or olanzapine and NSD between the 2 treatments. Results for individual subscales were equivalent to the overall analyses (data not reported).	None reported	No between-group differences in UKU scale or in somnolence adverse events.

Evidence Table 17. Adverse events in trials of patients with behavioral and psychological symptoms of dementia

Study, year	Interventions (Mean daily dose, range)	N	Duration	Method of adverse effects assessment?	Overall withdrawals	Withdrawals due to adverse events
Active-control trials						
Chan, 2001	risperidone (0.85 mg) vs haloperidol (0.90 mg)	58	12 weeks	AIMS, Simpson-Angus Extrapyramidal Symptoms Scale, Barnes Akathasia Scale	3% risperidone, 7% haloperidol	0 risperidone; 3% haloperidol (somnolence)
De Deyn, 1999	risperidone (1.1 mg) vs haloperidol (1.2 mg)	344	13 weeks	Extrapyramidal Symptom Rating Scale	41% risperidone, 30% haloperidol, 35% placebo	18% total, no significant differences between groups.
Meehan, 2002	rapidly-acting intramuscular olanzapine (2.5 mg or 5.0 mg) or lorazepam 1.0 mg	272	24 hours	Simpson-Angus Scale. Adverse events were detected by clinical evaluatin and spontaneous report. ECGs recorded at screening and endpoint (2 and 24 hours post first injection and/or upon discontinuatino after randomization)	olanzapine 2.5 mg: 5.6% olanzapine 5.0mg: 7.6% lorazepam 1.0 mg: 10.3% placebo: 11.1% (NS)	None

Evidence Table 17. Adverse events in trials of patients with behavioral and psychological symptoms of dementia

Study, year	Extrapyramidal symptoms	Cerebrovascular events	Other adverse effects reported
Active-control trials			
Chan, 2001	risperidone: no significant increase from baseline on Simpson-Angus, Barnes, or AIMS. haloperidol: significant increase in Simpson-Angus Scale ($p<0.001$)	None reported	risperidone: 1 nausea, 1 acute retention of urine (unrelated to study medication); haloperidol: 2 constipation, 3 drug-related daytime sleepiness.
De Deyn, 1999	Mean change in Extrapyramidal Symptoms Rating Scale score: risperidone 0.5 to 2 mg: -0.3 haloperidol 0.5 to 2 mg: +1.6 placebo: -1.4 ($p <0.05$ for risperidone vs haloperidol, NS for risperidone vs placebo)	None reported	76.5% risperidone, 80% haloperidol, and 72.8% of placebo patients reported and adverse events. Those occurring in 10% or more of patients were fall, injury, agitation, somnolence, and purpura (bruises caused by injuries or falls). Only somnolence more common in patients receiving active treatment than placebo (12.2% risperidone, 18.3% haloperidol, 4.4% placebo). No significant differences between groups in serious or severe adverse events.
Meehan, 2002	No significant change from baseline to endpoint.	None reported	Treatment-emergent AES not significantly different from placebo in any active-treatment group.

Evidence Table 17. Adverse events in trials of patients with behavioral and psychological symptoms of dementia

Study, year	Interventions (Mean daily dose, range)	N	Duration	Method of adverse effects assessment?	Overall withdrawals	Withdrawals due to adverse events
Suh, 2004	risperidone (range 0.5 mg-1.5 mg, mean daily dose 0.80 mg) vs haloperidol (range 0.5 mg-1.5 mg, mean daily dose 0.83 mg)	120	18 weeks (1 week washout, 8 weeks active treatment, 1 week washout, 8 weeks crossover treatment)	All reported adverse events were recorded, and the severity of EPS was assessed by use of the ESRS.	7% risperidone 3% haloperidol	7% risperidone 3% haloperidol
Tariot, 2004 (poster)	Not reported	284	10 weeks	AIMS, Simpson-Angus Extrapyramidal Symptoms Scale	32% quetiapine 41% haloperidol 35% placebo	11% quetiapine 18% haloperidol 13% placebo

Evidence Table 17. Adverse events in trials of patients with behavioral and psychological symptoms of dementia

Study, year	Extrapyramidal symptoms	Cerebrovascular events	Other adverse effects reported
Suh, 2004	Mean change from baseline on ESRS, risperidone vs haloperidol: Total: +4.8 vs +13.8 (p=0.0001) Parkinsonism: +3.5 vs +10.4 (p=0.0001) Dystonia: +1.0 vs +2.5 (p=0.6503) Dyskinetic movement: +0.5 vs +0.9 (p=0.4144)	None reported	Reasons for discontinuation: seizure (N=1) and nausea (N=2) in risperidone group, somnolence (N=3) in haloperidol group. Seizure was not considered drug-related.
Tariot, 2004 (poster)	"Quetiapine patients experienced statistically significantly fewer EPS adverse events than haloperidol and placebo patients did." (data not reported) "Patients taking quetiapine had significantly lower SAS scores compared with patients taking haloperidol (p<0.01). AIMS scores for patients taking quetiapine were similar to those for patients taking placebo." (Data not reported; AIMS scores for haloperidol not reported)	None reported	AEs with >10% incidence of which were statistically significantly different from placebo: somnolence, infection, rash, pain, conjunctivitis, vomiting, headache, cough increased, postural hypotension, dizziness, weight gain, weight loss, accidental injury. Of treatment-emergent adverse events, somnolence occurred statistically more often for quetiapine and haloperidol than for placebo.

Evidence Table 17. Adverse events in trials of patients with behavioral and psychological symptoms of dementia

Study, year	Interventions (Mean daily dose, range)	N	Duration	Method of adverse effects assessment?	Overall withdrawals	Withdrawals due to adverse events
Placebo-controlled trials						
Brodaty, 2003	risperidone (0.95 mg) vs placebo (1.06 mL)	345	12 weeks	Monitoring the presence and severity of EPS at each visit and ratings on the Extrapyramidal Symptom Rating Scale.	27% risperidone 33% placebo	13.2% risperidone 8.2% placebo

Evidence Table 17. Adverse events in trials of patients with behavioral and psychological symptoms of dementia

Study, year	Extrapyramidal symptoms	Cerebrovascular events	Other adverse effects reported
Placebo-controlled trials			
Brodaty, 2003	Mean change in Extrapyramidal Symptoms Rating Scale score: 0.5 to 2 mg: +0.7 placebo: +0.5 (p=0.407)	9% risperidone (5 stroke, 1 TIA) vs 1.8% placebo. 2 deaths from stroke in risperidone group.	Deaths: 3.6% risperidone (3 pneumonia, 2 stroke), 2.4% placebo (1 pneumonia). Serious adverse events: 16.8% risperidone vs 8.8% placebo. Most frequent were injury, cerebrovascular disorder, pneumonia, and accidental overdose. 94% risperidone, 92.4% placebo reported any adverse event. Somnolence and urinary tract infections more common in risperidone group (Somnolence 36.3% vs 25.3%, UTI 23.4% vs 14.7%), other events reported by at least 5% of patients in either group: injury, fall, agitation, purpura, conjunctivitis, constipation, skin disorder, vomiting, edema peripheral, rash, upper RTI, skin ulceration, extrapyramidal disorder, tremor, gait abnormal, fever, aggressive reaction, coughing, headache, infection, diarrhea, dyskinesia

Evidence Table 17. Adverse events in trials of patients with behavioral and psychological symptoms of dementia

Study, year	Interventions (Mean daily dose, range)	N	Duration	Method of adverse effects assessment?	Overall withdrawals	Withdrawals due to adverse events
de Deyn, 2004	olanzapine (1 mg, 2.5 mg, 5 mg, or 7.5 mg, fixed dose) vs placebo	652	10 weeks	Simpson-Angus Scale, AIMS, mobility (gait and balance) measured with Modified Performance-Oriented Mobility Assessment-II (POMA); spontaneously reported treatment-emergent adverse events.	34% olanzapine 1 mg 25% olanzapine 2.5 mg 25% olanzapine 5 mg 29% olanzapine 7.5 mg 29% placebo	9.3% olanzapine 1 mg 6.7% olanzapine 2.5 mg 7.2% olanzapine 5 mg 9.8% olanzapine 7.5 mg 3.9% placebo

Evidence Table 17. Adverse events in trials of patients with behavioral and psychological symptoms of dementia

Study, year	Extrapyramidal symptoms	Cerebrovascular events	Other adverse effects reported
de Deyn, 2004	Slight, non-significant improvement from baseline in each treatment group and placebo on AIMS and Simpson-Angus scales. Treatment-emergent abnormalities based on categorical analysis of the Simpson-Angus scale showed no overall differences among treatment groups (p=0.153), ranged from 15.6% in the placebo group to 4.7% in the olanzapine 1 mg group. No other assessments of treatment-emergent abnormal motor function were statistically significant, either on the Simpson-Angus scale, or AIMS.	None reported	48.5% of all patients experienced at least one adverse event. No significant differences between groups. Four events significantly different among treatment groups: increased weight, anorexia, urinary incontinence, and abnormal behavior (higher in olanzapine group). Olanzapine 5 mg and 7.5 mg groups had greater mean increases in weight than placebo (1 kg vs 0.8 kg vs 0.1 kg, p=0.016) Deaths occurring during treatment or within 30 days after ending study participation: olanzapine 1 mg: 4 olanzapine 2.5 mg: 3 olanzapine 5 mg: 5 olanzapine 7.5 mg: 3 placebo: 2 Most frequent cause pneumonia, no deaths considered related to study medication.

Evidence Table 17. Adverse events in trials of patients with behavioral and psychological symptoms of dementia

Study, year	Interventions (Mean daily dose, range)	N	Duration	Method of adverse effects assessment?	Overall withdrawals	Withdrawals due to adverse events
Katz, 1999	risperidone (0.5 mg, 1 mg, or 2 mg, fixed dose) vs placebo	625	12 weeks	Information regarding adverse events was obtained at each visit, Extrapyramidal Symptom Rating Scale.	21% risperidone 0.5 mg 30% risperidone 1 mg 42% risperidone 2 mg 27% placebo	8% risperidone 0.5 mg 16% risperidone 1 mg 24% risperidone 2 mg 12% placebo

Evidence Table 17. Adverse events in trials of patients with behavioral and psychological symptoms of dementia

Study, year	Extrapyramidal symptoms	Cerebrovascular events	Other adverse effects reported
Katz, 1999	Change from baseline to endpoint, Extrapyramidal Symptom Rating Scale scores (total and hypokinesia scales): risperidone 0.5 mg: -0.48 and 0.01 (NS vs placebo) risperidone 1 mg: 0.84 and 0.95 (NS vs placebo) risperidone 2 mg: 2.37 and 2.01 (p<0.001 vs placebo for both scales) placebo: -0.22 and 0.17 Tardive dyskinesia emerged in 1 placebo patient, 0 risperidone	None reported	Deaths: 4% risperidone 0.5 mg; 9% risperidone 1 mg; 4% risperidone 2 mg; 3% placebo Serious adverse events: 11% risperidone 0.5 mg; 16% risperidone 1 mg; 18% risperidone 2 mg; 13% placebo Any adverse event: 84% risperidone 0.5 mg; 82% risperidone 1 mg; 89% risperidone 2 mg; 85% placebo Dose-related increases somnolence: 10% risperidone 0.5 mg; 17% risperidone 1 mg; 28% risperidone 2 mg; 8% placebo peripheral edema: 16% risperidone 0.5 mg; 13% risperidone 1 mg; 18% risperidone 2 mg; 6% placebo

Evidence Table 17. Adverse events in trials of patients with behavioral and psychological symptoms of dementia

Study, year	Interventions (Mean daily dose, range)	N	Duration	Method of adverse effects assessment?	Overall withdrawals	Withdrawals due to adverse events
Mintzer, 2006	1.03 mg (range 0.4 to 1.9 mg)	416	8 weeks	Safety and tolerability measured by vital signs and occurrence of AEs, recorded weekly and clinical laboratory tests, ECGs and body weight at baseline and weeks 4 and 8. EPSs measured using Simpson Angus Rating Scale and AIMS at baseline and weeks 4 and 8.	25% risperidone, 25% placebo	11% risperidone, 10% placebo

Evidence Table 17. Adverse events in trials of patients with behavioral and psychological symptoms of dementia

Study, year	Extrapyramidal symptoms	Cerebrovascular events	Other adverse effects reported
Mintzer, 2006	8.5% risperidone vs 3.4% placebo	1.7% risperidone vs 0.4% placebo	Overall: 74% risperidone, 64% placebo Only somnolence was more common with risperidone vs placebo (16.2% vs 4.6%

Evidence Table 17. Adverse events in trials of patients with behavioral and psychological symptoms of dementia

Study, year	Interventions (Mean daily dose, range)	N	Duration	Method of adverse effects assessment?	Overall withdrawals	Withdrawals due to adverse events
Street, 2000	olanzapine (5 mg, 10 mg, or 15 mg, fixed dose) vs placebo	206	6 weeks	Simpson-Angus Scale, Barnes Akathisia Scale, AIMS	20% olanzapine 5 mg 28% olanzapine 10 mg 34% olanzapine 15 mg 23% placebo	11% olanzapine 5 mg 8% olanzapine 10 mg 17% olanzapine 15 mg 4% placebo
Zhong, 2004 (poster)	Flexible dosing, targets quetiapine 200 mg (n=114), quetiapine 100 mg (n=120), or placebo (n=92); mean daily dose not reported	333	10 weeks	Tolerability measures were incidence of adverse events, extrapyramidal symptoms related adverse events, clinically significant changes in laboratory tests and EKG; Simpson-Angus Scale, AIMS, and MMSE.	quetiapine 200 mg: 37% quetiapine 100 mg: 35% placebo: 35%	quetiapine 200 mg: 12% quetiapine 100 mg: 7.3% placebo: 35%: 7.6%

Evidence Table 17. Adverse events in trials of patients with behavioral and psychological symptoms of dementia

Study, year	Extrapyramidal symptoms	Cerebrovascular events	Other adverse effects reported
Street, 2000	No statistically significant mean changes on Simpson-Angus Scale, Barnes Akathisia Scale, AIMS. Incidence of spontaneously reported EPS (tremor, hypertonia, cogwheel rigidity, hyperkinesia, akathisia, dyskinesia, dystonia, parkinsonism, tardive dyskinesia) was not significantly different from placebo.	None reported	olanzapine 5 mg vs 10 mg vs 15 mg vs placebo accidental injury: 25% vs 24% vs 37.7% vs 27.7% somnolence: **25%** vs **26%** vs **35.8%** vs 6.4% pain: 14.3% vs 12% vs 24.5% vs 10.6% abnormal gait: **19.6%** vs 14% vs **17%** vs 2.1% anorexia: 1.8% vs 4% vs 15.1% vs 8.5% ecchymosis: 8.9% vs 12% vs 15.1% vs 14.9% fever: 8.9% vs 14% vs 13.2% vs 2.1% agitation: 8.9% vs 12% vs 11.3% vs 8.5% weight loss: 0 vs 4% vs 11.3% vs 6.4% cough increased: 12.5% vs 10% vs 7.5% vs 6.4% peripheral edema: 3.6% vs 12% vs 7.5% vs 6.4% nervousness: 7.1% vs 12% vs 1.9% vs 4.3% No differences between active treatment groups on any event (**Bold** indicates significantly different from placebo)
Zhong, 2004 (poster)	No significant difference in mean changes on SAS and AIMS among treatment groups (data not reported) Incidence of EPS-related adverse events: quetiapine 200 mg: 5% quetiapine 100 mg: 5% placebo: 4% Mean change in MMSE at end of treatment was 0 for all treatment groups.	1 transient ischemic attack in placebo group.	Adverse events occurring in >10% of patients, quetiapine 100 mg vs quetiapine 200 mg vs placebo: somnolence/sedation: 11.3% vs 17.1% vs 5.5% skin laceration: 15.3% vs 11.1% vs 14.1% urinary tract infection: 16.1% vs 7.7% vs 7.6% lethargy: 6.6% vs 11.1% vs 3.3% contusion (bruises): 9.7% vs 5.1% vs 6.5%

Evidence Table 18. Active-controlled trials in patients with autism

Author, year Country Trial Name (Quality Score)	N	Duration	Study design Setting	Eligibility criteria	Interventions (drug, dose, duration)	Run-in/Washout period
Olanzapine vs Haloperidol						
Malone, 2001 US (FAIR)	12	6 weeks	Randomized, open label, pilot study.	Children between ages 5 and 17 with a primary diagnosis of pervasive developmental disorder (DSM-IV criteria); at least moderate impairment on 2 or more of the first 28 items on the Children's Psychiatric Rating Scale at baseline.	Olanzapine starting dose 2.5 mg every other day for patients who weighed 40 kg or less and 2.5 mg per day for those who weighed more than 40 kg. Dosages could be increased in 2.5 mg increments up to 5 mg per week as needed. Maximum dose 20 mg/day. Haloperidol starting dose 0.25 mg/day for patients weighing 40 kg or less and 0.5 mg for those who weighed more than 40 kg. Dosages could be increased as clinically indicated in 0.5 mg increments up to 1 mg per week as needed. Maximum dose 5 mg/day.	1 week drug-free baseline washout period.

Evidence Table 18. Active-controlled trials in patients with autism

Author, year Country Trial Name (Quality Score)	Allowed other medications/ interventions	Age Gender Ethnicity	Other population characteristics (diagnosis, etc)	Number screened/ eligible/enrolled	Number withdrawn/ lost to fu/analyzed
Olanzapine vs Haloperidol					
Malone, 2001 US (FAIR)	No.	Mean age 7.8 (SD 2.1) years; range 4.8-11.8 years. 67% male 58% white, 25% African American, 17% Hispanic	11/12 (92%) autistic disorder, 1/12 (8%) pervasive developmental disorder, not otherwise specified. 8% normal cognitive functioning, 8% mild mental retardation, 42% moderate mental retardation, 42% severe mental retardation.	# screened not reported/ 13 eligible/ 12 enrolled (1 withdrew consent)	No withdrawals, losses to followup, 12 analyzed.

Evidence Table 18. Active-controlled trials in patients with autism

Author, year Country Trial Name (Quality Score)	Outcome measures	Method of outcome assessment and timing of assessment	Results
Olanzapine vs Haloperidol			
Malone, 2001 US (FAIR)	Primary outcome: CGI Secondary outcomes: Children's Psychiatric Rating Scale (CPRS)	Principal investigator and one other trained rater performed all ratings; assessments at baseline and end of study.	CGI Improvement from baseline olanzapine: 1/6 (16.7%) very much improved 4/6 (66.7%) much improved 1/6 (16.7% minimally improved haloperidol: 1/6 (16.7%) very much improved 2/6 (33.3%) much improved 3/6 (50% minimally improved (p=0.494) Mean change from baseline (olanzapine vs haloperidol) CGI (Severity): -1.08 vs -0.42 CPRS (Autism): -0.84 vs -0.53 CPRS (Anger/Uncooperative): -1.27 vs 0.15 CPRS (Hyperactivity): -1.1 vs 0.36 CPRS (Speech Deviance): 0.4 vs -0.25

Evidence Table 19. Placebo-controlled trials in patients with autism

Author, year Country Trial name (Quality score)	N	Duration	Study design setting	Eligibility criteria
Trials of risperidone				
McCracken, 2002 Arnold, 2003 US Research Units on Pediatric Psychopharmacology Autism Network (RUPP) (FAIR)	101	8 weeks	Double-blind, multicenter.	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; free of serious medical disorders and other psychiatric disorders requiring medication.

Evidence Table 19. Placebo-controlled trials in patients with autism

Author, year Country Trial name (Quality score)	Interventions (drug, dose, duration)	Run-in/washout period	Allowed other medications/interventions
Trials of risperidone			
McCracken, 2002 Arnold, 2003 US Research Units on Pediatric Psychopharmacology Autism Network (RUPP) (FAIR)	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.	Ineffective medications gradually withdrawn, drug-free interval of 7 to 28 days, depending on the drug, was required before enrollment.	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 19. Placebo-controlled trials in patients with autism

Author, year Country Trial name (Quality score)	Age Gender Ethnicity	Other population characteristics (diagnosis, etc)	Number screened/ eligible/enrolled
Trials of risperidone			
McCracken, 2002 Arnold, 2003 US Research Units on Pediatric Psychopharmacology Autism Network (RUPP) (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

Evidence Table 19. Placebo-controlled trials in patients with autism

Author, year Country Trial name (Quality score)	Number withdrawn/ lost to fu/analyzed	Outcome scales	Method of outcome assessment and timing of assessment
Trials of risperidone			
McCracken, 2002 Arnold, 2003 US Research Units on Pediatric Psychopharmacology Autism Network (RUPP) (FAIR)	18 withdrawn/3 lost to followup/101 analyzed/	Primary outcomes: Aberrant Behavior Checklist (Irritability subscale), CGI-Improvement (CGI-I Children who had at least a 25% reduction in the Irritability score and a rating of much improved or very much improved on the CGI-I scale were considered to have a positive response. Other outcomes: other subscales of the Aberrant Behavior Checklist (Social Withdrawal, Stereotypy, Hyperactivity, and Inappropriate Speech)	Irritability scale based on ratings by parent or primary caregiver, CGI-I determined by clinical evaluator, at baseline and 8 weeks.

Evidence Table 19. Placebo-controlled trials in patients with autism

Author, year Country Trial name (Quality score)	Results
Trials of risperidone	
McCracken, 2002 Arnold, 2003 US Research Units on Pediatric Psychopharmacology Autism Network (RUPP) (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)

Evidence Table 19. Placebo-controlled trials in patients with autism

Author, year Country Trial name (Quality score)	N	Duration	Study design setting	Eligibility criteria
Shea, 2004 Canada (FAIR)	80	8 weeks	Double-blind, multicenter	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.

Evidence Table 19. Placebo-controlled trials in patients with autism

Author, year Country Trial name (Quality score)	Interventions (drug, dose, duration)	Run-in/washout period	Allowed other medications/interventions
Shea, 2004 Canada (FAIR)	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.	None	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 inititated 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 19. Placebo-controlled trials in patients with autism

Author, year Country Trial name (Quality score)	Age Gender Ethnicity	Other population characteristics (diagnosis, etc)	Number screened/ eligible/enrolled
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% placbebo 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

Evidence Table 19. Placebo-controlled trials in patients with autism

Author, year Country Trial name (Quality score)	Number withdrawn/ lost to fu/analyzed	Outcome scales	Method of outcome assessment and timing of assessment
Shea, 2004 Canada (FAIR)	3 withdrawn/0 lost to followup/77 analyzed	Aberrant Behavior Checklist, Nisonger Child Behavior Rating Form (parent version), Visual Analog Scale for the most troublesome symptom, and the CGI-C.	Efficacy assessments scored at each clinic visit (baseline/screening, and end of treatment weeks 1, 2, 3, 5, 7, and 8).

Evidence Table 19. Placebo-controlled trials in patients with autism

Author, year Country Trial name (Quality score)	Results
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%

Evidence Table 19. Placebo-controlled trials in patients with autism

Author, year Country Trial name (Quality score)	N	Duration	Study design setting	Eligibility criteria
Pandina, 2004 (poster, subgroup analysis of Shea, 2004) Canada (FAIR)	55	8 weeks	Double-blind, multicenter	Subgroup of children enrolled in Shea, 2004. Healthy children ages 5-12 years with a DSM-IV diagnosis of autism, baseline Childhood Autism Rating Scale total score >30.
Troost, 2005 The Netherlands	24	8 weeks (placebo-controlled discontinuation phase)	Double-blind, single center	DSM-IV crieria for a pervasive developmental disorder. Patients were required to demonstrate clinically significant tantrums, aggressio, self-injurious behavior, or a combination of these problems. Age 5 to 17 years, a weight of at least 15 kg, and a mentalage 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 19. Placebo-controlled trials in patients with autism

Author, year Country Trial name (Quality score)	Interventions (drug, dose, duration)	Run-in/washout period	Allowed other medications/interventions
Pandina, 2004 (poster, subgroup analysis of Shea, 2004) Canada (FAIR)	Risperidone oral solution 1 mg/ml or plecebo. Initiated at 0.01 mg/kg/day, increased to 0.02 mg/kg on day 3, dosage adjusted based on efficacy and tolerability, could be increased by up to 0.02 mg/kg/day to a maximum total daily dose of 0.06 mg/kg/day.	Not reported	Not reported
Troost, 2005 The Netherlands	Children on effective psychotropic drug treatment for disruptive behavior were excluded.	7- to 28 day washout period to withdraw from ineffective medicaitons.	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 monhts.

Evidence Table 19. Placebo-controlled trials in patients with autism

Author, year Country Trial name (Quality score)	Age Gender Ethnicity	Other population characteristics (diagnosis, etc)	Number screened/ eligible/enrolled
Pandina, 2004 (poster, subgroup analysis of Shea, 2004) Canada (FAIR)	Mean age 7.4 years (SD 2.4 risperidone, 7.1 (SD 2.1) placebo. 70.4% risperidone, 85.7% placebo were male. 59.3% risperidone, 64.3% placebo white	Mean IQ 50.8 (SD 19.8) risperidone, 60.1 (SD 21.9) placebo	NR NR 55
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

Evidence Table 19. Placebo-controlled trials in patients with autism

Author, year Country Trial name (Quality score)	Number withdrawn/ lost to fu/analyzed	Outcome scales	Method of outcome assessment and timing of assessment
Pandina, 2004 (poster, subgroup analysis of Shea, 2004) Canada (FAIR)	2 withdrawn NR Not clear	Parent or caregiver Aberrant Behavior Checklist (ABC) total and subscale scores, Nisonger Child Behavior Rating Form (parent version) total and subscale scores, Visual Analog Scale for the most troublesome symptom (1=least troublesome, 100= least troublesome), and the CGI-C.	Efficacy measures assessed at baseline and at treatment weeks 1, 2, 3, 5, 7, and 8
Troost, 2005 The Netherlands	2 withdrew before randomization in discontinuation phase 24 analyzed	Primary outcome: Difference in relapse rate between groups, defined as CGI-C scores of "much worse" or "very much worse" for at least 2 consecutive weeks when compared with baseline of the discontinuation phase, and a minimum increase of 25% in Irritability scores on the most recent Aberrant Behavior Checklist (ABC).	See Outcome Scales

Evidence Table 19. Placebo-controlled trials in patients with autism

Author, year Country Trial name (Quality score)	Results
Pandina, 2004 (poster, subgroup analysis of Shea, 2004) Canada (FAIR)	Mean change from baseline to endpoint, risperidone vs placebo: ABC (Total): -43.83 vs -21.39 (p<0.001) ABC (Irritability): -13.41 vs -7.16 (p<0.001) ABC (Lethargy/social withdrawal): -7.74 vs -4.05 (p<0.05) ABC (Stereotypic behavior): -4.09 vs -1.98 (p<0.05) ABC (Hyperactivity/noncompliance): -16.07 vs -7.11 (p<0.001) ABC (Inappropriate speech): -2.44 vs -1.26 (NS) N-CBRF (Total) -31.99 vs -20.71 (p<0.05) N-CBRF (Adaptive social) 1.55 vs 0.54 (NS) N-CBRF (Compliant/calm) 2.15 vs 0.73 (NS) N-CBRF (Conduct problem) 12.43 vs -6.01 (p<0.01) N-CBRF (Hyperactive) -8.15 vs -4.36 (p<0.05) N-CBRF(Insecure/anxious) -4.03 vs -2.90 (NS) N-CBRF (Overly sensitive) -3.66 vs -2.22 (p<0.05) N-CBRF (Self injury/stereotypic) -2.38 vs -1.50 (NS) N-CBRF (Self-isolated/ritualistic) -4.24 vs -2.41 (NS)
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.

Evidence Table 20. Active control trials in patients with autism

Author, year Country Trial Name (Quality Score)	N	Duration	Study design Setting	Eligibility criteria	Interventions (drug, dose, duration)
olanzapine vs haloperidol					
Malone, 2001 US (FAIR)	12	6 weeks	Randomized, open label, pilot study.	Children between ages 5 and 17 with a primary diagnosis of pervasive developmental disorder (DSM-IV criteria); at least moderate impairment on 2 or more of the first 28 items on the Children's Psychiatric Rating Scale at baseline.	Olanzapine starting dose 2.5 mg every other day for patients who weighed 40 kg or less and 2.5 mg per day for those who weighed more than 40 kg. Dosages could be increased in 2.5 mg increments up to 5 mg per week as needed. Maximum dose 20 mg/day. Haloperidol starting dose 0.25 mg/day for patients weighing 40 kg or less and 0.5 mg for those who weighed more than 40 kg. Dosages could be increased as clinically indicated in 0.5 mg increments up to 1 mg per week as needed. Maximum dose 5 mg/day.

Evidence Table 20. Active control trials in patients with autism

Author, year Country Trial Name (Quality Score)	Run-in/Washout period	Allowed other medications/ interventions	Age Gender Ethnicity	Other population characteristics (diagnosis, etc)	Number screened/ eligible/enrolled
olanzapine vs haloperidol					
Malone, 2001 US (FAIR)	1 week drug-free baseline washout period.	No.	Mean age 7.8 (SD 2.1) years; range 4.8-11.8 years. 67% male 58% white, 25% African American, 17% Hispanic	11/12 (92%) autistic disorder, 1/12 (8%) pervasive developmental disorder, not otherwise specified. 8% normal cognitive functioning, 8% mild mental retardation, 42% moderate mental retardation, 42% severe mental retardation.	# screened not reported/13 eligible/12 enrolled (1 withdrew consent)

Evidence Table 20. Active control trials in patients with autism

Author, year Country Trial Name (Quality Score)	Number withdrawn/ lost to fu/analyzed	Outcome measures	Method of outcome assessment and timing of assessment	Results
olanzapine vs haloperidol				
Malone, 2001 US (FAIR)	No withdrawals, losses to followup, 12 analyzed.	Primary outcome: CGI Secondary outcomes: Children's Psychiatric Rating Scale (CPRS)	Principal investigator and one other trained rater performed all ratings; assessments at baseline and end of study.	CGI Improvement from baseline olanzapine: 1/6 (16.7%) very much improved 4/6 (66.7%) much improved 1/6 (16.7% minimally improved haloperidol: 1/6 (16.7%) very much improved 2/6 (33.3%) much improved 3/6 (50% minimally improved (p=0.494) Mean change from baseline (olanzapine vs haloperidol) CGI (Severity): -1.08 vs -0.42 CPRS (Autism): -0.84 vs -0.53 CPRS (Anger/Uncooperative): -1.27 vs 0.15 CPRS (Hyperactivity): -1.1 vs 0.36 CPRS (Speech Deviance): 0.4 vs -0.25

Evidence Table 20. Active control trials in patients with autism

Author, year Country Trial Name (Quality Score)
olanzapine vs haloperidol
Malone, 2001 US (FAIR)

Evidence Table 21. Quality assessment in trials in patients with autism or disruptive behavior disorder

	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?**
Studies in children with autism							
Active-control trials							
Malone et al, 2001 US	Yes	Not reported	Yes	Yes	No	No	No
Placebo-controlled trials							
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
Shea et al, 2004 Pandina et al, 2004 (subgroup analysis) Canada	Method not reported	Not reported	Yes	Yes	Yes	Not reported	Yes

Evidence Table 21. Quality assessment in trials in patients with autism or disruptive behavior disorder

Author, year Country	Reporting of attrition, crossovers, adherence, and contamination?	Loss to follow-up: differential/high?	Intention-to-treat (ITT) analysis?	Post-randomization exclusions?	Quality Rating
Studies in children with autism					
Active-control trials					
Malone et al, 2001 US	Not reported	No	Yes	No	Fair
Placebo-controlled trials					
McCracken et al, 2002 Arnold et al, 2003 Research Units on Pediatric Psychopharmacology Autism Network RUPP	Attrition yes, others no.	No	Yes	Yes- 4 patients.	Fair
Shea et al, 2004 Pandina et al, 2004 (subgroup analysis) Canada	Attrition yes, others no.	No	Yes (1 not analyzed)	No	Fair

Evidence Table 21. Quality assessment in trials in patients with autism or disruptive behavior disorder

	External Validity		
Author, year Country	**Number screened/eligible/enrolled**	**Exclusion criteria**	**Run-in/Washout**
Studies in children with autism			
Active-control trials			
Malone et al, 2001 US	Number screened, eligible not reported/12 enrolled	Major medical problems such as cardiac, liver, endocrine, or renal diseases, seizure disorder or gross neurological deficit, treatment with concomitant psychotropic medication, or a history of previous treatment with haloperidol or olanzapine	1 week drug-free baseline washout period.
Placebo-controlled trials			
McCracken et al, 2002 Arnold et al, 2003 Research Units on Pediatric Psychopharmacology Autism Network RUPP	270 screened/158 eligible/101 enrolled	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.	Ineffective medications gradually withdrawn, drug-free interval of 7 to 28 days, depending on the drug, was required before enrollment.
Shea et al, 2004 Pandina et al, 2004 (subgroup analysis) Canada	Number screened, eligible not reported/80 enrolled	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.	None reported.

Evidence Table 21. Quality assessment in trials in patients with autism or disruptive behavior disorder

Author, year Country	Class naïve patients only?	Control group standard of care?	Funding
Studies in children with autism			
Active-control trials			
Malone et al, 2001 US	Yes	Yes	Supported in part by a grant from Lilly Research Laboratories (Investigator-Initiated Study).
Placebo-controlled trials			
McCracken et al, 2002 Arnold et al, 2003 Research Units on Pediatric Psychopharmacology Autism Network RUPP	No	Yes	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.
Shea et al, 2004 Pandina et al, 2004 (subgroup analysis) Canada	No	Yes	Supported by Janssen-Ortho Inc, Canada, and Johnson & Johnson Pharmaceutical Research and Development.

Evidence Table 21. Quality assessment in trials in patients with autism or disruptive behavior disorder

	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?**
Studies in children with disruptive behavior disorders							
Placebo-controlled trials							
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
Snyder et al, 2002 Risperidone Conduct Study Group	Method not reported	Not reported	Yes	Yes	Yes	Yes	Yes

Evidence Table 21. Quality assessment in trials in patients with autism or disruptive behavior disorder

Author, year Country	Reporting of attrition, crossovers, adherence, and contamination?	Loss to follow-up: differential/high?	Intention-to-treat (ITT) analysis?	Post-randomization exclusions?	Quality Rating
Studies in children with disruptive behavior disorders					
Placebo-controlled trials					
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.	Not reported	Fair
Snyder et al, 2002 Risperidone Conduct Study Group	Attrition yes, others no.	Yes- 33.3% placebo, 11.3% risperidone withdrew (p=0.006)	No	No	Fair

Evidence Table 21. Quality assessment in trials in patients with autism or disruptive behavior disorder

	External Validity		
Author, year Country	**Number screened/eligible/enrolled**	**Exclusion criteria**	**Run-in/Washout**
Studies in children with disruptive behavior disorders			
Placebo-controlled trials			
Aman et al, 2002 Risperidone Disruptive Behavior Study Group US	142 screened/119 eligible/118 enrolled	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.	1-week placebo run-in to rule out placebo responders.
Snyder et al, 2002 Risperidone Conduct Study Group	Number screened not reported/133 eligible/110 enrolled	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.	One week placebo run-in to rule out placebo responders.

Evidence Table 21. Quality assessment in trials in patients with autism or disruptive behavior disorder

Author, year Country	Class naïve patients only?	Control group standard of care?	Funding
Studies in children with disruptive behavior disorders			
Placebo-controlled trials			
Aman et al, 2002 Risperidone Disruptive Behavior Study Group US	Yes	Yes	Supported by the Janssen Research Foundation.
Snyder et al, 2002 Risperidone Conduct Study Group	Yes	Yes	Funded by Janssen Research Foundation

Evidence Table 21. Quality assessment in trials in patients with autism or disruptive behavior disorder

	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?**
Buitelaar, 2001	Yes	Not reported	Yes	Yes	Yes	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 21. Quality assessment in trials in patients with autism or disruptive behavior disorder

Author, year Country	Reporting of attrition, crossovers, adherence, and contamination?	Loss to follow-up: differential/high?	Intention-to-treat (ITT) analysis?	Post-randomization exclusions?	Quality Rating
Buitelaar, 2001	Yes	No	Yes (LOCF)	No	Fair
Findling et al, 2000 US	Attrition and adherence yes, others no.	Withdrawals- 40% risperidone, 70% placebo	Yes	No	Fair

Evidence Table 21. Quality assessment in trials in patients with autism or disruptive behavior disorder

	External Validity		
Author, year Country	**Number screened/eligible/enrolled**	**Exclusion criteria**	**Run-in/Washout**
Buitelaar, 2001	145/48/38	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.	No run-in; 2 week washout after double-blind period.
Findling et al, 2000 US	Number screened, eligible not reported/20 enrolled.	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.	None reported.

Evidence Table 21. Quality assessment in trials in patients with autism or disruptive behavior disorder

Author, year Country	Class naïve patients only?	Control group standard of care?	Funding
Buitelaar, 2001	NR	Yes	Janssen-Cilag, The Netherlands
Findling et al, 2000 US	No	Yes	Supported in part by the Janssen Research Foundation, the Stanley Foundation, and NICHD Pediatric Pharmacology Research Unit contract.

Evidence Table 22. Placebo-controlled trials in patients with disruptive behavior disorder

Author, year Country Trial Name (Quality Score)	N	Duration	Study design Setting	Eligibility criteria
Trials of risperidone				
Aman et al, 2002 Risperidone Disruptive Behavior Study Group US (FAIR)	118	6 weeks	Double-blind, multicenter	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.

Evidence Table 22. Placebo-controlled trials in patients with disruptive behavior disorder

Author, year Country Trial Name (Quality Score)	Interventions (drug, dose, duration)	Run-in/washout period	Allowed other medications/interventions
Trials of risperidone			
Aman et al, 2002 Risperidone Disruptive Behavior Study Group US (FAIR)	Risperidone oral solution 0.01 mg/kg per day on days 1 and 2, increased to 0.02 mg/kg per day on day 3. Thereafter, dose adjusted at weekly intervals as judged necessary by the clinician. Increases or decreases in doses were made in increments of no more than 0.02 mg/kg per day. Maximum dose 0.06 mg/kg per day.	1-week placebo run-in to rule out placebo responders.	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.

Evidence Table 22. Placebo-controlled trials in patients with disruptive behavior disorder

Author, year Country Trial Name (Quality Score)	Age Gender Ethnicity	Other population characteristics (diagnosis, etc)	Number screened/ eligible/enrolled	Number withdrawn/ lost to fu/analyzed
Trials of risperidone				
Aman et al, 2002 Risperidone Disruptive Behavior Study Group US (FAIR)	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).

Evidence Table 22. Placebo-controlled trials in patients with disruptive behavior disorder

Author, year Country Trial Name (Quality Score)	Outcome scales	Method of outcome assessment and timing of assessment	Results
Trials of risperidone			
Aman et al, 2002 Risperidone Disruptive Behavior Study Group US (FAIR)	Primary outcome: Conduct problem subscale of the Nisonger Child Behavior Rating From problem behaviors section. Secondary measures: Other Nisonger Child Behavior Rating From problem behaviors section subscales and the social competence section subscales; Aberrant Behavior Checklist subscale scores, investigator's rating on the CGI severity scale, and CGI change scores. Change in a VAS rating of an individual target symptom for each patient (the symptoms considered most disturbing for the patient and his/her surroundings) was evaluated.	Method not reported; visits scheduled on day 0 (initiation of treatment), days 7, 14, 21, 28, 35, and 42 (final visit).	Change in Nisonger Child Behavior Rating Form conduct problem subscale score at 6 weeks (risperidone vs placebo): -15.2 vs -6.2 ($p<0.001$) 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% ($p<0.001$)

Evidence Table 22. Placebo-controlled trials in patients with disruptive behavior disorder

Author, year Country Trial Name (Quality Score)	N	Duration	Study design Setting	Eligibility criteria
Snyder et al, 2002 Risperidone Conduct Study Group Canada (FAIR)	110	6 weeks	Double-blind, multicenter	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 22. Placebo-controlled trials in patients with disruptive behavior disorder

Author, year Country Trial Name (Quality Score)	Interventions (drug, dose, duration)	Run-in/washout period	Allowed other medications/interventions
Snyder et al, 2002 Risperidone Conduct Study Group Canada (FAIR)	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	One week placebo run-in to rule out placebo responders.	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 22. Placebo-controlled trials in patients with disruptive behavior disorder

Author, year Country Trial Name (Quality Score)	Age Gender Ethnicity	Other population characteristics (diagnosis, etc)	Number screened/ eligible/enrolled	Number withdrawn/ lost to fu/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 22. Placebo-controlled trials in patients with disruptive behavior disorder

Author, year Country Trial Name (Quality Score)	Outcome scales	Method of outcome assessment and timing of assessment	Results
Snyder et al, 2002 Risperidone Conduct Study Group Canada (FAIR)	Primary outcome: Conduct problem subscale of the Nisonger Child Behavior Rating. Secondary measures: Subscales on the ABC, the Behavior Problems Inventory (BPI), CGI, Visual Analogue Scale of most troublesome symptoms, and Visual Analogue Scale of sedation.	Each child rated weekly (by parents?) at baseline, weeks 1, 2, 3, 4, 5, and 6 on NCBRF, ABC, BPI, CGI, ESRS, VAS/Sedation, and VAS/symptom. Cognitive function assessed at baseline and at the end of week 6.	Change in Nisonger Child Behavior Rating Form conduct problem subscale score at 6 weeks (risperidone vs placebo): -15.8 vs -6.8 ($p<0.001$)

Evidence Table 22. Placebo-controlled trials in patients with disruptive behavior disorder

Author, year Country Trial Name (Quality Score)	N	Duration	Study design Setting	Eligibility criteria
Findling et al, 2000 US (FAIR)	20	10 weeks	Double-blind, single, inner-city, academic medical center.	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 22. Placebo-controlled trials in patients with disruptive behavior disorder

Author, year Country Trial Name (Quality Score)	Interventions (drug, dose, duration)	Run-in/washout period	Allowed other medications/interventions
Findling et al, 2000 US (FAIR)	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.	None reported.	For patients in whom EPS developed, treatment with oral benztropine was available.

Evidence Table 22. Placebo-controlled trials in patients with disruptive behavior disorder

Author, year Country Trial Name (Quality Score)	Age Gender Ethnicity	Other population characteristics (diagnosis, etc)	Number screened/ eligible/enrolled	Number withdrawn/ lost to fu/analyzed
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 22. Placebo-controlled trials in patients with disruptive behavior disorder

Author, year Country Trial Name (Quality Score)	Outcome scales	Method of outcome assessment and timing of assessment	Results
Findling et al, 2000 US (FAIR)	Primary outcome: Rating of Aggression Against People and/or Property Scale (RAAPP) Secondary measures: CGI-S, CGI-I, Conners Parent Rating Scale (CPRS), Child Behavior Checklist (CBCL)	Method not reported; assessments weekly to week 10.	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)

Evidence Table 22. Placebo-controlled trials in patients with disruptive behavior disorder

Author, year Country Trial Name (Quality Score)	N	Duration	Study design Setting	Eligibility criteria
Buitelaar, 2001 The Netherlands (FAIR)	38	6 weeks	Double-blind, single center	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 Aggressn Scale (OAS-M) rated by nurses in the ward at the end of the baseline phase; their aggressive behavior failed to responsd to behavioral treatment approaches; there was a clinical indicaton 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 22. Placebo-controlled trials in patients with disruptive behavior disorder

Author, year Country Trial Name (Quality Score)	Interventions (drug, dose, duration)	Run-in/washout period	Allowed other medications/interventions
Buitelaar, 2001 The Netherlands (FAIR)	risperidone 1 mg or placebo	no run-in; 2 week washout after double-blind period.	Concomitant medication for acute or chronic somatic illnesses was allowed at the discretion of the clinician in charge.

Evidence Table 22. Placebo-controlled trials in patients with disruptive behavior disorder

Author, year Country Trial Name (Quality Score)	Age Gender Ethnicity	Other population characteristics (diagnosis, etc)	Number screened/ eligible/enrolled	Number withdrawn/ lost to fu/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)/0NR/38

Evidence Table 22. Placebo-controlled trials in patients with disruptive behavior disorder

Author, year Country Trial Name (Quality Score)	Outcome scales	Method of outcome assessment and timing of assessment	Results
Buitelaar, 2001 The Netherlands (FAIR)	CGI-Severity Secondary measures: OAS-M, ABC.	CGI-S at selection, end of baseline period, 2, 4, 6 weeks (endpoint), and end of washout period	risperidone vs placebo Markedly or severely disturbed: 21% vs 84% Mean (SD) CGI-Severity score: 2.7 (1.2) vs 4.4 (1.0)

Evidence Table 23. Adverse events in trials in patients with autism

Study, year	Interventions (Mean daily dose, range)	N	Duration	Method of adverse effects assessment	Overall withdrawals
Active-control trial					
Malone et al, 2001	olanzapine (7.9 mg, range 5-10 mg) vs haloperidol (1.4 mg, range 0.5-2.5 mg)	12	6 weeks	Weight, blood pressure, and pulse at baseline and each visit. Height recorded at baseline. Adverse effects monitored at each visit with the Dosage Record and Treatment Emergent Symptom Scale (DOTES), the Treatment Emergent Symptoms Scale-Write IN (TESS), AIMS, and the Neurologic Rating Scale (NRS). At baseline and end of treatment, complete blood count with differential, liver functions, and EKG.	None

Evidence Table 23. Adverse events in trials in patients with autism

Study, year	Withdrawals due to adverse events	Weight gain	Other adverse effects reported
Active-control trial			
Malone et al, 2001	No withdrawals	Mean weight gain at 12 weeks: olanzapine: 4.08 kg (SD 1.59, range 2.67 to 7.14) haloperidol: 1.45 kg (SD 2.22, range -2.49 to 3.97) (p=0.04) All 6 patients in olanzapine group vs 2 fo 6 in haloperidol group gained more than 2.27 kg (5 lbs)	No significant differences between groups on incidence of side effects. NRS: One haloperidol patient had transient mild rigidity, no olanzapine patient had extrapyramidal symptoms as rated by this measure. AIMS: No patients in either treatment group had dyskinesia as rated by this measure. No clinically significant changes in any of the laboratory studies or EKGs. Medication treatment was not associated with a prolongation of the QTc interval.

Evidence Table 23. Adverse events in trials in patients with autism

Study, year	Interventions (Mean daily dose, range)	N	Duration	Method of adverse effects assessment	Overall withdrawals
Placebo-controlled trials					
McCracken et al, 2002 Research Units on Pediatric Psychopharmacology Autism Network RUPP	risperidone (1.8 mg, range 0.5-3.5 mg) vs placebo (equivalent to 2.4 mg, range 1-3.5 mg)	101	8 weeks	Lab tests, EKG, and physical exam at baseline, 8 weeks, weight and vital signs assessed weekly. At each visit, primary clinician inquired about health problems, intercurrent illness, and concomitant medications and administered 32-item questionnaire concerning energy level, muscle stiffness, motor restlessness, bowel and bladder habits, sleep, and appetite. Neurologic side effects assessed weekly with the Simpson-Angus scale and AIMS. Adverse events noted as a result of any of these methods were documented with respect to severity, duration, management, and outcome.	3/49 (6%) risperidone 18/52 (35%) placebo (p=0.001)

Evidence Table 23. Adverse events in trials in patients with autism

Study, year	Withdrawals due to adverse events	Weight gain	Other adverse effects reported
Placebo-controlled trials			
McCracken et al, 2002 Research Units on Pediatric Psychopharmacology Autism Network RUPP	None	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 23. Adverse events in trials in patients with autism

Study, year	Interventions (Mean daily dose, range)	N	Duration	Method of adverse effects assessment	Overall withdrawals
Shea et al, 2004	risperidone 0.02 mg/kg/day-0.06 mg/kg/day. Mean daily dose 1.17 mg/day	80	8 weeks	Subjects attended clinic on 7 occasions: baseline screening visit and at the end of treatment weeks 1, 2, 3, 5, 7, and 8. Safety assessment measures, which included adverse event data, vital signs, and body weight, were collected at each visit. The presence and severity of EPSs were assessed at each visit by the investigator using the ESRS. A 12-lead EEG and routine biochemistry, hematology, and urinalysis were performed at baseline and at the end of treatment.	8.9% (2 risperidone, 5 placebo)

Evidence Table 23. Adverse events in trials in patients with autism

Study, year	Withdrawals due to adverse events	Weight gain	Other adverse effects reported
Shea et al, 2004	1 risperidone, 1 placebo.	Mean weight gain at 8 weeks: riisperidone: 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.

Evidence Table 23. Adverse events in trials in patients with autism

Study, year	Interventions (Mean daily dose, range)	N	Duration	Method of adverse effects assessment	Overall withdrawals
Pandina et al, 2004 (poster, subgroup analysis of Shea, 2004) Canada	Risperidone 1.17 mg (0.04 mg/kg), range not reported	55	8 weeks	Adverse events, vital signs, weight, ESRS at every visit; biochemistry, hematology, urinalysis,a nd 12-lead ECG at baseline and endpoint.	2 of 55 (4%)

Evidence Table 23. Adverse events in trials in patients with autism

Study, year	Withdrawals due to adverse events	Weight gain	Other adverse effects reported
Pandina et al, 2004 (poster, subgroup analysis of Shea, 2004) Canada	1 risperidone, 1 placebo.	Mean weight gain (SD) at 8 weeks: risperidone: 13.8 (5.4) to 14.9 (5.7) kg placebo: 12.4 (SD 4.0) to 12.9 (SD 4.4) kg	Most common adverse event was somnolence, more frequent with risperidone (74% vs 7%) Other AEs occurring in >10%, risperidone (N=27) vs placebo (N=28): diarrhea: 7.4% vs 17.9% vomiting: 11.1% vs 21.4% increased saliva: 14.8% vs 3.6% increased appetite: 11.1% vs 3.6% aggression: 3.7% vs 10.7% agitation: 3.7% vs 10.7% anorexia: 11.1% vs 3.6% somnolence: 74.1% vs 7.1% insomnia: 3.7% vs 17.9% cough: 14.8% vs 10.7% rhinitis: 25.9% vs 7.1% fever: 25.9% vs 17.9% influenza-like symptoms: 11.1% vs 3.6% upper respiratory infection: 40.7% vs 17.9% urinary incontinence: 7.4% vs 14.3%

Evidence Table 24. Adverse events in trials in patients with disruptive behavior disorder

Study, year	Interventions (Mean daily dose, range)	N	Duration	Method of adverse effects assessment	Overall withdrawals	Withdrawals due to adverse events
Placebo-controlled trials						
Aman et al, 2002 Risperidone Disruptive Behavior Study Group US	Risperidone 1.16 mg	118	6 weeks	Physical exams and EKGs at screening and the end of treatment. Weekly safety assessments included a visual analogue scale rating of sedation, Extrapyramidal Symptom Rating Scale score for the severity of extrapyramidal symptoms, and measures of vital signs and weight.	22% risperidone, 30% placebo	4% risperidone (somnolence), 0 placebo

Evidence Table 24. Adverse events in trials in patients with disruptive behavior disorder

Study, year	Weight gain	Extrapyramidal symptoms	Other adverse effects reported
Placebo-controlled trials			
Aman et al, 2002 Risperidone Disruptive Behavior Study Group US	15% risperidone vs 2% placebo reported weight increase Mean weight increase risperidone: 2.2 kg (SD 1.8 kg) placebo: 0.9 kg (SD 1.5 kg) (p<0.001)	Extrapyramidal Symptom Rating Scale score, mean change from baseline to 6 weeks (risperidone vs placebo) Total score on interview questionnaire: -0.2 vs -0.2 (p=0.72) Score on neurologic examination, mean change from baseline to 6 weeks Total: -0.2 vs -0.2 (p=0.72) Parkinsonism: -0.6 vs -0.1 (p=0.48) Dystonia: -- vs 0.2 (p=0.32) Dyskinesia: -0.1 vs 0.1 (p=0.09) Buccolinguomasticatory: 0.0 vs 0.1 (p=0.16) Choreoathetoid movements: -0.1 vs 0.0 (p=0.27)	98% of risperidone, 70% placebo reported any adverse event. Most common AEs (risperidone vs placebo): somnolence (51% vs 10%); headache (29% vs 14%); vomiting (20% vs 6%); dyspepsia (15% vs 6%); weight increase (15% vs 2%); elevated serum prolactin (13% vs 2%); increased appetite (11% vs 6%); rhinitis (11% vs 5%) Temporary 11 beats-per-minute increase in heart rate occurred during first 2 weeks of treatment in risperidone group compared with placebo (p=0.006). No QTc abnormalities. At endpoint, mean visual analogue scale score for sedation (higher score indicative of sedation) was 5.9 for risperidone and -2.02 for placebo (p=0.008).

Evidence Table 24. Adverse events in trials in patients with disruptive behavior disorder

Study, year	Interventions (Mean daily dose, range)	N	Duration	Method of adverse effects assessment	Overall withdrawals	Withdrawals due to adverse events
Buitelaar, 2001 The Netherlands	Risperidone 2.9 mg (range 1.5 to 4 mg)	36	6 weeks	Extrapyramidal Symptom Rating Scale (ESRS). Completed by the psychiatrist at the end of 2-week baseline period, end of 6-week double-blind period, and end of 2-week washout. At each clinical visit, patients asked if they had experienced any dicomfort since the last visit, patients weighed at each clinical visit, Cognitive function assessed, but results not reported (states results will be reported separately).	0 risperidone (1 patient withdrew after washout) 10.5% placebo	None
Findling et al, 2000 US	Risperidone 0.028 mg per kg (range 0.75-1.5 mg)	20	10 weeks	Neurological side effects measured with the AIMS, Neurological Rating Scale at baseline and at each study visit. Other side effects assessed at each study visit using the Dosage Record and Treatment Emergent Symptom scale. Vital signs and weight obtained at baseline and each study visit. Physical exam and EKG at screening and study's end. Third EKG at week 5.	40% risperidone, 70% placebo.	1/10 (10%) risperidone (rash); 0 placebo.

Evidence Table 24. Adverse events in trials in patients with disruptive behavior disorder

Study, year	Weight gain	Extrapyramidal symptoms	Other adverse effects reported
Buitelaar, 2001 The Netherlands	Mean increase: risperidone: 2.3 kg (3.5%, range, −1 to +6 kg) placebo: 0.6 kg (1.1% range −4 to +6 kg)	Increase in parkinsonism (risperidone vs placebo) on ESRS: 0.6 vs vs −0.5 ($p<0.05$) NSD for other ESRS clusters. 21% risperidone vs 0 placebo had mild difficulty swallowing or talking ($p<0.05$). At washout, ESRS scores of cluster I and II decreased significantly for risperidone group ($p<0.05$)	Prolactin concentration increased signficantly in risperidone group. No prolactin-related AES reported. No clinically relevant ECG abnormalities, no effect on TT interval.
Findling et al, 2000 US	Mean predicted weight gain: risperidone: 4.2 kg placebo: 0.74 kg ($p=0.003$)	No parkinsonian symptoms or acute dystonic reactions. No patient developed any abnormal involuntary movements.	80% of risperidone and 40% placebo patients experienced at least one side effect. Side effects attributable to study medication: increased appetite (3 risperidone) sedation (3 risperidone, 2 placebo) headache (1 risperidone, 1 placebo) initial insomnia (1 risperidone) restlessness (1 risperidone) irritability (1 risperidone) enuresis (1 placebo) nausea/emesis (1 risperidone, 1 placebo) No clinically significant changes in any laboratory value or electrocardiogram. No elevations in serum transaminase or bilirubin levels.

Evidence Table 24. Adverse events in trials in patients with disruptive behavior disorder

Study, year	Interventions (Mean daily dose, range)	N	Duration	Method of adverse effects assessment	Overall withdrawals	Withdrawals due to adverse events
Snyder et al, 2002 Risperidone Conduct Study Group	Risperidone 0.98 mg (range 0.40-3.8 mg)	110	6 weeks	Extrapyramidal Symptom Rating Scale (ESRS).	11.3% risperidone, 33.3% placebo	None

Evidence Table 24. Adverse events in trials in patients with disruptive behavior disorder

Study, year	Weight gain	Extrapyramidal symptoms	Other adverse effects reported
Snyder et al, 2002 Risperidone Conduct Study Group	Weight gain risperidone: 2.2 kg placebo: 0.2 kg (p<0.001) Body mass increase risperidone: 1.2 placebo: 0.1 (p<0.001)	Extrapyramidal Symptom Rating Scale score, mean change from baseline to 6 weeks (risperidone vs placebo) Total score: -03 vs -0.2 (NS) Bucco-linguo-masticatory: remained at 0.0 for both groups Parkinsonism: -0.3 vs -0.2 (NS) 7 risperidone vs 3 placebo patients rated as having some EPS. 0 risperidone vs 1 placebo patient rated as having emergence of tardive dyskinesia.	86.8% risperidone vs 73.7% placebo patients had at least one adverse event. Most common were somnolence, increased appetite, dyspepsia, abnormal crying, headaches, urinary incontinence, hyperprolactinemia, and weight increase. No drug-related changes in heart rate and QTc. No ECG changes judged to be clinically significant.