Drug Class Review on Newer Drugs for Insomnia

Final Report

EVIDENCE TABLES

July 2006

The Agency for Healthcare Research and Quality has not yet seen or approved this report

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.

Susan Carson, MPH Po-Yin Yen, MS Marian S. McDonagh, PharmD

Oregon Evidence-based Practice Center Oregon Health & Science University Mark Helfand, MD, MPH, Director

Copyright © 2006 by Oregon Health & Science University Portland, Oregon 97239. All rights reserved.



TABLE OF CONTENTS

Evidence Table 1. Head to head controlled trials: Efficacy	3
Evidence Table 2. Head to head controlled trials: Rebound	15
Evidence Table 3. Head to head controlled trials: Adverse Events	
Evidence Table 4. Active controlled trials (Adult): Efficacy	27
Evidence Table 5. Active controlled trials (Adult): Rebound	65
Evidence Table 6. Active controlled trials (Adult): Adverse Events	79
Evidence Table 7. Active controlled trials (Elderly): Efficacy	
Evidence Table 8. Active controlled trials (Elderly): Rebound	
Evidence Table 9. Active controlled trials (Elderly): Adverse Events	
Evidence Table 10. Active controlled trials (Other Subgroups): Efficacy	
Evidence Table 11. Active controlled trials (Other Subgroups): Rebound	
Evidence Table 12. Active controlled trials (Other Subgroups): Adverse Ever	nts145
Evidence Table 13. Placebo controlled trials: Efficacy	
Evidence Table 14. Placebo controlled trials: Rebound	
Evidence Table 15. Placebo controlled trials: Adverse Events	
Evidence Table 16. Quality Assessment of Efficacy Trials	241
Evidence Table 17. Observational Studies	
Evidence Table 18. Case Reports	

Suggested citation for this report:

Carson S, Yen P, McDonagh MS. Drug Class Review on Newer Sedative Hypnotics. Final Report. 2006

Funding:

The funding source, the Center for Evidence-based Policy, is supported by 17 organizations, including 15 state Medicaid programs. These organizations selected the topic and had input into the Key Questions for this review. The content and conclusions of the review are entirely determined by the Evidence-based Practice Center researchers. The authors of this report have no financial interest in any company that makes or distributes the products reviewed in this report.

lain, 2003							Quality	rating:	Fair
esign:									
Study design:	RCT	DB	Crossov		0 days t: 0 days		Setting: Country:	Single C France	enter
Sample:	Numt	er Scre	eened/ Elio NR/	gible/ Enrolled NR/ 53	•	er Withdrawn/ 0/		w-up/ An 0/	alyzed 53
Inclusion crite	ria:		110			0/		0,	
					tion judged com g the prescriptior				
patients who drugs the da	ode ha o follow ay befor zaleplo	ed a co re inclu on; nigh	ontinuous tr sion; patier nt-shift work	eatment with the nts who took hyp x; current medica	; any secondary same hypnotic f notic drugs the d I treatment includ	or more than s ay before inclu	six months; p usion, patien	batients what is currently	y treated by
Population:	Mean	age:	52 years	Ethnici	ty: NR				
tervention: Drug name	Gend dos		49% Fema N=	lle Duration		Primary outcome	Outcome:		
Zolpidem	10	mg	53	1 day		\checkmark	Patient's p	reference	for drug
Zaleplon	10	mg	53	1 day			Getting to	sleep	
					_		Quality of	sleep (LSE	EQ)
							Ease of wa	aking up	
							Behavior f	ollowing w	akefulness
							Day quality		
							Quality of		5)
fficacy:									
Patient pre	eferenc	e							
	Zolpide	m	Zale	plon					
Percenta	age of p	atients	preferring	a drug: (%)					
	62		3	8					P: 0.81
LSEQ									
	Zolpide	ŧm	Zale	plon					
Getting t	o sleep	mean	score (low	er is better): Sco	re (SD)				
3	35.9 (20).0)	45.3 ((20.7)					P: 0.03
Quality	of sleep	mean	score (lowe	er is better): Scor	e (SD)				
Quality c	30.6 (18		44.3 (P: <0.0001
-					core (SD)				
3		up mea	an score (lo	ower is better): S					
3 Ease of v			an score (lo 43.8 (ower is better): S (21.8)					P: 0.27
3 Ease of v 4	waking 13.6 (22	2.8)	43.8	(21.8)	r is better): Score	e (SD)			P: 0.27

n, 2003		Quality rating: Fair
VAS for day quality (0-10	00, higher is better)	
Zolpidem	Zaleplon	
Quality of sleep mean s	score: Score (SD)	
68.8 (21.8)	50.2 (28.1)	P: <0.0001
Consciousness mean s	score: Score (SD)	
73.9 (21.3)	73.1 (19.7)	P: 0.18
Dynamism mean score	: Score (SD)	
62.6 (26.0)	61.8 (24.9)	P: 0.47
Drowsiness mean scor	e: Score (SD)	
28 (27.4)	27.7 (26.5)	P: 0.53
Anxiety mean score: So	core (SD)	
29.3 (30.1)	26.7 (27.7)	P: 0.34
Mood mean score: Sco	re (SD)	
21.6 (25.5)	20.1 (21.6)	P: 0.92
Drowsiness duration (n	ninutes): Number (SD)	
43 (43.8)	38 (21.2)	P: 0.83

	1999							Quality	rating	j: Fa	ir	
Design:												
Study design:	RCT	DB	Parallel		Run-in : Wash out :	7 days 7-21 days		Setting: Country:	Multice US	enter		
Sample:	Numbe	er Scre	eened/ Eli 1224/	gible/ 551/	Enrolled 549	Numb	oer Withdrawn/ 2/	Lost to follo	w-up/ A NR/		ed 549	
Inclusion crite	ria:											
IV at study e	entry. Th	is his	tory must h	nave in		al sleep laten	th history of prin cy of 30 minute hours.					-
Depression restless legs	medical scales a s syndror results o	dmini: ne, if	stered duri their sleep	ng scr comp	eening were a laint was cons	=50. Patien sidered to be	aw scores on th ts were also exists secondary to n ory assessment	cluded if the icotine use,	ey had sle or if the	eep a _l study	onea or physician	
Population:	Mean a	age:	72 years		Ethnicity:	3.3% Blac	k; 1.6% Hispani	c; 1.3 Asiar	ı; 93.6%	White	•	
	Gende		58% Fema	ale	-							
Drug name	dosa	ge	N=		Duration		Primary outcome	Outcome	:			
Placebo	NA n	ng	107		2 week			Sleep late	ncy			
Zaleplon	5 n	ng	166		2 week			Total slee	o time			
Zaleplon	10 n	ng	165		2 week			Number of	fawaken	nings		
Zolpidem	5 n	ng	111		2 week			Sleep qua	lity			
Efficacy:												
	leplon 5	•			es) at week 1:	em 5 mg Number (p v).05)	Placebo rs placebo)					
Za	leplon 5 subjectiv NS)	e slee	p latency (<0.	(minute 001)	es) at week 1:	Number (p v).05)	rs placebo)					
Za Median s Median s	leplon 5 subjectiv NS)	e slee e slee	p latency (<0. p latency ((minute 001)	es) at week 1: <(es) at week 2:	Number (p v).05)	rs placebo)					
Za Median s Median s	leplon 5 subjectiv NS) subjectiv 9 (<0.00	e slee e slee	p latency (<0. p latency ((minute 001) (minute	es) at week 1: <(es) at week 2:	Number (p v).05) Number (p v	rs placebo) rs placebo)					
Za Median s Median s 3 Total sleep	leplon 5 subjectiv NS) subjectiv 9 (<0.00	e slee e slee 1)	p latency (<0. p latency ((minute 001) (minute 001)	es) at week 1: <(es) at week 2: <(Number (p v).05) Number (p v	rs placebo) rs placebo)					
Za Median s Median s 3 Total sleep Za	leplon 5 subjectiv NS) subjectiv 9 (<0.00 o time leplon 5	e slee e slee 1) mg	p latency (<0. p latency (<0. Zaleplo	(minute 001) (minute 001) n 10 n	es) at week 1: <(es) at week 2: <(Number (p v).05) Number (p v).01) em 5 mg	rs placebo) rs placebo) 56 Placebo					
Za Median s Median s 3 Total sleep Za	leplon 5 subjectiv NS) subjectiv 9 (<0.00 o time leplon 5	e slee e slee 1) mg	p latency (<0. p latency (<0. Zaleplo	(minute 001) (minute 001) n 10 n	es) at week 1: <(es) at week 2: <(ng Zolpid eek 1: Numbe	Number (p v).05) Number (p v).01) em 5 mg	rs placebo) rs placebo) 56 Placebo					
Za Median s Median s 3 Total sleep Za Median s	subjectiv NS) subjectiv 9 (<0.00 o time lepton 5 subjectiv NS)	e slee 1) mg e total	p latency (<0. p latency (<0. Zaleplo sleep time 345 (p	(minute 001) (minute 001) n 10 n e at we p<0.05	es) at week 1: <(es) at week 2: <(ng Zolpid eek 1: Numbe	Number (p v).05) Number (p v).01) em 5 mg r (p vs placet <0.001)	rs placebo) rs placebo) 56 Placebo po) 318 (NA)					
Za Median s Median s 3 Total sleep Za Median s	subjectiv NS) subjectiv 9 (<0.00 o time lepton 5 subjectiv NS)	e slee 1) mg e total	p latency (<0. p latency (<0. Zaleplo sleep time 345 (p	(minute 001) (minute 001) n 10 n e at we p<0.05	es) at week 1: <(es) at week 2: <(ng Zolpid eek 1: Numbe) 360 (eek 2: Numbe	Number (p v).05) Number (p v).01) em 5 mg r (p vs placet <0.001)	rs placebo) rs placebo) 56 Placebo po) 318 (NA)					
Za Median s 3 Total sleep Za Median s Median s	leplon 5 subjectiv NS) subjectiv 9 (<0.00 9 (<0.00 9 time leplon 5 subjectiv NS) subjectiv NS)	e slee 1) mg e total e total	p latency (<0. p latency (<0. Zaleplo sleep time 345 (p	(minute 001) (minute 001) n 10 n e at we 0<0.05 e at we IS)	es) at week 1: <(es) at week 2: <(ng Zolpid eek 1: Numbe) 360 (eek 2: Numbe 360	Number (p v).05) Number (p v).01) em 5 mg r (p vs placet <0.001) r (p vs placet	rs placebo) 56 Placebo 00) 318 (NA)					
Za Median s 3 Total sleep Za Median s Median s	subjectiv NS) subjectiv 9 (<0.00 o time leplon 5 subjectiv NS) subjectiv NS) awaker leplon 5	e slee e slee 1) mg e total e total nings mg	p latency (<0. p latency (<0. Zaleplo sleep time 345 (p sleep time N Zaleplo	(minute 001) (minute 001) n 10 n e at we ><0.05 e at we IS) n 10 n	es) at week 1: <(es) at week 2: <(ng Zolpid eek 1: Numbe) 360 (eek 2: Numbe 360	Number (p v).05) Number (p v).01) em 5 mg r (p vs placet <0.001) r (p vs placet (<0.01) em 5 mg	rs placebo) 56 Placebo 00) 318 (NA) 00) 326 (NA)					
Za Median s 3 Total sleep Za Median s Median s	subjectiv NS) subjectiv 9 (<0.00 o time leplon 5 subjectiv NS) subjectiv NS) awaker leplon 5	e slee 1) mg e total e total mg enings	p latency (<0. p latency (<0. Zaleplo sleep time 345 (p sleep time N Zaleplo	(minute 001) (minute 001) n 10 n e at we ><0.05 e at we IS) n 10 n	es) at week 1: <(es) at week 2: <(ng Zolpid eek 1: Numbe) 360 (eek 2: Numbe 360 ng Zolpid ber (p vs plac	Number (p v).05) Number (p v).01) em 5 mg r (p vs placet <0.001) r (p vs placet (<0.01) em 5 mg	rs placebo) 56 Placebo 00) 318 (NA) 00) 326 (NA)					
Za Median s 3 Total sleep Za Median s Median s Number of Za	leplon 5 subjectiv NS) subjectiv 9 (<0.00 0 time leplon 5 subjectiv NS) subjectiv NS) awaker leplon 5 of awake 1.8 (NS)	e slee e slee 1) mg e total e total hings mg enings	p latency (<0. p latency (<0. Zaleplo 345 (p sleep time 345 (p N Zaleplo at week 1 1.8	(minute 001) (minute 001) (m 10 n e at we o<0.05 e at we IS) (n 10 n : Num (NS)	es) at week 1: <(es) at week 2: <(ng Zolpid eek 1: Numbe) 360 (eek 2: Numbe 360 ng Zolpid ber (p vs plac	Number (p v 0.05) Number (p v 0.01) em 5 mg r (p vs placet <0.001) r (p vs placet <0.001) r (p vs placet (<0.01) em 5 mg ebo) <0.01)	rs placebo) 56 Placebo 00) 318 (NA) 00) 326 (NA) Placebo					

Ancoli-Israel, 1999

Quality rating: Fair

leep	quality			
	Zaleplon 5 mg	Zaleplon 10 mg	Zolpidem 5 mg	Placebo
Med	dian sleep quality at	week 1 (1=excellent	t, 7=extremely poor): S	Score (p vs placebo)
	3.83 (NS)	3.67 (<0.05)	3.50 (<0.001)	4.00 (NA)
Med	dian sleep quality at	week 2 (1=excellent	t, 7=extremely poor): S	Score (p vs placebo)
	3.75 (NS)	3.63 (NS)	3.50 (<0.001)	4.00 (NA)

Elie, 1999						Quality rating: Fair					
Design:											
Study design:	RCT	DB	Para	llel	Run-in :	7-21 days	Setting:	Multicer	nter		
					Wash out :	7 days	Country:	Canada	and Europe		
Sample:	Numbe	er Scre	ened/	Eligible/	Enrolled	Number Withdrawn	/ Lost to follo	w-up/ A	nalyzed		
			NR/	NR/	615	41	/	NR/	574		

Inclusion criteria:

Met criteria for primary insomnia or insomnia associated with mild nonpsychotic psychiatric disorders based on DSM-III-R; ages 18 to 65 years, men or nonpregnant women who were using a medically acceptable method of contraception, or postmenopausal women. During the month preceding study enrollment, patients must have experienced the following symptoms: a typical sleep latency of 30 minutes or longer, daytime impairment due to sleep disturbance, and either a mean total sleep duration per night of less than or equal to 6.5 hours or prolonged (at least 30 minutes) or frequent (3 or more per night) nocturnal awakenings with difficulty returning to sleep.

Exclusion criteria:

Transient insomnia, situational insomnia, or insomnia associated with sleep-wake schedules (e.g., shift work) or the use of alcohol or drugs. Also excluded were patients with a history or current manifestations of sleep apnea, restless legs syndrome, or a major psychiatric disorder and patients whose raw score on either the Zung Self-Rating Anxiety Scale or the Zung Self-Rating Depression Scale was >49.

Population:	Mear Geno		42.8 years 64% Female	Ethnicity:	99% white <1% black		
Intervention: Drug name	dos	sage	N=	Duration		Primary outcome	Outcome:
Zaleplon	5	mg	113	4 week		\checkmark	Sleep latency
Zaleplon	10	mg	112	4 week			Sleep duration
Zaleplon	20	mg	116	4 week			Number of awakenings
Zolpidem	10	mg	115	4 week			Sleep quality
Placebo	NA	mg	118	4 week			

Efficacy:

leep duration				
Zaleplon 5 mg	Zaleplon 10 mg	Zaleplon 20 mg	Zolpidem 10 mg	Placebo
Median sleep duration	at baseline (minutes)	: Number (p vs place	ebo)	
313 (NS)	331 (NS)	328 (NS)	330 (NS)	334
Median sleep duration	at week 1 (minutes):	Number (p vs placel	00)	
351 (NS)	370 (NS)	370 (p<0.05)	379 (p<0.001)	351
Median sleep duration	at week 2 (minutes):	Number (p vs placel	00)	
359 (NS)	368 (NS)	369 (p<0.05)	387 (p<0.001)	359
Median sleep duration	at week 3 (minutes):	Number (p vs placel	00)	
384 (NS)	371 (NS)	374 (NS)	385 (<0.001)	365
Median sleep duration	at week 4 (minutes):	Number (p vs placel	00)	
372 (NS)	384 (NS)	385 (<0.05)	400 (<0.001)	377

999			Q	uality rating: Fair	
Number of awakenings Zaleplon 5 mg	Zaleplon 10 mg	Zaleplon 20 mg	Zolpidem 10 mg	Baseline	
Median number of awa	kenings at baseline:	Number (p vs placet	00)		
2 (NS)	2 (NS)	2 (NS)	2 (NS)	2	
Median number of awa	kenings at week 1: N	lumber (p vs placebo))		
2 (NS)	2 (NS)	2 (NS)	2 (NS)	2	
Median number of awa	kenings at week 2: N	lumber (p vs placebo))		
2 (NS)	2 (NS)	2 (NS)	2 (NS)	2	
Median number of awa	kenings at week 3: N	lumber (p vs placebo))		
2 (NS)	2 (NS)	1 (NS)	2 (NS)	2	
Median number of awa	kenings at week 4: N	lumber (p vs placebo))		
2 (NS)	2 (NS)	1 (NS)	2 (NS)	2	
Sleep quality (1=excelle Zaleplon 5 mg	nt, 7=extremely poo	or) Zaleplon 20 mg	Zolpidem 10 mg	Baseline	
Sleep quality mean sco	ore at baseline: Score	e (p vs placebo)			
4.6 (NS)	4.5 (NS)	4.5 (NS)	4.4 (NS)	4.5	
Sleep quality mean sc	ore at week 1: Score	(p vs placebo)			
4.1 (NS)	3.9 (p<0.05)	3.8 (p<0.001)	3.7 (p<0.001)	4.1	
Sleep quality mean sc	ore at week 2: Score	(p vs placebo)			
4.0 (NS)	3.9 (NS)	3.8 (NS)	3.6 (p<0.001)	3.9	
Sleep quality mean sco	ore at week 3: Score	(p vs placebo)			
3.8 (NS)	3.8 (NS)	3.6 (NS)	3.6 (p<0.05)	3.9	
Sleep quality mean sco	ore at week 4: Score	(p vs placebo)			
3.8 (NS)	3.7 (NS)	3.6 (NS)	3.4 (p<0.01)	3.8	
Sleep latency Zaleplon 5 mg	Zaleplon 10 mg	Zaleplon 20 mg	Zolpidem 10 mg	placebo	
Time to sleep onset at	week 1 (median, mir	nutes): Number (p vs	placebo)		
42 (0.005)	36 (<0.001)	33 (<0.001)	45 (0.47)	50	
Median time to sleep o	nset at week 2 (med	ian, minutes): Numbe	er (p vs placebo)		
35 (0.002)	32 (0.001)	31 (<0.001)	37 (0.006)	47	
Median time to sleep o	nset at week 3 (med	ian, minutes): Numbe	er (p vs placebo)		
31 (0.004)	30 (0.004)	28 (<0.001)	34 (0.043)	41	
Median time to sleep c	nset at week 4 (med	ian, minutes): Numbe	er (p vs placebo)		
31 (0.093)	28 (0.010)	27 (0.001)	36 (0.054)	36	

y, 2000								Quality	ratin	g: F	air	
sign:												
Study design:	RCT	DB	Para	llel	Run-in :	7 days		Setting:	Multic	ente	r	
					Wash out	: 0 days		Country:	US			
Sample:	Num	oer Scr	eened/	Eligible/	Enrolled	Nun	nber Withdrawn/	Lost to follo	w-up/	Anal	yzed	
			NR/	830/	595		9/		NR/		586	
Inclusion crite	ria:											
psychotic ps medically ac symptoms fr typical sleep	sychiatic ceptatic requent latence night of	ric diso ble met tly (at le cy of 30 of 6.5 h	rders ba hod of c east 3 til) minute lours or	ised on th ontracept mes per v s or more less or pr	ie DSM-III-F ion. At initiaveek, accor , daytime in	R. Women wh al screening, ding to DSM-I npairment due	rimary insomnia no were capable patients had to re III-R) during the r e to sleep disturb nore) or frequent	of becoming eport having month prece ance, and e	pregna experi ding stu ither ar	ant h ence udy e n ave	ad to us d the fol nrollme rage tot	e a llowing nt: a al sleep
schedules (e	cluded e.g., sh	ift-worl	k) or the	use of al	cohol or dru	igs. Also excl	l insomnia, or ins luded were patie sychiatric disord	nts with a hi	story or	· curr	ent	
						s was 50 or gi	reater.	, I			411 0001	eon
	ung an	kiety or		sion self-r	ating scales	s was 50 or gi y: 11% Blac	ck; 3% Hispanic;	<1% Native	Amerio	can; ²		
either the Zu Population:	ung an	kiety or age:	depres	sion self-r rs	ating scales	s was 50 or gi	ck; 3% Hispanic;	<1% Native	Amerio	can; [,]		
either the Zu	ung an: Mear Geno	kiety or age:	depres 42 year	sion self-r rs emale	ating scales	s was 50 or gi y: 11% Blac	ck; 3% Hispanic;	<1% Native		can; ŕ		
either the Zu Population: ervention:	ung an: Mear Geno	kiety or nage: ler:	depres 42 yea 59% Fe	sion self-r rs emale	ating scales Ethnicit	s was 50 or gi y: 11% Blac	ck; 3% Hispanic; ite Primary		:	can; [,]		
either the Zu Population: ervention: Drug name	ung an: Mear Geno dos	kiety or n age: ler: age	depress 42 year 59% Fe N=	sion self-r rs emale	Ethnicit	s was 50 or gi y: 11% Blac	ck; 3% Hispanic; ite Primary outcome	Outcome	ncy	can; ŕ		
either the Zu Population: ervention: Drug name Zaleplon	ung an: Mear Geno dos 5	kiety or nage: ler: age mg	depress 42 year 59% Fe N= 118	sion self-r rs emale	Ethnicit	s was 50 or gi y: 11% Blac	ck; 3% Hispanic; ite Primary outcome	Outcome Sleep late	ncy time		1.5% As	
either the Zu Population: ervention: Drug name Zaleplon Zaleplon	ung an: Mear Geno dos 5 10	kiety or n age: ler: age mg mg	depress 42 year 59% Fe N= 118 119	sion self-r rs emale	Ethnicit Duration 4 week 4 week	s was 50 or gi y: 11% Blac	ck; 3% Hispanic; ite Primary outcome	Outcome Sleep late Total slee	ncy o time f awake		1.5% As	
either the Zu Population: ervention: Drug name Zaleplon Zaleplon Zaleplon Zolpidem	Mean Gence dos 5 10 20 10	mg mg mg mg mg mg	depress 42 year 59% Fe N= 118 119 116 115	sion self-r rs emale	Ethnicit Duration 4 week 4 week 4 week 4 week 4 week	s was 50 or gi y: 11% Blac	ck; 3% Hispanic; ite Primary outcome	Outcome Sleep late Total slee Number o	ncy o time f awake		1.5% As	
either the Zu Population: ervention: Drug name Zaleplon Zaleplon Zaleplon	ung an: Mear Geno dos 5 10 20	mg mg mg mg mg mg	depress 42 year 59% Fe N= 118 119 116	sion self-r rs emale	Ethnicit Duration 4 week 4 week 4 week	s was 50 or gi y: 11% Blac	ck; 3% Hispanic; ite Primary outcome	Outcome Sleep late Total slee Number o	ncy o time f awake		1.5% As	
either the Zu Population: ervention: Drug name Zaleplon Zaleplon Zaleplon Zolpidem	Mean Gence dos 5 10 20 10	mg mg mg mg mg mg	depress 42 year 59% Fe N= 118 119 116 115	sion self-r rs emale	Ethnicit Duration 4 week 4 week 4 week 4 week 4 week	s was 50 or gi y: 11% Blac	ck; 3% Hispanic; ite Primary outcome	Outcome Sleep late Total slee Number o	ncy o time f awake		1.5% As	
either the Zu Population: ervention: Drug name Zaleplon Zaleplon Zaleplon Zolpidem Placebo	Mear Gend dos 5 10 20 10 NA	mg mg mg mg mg mg	depress 42 year 59% Fe N= 118 119 116 115	sion self-r rs emale	Ethnicit Duration 4 week 4 week 4 week 4 week 4 week	s was 50 or gi y: 11% Blac	ck; 3% Hispanic; ite Primary outcome	Outcome Sleep late Total slee Number o	ncy o time f awake		1.5% As	
either the Zu Population: Drug name Zaleplon Zaleplon Zaleplon Zolpidem Placebo ficacy: Sleep later	Mear Gend dos 5 10 20 10 NA	kiety or n age: ler: mg mg mg mg mg mg	depress 42 yea 59% Fe N= 118 119 116 115 118	sion self-r rs emale	Ethnicit Ethnicit Uuration 4 week 4 week 4 week 4 week 4 week 4 week	s was 50 or gi y: 11% Blac	ck; 3% Hispanic; ite Primary outcome	Outcome Sleep late Total slee Number o Sleep qua	ncy o time f awake		1.5% As	
either the Zu Population: ervention: Drug name Zaleplon Zaleplon Zaleplon Zolpidem Placebo ficacy: Sleep later Za	Mear Geno dos 5 10 20 10 NA	xiety or n age: ler: mg mg mg mg mg 5 mg	depress 42 year 59% Fe N= 118 119 116 115 118 Zale	sion self-r rs emale	Ethnicit Ethnicit Duration 4 week 4 week 4 week 4 week 4 week 4 week	s was 50 or gi y: 11% Blac 84% Whi	ck; 3% Hispanic; ite Primary outcome	Outcome Sleep late Total sleep Number o Sleep qua	ncy o time f awake lity		1.5% As	
either the Zu Population: Drug name Zaleplon Zaleplon Zaleplon Zolpidem Placebo ficacy: Sleep later Za Time to s	Mear Geno dos 5 10 20 10 NA	xiety or a age: ler: age mg mg mg mg 5 mg 5 mg	depress 42 year 59% Fe N= 118 119 116 115 118 Zale	sion self-r rs emale	Ethnicit Ethnicit Uuration 4 week 4 week 4 week 4 week 4 week 4 week	s was 50 or gi y: 11% Blac 84% Whi	ck; 3% Hispanic; ite Primary outcome	Outcome Sleep late Total slee Number o Sleep qua	ncy o time f awake lity	ening	1.5% As	

 Time to sleep onset at week 3 (median, minutes): Number (p vs zolpidem 10 mg)

 40.71 (0.323)
 35.71 (0.110)
 30.00 (<0.001)</td>
 44.29
 45.00 (0.236)

 Time to sleep onset at week 4 (median, minutes): Number (p vs zolpidem 10 mg)
 45.63 (0.124)
 35.00 (0.988)
 30.00 (0.037)
 34.29
 47.14 (0.033)

31.67 (<0.001)

46.43

49.29 (0.502)

36.43 (0.183)

43.57 (0.959)

000			Qı	uality rating: Fair	
Total sleep time					
Zaleplon 5 mg	Zaleplon 10 mg	Zaleplon 20 mg	Zolpidem 10 mg	placebo	
Total sleep time at wee	ek 1 (median, minute	s): Number (p vs pla	cebo)		
360.0 (NS)	360.6 (NS)	368.6 (<0.05)	377.1 (<0.001)	346.8	
Total sleep time at wee	ek 2 (median, minute	s): Number (p vs pla	cebo)		
366.4 (NS)	364.3 (NS)	368.6 (NS)	384.4 (<0.05)	360.0	
Total sleep time at wee	ek 3 (median, minute	s): Number (p vs pla	cebo)		
361.4 (NS)	377.1 (NS)	386.8 (<0.05)	392.1 (<0.01)	366.4	
Total sleep time at wee	ek 4 (median, minute	s): Number (p vs pla	cebo)		
360.0 (NS)	376.3 (NS)	377.5 (NS)	392.9 (<0.05)	364.3	
Number of awakenings					
Zaleplon 5 mg	Zaleplon 10 mg	Zaleplon 20 mg	Zolpidem 10 mg	placebo	
Number of awakenings	at week 1 (median):	Number (p vs place	bo)		
1.93 (NS)	1.69 (NS)	1.75 (NS)	1.59 (<0.01)	1.71	
Number of awakenings	at week 2 (median):	Number (p vs place	bo)		
1.67 (NS)	1.69 (NS)	1.50 (<0.001)	1.50 (<0.001)	2.00	
Number of awakenings	at week 3 (median):	Number (p vs place	bo)		
1.71 (NS)	1.71 (NS)	1.43 (<0.05)	1.71 (NS)	1.86	
Number of awakenings	at week 4 (median):	Number (p vs place	bo)		
1.71 (NS)	1.57 (NS)	1.60 (NS)	1.67 (NS)	1.71	
Sleep quality (1=excelle	nt, 7=extremely poo	or)			
Zaleplon 5 mg	Zaleplon 10 mg	Zaleplon 20 mg	Zolpidem 10 mg	placebo	
Sleep quality at week 1	(median): Score (p	vs placebo)			
3.43 (NS)	3.57 (NS)	3.43 (<0.01)	3.38 (<0.001)	3.73	
Sleep quality at week 2	(median): Score (p	vs placebo)			
3.43 (NS)	3.57 (NS)	3.43 (NS)	3.29 (<0.05)	3.57	
Sleep quality at week 3	(median): Score (p	vs placebo)			
3.43 (NS)	3.43 (NS)	3.29 (NS)	3.29 (<0.05)	3.57	
Sleep quality at week 4	(median): Score (p	vs placebo)			
3.38 (NS)	3.54 (NS)	3.29 (NS)	3.15 (<0.05)	3.43	

epracor Stud	ly #1	90-04	5					Quality	ratin	g: Fair	
esign:											
Study design:	RCT	DB	Crossov	/er Ri	un-in :	3-7 days		Setting:	Multic	enter	
				w	ash out :	3-7 days		Country:	US		
Sample:	Num	ber Sc	reened/ Eli	gible/ En	rolled	Nun	nber Withdrawn/	Lost to follo	w-up/	Analyzed	t
			NR/	NR/	64		NR/		NR/	6	4
Inclusion crite											
minutes each	ch nigh east 2 utes, o minute	t to fall nights : r (3) wa	asleep for a >= 20 minut	at least or tes with no	ne month), one of 3 nig	who also n ghts < 15 n	SM-IV (<= 6.5 ho net the following s ninutes, plus (2) e ASO): at least 2 ni	creening P	SG crite	eria: (1) s ne: at lea	leep st 2 nights
NR											
Population:	Mea	n age:	40.6 years	; I	Ethnicity:						
tonyontion	Gen	der:	25% Fema	ale		13 (20.09	%) black				
Drug name	dos	sage	N=	Dui	ration		Primary outcome	Outcome:			
Eszopiclone	1	mg	64	20	day		\checkmark	sleep later	псу		
Eszopiclone	2	mg	64	20	day			sleep effici	iency		
Eszopiclone	2.5	mg	64	20	day			total sleep	time		
Eszopiclone	3	mg	64	20	day			wake after	sleep	onset	
Zolpidem	10	mg	64	20	day			wake time	during	sleep	
Placebo	NA	mg	64	20	day			number of	awake	nings	
Efficacy:											
questionna	aire										
•		ne 1mg	Eszopic	lone 2mg	Eszopicle	one 2.5mg	Eszopiclone 3m	ng Zo	lpidem		
morning	sleepi	ness: N	/lean (p vs p	olacebo)		-	· · ·	-			
e e	3.8 (0.1			0.0670)	44.7 (0.0416)	45.4 (0.0307)	43.5	(0.125	7)	
mornina	sleepi	ness: N	/ledian (SD)		,		. ,				
-	42.3 (2			21.3)	45.3	(19.9)	44.5 (22.8)	43	.3 (22)		
			an (p vs pla	,		. ,	· · ·		. /		
		1068)			50 7 (0 2731)	52 2 (0 0567)	EE 0	(0.001	ר	

46 (<0.05)	56.5 (<0.0001)	53 (<0.0001)	59.9 (<0.0001)	56.5 (<0.0001)
depth of sleep: Median	(p vs placebo)			
47 (<0.05)	58 (<0.0001)	55 (<0.05)	62 (<0.0001)	56 (<0.0001)
quality of sleep: Mediar	n (p vs placebo)			
58 (21.9)	59 (22.4)	51 (23.8)	60 (26.2)	53 (26.4)
daytime ability to function	on: Media (SD)			
58.7 (0.0134)	59.5 (0.0046)	54.1 (0.4606)	56.6 (0.0424)	56.2 (0.0494)
daytime ability to function	on: Mean (p vs place	bo)		
57 (24.6)	56.5 (24.3)	50 (25.6)	56 (27.5)	27.7 (62.5)
daytime alertness: Med	lian (SD)			
52.5 (0.0968)	55.2 (0.0094)	50.7 (0.2731)	52.2 (0.0567)	55.8 (0.0012)
daytime alertness: Mea	in (p vs placebo)			

Sepracor Study #190-045

or Study #190-04	5		Q	uality rating: Fair	
olysomnography					
Eszopiclone 1mg	Eszopiclone 2mg	Eszopiclone 2.5mg	Eszopiclone 3mg	Zolpidem	
number of awakenings	: Mean (p vs placebo	b)			
7.8 (0.4795)	7.6 (0.5983)	7.1 (0.1587)	6.5 (0.0031)	7.2 (0.1838)	
sleep latency (min): Me	ean (p vs placebo)				
25.2 (<0.0001)	20.1 (<0.0001)	18.6 (<0.0001)	18.3 (<0.0001)	16.6 (<0.0001)	
sleep efficiency (%): M	ean (p vs placebo)				
86.8 (<0.05)	88.9 (<0.0001)	89.7 (<0.0001)	89.2 (<0.0001)	88.8 (<0.0001)	
total sleep time (min): I	Median (p vs placebo))			
381.3 (NS)	412.5 (<0.05)	420.0 (<0.05)	420.0 (<0.05)	410 (<0.05)	
wake after sleep onset	(min): Mean (p vs pl	acebo)			
41.4 (NS)	36.0 (NS)	33.1 (<0.05)	35.9 (<0.05)	39.3 (NS)	
wake time during sleep	o (min): Median (p vs	placebo)			
28 (NS)	26 (NS)	25.3 (<0.05)	23.3 (<0.05)	24.7 (NS)	
number of awakenings	: Median (SD)				
7.5 (3.5)	6.5 (4.5)	7.0 (4.4)	5.3 (4.4)	7.5 (3.5)	
sleep latency (min): Me	edian (SD)				
16.8 (24.1)	15.5 (17.6)	13.8 (18.7)	13.1 (19.6)	13.1 (14.4)	
sleep efficiency (%): M	edian (SD)				
88.6 (7.1)	89.6 (7.0)	90.4 (6.4)	92.0 (8.1)	89.1 (6.3)	
wake after sleep onset	(min): Median (SD)				
35.5 (26.5)	30.5 (25)	29.5 (23.2)	25.3 (31.7)	30.5 (28.5)	

aner, 2005								Quality rating: Poor
sign:								
Study design:	RCT	DB	Cross	over	Run-in :	NR		Setting: Single Center
					Wash out :	•		Country: France
Sample:	Num	ber Sc	reened/ E	0		Nun		Lost to follow-up/ Analyzed
Inclusion criter			NR/	NR/	23		NR/	NR/ 23
To be include during the me	ed in t onth p for at	orecedi least fo	ng the scr our nights	eening vi each wee	sit, at least t ek, (2) duratio	wo of the th	ree following syn after sleep onset	ry insomnia (307.42) and have had, nptoms: (1) sleep-onset latency greater of 60 min or more for at least four
Exclusion crite	ria:							
Population:	Mea	n age:	38.8 yea	rs	Ethnicity:	NR		
	Gen	der:	61% Fen	nale				
ervention: Drug name	dos	sage	N=	D	ouration		Primary outcome	Outcome:
Zolpidem	10	mg	23		8 day			ease to get asleep
Zopiclone	7.5	mg	23		8 day			sleep quality
Lormetazepam	1	mg	23		8 day			awakening from sleep
Placebo	NA	mg	23		8 day			behavior after waking
								driving abilities
	Zolpid et asl		Zoj core (p vs	piclone placebo)		tazepam	Placebo	
•	.4 (<0	•	u.	(<0.05)		(<0.05)	45.8 (NA)	
sleep qua	ality: S	core (p	o vs placel	00)				
	, 1) 8.8			, (<0.01)	70.0	(<0.05)	61.1 (Na)	
awakenin	g fror	n sleep	: Score (p	vs place	bo)			
6	6.1 (N	NS)	62.	6 (NS)	70.6	6 (NS)	65.7 (NA)	
behavior	after v	waking	: Score (p	vs placel	00)			
6	i3.1 (N	NS)	62	5 (NS)	69.2	2 (NS)	63.7 (NA)	
Driving abi	lities							
Z	Zolpid	em	Zoj	oiclone	Lorme	tazepam	Placebo	
absolute	speed	l devia	tion: Score	e (p vs pla	acebo)			
1:	23.3 (NS)	122	.8 (NS)	125.	1 (NS)	123.7 (MA)	
speed lim	it dev	iation:	Score (p v	s placeb	o)			
-	5.7 (N	1S)	-5.	9 (NS)	-3.0	(<0.05)	-4.6 (NA)	
Ideal rout	e dev	iation:	Score (p v	s placeb	0)			
().17 (NS)	-0.3	81 (NS)	-0.1	5 (NS)	-0.18 (NA)	
-(
	f colli	sions:	Score (p v	s placebo))			

sutsui, 2001							Quality	rating:	Fair
esign:									
Study design:	RCT	DB	Parallel	Run-in :	0 days		Setting:	Multicen	ter
				Wash out :	7 days		Country:	Japan	
Sample:	Numb	er Scr	eened/ Elig	ible/ Enrolled	Numbe	er Withdrawn/	Lost to follo	w-up/ Ar	nalyzed
			NR/	NR/ 479		77/		NR/	428
Inclusion crite									
				a (I.e., experiencin fficulties more thar				ore than a	a month in initiating
unstable syr severe respi intelligence. benzodiazep dose exceed likelihood of	nia, dep mptoms iratory c Sympt bines ar ding the pregna	s, orgar dysfund toms ir nd ana e stand ancy, b	nic cerebral ction, myast nterfering wi logous drug lard single d reast feedin	pression, clinically disorders (diagnos henia gravis or act th sleep (e.g., pain s, zopiclone intake ose, history of drug g, participation in o ator's judgment.	ed or suspecte ute narrow-ang , fever, diarrhe within 3 montl g dependence,	ed), serious he le glaucoma a a, pollakiuria, hs prior to the operation of r	art, liver, kio nd cognitive cough), hyp study, requi nachinery in	dney, or bl disorders ersensitiv rement fo volving ris	lood disorders, s or impaired ity to r hypnotics at a sk, pregnancy or
Population:	Mean	age:	42.2 years	Ethnicity	NR				
	Gend		58% Femal	le					
tervention: Drug name	dosa	age	N=	Duration		Primary outcome	Outcome:		
Zolpidem	10	mg	209	2 week			Global imp	rovement	of sleep disorders
-		ent of	219 sleep disor				Patient's ir	npression	of treatment efficac
fficacy: Global imp	Provem Zolpide rated by	ent of em by the ir	sleep diso Zopic	r ders Ilone as "markedly impro	oved": (%)		Patient's ir	npression	
fficacy: Global imp	Zolpide rated by 18.7	ent of em by the ir	sleep disor Zopic nvestigator a 16	r ders Ilone as "markedly impro			Patient's ir	npression	P: NS
fficacy: Global imp	rovem Zolpide rated by 18.7 rated by	ent of em by the ir	sleep diso r Zopic nvestigator a 16 nvestigator a	r ders Ilone as "markedly impro .4 as "moderately imp			Patient's ir	npression	P: NS
fficacy: Global imp	Zolpide rated by 18.7	ent of em by the ir	sleep disor Zopic nvestigator a 16	r ders Ilone as "markedly impro .4 as "moderately imp			Patient's ir	npression	
fficacy: Global imp Patients Patients	rovem Zolpide rated b 18.7 rated b 49.3	ent of em by the ir	sleep disor Zopic nvestigator a 16 nvestigator a 45	r ders Ilone as "markedly impro .4 as "moderately imp	proved": (%)		Patient's ir	npression	P: NS
fficacy: Global imp Patients Patients	rovem Zolpide rated b 18.7 rated b 49.3	ent of em by the ir	sleep disor Zopic nvestigator a 16 nvestigator a 45	r ders Islone as "markedly impro .4 as "moderately imp .2 as "slightly improve	proved": (%)		Patient's ir	npression	P: NS
fficacy: Global imp Patients Patients Patients	rated b 18.7 rated b 49.3 rated b 26.8	ent of em by the ir	sleep disor Zopic nvestigator a 16 nvestigator a 45 nvestigator a 31	rders clone as "markedly impro .4 as "moderately imp .2 as "slightly improve .1	oroved": (%) ed": (%)		Patient's ir	npression	P: NS P: NS
fficacy: Global imp Patients Patients Patients	rated b 18.7 rated b 49.3 rated b 26.8	ent of em by the ir	sleep disor Zopic nvestigator a 16 nvestigator a 45 nvestigator a 31	r ders Ione as "markedly impro .4 as "moderately imp .2 as "slightly improve .1 as "unchanged": (%	oroved": (%) ed": (%)		Patient's ir	npression	P: NS P: NS
fficacy: Global imp Patients Patients Patients Patients Patients in	rated by 18.7 rated by 49.3 rated by 26.8 rated by 5.3	ent of my the ir by the ir by the ir by the ir by the ir	sleep disor Zopic nvestigator a 16 nvestigator a 45 nvestigator a 31 nvestigator a 6.	rders done as "markedly impro .4 as "moderately imp .2 as "slightly improve .1 as "unchanged": (% 4 efficacy	oroved": (%) ed": (%)		Patient's ir	npression	P: NS P: NS P: NS
fficacy: Global imp Patients Patients Patients Patients Patients in	rated b 18.7 rated b 49.3 rated b 26.8 rated b 5.3 npress Zolpide	ent of em by the ir by the ir by the ir by the ir sion of em	sleep disor Zopic nvestigator a 16 nvestigator a 45 nvestigator a 31 nvestigator a 6. treatment o Zopic	rders done as "markedly impro .4 as "moderately imp .2 as "slightly improve .1 as "unchanged": (% 4 efficacy	oroved": (%) ed": (%) %)		Patient's ir	npression	P: NS P: NS P: NS
fficacy: Global imp Patients Patients Patients Patients Patients in	rated b 18.7 rated b 49.3 rated b 26.8 rated b 5.3 npress Zolpide	eent of em by the ir by the ir by the ir by the ir sion of em the treat	sleep disor Zopic nvestigator a 16 nvestigator a 45 nvestigator a 31 nvestigator a 6. treatment o Zopic	rders clone as "markedly impro .4 as "moderately imp .2 as "slightly improve .1 as "unchanged": (% 4 efficacy clone markedly effective":	oroved": (%) ed": (%) %)		Patient's ir	npression	P: NS P: NS P: NS
fficacy: Global imp Patients Patients Patients Patients in Patients in Patients	rated by 18.7 rated by 49.3 rated by 26.8 rated by 5.3 mpress Zolpide rating th 18.2	eent of em by the ir by the ir by the ir by the ir sion of em the treat	sleep disor Zopic nvestigator a 16 nvestigator a 45 nvestigator a 31 nvestigator a 6. treatment o Zopic atment as "m	rders clone as "markedly impro- .4 as "moderately imp .2 as "slightly improve .1 as "unchanged": (% 4 efficacy clone markedly effective": .0	oroved": (%) ed": (%) %)		Patient's ir	npression	P: NS P: NS P: NS P: NS
fficacy: Global imp Patients Patients Patients Patients in Patients in Patients	rated by 18.7 rated by 49.3 rated by 26.8 rated by 5.3 npress Zolpide rating th 18.2	eent of em by the ir by the ir by the ir by the ir by the ir by the ir by the treat	sleep disor Zopic nvestigator a 16 nvestigator a 45 nvestigator a 31 nvestigator a 6. treatment as "m 16 atment as "m	rders clone as "markedly impro- .4 as "moderately imp .2 as "slightly improve .1 as "unchanged": (% 4 efficacy clone markedly effective": .0	oroved": (%) ed": (%) %)		Patient's ir	npression	P: NS P: NS P: NS P: NS P: NS
fficacy: Global imp Patients Patients Patients Patients Patients Patients Patients	rated by 18.7 rated by 49.3 rated by 26.8 rated by 5.3 mpress Zolpide rating th 18.2 rating th 46.4	eent of em by the in by the in by the in by the in en sion of em the treat	sleep disor Zopic nvestigator a 16 nvestigator a 45 nvestigator a 31 nvestigator a 6. treatment a Zopic atment as "m 16 atment as "m 45	rders lone as "markedly impro .4 as "moderately imp .2 as "slightly improve .1 as "unchanged": (% 4 efficacy clone harkedly effective": .0 hoderately effective .2	oroved": (%) od": (%) (%) (%)		Patient's ir	npression	P: NS P: NS P: NS P: NS
fficacy: Global imp Patients Patients Patients Patients Patients Patients Patients	rated by 18.7 rated by 49.3 rated by 26.8 rated by 26.8 rated by 5.3 mpress Zolpide rating th 18.2 rating th 46.4	eent of em by the ir by the ir by the ir by the ir sion of em the treat the treat	sleep disor Zopic nvestigator a 16 nvestigator a 45 nvestigator a 31 nvestigator a 6. treatment a Zopic atment as "m 16 atment as "m 45	rders clone as "markedly impro- .4 as "moderately imp .2 as "slightly improve .1 as "unchanged": (% 4 efficacy clone markedly effective": .0	oroved": (%) od": (%) (%) (%)		Patient's ir	npression	P: NS P: NS P: NS P: NS P: NS P: NS
fficacy: Global imp Patients Patients Patients Patients Patients Patients Patients	rated by 18.7 rated by 49.3 rated by 26.8 rated by 5.3 mpress Zolpide rating th 18.2 rating th 46.4	eent of em by the ir by the ir by the ir by the ir sion of em the treat the treat	sleep disor Zopic nvestigator a 16 nvestigator a 45 nvestigator a 31 nvestigator a 6. treatment a Zopic atment as "m 16 atment as "m 45	rders clone as "markedly impro- .4 as "moderately imp .2 as "slightly improve .1 as "unchanged": (% 4 efficacy clone narkedly effective": .0 noderately effective": (%	oroved": (%) od": (%) (%) (%)		Patient's ir	npression	P: NS P: NS P: NS P: NS P: NS
fficacy: Global imp Patients Patients Patients Patients Patients Patients Patients Patients Patients	rated by 18.7 rated by 49.3 rated by 26.8 rated by 26.8 rated by 5.3 mpress Zolpide rating th 18.2 rating th 46.4 rating th 29.7	eent of my the ir by the ir by the ir by the ir by the ir sion of em the treat the treat	sleep disor Zopic nvestigator a 16 nvestigator a 31 nvestigator a 6. treatment as "m 16 atment as "m 45 atment as "s 33	rders clone as "markedly impro- .4 as "moderately imp .2 as "slightly improve .1 as "unchanged": (% 4 efficacy clone narkedly effective": .0 noderately effective": (%	oroved": (%) od": (%) (%) (%)		Patient's ir	npression	P: NS P: NS P: NS P: NS P: NS P: NS

coli-Israel, 1	999					Qualit	y rating:	: Fair
sign:								
Study design:	RCT	DB	Parallel	Run-in : Wash out :	7 days 7-21 days	Setting: Country		enter
Sample:	Num	ber Scr	-	jible/ Enrolled 551/ 549		ndrawn/ Lost to fo		Analyzed 549
Inclusion crite	ria:							
IV at study e	entry.	This his	story must ha	romen who had at le ave included a usua a usual total sleep ti	al sleep latency of 3	0 minutes or more	mnia as de and either	fined by the DSM- r 3 or more
Depression restless legs	medica scales s syndi results	admin rome, if	istered durin their sleep	uld affect the study og screening were > complaint was cons nations or routine cli	=50. Patients were idered to be secon	also excluded if t dary to nicotine us	hey had sle	eep apnea or study physician
Population:	Mear Gene		72 years 58% Femal	-	3.3% Black; 1.6%	Hispanic; 1.3 Asi	an; 93.6%	White
ervention: Drug name		sage	N=	Duration				
Placebo	NA	mg	107	2 week				
Zaleplon	5	mg	166	2 week				
	10	mg	165	2 week				
Zaleplon				0				
Zaleplon Zolpidem	5	mg	111	2 week				
Zolpidem	5	mg 		2 week				
	5	mg 		2 week				
Zolpidem bound: rebound	5 eplon		Zaleplon		m 5mg Pla	серо		
Zolpidem bound: rebound Zal	eplon	5 5mg	Zaleplon	10mg Zolpide	•		placebo)	
Zolpidem bound: rebound Zal rebound in	eplon	5mg nia: slee	Zaleplon	10mg Zolpide	y 1 (minutes, medi		placebo)	
Zolpidem bound: rebound Zal	eplon nsomn 30 (NS	5mg nia: slee S)	Zaleplon ep latency or 45 (N	10mg Zolpide	y 1 (minutes, medi 0.01) 44	an): Number (p vs (NA)	. ,	er (p vs placebo)
Zolpidem bound: rebound Zal rebound in rebound in	eplon nsomn 30 (NS	5mg nia: slee S)	Zaleplon ep latency or 45 (N	10mg Zolpide n discontinuation da IS) 60 (< total sleep time on d	y 1 (minutes, medi 0.01) 44 discontinuation day	an): Number (p vs (NA)	. ,	er (p vs placebo)
Zolpidem bound: rebound Zal rebound in rebound in 3	eplon nsomr 30 (NS nsomr 330 (NS	5mg nia: slee S) nia: slee S)	Zaleplon ep latency or 45 (N ep duration, f 315 (<0	10mg Zolpide n discontinuation da IS) 60 (< total sleep time on d	y 1 (minutes, medi 0.01) 44 discontinuation day 0.001) 317.	an): Number (p vs (NA) 1 (minutes, media 50 (NA)	in): Numbe	er (p vs placebo)

Elie, 1999							Quality	rating	g: Fair
Design:									
Study design:	RCT	DB	Para	llel	Run-in :	7-21 days	Setting:	Multio	center
					Wash out :	7 days	Country:	Cana	da and Europe
Sample:	Numbe	er Scre	ened/	Eligible/	Enrolled	Number Withdrawn/	Lost to follo	w-up/	Analyzed
			NR/	NR/	615	41/		NR/	574

Inclusion criteria:

Met criteria for primary insomnia or insomnia associated with mild nonpsychotic psychiatric disorders based on DSM-III-R; ages 18 to 65 years, men or nonpregnant women who were using a medically acceptable method of contraception, or postmenopausal women. During the month preceding study enrollment, patients must have experienced the following symptoms: a typical sleep latency of 30 minutes or longer, daytime impairment due to sleep disturbance, and either a mean total sleep duration per night of less than or equal to 6.5 hours or prolonged (at least 30 minutes) or frequent (3 or more per night) nocturnal awakenings with difficulty returning to sleep.

Exclusion criteria:

Transient insomnia, situational insomnia, or insomnia associated with sleep-wake schedules (e.g., shift work) or the use of alcohol or drugs. Also excluded were patients with a history or current manifestations of sleep apnea, restless legs syndrome, or a major psychiatric disorder and patients whose raw score on either the Zung Self-Rating Anxiety Scale or the Zung Self-Rating Depression Scale was >49.

Population:	Mear Gene	n age: der:	42.8 years 64% Female	Ethnicity:	99% white <1% black
Drug name	dos	sage	N=	Duration	
Zaleplon	5	mg	113	4 week	
Zaleplon	10	mg	112	4 week	
Zaleplon	20	mg	116	4 week	
Zolpidem	10	mg	115	4 week	
Placebo	NA	mg	118	4 week	

Rebound:

Rebound insomnia

Zaleplon 5mg	Zaleplon 10mg	Zaleplon 20mg	Zolpidem 10mg
Rebound: Sleep latency	y on night +1 (media	an, minutes): Numbe	er (p vs placebo)
51.7 (NS)	57.6 (NS)	50.4 (NS)	91.6 (<0.001)
Rebound: Sleep duration	on on night +1 (media	an, minutes): Numbe	er (p vs placebo)
344.3 (NS)	349.6 (NS)	339.2 (NS)	324.7 (<0.05)
Rebound: Number of a	wakenings on night +	-1 (median): Numbe	r (p vs placebo)
2.3 (NS)	2.0 (NS)	1.8 (NS)	2.6 (<0.01)

Fry, 2000							Quality	rating:	Fair	
Design:										
Study design:	RCT	DB	Para	allel	Run-in :	7 days	Setting:	Multicer	nter	
					Wash out :	0 days	Country:	US		
Sample:	Numbe	er Scre	ened/	Eligible/	Enrolled	Number W	/ithdrawn/ Lost to foll	ow-up/ A	nalyzed	
			NR/	830/	595		9/	NR/	586	
Inclusion crite	ria [.]									

Inclusion criteria:

Men or non-pregnant women, 18-65 years who met the criteria for primary insomnia or insomnia associated with mild nonpsychotic psychiatric disorders based on the DSM-III-R. Women who were capable of becoming pregnant had to use a medically acceptable method of contraception. At initial screening, patients had to report having experienced the following symptoms frequently (at least 3 times per week, according to DSM-III-R) during the month preceding study enrollment: a typical sleep latency of 30 minutes or more, daytime impairment due to sleep disturbance, and either an average total sleep duration per night of 6.5 hours or less or prolonged (30 minutes or more) or frequent nocturnal awakenings (three or more per night) with difficulty returning to sleep.

Exclusion criteria:

Patients excluded if they experienced transient insomnia, situational insomnia, or insomnia associated with sleep-wake schedules (e.g., shift-work) or the use of alcohol or drugs. Also excluded were patients with a history or current manifestations of sleep apnea, restless legs syndrome, or a major psychiatric disorder, and patients whose raw score on either the Zung anxiety or depression self-rating scales was 50 or greater.

Population:	Mea Gen		42 years 59% Female	Ethnicity:	11% Black; 3% Hispanic; <1% Native American; 1.5% Asian; <1% Othe 84% White
Drug name	dos	sage	N=	Duration	
Zaleplon	5	mg	118	4 week	
Zaleplon	10	mg	119	4 week	
Zaleplon	20	mg	116	4 week	
Zolpidem	10	mg	115	4 week	
Placebo	NA	mg	118	4 week	

Rebound

Zaleplon 5mg	Zaleplon 10mg	Zaleplon 20mg	Zolpidem 10mg	
rebound : Sleep latency	on discontinuation r	night 1 (minutes, med	dian): Number (p vs placebo)	
45 (NS)	40 (NS)	30 (NS)	60 (<0.01)	
rebound : Number of av	vakenings on discont	tinuation night 1: Nur	nber (p vs placebo)	
2 (NS)	2 (NS)	2 (NS)	2 (<0.05)	
rebound : Sleep duratio	n on discontinuation	night 1 (median, mir	nutes): Number (p vs placebo)	
360 (NS)	360 (NS)	360 (NS)	330 (<0.001)	

utsui, 2001					G	Quality	rating:	Fair
esign:								
Study design:	RCT	DB Parallel	Run-in :	0 days	S	etting:	Multicent	ter
			Wash out :	7 days	C	ountry:	Japan	
Sample:	Number	Screened/ Elig	ible/ Enrolled	Number	Withdrawn/ Lo	ost to follo	w-up/ An	alyzed
		NR/	NR/ 479		77/		NR/	428
Inclusion crite	ria:							
			a (I.e., experiencing fficulties more than				ore than a	month in initiating
severe respi intelligence. benzodiazer	ratory dys Symptom bines and	function, myast is interfering wit analogous drug andard single d	disorders (diagnos henia gravis or acu th sleep (e.g., pain, s, zopiclone intake ose, history of drug	te narrow-angle fever, diarrhea, within 3 months	glaucoma and pollakiuria, co prior to the stu	cognitive ugh), hyp udy, requi	disorders ersensitivi rement for	s or impaired ty to r hypnotics at a
likelihood of			g, participation in o	ther clinical trials				
likelihood of for the study	according	to the investig	ator's judgment.					
likelihood of	according Mean ag	to the investig e: 42.2 years	ator's judgment. Ethnicity:					
likelihood of for the study	according	to the investig e: 42.2 years	ator's judgment. Ethnicity:					
likelihood of for the study Population:	according Mean ag	to the investig e: 42.2 years 58% Femal	ator's judgment. Ethnicity:					
likelihood of for the study Population: tervention:	According Mean ag Gender:	to the investig le: 42.2 years 58% Femal e N=	ator's judgment. Ethnicity: le					
likelihood of for the study Population: tervention: Drug name	Mean ag Gender: dosage	y to the investig 10: 42.2 years 58% Femal 209	ator's judgment. Ethnicity: le Duration					
likelihood of for the study Population: tervention: Drug name Zolpidem	according Mean ag Gender: dosage	y to the investig 10: 42.2 years 58% Femal 209	ator's judgment. Ethnicity: le Duration 2 week					
likelihood of for the study Population: tervention: Drug name Zolpidem Zopiclone ebound:	according Mean ag Gender: dosage 10 mg 7.5 mg	y to the investig 10: 42.2 years 58% Femal 209	ator's judgment. Ethnicity: le Duration 2 week					
likelihood of for the study Population: tervention: Drug name Zolpidem Zopiclone ebound: Rebound in	according Mean ag Gender: dosage 10 mg 7.5 mg	y to the investig 10: 42.2 years 58% Femal 209 219	ator's judgment. Ethnicity: le Duration 2 week 2 week					
likelihood of for the study Population: tervention: Drug name Zolpidem Zopiclone ebound: Rebound in Z	according Mean ag Gender: dosage 10 mg 7.5 mg somnia: s	to the investig 10: 42.2 years 58% Femal 209 219 31eep latency Zopick	ator's judgment. Ethnicity: le Duration 2 week 2 week	NR	s within the pas	st 6 month	ns, and ina	appropriateness
likelihood of for the study Population: tervention: Drug name Zolpidem Zopiclone ebound: Rebound in Z	according Mean ag Gender: dosage 10 mg 7.5 mg somnia: s	to the investig 10: 42.2 years 58% Femal 209 219 31eep latency Zopick	ator's judgment. Ethnicity: le <u>Duration</u> 2 week 2 week 2 week one	NR	s within the pas	st 6 month	ns, and ina	appropriateness

ain, 2003						C	Quality	rating	: Fa	air	
esign:											
Study design:	RCT	DB	Crossover	Run-in :	0 days	S	etting:	Single	Cen	ter	
				Wash out :	0 days	C	country:	Franc	е		
Sample:	Numb	er Scr	eened/ Eligibl	e/ Enrolled	Number V	Vithdrawn/ Lo	ost to follo	w-up/	Analy	/zed	
			NR/ NI	R/ 53		0/		0/		53	
Inclusion crite											
					n judged compati ne prescription of						S
patients who drugs the da	o followe ay befor	ed a co e inclu	ontinuous treat ision; patients	tment with the sa who took hypnot	ny secondary ins ame hypnotic for r ic drugs the day l	nore than six pefore inclusio	months; pon, patien	oatients ts curre	who ntly ti	took hypno reated by	
					eatment including	antidepressa	ints, neur	oleptics	, anx	iolytics, H1	l
	es, bark	oiturat	es or hypnotics	3.	-	l antidepressa	ints, neur	oleptics	, anxi	iolytics, H1	I
antihistamin	es, bark	oiturate age:			-	j antidepressa	ints, neur	oleptics	, anxi	iolytics, H1	I
antihistamin Population: tervention:	es, barb Mean Gend	age: er:	es or hypnotics 52 years 49% Female	S. Ethnicity:	-	ı antidepressa	ints, neur	oleptics	, anxi	iolytics, H1	I
antihistamin Population:	es, bart Mean	age: er:	es or hypnotics 52 years	3.	-	ı antidepressa	ints, neur	oleptics	, anxi	iolytics, H1	I
antihistamin Population: tervention:	es, bark Mean Gend dosa	age: er:	es or hypnotics 52 years 49% Female	S. Ethnicity:	-	ı antidepressa	nts, neur	oleptics	, anxi	iolytics, H1	I
antihistamin Population: tervention: Drug name	es, bark Mean Gend dosa 10	age: er: age	es or hypnotics 52 years 49% Female N=	Ethnicity:	-	ı antidepressa	nts, neur	oleptics	, anxi	iolytics, H1	I
antihistamin Population: tervention: Drug name Zolpidem	es, bart Mean Gend dosa 10	age: er: age mg	es or hypnotics 52 years 49% Female N= 53	Ethnicity: Duration 1 day	-	ı antidepressa	nts, neur	oleptics	, anxi	iolytics, H1	I
antihistamin Population: tervention: Drug name Zolpidem Zaleplon	es, bart Mean Gend dosa 10 10 ts:	age: er: age mg mg	es or hypnotics 52 years 49% Female N= 53 53	Ethnicity: Duration 1 day	-	ı antidepressa	nts, neur	oleptics	, anxi	iolytics, H1	I
antihistamin Population: tervention: Drug name Zolpidem Zaleplon dverse Even Adverse ev	es, bart Mean Gend dosa 10 10 ts:	age: er: age mg mg ported	es or hypnotics 52 years 49% Female N= 53 53	Ethnicity: Duration 1 day 1 day	-	ı antidepressa	nts, neur	oleptics	, anxi	iolytics, H1	I
antihistamin Population: tervention: Drug name Zolpidem Zaleplon dverse Even Adverse ev	es, bart Mean Gend 10 10 ts: ents re Zolpiden	age: er: age mg mg porteo	es or hypnotics 52 years 49% Female N= 53 53 53 Zaleplor	Ethnicity: Duration 1 day 1 day	-	ı antidepressa	nts, neur	oleptics	, anxi	iolytics, H1	

Total withdrawals: none

Withdrawals due to adverse events: none

Ancoli-Israel, 1	999						Quality	rating:	Fair	
Design:										
Study design:	RCT	DB	Para	llel	Run-in :	7 days	Setting:	Multice	nter	
					Wash out :	7-21 days	Country:	US		
Sample:	Numbe	er Scre	ened/	Eligible/	Enrolled	Number Withdrawn/	Lost to follo	w-up/ A	nalyzed	
			1224/	551/	549	2/		NR/	549	
Inclusion crite	ria:									

Elderly (65 years or older) men and women who had at least a 3-month history of primary insomnia as defined by the DSM-IV at study entry. This history must have included a usual sleep latency of 30 minutes or more and either 3 or more awakenings per night on average or a usual total sleep time of <= 6.5 hours.

Exclusion criteria:

Preexisting medical condition that would affect the study results or if raw scores on the Zung Self-Rating Anxiety and Depression scales administered during screening were >=50. Patients were also excluded if they had sleep apnea or restless legs syndrome, if their sleep complaint was considered to be secondary to nicotine use, or if the study physician judged that results of physical examinations or routine clinical laboratory assessments included a clinically important abnormality.

Population:	Mean age: Gender:	72 years 58% Female	Ethnicity:	3.3% Black; 1.6% Hispanic; 1.3 Asian; 93.6% White
Intervention: Drug name	dosage	N=	Duration	
Placebo	NA mg	107	2 week	
Zaleplon	5 mg	166	2 week	
Zaleplon	10 mg	165	2 week	
Zolpidem	5 mg	111	2 week	

Adverse Events:

Adverse events

Placebo	Zaleplon 5 mg	Zaleplon 10 mg	Zolpidem 5 mg	
y of treatment-	-emergent adverse ev	ents: %		
56	56	59	63	P: NS
erse events: %	o (p vs placebo)			
14	NR	NR	25 (P<0.05)	
nce: % (p vs pl	acebo)			
2	4	NR	10 (p<0.05)	
	y of treatment 56 erse events: % 14 nce: % (p vs pl	y of treatment-emergent adverse ev 56 56 erse events: % (p vs placebo) 14 NR nce: % (p vs placebo)	y of treatment-emergent adverse events: % 56 56 59 erse events: % (p vs placebo) 14 NR NR nce: % (p vs placebo)	y of treatment-emergent adverse events: % 56 56 59 63 erse events: % (p vs placebo) 14 NR NR 25 (P<0.05) nce: % (p vs placebo)

Total withdrawals: NR

Withdrawals due to adverse events: NR

Elie, 1999							Quality	rating	g: Fair	
Design:										
Study design:	RCT	DB	Paral	llel	Run-in :	7-21 days	Setting:	Multic	center	
					Wash out :	7 days	Country:	Cana	da and Europe	
Sample:	Numbe	er Scre	ened/	Eligible/	Enrolled	Number Withdrawn	/ Lost to follo	w-up/	Analyzed	
			NR/	NR/	615	41,	/	NR/	574	

Inclusion criteria:

Met criteria for primary insomnia or insomnia associated with mild nonpsychotic psychiatric disorders based on DSM-III-R; ages 18 to 65 years, men or nonpregnant women who were using a medically acceptable method of contraception, or postmenopausal women. During the month preceding study enrollment, patients must have experienced the following symptoms: a typical sleep latency of 30 minutes or longer, daytime impairment due to sleep disturbance, and either a mean total sleep duration per night of less than or equal to 6.5 hours or prolonged (at least 30 minutes) or frequent (3 or more per night) nocturnal awakenings with difficulty returning to sleep.

Exclusion criteria:

Transient insomnia, situational insomnia, or insomnia associated with sleep-wake schedules (e.g., shift work) or the use of alcohol or drugs. Also excluded were patients with a history or current manifestations of sleep apnea, restless legs syndrome, or a major psychiatric disorder and patients whose raw score on either the Zung Self-Rating Anxiety Scale or the Zung Self-Rating Depression Scale was >49.

In	Population:	Mear Geno	n age: der:	42.8 years 64% Female	Ethnicity:	99% white <1% black
	Drug name	dos	sage	N=	Duration	
	Zaleplon	5	mg	113	4 week	
	Zaleplon	10	mg	112	4 week	
	Zaleplon	20	mg	116	4 week	
	Zolpidem	10	mg	115	4 week	
	Placebo	NA	mg	118	4 week	

Adverse Events:

Withdrawal effects

Zolpidem 10 mg	Zaleplon 10 mg			
Incidence of 3 or more n	ew withdrawal sympt	oms after discontinu	ation of treatment: NR (p vs placeb	o)
NR (<0.05)	NR (NS)			
Adverse events				
Zaleplon 5 mg	Zaleplon 10 mg	Zaleplon 20 mg	Zolpidem 10 mg	
Patients with treatment-e	emergent adverse ev	ents: % (N)		
59 (71)	73 (87)	61 (76)	64 (78)	
Total withdrawals NR				
Withdrawals due to adv	erse events			
Zaleplon 5 mg	Zaleplon 10 mg	Zaleplon 20 mg	Zolpidem 10 mg	
Withdrawals due to adve	erse events: % (N)			
2 (2)	6 (7)	2 (2)	6 (7)	

Fry, 2000							Quality	rating	: Fair	
Design:										
Study design:	RCT	DB	Paral	lel	Run-in :	7 days	Setting:	Multice	enter	
					Wash out :	0 days	Country:	US		
Sample:	Numbe	er Scree	ened/	Eligible/	Enrolled	Number W	thdrawn/ Lost to foll	ow-up/ A	Analyzed	
			NR/	830/	595		9/	NR/	586	

Inclusion criteria:

Men or non-pregnant women, 18-65 years who met the criteria for primary insomnia or insomnia associated with mild nonpsychotic psychiatric disorders based on the DSM-III-R. Women who were capable of becoming pregnant had to use a medically acceptable method of contraception. At initial screening, patients had to report having experienced the following symptoms frequently (at least 3 times per week, according to DSM-III-R) during the month preceding study enrollment: a typical sleep latency of 30 minutes or more, daytime impairment due to sleep disturbance, and either an average total sleep duration per night of 6.5 hours or less or prolonged (30 minutes or more) or frequent nocturnal awakenings (three or more per night) with difficulty returning to sleep.

Exclusion criteria:

Patients excluded if they experienced transient insomnia, situational insomnia, or insomnia associated with sleep-wake schedules (e.g., shift-work) or the use of alcohol or drugs. Also excluded were patients with a history or current manifestations of sleep apnea, restless legs syndrome, or a major psychiatric disorder, and patients whose raw score on either the Zung anxiety or depression self-rating scales was 50 or greater.

Population:	Mea Gen		42 years 59% Female	Ethnicity:	11% Black; 3% Hispanic; <1% Native American; 1.5% Asian; <1% Oth 84% White
tervention: Drug name	dos	sage	N=	Duration	
Zaleplon	5	mg	118	4 week	
Zaleplon	10	mg	119	4 week	
Zaleplon	20	mg	116	4 week	
Zolpidem	10	mg	115	4 week	
Placebo	NA	mg	118	4 week	

	7	7	7	
Zaleplon 5 mg	Zaleplon 10 mg	Zaleplon 20 mg	Zolpidem 10 mg	
Total withdrawals: %				
16.9	15.0	14.5	17.2	
Vithdrawals due to adv	erse effects			
	7	Zaleplon 20mg	Zolpidem 10mg	
Zaleplon 5mg	Zaleplon 10mg	Zalepion Zong		
Zaleplon 5mg Withdrawals due to adve				

emoine, 1995							Quali	ty rating:	Fair	
Design:										
Study design:	RCT	DB I	Paralle	əl	Run-in :	0 days	Setting	g: Multice	nter	
					Wash out :	0 days	Count	ry: France		
Sample:	Number	Screen	ed/ E	ligible/	Enrolled	Number With	drawn/ Lost to	follow-up/ A	nalyzed	
		1	IR/	NR/	394		15/	2/	390	
Inclusion crite	ria:									
Males and f zolpidem 10 Exclusion crite) mg.	ed 18 t	o 65 y	ears wh	no were treate	d for insomnia for at	least 3 months	with zopiclor	ne 7.5 mg or	
zolpidem 10 Exclusion crite History of de >=7) or any acute pain.) mg. eria: epression other curr Patients v	or other ent psy- vere als	psyc chiatri o exc	hiatric c c disorc luded if	lisorder, a cur der, severe an they had bee	d for insomnia for at rent depressive epis d evolving physical i n taking any psychol excluded if pregnant	ode (total score llness, dementia ropic drug (with	on the QD2A , alcoholism the exceptio	A questionnaire , drug abuse, or n of zopiclone or	
zolpidem 10 Exclusion crite History of de >=7) or any acute pain.) mg. eria: epression other curr Patients v	or other ent psy- vere als revious	psyc chiatri o exc	hiatric c c disorc luded if	lisorder, a cur der, severe an they had bee Women were	rent depressive epis d evolving physical i n taking any psychot excluded if pregnant	ode (total score llness, dementia ropic drug (with	on the QD2A , alcoholism the exceptio	A questionnaire , drug abuse, or n of zopiclone or	
zolpidem 10 Exclusion crite History of de >=7) or any acute pain. zolpidem) w) mg. eria: epression other curr Patients v ithin the p	or other ent psy- vere als revious je: ye	psyc chiatri o exc two w	hiatric c c disoro luded if /eeks.	lisorder, a cur der, severe an they had bee	rent depressive epis d evolving physical i n taking any psychot excluded if pregnant	ode (total score llness, dementia ropic drug (with	on the QD2A , alcoholism the exceptio	A questionnaire , drug abuse, or n of zopiclone or	
zolpidem 10 Exclusion crite History of de >=7) or any acute pain. zolpidem) w Population:) mg. eria: epression other curr Patients v ithin the p Mean ag	or other ent psy- vere als revious ge: ye %	psyc chiatri o exc two w ars -emal	hiatric c c disoro luded if /eeks.	lisorder, a cur der, severe an they had bee Women were	rent depressive epis d evolving physical i n taking any psychot excluded if pregnant	ode (total score llness, dementia ropic drug (with	on the QD2A , alcoholism the exceptio	A questionnaire , drug abuse, or n of zopiclone or	

Adverse Events:

Withdrawals: NR

Sepracor Study	y #190	-045					Qual	ty rating:	Fair
Design:									
Study design:	RCT	DB	Crosso	over	Run-in :	3-7 days	Setting	g: Multice	nter
					Wash out :	3-7 days	Count	ry: US	
Sample:	Numbe	er Scre	ened/ E	ligible/	Enrolled	Number Wi	hdrawn/ Lost to	follow-up/ A	nalyzed
			NR/	NR/	64		NR/	NR/	64

Inclusion criteria:

Patients aged 21 to 65 years with primary insomnia as defined by DSM-IV (<= 6.5 hours of sleep per night, and >= 30 minutes each night to fall asleep for at least one month), who also met the following screening PSG criteria: (1) sleep latency: at least 2 nights >= 20 minutes with none of 3 nights < 15 minutes, plus (2) either total sleep time: at least 2 nights <= 420 minutes, or (3) wake time after onset of persistent sleep (WASO): at least 2 nights >= 20 minutes with none of 3 nights < 15 minutes.

Exclusion criteria:

NR

Population:	Mear Geno	n age: der:	40.6 years 25% Female	Ethnicity:	44 (67.7%) white 13 (20.0%) black
 Drug name	dos	sage	N=	Duration	
Eszopiclone	1	mg	64	2 day	
Eszopiclone	2	mg	64	2 day	
Eszopiclone	2.5	mg	64	2 day	
Eszopiclone	3	mg	64	2 day	
Zolpidem	10	mg	64	2 day	
Placebo	NA	mg	64	2 day	

Adverse Events:

Eszopiclone 1mg	Eszopiclone 2mg	Eszopiclone 2.5mg	Eszopiclone 3mg	Zolpidem	
dizziness (placebo=7.9):	%				
3.2	0	0	4.9	23.4	
hallucinations (placebo=0	0): %				
0	0	0	0	10.9	
somnolence (placebo=3.2	2): %				
4.8	3.2	3.1	4.7	9.4	
headache (placebo=9.5):	%				
4.8	6.3	3.1	9.4	9.4	
nausea (placebo=3.2): %)				
3.2	1.6	3.1	3.1	6.3	
unpleasant taste (placebo	o=1.6): %				
4.8	4.8	9.2	7.8	0	

							G	Quality r	ating:	Poor
sign:										
Study design:	RCT	DB	Cross	sover	Run-in :	NR	S	etting:	Single (Center
					Wash out :	7 days	С	country:	France	
Sample:	Numb	ber Sci	reened/	Eligible/	Enrolled	Numb	er Withdrawn/ Lo	ost to follow	w-up/ A	nalyzed
			NR/	NR/	23		NR/		NR/	23
Inclusion criteri							94) for primary inso			
than 30 min f	or at l	east fo	our nights	each we		on of wake af	ter sleep onset of			set latency greater r at least four
Exclusion criter	ria:									
Population:	Mean	age:	38.8 yea	ars	Ethnicity:	NR				
	Gend	ler:	61% Fe	male						
ervention: Drug name	dos	ane	N=		Duration					
	10	mg	23		8 day					
Zolpidem	10	0								
Zolpidem Zopiclone	7.5	mg	23		8 day					
•	7.5	mg mg	23 23		8 day 8 day					
Zopiclone	7.5 1	mg								
Zopiclone Lormetazepam	7.5	mg	23		8 day					
Zopiclone Lormetazepam	7.5 1 NA	mg	23		8 day					
Zopiclone Lormetazepam Placebo	7.5 1 NA S:	mg	23		8 day					
Zopiclone Lormetazepam Placebo Verse Events Withdrawals	7.5 1 NA S:	mg mg	23 23	piclone	8 day	azepam	Placebo			
Zopiclone Lormetazepam Placebo Verse Events Withdrawals	7.5 1 NA S:	mg mg m	23 23 Zoj	Diclone	8 day 8 day	azepam	Placebo			

0

Withdrawals due to adverse events: Number

0

0

0

utsui, 2001						Quality	rating: Fair	
esign:								
Study design:	RCT	DB	Parallel	Run-in : Wash out :	0 days 7 days	Setting: Country:	Multicenter Japan	
Sample:	Numb	er Scr	eened/ Eligible/ NR/ NR/		Number Withdrawn/ 77/	Lost to follo	w-up/ Analyzed NR/ 428	
Inclusion crite	ria:							
					non-restorative sleep or dif three times a week in sleep		ore than a month in initi	iating
Exclusion crite					liagnosed diseases in the ac			
severe respi intelligence. benzodiazer dose exceed likelihood of	ratory c Sympt bines ar ling the pregna	dysfun toms ir nd ana stand incy, b	ction, myastheni nterfering with sl llogous drugs, zo lard single dose,	a gravis or acu eep (e.g., pain, ppiclone intake history of drug articipation in o	ed or suspected), serious he te narrow-angle glaucoma au fever, diarrhea, pollakiuria, o within 3 months prior to the dependence, operation of m ther clinical trials within the p	nd cognitive cough), hyp study, requi nachinery in	disorders or impaired ersensitivity to rement for hypnotics at volving risk, pregnancy	a or
Population:	Mean	age:	42.2 years	Ethnicity:	NR			
	Gend	er:	58% Female	-				
tervention: Drug name	dosa	age	N=	Duration				
Zolpidem	10	mg	209	2 week				
Zopiclone	7.5	mg	219	2 week				
dverse Event	ts:							
Total withd	rawals							
	olpiden		Zopiclone					
Z								
Z Total withdr	awals:	%						
Total withdr	awals: 13.9	%	18.1				P: NS	
Total withdr	13.9						P: NS	
Total withdr Withdrawal	13.9	o advo					P: NS	
Total withdr Withdrawal	13.9 s due to olpiden	o adve n	erse events				P: NS	
Total withdr Withdrawal Z Withdrawal	13.9 s due to olpiden	o adve n	erse events Zopiclone				P: NS P: NR	
Total withdr Withdrawal Z Withdrawal	13.9 s due t e colpiden s due te 6.1	o adve n	erse events Zopiclone rse events: %					
Total withdr Withdrawal Z Withdrawals	13.9 s due t e colpiden s due te 6.1	o adv o n o adve	erse events Zopiclone rse events: %					
Total withdr Withdrawal Withdrawals Adverse even Z	13.9 s due tr colpiden s due tr 6.1 ents colpiden	o adve n o adve n	erse events Zopiclone rse events: % 8.1 Zopiclone	lated", "possib	y related" or "probably relate	d" to study		

Anderson, 1987									Quality rating: Fair			
Design:												
Study design:	RCT	DB	Parall	el	Run-in :	7 days		Setting:	Multic	enter		
					Wash out :	7 days		Country:	UK			
Sample:	Numbe	er Scre	ened/ E	Eligible/	Enrolled	Number	Withdrawn/	Lost to follo	w-up/	Analyz	zed	
			NR/	NR/	119		5/		15/		99	

Inclusion criteria:

Patients were suffering from at least one of the following symptoms: unable to fall asleep within 45 minutes, more than two nocturnal awakenings with difficulty in returning to sleep without known cause, or sleeping <6 hours per night

Exclusion criteria:

Patients were not eligible for the trial if there was evidence for the presence (or previous history) of psychiatric disease, hepatic or renal dysfunction, heart block or cardiovascular disease with significant symptomatology, gastrointestinal disease, drug addiction or chronic alcoholism, a history of hypersensitivity to drugs or continuous use of high doses of a hypnotic for a period in excess of 6 months. Other groups excluded were pregnant women, nursing mothers, women of childbearing potential, and night shift workers.

Population:	Mean age: Gender:	NR years 0% Female	Ethnicity:	NR		
Intervention: Drug name	dosage	N=	Duration		Primary outcome	Outcome:
Zopiclone	7.5 mg	37	14 day			The time they took medicine
Nitrazepam	5 mg	NR	14 day			Sleep duration
Placebo	NA mg	NR	14 day			No. of times woke-up
						Wake up earlier then wished
						Sleep latency
						How much they dreamed
						Slept well - sleep quality
						Feeling wide awake

Efficacy:

Zopiclone	Nitrazepam	Placebo	
sleep quality at week 3	(in figure), higher sco	re=better: Score (p vs placebo)	
68 (<0.05)	66 (<0.05)	49 (NA)	
time to fall asleep at we	ek 3 (in figure), highe	r score=better: Score (p vs placebo)	
61 (<0.05)	63 (<0.05)	44 (NA)	
all sleep parameters: S	core		
NR	NR		P: NS
eep questionnaire			
Zopiclone	Nitrazepam	Placebo	
early morning awakenir	ngs at week 3 (in figu	e), higher score=worse: proportion (p	vs placebo)
0.38 (<0.05)	0.35 (<0.05)	0.78 (NA)	
physicians global asses	ssment: Score		
NR	NR		P: NS
wide-awake in the morr	ning: Score		
better	-		P: 0.02

utret, 1987								Quality	rating:	Poor
esign:										
Study design:	СТ	DB	Cross		Run-in : Wash out :	4 days 3 days		Setting: Country:	Single C France	Center
Sample:	Numb	ber Sc	reened/ E NR/			•	Withdrawn/ NR/	Lost to follo	w-up/Ar 8/	nalyzed 113
Inclusion crite	ria:									
greater than	2 hour e than 2	rs; wał	king up mo	ore than t	wice at night;		gth of night w	vakefulness		od of falling asleep an 30 minutes;
Population:	Mean	age:	46.3 yea	rs	Ethnicity:	NR				
-	Gend		, 70% Fer							
tervention:							Primary			
Drug name	dos	age	N=		Duration		outcome	Outcome:		
Zopiclone	7.5	mg	121		7 day		\checkmark	Sleep later	ncy	
Triazalam	0.5	mg	121		7 day					
Triazolam					. uuj		\checkmark	Sleep qual	lity	
							\checkmark	Sleep qual Sleep dura	,	
									ation	
								Sleep dura	ation	
								Sleep dura Night waki	ation ng	
								Sleep dura Night waki Dreams	ation ng tate	
							> > >	Sleep dura Night waki Dreams Morning st	ation ng tate aluation	
							> > >	Sleep dura Night waki Dreams Morning st Global eva	ation ng ate aluation insomnia	

Efficacy:

Spiegel and Norris'	visual analogue scale
Zopiclone	Triazolam

Zopicione	Iriazolam	
Delay in falling asleep	(higher score=better)- change from baseline: Score (SD)	
1.86 (1.35)	1.43 (1.12)	P: <0.01
quality of sleep (higher	score=better)- change from baseline: Score (SD)	
1.98 (1.25)	1.47 (1.06)	P: <0.01
length of sleep (higher	score=better)- change from baseline: Score (SD)	
1.47 (1.26)	1.26 (0.97)	P: NS
night waking (higher sc	ore=better)- change from baseline: Score (SD)	
1.64 (1.38)	1.34 (1.11)	P: <0.05
dream (higher score=b	etter)- change from baseline: Score (SD)	
0.40 (1.44)	0.32 (1.10)	P: NS
morning state (higher s	core=better)- change from baseline: Score (SD)	
1.66 (1.46)	1.13 (1.04)	P: <0.001
global evaluation (high	er score=better)- change from baseline: Score (SD)	
1.96 (1.40)	1.43 (1.04)	P: <0.001

t, 1987		Quality rating: Poor		
rated by physicians				
Zopiclone	Temazepam			
therapeutic efficacy- p	references of the patients: Number (%)			
62 (54.9)	26 (23)	P: <0.01		

8egg, 1992								Quality	rating	g: Po	oor	
Design:												
Study design:	RCT	SB	Parall	el	Run-in :	2 days		Setting:	Single	e Cen	ter	
					Wash out :			Country:	NR			
Sample:	Numl	ber Sc	reened/ E	•		Number	Withdrawn/ I	ost to follo		Analy		
			NR/	NR/	88		4/		33/		51	
Inclusion crite						• • • • •						
						more of the foll total reported sl				g 30 m	ninutes or more	
Exclusion crite			o amaitoin	ngo aan	ing the highl,				nouro.			
		ations I	known to a	affect sle	eep or on drug	gs known to alte	r drug metabo	lism during	g and w	vithin t	two weeks prior	
					on within four	hours of retiring	or more than	one glass	(10 g)	alcoh	ol in the	
previous 24			•									
Population:			NR years		Ethnicity:	NR						
ntervention:	Gend	der:	0% Fem	ale								
Drug name	dos	age	N=		Duration							
Zopiclone	7.5	mg	28		11 day							
Midazolam	15	mg	23		11 day							
Midazolam												
Efficacy:												
Efficacy: LSEQ - pre		•										
Efficacy: LSEQ - pre	vs. du Baselin	•		n azolam	Zopi	clone						
Efficacy: LSEQ - pre	Baselin	ie	Mida	azolam	Zopi e (p vs zopick							
Efficacy: LSEQ - pre E all 10 item	Baselin	ie =bene	Mida ficial effect	azolam	e (p vs zopiclo						P: p<0.01	
Efficacy: LSEQ - pre all 10 iten Hig	Baselin ns (low gh (<0.	e =bene 01)	Mida ficial effec Lov	azolam xt): Scor v (NS)	e (p vs zopiclo Low	one) (NA)	und)				P: p<0.01	
Efficacy: LSEQ - pre all 10 item Hig LSEQ - pre	Baselin ns (low gh (<0.	ie ≔bene 01) o nigh	Mida ficial effect Lov hts after m	azolam xt): Scor v (NS)	e (p vs zopick Low on was disco	one)	ind)				P: p<0.01	
Efficacy: LSEQ - pre all 10 item Hig LSEQ - pre	Baselin ns (low gh (<0. vs. tw Baselin	e =bene 01) o nigh	Mida ficial effec Lov nts after m Mida	azolam ct): Scor v (NS) nedicati azolam	e (p vs zopick Low on was disco	one) (NA) ontinued (rebo	ınd)				P: p<0.01	
Efficacy: LSEQ - pre all 10 iten Hig LSEQ - pre E 5 of 10 ite	Baselin ns (low gh (<0. vs. tw Baselin	e =bene 01) o nigh e core (p	Mida ficial effec Lov nts after m Mida o vs zopicle	azolam ct): Scor v (NS) nedicati azolam	e (p vs zopick Low on was disco Zopi	one) (NA) ontinued (rebo	ınd)				P: p<0.01	
Efficacy: LSEQ - pre all 10 item Hig LSEQ - pre 5 of 10 ite Lo	Baselin ns (low gh (<0. vs. tw Baselin ems: So ww (<0.	e =bene 01) o nigh e core (p 01)	Mida ficial effec Lov nts after m Mida o vs zopicle	azolam ct): Scor v (NS) nedicati azolam one) t (NR)	e (p vs zopick Low on was disco Zopi	one) (NA) ontinued (rebor clone	ind)				P: p<0.01	

)					Quality rating: Fair
esign:						
Study design:	RCT DE	8 Parallel	Run-in : Wash out :	no days 7 days		Setting: Multicenter Country: UK
Sample:	Number Sc	reened/ Eligible		-	Withdrawn/	Lost to follow-up/ Analyzed
		NR/ NF			4/	NR/ 38
	somnia with a					o fall asleep longer than 30 minutes, vn cause, sleep duration of less than 6
with assess	concomitant ment; womer		nant, nursing, or	of child-bearin		hol consumption that might interfere ing to become pregnant. No patient was
Population:	Mean age: Gender:	50.9 years 71% Female	Ethnicity:	100% Cauca	sian	
Drug name	dosage	N=	Duration		Primary outcome	Outcome:
Zopiclone	7.5 mg	19	1 week			LSEQ: Ease of getting to sleep
Triazolam	0.25 mg	19	1 week			LSEQ: Quality of sleep
			,			LSEQ: Ease of awakening
						LSEQ: Behavior following wakefulness
						Global assessment of efficacy
ficacy:						
	e of getting t	-				
Z	Copiclone	Triazolar	1			
Z	Copiclone ore at week 1	Triazolarr : Score	1			
Z Mean sco	Zopiclone ore at week 1 57.91	Triazolar	1			P: NS (NR
Z Mean sco LSEQ: Qua	Zopiclone ore at week 1 57.91 lity of sleep	Triazolam : Score 65.18				P: NS (NR
Z Mean sco LSEQ: Qua Z	Copiclone ore at week 1 57.91 lity of sleep Copiclone	Triazolam : Score 65.18 Triazolam				P: NS (NR
Z Mean sco LSEQ: Qua Z	Copiclone ore at week 1 57.91 lity of sleep Copiclone ore at week 1	Triazolam : Score 65.18 Triazolam : Score				,
Z Mean sco LSEQ: Qua Z Mean sco	Copiclone ore at week 1 57.91 lity of sleep Copiclone ore at week 1 67.13	Triazolam : Score 65.18 Triazolam : Score 72.13				P: NS (NR P: NS (NR
Z Mean sco LSEQ: Qua Z Mean sco LSEQ Ease	Copiclone ore at week 1 57.91 lity of sleep Copiclone ore at week 1 67.13 of awakenin	Triazolam : Score 65.18 Triazolam : Score 72.13	1			
Z Mean sco LSEQ: Qua Z Mean sco LSEQ Ease Z	Copiclone ore at week 1 57.91 lity of sleep Copiclone ore at week 1 67.13 of awakenin Copiclone	Triazolam : Score 65.18 Triazolam : Score 72.13 ng Triazolam	1			,
Z Mean sco LSEQ: Qua Z Mean sco LSEQ Ease Z	Copiclone ore at week 1 57.91 lity of sleep Copiclone ore at week 1 67.13 of awakenin	Triazolam : Score 65.18 Triazolam : Score 72.13 ng Triazolam	1			
Z Mean sco LSEQ: Qua Z Mean sco Z Mean sco	Copiclone ore at week 1 57.91 lity of sleep Copiclone ore at week 1 67.13 of awakenin Copiclone ore at week 1 68.79	Triazolam : Score 65.18 Triazolam : Score 72.13 ng Triazolam : Score 53.03	1 1			P: NS (NR
Z Mean sco LSEQ: Qua Z Mean sco LSEQ Ease Z Mean sco LSEQ Beha	Copiclone ore at week 1 57.91 lity of sleep Copiclone ore at week 1 67.13 of awakenin Copiclone ore at week 1 68.79	Triazolam : Score 65.18 Triazolam : Score 72.13 ng Triazolam : Score	1 1 1			P: NS (NR
Z Mean sco LSEQ: Qua Z Mean sco LSEQ Ease Z Mean sco LSEQ Beha Z	Copiclone ore at week 1 57.91 lity of sleep Copiclone ore at week 1 67.13 of awakenin Copiclone ore at week 1 68.79 wior followin	Triazolam : Score 65.18 Triazolam : Score 72.13 mg Triazolam : Score 53.03 mg wakefulness Triazolam	1 1 1			P: NS (NR

ıdoir, 1990		Quality rating: Fair
Global assessment of ef	ficacy	
Zopiclone	Triazolam	
Physicians' global asse	ssment of efficacy: Score	
NR, high	NR, high	P: NS
Patients' global assessr	nent of efficacy: Score	
NR, high	NR, high	P: NS

Drake (1), 2001							Quality	rating	g: Fair	
Design:										
Study design:	RCT	DB	Cros	ssover	Run-in :	NR	Setting:	Multio	center	
					Wash out :	5-12 days	Country:	US		
Sample:	Numbe	er Scre	ened/	Eligible/	Enrolled	Number Withdrawn/	Lost to follo	w-up/	Analyzed	
			NR/	NR/	47	0/		0/	47	

Inclusion criteria:

Age 21-60, with a recent, six-month, history or primary insomnia as defined by the DSM-III. To be eligible for polysomnographic (PSG) screening, participants must have reported at least two of the following: 6 months of sleep disturbance with a sleep latency of >30 minutes, three or more awakenings per night, or a sleep time of 4 to 6 hours. All patients had to meet the following PSG screening criteria for study eligibility: 1) latency to persistent sleep greater than 20 minutes on at least two of the screening nights, with no latency of less than 15 minutes, 2) Total sleep time between 240 and 420 on at least two of the screening nights, 3) less than five apneas per hour of sleep, 4) less than 10 leg movements per hour of sleep.

Exclusion criteria:

Individuals with medical or psychiatric diagnoses (including any history of alcoholism or drug abuse), abnormal laboratory results (urinalysis, hematology, and blood chemistries), an irregular sleep-wake schedule, or who regularly consumed greater than 750 mg of caffeinated beverages.

Population:	Mean age: Gender:	41.6 years 51% Female	Ethnicity:	NR		
Intervention: Drug name	dosage	N=	Duration		Primary outcome	Outcome:
Zaleplon	10 mg	47	2 day			latency to persistent sleep
Zaleplon	40 mg	47	2 day			total sleep time
Triazolam	0.25 mg	47	2 day			sleep quality
Placebo	NA mg	47	2 day			ease of falling asleep

Efficacy:

polysomnography

Zaleplon 10mg	Zaleplon 40mg	Triazolam 0.25mg
latency to persistent sle	ep: minutes (p vs tr	iazolam)
22.5 (NS)	18.6 (<0.05)	27.5 (NA)
total sleep time: minutes	s (p vs triazolam)	
386.3 (<0.05)	392.6 (<0.05)	407.8 (NA)
patient reports		
Zaleplon 10mg	Zaleplon 40mg	Triazolam 0.25mg
latency to sleep: minute	es (p vs triazolam)	
38.8 (NS)	29.3 (NS)	36.4 (NA)
total sleep time: minutes	s (p vs triazolam)	
358.1 (NS)	375.5 (NS)	386.8 (NA)
sleep quality: Score (p v	/s triazolam)	
2.5 (NS)	2.7 (NS)	2.7 (NA)
ease of falling asleep: S	Score (p vs triazolan	ר)
65.4 (NS)	74.1 (NS)	67.3 (NA)

Drake (2), 2000							Quality	rating:	Fair	
Design:										
Study design:	RCT	DB	Cros	ssover	Run-in :	NR	Setting:	Multice	nter	
					Wash out :	5-12 days	Country:	US		
Sample:	Numbe	er Scre	ened/	Eligible/	Enrolled	Number Withdrawn	/ Lost to follo	w-up/A	nalyzed	
			NR/	NR/	36	0.	1	0/	36	

Inclusion criteria:

Age 21-60, with a recent, six-month, history or primary insomnia as defined by the DSM-III. To be eligible for polysomnographic (PSG) screening, participants must have reported at least two of the following: 6 months of sleep disturbance with a sleep latency of >30 minutes, three or more awakenings per night, or a sleep time of 4 to 6 hours. All patients had to meet the following PSG screening criteria for study eligibility: 1) latency to persistent sleep greater than 20 minutes on at least two of the screening nights, with no latency of less than 15 minutes, 2) Total sleep time between 240 and 420 on at least two of the screening nights, 3) less than five apneas per hour of sleep, 4) less than 10 leg movements per hour of sleep.

Exclusion criteria:

Individuals with medical or psychiatric diagnoses (including any history of alcoholism or drug abuse), abnormal laboratory results (urinalysis, hematology, and blood chemistries), an irregular sleep-wake schedule, or who regularly consumed greater than 750 mg of caffeinated beverages.

Population:	Mean age: Gender:	38.1 years 39% Female	Ethnicity:	NR		
Intervention: Drug name	dosage	N=	Duration		Primary outcome	Outcome:
Zaleplon	20 mg	36	2 day			latency to persistent sleep
Zaleplon	60 mg	36	2 day			total sleep time
Triazolam	0.25 mg	36	2 day			sleep quality
Placebo	NA mg	36	2 day			ease of falling asleep

Efficacy:

polysomnography

Zaleplon 20mg	Zaleplon 60mg	Triazolam 0.25mg
latency to persistent slee	ep: minutes (p vs tr	iazolam)
30.5 (NS)	21.7 (<0.05)	27.6 (NA)
total sleep time: minutes	s (p vs triazolam)	
391.3 (<0.05)	404.7 (<0.05)	422.8 (NA)
patient reports		
Zaleplon 20mg	Zaleplon 60mg	Triazolam 0.25mg
latency to sleep: minute	s (p vs triazolam)	
45.5 (NS)	36.6 (NS)	41.9 (NA)
total sleep time: minutes	s (p vs triazolam)	
356 (<0.05)	376.3 (NS)	393.5 (NA)
sleep quality (higher sco	ore=better): Score (p vs triazolam)
2.3 (<0.05)	2.4 (NS)	2.7 (NA)
ease of falling asleep (Ic	ower score=better):	Score (p vs triazolam)
58.8 (NS)	64.5 (NS)	61 (NA)

ie, 1990b								Quality	rating: F	Fair	
esign:											
Study design:	RCT	DB	Parall		Run-in : Wash out :	7 days 3 days		Setting: Country:	Single Ce Canada	enter	
Sample:	Numb	ber Scr	eened/ E NR/	Eligible/ E NR/	Enrolled 36	Nur	nber Withdrawn/ 0/	Lost to follo	w-up/Ana 0/	alyzed 36	
Inclusion crite	eria:										
	(1) requ	uiring lo	onger thai	n 30 min t			ship to another a leep time less tha				
hypersensit a medically	ivity, ab recogn	ouse of ized co	alcohol o	or other dr ve progra	rugs were ex am and patie	cluded fron	ression or presen n the study. Worr g any treatment	nen of childb	earing pote	ential not	following
naving iccc	eived en	zyme i	nducing c	drugs in th	ne previous	month were	also excluded.				or
Population:			nducing c 37.6 yea	•	ne previous Ethnicity		also excluded.				or
•	Mean Gend	age:	•	nrs male	•		also excluded. Primary outcome	Outcome:			or
Population:	Mean Gend	age: ler: age	37.6 yea 67% Fer	nrs male D	Ethnicity		Primary		sleep onse	t	or
Population: tervention: Drug name	Mean Gend dos	age: ler: age	37.6 yea 67% Fer N=	nale	Ethnicity Duration		Primary outcome		sleep onse	ıt	or
Population: tervention: Drug name Zopiclone	Mean Gend dos 7.5	mage: ler: age mg mg	37.6 yea 67% Fer N= 12	nrs male 24 24	Ethnicity Duration		Primary outcome	rapidity of duration of	sleep onse		or
Population: tervention: Drug name Zopiclone Flurazepam	Mean Gend dos 7.5 30	mage: ler: age mg mg	37.6 yea 67% Fer N= 12 12	nrs male 24 24	Ethnicity Duration 28 day 28 day		Primary outcome	rapidity of duration of	sleep onse f sleep		or
Population: tervention: Drug name Zopiclone Flurazepam Placebo	Mean Gend dos 7.5 30 NA	mage: mg mg mg	37.6 yea 67% Fer N= 12 12 12	nrs male 24 24	Ethnicity Duration 28 day 28 day		Primary outcome	rapidity of duration of	sleep onse f sleep		or
Population: tervention: Drug name Zopiclone Flurazepam Placebo fficacy: post-sleep	Mean Gend dos 7.5 30 NA	mage: mage mg mg mg	37.6 yea 67% Fer N= 12 12 12	nrs male 24 24	Ethnicity Duration 18 day 18 day 18 day		Primary outcome	rapidity of duration of	sleep onse f sleep		or
Population: tervention: Drug name Zopiclone Flurazepam Placebo fficacy: post-sleep	Mean Gend dos 7.5 30 NA questia Zopiclor	mage: ler: mg mg mg mg onnair	37.6 yea 67% Fer N= 12 12 12 12 e Flura	azepam	Ethnicity Duration 18 day 18 day 18 day	: NR	Primary outcome	rapidity of duration of	sleep onse f sleep		or
Population: tervention: Drug name Zopiclone Flurazepam Placebo fficacy: post-sleep	Mean Gend dos 7.5 30 NA questia Zopiclor	mg mg mg onnair ne onset a	37.6 yea 67% Fer N= 12 12 12 e Flura at week 4	azepam	Ethnicity Duration 8 day 8 day 8 day Pla Pla	: NR	Primary outcome	rapidity of duration of	sleep onse f sleep		or
Population: tervention: Drug name Zopiclone Flurazepam Placebo fficacy: post-sleep rapidity c	Mean Gend dos 7.5 30 NA questid Zopiclor of sleep 11.6 (NS	mg mg mg onnair ne S)	37.6 yea 67% Fer N= 12 12 12 12 e Flura at week 4 11.2	azepam (higher s 2 (NS)	Ethnicity Duration 8 day 8 day 8 day Pla Pla	cebo): Score (p v 5 (NA)	Primary outcome	rapidity of duration of	sleep onse f sleep		or

3.5 (<0.01)

3.5 (<0.01)

5.5 (NA)

eming, 1990						Quality	rating: F	air	
esign:									
Study design:	RCT DE	8 Paralle		: 3 days ut : 4 days		Setting: Country:	Multicent Canada	er	
Sample:	Number So	reened/ F	ligible/ Enrolled		er Withdrawn/	•		alvzod	
oumpie.		NR/	NR/ 52	Numbe	4/		0/	48	
Inclusion crite	ria:								
period. Exclusion crite	ria							-	
Females exc whose sleep antidepressa	cluded if they performance ants or with a red seconda	e was disru a history of ry to a psy	upted by external hypersensitivity to	r were not using a factors and those o one or more hyp al disorder were als	taking neurole notic drugs we	eptics, sedat ere excluded	ives, analg I. Subjects	jesics, or s whose inse	omnia
Females exc whose sleep antidepressa was conside	cluded if they performand ants or with red seconda iffeine overu	e was disru a history of ry to a psy se.	upted by external hypersensitivity to chiatric or medica	factors and those o one or more hyp	taking neurole notic drugs we	eptics, sedat ere excluded	ives, analg I. Subjects	jesics, or s whose inse	omnia
Females exc whose sleep antidepress was conside abuse, or ca Population:	cluded if they performance ants or with a red seconda	e was disru a history of ry to a psy se.	upted by external hypersensitivity to chiatric or medica rs Ethnic	factors and those o one or more hyp al disorder were als	taking neurole notic drugs we	eptics, sedat ere excluded	ives, analg I. Subjects	jesics, or s whose inse	omnia
Females exc whose sleep antidepress was conside abuse, or ca	cluded if the performand ants or with ared seconda affeine overu Mean age	e was disri a history of ry to a psy se. 45.5 yea	upted by external hypersensitivity to chiatric or medica rs Ethnic	factors and those o one or more hyp al disorder were als sity: NR	taking neurole notic drugs we	eptics, sedat ere excluded	ives, analg I. Subjects	jesics, or s whose inse	omnia
Females exc whose sleep antidepress was conside abuse, or ca Population: tervention:	cluded if they performand ants or with red seconda iffeine overu Mean age Gender:	e was disri a history of ry to a psy se. 45.5 yea % Femal	upted by external hypersensitivity to chiatric or medica rs Ethnic e	factors and those o one or more hyp al disorder were als sity: NR	taking neurole notic drugs we so excluded a Primary	ptics, sedat ere excluded s those with Outcome:	ives, analg I. Subjects a history o	jesics, or s whose inse	omnia n, drug
Females exc whose sleep antidepress was conside abuse, or ca Population: tervention: Drug name	cluded if they performand ants or with red seconda iffeine overu Mean age Gender: dosage	e was disri a history of ry to a psy se. 45.5 yea % Femal N=	upted by external hypersensitivity to chiatric or medica rs Ethnic e Duration	factors and those o one or more hyp al disorder were als sity: NR	taking neurole notic drugs we so excluded a Primary	ptics, sedat ere excluded s those with Outcome:	ives, analg I. Subjects a history o	lesics, or s whose inso f alcoholisn	omnia n, drug
Females exc whose sleep antidepressa was conside abuse, or ca Population: tervention: Drug name Zopiclone	cluded if they operformance ants or with a ored seconda offeine overu Mean age: Gender: dosage 7.5 mg	e was disri a history of ry to a psy se. 45.5 yea % Femal N= 24	upted by external hypersensitivity to chiatric or medica rs Ethnic e Duration 21 day	factors and those o one or more hyp al disorder were als sity: NR	taking neurole notic drugs we so excluded a Primary	ptics, sedat ere excluded s those with Outcome: speed and	ives, analg I. Subjects a history o quality of s sleep	lesics, or s whose inso f alcoholisn sleep onset	omnia n, drug
Females exc whose sleep antidepressa was conside abuse, or ca Population: tervention: Drug name Zopiclone	cluded if they operformance ants or with a ored seconda offeine overu Mean age: Gender: dosage 7.5 mg	e was disri a history of ry to a psy se. 45.5 yea % Femal N= 24	upted by external hypersensitivity to chiatric or medica rs Ethnic e Duration 21 day	factors and those o one or more hyp al disorder were als sity: NR	taking neurole notic drugs we so excluded a Primary	Dutcome: speed and duration of	ives, analg I. Subjects a history of quality of s sleep quality of s	lesics, or s whose inso f alcoholisn sleep onset	omnia n, drug
Females exc whose sleep antidepressa was conside abuse, or ca Population: tervention: Drug name Zopiclone	cluded if they operformance ants or with a ored seconda offeine overu Mean age: Gender: dosage 7.5 mg	e was disri a history of ry to a psy se. 45.5 yea % Femal N= 24	upted by external hypersensitivity to chiatric or medica rs Ethnic e Duration 21 day	factors and those o one or more hyp al disorder were als sity: NR	taking neurole notic drugs we so excluded a Primary	Outcome: speed and duration of perceived	ives, analg I. Subjects a history of quality of s sleep quality of s	lesics, or s whose inso f alcoholisn sleep onset	omnia n, drug
Females exc whose sleep antidepressa was conside abuse, or ca Population: tervention: Drug name Zopiclone	cluded if they operformance ants or with a ored seconda offeine overu Mean age: Gender: dosage 7.5 mg	e was disri a history of ry to a psy se. 45.5 yea % Femal N= 24	upted by external hypersensitivity to chiatric or medica rs Ethnic e Duration 21 day	factors and those o one or more hyp al disorder were als sity: NR	taking neurole notic drugs we so excluded a Primary	Outcome: speed and duration of perceived on no. of awal	quality of s sleep quality of s kenings	lesics, or s whose inso f alcoholisn sleep onset	omnia n, drug

Efficacy:

Hamilton Anxiety Scale			
Zopiclone	Triazolam		
total score: Score			
NR	NR	F	P: NS

daytime alertness

Fleming, 1995						Quality	rating: Fair
Design:							
Study design:	RCT	DB	Parallel	Run-in :	1 days	Setting:	Multicenter
				Wash out :	NR	Country:	Canada
Sample:	Numbe	r Scre	ened/ Eligible/	Enrolled	Number Withdrawn/	Lost to follo	ow-up/ Analyzed
			222/ 144/	144	7/		1/ 141
Inclusion crite	ria:						

sion criteria:

(a) a subjective usual sleep duration of at least 4 hours but less than 6 hours per night; (b) a usual sleep latency of >= 30minutes; (c) daytime complaints associated with disturbed asleep. Each of there criteria was to be present for at least 6 months prior to study entry.

Exclusion criteria:

Any significant medical or psychiatric disorder or mental retardation; use of any other investigational drug within 30 days prior to the start of the study; use of flurazepam within 30 days of the first sleep laboratory night; regular use of any medication that would interfere with the assessment, absorption or metabolism of the study hypnotic; use of alcohol or short-acting central nervous system medication within 12 hours of any study night; use of triazolam within 4 nights, other short- or intermediate-acting hypnotics within 7 nights, or long-acting hypnotics within 14 nights of the first sleep laboratory night; history of exaggerated response or hypersensitivity to benzodiazepines or other CNS depressants; history of drug addiction, alcoholism, drug abuse, sleep apnoea, or nocturnal myoclonus; or a work or sleep schedule that regularly changed by at least 6 hours within 7 days of study initiation.

Population:	Mean age: Gender:	NR years 48% Female	Ethnicity:	NR		
Intervention: Drug name	dosage	N=	Duration		Primary outcome	Outcome:
Zolpidem	10 mg	35	3 day			sleep latency
Zolpidem	20 mg	35	3 day			wake time
Flurazepam	30 mg	36	3 day			sleep quality
Placebo	NA mg	35	3 day			sleep efficiency

oolysomnography			
Zolpidem 10mg	Zolpidem 20mg	Flurazepam	
sleep latency: minutes	(p vs flurazepam)		
-14.7 (<0.05)	-28.4 (<0.05)	-11.8 (NA)	
sleep efficiency: minute	s (p vs placebo)		
NR (NS)	NR (NS)	NR (NS)	
wake time during sleep	: minutes (p vs placet	00)	
NR (NS)	NR (NS)	NR (NS)	
uestionnaire			
Zolpidem 10mg	Zolpidem 20mg	Flurazepam	
sleep quality at day 3, (higher score=better):	Score (p vs flurazepam)	
2.4 (<0.05)	2.5 (<0.05)	1.9 (NA)	P: <0.05

ajak, 1998, 19	95, 1	994							Quality	rating	: Fai	ir	
esign:													
Study design:	RCT	DB	Paralle	el	Run-in : Wash out	7 days : 3 days			Setting: Country:	Multice Germa			
Sample:	Num	ber Sci	reened/ El NR/	ligible/ NR/		-	umber With	drawn/ 0/	Lost to follo		Analyz	zed 507	
Inclusion criter	ria:												
Insomnia of a treatment (no times.													
Exclusion crite Any patients during the 14 neuroses), o	who h 4 days	prior to	o admissio	n, or ar	ny patients v	/ith psychia	atric disorde	ers (e.g.,	depression	, schizo	phren	ia, severe	
Population:			51 years		Ethnicity	r: 99.3% (0.9% O	Caucasian						
	Gend	ler:	62% Fem	nale		0.9% 0	others						
Drug name		ler: age	62% Fem		Duration	0.9% 0	Pri	imary tcome	Outcome:				
		age			Duration 28 day	0.9% 0	Pri ou		Outcome: daytime ar				
Drug name	dos	age mg	N=			0.9% 0	Pri ou	tcome		nxiety			
Drug name Zopiclone	dos 7.5	mg mg	N= 612		28 day	0.9% 0	Pri ou	tcome	daytime ar	nxiety time	al awa	akenings	
Drug name Zopiclone Triazolam	dos 7.5 0.2	mg mg	N= 612 307		28 day 28 day	0.9% 0	Pri ou	tcome	daytime an total sleep number of	nxiety time nocturna		akenings ned on awa	kening
Drug name Zopiclone Triazolam	dos 7.5 0.2	mg mg	N= 612 307		28 day 28 day	0.9% 0	Pri ou	tcome	daytime an total sleep number of	nxiety time nocturna f being r		Ũ	kening
Drug name Zopiclone Triazolam	dos 7.5 0.2	mg mg	N= 612 307		28 day 28 day	0.9% 0	Pri ou		daytime an total sleep number of a feeling of	nxiety time nocturna f being r edness		Ũ	kening
Drug name Zopiclone Triazolam	dos 7.5 0.2	mg mg	N= 612 307		28 day 28 day	0.9% 0	Pri ou		daytime ar total sleep number of a feeling of daytime tire	nxiety time nocturna f being r edness		Ũ	kening
Drug name Zopiclone Triazolam	dos 7.5 0.2	mg mg	N= 612 307		28 day 28 day	0.9% 0	Pri ou		daytime ar total sleep number of a feeling of daytime tire	nxiety time nocturna f being r edness		Ũ	kening
Drug name Zopiclone Triazolam Placebo	dos 7.5 0.2 NA	mg mg	N= 612 307		28 day 28 day	0.9% 0	Pri ou		daytime ar total sleep number of a feeling of daytime tire	nxiety time nocturna f being r edness		Ũ	kening

Improved sleep quality	and daytime well-b	peing- treatment period: %	
42.3	36.3		P: 0.1133

26.8 (NA)

37.4 (<=0.0017)

32.2 (NS)

ayoun, 1989							Quality	rating:	Fair	
esign:										
Study design:	RCT	DB Para	allel	Run-in : Wash out :	NR NR		Setting: Country:	Single France		
Sample:	Number	Screened/	Eligible/			Number Withdrawn/				
·		NR/	NR/	136		9/		0/	127	
Inclusion crite	ria:									
two of the th	nree follow	ng criteria	for most o		ights: tin	int of unsatisfactory ne to fall asleep exc ding).				
need such o	ig patients drugs durir	g study; pr	egnant or	lactating fema	ales, or fe	dative drug within s emales of childbear	ing age with	out reliat	ole contracept	ion;
The followir need such o patients suf impairment with myasth	ing patients drugs durir fering from with unco lenia or kn ose unable Mean ag	g study; pr insomnia v ntrolled and own intoler to read an le: 47.9 ye	egnant or with exterr d significar ance to eit d understa ears	lactating fema nal causes; pa nt organic diso ther study dru	ales, or fe atients wi ease, wit g; shift w ating scal		ing age with ulsive disord or with a ps or drug-abu	out reliat ders, with sychiatric sers; non	ble contracept renal or resp affection; pat	ion; iratory
The followir need such o patients suf impairment, with myasth patients; the	ng patients drugs durir fering from with unco lenia or kn ose unable	g study; pr insomnia v ntrolled and own intoler to read an le: 47.9 ye 66% F	egnant or with extern d significan ance to eit d understa ears emale	lactating fema nal causes; pa nt organic dise ther study dru and the self-ra Ethnicity:	ales, or fe atients wi ease, wit g; shift w ating scal	emales of childbear ith a history of conv th uncontrolled pair vorkers, alcoholics, les; known resistan	ing age with ulsive disord or with a ps or drug-abu	out reliat ders, with sychiatric sers; non	ble contracept renal or resp affection; pat	ion; iratory
The followir need such of patients suf impairment, with myasti- patients; the Population:	ing patients drugs durir fering from with unco lenia or kn ose unable Mean ag	g study; pr insomnia v ntrolled and own intoler to read an le: 47.9 ye 66% F	egnant or with extern d significan ance to eit d understa ears emale	lactating fema nal causes; pa nt organic diso ther study dru and the self-ra	ales, or fe atients wi ease, wit g; shift w ating scal	emales of childbean ith a history of conv th uncontrolled pair vorkers, alcoholics,	ing age with ulsive disord or with a ps or drug-abu	nout reliat ders, with sychiatric sers; non tics.	ble contracept renal or resp affection; pat	ion; iratory
The followir need such o patients suf impairment, with myasth patients; the Population:	g patients drugs durir fering from with unco enia or kn ose unable Mean ag Gender	g study; pr insomnia htrolled and own intolera to read an e: 47.9 ye 66% F 66% F	egnant or with extern d significan ance to eit d understa ears emale	lactating fema nal causes; pa nt organic dise ther study dru and the self-ra Ethnicity:	ales, or fe atients wi ease, wit g; shift w ating scal	emales of childbeau ith a history of conv th uncontrolled pair vorkers, alcoholics, les; known resistan Primary	ing age with ulsive disord or with a ps or drug-abu ce to hypnot	nout reliat ders, with sychiatric sers; non iics.	ble contracept renal or resp affection; pat	ion; iratory
The followir need such o patients suf impairment, with myasth patients; the Population: Intervention: Drug name	drugs durir fering from with unco enia or kn ose unable Mean ag Gender dosag	g study; pr insomnia o htrolled and own intoler to read an de: 47.9 ye 66% F e N= 1 67	egnant or with extern d significan ance to eit d understa ears emale	lactating fema nal causes; pa nt organic disc ther study dru and the self-ra Ethnicity: Duration	ales, or fe atients wi ease, wit g; shift w ating scal	emales of childbeau ith a history of conv th uncontrolled pair vorkers, alcoholics, les; known resistan Primary outcome	ing age with ulsive disord or with a ps or drug-abu ce to hypnot	nout reliat ders, with sychiatric sers; non ics.	ble contracept renal or resp affection; pat	ion; iratory
The followir need such o patients suf impairment, with myasth patients; tho Population: ntervention: Drug name Zopiclone	ring patients drugs durir fering from with unco- lenia or kn bse unable Mean ag Gender dosag 7.5 mg	g study; pr insomnia o htrolled and own intoler to read an de: 47.9 ye 66% F e N= 1 67	egnant or with extern d significan ance to eit d understa ears emale	lactating fema hal causes; pa ht organic disc ther study dru and the self-ra Ethnicity: Duration 7 day	ales, or fe atients wi ease, wit g; shift w ating scal	emales of childbeau ith a history of conv th uncontrolled pair vorkers, alcoholics, les; known resistan Primary outcome	ing age with ulsive disord or with a ps or drug-abu ce to hypnot Outcome: sleep later	nout reliat ders, with sychiatric sers; non ics. : : ncy	ble contracept renal or resp affection; pat	ion; iratory
The followir need such o patients suf impairment, with myasth patients; tho Population: ntervention: Drug name Zopiclone	ring patients drugs durir fering from with unco- lenia or kn bse unable Mean ag Gender dosag 7.5 mg	g study; pr insomnia o htrolled and own intoler to read an de: 47.9 ye 66% F e N= 1 67	egnant or with extern d significan ance to eit d understa ears emale	lactating fema hal causes; pa ht organic disc ther study dru and the self-ra Ethnicity: Duration 7 day	ales, or fe atients wi ease, wit g; shift w ating scal	emales of childbeau ith a history of conv th uncontrolled pair vorkers, alcoholics, les; known resistan Primary outcome	ing age with ulsive disord or with a ps or drug-abu ce to hypnot Outcome: sleep later sleep dura	nout reliat ders, with sychiatric sers; non ics. :	ble contracept renal or resp affection; pat	ion; iratory

Zopiclone	Triazolam	
overall: Score		
NR	NR	P: NS
global physicians' evalu	ation scale	
Zopiclone	Triazolam	
Efficacy- good or excel	ent: %	
73	69	P: NS

un, 1989		Quality rating: Fair
self-evaluation question	naire	
Zopiclone	Triazolam	
falling asleep in less the	n 30 minutes: %	
63	84	P: NS
sleep more than 7 hour	S: %	
50	69	P: NS
awakening at night onc	e or not at all: %	
64	89	P: NS
sleep heavily while still	reporting a good awakening state: %	
55	70	P: NS
feel more rest: %		
80	92	P: NS
awakening with no con interaction, p<0.01): %	entration difficulties (with a significant investiga	tor-by-treatment group
56	82	P: 0.04
medication aided sleep	%	
multiple data	multiple data	P: NS

, 1997						Quality	rating:	Poor
sign:								
Study design:	RCT DE	3 Crossover	Run-in : Wash out :	0 days 7 days		Setting: Country:	Single C Taiwan	enter
Sample:	Number Sc	reened/ Eligible/ NR/ NR/	Enrolled	-	r Withdrawn/ 0/	Lost to follo	w-up/ An 0/	alyzed 15
Inclusion crite	ria:							
	1 hour, total	d from insomnia fo sleep duration o						
Exclusion crite Patients with		or mood disorder	s, history of se	vere physical i	lness, alcoho	I arouse or	drug abuse	э.
Population:	Mean age:	40.1 years	Ethnicity:	NR				
	Gender:	73% Female						
ervention: Drug name	dosage	N=	Duration		Primary	•		
	uusage				outcome	Outcome:		
Zopiclone	7.5 mg	15	14 day			therapeuti	c efficacy	
Triazolam	0.25 mg	15	14 day			delay in fa	lling aslee	р
Placebo	NA mg	15	14 day			quality of s	sleep	
						length of s	leep	
						night waki	ng	
						dream		
						morning st	tate	
						global eva	luation	
						0		
icacy:								
-	hal Impress	ion Scale (CGI)						

Zopiclone	Triazolam	
erapeutic efficacy: So	core (p vs baseline)	
NR (<0.005)	NR (<0.005)	P: NS

997		Quality rating: Poor
Spiegel's sleep question	nnaire (SSQ)	
Zopiclone	Triazolam	
therapeutic efficacy: Sc	ore (p vs baseline)	
NR (<0.005)	NR (<0.005)	P: NS
delay in falling asleep a	t day 14: Score (SD)	
3.94 (0.70)	4.13 (0.64)	P: NS
quality of sleep at day 1	4: Score (SD)	
4.33 (0.62)	3.47 (0.64)	P: <0.05
length of sleep at day 1	4: Score (SD)	
3.73 (0.70)	3.53 (0.74)	P: NS
night waking at day 14:	Score (SD)	
4.20 (0.68)	3.33 (0.62)	P: <0.05
dream at day 14: Score	e (SD)	
3.93 (0.70)	3.73 (1.03)	P: NS
morning state at day 14	: Score (SD)	
3.93 (0.80)	3.60 (0.91)	P: NS
global evaluation at day	/ 14: Score (SD)	
4.13 (0.92)	3.93 (0.96)	P: NS
Leed's sleep evaluation	questionnaire (LSEQ)	
Zopiclone	Triazolam	
2 out of 10 items shows	s more effectiveness in zopiclone: quality of sleep: Score	
NR	NR	P: <0.05

	•						Quality rating: Fair
sign:							
Study design:	RCT	DB	Parallel	Run-in :	2 days		Setting: Single Center
				Wash out :	3 days		Country: Canada
Sample:	Num	ber Sc	reened/ Eligi	ble/ Enrolled	Num	ber Withdrawn/	Lost to follow-up/ Analyzed
			NR/ I	NR/ 30		0/	0/ 30
Inclusion crite					den al cara de la		lauda a stara d'arandara ata a tata ara d
>= 45 min, t more noctur	otal no nal aw	octurna vakenin	l sleep time o Igs. All subjec	f <6 hours, mornin ts were required to	ng awakening o be free of	g at least 90 min centrally acting o	lowing sleep disorders: sleep latency of earlier than expected time, or three or drugs for at least 3 months before derate users of alcohol.
Exclusion crite	eria:						
							er disqualifying cases specifically or allergic reactions to hypnotic-sedative
Population:	Mear	n age:	50 years	Ethnicity:	NR		
	Gene	der:	70% Female	9			
ervention: Drug name	dos	sage	N=	Duration		Primary outcome	Outcome:
Zopiclone	7.5	mg	10	12 day			total sleep time
Flurazepam	30	mg	10	12 day			sleep latency
Discut	NA	mg	10	12 day			no. of awakenings
Placebo							duration of early wakefulness
Placebo							
icacy: sleep ques	tionna Zopiclo		Flurazep	pam Plac	cebo		
icacy: sleep ques Z	Copiclo	ne	•	pam Plac		eline)	
icacy: sleep ques Z total slee	Copiclo	ne at day	•	f treatment: minute		eline)	
icacy: sleep ques Z total slee 41	Copiclo p time 7.5 (<0	ne at day).05)	14, the end o 410.5 (<0	f treatment: minute 0.05) 328.0	es (p vs bas (<0.05)	,	
icacy: sleep ques Z total slee 41 sleep late	Copiclo p time 7.5 (<0	ne at day 0.05) day 14	14, the end o 410.5 (<0	f treatment: minute 0.05) 328.0 reatment: minutes	es (p vs bas (<0.05)	,	
icacy: sleep ques Z total sleep 41 sleep late 28	Zopiclo p time 7.5 (<0 ency at 8.8 (<0.	ne at day 0.05) day 14 .05)	14, the end o 410.5 (<(4, the end of t 31.5 (<0	f treatment: minute 0.05) 328.0 reatment: minutes	es (p vs bas (<0.05) (p vs baseli (NS)	ne)	
icacy: sleep ques total slee 41 sleep late 28 no of awa	Zopiclo p time 7.5 (<0 ency at 8.8 (<0.	ne at day 0.05) day 14 .05) gs at da	14, the end o 410.5 (<(4, the end of t 31.5 (<0	f treatment: minute 0.05) 328.0 reatment: minutes .05) 69.8 I of treatment: Nur	es (p vs bas (<0.05) (p vs baseli (NS)	ne)	
icacy: sleep ques total sleep 41 sleep late 28 no of awa 1.	Zopiclo p time 7.5 (<0 ency at 3.8 (<0. akening 15 (<0.	ne at day 0.05) day 14 .05) gs at da .05)	14, the end o 410.5 (<(4, the end of t 31.5 (<0 ay 14, the end 1.55 (<0	f treatment: minute 0.05) 328.0 reatment: minutes .05) 69.8 I of treatment: Nur	es (p vs base (<0.05) (p vs baseli (NS) nber (p vs b <0.05)	ne) aseline)	
icacy: sleep ques total sleep 41 sleep late 28 no of awa 1. duration of	Zopiclo p time 7.5 (<0 ency at 3.8 (<0. akening 15 (<0.	ne at day 0.05) day 14 .05) gs at da .05) y wakef	14, the end o 410.5 (<(4, the end of t 31.5 (<0 ay 14, the end 1.55 (<0	f treatment: minute 0.05) 328.0 reatment: minutes .05) 69.8 I of treatment: Nur .05) 1.65 (14, the end of tre	es (p vs base (<0.05) (p vs baseli (NS) nber (p vs b <0.05)	ne) aseline)	
icacy: sleep ques total sleep 41 sleep late 28 no of awa 1. duration o	Zopiclo p time 7.5 (<0 ency at 8.8 (<0. akening 15 (<0. of early 87.0 (N	ne at day 0.05) day 14 .05) gs at da .05) v wakef S)	14, the end o 410.5 (< 4, the end of t 31.5 (<0 ay 14, the end 1.55 (<0 fulness at day 14.7 (N	f treatment: minute 0.05) 328.0 reatment: minutes .05) 69.8 I of treatment: Nur .05) 1.65 (14, the end of tre	es (p vs base (<0.05) (p vs baseli (NS) nber (p vs b <0.05) atment: mine (NS)	ne) aseline)	

nti, 1994								Quality	rating:	Fair	
esign:											
Study design:	RCT	DB	Parall	el	Run-in :	3 days		Setting:	Single C	enter	
					Wash out :	3 days		Country:	Uruguay	,	
Sample:	Numb	er Scre		•	Enrolled	Num	hber Withdrawn/	Lost to follo	ow-up/ An	alyzed	
			NR/	NR/	24		1/		0/	24	
Inclusion crite	ria:										
							rbances: time to		>30 minute	es; total	sleep time
	otal noct	urnai v	vake tim	e >20 m	ninutes; numb	er of nocturr	nal awakenings >	•3.			
Exclusion crite											
		/omen	of child-	bearing	age with inad	dequate cont	raception, breas	tfeeding ma	thers, pati	ents sul	ifering from
Pregnant w	omen, v						raception, breas m insufficient co				
Pregnant wo	omen, v ase or s	evere	psychiat	ric diso	rders, and pa	tients in who	m insufficient co	mpliance wa	as to be ex	pected.	Alcohol
Pregnant wo	omen, v ase or s	evere	psychiat	ric diso	rders, and pa	tients in who		mpliance wa	as to be ex	pected.	Alcohol
Pregnant wo organic dise abuse or inta exclusion.	omen, v ase or s ake of h	evere ypnotio	psychiat cs or any	ric diso ciolytics	rders, and pa and/or antide	tients in who pressants in	m insufficient co	mpliance wa	as to be ex	pected.	Alcohol
Pregnant wo organic dise abuse or inta	omen, v ase or s ake of h Mean	evere ypnotio age:	psychiat cs or any 47.3 yea	ric diso ciolytics	rders, and pa	tients in who pressants in	m insufficient co	mpliance wa	as to be ex	pected.	Alcohol
Pregnant w organic dise abuse or inta exclusion. Population:	omen, v ase or s ake of h	evere ypnotio age:	psychiat cs or any	ric diso ciolytics	rders, and pa and/or antide	tients in who pressants in	m insufficient co the seven days	mpliance wa	as to be ex	pected.	Alcohol
Pregnant we organic dise abuse or inta exclusion. Population: tervention:	omen, v ase or s ake of h Mean Gende	evere ypnotio age: er:	psychiat cs or anx 47.3 yea 88% Fer	ric diso ciolytics	rders, and pa and/or antide Ethnicity	tients in who pressants in	m insufficient co the seven days Primary	mpliance wa	as to be ex baseline p	pected.	Alcohol
Pregnant w organic dise abuse or inta exclusion. Population:	omen, v ase or s ake of h Mean	evere ypnotio age: er:	psychiat cs or any 47.3 yea	ric diso ciolytics	rders, and pa and/or antide	tients in who pressants in	m insufficient co the seven days	mpliance wa	as to be ex baseline p	pected.	Alcohol
Pregnant we organic dise abuse or inta exclusion. Population: tervention:	omen, v ase or s ake of h Mean Gende dosa	evere ypnotio age: er:	psychiat cs or anx 47.3 yea 88% Fer	ric diso ciolytics	rders, and pa and/or antide Ethnicity	tients in who pressants in	m insufficient co the seven days Primary	mpliance wa	as to be e> baseline p	pected.	Alcohol
Pregnant we organic dise abuse or inta exclusion. Population: tervention: Drug name	Mean, w ase or s ake of h Mean Gende dosa	evere ypnotio age: er: age	psychiat cs or anx 47.3 yea 88% Fer N=	ric diso ciolytics	rders, and pa and/or antide Ethnicity Duration	tients in who pressants in	m insufficient co the seven days Primary outcome	mpliance wa prior to the Outcome:	as to be e> baseline p : ncy	pected.	Alcohol
Pregnant we organic dise abuse or inta exclusion. Population: tervention: Drug name Zolpidem	Mean Mean Gende dosa	age: age: er: ng mg	psychiat cs or any 47.3 yea 88% Fer N= 8	ric diso ciolytics	rders, and pa and/or antide Ethnicity Duration 27 day	tients in who pressants in	m insufficient co the seven days Primary outcome	mpliance wa prior to the Outcome: sleep later	as to be e> baseline p : : ncy time	kpected.	Alcohol
Pregnant we organic dise abuse or inta exclusion. Population: tervention: Drug name Zolpidem Triazolam	Mean Mean Gende dosa	age: age: er: ng mg	psychiat cs or anx 47.3 yea 88% Fer N= 8 8	ric diso ciolytics	rders, and pa and/or antide Ethnicity Duration 27 day 27 day	tients in who pressants in	m insufficient co the seven days Primary outcome	mpliance wa prior to the Outcome: sleep later total sleep	as to be e> baseline p ncy time after slee	kpected.	Alcohol

Zolpidem	Triazolam	Placebo	
wake time (change from	n baseline) - night 15	-16: minutes (SD)	
-130 (135.9)	-32 (36.10)		P: NR
wake time (change from	n baseline) - night 29	-30: minutes (SD)	
-117 (114.6)	-39 (44.5)		P: NR
total sleep time (change	e from baseline) - nig	ht 15-16: minutes (SD)	
127 (136.7)	33 (35.8)		P: NR
total sleep time (change	e from baseline) - nig	ht 29-30: minutes (SD)	
113 (116.2)	41 (44.1)		P: NR
number of sleep cycles	(change from baselin	ne) - night 4-5: Number (SD)	
1.8 (2.1)	0.3 (1.3)		P: NR
number of sleep cycles	(change from baselin	ne) - night 15-16: Number (SD)	
1.7 (2.0)	0 (1)		P: NR
number of sleep cycles	(change from baselin	ne) - night 29-30: Number (SD)	
1.2 (1.3)	0.3 (1.5)		P: NR

ir, 1990						Quality	rating: Fair
esign:							
Study design:	RCT D	B Paralle	Run-in : Wash out	1 day : NR	S	Setting: Country:	Single Center Canada
Sample:	Number S	Creened/ El NR/	igible/ Enrolled NR/ 60		Number Withdrawn/	Lost to follo	ow-up/ Analyzed
Inclusion crite (a) sleep late		nin or more, ((b) two or more noc	turnal av	wakenings with difficu	Ilty falling ba	ack to sleep, (c) early final
morning awa hours.	akening in t	he absence o	of depression, and	(d) total	sleep time usually les	s than 5 ho	urs and always less than 6
abnormal la	ess interferin poratory fine	dings, other i	nterfering treatmen	ts or dis	orders, women of chi	ldbearing po	vere head trauma, significant otential not following e, or drug hypersensitivity.
Population:	Mean age	: 46.9 years	s Ethnicity	: NR			
	Gender:	47% Fem	-				
tervention: Drug name	dosage	N=	Duration		Primary outcome	Outcome	:
Zopiclone	3.75 mg	10	7 day			sleep indu	iction time
Zopiclone	7.5 mg	10	7 day			quality of s	sleep
Zopiclone	11.2 mg	10	7 day			quality of r	morning awakening
Zopiclone	15 mg	10	7 day			hangover	effects
Flurazepam	30 mg	10	7 day				
Placebo	NA mg	10	7 day				
ficacy:							
sleep quest Z	opiclone	Fluraz	zepam				
sleep indu	uction time:	Score					
	NR	Ν	IR				P: NS
quality of	sleep: Scor	е					
	NR	Ν	IR				P: NS
quality of	morning aw	vakening: Sco	ore				
	NR	Ν	IR				P: NS
	effects (exc	cept zopiclon	e 3.75mg): Score				
hangover							P: NS
hangover	NR	N	IR				F. N3
-			IR ng only), (higher sc	ore=bet	er): Score		F. N3

nangover enects (zopi	sone 3.75mg only), (nigher score=beller): Score	
7	5.5	P: <0.05
CGI		
Zopiclone	Flurazepam	
Severity of illness (exc	ept Zopiclone 3.75mg): Score	
NR	NR	P: NS
Severity of illness (Zop	iclone 3.75mg only): Score	
NR	better	P: NR
global improvement, (Z	opiclone at any dose): Score	
NR	NR	P: NS

								Quality	rating: Fair
Design:									
Study design:	RCT	DB	Parallel	Run-in : Wash out :	7 day: NR	6		Setting: Country:	Single Center Malaysia
Sample:	Num	ber Sc	reened/ Eligible NR/ NF			Number	/Withdrawn 16	-	ow-up/ Analyzed 0/ 44
Inclusion crite	ria:								
longer than	45 min	to fall		e than two noctu	irnal av	vakening			st 2 weeks duration; (a) takes own cause and difficulty in
a history of h	oncom	ensitiv		epines, (e) drug	and/or				owsiness, (c) psychosis, (d) ursing mother or intending to
Population:	Mear	n age:	38.4 years	Ethnicity:	NR				
	Geno		52% Female						
Drug name	dos	sage	N=	Duration			Primary outcome	Outcome	:
Zopiclone	7.5	mg	20	14 day				sleep late	ncy
Temazepam	20	mg	20	14 day				no. of time	es of awakening
Placebo	NA	mg	20	14 day				total dura	tion sleep
Efficacy:									
	opiclo		Temazepa at treatment we		s baseli	ne)			
Z total durat	•	sleep		ek 1: hours (p ve	s baseli	ne)			
total durat	ion of)7 (<0.	sleep .01)	at treatment we	ek 1: hours (p vs 5)					
z total durat 5.9 total durat	ion of)7 (<0.	sleep .01) sleep	at treatment we 5.90 (<0.0	ek 1: hours (p vs 5) ek 2: hours (p vs					
z total durat 5.9 total durat 6.0	ion of)7 (<0. ion of)3 (<0.	sleep .01) sleep .01)	at treatment we 5.90 (<0.09 at treatment we	ek 1: hours (p vs 5) ek 2: hours (p vs	s baseli				
z total durat 5.9 total durat 6.0 sleep late	ion of)7 (<0. ion of)3 (<0.	sleep .01) sleep .01) treatm	at treatment we 5.90 (<0.0 at treatment we 5.62 (NS)	ek 1: hours (p vs 5) ek 2: hours (p vs utes (p vs base	s baseli				
z total durat 5.9 total durat 6.0 sleep late 84	ion of 7 (<0. ion of 3 (<0. ncy at 4 (<0.0	sleep .01) sleep .01) treatm 05)	at treatment we 5.90 (<0.0 at treatment we 5.62 (NS) ent week 1: Mir	ek 1: hours (p vs 5) ek 2: hours (p vs utes (p vs base 5)	s baseli line)				
z total durat 5.9 total durat 6.0 sleep late 84 sleep late	ion of 7 (<0. ion of 3 (<0. ncy at 4 (<0.0	sleep .01) sleep .01) treatm .05) treatm	at treatment we 5.90 (<0.0 at treatment we 5.62 (NS) ent week 1: Mir 25.9 (<0.0	ek 1: hours (p vs 5) ek 2: hours (p vs utes (p vs base 5) utes (p vs base	s baseli line)				
z total durat 5.9 total durat 6.0 sleep late 84 sleep late 64	ion of 7 (<0. ion of 3 (<0. ncy at 4 (<0.0 ncy at .5 (<0.	sleep .01) sleep .01) treatm .05) treatm .05)	at treatment wer 5.90 (<0.0 at treatment wer 5.62 (NS) ent week 1: Mir 25.9 (<0.0 ent week 2: Mir	ek 1: hours (p vs 5) ek 2: hours (p vs utes (p vs base 5) utes (p vs base	s baseli line) line)	ne)			
z total durat 5.9 total durat 6.0 sleep late 84 sleep late 64 no. of awa	ion of 7 (<0. ion of 3 (<0. ncy at 4 (<0.0 ncy at .5 (<0.	sleep .01) sleep .01) treatm .05) treatm .05) gs at tr	at treatment we 5.90 (<0.0) at treatment we 5.62 (NS) ent week 1: Mir 25.9 (<0.0) ent week 2: Mir 26.1 (NS)	ek 1: hours (p vs 5) ek 2: hours (p vs utes (p vs base 5) utes (p vs base : Number (p vs	s baseli line) line)	ne)			
z total durat 5.9 total durat 6.0 sleep late 84 sleep late 64 no. of awa 0	ion of 7 (<0. ion of 03 (<0. ncy at 4 (<0.0 ncy at .5 (<0. akenin	sleep (.01) sleep (.01) treatm .05) treatm .05) gs at tr S)	at treatment we 5.90 (<0.0) at treatment we 5.62 (NS) ent week 1: Mir 25.9 (<0.0) ent week 2: Mir 26.1 (NS) reatment week 1	ek 1: hours (p vs 5) ek 2: hours (p vs utes (p vs base 5) utes (p vs base : Number (p vs)	ine) ine) baselin	ne) e)			
z total durat 5.5 total durat 6.0 sleep late 84 sleep late 64 no. of awa 0 no. of awa	ion of 7 (<0. ion of 03 (<0. ncy at 4 (<0.0 ncy at .5 (<0. akenin	sleep : .01) sleep : .01) treatm .05) gs at tr S) gs at tr	at treatment we 5.90 (<0.0) at treatment we 5.62 (NS) ent week 1: Mir 25.9 (<0.0) ent week 2: Mir 26.1 (NS) reatment week 1 1.2 (<0.05	ek 1: hours (p vs 5) ek 2: hours (p vs utes (p vs base 5) utes (p vs base : Number (p vs) :: Number (p vs	ine) ine) baselin	ne) e)			
z total durat 5.5 total durat 6.0 sleep late 84 sleep late 64 no. of awa 0 no. of awa	ion of 7 (<0. ion of 3 (<0. ncy at 4 (<0.0 ncy at 5 (<0. akenin .77 (N akenin 52 (<0.	sleep (.01) sleep (.01) treatm .05) treatm .05) gs at tr S) gs at tr .05)	at treatment we 5.90 (<0.0) at treatment we 5.62 (NS) ent week 1: Mir 25.9 (<0.0) ent week 2: Mir 26.1 (NS) reatment week 1 1.2 (<0.05 reatment week 2 1.28 (NS)	ek 1: hours (p vs 5) ek 2: hours (p vs utes (p vs base 5) utes (p vs base : Number (p vs) :: Number (p vs	ine) ine) baselin	ne) e)			
z total durat 5.9 total durat 6.0 sleep late 84 sleep late 64 no. of awa 0.6 global asse	ion of 7 (<0. ion of 3 (<0. ncy at 4 (<0.0 ncy at 5 (<0. akenin .77 (N akenin 52 (<0.	sleep : .01) sleep : .01) treatm .05) gs at tr S) gs at tr .05) mt effic	at treatment we 5.90 (<0.0) at treatment we 5.62 (NS) ent week 1: Mir 25.9 (<0.0) ent week 2: Mir 26.1 (NS) reatment week 1 1.2 (<0.05 reatment week 2 1.28 (NS)	ek 1: hours (p vs 5) ek 2: hours (p vs utes (p vs base 5) utes (p vs base : Number (p vs) :: Number (p vs	ine) ine) baselin	ne) e)			
z total durat 5.9 total durat 6.0 sleep late 64 no. of awa 0 no. of awa 0.6 global asse Z	ion of 7 (<0. ion of 3 (<0. 10 (<0.	sleep : .01) sleep : .01) treatm .05) gs at tr .05) gs at tr .05) nt effic ne	at treatment we 5.90 (<0.0 at treatment we 5.62 (NS) ent week 1: Mir 25.9 (<0.0 ent week 2: Mir 26.1 (NS) reatment week 1 1.2 (<0.05 reatment week 2 1.28 (NS)	ek 1: hours (p vs 5) ek 2: hours (p vs utes (p vs base 5) utes (p vs base : Number (p vs) :: Number (p vs	ine) ine) baselin	ne) e)			

Ponciano, 1990	onciano, 1990								Quality rating: Fair			
Design:												
Study design:	RCT	DB	Para	llel	Run-in :	7 days	Setting:	Single C	enter			
					Wash out :	7 days	Country:	Portugal				
Sample:	Numbe	er Scre	ened/	Eligible/	Enrolled	Number Withdra	awn/ Lost to folle	ow-up/ An	alyzed			
			NR/	NR/	26		2/	0/	24			

Inclusion criteria:

Patients were included in the study if they were unable to sleep without medication and had at least 3 of the following symptoms: sleep onset greater than 30 min, total sleep duration of less than 6 hours, poor subjectively reported sleep quality, and/or more than 2 nocturnal awakenings. Patients had to be within normal ranges for body weight, cardiac and haematological variables.

Exclusion criteria:

Those patients with a clinically significant history of psychiatric illness and those with a concurrent medical condition or therapy likely to interfere with the medication to be used were excluded. Patients with a history of drug use, those with excessive alcohol consumption (<1 litre of wine/day, or equivalent) pregnant or nursing women and all females of child bearing age without adequate contraception were also excluded.

Population:	Mean age: Gender:	30 years 46% Female	Ethnicity:	NR		
Intervention: Drug name	dosage	N=	Duration		Primary outcome	Outcome:
Zopiclone	7.5 mg	8	21 day			the ease of getting to sleep
Flurazepam	30 mg	8	21 day			quality of sleep
Placebo	NA mg	10	21 day			ease of awakening
						integrity of daytime behavior
						mood changes
						sleep onset
						sleep duration time

inical interview			
Zopiclone	Flurazepam	Placebo	
sleep onset latency at	day 21: minutes (p vs	placebo)	
30 (0.02)	28 (0.04)	60 (NA)	
sleep duration: minute	s (p vs placebo)		
393 (NS)	425 (0.05)	410 (NA)	
sleep duration: minute	es (p vs placebo) 425 (0.05)		
mood changes: Score			
NR	NR	NR	P: NS

adens, 1983	\$						Quality	rating:	Poor	
esign:										
Study design:	RCT	DB	Crossove		n: 6 days out: 35 days		Setting: Country:	Single C Belgium		
Sample:	Numb	er Scr		ible/ Enrolleo NR/ 12		hber Withdrawn/ 0/	Lost to follo	w-up/An 0/	alyzed 12	
Inclusion crite	ria:									
complaints v total sleepin	were to g time o	includ during;	e two or moi (3) number	re of the follow	59 years and com wing criteria: (1) s awakenings equa ified as poorly res	leep onset laten I to or higher tha	cy equal to c in 3; (4) total	or longer ti I waking ti	han 30 min; me during tl	(2) he
	nder 45				se of drugs or alco					i
					irdation; (5) physic and susceptible to	cal or psychiatric alter the evalua				
	metabo	lism, o	or excretion of	of the drugs a	ind susceptible to					
absorption, Population:	metabo	lism, o age:		of the drugs a Ethn						
absorption,	metabo Mean	lism, o age: er:	or excretion of NR years	of the drugs a Ethn	icity: NR			ypnotic eff		
absorption, Population: tervention:	metabo Mean Gend dos	lism, o age: er:	or excretion of NR years 100% Fema	of the drugs a Ethn ale	icity: NR	alter the evalua	tion of the hy	ypnotic eff		
absorption, Population: tervention: Drug name	Mean Gend dos 7.5	lism, o age: er: age	NR years 100% Fema N=	of the drugs a Ethn ale Duratio	icity: NR	alter the evalua	tion of the hy Outcome:	ypnotic eff		
absorption, Population: tervention: Drug name Zopiclone	Mean Gend dos 7.5	lism, o age: er: age mg	NR years 100% Fema N= 12	of the drugs a Ethn ale Duratio 13 day	icity: NR	alter the evalua	tion of the hy Outcome: no. of awa	ypnotic eff kenings time		
absorption, Population: tervention: Drug name Zopiclone	Mean Gend dos 7.5	lism, o age: er: age mg	NR years 100% Fema N= 12	of the drugs a Ethn ale Duratio 13 day	icity: NR	alter the evalua	tion of the hy Outcome: no. of awa total sleep	ypnotic eff kenings time et latency	ects.	
absorption, Population: tervention: Drug name Zopiclone	Mean Gend dos 7.5	lism, o age: er: age mg	NR years 100% Fema N= 12	of the drugs a Ethn ale Duratio 13 day	icity: NR	alter the evalua	Outcome: no. of awa total sleep sleep onse	ypnotic eff kenings time et latency	ects.	
absorption, Population: tervention: Drug name Zopiclone	Mean Gend dos 7.5	lism, o age: er: age mg	NR years 100% Fema N= 12	of the drugs a Ethn ale Duratio 13 day	icity: NR	alter the evalua	Outcome: no. of awa total sleep sleep onse	ypnotic eff kenings time et latency	ects.	
absorption, f Population: tervention: Drug name Zopiclone Flurazepam ficacy: sleep quest	metabo Mean Gend dos 7.5 30	lism, o age: er: age mg mg	NR years 100% Fema N= 12	of the drugs a Ethn ale Duratio 13 day	nd susceptible to icity: NR 	alter the evalua	Outcome: no. of awa total sleep sleep onse	ypnotic eff kenings time et latency	ects.	
absorption, f Population: tervention: Drug name Zopiclone Flurazepam ficacy: sleep quest	metabo Mean Gend dos 7.5 30	lism, o age: er: age mg mg	NR years 100% Fema N= 12	of the drugs a Ethn ale 13 day 13 day	icity: NR	alter the evalua	Outcome: no. of awa total sleep sleep onse	ypnotic eff kenings time et latency	ects.	
absorption, f Population: tervention: Drug name Zopiclone Flurazepam ficacy: sleep quest	metabo Mean Gend dos 7.5 30 tionnai	re	NR years 100% Fema N= 12 12	of the drugs a Ethn ale 13 day 13 day	nd susceptible to icity: NR 	alter the evalua	Outcome: no. of awa total sleep sleep onse	ypnotic eff kenings time et latency	ects.	

24903 (<0.01)

1117 (<0.05)

91.4 (<0.01)

as below

sleep onset latency: seconds (p vs placebo)

sleep efficiency index: Score (p vs placebo)

All sleep items comparing two treatment: Number

25129 (<0.05)

1174 (<0.1)

92.2 (<0.05)

as below

23225 (NA)

1452 (NA)

83.6 (NA)

P: NS

osenberg, 19	94			Quality rating: Poor		
Design:						
Study design:	RCT	DB	Parallel	Run-in :	NR	Setting: Multicenter
				Wash out :	NR	Country: Denmark
Sample:	Numbe	er Scre	ened/ Eligible	e/ Enrolled		Number Withdrawn/ Lost to follow-up/ Analyzed
			NR/ NF	R/ 178		5/ 34/ 139
Inclusion criter	ria:					
criteria: 1) ha	ave more	e thán	three awaken) slee	ase one week complying with at least two of the following ping time less than six hours per night, 3) time to fall asleep ring the night.

Exclusion criteria:

General exclusion criteria were psychiatric disease requiring medication, insomnia because of well-defined illness, and treatment with hypnotics or BZDs within four weeks prior to the study. The patients was excluded from data analysis if his diary consisted of comments from less than three days, if his case record form was incompletely filled in by the doctor, or if he had taken hypnotics other than blinded drugs in the study

Population:	Mean age: Gender:	54 years 0% Female	Ethnicity:	NR		
Intervention: Drug name	dosage	N=	Duration		Primary outcome	Outcome:
Zolpidem	10 mg	71	14 day			duration of sleep
Triazolam	0.25 mg	68	14 day			no. of nocturnal awakenings
						sleep quality
						day quality

eported by patients								
Zolpidem	Triazolam							
total sleep times: hours (range)								
6.9 (4.8-9.1)	7.1 (5.0-8.4)	P: NS						
No. of awakenings: Nu	nber (range)							
1 (0-4)	1 (0-5)	P: NS						
isual analogue scales								
Zolpidem	Triazolam							
sleep quality, bad-good	: Score (Range)							
69 (15-96)	69 (18-98)	P: NS						
morning feeling, bad-go	ood: Score (Range)							
64 (8-94)	56 (9-98)	P: NS						
daytime alertness. una	ert-alert: Score (Range)							
65 (6-92)	63 (26-92)	P: NS						
subjective day feeling:	Score (Range)							
64 (6-93)	60 (9-92)	P: NS						

vestri, 1996				Quality rating: Fair						
esign:										
Study design:	RCT	DB	Para	llel	Run-in :	3 days	Setting:	Multicent	er	
					Wash out :	No days	Country:	Italy		
Sample:	Numbe	r Scre	ened/	Eligible/	Enrolled	Number W	ithdrawn/ Lost to foll	ow-up/ Ana	alyzed	
			NR/	NR/	22		0/	2/	20	
Inclusion crite	ria:									
a recurrence	e of short	-term s	situatic	onal insor	nnia) or poor s	sleepers with subje	siological insomnia (e ective reporting of at l	east two ou	it of these four	
a recurrence complaints:	e of short time to fa >3. The	-term s all asle	situatio ep >30	onal insor) minutes	nnia) or poor s , total sleep d	sleepers with subject uration <6 hours, t	0	east two ou iinutes, and	it of these four l/or number or	
a recurrence complaints: awakenings polysomnog Exclusion crite	e of short time to fa >3. The raphy. eria:	term : all asle se sub	situatic ep >30 ojective	onal insor) minutes e inclusio	nnia) or poor s , total sleep d n criteria had t	sleepers with subje uration <6 hours, t to be confirmed by	ective reporting of at I cotal wake time >20 m the objective assess	east two ou inutes, and ment throug	it of these four I/or number or gh	
a recurrence complaints: awakenings polysomnog Exclusion crite Pregnant or psychiatric of Rating Scale syndrome, s	e of short time to fa >3. The raphy. eria: lactating diseases, e for Dep deep obs duick's tim	-term s all asle se sub wome also s ression tructive ne <70	situatic ep >30 ojective en; wor screene n (tota e apne %); int	men of ch ed by me l score > 7 a of >7 n take of ar	nnia) or poor total sleep d n criteria had ild-bearing ag ans of both Ha 16); neurologic ninutes duration ny psychotropi	sleepers with subje uration <6 hours, t to be confirmed by ge without adequat amilton Rating Sca cal diseases (myoo on); severe interna	ective reporting of at I total wake time >20 m	east two ou inutes, and ment throug coperative p core >16) a lisorders, re liseases; he	it of these four l/or number or gh patients; severe nd Hamilton estless legs emocoagulation	

• • •	Gender:	55% Female			
Intervention: Drug name	dosage	N=	Duration	Primary outcome	Outcome:
Zolpidem	10 mg	10	2 week		total sleep time
Triazolam	0.25 mg	12	2 week		sleep onset latency
					sleep efficiency
					no. of awakenings
					wake time after sleep onset
					REM sleep
					quiet-disturbed sleep
					alert-drowsy awakening

olysomnography		
Zolpidem	Triazolam	
sleep onset latency- ch	ange from baseline- night 14: minutes (SD)	
-23 (21.38)	-14.8 (30.92)	P: NS
total sleep time- change	e from baseline- night 14: minutes (SD)	
61.1 (43.97)	54.4 (49.70)	P: NS
sleep efficiency- change	e from baseline- night 14: % (SD)	
14.3 (10.39)	10.7 (7.35)	P: NS
wake time after sleep o	nset- change from baseline- night 14: minutes (SD)	
-44.9 (44.82)	-37 (25.62)	P: NS
no. of awakenings- cha	nge from baseline- night 14: Number (SD)	
-2.2 (3.51)	-3.5 (2.45)	P: NS

stri, 1996		Quality rating: Fair
questionnaire		
Zolpidem	Triazolam	
time to fall asleep- char	nge from baseline- night 14: minutes (SD)	
-41.8 (32.51)	-19.9 (36.83)	P: NS
total sleep time- change	e from baseline- night 14: minutes (SD)	
66.9 (44.53)	81.4 (46.9)	P: NS
total wake time- change	e from baseline- night 14: minutes (SD)	
-12.1 (9.88)	-11.4 (8.53)	P: NS
no. of nocturnal awaker	nings- change from baseline- night 14: Number (SD)	
-1.4 (0.75)	-1.2 (1.63)	P: NS
visual analogue scale		
Zolpidem	Triazolam	
sleep quality- change fr	rom baseline- night 14: Score (SD)	
-22.8 (17.90)	-31.8 (20.66)	P: NS
awakening quality- cha	nge from baseline- night 14: Score (SD)	
-16.3 (18.14)	-26.9 (23.32)	P: NS

ngh, 1990						Quality rating: Fair
esign:						
Study design:	RCT DE	B Parallel	Run-in : Wash out :	4 days NR		Setting: Single Center Country: Canada
Sample:	Number Sc	reened/ Eligibl	e/ Enrolled	Numb	er Withdrawn/	Lost to follow-up/ Analyzed
		NR/ 6	1/ 60		3/	0/ 57
Inclusion crite NR	ria:					
abuse, coffe significant m	nd neurotic p e or tea abus nedical condi gnancy, lacta	se, neurological tion interfering v	disorders, estat with sleep, those	blished sleep treatment wh	apnoea and dru ich could modi	ntal retardation, chronic alcoholism, dr ug hypersensitivity. Patients with any ify drug kinetics were also excluded. zed contraceptive programme preclud
Population:	Mean age:	39.6 years	Ethnicity:	NR		
	Gender:	53% Female	·			
Drug name	dosage	N=	Duration		Primary outcome	Outcome:
Zopiclone	7.5 mg		24 day			duration of sleep onset
Zopiclone	11.2 mg		24 day			sleep soundness
Flurazepam	30 mg		24 day			quality of sleep
Zopi		Zopiclone 11.	25mg Flurazep			
	7 (<0.01)	6.9 (<0.0 ²		<0.01)		
sleep sou	ndness at w	eek 4: Score (p	vs placebo)	,		
•	7 (<0.01)	6.6 (<0.0 ²	• •	<0.01)		
6.		k A: Score (n vs	s placebo)			
	sleep at wee		1	0.04)		
quality of	sleep at wee .2 (<0.01)		1) 12.2 (<0.01)		
quality of 11	.2 (<0.01)	11.0 (<0.0		,	l: Score (p vs f	lurazepam)
quality of 11 duration o	.2 (<0.01)	11.0 (<0.0	ess, quality of sl	,	l: Score (p vs f	lurazepam)
quality of 11 duration o as a	.2 (<0.01) of sleep onse	11.0 (<0.0 t, sleep soundn	ess, quality of sl	eep at week 4	l: Score (p vs fl	lurazepam)
quality of 11 duration o as a CGI	.2 (<0.01) of sleep onse	11.0 (<0.0 t, sleep soundn as above (۱	ess, quality of sl	eep at week 4 ve (NA)	I: Score (p vs fl	lurazepam)
quality of 11 duration o as a CGI Zopi	.2 (<0.01) of sleep onse above (NS) clone 7.5mg	11.0 (<0.0 t, sleep soundn as above (f Zopiclone 11.	ess, quality of sl NS) as abo	eep at week 4 ve (NA) am 30mg	I: Score (p vs f	lurazepam)

tip, 1999								Quality	rating:	Fair
Design:										
Study design:	RCT	DB	Parallel		un-in : ash out :	7 days 7 days		Setting: Country:	Single C Canada	enter
Sample:	Number	Scre	ened/ Eligi NR/	ble/ En NR/	rolled 60	1	lumber Withdraw	vn/ Lost to follo 2/	ow-up/ An 8/	alyzed 50
Inclusion crite	ria:									
Daytime fati	gability, d	iminis	shed power	of conce	entration at	t work a	n mild non-psych nd at least two of than two awaker	f the following s	symptoms:	falling asleep
Exclusion crite	eria:									
Population:	Mean a	ge:	42.6 years	I	Ethnicity:	NR				
	Gender	:	% Female							
Drug name	dosag	e	N=	Dui	ration		Primar outcon		:	
Zopiclone	7.5 m	g	19	21 0	day			anxiety		
Temazepam	30 m	g	16	21 (day			quality of	sleep	
Placebo	NA m	g	15	21 (day			sleep ons	et	
								sleep dep	oth	
								wakefulne	ess and atte	ention
Efficacy:										
Hamilton se	cale for a	nxiet	y							
Z	opiclone		Temaze	pam	Plac	cebo				
anxiety: S	core									
	NR		NR		N	R				P: NS
Self-rating	question	naire	for sleep							
Z	opiclone		Temaze	pam						
sleep ons	et at trea	tment	t week 1: So	ore (p v	s placebo)					
N	R (<0.01)		NR (<0	.01)						
sleep dep	th at trea	tmen	t week 1: So	core (p v	s placebo))				
	R (<0.01)		NR (<0	.01)						
Ν										
N auditory an	d visual	span	test							
auditory an	d visual opiclone	span	test Nitrazej	bam	Plac	cebo				
auditory an	opiclone		Nitrazej	oam	Plac	cebo				

mminen, 198	37		Quality rating: Poor						
esign:									
Study design:	RCT I	DB Parallel	Run-in :	7 days	S	etting:	Multicent	er	
			Wash out :	NR	С	ountry:	Finland		
Sample:	Number	Screened/ Eligibl	e/ Enrolled	Number Wit	hdrawn/ Lo	st to follow	w-up/ Ana	alyzed	
		NR/ 13	0/ 94		0/		0/	94	
Inclusion crite	ria:								
duration <6	ey also had	to have been pre	esent prior to trea	itment in treated ca	ses): latenc	y or sieep	urnal awak)min, tota oning >3(l sleep
duration <6. awakening : Exclusion crite Known hype	5hours, no >2hour bef eria: ersensitivity	cturnal awakening ore scheduled tim to benzodiazepir	gs >2 per night, t e. nes, major psych	ime to fall asleep a iatric disorders, sor	ter at least	one noctu ers directl	ırnal awak y causing	ening >30 insomnia	or likely
duration <6. awakening : Exclusion crite Known hype to interfere pregnant du	5hours, no >2hour before eria: ersensitivity with the ass ring the tria	cturnal awakening ore scheduled tim to benzodiazepir essments, knowr II, frequent intake	gs >2 per night, t e. nes, major psych n alcoholism or d s of other medica	ime to fall asleep a iatric disorders, sor Irug addiction, preg ation likely to interfe	ter at least natic disord nant women	one noctu ers directl	ırnal awak y causing	ening >30 insomnia	or likely
duration <6. awakening = Exclusion crite Known hype to interfere	5hours, no >2hour before eria: ersensitivity with the ass ring the tria Mean ag	cturnal awakening ore scheduled tim to benzodiazepir essments, knowr I, frequent intake 2: 47 years	gs >2 per night, t e. nes, major psych n alcoholism or d	ime to fall asleep a iatric disorders, sor Irug addiction, preg ation likely to interfe	ter at least natic disord nant women	one noctu ers directl	ırnal awak y causing	ening >30 insomnia	or likely
duration <6. awakening s Exclusion crite Known hype to interfere pregnant du Population:	5hours, no >2hour before eria: ersensitivity with the ass ring the tria	cturnal awakening ore scheduled tim to benzodiazepir essments, knowr II, frequent intake	gs >2 per night, t e. nes, major psych n alcoholism or d s of other medica	ime to fall asleep a iatric disorders, sor lrug addiction, preg ation likely to interfe NR	ter at least natic disord nant womer are with slee	one noctu ers directl	ırnal awak y causing	ening >30 insomnia	or likely
duration <6. awakening : Exclusion crite Known hype to interfere pregnant du	5hours, no >2hour before eria: ersensitivity with the ass ring the tria Mean ag	cturnal awakening ore scheduled tim to benzodiazepir essments, knowr I, frequent intake 2: 47 years 77% Female	gs >2 per night, t e. nes, major psych n alcoholism or d s of other medica	ime to fall asleep a iatric disorders, sor lrug addiction, preg ation likely to interfe NR P	iter at least natic disord nant womer re with slee rimary	one noctu ers directl	ırnal awak y causing	ening >30 insomnia	or likely
duration <6. awakening s Exclusion crite Known hype to interfere pregnant du Population: tervention:	Shours, no >2hour beforeria: Prsensitivity with the ass ring the triat Mean ag Gender:	cturnal awakening ore scheduled tim to benzodiazepir essments, knowr I, frequent intake 2: 47 years 77% Female	gs >2 per night, t e. nes, major psych n alcoholism or d s of other medica Ethnicity:	ime to fall asleep a iatric disorders, sor lrug addiction, preg ation likely to interfe NR P	iter at least natic disord nant womer are with slee rimary utcome O	one noctu ers directl n or wome p.	irnal awak y causing n who ma	ening >30 insomnia	or likely
duration <6. awakening : Exclusion crite Known hype to interfere pregnant du Population: tervention: Drug name	5hours, no >2hour beforeria: ersensitivity with the ass ring the tria Mean ag Gender: dosage	cturnal awakening ore scheduled tim to benzodiazepir essments, known I, frequent intake 2: 47 years 77% Female N=	gs >2 per night, t e. nes, major psych n alcoholism or d s of other medica Ethnicity: Duration	ime to fall asleep a iatric disorders, sor lrug addiction, preg ation likely to interfe NR P	ter at least natic disord hant womer ere with slee rimary utcome O	one noctu ers directl o r wome p. utcome:	rnal awak y causing n who ma t latency	ening >30 insomnia	or likely
duration <6. awakening s Exclusion crite Known hype to interfere pregnant du Population: tervention: Drug name Zopiclone	Shours, no >2hour beforeria: ersensitivity with the ass ring the tria Mean ag Gender: dosage 7.5 mg	cturnal awakening ore scheduled tim to benzodiazepin essments, known I, frequent intake 2: 47 years 77% Female N= 52	gs >2 per night, t e. hes, major psych n alcoholism or d s of other medica Ethnicity: Duration 42 day	ime to fall asleep a iatric disorders, sor lrug addiction, preg ation likely to interfe NR P	rimary utcome O	ers directl or wome p. utcome: eep onset	rnal awak y causing n who ma t latency	ening >30 insomnia	or likely

lary		
Zopiclone	Nitrazepam	
sleep onset latency, me	an score: Score	
32.6	33.1	P: NS
quality of sleep, mean	core: Score	
34	30.2	
lobal evaluation		
Zopiclone	Nitrazepam	
efficacy (1=poor; 5=exc	ellent): Score	
3.2	3.1	P: NS

ninen, 1987		Quality rating: Poor
sleep questionnaire		
Zopiclone	Nitrazepam	
latency of sleep onset	>30 min: %	
38	44.4	P: 0.07
duration of sleep <6.5	hours: %	
37.5	37.7	P: NS
>2 night awakenings: 9	6	
18.4	24.4	P: NS
time to fall asleep after	a night awakenings >30 min: %	
14.6	22.2	P: NS
awakening at least 2 h	ours before expected time: %	
20.4	20	P: NS
Norris Mood Rating		
Zopiclone	Nitrazepam	
overall: Score		
-	better	P: <0.05

					•	, .			
an der Kleijn,	1989					Qualit	y rating:	Fair	
Design:									
Study design:	RCT	DB	Crossover	Run-in :	2 days	Setting:	NR		
				Wash out :	7 days	Country	: Nijmege	en	
Sample:	Numbe	er Scre	ened/ Eligible/	Enrolled	Number	·Withdrawn/Lost to fo	llow-up/ Ar	nalyzed	
			NR/ 60/	55		2/	0/	53	
Inclusion crite	ria:								
	severa	l times	at night and dif		g asleep afterwa	ards			
Exclusion crite	eria:								
time, or patie 2. Patients v 3. Patients s 4. Patients u physical stre	ents who who took suffering inable to ess situa	bse psy benzo from p fill in tions li	ychotropic medi odiazepine tranco oainful disorder a sleep questio	cine was chan quillizers or hy nnaire, those v during the stu	iged during the photics in doses with a history of	e who received anothe study period. s at least twice that rec alcohol and/or drug ab r kidney disorders, mya	ommended use, who liv	before the st ved in psychia	tudy. atric or

Population:	Mean age: Gender:	53 years 71% Female	Ethnicity:	NR		
Intervention: Drug name	dosage	N=	Duration		Primary outcome	Outcome:
Zopiclone	7.5 mg	53	5 day		\checkmark	Sleep quality
Temazepam	20 mg	53	5 day		\checkmark	Latency of sleep onset
					\checkmark	Status after awaking

Efficacy:

Questionnaire in the morning about sleep

Zopiclone	Temazepam	Placebo		
Sleep quality - average	score: Score (p vs z	opiclone)		
3.9 (NA)	3.9 (0.096)	3.4 (<0.001)		
Latency of sleep onset	- average score: Sco	re (p vs zopiclone)		
3.8 (NA)	3.7 (0.106)	3.1 (<0.01)		
Status after awaking - a	average score: Score	(p vs zopiclone)		
3.5 (NA)	3.4 (0.45)	3.2 (<0.01)		
eference				
Zopiclone	Temazepam	Placebo	Z and T	
Sleep better: Number				
16	10	6	2	P: NR
Better status during the	e day: Number			
29	23	0	0	P: NR
8	3	5	2	P: NR

oshaar, 2004							Quality rating: Fair
esign:							
Study design:	RCT	DB	Parallel	Run-in : Wash out :	NR 4 days		Setting: Multicenter Country: Netherlands
Sample:	Num	ber Sci	reened/ Eligible NR/ NF		Ν	lumber Withdrawn/ 9/	Lost to follow-up/ Analyzed 5/ 159
Inclusion criter Patients wer between 18	e inclu			y were diagnose	d with p	rimary insomnia acc	cording to DSM-III-R and were aged
	n othei			re somatic disor study or occupa			e of psychotropic medication, complaints
Population:	Mea	n age:	46.1 years	Ethnicity:	NR		
	Gen	der:	0% Female				
ntervention: Drug name	dos	sage	N=	Duration		Primary outcome	Outcome:
Zolpidem	10	mg	74	28 day		\checkmark	Total sleep time (TST)
Temazepam	20	mg	85	28 day		\checkmark	Sleep onset latency (SOL)
							Wake time after sleep onset (WASO)
							Time in bed (TIB)
fficacy:							
Sleep/wake	diarie	es					
•	olpide		Temazepa	m			
total sleep	time:	minute	es (SD)				
2	13 (7	8)	386 (82)				P: NS
sleep ons	et late	ncy: m	inutes (SD)				
	46 (33	•	46 (34)				P: NS
wake time	after	sleep:	minutes (SD)				
	40 (36	•	39 (38)				P: NS
	d	utes (S	SD)				
time in be	a. min	- (-	,				P: NS
time in be بر	530 (7	7)	508 (58)				
	530 (7	,	()				
swel tot	530 (7	re: Sco	()				P: NS
sWEL tot 3	530 (7 al sco 5.7 (7	, re: Sco .7)	re (SD)				P: NS

esign: Study design: RCT DB Parallel Run-in: 7 days Setting: Multicenter Sample: Number Screened/ Eligible/ Enrolled Number Withdrawn/ Lost to follow-up/ Analyzed NR/ 589/ 306 28/ 0/ 278 Inclusion criteria: Patients had to have a minimum of a 1-month history of disturbed sleep, characterized by a self-reported sleep latency (SSL) of 4-6 hours at least three nights per week. Exclusion criteria: Any significant medical or psychiatric disorder (as determined by clinical interview by a physician), a history suggestive of sleep apnea or periodic limb movement disorder, smoking of more than 10 cigarettes per day, weight varying by more than 25% from desirable weight based on the Metro-politan Life Insurance Table, pregnancy or risk of becoming pregnant, and lactation. Population: Mean age: NR years Ethnicity: NR Gender: 0% Female V Itrazodone 50 mg 100 14 day Placebo NA mg 104 14 day Placebo NA mg 104 14 day Illouity of sleep incuring sleepiness ability to concentrate in the morning ingradue ingradue ingradue ingradue Idlo 14 day iseep duration iseep ouration industry <th>alsh, 1998a</th> <th></th> <th></th> <th></th> <th></th> <th></th> <th></th> <th>Quality</th> <th>rating</th> <th>: Fair</th>	alsh, 1998a							Quality	rating	: Fair
Wash out : NR Country: US Sample: Number Screened/ Eligible/ Enrolled NR/ 589/ 306 Number Withdrawn/ Lost to follow-up/ Analyzed 28/ 0/ 278 Inclusion criteria: Patients had to have a minimum of a 1-month history of disturbed sleep, characterized by a self-reported sleep latency (SSL of at least 30 min, and a self-reported sleep duration (SSD) of 4-6 hours at least three nights per week. Exclusion criteria: Any significant medical or psychiatric disorder (as determined by clinical interview by a physician), a history suggestive of sleep apnea or periodic limb movement disorder, smoking of more than 10 cigarettes per day, weight varying by more than 25% from desirable weight based on the Metro-politan Life Insurance Table, pregnancy or risk of becoming pregnant, and lactation. Population: Mean age: NR years Gender: 0% Female Ethnicity: NR Gender: 0% Female tervention: Primary Outcome Outcome: Zolpidem 10 mg 102 14 day Placebo NA mg 104 14 day Placebo NA mg 104 14 day Wase time after sleep onset quality of sleep morning sleepiness ability to concentrate in the morning ability to concentrate in the morning disruption caused by insomnia	esign:									
Sample: Number Screened/ Eligible/ Enrolled NR/ 589/ 306 Number Withdrawn/ Lost to follow-up/ Analyzed 28/ 0/ 278 Inclusion criteria: Patients had to have a minimum of a 1-month history of disturbed sleep, characterized by a self-reported sleep latency (SSL of at least 30 min, and a self-reported sleep duration (SSD) of 4-6 hours at least three nights per week. Exclusion criteria: Any significant medical or psychiatric disorder (as determined by clinical interview by a physician), a history suggestive of sleep apnea or periodic limb movement disorder, smoking of more than 10 cigarettes per day, weight varying by more than 25% from desirable weight based on the Metro-politan Life Insurance Table, pregnancy or risk of becoming pregnant, and lactation. Population: Mean age: NR years Ethnicity: NR Gender: 0% Female Primary outcome Outcome: Image: sleep latency Zolpidem 10 mg 102 14 day sleep latency sleep latency Placebo NA mg 104 14 day sleep latency sleep latency Placebo NA mg 104 14 day sleep latency sleep latency Placebo NA mg 104 14 day sleep latency moming sleep onset guality of sleep more of awakenings wake time after sleep onset	Study design:	RCT	DB	Paralle	el Run-in :	7 days		Setting:	Multice	enter
NR/ 589/ 306 28/ 0/ 278 Inclusion criteria: Patients had to have a minimum of a 1-month history of disturbed sleep, characterized by a self-reported sleep latency (SSL of at least 30 min, and a self-reported sleep duration (SSD) of 4-6 hours at least three nights per week. Exclusion criteria: Any significant medical or psychiatric disorder (as determined by clinical interview by a physician), a history suggestive of sleep apnea or periodic limb movement disorder, smoking of more than 10 cigarettes per day, weight varying by more than 25% from desirable weight based on the Metro-politan Life Insurance Table, pregnancy or risk of becoming pregnant, and lactation. Population: Mean age: NR years Ethnicity: NR Gender: 0% Female tervention: 0/0 14 day Placebo NA mg 104 14 day Placebo NA mg 104 14 day Placebo NA mg 104 14 day Inclusion 9 sleep latency Inclusion Inumber of awakenings Inumber of awakenings Industrian Industrian Industrian Inclusion Industrian Industrian Primary Industrian Industrian Industrian Industrian Industrian Vistigation Indu					Wash out :	NR		Country:	US	
Inclusion criteria: Patients had to have a minimum of a 1-month history of disturbed sleep, characterized by a self-reported sleep latency (SSL of at least 30 min, and a self-reported sleep duration (SSD) of 4-6 hours at least three nights per week. Exclusion criteria: Any significant medical or psychiatric disorder (as determined by clinical interview by a physician), a history suggestive of sleep apnea or periodic limb movement disorder, smoking of more than 10 cigarettes per day, weight varying by more than 25% from desirable weight based on the Metro-politan Life Insurance Table, pregnancy or risk of becoming pregnant, and lactation. Population: Mean age: NR years Ethnicity: NR Gender: 0% Female Primary Outcome Outcome: Zolpidem 10 mg 102 14 day Image: sleep duration Primary Placebo NA mg 104 14 day Image: sleep duration ease of falling asleep Placebo NA mg 104 14 day Image: sleep duration ease of falling asleep Image: sleep latency	Sample:	Num	ber Sci		0	Num		Lost to follo	•	,
Patients had to have a minimum of a 1-month history of disturbed sleep, characterized by a self-reported sleep latency (SSL of at least 30 min, and a self-reported sleep duration (SSD) of 4-6 hours at least three nights per week. Exclusion criteria: Any significant medical or psychiatric disorder (as determined by clinical interview by a physician), a history suggestive of sleep apnea or periodic limb movement disorder, smoking of more than 10 cigarettes per day, weight varying by more than 25% from desirable weight based on the Metro-politan Life Insurance Table, pregnancy or risk of becoming pregnant, and lactation. Population: Mean age: NR years Ethnicity: NR Gender: 0% Female tervention: Duration Zolpidem 10 mg 10 mg 102 14 day Trazodone 50 mg 100 14 day Placebo NA mg 104 14 day Placebo NA mg 104 14 day Image: Image: Image: Image: Image: Image: Image: Image: Image: Image: Image: Image: Image: Image: Image: Image: Image: And the date: Image: Image: Image: <td< td=""><td></td><td></td><td></td><td>NR/</td><td>589/ 306</td><td></td><td>28/</td><td></td><td>0/</td><td>278</td></td<>				NR/	589/ 306		28/		0/	278
of at least 30 min, and a self-reported sleep duration (SSD) of 4-6 hours at least three nights per week. Exclusion criteria: Any significant medical or psychiatric disorder (as determined by clinical interview by a physician), a history suggestive of sleep apnea or periodic limb movement disorder, smoking of more than 10 cigarettes per day, weight varying by more than 25% from desirable weight based on the Metro-politan Life Insurance Table, pregnancy or risk of becoming pregnant, and lactation. Population: Mean age: NR years Gender: 0% Female tervention: Drug name dosage N= Duration Zolpidem 10 mg 102 14 day Frazodone 50 mg 100 14 day Placebo NA mg 104 14 day N Gender: V Second State Sta				inimum of	a 1 month history of	diaturbadal		ad by a calf	roportor	d alaan latanay (CCL)
Any significant medical or psychiatric disorder (as determined by clinical interview by a physician), a history suggestive of sleep apnea or periodic limb movement disorder, smoking of more than 10 cigarettes per day, weight varying by more than 25% from desirable weight based on the Metro-politan Life Insurance Table, pregnancy or risk of becoming pregnant, and lactation. Population: Mean age: NR years Ethnicity: NR Gender: 0% Female tervention: Duration Zolpidem 10 mg 102 14 day Image: sleep latency Trazodone 50 mg 100 14 day Image: sleep duration sleep latency Placebo NA mg 104 14 day Image: sleep duration number of awakenings uality of sleep number of awakenings Image: sleep latency Image: sleep latency Image: sleep latency Value Value Value Image: sleep latency Image: sleep latency Image: sleep latency Placebo NA mg 104 14 day Image: sleep latency Image: sleep latency Image: sleep latency Image: sleep latency Image: sleep latency Image: sleep latency Image: sleep latency Image: sleep latency Image: sleep latency Image: sleep latency										sleep latency (SSL)
Gender: 0% Female Drug name dosage N= Duration Zolpidem 10 mg 102 14 day Trazodone 50 mg 100 14 day Placebo NA mg 104 14 day Image: Note that the more the more the more that the more the mor	sleep apnea 25% from de	or per	riodic li	mb moven	nent disorder, smoki	ng of more th	an 10 cigarettes	s per day, w	eight va	rying by more than
Gender: 0% Female Drug name dosage N= Duration Zolpidem 10 mg 102 14 day Trazodone 50 mg 100 14 day Placebo NA mg 104 14 day Image: Note that the more the more the more that the more the mor	Population:	Mea	n age:	NR years	Ethnicity	: NR				
Drug name dosage N= Duration Zolpidem 10 mg 102 14 day Trazodone 50 mg 100 14 day Placebo NA mg 104 14 day Image: New of the second sec				-	-					
Trazodone 50 mg 100 14 day ✓ sleep duration Placebo NA mg 104 14 day □ ease of falling asleep		dos	sage	N=	Duration			Outcome	:	
Placebo NA mg 104 14 day ease of falling asleep	Zolpidem	10	mg	102	14 day		\checkmark	sleep later	ncy	
	Trazodone	50	mg	100	14 day		\checkmark	sleep dura	ation	
wake time after sleep onset quality of sleep morning sleepiness ability to concentrate in the morning disruption caused by insomnia	Placebo	NA	mg	104	14 day			ease of fa	lling asle	eep
quality of sleep morning sleepiness ability to concentrate in the morning disruption caused by insomnia								number of	awaken	nings
morning sleepiness ability to concentrate in the morning disruption caused by insomnia								wake time	after sle	eep onset
ability to concentrate in the morning disruption caused by insomnia								quality of	sleep	
disruption caused by insomnia								morning s	leepines	S
								ability to c	oncentra	ate in the morning
social life or family life										
								disruption	caused	by insomnia

Zolpidem	Trazodone	
leep latency at week 1	: minutes (SD)	
48.2 (2.7)	57.7 (4.0)	P: <0.037
leep latency at week 2	:: minutes (SD)	
48.1 (3.1)	54.5 (4.1)	P: NS
leep duration at week	1: minutes (SD)	
378.8 (5.3)	366.4 (6.4)	P: NR
leep duration at week	2: minutes (SD)	
NR (NR)	NR (NR)	P: NS
ease of falling asleep a	t week 2: Score (SD)	
44.3 (1.8)	44.0 (2.3)	P: NS
number of awakenings	at week 2: minutes (SD)	
1.5 (0.2)	1.4 (0.1)	P: NS
subjective waking time	after sleep onset at week 2: minutes (SD)	
39.5 (3.6)	42.1 (4.3)	P: NS

h, 1998a		Quality rating: Fair
sleep quality at week 2	minutes (SD)	
2.45 (0.05)	2.43 (0.07)	P: NS
patients global impressi	ons	
Zolpidem	Trazodone	
sleep status (excellent	and good) at week 2: Number (%)	
49 (53.8)	47 (52.2)	P: NS
sleep improvement (a l	ot and somewhat) at week 2: Number (%)	
60 (66)	62 (68.8)	P: NS
time to fall asleep (sho	tened a lot and shortened somewhat) at week 2:	Number (%)
56 (61.5)	50 (55.5)	P: NS
sleep time (increased a	lot and increased somewhat) at week 2: Number	r (%)
56 (61.5)	61 (67.8)	P: NS
Sheehan Disability Scal		
Zolpidem	Trazodone	
overall: Score		
NR	NR	P: NS

Valsh, 1998b					Quality rating: Good	
Design:						
Study design:	DB	Parallel	Run-in :	3 days	Setting:	
			Wash out :	2 days	Country: US	
Sample:	Number Scre	ened/ Eligible/	Enrolled	Number Wit	ndrawn/ Lost to follow-up/ Analyzed	
		673/ 456/	132		7/ 0/ 125	
Inclusion criter	ia:					
sleep reports	a modal slee	p latency >=45	minutes, mea	n awakenings per n	ring four (including one of the first two) subjective ight >=3, a mean total sleep time of <6.5 s, impaired functioning, irritability).	
Exclusion crite Individuals w		medical or psyc	hiatric illness,	as determined by h	istory and physical examination, clinical	

Individuals with significant medical or psychiatric illness, as determined by history and physical examination, clinical laboratory tests, the Zung Anxiety and Depression scales (scores >40) were excluded, as were those using CNS active medication. Individuals with prior exposure to zaleplon, or sensitivity to benzodiazepines or other psychotropic drugs, were excluded.

Population:	Mean age: Gender:	40.3 years 58% Female	Ethnicity:	NR		
Intervention: Drug name	dosage	N=	Duration		Primary outcome	Outcome:
Zaleplon	5 mg	34	14 day			Total sleep time
Zaleplon	10 mg	33	33 day			Sleep duration
Triazolam	0.25 mg	31	14 day			No. of awakenings
Placebo	NA mg	34	14 day			% of total sleep time spent in each sleep st

Efficacy:

Polysomnography

Zaleplon 5mg	Zaleplon 10mg	Triazolam 0.25mg	Placebo	
Total sleep time day 4-	5 and day 16-17, mi	nutes: during (after)		
413.6 (18)	402 (396.8)	NR (NR)	400 (411.3)	P: NS
Total sleep time- day 4	-5: Minute (p vs triaz	zolam)		
413.6 (<0.001)	402 (0.014)	431 (NA)	400 (<0.001)	
Total sleep time- day 1	6-17: Minute (p vs tr	iazolam)		
418 (0.63)	396.8 (0.22)	420 (NA)	411.3 (0.35)	
Latency to persistent sl	eep- day 4-5: Minut	e (p vs placebo)		
17 (0.019)	19.25 (0.039)	18.5 (NR)	25.38 (NA)	
Latency to persistent sl	eep- day 16-17: Mir	ute (p vs placebo)		
18 (0.019)	16.75 (0.039)	23.75 (NR)	20.5 (NA)	
No. of awakenings- day	/ 4-5 and day 16-17:	Number		
NR	NR	NR	NR	P: NS
% of total sleep time sp	ent in each sleep st	age- day 4-5 and day	16-17: Number	
NR	NR	NR	NR	P: NS
Latency to persistent sl	eep- day 16-17: Mir	ute (p vs placebo)		
416.5 (NS)	400 (NS)	406.75 (NS)	408.5 (NA)	P: NS

h, 1998b			Quality rating: Good
Sleep questionnaire			
Zaleplon 5mg	Zaleplon 10mg	Triazolam 0.25mg	Placebo
Subjective sleep latence	cy- day 4-5, score: vs	s placebo (p vs placebo)
shorter (0.003)	shorter (0.056)	shorter (0.015)	NR (NA)
Subjective sleep latence	y- day 6-14, score: v	/s placebo (p vs placeb	o)
shorter (0.67)	shorter (0.03)	shorter (0.168)	NR (NA)
Subjective total sleep to	ime- day 1-2, score:	vs placebo (p vs placel	bo)
NR (NS)	NR (NS)	NR (<0.001)	NR (NA)
Subjective total sleep ti	ime- day 3-19, score	: vs placebo (p vs place	ebo)
NR (NS)	NR (NS)	NR (NS)	NR (NA)
Subjective no. of awak	enings- day 6-14, nu	mber: vs placebo (p vs	placebo)
NR (NS)	NR (NS)	NR (0.046)	NR (NA)
Subjective sleep latence	y after discontinuation	on night, score: vs plac	ebo (p vs placebo)
NR (NS)	NR (NS)	longer (0.036)	NR (NA)
Subjective total sleep ti	ime after discontinua	ation night, score: vs pla	acebo (p vs placebo)
NR (NS)	NR (NS)	shorter (0.022)	NR (NA)

Valsh, 2000								Quality	rating	: Poor
Design:										
Study design:	RCT	DB	B Cros	sover	Run-in : Wash out	NR : NR		Setting: Country:	0	Center
Sample:	Num	ber Sc	reened/ 73/	Eligible/ 39/	Enrolled		Number Withdrawn/ 2/	•		Analyzed 22
Inclusion crite	ria:									
Men and wo	men w	ith sle	ep mainte	enance i	nsomnia, 18	to 60 y	ars of age.			
Exclusion crite	ria:									
ethanol per v another inve	week, stigati	curren onal dı	tly pregna rug, psyc	ant or br hotropic	east-feeding, medication,	, precio tryptopł	consumption of 20 c exposure to zaleplo n, or melatoantihista sm of the study drugs	n, benzodia mine in the	zepine s	sensitivity, use of
Population:	Mea	n age:	42 year	s	Ethnicity	: NR				
	Gene		% Fem		-					
Intervention: Drug name	dos	sage	N=		Duration		Primary outcome	Outcome	:	
Zaleplon	10	mg	22		2 day		\checkmark	Sleep late	ncy	
Flurazepam	30	mg	22		2 day		\checkmark	Number o	f minutes	s sleep
Placebo	NA	mg	22		2 day					
Efficacy:										
Sleep laten	cy tes	ting								
Z	Zaleplo	n	Flu	razepam	Pl	acebo				
5 hours at	ter dru	ug adm	ninistratio	n, score:	: Mean (p vs	zaleplo)			
1	6.6 (N	A)	6.8	(<0.001)	14.4	4 (0.07)				
6.5 hours	after o	łrua ad	Iministrat	tion, scor	re: Mean (p v	s zalen	n)			
	4.7 (N	0		(<0.001)		(0.111	.,			
sleep quest	ionna	ire								
Z	Zaleplo	n	Flui	razepam	Pl	acebo				
time to sle	ep (m	inute):	Median							
	27.5			22.5	:	27.5				P: NR
number o	f minu	tes sle	ep: Media	an (p vs	placebo)					

Ware, 1997								Quality	rating	j: Fair	
Design:											
Study design:	RCT	DB	Para	llel	Run-in :	2 days		Setting:	Multic	enter	
					Wash out :	3 days		Country:	US		
Sample:	Numbe	er Scre	ened/	Eligible/	Enrolled	Number W	ithdrawn/	Lost to follo	w-up/	Analyzed	
			358/	NR/	110		11/		NR/	99	

Inclusion criteria:

Adults 21-55 years old with a complaint of chronic insomnia and polysomnographically disturbed sleep; minimum of a 3month history of disturbed sleep characterized by a usual sleep time of 4 to 6 hours, a usual sleep latency of at least 30 minutes, and associated daytime complaints.

Exclusion criteria:

Any significant medical or psychiatric disorder, history or polysomnographically findings of sleep apnea or periodic leg movements, pregnancy or risk of becoming pregnant, and lactation. History of sensitivity to CNS depressants, regular use of any medication that would interfere with the study, a recent history of alcohol or drug abuse, use of any investigational drug within 30 days of study entry, and previous use of zolpidem also excluded patients. Finally, shift work or any other regularly changing sleep schedule excluded study participation.

Population:	Mean age: Gender:	NR years 58% Female	Ethnicity:	69% white		
Intervention: Drug name	dosage	N=	Duration		Primary outcome	Outcome:
Zolpidem	10 mg	37	28 day		\checkmark	Sleep Latency
Triazolam	0.5 mg	30	28 day		\checkmark	Sleep Efficiency
Placebo	NA mg	35	28 day			no. of awakenings
						waking time during sleep
						wake time after sleep
						% of time spent in REM and deep sleep
						quality of sleep
						morning sleepiness
						ability to concentrate

olysomnography		
Zolpider	n Triazolam	Placebo
latency to persist	ent sleep- night 27 & 28: m	inutes (p vs baseline)
-7 (NS)	0 (NS)	-15 (<0.05)
sleep efficiency-	night 27 & 28: % (p vs base	eline)
1 (NS)	3 (<0.05)	5 (<0.05)
no. of awakening	s- night 27 & 28: Number (p vs baseline)
1 (NS)	-2 (<0.05)	-1 (NS)
waking time duri	ng sleep: minutes (p vs bas	eline)
0 (NS)	-20 (<0.05)	2 (NS)

Vheatley, 1985							Quality rating: Fair				
esign:											
Study design:	RCT	DB	Cros	sover	Run-in :	3 days		Setting:	NR		
					Wash out :	NR		Country:	NR		
Sample:	Num	ber Sc	reened/	Eligible/	Enrolled	Nu	umber Withdrawn/	Lost to follo	ow-up/	Analyzed	
			NR/	NR/	36		2/		0/	36	
Inclusion crite	ria:										
Patients age one week.	ed 18 y	ears a	nd over	suffering	from difficulty	in sleepin	g, provided that sy	mptoms had	d been	present for at lea	ast
Exclusion crite	eria:										
Population:	Mear	n age:	53.2 ye	ears	Ethnicity:	NR					
	Geno		61% Fe		-						
ntervention:					_		Primary				
Drug name	dos	sage	N=		Duration		outcome	Outcome	:		
Zopiclone	7.5	mg	36		7 day		\checkmark	Sleep late	ncy		
Temazepam	20	mg	36		7 day		\checkmark	No. time w	aking		
							\checkmark	Quality of	sleep		
							\checkmark	Duration o	of sleep		
							\checkmark	Dreaming			
							\checkmark	State on w	vaking		

atient Questionnaires Zopiclone	Temazepam	Placebo
Sleep latency: Minutes	(p vs baseline)	
30.8 (<0.01)	NR (NR)	29.1 (<0.01)
No. time waking: Numb	er (p vs baseline)	
0.75 (<0.01)	0.66 (<0.01)	
Quality of sleep (0-4): S	core (p vs baseline)	
0.93 (<0.01)	0.87 (<0.01)	
Duration of sleep: Hour	s (p vs baseline)	
6.6 (<0.01)	6.6 (<0.01)	
Dreaming (0-4): Score ((p vs baseline)	
0.46 (NS)	0.46 (NS)	
State on waking (0-3): \$	Score (p vs baseline)	
0.39 (NS)	0.38 (NS)	
At work (0-3): Score (p	vs baseline)	
0.51 (<0.05)	0.54 (NS)	
With others (0-3): Score	e (p vs baseline)	
0.63 (NS)	0.67 (NS)	
Driving (0-3): Score (p v	/s baseline)	
0.35 (NS)	0.57 (NS)	
All measures: Score		
as above	as above	

Elie, 1990b							Qu	Quality rating: Fair			
Design:											
Study design:	RCT	DB	Para	allel	Run-in :	7 days	Sett	ting: Si	ngle	Center	
					Wash out :	3 days	Cou	untry: Ca	anada	a	
Sample:	Numbe	er Scre	ened/	Eligible/	Enrolled	Number	Withdrawn/ Lost	to follow-u	p/ A	nalyzed	
			NR/	NR/	36		0/		0/	36	

Inclusion criteria:

Subjects had to present a history of insomnia without direct relationship to another ailment plus at least three of the following symptoms: (1) requiring longer than 30 min to fall asleep, (2) total sleep time less than 6 hours, (3) more than two nocturnal awakenings and (4) poor quality of sleep,

Exclusion criteria:

Patients suffering from any other psychiatric disorder including depression or presenting a history of blood dyscrasia, drug hypersensitivity, abuse of alcohol or other drugs were excluded from the study. Women of childbearing potential not following a medically recognized contraceptive program and patients receiving any treatment which could modify drug kinetics or having received enzyme inducing drugs in the previous month were also excluded.

Population:	Mean age: Gender:	37.6 years 67% Female	Ethnicity:	NR
Drug name	dosage	N=	Duration	
Zopiclone	7.5 mg	12	28 day	
Flurazepam	30 mg	12	28 day	
Placebo	NA mg	12	28 day	

Rebound:

post-sleep questionnaire

Zopiclone	Flurazepam	Placebo	
rebound: rapidity of sle	ep onset at day 29 (h	igher score=better): Score (p vs baseline)	
5.8 (NS)	7.3 (NS)	10 (<0.01)	
rebound: duration of sl	eep at day 29 (higher	score=better): Score (p vs baseline)	
3.6 (NS)	6.2 (NS)	7.3 (<0.05)	
rebound: nocturnal awa	akenings at day 29(h	igher score=worse): Score (p vs baseline)	
5.0 (NS)	6.3 (NS)	8.0 (NS)	

eming, 1990				Quality rating: Fair				
esign:								
Study design:	RCT DE	B Parallel	Run-in : Wash out :	3 days 4 days	Setting: Country:	Multicenter Canada		
Sample:	Number Sc	reened/ Eligible NR/ NR		Number W	thdrawn/ Lost to follo 4/	ow-up/ Analyzed 0/ 48		
Inclusion crite	ria:							
and charact awakenings	erized by at I with difficulty	east 3 of the follo	owing 4 criteria sleep, 3) a total	: 1) a sleep latency sleep time of less	of 45 minutes or mor than 6 hours, and 4) a	at least 3 months duration re, 2) 2 or more nightly a poor quality of sleep. met after a 7 day washout		
whose sleep antidepress was conside	cluded if they performanc ants or with a	e was disrupted a history of hyper ry to a psychiatr	by external factors sensitivity to or	tors and those taking the or more hypnotic	ng neuroleptics, seda c drugs were excluded	traceptive method. Subjects tives, analgesics, or d. Subjects whose insomnia a history of alcoholism, drug		
Population:	Mean age:	45.5 years	Ethnicity:	NR				
toniontion.	Gender:	% Female						
tervention: Drug name	dosage	N=	Duration					
Zopiclone	7.5 mg	24	21 day					
Triazolam	0.25 mg	24	21 day					
Z	questionnai Copiclone sleep duratic 4.3	Triazolam on at the last with 5.9		ore		P: <0.05		
						P. <0.05		
rebound:	4.7	on at the last wit 6.1	ndrawal day: S	core		P: NS		
roboundu			with drawal day u	Coore		1.10		
rebound:	sieep soundr 7.4	ness at the last v 8.6	minurawai day:	Score		P: NS		
		0.0				1.110		
withdrawal Z	effects Copiclone	Triazolam						
	nsomnia: %							
resound i	73	71				P: NS		
rebound:	sleep inducti	on, duration and	soundness at	the first withdrawal	nights: Score (p vs ba	aseline)		
	NR (NS)	NR, worse (<0				-,		
rebound:	sleep soundr	ness: Score						
	NR	NR, better				P: <0.05		
rebound:	withdrawal s	ymptoms: Numb	er					
	3	2				P: NS		

	95, 1994				Qu	ality ra	ating: I	Fair	
)esign:									
Study design:	RCT DE	B Parallel	Run-in :	7 days	Sett	ing:	Multicent	er	
			Wash out :	•		•	Germany		
Sample:	Number So	reened/ Eligible NR/ NR		Number Wi	thdrawn/ Lost 0/	to follow	up/Ana 0/	alyzed 1507	
Inclusion crite	ria·		1507		0/		0/	1507	
Insomnia of	at least 4-we	eek duration and e): (a) sleep late	the presence o ency >= 45 min,	f at least two of the (b) total sleep time	following as a < <= 6 hours, ar	mean o nd © noo	f 3 days b turnal aw	before sta vakening	arting >= 3
during the 1	who had tal 4 days prior	to admission, or	any patients wit	zodiazepine or any h psychiatric disoro zopiclone, flunitraz	ders (e.g., depr	ession,	schizoph	renia, sev	vere
Population:	Mean age:		Ethnicity:						
_	Gender:	62% Female		0.9% Others					
ntervention: Drug name	dosage	N=	Duration						
Zopiclone	7.5 mg	612	28 day						
Triazolam	0.2 mg	307	28 day						
Placebo	NA mg	298	28 day						
	-		·						
Total respo	nse Copiclone	Triazolam	n Plac	cebo					
Z	opiclone	Triazolam eep quality and d 18.8						P: 0.00	126
Total respo Z rebound:	Copiclone Improved sle 27.0	eep quality and d 18.8	aytime well-bei					P: 0.00	126
Total respo Z rebound: Rebound ra	Copiclone Improved sle 27.0	ep quality and d	aytime well-beii					P: 0.00	126
Total respo Z rebound: Rebound ra Z	Copiclone Improved sle 27.0 Intes in treatr Copiclone	eep quality and d 18.8 nent responder Triazolam	laytime well-beir s n Plac	ng: %				P: 0.00	126
Total respo Z rebound: Rebound ra Z Rebound:	Copiclone Improved sle 27.0 Intes in treatr Copiclone	eep quality and d 18.8 ment responder	laytime well-bein s n Plac piclone)	ng: %				P: 0.00	126
Total respo Z rebound: Rebound ra Z Rebound: 46	Copiclone Improved sle 27.0 Intes in treatr Copiclone Copiclone Coverall rebo	eep quality and d 18.8 ment responder Triazolam rund: % (p vs zop 46.63 (NS	aytime well-bein s Plac biclone)) 48.56 (ng: %				P: 0.00	126
Total respo Z rebound: Rebound ra Z Rebound: 46 Rebound:	Copiclone Improved sle 27.0 Intes in treatr Copiclone Copiclone Coverall rebo	eep quality and d 18.8 nent responder Triazolam und: % (p vs zop	aytime well-bein s Plac biclone)) 48.56 (ne)	ng: %				P: 0.00	
Total respo Z rebound: Rebound ra Z Rebound: 46 Rebound: 9	Copicione Improved sle 27.0 Intes in treatr Copicione Coverall rebo 5.07 (NA) Responder:	eep quality and d 18.8 ment responder Triazolam und: % (p vs zop 46.63 (NS % (p vs zopiclor 7.70 (<=0.0	aytime well-bein s Plac biclone)) 48.56 (ne)	ng: % cebo <=0.01)					
Total respo Z rebound: Rebound ra Z Rebound: 46 Rebound: 9 Rebound:	Improved sle 27.0 Intes in treatr Copicione Intes in treatr Copicione Copicione Intes in treatr Copicione Copi	eep quality and d 18.8 ment responder Triazolam und: % (p vs zop 46.63 (NS % (p vs zopiclor 7.70 (<=0.0	laytime well-bein s Place biclone)) 48.56 (ne) 1) 4.92 (<	ng: % cebo <=0.01)					01
Total respo Z rebound: Rebound ra Z Rebound: 46 Rebound: 9 Rebound: 36	Improved sle 27.0 Intes in treatr Copicione Coverall rebo 5.07 (NA) Responder: 0.05 (NA) Nonrespond 0.02 (1.35)	eep quality and d 18.8 ment responder Triazolam und: % (p vs zop 46.63 (NS % (p vs zopiclor 7.70 (<=0.0 der: % (SD) 38.93 (1.45	aytime well-bein s biclone)) 48.56 (ne) 1) 4.92 (ng: % cebo <=0.01)				P: <=0.	01
Total respo	Improved sle 27.0 Intes in treatr Copicione Coverall rebo 5.07 (NA) Responder: 0.05 (NA) Nonrespond 0.02 (1.35)	eep quality and d 18.8 ment responder Triazolam und: % (p vs zop 46.63 (NS % (p vs zopiclor 7.70 (<=0.0 der: % (SD)	laytime well-bein s Place biclone)) 48.56 (ne) 1) 4.92 (- 5) ty	ng: % cebo <=0.01)				P: <=0.	01
Total respo	Improved sle 27.0 Intes in treatr Copicione Coverall rebo 6.07 (NA) Responder: 0.05 (NA) Nonrespond 0.02 (1.35) Intes for item Copicione	eep quality and d 18.8 ment responder Triazolam und: % (p vs zop 46.63 (NS % (p vs zopiclor 7.70 (<=0.0 der: % (SD) 38.93 (1.45 s of sleep quali Triazolam	aytime well-bein s piclone)) 48.56 (ne) 1) 4.92 (5) ty	ng: % cebo <=0.01)				P: <=0.	01
Total respo	Improved sle 27.0 Intes in treatr Copicione Copicione Coverall rebo 5.07 (NA) Responder: 0.05 (NA) Nonrespond 0.02 (1.35) Intes for item Copicione	eep quality and d 18.8 ment responder Triazolam und: % (p vs zop 46.63 (NS % (p vs zopiclor 7.70 (<=0.0 der: % (SD) 38.93 (1.45 s of sleep quali	laytime well-bein s biclone)) 48.56 (ne) 1) 4.92 (< 5) ty BD)	ng: % cebo <=0.01)				P: <=0.	01
Total respo Z rebound: Rebound ra Z Rebound: 46 Rebound: 36 Rebound ra Z Rebound ra Z Rebound: 36	Improved sle 27.0 Intes in treatr Copicione Coverall rebo 6.07 (NA) Responder: 0.05 (NA) Nonrespond 0.02 (1.35) Intes for item Copicione Sleep qualit .33 (1.11)	eep quality and d 18.8 ment responder Triazolam ound: % (p vs zop 46.63 (NS % (p vs zopiclor 7.70 (<=0.0 der: % (SD) 38.93 (1.45 s of sleep quali Triazolam y - 1 item: (%) (S 16.32 (1.33	aytime well-bein s n Place biclone)) 48.56 (ne) 1) 4.92 (1) 4.92 (5) ty 5) 5)	ng: % cebo <=0.01)				P: <=0. P: <=0.	01
Total respo	Improved sle 27.0 Intes in treatr Copicione Coverall rebo 6.07 (NA) Responder: 0.05 (NA) Nonrespond 0.02 (1.35) Intes for item Copicione Sleep qualit .33 (1.11)	eep quality and d 18.8 ment responder Triazolam rund: % (p vs zop 46.63 (NS % (p vs zopiclor 7.70 (<=0.0 der: % (SD) 38.93 (1.45 s of sleep quali Triazolam y - 1 item: (%) (S 16.32 (1.33 y - 2 items: (%) (aytime well-bein s h Place biclone)) 48.56 (he) 1) 4.92 (5) ty 5) ty 50) 3) SD)	ng: % cebo <=0.01)				P: <=0. P: <=0.	01 01 01
Total respo	appicione Improved size 27.0 Ates in treatr appicione coverall rebo 6.07 (NA) Responder: 0.05 (NA) Nonrespond 0.02 (1.35) Ates for item appicione size pqualit .33 (1.11) size pqualit 76 (0.83)	eep quality and d 18.8 ment responder Triazolam ound: % (p vs zop 46.63 (NS % (p vs zopiclor 7.70 (<=0.0 der: % (SD) 38.93 (1.45 s of sleep quali Triazolam y - 1 item: (%) (S 16.32 (1.33	s Place biclone) 48.56 (n 48.56 (ne) 4.92 (5) 5) ty 5) SD))	ng: % cebo <=0.01)				P: <=0. P: <=0.	01 01 01

, 1998, 1995, 1994		Quality rating: Fair		
Rebound rates for items	of daytime well-being			
Zopiclone	Triazolam			
Rebound: daytime well-	being - 1 item: % (SD)			
18.52 (1.44)	19.04 (2.00)	P: NS		
Rebound: daytime well-	being - 2 items: % (SD)			
14.09 (1.11)	13.10 (1.91)	P: NS		
Rebound: daytime well-	being - 3 items: % (SD)			
7.89 (0.82)	7.73 (1.33)	P: NS		

u, 1997					Quality I	rating: Poo	r
esign:							
Study design:	RCT DE	3 Crossover	Run-in : Wash out :	0 days 7 days	Setting: Country:	Single Center Taiwan	
Sample:	Number So	reened/ Eligibl		•	drawn/ Lost to follo	w-up/ Analyze	d
		NR/ NI	R/ 15		0/	0/ 1	5
Inclusion crite							
	1 hour, tota			months, with at least ours, more than 2 noc			
Exclusion crite Patients wit		or mood disord	ers, history of se	vere physical illness,	alcohol arouse or c	lrug abuse.	
Population:	Mean age:	40.1 years	Ethnicity:	NR			
	Gender:	73% Female					
tervention:	decere	N	Duration				
Drug name	dosage	N=	Duration				
Zopiclone	7.5 mg	15	14 day				
Triazolam	0.25 mg	15	14 day				
Placebo	NA mg	15	14 day				
ebound:							
Spiegel's s	leep questic	onnaire (SSQ)					
Z	Zopiclone	Triazolar	n				
rebound:	6 out of 7 ite	ms shows less	rebound effects i	n Zopiclone: Score			
	ultiple data	multiple da				P: •	<0.05
		•					
Leed's slee	•	n questionnaire	. ,				
	Zopiclone	Triazolar	n				
					-		
Z	9/10 items s	how more withd	rawal sleep distu	irbance of triazolam:	Score		

Mamelak, 1987							Qualit	Quality rating: Fair			
Design:											
Study design:	RCT	DB	Para	allel	Run-in :	2 days	Setting	Single	e Center		
					Wash out :	3 days	Country	: Cana	da		
Sample:	Numbe	r Scre	ened/	Eligible/	Enrolled	Number V	Vithdrawn/ Lost to fo	llow-up/	Analyzed	l	
			NR/	NR/	30		0/	0/	30)	

Inclusion criteria:

Each subject had to have a history of at least 3-month's duration of any two of the following sleep disorders: sleep latency of >= 45 min, total nocturnal sleep time of <6 hours, morning awakening at least 90 min earlier than expected time, or three or more nocturnal awakenings. All subjects were required to be free of centrally acting drugs for at least 3 months before starting the study. Subjects had to be within 20% of normal body weight and only moderate users of alcohol.

Exclusion criteria:

Any major medical or psychiatric disorder disqualified the subject from the study. Other disqualifying cases specifically included women of child bearing potential and subjects with histories of drug abuse or allergic reactions to hypnotic-sedative drugs.

Population:	Mean age: Gender:	50 years 70% Female	Ethnicity:	NR
Drug name	dosage	N=	Duration	
Zopiclone	7.5 mg	10	12 day	
Flurazepam	30 mg	10	12 day	
Placebo	NA mg	10	12 day	

Rebound:

sleep questionnaire

eep questionnaire			
Zopiclone	Flurazepam	Placebo	
rebound: total sleep tim	e at day 15: minutes	(p vs baseline)	
313.5 (NS)	356.5 (NS)	313.5 (NS)	
rebound: sleep latency	at day 15: minutes (p	vs baseline)	
105.0 (<0.05)	39.7 (<0.05)	75.5 (NS)	
rebound: no. of awaken	ings at day 15: minu	es (p vs baseline)	
2.10 (NS)	2.05 (<0.05)	1.70 (<0.05)	
rebound: duration of ea	rly wakefulness at da	y 15: minutes (p vs baseline)	
41.5 (NS)	27.8 (NS)	46.9 (NS)	
rebound: sleep latency	at day 15: minutes		
105.0	39.7		P: <0.05
rebound: no. of awaken	ings at day 17: Num	ber	
3.15	2.05		P: <0.05
other rebounds: numbe	r		
multiple data	multiple data		P: NS

onti, 1994					Quality rating: Fair						
esign:											
Study design:	RCT	DB	Parallel	Run-in : Wash out :	3 days 3 davs		Setting: Country:	Singl Urugi		nter	
Sample:	Numbe	er Scre	eened/ Eligibl		-	Withdrawn/I	-	-	•	yzed	
			NR/ N	R/ 24		1/		0/		24	
Inclusion crite											
				2 of the following minutes; numbe				>30 mir	nutes	; total sle	ep time
organic dise	omen, w ase or se	evere	psychiatric dis	ng age with inade sorders, and pati cs and/or antidep	ents in whom in	sufficient com	npliance wa	as to be	e exp	ected. Al	cohol
Population:	Mean a	age:	47.3 years	Ethnicity:	NR						
_	Gende		88% Female								
ntervention: Drug name	dosa	ge	N=	Duration							
Zolpidem	10 n	ng	8	27 day							
Triazolam	0.5 n	ng	8	27 day							
Placebo	NA n	ng	8	27 day							
polysomno Z	gram Zolpidem	1	Triazolar	n Plac	ebo						
rebound:	mean wa	ake tin	ne (change fro	om baseline): mir	nutes (SD)						
	80 (118)		43 (47.4)						P: NR	
rebound:	mean to	tal sle	ep time (chan	ge from baseline): minutes (SD)						
8	0 (118.5))	-40 (52.2	2)						P: NR	
rebound:	mean nu	umber	of sleep cycle	es (change from b	baseline): Num	ber (SD)					
	1.3 (1.5)		-0.7 (0.7)	-	-				P: NR	
sleep quest	tionnaire										
	Zolpidem		Triazolar	n Plac	ebo						
rehound	increase	d nun	ober of awake	nings- day 32: N	umber (%)						
	3 (37.5)	a nun	5 (62.5)	0 ,	. ,					P: NR	
	····/			ay 32: Number (
:	decrease	ed sle	$e_0 $ m_{amon} n_{amon}		/0/						
rebound:		ed sle			25)					P: NR	
rebound: :	3 (37.5)		6 (75)	2 (2						P: NR	
rebound: ; ; rebound:	3 (37.5)		6 (75)		(%)					P: NR P: NR	

sign: Study design: RCT DB Crossover Run-in : 6 days Setting: Single Center Sample: Number Screened/ Eligible/ Enrolled Number Withdrawn/ Lost to follow-up/ Analyzed NR/ NR/ 12 0/ 0/ 12 Inclusion criteria: The subjects accepted for the study were aged 50-59 years and complained of insomnia for at least 2 month. To be valid th complaints were to include two or more of the following criteria: (1) sleep onset latency equal to or longer than 30 min; (2) total sleeping time during the of noctrunal awakenings equal to or ligher than 3; (4) total waking time during the night equal to or longer than 30 min; (5) sleep qualified as poorly restoring, and (6) repetitiveness of the complaint if no druw were taken Exclusion criteria: (1) weight under 45 kg or over 75 kg; (2) chronic use of drugs or alcohol; (3) admission to hospital within the 3 months preceding the recruiting for the trial; (4) mental retardation; (5) physical or psychiatric disability, and (6) treatment altering the absorption, metabolism, or excretion of the drugs and susceptible to alter the evaluation of the hypnotic effects. Population: Mean age: NR Duration Zopiclone 7.5 mg 12 13 day Flurazepam 30 mg 12 13 day Flurazepam Placebo rebound: no. of awakenings: Number (p vs treatment data	ian:		uadens, 1983				Quality rating: Poor					
Wash out: 35 days Country: Belgium Sample: Number Screened/ Eligible/ Enrolled NR/ NR/ 12 Number Withdrawn/ Lost to follow-up/ Analyzed NR/ NR/ 12 0/ 0/ 12 Inclusion criteria: The subjects accepted for the study were aged 50-59 years and complained of insomnia for at least 2 month. To be valid th complaints were to include two or more of the following criteria: (1) sleep onset latency equal to or longer than 30 min; (2) total sleeping time during; (3) number of nocturnal awakenings equal to or higher than 3; (4) total waking time during the night equal to or longer than 30 min; (5) sleep qualified as poorly restoring, and (6) repetitiveness of the complaint if no drug were taken Exclusion criteria: (1) weight under 45 kg or over 75 kg; (2) chronic use of drugs or alcohol; (3) admission to hospital within the 3 months preceding the recruiting for the trial; (4) mental retardation; (5) physical or psychiatric disability, and (6) treatment altering the absorption, metabolism, or excretion of the drugs and susceptible to alter the evaluation of the hypnotic effects. Population: Mean age: Mean age: NR years Ethnicity: NR NR Zopiclone 7.5 mg 12 13 day Flurazepam 30 mg 12 13 day bound: Zopiclone Flurazepam Placebo rebound: no. of awakenings: Number (p vs treatment data) 5.5 (<0.05)	ign.											
Sample: Number Screened/ Eligible/ Enrolled NR/ Number Withdrawn/ Lost to follow-up/ Analyzed NR/ NR/ 12 0/ 0/ 12 Inclusion criteria: The subjects accepted for the study were aged 50-59 years and complained of insomnia for at least 2 month. To be valid th complaints were to include two or more of the following criteria: (1) sleep onset latency equal to or longer than 30 min; (2) total sleeping time during; (3) number of nocturnal awakenings equal to or higher than 3; (4) total waking time during the night equal to or longer than 30 min; (5) sleep qualified as poorly restoring, and (6) repetitiveness of the complaint if no dru- were taken Exclusion criteria: (1) weight under 45 kg or over 75 kg; (2) chronic use of drugs or alcohol; (3) admission to hospital within the 3 months preceding the recruiting for the trial; (4) mental retardation; (5) physical or psychiatric disability, and (6) treatment altering the absorption, metabolism, or excretion of the drugs and susceptible to alter the evaluation of the hypnotic effects. Population: Mean age: NR years Ethnicity: NR Gender: 100% Female ervention: Duration Zopiclone 7.5 mg 12 J3 day Ita adage Flurazepam 30 mg 12 Seep questionnaire Zopiclone Flurazepam Zopiclone Flurazepam Placebo rebound: 0.5 (c0.05) 6.1 (<0.01)<	tudy design:	RCT DE	B Crossover				•	0	r			
Inclusion criteria: The subjects accepted for the study were aged 50-59 years and complained of insomnia for at least 2 month. To be valid the complaints were to include two or more of the following criteria: (1) sleep onset latency equal to or longer than 30 min; (2) total sleeping time during; (3) number of nocturnal awakenings equal to or higher than 3; (4) total waking time during the night equal to or longer than 30 min; (5) sleep qualified as poorly restoring, and (6) repetitiveness of the complaint if no drue were taken Exclusion criteria: (1) weight under 45 kg or over 75 kg; (2) chronic use of drugs or alcohol; (3) admission to hospital within the 3 months preceding the recruiting for the trial; (4) mental retardation; (5) physical or psychiatric disability, and (6) treatment altering the absorption, metabolism, or excretion of the drugs and susceptible to alter the evaluation of the hypnotic effects. Population: Mean age: NR years Ethnicity: NR Gender: 100% Female ervention: Duration Zopiclone 7.5 mg 12 13 day Flurazepam 30 mg 12 13 day Flurazepam 30 mg 12 13 day Flurazepam 30 mg 12 13 day Free colone Flurazepam Placebo rebound: sleep questionnaire Zopiclone Flurazepam Placebo rebound: 5.5 (<0.05)	ample:	Number So	-		Numbe		ost to follo					
complaints were to include two or more of the following criteria: (1) sleep onset latency equal to or longer than 30 min; (2) total sleeping time during; (3) number of nocturnal awakenings equal to or higher than 3; (4) total waking time during the night equal to or longer than 30 min; (5) sleep qualified as poorly restoring, and (6) repetitiveness of the complaint if no drug were taken Exclusion criteria: (1) weight under 45 kg or over 75 kg; (2) chronic use of drugs or alcohol; (3) admission to hospital within the 3 months preceding the recruiting for the trial; (4) mental retardation; (5) physical or psychiatric disability, and (6) treatment altering the absorption, metabolism, or excretion of the drugs and susceptible to alter the evaluation of the hypnotic effects. Population: Mean age: NR years Ethnicity: NR Gender: 100% Female ervention: Drug name dosage N= Duration Zopiclone 7.5 mg 12 13 day Flurazepam 30 mg 12 13 day Flurazepam 50 50 50 50 50 50 50 50 50 50 50 50 50	clusion crite	eria:										
(1) weight under 45 kg or over 75 kg; (2) chronic use of drugs or alcohol; (3) admission to hospital within the 3 months preceding the recruiting for the trial; (4) mental retardation; (5) physical or psychiatric disability, and (6) treatment altering the absorption, metabolism, or excretion of the drugs and susceptible to alter the evaluation of the hypnotic effects. Population: Mean age: NR years Ethnicity: NR Gender: 100% Female ervention: Drug name dosage N= Duration Zopiclone 7.5 mg 12 13 day Flurazepam 30 mg 12 13 day Flurazepam 30 mg 12 13 day bound: sleep questionnaire Zopiclone Flurazepam Placebo rebound: no. of awakenings: Number (p vs treatment data) 5.5 (<0.05) 6.1 (<0.01)	complaints total sleepir night equal	were to inclue	de two or more o g; (3) number of	f the following nocturnal awak	criteria: (1) slee enings equal to	ep onset latency o or higher than	equal to o 3; (4) total	or longer than waking time of	30 min; (2) during the			
Gender: 100% Female Drug name dosage N= Duration Zopiclone 7.5 mg 12 13 day Flurazepam 30 mg 12 13 day bound: Sleep questionnaire Zopiclone Flurazepam Placebo rebound: no. of awakenings: Number (p vs treatment data) 5.5 (<0.05)	(1) weight u preceding t	under 45 kg o he recruiting	for the trial; (4) m	nental retardation	on; (5) physical	or psychiatric d	lisability, a	nd (6) treatme	nt altering the			
Gender: 100% Female Drug name dosage N= Duration Zopiclone 7.5 mg 12 13 day Flurazepam 30 mg 12 13 day bound: Sleep questionnaire Zopiclone Flurazepam Placebo rebound: no. of awakenings: Number (p vs treatment data) 5.5 (<0.05)	opulation:	Mean age:	NR years	Ethnicity	NR							
Drug namedosageN=DurationZopiclone7.5 mg1213 dayFlurazepam30 mg1213 day bound: Sleep questionnaire $\frac{Zopiclone}{rebound: no. of awakenings: Number (p vs treatment data)5.5 (<0.05)$	-		•									
Zopiclone 7.5 mg 12 13 day Flurazepam 30 mg 12 13 day bound:		docogo	N	Duration								
Flurazepam 30 mg 12 13 day bound: sleep questionnaire Zopiclone Flurazepam Placebo rebound: no. of awakenings: Number (p vs treatment data) 5.5 (<0.05) 6.1 (<0.01)		uosaye										
bound: Sleep questionnaire Zopiclone Flurazepam Placebo rebound: no. of awakenings: Number (p vs treatment data) 5.5 (<0.05) 6.1 (<0.01)	Zopiclone	7.5 mg	12	13 day								
Sleep questionnaire Zopiclone Flurazepam Placebo rebound: no. of awakenings: Number (p vs treatment data) 5.5 (<0.05)	Iurazepam	30 mg	12	13 day								
Zopiclone Flurazepam Placebo rebound: no. of awakenings: Number (p vs treatment data) 5.5 (<0.05)	ound:											
rebound: no. of awakenings: Number (p vs treatment data) 5.5 (<0.05) 6.1 (<0.01)	sleep ques	stionnaire										
5.5 (<0.05) 6.1 (<0.01)		Zopiclone	Flurazepar	n Pla	cebo							
5.5 (<0.05) 6.1 (<0.01)	rebound:	no. of awake	enings: Number (p vs treatment	data)							
rebound: total sleep time: seconds (p vs treatment data)			0	•	,							
	rebound:	total sleep ti	me: seconds (p)	/s treatment da	ita)							
23490 (<0.05) 23184 (<0.05)		•	ŭ									
rebound: sleep onset latency: seconds (p vs treatment data)		, ,	,	,	nt data)							
1255 (NS) 1042 (NR)	rebound.	•		u .	n data)							
	1			/								
rebound: sleep efficiency index: Score (p vs treatment data) 86.9 (NS) 84.9 (<0.01)			novindov: Coore	(n vo tractman	t data)							

vestri, 1996					Quality	rating: Fa	ir
esign:							
Study design:	RCT DE	B Parallel	Run-in :	3 days	Setting:	Multicenter	
			Wash out :	No days	Country:	Italy	
Sample:	Number Sc	creened/ Eligibl		Number Withdra			
		NR/ NF	R/ 22		0/	2/	20
Inclusion crite		40			· I ·	ille and a construction of the second	
a recurrence complaints:	e of short-terr time to fall as >3. These s	m situational ins sleep >30 minut	omnia) or poor s es, total sleep du	osis of psychophysiolog leepers with subjective uration <6 hours, total w o be confirmed by the o	reporting of at le ake time >20 m	east two out o inutes, and/or	f these four
Exclusion crite							
psychiatric o Rating Scale syndrome, s disorders (Q	liseases, also e for Depress leep obstruc luick's time <	o screened by n sion (total score tive apnea of >7	neans of both Ha >16); neurologic ' minutes duratio any psychotropi	e without adequate cont amilton Rating Scale for al diseases (myoclonus an); severe internal (hea c drug during 2 weeks p	Anxiety (total so , kinaesthesis d rt, renal, liver) d	core >16) and lisorders, restl iseases; hemo	Hamilton ess legs ocoagulation
Population:	Mean age:	33.6 years	Ethnicity:	NR			
•	Gender:	55% Female	Eumony.				
tervention:							
Drug name	dosage	N=	Duration				
Zolpidem	10 mg	10	2 week				
Triazolam	0.25 mg	12	2 week				
ebound:							
polysomno	graphy						
Z	Colpidem	Triazolar	า				
rebound:	sleep onset l	latency- change	from baseline- r	hight 15: minutes (SD)			
-11	I.6 (31.98)	7.1 (30.73	3)			F	P: NS
rebound:	total sleep tir	me- change fror	n baseline- night	15: minutes (SD)			
	.8 (62.54)	-34.5 (50.2	e e	× /		F	P: <0.01
rebound:	sleep efficier	ncy- change fror	n baseline- night	: 15: % (SD)			
	9 (13.63)	-6.3 (8.55	0			F	P: <0.01
rebound:	wake time af	fter sleep onset-	change from ba	seline- night 15: minute	s (SD)		
9.9-3	37.5 (49.01)	17.3 (31.8	9)			F	P: <0.01
rebound:	no. of awake	enings- change f	rom baseline- ni	ght 15: Number (SD)			
						_	

-1.9 (7.16)

-1.2 (4.67)

P: NS

stri, 1996		Quality rating: Fair
questionnaire		
Zolpidem	Triazolam	
rebound: time to fall as	eep- change from baseline- night 15: minute	es (SD)
-20.8 (28.23)	8.6 (31.65)	P: <0.05
rebound: total sleep tim	e- change from baseline- night 15: minutes	(SD)
51.9 (45.4)	-35.6 (127.92)	P: <0.01
rebound: total wake tim	e- change from baseline- night 15: minutes	(SD)
-2.2 (12.96)	13.2 (38.71)	P: NS
rebound: no. nocturnal	awakenings- change from baseline- night 1	5: Number (SD)
-0.3 (2.32)	0.4 (0.86)	P: NS
visual analogue scale		
Zolpidem	Triazolam	
rebound: sleep quality-	change from baseline- night 15: Score (SD)	
-12.9 (20.59)	0.8 (22.88)	P: NS
rebound: awakening qu	ality- change from baseline- night 15: Score	(SD)
-12.9 (21.34)	-1.5 (21.36)	P: NS

ip, 1999						Quality	rating: F	Fair
esign:								
Study design:	RCT	DB Para	allel	Run-in : Wash out :	7 days 7 days	Setting: Country:	Single Ce Canada	enter
Sample:	Number	Screened/ NR/	•	Enrolled 60	Number Withd	rawn/ Lost to follo 2/	w-up/ Ana 8/	alyzed 50
Inclusion crite	ria:							
Daytime fati	gability, di than 30 n	minished p	ower of co	oncentration at	ated with mild non-psy t work and at least two s, more than two awa	o of the following s	ymptoms:	falling asleep
Population:	Mean ag	je: 42.6 y	ears	Ethnicity:	NR			
tervention:	Gender:		nale	D (1				
Drug name	dosag	e N=		Duration				
Zopiclone	7.5 mg	g 19		21 day				
Temazepam	30 mỹ	g 16		21 day				
romazopam	NIA ma	j 15		21 day				
Placebo	NA mợ							
Placebo	INA MŲ							
Placebo ebound:								
Placebo ebound: Self-rating	questionr	naire for sl	•					
Placebo ebound: Self-rating		naire for sl	eep mazepam					
Placebo ebound: Self-rating	questionr Copiclone	naire for sl Te	mazepam	nd: Score (p v	s placebo)			

oshaar, 2004							Quality	rating	: Fair
esign:									
Study design:	RCT	DB	Parallel	Run-in : Wash out :	NR 4 days		Setting: Country:	Multice Nether	
Sample:	Numb	oer Sci	reened/ Eligible NR/ NR	/ Enrolled	•	//Withdrawn	-		Analyzed 159
Inclusion crite	ria:					0,		0,	
Patients wer between 18	e inclue and 65	ded in years	the study if they	/ were diagnose	d with primary i	nsomnia acc	cording to D	SM-III-R	and were aged
	n other		disorders, sever				e of psychol	tropic me	edication, complaints
Population:	Mean	age:	46.1 years	Ethnicity:	NR				
	Gend	ler:	0% Female	-					
Drug name	dos	age	N=	Duration					
Zolpidem	10	mg	74	28 day					
Temazepam	20	mg	85	28 day					
ebound:									
rebound									
Z	olpider	m	Temazepar	n					
rebound-	mean t	otal sl	eep time: minute	es (SD)					
3	370 (84	·)	352 (89)						P: NS
rebound-	prevale	ence re	ebound insomnia	a (TST): %					
	27		25.9						P: NS
rebound-	sleep o	onset la	atency: minutes	(SD)					
	60 (51))	73 (53)						P: NS
		noo ra	ebound insomnia	a (SOL): %					
	prevale			()					

are, 1997						Quality	rating: I	Fair	
esign:									
Study design:	RCT	DB F	Parallel	Run-in :	2 days	Setting:	Multicent	er	
				Wash out :	3 days	Country:	US		
Sample:	Number	Screen	ed/ Eligibl	e/ Enrolled	Number Withd	rawn/ Lost to follo	ow-up/ Ana	alyzed	
		3	58/ N	R/ 110		11/	NR/	99	
Inclusion criter	ia:								
month histor	y of distu	rbed sle	ep charact	erized by a usua	nnia and polysomnogra al sleep time of 4 to 6 h				
month histor minutes, and Exclusion crite Any significa movements, any medicati within 30 day	y of distu l associa ria: nt medic pregnan on that w /s of stuc	rbed sle ted dayt al or psy cy or risl vould inte ly entry,	ep charact me complechiatric dis of becomerfere with and previo	erized by a usua aints. sorder, history of ing pregnant, ar the study, a rec		findings of sleep sensitivity to CNS r drug abuse, use	apnea or p depressa of any inve	of at least 30 periodic leg nts, regular use estigational drug	g
month histor minutes, and Exclusion crite Any significa movements, any medicati within 30 day	y of distu l associa ria: nt medic pregnan on that w /s of stuc	rbed sle ted dayt al or psy cy or risl vould inte ly entry, dule excl	ep charact me compl chiatric dis of becom erfere with and previce uded stud	erized by a usua aints. sorder, history o ning pregnant, ar the study, a rec bus use of zolpid	al sleep time of 4 to 6 h r polysomnographically nd lactation. History of ent history of alcohol o lem also excluded patie	findings of sleep sensitivity to CNS r drug abuse, use	apnea or p depressa of any inve	of at least 30 periodic leg nts, regular use estigational drug	g
month histor minutes, and Exclusion crite Any significa movements, any medicati within 30 day changing sle	y of distu l associa ria: nt medic pregnan on that w /s of stuc ep scheo	rbed sle ted dayt al or psy cy or risl vould inte dy entry, dule excl ge: NR	ep charact me compl chiatric dis of becom erfere with and previce uded stud	erized by a usua aints. sorder, history o ing pregnant, ar the study, a rec ous use of zolpid y participation.	al sleep time of 4 to 6 h r polysomnographically nd lactation. History of ent history of alcohol o lem also excluded patie	findings of sleep sensitivity to CNS r drug abuse, use	apnea or p depressa of any inve	of at least 30 periodic leg nts, regular use estigational drug	g

Zolpidem 10 mg 37 28 da	
Triazolam 0.5 mg 30 28 da	y
Placebo NA mg 35 28 da	y

Rebound:

polysomnography			
Zolpidem	Triazolam	Placebo	
rebound: latency to pe	rsistent sleep- discont	inuation night 1: minutes (p vs baseline)	
6 (NS)	47 (<0.05)	-11 (NS)	
rebound: latency to pe	rsistent sleep- discont	inuation night 1: minutes (p vs baseline)	
6 (NS)	47 (<0.05)	-11 (NS)	
rebound: sleep efficier	ncy- discontinuation ni	ght 1: % (p vs baseline)	
-3 (NS)	-15 (<0.05)	5 (<0.05)	
-3 (NS)	-15 (<0.05)	5 (<0.05)	

, 1997			Quality rating: Fair
rebound questionnaire-	discontinuation nig	Jht 1	
Zolpidem	Triazolam	Placebo	
rebound: sleep latency	: minutes (p vs basel	ine)	
14 (NS)	72 (<0.05)	-16	
rebound: total sleep tin	ne: minutes (p vs bas	eline)	
-4 (NS)	-63 (<0.05)	49 (0.05)	
rebound: no. of awake	nings: Number (p vs	paseline)	
1 (NS)	1 (NS)	-1 (<0.05)	
rebound: wake min du	ring sleep: minutes (p	vs baseline)	
-4 (NS)	48 (<0.05)	-29 (<0.05)	
rebound: quality latenc	y: Score (p vs baseli	ne)	
0.3 (NS)	0.8 (<0.05)	-0.4 (<0.05)	
rebound: morning slee	piness: Score (p vs b	aseline)	
-5 (NS)	-6.7 (NS)	4.5 (NS)	
rebound: ability to cond	centrate: Score (p vs	baseline)	
0.2 (<0.05)	0.1 (NS)	-0.1 (NS)	
rebound: over all rebou	ınds: %		
15	43	11	

Anderson, 1987	7						(Quality rating: Fair			
Design:											
Study design:	RCT	DB	Para	llel	Run-in :	7 days	S	Setting:	Multicer	nter	
					Wash out :	7 days	C	Country:	UK		
Sample:	Numbe	er Scre	ened/	Eligible/	Enrolled	Number V	Vithdrawn/ Lo	ost to follo	w-up/ Ai	nalyzed	
			NR/	NR/	119		5/		15/	99	

Inclusion criteria:

Patients were suffering from at least one of the following symptoms: unable to fall asleep within 45 minutes, more than two nocturnal awakenings with difficulty in returning to sleep without known cause, or sleeping <6 hours per night

Exclusion criteria:

Patients were not eligible for the trial if there was evidence for the presence (or previous history) of psychiatric disease, hepatic or renal dysfunction, heart block or cardiovascular disease with significant symptomatology, gastrointestinal disease, drug addiction or chronic alcoholism, a history of hypersensitivity to drugs or continuous use of high doses of a hypnotic for a period in excess of 6 months. Other groups excluded were pregnant women, nursing mothers, women of childbearing potential, and night shift workers.

Population:	Mean age: Gender:	NR years 0% Female	Ethnicity: NR
Drug name	dosage	N=	Duration
Zopiclone	7.5 mg	37	14 day
Nitrazepam	5 mg	NR	14 day
Placebo	NA mg	NR	14 day

Adverse Events:

bitter tas	stes		
	Zopiclone	Nitrazepam	
no, of pa	atients: Number	(%)	
	9 (24.3)	NR (NR)	
withdraw	wals		
	Zopiclone	Nitrazepam	Placebo
total with	hdrawals: Numbe	er	
	2	1	2
withdrav	wals due to AEs:	Number	
	1		1

utret, 1987					Quality	rating: Poor	
Design:							
Study design:	CT DB	Crossover	Run-in :	4 days	Setting:	Single Center	
			Wash out :	3 days	Country:	France	
Sample:	Number Sc	reened/ Eligible	/ Enrolled	Number	Nithdrawn/ Lost to follo	ow-up/ Analyzed	
		NR/ NR	/ 121		NR/	8/ 113	
Inclusion crite	ria:						
greater than	2 hours; wal	king up more tha	n twice at night	; subjective leng		ctive period of falling asle greater than 30 minutes;	ер
Exclusion crite	eria:						
Population:	Mean age:	46.3 years	Ethnicity:	NR			
	Gender:	70% Female	-				
ntervention:							
Drug name	dosage	N=	Duration				
Zopiclone	7.5 mg	121	7 day				
Triazolam	0.5 mg	121	7 day				
Adverse Event	ts:						
Guelfi side-	effects chec	k list					
	opiclone	Triazolam					
Z							
	items show	s favour Zopiclor	ne: Score				

						Quality	rating	: Poor	
esign:									
Study design:	RCT S	B Parallel	Run-in : Wash out :	2 days 2 days		Setting: Country:	Single NR	Center	
Sample:	Number S	creened/ Eligible		•	er Withdrawn/	•		Analyzed	
		NR/ NR	/ 88		4/		33/	51	
Inclusion crite									
		rears or older and re awakenings du						30 minute	s or more
	medications were exclud	known to affect s led. Alcohol inges itted.							
Population:	Mean age	NR years	Ethnicity:	NR					
	Gender:	0% Female	-						
tervention:									
Drug name	dosage	N=	Duration						
Zopiclone	7.5 mg	28	11 day						
Midazolam	15 mg	23	11 day						
dverse Even	ts:								
Averse Eve		Midazolam	1						
Averse Eve Z	nts Copiclone	Midazolam							
Averse Eve Z No. of patie	nts Copiclone ents experier 5 (31)							P: >0.0	5
Averse Eve Z No. of patie	nts Copiclone ents experier 5 (31)	ncing AEs (overal 16 (40)						P: >0.0	5
Averse Eve Z No. of patie 1 No. of AEs	nts Copicione ents experien 5 (31) Number 21	ncing AEs (overal 16 (40) 28	I): Number (%)					P: >0.0	
Averse Eve Z No. of patie 1 No. of AEs: No. of patie	nts Copicione ents experier 5 (31) Number 21 ents experier	ncing AEs (overal 16 (40) 28 ncing AEs - Daytin	I): Number (%)	umber (%)				P: >0.0	
Averse Eve Z No. of patie No. of AEs: No. of patie	nts Copicione ents experier 5 (31) Number 21 ents experier (12.5)	ncing AEs (overal 16 (40) 28 ncing AEs - Daytin 6 (15)	I): Number (%) me tiredness: Ni						
Averse Eve Z No. of patie 1 No. of AEs No. of patie 6 No. of patie	nts Copicione ents experier 5 (31) Number 21 ents experier (12.5) ents experier	ncing AEs (overal 16 (40) 28 ncing AEs - Daytin 6 (15) ncing AEs - Taste	I): Number (%) me tiredness: Ni					P: >0.0	
Averse Eve Z No. of patie 1 No. of AEs: No. of patie 6 No. of patie	nts Copicione ents experier 5 (31) Number 21 ents experier (12.5) ents experier (12.5)	ncing AEs (overal 16 (40) 28 ncing AEs - Daytin 6 (15) ncing AEs - Taste 0 (0)	I): Number (%) me tiredness: No disturbance: No	umber (%)				P: >0.0	
Averse Eve Z No. of patie No. of AEs: No. of patie 6 No. of patie 6 No. of patie	nts Copicione ents experier 5 (31) Number 21 ents experier (12.5) ents experier (12.5) ents experier	ncing AEs (overal 16 (40) 28 ncing AEs - Daytin 6 (15) ncing AEs - Taste 0 (0) ncing AEs - Dry m	I): Number (%) me tiredness: No disturbance: No	umber (%)				P: >0.0 P: NR P: NR	
Averse Eve Z No. of patie 1 No. of AEs No. of patie 6 No. of patie 6 No. of patie	nts Copicione ents experier 5 (31) Number 21 ents experier (12.5) ents experier (12.5) ents experier (12.5) ents experier (12.2)	ncing AEs (overal 16 (40) 28 ncing AEs - Daytin 6 (15) ncing AEs - Taste 0 (0) ncing AEs - Dry m 3 (7.5)	I): Number (%) me tiredness: Nr disturbance: Nr nouth: Number (*	umber (%) %)				P: >0.0	
Averse Eve Z No. of patie No. of AEs: No. of patie 6 No. of patie 6 No. of patie 2 No. of patie	nts Copicione ents experier 5 (31) Number 21 (12.5) ents experier (12.5) ents experier (12.5) ents experier (12.5) ents experier (12.5)	ncing AEs (overal 16 (40) 28 ncing AEs - Daytin 6 (15) ncing AEs - Taste 0 (0) ncing AEs - Dry m 3 (7.5) ncing AEs - Indige	I): Number (%) me tiredness: Nr disturbance: Nr nouth: Number (*	umber (%) %)				P: >0.0 P: NR P: NR P: NR	
Averse Eve Z No. of patie 1 No. of AEs: No. of patie 6 No. of patie 2 No. of patie 2 No. of patie	nts copicione ents experier 5 (31) Number 21 (12.5) ents experier (12.5) ents experier (12.5) ents experier (4.2) ents experier (4.2)	ncing AEs (overal 16 (40) 28 ncing AEs - Daytin 6 (15) ncing AEs - Taste 0 (0) ncing AEs - Dry m 3 (7.5) ncing AEs - Indige 5 (12.5)	I): Number (%) me tiredness: No disturbance: No nouth: Number (* estion/nausea/vo	umber (%) %) omiting: Numb	ber (%)			P: >0.0 P: NR P: NR	
Averse Eve Z No. of patie No. of patie 6 No. of patie 6 No. of patie 2 No. of patie 1 No. of patie	nts Copicione ents experier 5 (31) Number 21 ents experier (12.5) ents experier (12.5) ents experier (4.2) ents experier (2.1) ents experier	ncing AEs (overal 16 (40) 28 ncing AEs - Daytin 6 (15) ncing AEs - Taste 0 (0) ncing AEs - Dry m 3 (7.5) ncing AEs - Indige 5 (12.5) ncing AEs - Clum	I): Number (%) me tiredness: No disturbance: No nouth: Number (* estion/nausea/vo	umber (%) %) omiting: Numb	per (%)			P: >0.0 P: NR P: NR P: NR P: NR	
Averse Eve Z No. of patie 1 No. of patie 6 No. of patie 2 No. of patie 1 No. of patie	nts Copicione ents experier 5 (31) Number 21 ents experier (12.5) ents experier (12.5) ents experier (4.2) ents experier (2.1) ents experier (2.1)	ncing AEs (overal 16 (40) 28 ncing AEs - Daytin 6 (15) ncing AEs - Taste 0 (0) ncing AEs - Dry m 3 (7.5) ncing AEs - Indige 5 (12.5) ncing AEs - Clums 4 (10)	I): Number (%) me tiredness: No disturbance: No nouth: Number (estion/nausea/vo siness: Number	umber (%) %) omiting: Numb (%)				P: >0.0 P: NR P: NR P: NR	
Averse Eve Z No. of patie 1 No. of AEs: No. of patie 6 No. of patie 2 No. of patie 1 No. of patie	nts Copicione ents experier 5 (31) Number 21 (12.5) ents experier (12.5) ents experier (4.2) ents experier (2.1) ents experier (0.0) ents experier	ncing AEs (overal 16 (40) 28 ncing AEs - Daytin 6 (15) ncing AEs - Taste 0 (0) ncing AEs - Dry m 3 (7.5) ncing AEs - Indige 5 (12.5) ncing AEs - Clum	I): Number (%) me tiredness: No disturbance: No nouth: Number (estion/nausea/vo siness: Number	umber (%) %) omiting: Numb (%)				P: >0.0 P: NR P: NR P: NR P: NR P: NR	
Averse Eve Z No. of patie 1 No. of AEs No. of patie 6 No. of patie 2 No. of patie 1 No. of patie 1 No. of patie 2 No. of patie	nts Copicione ents experien 5 (31) Number 21 ents experien (12.5) ents experien (4.2) ents experien (2.1) ents experien 0 (0) (4.2)	ncing AEs (overal 16 (40) 28 ncing AEs - Daytin 6 (15) ncing AEs - Taste 0 (0) ncing AEs - Dry m 3 (7.5) ncing AEs - Indige 5 (12.5) ncing AEs - Clums 4 (10) ncing AEs - Distu	I): Number (%) me tiredness: Na disturbance: Na nouth: Number (estion/nausea/vo siness: Number bed sleep patte	umber (%) %) omiting: Numb (%)				P: >0.0 P: NR P: NR P: NR P: NR	

audoir, 1990)				Quality	rating: Fair
esign:						
Study design:	RCT DI	B Parallel	Run-in :	no days	Setting:	Multicenter
			Wash out :	7 days	Country:	UK
Sample:	Number Se	creened/ Eligit	ole/ Enrolled	Number V	Vithdrawn/ Lost to follo	ow-up/ Analyzed
		NR/ N	NR/ 38		4/	NR/ 38
Inclusion crite						
						longer than 30 minutes, more uration of less than 6 hours.
Exclusion crite		crinigs with un	nearly in returning	to sicep, without	Kilowii cause, sieep u	
		t disease, psyc	hosis, hypersensi	tivity, drug addict	ion, or alcohol consum	ption that might interfere with
					intending to become p	regnant. No patient was
	•		on known to induc			
Population:		50.9 years	•	100% Caucasi	an	
tervention:	Gender:	71% Female				
Drug name	dosage	N=	Duration			
	uosaye	N -	Duration			
Zopiclone	7.5 mg	19	1 week			
Triazolam	0.25 mg	19	1 week			
dverse Even	te:					
reported by	•					
Z	Zopiclone	Triazola	m			
no. of patie	nts experier	icing severe sid	le effect: Number			
	1	1				
		· · ·				
withdrawal	s					
Z	Copiclone	Triazola	im			
total withdr	awals: Numl	ber				
	1	3				
withdrawals	s due to AEs	-				
	0	1				

Drake (1), 2001							Qual	Quality rating: Fair		
Design:										
Study design:	RCT	DB	Crossov	ver	Run-in :	NR	Settin	g: Multicen	ter	
					Wash out :	5-12 days	Count	ry: US		
Sample:	Sample: Number Screened/ Eligible/ Enrolled			Enrolled	Number V	Vithdrawn/ Lost to	follow-up/ Ar	nalyzed		
			NR/	NR/	47		0/	0/	47	

Inclusion criteria:

Age 21-60, with a recent, six-month, history or primary insomnia as defined by the DSM-III. To be eligible for polysomnographic (PSG) screening, participants must have reported at least two of the following: 6 months of sleep disturbance with a sleep latency of >30 minutes, three or more awakenings per night, or a sleep time of 4 to 6 hours. All patients had to meet the following PSG screening criteria for study eligibility: 1) latency to persistent sleep greater than 20 minutes on at least two of the screening nights, with no latency of less than 15 minutes, 2) Total sleep time between 240 and 420 on at least two of the screening nights, 3) less than five apneas per hour of sleep, 4) less than 10 leg movements per hour of sleep.

Exclusion criteria:

Individuals with medical or psychiatric diagnoses (including any history of alcoholism or drug abuse), abnormal laboratory results (urinalysis, hematology, and blood chemistries), an irregular sleep-wake schedule, or who regularly consumed greater than 750 mg of caffeinated beverages.

Population:	Mean age: Gender:	41.6 years 51% Female	Ethnicity:	NR
Drug name	dosage	N=	Duration	
Zaleplon	10 mg	47	2 day	
Zaleplon	40 mg	47	2 day	
Triazolam	0.25 mg	47	2 day	
Placebo	NA mg	47	2 day	

Adverse Events:

reported by patients

-	Zaleplon 10mg	Zaleplon 40mg	Triazolam
no. o	f patients experienci	ng AEs: Number	
	9	18	8
withd	Irawals		
	Zaleplon 10mg	Zaleplon 40mg	Triazolam 0.25mg
total	withdrawals: Numbe	r	
	NR	NR	NR
withd	Irawals due to AEs: I	Number	
	0	0	0

Drake (2), 2000)					Quality	Quality rating: Fair		
Design:									
Study design:	RCT	DB	Crossove	Run-in :	NR	Setting:	Multicenter		
				Wash out	t: 5-12 days	Country:	US		
Sample:	Sample: Number Screened/ Eligible/ Er		ole/ Enrolled	Enrolled Number Withdrawn/		ow-up/ Ar	nalyzed		
			NR/ I	NR/ 36		0/	0/	36	

Inclusion criteria:

Age 21-60, with a recent, six-month, history or primary insomnia as defined by the DSM-III. To be eligible for polysomnographic (PSG) screening, participants must have reported at least two of the following: 6 months of sleep disturbance with a sleep latency of >30 minutes, three or more awakenings per night, or a sleep time of 4 to 6 hours. All patients had to meet the following PSG screening criteria for study eligibility: 1) latency to persistent sleep greater than 20 minutes on at least two of the screening nights, with no latency of less than 15 minutes, 2) Total sleep time between 240 and 420 on at least two of the screening nights, 3) less than five apneas per hour of sleep, 4) less than 10 leg movements per hour of sleep.

Exclusion criteria:

Individuals with medical or psychiatric diagnoses (including any history of alcoholism or drug abuse), abnormal laboratory results (urinalysis, hematology, and blood chemistries), an irregular sleep-wake schedule, or who regularly consumed greater than 750 mg of caffeinated beverages.

Population:	Mean age: Gender:	38.1 years 39% Female	Ethnicity:	NR
Drug name	dosage	N=	Duration	
Zaleplon	20 mg	36	2 day	
Zaleplon	60 mg	36	2 day	
Triazolam	0.25 mg	36	2 day	
Placebo	NA mg	36	2 day	

Adverse Events:

reported by patients

Zaleplon 20mg	Zaleplon 60mg	Triazolam
no. of patients experienci	ng AEs: Number	
6	17	8
withdrawals		
Zaleplon 20mg	Zaleplon 60mg	Triazolam
total withdrawals: Numbe	r	
NR	NR	NR
withdrawals due to AEs: N	Number	
0	1	0

Elie, 1990b							Quality	rating	: Fair	
Design:										
Study design:	RCT	DB	Para	allel	Run-in :	7 days	Setting:	Single	Center	
					Wash out :	3 days	Country:	Canac	la	
Sample:	Numbe	r Scre	ened/	Eligible/	Enrolled	Number Withdr	awn/ Lost to foll	low-up/	Analyzed	
			NR/	NR/	36		0/	0/	36	

Inclusion criteria:

Subjects had to present a history of insomnia without direct relationship to another ailment plus at least three of the following symptoms: (1) requiring longer than 30 min to fall asleep, (2) total sleep time less than 6 hours, (3) more than two nocturnal awakenings and (4) poor quality of sleep,

Exclusion criteria:

Patients suffering from any other psychiatric disorder including depression or presenting a history of blood dyscrasia, drug hypersensitivity, abuse of alcohol or other drugs were excluded from the study. Women of childbearing potential not following a medically recognized contraceptive program and patients receiving any treatment which could modify drug kinetics or having received enzyme inducing drugs in the previous month were also excluded.

Population:	Mean age: Gender:	37.6 years 67% Female	Ethnicity:	NR
Intervention:				
Drug name	dosage	N=	Duration	
Zopiclone	7.5 mg	12	28 day	
Flurazepam	30 mg	12	28 day	
Placebo	NA mg	12	28 day	

Adverse Events:

overall AEs

Zopiclone	Flurazepam	Placebo	
somnolence: Number			
11	12	9	P: NS
loss of concentration: Nu	Imber		
8	8	5	P: NS
excitation: Number			
10	2	7	P: NS
tension: Number			
10	7	9	P: NS
taste disturbance: Numb	er		
10	10	4	P: <0.05
try mouth: Number			
11	7	8	P: NS
thick tongue: Number			
9	7	5	P: NS
withdrawals			
Zopiclone	Flurazepam	Placebo	
total withdrawals: Numbe	er		
0	0	0	
withdrawals due to AEs:	Number		
0	0	0	

Fleming, 1990					Quality	Quality rating: Fair			
Design:									
Study design:	RCT	DB	Parall	el	Run-in :	3 days	Setting:	Multicer	nter
					Wash out :	4 days	Country:	Canada	
Sample:	Numb	er Scre	ened/ E	Eligible/	Enrolled	Number W	/ithdrawn/ Lost to follo	ow-up/Ar	nalyzed
			NR/	NR/	52		4/	0/	48

Inclusion criteria:

Ages 18 to 64 with body weight within 20% of normal for their age, with a history of insomnia of at least 3 months duration and characterized by at least 3 of the following 4 criteria: 1) a sleep latency of 45 minutes or more, 2) 2 or more nightly awakenings with difficulty in returning to sleep, 3) a total sleep time of less than 6 hours, and 4) a poor quality of sleep. Subjects previously receiving hypnotic medication were eligible provided the above criteria were met after a 7 day washout period.

Exclusion criteria:

Females excluded if they were pregnant, lactating, or were not using a medically recognized contraceptive method. Subjects whose sleep performance was disrupted by external factors and those taking neuroleptics, sedatives, analgesics, or antidepressants or with a history of hypersensitivity to one or more hypnotic drugs were excluded. Subjects whose insomnia was considered secondary to a psychiatric or medical disorder were also excluded as those with a history of alcoholism, drug abuse, or caffeine overuse.

Population:	Mean age: Gender:	45.5 years % Female	Ethnicity:	NR
Drug name	dosage	N=	Duration	
Zopiclone	7.5 mg	24	21 day	
Triazolam	0.25 mg	24	21 day	

Adverse Events:

Zopiclone	Triazolam	
o. of patients experier	cing adverse effect: Number (%)	
18 (75)	20 (83.3)	P: NS
aste perception: Numb	er	
NR	NR, more	P: <0.05
noderate or severe ad	verse effects reported: %	
18	42	P: <0.05

Fleming, 1995								Quality	rating	Fair	
Design:											
Study design:	RCT	DB	Para	llel	Run-in :	1 dag	ys	Setting:	Multice	enter	
					Wash out :	NR		Country:	Canad	а	
Sample:	Numbe	er Scre	ened/	Eligible/	Enrolled		Number Withdrawn/	Lost to follo	w-up/ A	Analyzed	
			222/	144/	144		7/		1/	141	

Inclusion criteria:

(a) a subjective usual sleep duration of at least 4 hours but less than 6 hours per night; (b) a usual sleep latency of >= 30minutes; (c) daytime complaints associated with disturbed asleep. Each of there criteria was to be present for at least 6 months prior to study entry.

Exclusion criteria:

Any significant medical or psychiatric disorder or mental retardation; use of any other investigational drug within 30 days prior to the start of the study; use of flurazepam within 30 days of the first sleep laboratory night; regular use of any medication that would interfere with the assessment, absorption or metabolism of the study hypnotic; use of alcohol or short-acting central nervous system medication within 12 hours of any study night; use of triazolam within 4 nights, other short- or intermediate-acting hypnotics within 7 nights, or long-acting hypnotics within 14 nights of the first sleep laboratory night; history of exaggerated response or hypersensitivity to benzodiazepines or other CNS depressants; history of drug addiction, alcoholism, drug abuse, sleep apnoea, or nocturnal myoclonus; or a work or sleep schedule that regularly changed by at least 6 hours within 7 days of study initiation.

Mean age: Gender:	NR years 48% Female	Ethnicity:	NR
dosage	N=	Duration	
10 mg	35	3 day	
20 mg	35	3 day	
30 mg	36	3 day	
NA mg	35	3 day	
	Gender: dosage 10 mg 20 mg 30 mg	dosage N= 10 mg 35 20 mg 35 30 mg 36	Gender: 48% Female dosage N= Duration 10 mg 35 3 day 20 mg 35 3 day 30 mg 36 3 day

Adverse Events:

reported by patients

eponed by patients				
Zolpidem 10mg	Zolpidem 20mg	Flurazepam 30mg	Placebo	
any event: Number (%)				
14 (40)	23 (6537)	15 (41.7)	15 (42.9)	P: <0.05
dry mouth: Number (%)				
0 (0)	1 (2.9)	2 (5.6)	0 (0)	
back pain: Number (%)				
0 (0)	2 (5.7)	0 (0)	0 (0)	
fatigue: Number (%)				
3 (8.6)	2 (5.7)	0 (0)	1 (2.9)	
ataxia: Number (%)				
1 (2.9)	3 (8.6)	0 (0)	1 (2.9)	
confusion: Number (%)				
0 (0)	2 (5.7)	0 (0)	0 (0)	
difficulty concentrating: N	lumber (%)			
0 (0)	0 (0)	1 (2.8)	2 (5.7)	
dizziness: Number (%)				
0 (0)	3 (8.6)	1 (2.8)	0 (0)	
drugged feeling: Number	· (%)			
0 (0)	2 (5.7)	1 (2.8)	0 (0)	

ng, 1995				Quality rating: Fair
dysarthria: Number (%)				
1 (2.9) headache: Number (%)	3 (8.6)	0 (0)	0 (0)	
4 (11.4) light-headedness: Numbe	2 (5.7)	4 (11.1)	3 (8.6)	
0 (0) vomiting: Number (%)	0 (0)	2 (5.6)	0 (0)	
0 (0) myalgia: Number (%)	3 (8.6)	0 (0)	0 (0)	
0 (0) amnesia: Number (%)	2 (5.7)	1 (2.8)	1 (2.9)	
1 (2.9) nervousness: Number (%	3 (8.6) 5)	1 (2.8)	0 (0)	
1 (2.9) pharyngitis: Number (%)	2 (5.7)	1 (2.8)	0 (0)	
2 (5.7) abnormal vision: Number	0 (0) (%)	1 (2.8)	0 (0)	
0 (0)	2 (5.7)	0 (0)	0 (0)	
withdrawals				
Zolpidem 10mg	Zolpidem 20mg	Flurazepam 30mg	Placebo	
total withdrawals: Numbe	r			
0 withdrawal due to AEs: N	7 umber	1	0	P: NR
0	6	0	0	P: NR

jak, 1998, 19	95, 1	994							Quality	rating:	Fair
esign:											
Study design:	RCT	DB	Parall	lel	Run-in : Wash ou		′ days 3 days		Setting: Country:	Multice Germa	
Sample:	Numb	er Scr	reened/ I NR/	/Eligible /NR			•	//Withdrawn 0	Lost to follo	w-up/ A 0/	nalyzed 1507
Inclusion criter	ria:										
											s before starting awakening >= 3
during the 14	who h 4 days	prior to	o admissi	ion, or a	ny patients	with	psychiatric di	orders (e.g.	, depression	, schizoj	e times per week ohrenia, severe uded from this study
Population:	Mean Gend		51 years 62% Fei		Ethnic		99.3% Cauca 0.9% Others	sian			
tervention:			02,010								
Drug name	dos	age	N=		Duration						
Zenielene	7.5	mg	612		28 day						
Zopiclone					28 dav						
Zopicione Triazolam	0.2	mg	307		20 uay						
•	0.2 NA	0	307 298		28 day						
Triazolam	NA	0			,	_					
Triazolam Placebo	NA	0			,	_					
Triazolam Placebo dverse Event withdrawals	NA	mg	298	azolam	28 day	 Placel	00				
Triazolam Placebo dverse Event withdrawals	NA t s: s opiclor	mg	298 Tria	azolam	28 day	- Placel	00				
Triazolam Placebo dverse Event withdrawals Z total withdra	NA t s: s opiclor	mg	298 Tria	azolam 37	28 day	– Placel	00				
Triazolam Placebo dverse Event withdrawals Z total withdra	NA t s: opiclor awals: I	mg ne Numbe	298 Tria er 18		28 day		00				

Hayoun, 1989							Quality rating: Fair
Design:							
Study design:	RCT	DB	Paral	lel	Run-in :	NR	Setting: Single Center
					Wash out :	NR	Country: France
Sample:	Numbe	er Scree	ened/	Eligible/	Enrolled		Number Withdrawn/ Lost to follow-up/ Analyzed
			NR/	NR/	136		9/ 0/ 127

Inclusion criteria:

Patients aged between 18 and 65 years were recruited over a one-year period by 11 general practitioners. All of them had been experiencing insomnia, for at least two weeks, with complaint of unsatisfactory quality of sleep, associated with at least two of the three following criteria for most of the last 15 nights: time to fall asleep exceeding 30 minutes, total duration of sleep less than six hours, waking up at least twice (except for voiding).

Exclusion criteria:

The following patients were excluded: patients having taken a sedative drug within seven days before inclusion or likely to need such drugs during study; pregnant or lactating females, or females of childbearing age without reliable contraception; patients suffering from insomnia with external causes; patients with a history of convulsive disorders, with renal or respiratory impairment, with uncontrolled and significant organic disease, with uncontrolled pain or with a psychiatric affection; patients with myasthenia or known intolerance to either study drug; shift workers, alcoholics, or drug-abusers; noncooperative patients; those unable to read and understand the self-rating scales; known resistance to hypnotics.

Population:	Mean age: Gender:	47.9 years 66% Female	Ethnicity:	NR
Drug name	dosage	N=	Duration	
Zopiclone	7.5 mg	67	7 day	
Triazolam	0.25 mg	69	7 day	

Adverse Events:

reported by patients		
Zopiclone	Zaleplon	
overall side effects: %		
NR	NR	P: NS
global evaluation		
Zopiclone	Triazolam	
safety- good or excellent	%	
86	82	P: NS

, 1997						Quality	rating: Poo	r
sign:								
Study design:	RCT	DB	Crossove		0 days It: 7 days	Setting: Country:	Single Center Taiwan	
Sample:	Number	Scre	-	ble/ Enrolled NR/ 15	Numbe	r Withdrawn/ Lost to follo 0/	1 2	d 5
Inclusion crite	ia:							
						t least 3 of the following s irnal awakenings, and po		
Exclusion crite Patients with		es or	mood disor	ders, history of	severe physical il	Iness, alcohol arouse or	drug abuse.	
Population:	Mean ag Gender		40.1 years 73% Female		ity: NR			
ervention:								
Drug name	dosag	е	N=	Duration				
Zopiclone	7.5 m	g	15	14 day	_			
Triazolam	0.25 m	g	15	14 day				
Placebo	NA m	g	15	14 day				
verse Even	s:				_			
rebound ins	omnia							
Z	opiclone		Triazola	am				
rebound ins	omnia- m	nild de	egree of poc	or sleep: Numb	er (%)			
6	(40)		1 (6.7)					
rebound ins	omnia- m	noder	ate degree o	of poor sleep: N	Number (%)			
6	(40)		4 (26.7)					
rebound ins	omnia- s	evere	e degree of p	oor sleep: Nur	nber (%)			
3	(20)		10 (67.6))				
overall AEs								
Z	opiclone		Triazola	am				
number of a	wonte ror	orter	d: Number					
number of e	svenus iet							

Mamelak, 1987							Qu	Quality rating: Fair			
Design:											
Study design:	RCT	DB	Parall	el	Run-in :	2 days	Sett	ting:	Single	Center	
					Wash out :	3 days	Cou	untry:	Canad	а	
Sample:	Numb	er Scre	ened/ E	Eligible/	Enrolled	Number W	/ithdrawn/ Lost	to follov	w-up/ A	Analyzed	
			NR/	NR/	30		0/		0/	30	

Inclusion criteria:

Each subject had to have a history of at least 3-month's duration of any two of the following sleep disorders: sleep latency of >= 45 min, total nocturnal sleep time of <6 hours, morning awakening at least 90 min earlier than expected time, or three or more nocturnal awakenings. All subjects were required to be free of centrally acting drugs for at least 3 months before starting the study. Subjects had to be within 20% of normal body weight and only moderate users of alcohol.

Exclusion criteria:

Any major medical or psychiatric disorder disqualified the subject from the study. Other disqualifying cases specifically included women of child bearing potential and subjects with histories of drug abuse or allergic reactions to hypnotic-sedative drugs.

	opulation: rvention:	Mear Geno		50 years 70% Female	Ethnicity:	NR
[Drug name	dos	sage	N=	Duration	
Z	Zopiclone	7.5	mg	10	12 day	
F	Iurazepam	30	mg	10	12 day	
F	Placebo	NA	mg	10	12 day	

Adverse Events:

withdrawals

witharaw	laio							
	Zopiclone	Flurazepam	Placebo					
total with	otal withdrawals: Number							
	0	1	0					
withdraw	vithdrawals due to AEs: Number							
	0	1	0					

nti, 1994						C	Quality	rating: Fair	
sign:									
Study design:	RCT	DB	Parallel	Run-in : Wash out :	3 days 3 days		Setting: Country:	Single Center Uruguay	
Sample:	Num	ber Sc	reened/ Eligible/ NR/ NR/	Enrolled	-		-	w-up/ Analyzed 0/ 24	
Inclusion crite	ria:								
All patients v <6 hours,; to	vere s otal no	uffering cturnal	g from at least 2 wake time >20 r	of the following ninutes; numbe	sleep disturban r of nocturnal av	ces: time to fa wakenings >3.	ll asleep >	30 minutes; total slee	ep time
organic dise	omen, ase or	severe	e psychiatric disc	orders, and pati	ents in whom in	sufficient comp	oliance wa	thers, patients sufferin to be expected. All baseline period also le	cohol
Population:	Mea	n age:	47.3 years	Ethnicity:	NR				
	Gene		88% Female	-					
ervention:									
Drug name	dos	sage	N=	Duration					
Zolpidem	10	mg	8	27 day					
Triazolam	0.5	mg	8	27 day					
Placebo	NA	mg	8	27 day					
verse Event									
overall AEs	olpide	m	Triazolam	Plac	aha				
Z	.oipiue	111	TTId20IdTT	Flat	ebu				
Emergent a	dverse	e event	ts: Number						
	13		16	10				P: NR	
AEs with sig	gnifica	ant diff	ferences						
Z	olpide	m	Triazolam						
rebound: pe	essimi	st: Nun	nber						
	ower		higher					P: 0.096	
rebound: te		lumber	•						
le	ower		higher					P: 0.061	
rebound: pe	essimi	st: Nun	-						
le	ower		higher					P: 0.040	
withdrawals	5								
Z	olpide	m	Triazolam	Plac	ebo				
total withdra	awals:	Numbe	er						
	0		1	0					
	. d		Number						
withdrawals	aue i	U ALS.	Number						

Nair, 1990									Quality rating: Fair			
Design:												
Study design:	RCT DB Parallel		Run-in :	1 day	/S	Setting:	Single Center					
					Wash out :	NR		Country:	Canada			
Sample:	Number	Scree	ened/	Eligible/	Enrolled		Number Withdraw	n/ Lost to follo	w-up/ Analyzed			
			NR/	NR/	60							

Inclusion criteria:

(a) sleep latency of 30min or more, (b) two or more nocturnal awakenings with difficulty falling back to sleep, (c) early final morning awakening in the absence of depression, and (d) total sleep time usually less than 5 hours and always less than 6 hours.

Exclusion criteria:

Organic illness interfering with sleep, serious psychiatric illness, mental retardation, epilepsy, severe head trauma, significant abnormal laboratory findings, other interfering treatments or disorders, women of childbearing potential not following medically recognized contraceptive methods, pregnancy and/or breastfeeding, amphetamine use, or drug hypersensitivity.

Population: ervention:	Mean age: Gender:	46.9 years 47% Female	Ethnicity:	NR
Drug name	dosage	N=	Duration	
Zopiclone	3.75 mg	10	7 day	
Zopiclone	7.5 mg	10	7 day	
Zopiclone	11.2 mg	10	7 day	
Zopiclone	15 mg	10	7 day	
Flurazepam	30 mg	10	7 day	
Placebo	NA mg	10	7 day	

Adverse Events:

overall AEs

Zopiclone 3.75mg	Zopiclone 7.5mg	Zopiclone 11.25mg	Zopiclone 15mg	Flurazepam	
Total number of patients,	(Placebo=5): Numb	er			
4	4	11	5	10	
withdrawals					
Zopiclone 3.75mg	Zopiclone 7.5mg	Zopiclone 11.5mg	Zopiclone 15mg	Flurazepam	
total withdrawals, (placeb	o = 2): Number				
0	0	1	1	0	
withdrawals due to AEs, (placebo = 1): Numb	ber			
0	0	1	1	0	

en, 1990						Q	uality	rating:	Fai	r
sign:										
Study design:	RCT	DB	Parallel	Run-in : Wash out :	7 days NR		etting: ountry:	Single Malays		r
Sample:	Num	oer Scr	eened/ Eligible NR/ NR		Number	Withdrawn/ Lo 16/	st to follo	w-up/ A 0/		ed 44
Inclusion crite	ria:									
longer than	45 min	to fall a		e than two noct	nust have one o urnal awakening s a night					
history of hy	oncom	sitivity		ines, (e) drug a	comitant medica Ind/or alcohol ab					
Population:	Mear	age:	38.4 years	Ethnicity:	NR					
ervention:	Gend	ler:	52% Female							
Drug name	dos	age	N=	Duration						
Zopiclone	7.5	mg	20	14 day						
Temazepam	20	mg	20	14 day						
Placebo	NA	mg	20	14 day						
lverse Even	ts:									
reported by	patier	nts								
Z	opiclor	ne	Temazepa	m Pla	cebo					
excessive s	edatio	n: Num	iber							
	2		0	1						
withdrawal	S									
	opiclor	ne	Temazepa	m Pla	cebo					
Z										
Z total withdr	awals:	Numbe	er							
	awals: 7	Numbe	er 7	10	1					
	7		7	10						

Ponciano, 1990)					Qua	Quality rating: Fair			
Design:										
Study design:	RCT	DB	Paral	lel	Run-in :	7 days	Setti	ng:	Single C	Center
					Wash out :	7 days	Cour	try:	Portuga	I
Sample:	Numbe	er Scre	ened/	Eligible/	Enrolled	Number W	/ithdrawn/ Lost to	o follow	v-up/ Ar	nalyzed
			NR/	NR/	26		2/		0/	24

Inclusion criteria:

Patients were included in the study if they were unable to sleep without medication and had at least 3 of the following symptoms: sleep onset greater than 30 min, total sleep duration of less than 6 hours, poor subjectively reported sleep quality, and/or more than 2 nocturnal awakenings. Patients had to be within normal ranges for body weight, cardiac and haematological variables.

Exclusion criteria:

Those patients with a clinically significant history of psychiatric illness and those with a concurrent medical condition or therapy likely to interfere with the medication to be used were excluded. Patients with a history of drug use, those with excessive alcohol consumption (<1 litre of wine/day, or equivalent) pregnant or nursing women and all females of child bearing age without adequate contraception were also excluded.

Mean age: Gender:	30 years 46% Female	Ethnicity:	NR
dosage	N=	Duration	
7.5 mg	8	21 day	
30 mg	8	21 day	
NA mg	10	21 day	
	Gender: dosage 7.5 mg 30 mg	dosage N= 7.5 mg 8 30 mg 8	Gender: 46% Female dosage N= Duration 7.5 mg 8 21 day 30 mg 8 21 day

Adverse Events:

withdrawals

	Zopiclone	Flurazepam	Placebo
total	withdrawals: Numbe	er	
	0	0	2
withd	frawals due to AEs:	Number	
	0	0	1

Quadens, 1983						Quality rating: Poor				
Design:										
Study design:	RCT	DB	Crossover	Run-i	n :	6 days	Setting:	Single Co	enter	
				Wash	out :	35 days	Country:	Belgium		
Sample:	Numbe	r Scre	ened/ Eligib	le/ Enrolle	d	Number Withdrawn/	Lost to follo	ow-up/ An	alyzed	
			NR/ N	R/ 1	2	0/		0/	12	
Inclusion orito										

Inclusion criteria:

The subjects accepted for the study were aged 50-59 years and complained of insomnia for at least 2 month. To be valid the complaints were to include two or more of the following criteria: (1) sleep onset latency equal to or longer than 30 min; (2) total sleeping time during; (3) number of nocturnal awakenings equal to or higher than 3; (4) total waking time during the night equal to or longer than 30 min; (5) sleep qualified as poorly restoring, and (6) repetitiveness of the complaint if no drugs were taken

Exclusion criteria:

(1) weight under 45 kg or over 75 kg; (2) chronic use of drugs or alcohol; (3) admission to hospital within the 3 months preceding the recruiting for the trial; (4) mental retardation; (5) physical or psychiatric disability, and (6) treatment altering the absorption, metabolism, or excretion of the drugs and susceptible to alter the evaluation of the hypnotic effects.

Population:	Mean age: Gender:	NR years 100% Female	Ethnicity:	NR	
Drug name	dosage	N=	Duration		
Zopiclone	7.5 mg	12	13 day		
Flurazepam	30 mg	12	13 day		

Adverse Events:

Norris questionnaire

Zopiclone	Flurazepam	
clear headed-mussy: So	core (SD)	
28.1 (9.3)	34.6 (13.4)	P: <0.05
energic-lethargic: Score	e (SD)	
29.2 (12.7)	34.9 (10.1)	P: <0.05
tranquil-troubled: Score	(SD)	
19.8 (11.2)	24.7 (9.4)	P: <0.05
relaxed-tense: Score (S	D)	
21.4 (11.7)	25.9 (10.8)	P: <0.05
elated-depressed: Scor	e (SD)	
48.1 (15.3)	50.5 (14.0)	P: <0.05
sociable-introverted: Sc	ore (SD)	
53.6 (15.3)	52.3 (13.4)	P: <0.05
other 12 items show no	difference: Score	
multiple data	multiple data	P: NS
withdrawals		
Zopiclone	Flurazepam	
total: Number		
0	0	P: NR
due to AEs: Number		
0	0	P: NR

Rosenberg, 19	94						Quality rating: Poor
Design:							
Study design:	RCT	DB	Parall	el	Run-in :	NR	Setting: Multicenter
					Wash out :	NR	Country: Denmark
Sample:	Numbe	er Scre	ened/ E	Eligible/	Enrolled		Number Withdrawn/ Lost to follow-up/ Analyzed
			NR/	NR/	178		5/ 34/ 139

Inclusion criteria:

Patients between 18-80 years old, have had insomnia for at lease one week complying with at least two of the following criteria: 1) have more than three awakenings per night, 2) sleeping time less than six hours per night, 3) time to fall asleep more than 30 minutes, and 4) awake more than 20 minutes during the night.

Exclusion criteria:

General exclusion criteria were psychiatric disease requiring medication, insomnia because of well-defined illness, and treatment with hypnotics or BZDs within four weeks prior to the study. The patients was excluded from data analysis if his diary consisted of comments from less than three days, if his case record form was incompletely filled in by the doctor, or if he had taken hypnotics other than blinded drugs in the study

Population:	Mean age: Gender:	54 years 0% Female	Ethnicity:	NR
Drug name	dosage	N=	Duration	
Zolpidem	10 mg	71	14 day	
Triazolam	0.25 mg	68	14 day	

Adverse Events:

Overall AEs		
Zolpidem	Triazolam	
CNS-related adverse ev	ents: Number (%)	
8 (11.3)	10 (14.7)	P: NS
GI-related adverse ever	ts: Number (%)	
2 (2.8)	3 (4.4)	P: NS
other adverse events: N	umber (%)	
5 (7)	2 (2.9)	P: NS
total: Number (%)		
15 (21.1)	15 (22)	P: NS

vestri, 1996								Qu	ality	rating	: Fai	r	
esign:													
Study design:	RCT	DB	Parall	el	Run-in :	3 days			ting:	Multic	enter		
		_			Wash out :				untry:	Italy			
Sample:	Numbe	r Scre		•	Enrolled	Numb	er Withdra		to follo	•	Analyz		
Inclusion crite	rio		NR/	NR/	22			0/		2/		20	
Both sexes, recurrence c complaints:	age betw of short-te time to fa >3. The	erm si all asle	tuationa eep >30	l insomr minutes	, clinical diagn nia) or poor sle s, total sleep di n criteria had t	epers with su uration <6 hou	bjective re	eporting o vake time	f at lea: >20 mi	st two o nutes, a	ut of th and/or	nese fo	ur
psychiatric of Scale for De sleep obstru	diseases, epression uctive apr	also (total iea of	screene score > >7 minu	d by me 16); neu utes dura	hild-bearing ag ans of both Ha urological dise ation); severe tropic drug dur	amilton Rating ases (myoclor internal (hear	Scale for ius, kinae , renal, liv	Anxiety (sthesis di er) diseas	total sc sorders ses; he	ore >16 s, restle mocoag) and ss legs ulatior	Hamilto s syndr n disoro	on Ratin ome, ders
blockars or	corticocto					o 1	locoung						
blockers or Population:		eroids		are	Ethnicity	0	locounig						
Population:		eroids i ge:	33.6 yea 55% Fer		Ethnicity:	0							
	Mean a	eroids I ge: I	33.6 yea		Ethnicity: Duration	0							
Population: tervention:	Mean a Gender	eroids I ge: r: ge	33.6 yea 55% Fer		Ĩ	0							
Population: tervention: Drug name	Mean a Gender dosag	eroids i ge: r: ge ng	33.6 yea 55% Fer N=		Duration	0							
Population: tervention: Drug name Zolpidem	Mean a Gender dosag 10 m 0.25 m	eroids i ge: r: ge ng	33.6 yea 55% Fer N= 10		Duration 2 week	0							
Population: tervention: Drug name Zolpidem Triazolam	Mean a Gender dosag 10 m 0.25 m ts:	eroids i ge: r: ge ng	33.6 yea 55% Fer N= 10		Duration 2 week	0							
Population: tervention: Drug name Zolpidem Triazolam dverse Even withdrawal	Mean a Gender dosag 10 m 0.25 m ts:	eroids i ge: r: ge ng	33.6 yea 55% Fer N= 10 12		Duration 2 week	0							
Population: tervention: Drug name Zolpidem Triazolam dverse Even withdrawal	Mean a Gender dosag 10 m 0.25 m ts: s Zolpidem	aroids age: r: ge ng	33.6 yea 55% Fer N= 10 12 Tria	male	Duration 2 week	0							
Population: tervention: Drug name Zolpidem Triazolam dverse Even withdrawal Z	Mean a Gender dosag 10 m 0.25 m ts: s Zolpidem	aroids age: r: ge ng	33.6 yea 55% Fer N= 10 12 Tria	azolam	Duration 2 week	0							
Population: tervention: Drug name Zolpidem Triazolam dverse Even withdrawal Z	Mean a Gender dosag 10 m 0.25 m ts: s Zolpidem awals: Nu 0 (0)	ge: ge ge gg gg gg	33.6 yea 55% Fer 10 12 Tria	azolam	Duration 2 week	0							
Population: tervention: Drug name Zolpidem Triazolam dverse Even withdrawal Z total withdra	Mean a Gender dosag 10 m 0.25 m ts: s Zolpidem awals: Nu 0 (0)	ge: ge ge gg gg gg	33.6 yea 55% Fer 10 12 Tria	azolam 6.7)	Duration 2 week	0							
Population: tervention: Drug name Zolpidem Triazolam dverse Even withdrawal Z total withdra	Mean a Gender dosag 10 m 0.25 m ts: s Zolpidem awals: Nu 0 (0) s due to A 0	ge: ge ge gg gg gg	33.6 yea 55% Fer 10 12 Tria (%) 2 (1 Jumber	azolam 6.7)	Duration 2 week	0							

1

1

P: NR

gh, 1990					Quality	rating: Fair	
sign:							
Study design:	RCT DE	B Parallel	Run-in :	4 days	Setting:	Single Center	
			Wash out :		Country:		
Sample:	Number Sc	reened/ Eligible		Number Wi	thdrawn/ Lost to follo		
		NR/ 61	60		3/	0/ 57	
Inclusion crite NR	ria:						
Exclusion crite Psychotic an abuse, coffe significant n	nd neurotic pa ee or tea abus nedical condit gnancy, lacta	se, neurological of tion interfering w	disorders, estab th sleep, those	lished sleep apnoe treatment which co	ry of mental retardati a and drug hyperser buld modify drug kine recognized contrace	nsitivity. Patients v etics were also exe	with any cluded.
Population:	-	39.6 years	Ethnicity:	NR			
-	Gender:	53% Female					
ervention:							
Drug name	dosage	N=	Duration				
Zopiclone	7.5 mg		24 day				
Zopiclone	11.2 mg		24 day				
Flurazepam	30 mg		24 day				
withdrawal Zopi		Zopiclone 11.2	5mg Elurazep	am 30mg			
				g			
	ber						
total: Numb	0	0	4				
	0 · Number	2	1				
total: Numb	: Number						
due to AEs	: Number 0	2	1				
due to AEs overall AEs	: Number 0	1	0				
due to AEs overall AEs	: Number 0		0	am 30mg			
due to AEs overall AEs Zopi	: Number 0	1 Zopiclone 11.2	0	am 30mg			
due to AEs overall AEs Zopi	: Number 0 clone 7.5mg	1 Zopiclone 11.2	0	am 30mg		P: NR	
due to AEs overall AEs Zopi	Number 0 clone 7.5mg rrsion: Number 7	1 Zopiclone 11.2 er	0 5mg Flurazepa	am 30mg		P: NR	
due to AEs overall AEs Zopi taste perve	Number 0 clone 7.5mg rrsion: Number 7	1 Zopiclone 11.2 er	0 5mg Flurazepa	am 30mg		P: NR P: <0.	
due to AEs overall AEs Zopi taste perve	: Number 0 clone 7.5mg rsion: Number 7 :: Number 0	1 Zopiclone 11.2 er 10	0 5mg Flurazepa 7	am 30mg			
due to AEs overall AEs Zopi taste perve drowsiness	: Number 0 clone 7.5mg rsion: Number 7 :: Number 0	1 Zopiclone 11.2 er 10	0 5mg Flurazepa 7	am 30mg			05
due to AEs overall AEs Zopi taste perve drowsiness headache:	Number 0 clone 7.5mg rrsion: Number 7 :: Number 0 Number 0	1 Zopiclone 11.2 er 10 1	0 5mg Flurazepa 7 9 4	am 30mg		P: <0.	05

p, 1999					Quality	rating: Fair
sign:						
Study design:	RCT DE	B Parallel	Run-in :	7 days	Setting:	Single Center
			Wash out :	7 days	Country:	Canada
Sample:	Number Sc	creened/ Eligible	/ Enrolled	Number Wi	thdrawn/ Lost to follo	w-up/ Analyzed
		NR/ NR	/ 60		2/	8/ 50
Inclusion criter						
Daytime fatig	gability, dimi	nished power of a	concentration a	t work and at least	two of the following s	disorders (DSM III-R). symptoms: falling asleep time early wake up in the morning
Exclusion crite	eria:					
Population:	Mean age:	42.6 years	Ethnicity:	NR		
ervention:	Gender:	% Female				
Drug name	dosage	N=	Duration			
Zopiclone	7.5 mg	19	21 day			
Temazepam	30 mg	16	21 day			
Placebo	NA mg	15	21 day			
lverse Event	ts:					
withdrawals	6					
Z	opiclone	Temazepar	n Plac	cebo		
total withdra	awals: Numb	er				
	0	1	1			
	0					
withdrawals	due to AEs	: Number				

Tamminen, 198	87							Quality	rating:	Poor	
Design:											
Study design:	RCT	DB	Para	llel	Run-in :	7 days		Setting:	Multicen	ter	
					Wash out :	NR		Country:	Finland		
Sample:	Numbe	r Screei	ned/	Eligible/	Enrolled	Num	ber Withdrawn/	Lost to follo	w-up/ An	alyzed	
			NR/	130/	94		0/		0/	94	

Inclusion criteria:

Patients aged 18 to 70 years with sleep disturbances for at least 3 months prior to entrance into the trial were included. Both untreated and preciously treated patients were included. At least two of the following criteria had to be present in untreated patients (they also had to have been present prior to treatment in treated cases): latency of sleep onset >30min, total sleep duration <6.5hours, nocturnal awakenings >2 per night, time to fall asleep after at least one nocturnal awakening >30min, awakening >2hour before scheduled time.

Exclusion criteria:

Known hypersensitivity to benzodiazepines, major psychiatric disorders, somatic disorders directly causing insomnia or likely to interfere with the assessments, known alcoholism or drug addiction, pregnant women or women who may become pregnant during the trial, frequent intakes of other medication likely to interfere with sleep.

Population:	Mean age: Gender:	47 years 77% Female	Ethnicity:	NR
Drug name	dosage	N=	Duration	
Zopiclone	7.5 mg	52	42 day	
Nitrazepam	5 mg	46	42 day	

Adverse Events:

somatic complaint check list (higher score=more severe)- change from b

Zopiclone	Nitrazepam	
anxiety: Score (p vs ba	seline)	
3.8 (<0.06)	-6.8 (<0.001)	P: <0.05
sweating: Score (p vs b	aseline)	
5.7 (<0.001)	-7.1 (<0.05)	P: NS
nausea: Score (p vs ba	seline)	
4.3 (NS)	-3.2 (NS)	P: <0.05
loss of appetite: Score	(p vs baseline)	
0 (NS)	-6.5 (<0.05)	P: NS
restlessness: Score (p	vs baseline)	
2.2 (NS)	-5.9 (<0.05)	P: NS
physical tiredness: Sco	re (p vs baseline)	
-3.5 (<0.0001)	-10.3 (<0.0001)	P: NS
dizziness: Score (p vs l	baseline)	
3.5 (NS)	-7.8 (<0.001)	P: <0.05
indigestion: Score (p vs	baseline)	
8.8 (<0.05)	-10 (<0.01)	P: <0.05
reported by patients		
Zopiclone	Nitrazepam	

number of events reported: Number

24 13 number of patients experiencing unwanted effects: Number

46

ninen, 1987		Quality rating: Poor
global evaluation		
Zopiclone	Nitrazepam	
safety score (1=poor; 5=	excellent): Score	
3.4	3.5	P: NS

n der Kleijn,	1989						Qua	lity rat	ing: F	air	
esign:											
Study design:	RCT	DB	Cros	sover	Run-in : Wash out :	2 days 7 days	Setti Cour	•	२ jmegen		
Sample:	Numbe	r Scree	ened/ NR/	Eligible/ 60/	Enrolled 55	Number \	Vithdrawn/ Lost to 2/		ip/ Anal 0/	lyzed 53	
Inclusion criter	ria:										
1. latency of	sleep on	set ex	ceedir	na 30 min							
0,	too early several	y times :	at nigh	nt and diff		g asleep afterwar	ds				

Population:	Mean age: Gender:	53 years 71% Female	Ethnicity:	N
Drug name	dosage	N=	Duration	
Zopiclone	7.5 mg	53	5 day	
Temazepam	20 mg	53	5 day	

Adverse Events:

Reported	by	patients
----------	----	----------

Zopiclone	Temazepam	Placebo	
Bad headache: %			
8	12	14	P: NR
Very severe perspiration	: %		
8	18	10	P: NR

er Kleijn, 1989		Quality rating: Fair					
Opinion of the patient about day-time status							
Zopiclone	Temazepam	Placebo					
Well/normal: Number (%	5)						
30 (57)	35 (66)	27 (51)	P: NR				
Sleepy/dull/tired: Numbe	er (%)						
7 (13)	6 (11)	12 (23)	P: NR				
Headache: Number (%)							
3 (6)	3 (6)	1 (2)	P: NR				
Irritable/unstable: Numb	er (%)						
4 (8)	4 (8)	6 (11)	P: NR				
Trembling/palpitation: N	umber (%)						
2 (4)	4 (8)	2 (4)	P: NR				
Difficulties to concentrat	e: Number (%)						
2 (4)	0 (0)	0 (0)	P: NR				
Depressive: %							
3 (6)	1 (2)	2 (4)					
Unknown: %							
2 (4)	0 (0)	3 (6)					
withdrawals							
Zopiclone	Temazepam						
Total withdrawals: Numb	ber						
1	1		P: NR				
withdrawals due to AEs:	Number						
1	1		P: NR				

oshaar, 2004						Quality rating: Fair					
sign:											
Study design:	RCT	DB	Paralle	el	Run-in : Wash out :	NR 4 days		Setting: Country:	Multice Nether		
Sample:	Numb	er Scr	eened/ E NR/	ligible/ NR/	Enrolled 221	Number V	/ithdrawn/ 9/	Lost to follo	w-up/ A 5/	Analyzed 159	
Inclusion criter	ia:										
Patients wer between 18				if they v	were diagnose	d with primary in	somnia acc	ording to DS	SM-III-R	and were ag	ged
	other a					ders, pregnancy, ion requiring shit		of psychoti	ropic me	edication, co	mplaints
Population:	Mean Gende		46.1 yea 0% Fema		Ethnicity:	NR					
ervention:	Conta		0701 0116								
Drug name	dosa	age	N=		Duration						
Zolpidem	10	mg	74		28 day						
Temazepam	20	mg	85		28 day						
remazepani											
verse Event	s:										
verse Event		n	Tema	azepam							
verse Event	s olpiden			azepam							
verse Event withdrawals Z total withdra	s olpiden										
verse Event withdrawals Z total withdra	s olpiden awals: N NR	lumbe	er Ni								

lsh, 1998a									Quality	rating	g: Fa	air
sign:												
Study design:	RCT	DB	Parallel	Run-in : Wash ou	7 da nt: NR	ays			Setting: Country:	Multio US	center	
Sample:	Num	ber Scr	eened/ Eligib NR/ 58	le/ Enrolled 39/ 306		Numbe	er Withdr	awn/ L 28/	_ost to follo	ow-up/ 0/	Analy	yzed 278
Inclusion crite	ria:											
			nimum of a 1- self-reported s								d slee	ep latency (S
sleep apnea	ant me or per	riodic lii	psychiatric di mb movement nt based on th	disorder, smo	oking of	more tha	n 10 ciga	rettes	per day, w	eight va	arying	by more that
Population:	Mea	n age:	NR years	Ethnic	ity: NF	ł						
ervention:	Gene		0% Female									
Drug name	dos	sage	N=	Duration								
Zolpidem	10	mg	102	14 day								
Trazodone	50	mg	100	14 day								
Placebo	NA	mg	104	14 day								
lverse Even	ts:											
reported by	patie	nts										
Ζ	Colpide	m	Trazodo	ne l	Placebo							
total numbe	er of ev	/ents: N	lumber (%)									
	(76.5)	1	75 (75)								Р	: NS
		st incide	ence): %									
	highes											
78	highes 24		30		19							
78	24				19							
78 headache (24				19 8							
78 headache (24 e (high 16		idence): %		-							

7

2

10

5

total withdrawals: Number

11

withdrawals due to AEs: Number 5

Walsh, 1998b							C	Quality I	rating	g: Go	boc	
Design:												
Study design:		DB	Para	allel	Run-in :	3 days	S	Setting:				
					Wash out :	2 days	C	Country:	US			
Sample:	Number	Scre	ened/	Eligible/	Enrolled	Number \	Nithdrawn/ Lo	ost to follo	w-up/	Analy	zed	
			673/	456/	132		7/		0/		125	
Inclusion crite	ria:											

Patients with a DSM-IIIR diagnosis of primary insomnia and two of the following four (including one of the first two) subjective sleep reports: a modal sleep latency >=45 minutes, mean awakenings per night >=3, a mean total sleep time of <6.5 hours/night, and daytime symptoms related to disturbed sleep (e.g. tiredness, impaired functioning, irritability).

Exclusion criteria:

Individuals with significant medical or psychiatric illness, as determined by history and physical examination, clinical laboratory tests, the Zung Anxiety and Depression scales (scores >40) were excluded, as were those using CNS active medication. Individuals with prior exposure to zaleplon, or sensitivity to benzodiazepines or other psychotropic drugs, were excluded.

Population:	Mean age Gender:	: 40.3 years 58% Female	Ethnicity:	NR
Drug name	dosage	N=	Duration	
Zaleplon	5 mg	34	14 day	
Zaleplon	10 mg	33	33 day	
Triazolam	0.25 mg	31	14 day	
Placebo	NA mg	34	14 day	

Adverse Events:

Treatment emergent adverse effects

Placebo	Zaleplon 5mg	Zaleplon 10mg	Triazolam	
Overall number of report	s: Number (%)			
13 (38)	12 (35)	14 (42)	17 (55)	P: NS
Nausea: Number (p vs tr	iazolam)			
0 (<0.046)	0 (<0.046)	1 (NR)	4 (NA)	
headache- the most com	mon adverse event:	Number (%)		
5 (15)	5 (15)	6 (18)	7 (23)	
withdrawals				
Zaleplon 5mg	Zaleplon 10mg	Triazolam	Placebo	
total withdrawals: Numbe	er			
3	1	0	3	
withdrawals due to AEs:	Number			
1	0	0	0	

Evidence Table 6. Active controlled trials (Adult): Adverse Events

/alsh, 2000	h, 2000							Quality rating: Poor			
Design:											
Study design:	RCT	DB (Crossover	Run-in :	NR	Setting:	Sing	le Center			
				Wash out :	NR	Country:	US				
Sample:	Number	Screen	ed/ Eligible/	Enrolled		Number Withdrawn/ Lost to follo	ow-up/	Analyzed			
			73/ 39/	30		2/	0/	22			
Inclusion crite	ria:										

Men and women with sleep maintenance insomnia, 18 to 60 years of age.

Exclusion criteria:

individuals for any of the following: >120% of ideal body weight, consumption of 20 cigarettes per day or >21 ounces of ethanol per week, currently pregnant or breast-feeding, precious exposure to zaleplon, benzodiazepine sensitivity, use of another investigational drug, psychotropic medication, tryptophan, or melatoantihistamine in the past week, or use of medications that would interfere with the absorption or metabolism of the study drugs.

Population:	Mean age: Gender:	42 years % Female	Ethnicity:	NR
Drug name	dosage	N=	Duration	
Zaleplon	10 mg	22	2 day	
Flurazepam	30 mg	22	2 day	
Placebo	NA mg	22	2 day	

Adverse Events:

NR

Ware, 1997							Qu	uality ra	ting	: Fair	
Design:											
Study design:	RCT	DB	Para	allel	Run-in :	2 days	Set	tting: N	lultic	enter	
					Wash out :	3 days	Со	<mark>untry:</mark> Լ	IS		
Sample:	Numbe	er Scre	ened/	Eligible/	Enrolled	Number \	Vithdrawn/ Lost	t to follow-	up/	Analyzed	
			358/	NR/	110		11/	I	NR/	99	

Inclusion criteria:

Adults 21-55 years old with a complaint of chronic insomnia and polysomnographically disturbed sleep; minimum of a 3-month history of disturbed sleep characterized by a usual sleep time of 4 to 6 hours, a usual sleep latency of at least 30 minutes, and associated daytime complaints.

Exclusion criteria:

Any significant medical or psychiatric disorder, history or polysomnographically findings of sleep apnea or periodic leg movements, pregnancy or risk of becoming pregnant, and lactation. History of sensitivity to CNS depressants, regular use of any medication that would interfere with the study, a recent history of alcohol or drug abuse, use of any investigational drug within 30 days of study entry, and previous use of zolpidem also excluded patients. Finally, shift work or any other regularly changing sleep schedule excluded study participation.

Population:	Mean age: Gender:	NR years 58% Female	Ethnicity:	69% white
Drug name	dosage	N=	Duration	
Zolpidem	10 mg	37	28 day	
Triazolam	0.5 mg	30	28 day	
Placebo	NA mg	35	28 day	

Adverse Events:

withdrawals

	Zolpidem	Triazolam	Placebo
withdra	wals due to AEs:	Number (%)	
	3 (8.1)	4 (11.1)	0 (0)
total wit	thdrawals: Numbe	er	
	NR	NR	NR

heatley, 1985	5							Quality	rating	g: Fair
esign:										
Study design:	RCT	DB	Cross	sover	Run-in : Wash out :	3 day NR	/S	Setting: Country:	NR NR	
Sample:	Num	ber Sci	reened/ I NR/	Eligible/ NR/	Enrolled 36		Number Withdrawn/ 2/	Lost to follo	ow-up/ /0	
Inclusion crite Patients age week.		ears a	nd over s	uffering	from difficulty	in slee	ping, provided that sy	mptoms ha	d been	present for at least one
Exclusion crite	eria:									
Population:	Mear Geno		53.2 yea 61% Fe		Ethnicity:	NR				
ntervention: Drug name	hos	sage	N=		Duration					
Zopiclone	7.5	mg	36		7 day					
Temazepam	20	mg	36		7 day					
dverse Even	ts:									
Reported b	y patie	ents								
Z	opiclo	ne	Tem	azepam						
Overall AE	s, no. c	of patie	nts: Num	ber (%)						
1	0 (28)		9 (25)				2 (6)	P: NR
Daytime dro	owsine	ss: Nu	mber							
_	3		:	2						P: NR
withdrawal	5									
Z	opiclo	ne	Tem	azepam						
total withdra	awals:	Numbe	ər							
	2		(C						
withdrawals	due t	o AEs:	Number							
	2			C						

ergener, 1989)						Quality	rating	: Fai	r
esign:										
Study design:	RCT	DB	Parallel	Run-in: Wash out:	4 days 7 days		Setting: Country:	NR Germa	in	
Sample:	Num	ber Sci	-	ible/ Enrolled NR/ 42	Num	ber Withdrawn/ NR/	Lost to follo	w-up/ / NR/	,	ed 42
Inclusion crite	ria:									
Patients who the initial pla				of 14 points on the	Sleep Disord	ler intensity Sca	le (SDIS) w	ith no im	prove	ment during
	n a hist psych	,		a predelirium a sev with drugs affectin		'	· ·			,
were exclude	cu									
Population:		n age:	NR years	Ethnicity:	NR					
Population:			NR years 86% Femal	•	NR					
	Mear Geno		-	•	NR	Primary outcome	Outcome:			
Population:	Mear Geno	ler: age	86% Femal	e	NR				ensity	Scale (SDIS
Population: ntervention: Drug name	Mear Genc dos	ler: age	86% Femal N=	e Duration	NR				ensity	Scale (SDIS
Population: htervention: Drug name Zopiclone	Mear Genc dos 7.5	ler: age mg	86% Femal N= 20	e Duration 21 day	NR				ensity	Scale (SDIS
Population: htervention: Drug name Zopiclone	Mear Genc dos 7.5	ler: age mg	86% Femal N= 20	e Duration 21 day	NR				ensity	Scale (SDIS
Population: ntervention: Drug name Zopiclone Flurazepam	Mear Genc dos 7.5 30	ler: age mg mg	86% Femal N= 20 22	e Duration 21 day 21 day	NR				ensity	Scale (SDIS
Population: ntervention: Drug name Zopiclone Flurazepam fficacy: SDIS (6=bes	Mear Genc dos 7.5 30	ler: age mg mg p; 30=	86% Femal N= 20 22	Duration 21 day 21 day	NR				ensity	Scale (SDIS
Population: ntervention: Drug name Zopiclone Flurazepam Sflicacy: SDIS (6=be: Z	Mear Genc dos 7.5 30 st slee	ler: age mg mg p; 30= ne	86% Femal N= 20 22 worst sleep	Duration 21 day 21 day 21 day	NR				ensity	Scale (SDIS

Elie, 1990a						Quality ra	ating: I	Fair
Design:								
Study design:	RCT D	DB Parallel	Run-in : Wash out :	7 days 4 days		•	Multicent Canada	er
Sample:	Number S	Screened/ Elig NR/	jible/ Enrolled NR/ 44	Numb	er Withdrawn/ 0/	Lost to follow	-up/ Ana 0/	alyzed 44
Inclusion crite	ria:							
Age betwee	n 60 and 90) years, living i	in residential home	s and sufferin	g from chronic	insomnia.		
Exclusion crite								
drug abuse	and coffee	or tea abuse.	ry of blood dyscras Patients with seven dify drug kinetics we	re medical co	nditions, those			
Population:	Mean age	76.0 years	Ethnicity:	NR				
	Gender:	75% Fema	•					
Intervention: Drug name	dosage	N=	Duration		Primary outcome	Outcome:		
Zopiclone	5-7. mg	15	21 day			Sleep latenc	;y	
Triazolam	0.12 mg	14	21 day			Sleep sound	lness	
Placebo	NA mg	15	21 day			Sleep quality	/	
						Status of wa	kefulnes	s upon arising
						Hangover		
Efficacy:								
Post-sleep	questionna	aire						
-	opiclone	Triazo	lam					
sleep late	ncy, mean	score: Score (p vs placebo)					
6.	7 (<0.05)	6.8 (<0	0.05)					
sleep sou	indness, me	ean score: Sco	ore (p vs placebo)					
	8 (<0.01)	6.4 (<0	<i>,</i>					
quality of	sleep, mea	n score: Score	e (p vs placebo)					
	0.8 (<0.08)	11.0 (<	,					P: NS
	. ,		ore (p vs placebo)					
0	0.5 (NS)	10.5 (· · /					P: NS
	· · ·	re: Score (p vs	,					
								D. NO
1	6.6 (NS)	16.7 (100)					P: NS

Klimm, 1987							Qual	ity ratin	g: Fai	r	
Design:											
Study design:	RCT	DB	Para	allel	Run-in :	7 days	Settin	g: Com	munity	practic	
					Wash out :	7 days	Count	ry: Fran	ce		
Sample:	Numbe	er Scre	ened/	Eligible/	Enrolled	Number \	Vithdrawn/ Lost to	follow-up/	Analyz	ed	
			NR/	NR/	74		2/	2/		72	

Inclusion criteria:

For the purpose of this trial, chronic insomnia was defined as the presence of two of the following criteria: hypnotics taken five times a week for the last 3 months, sleep onset latency > 1 h, total duration of sleep < 6 h, and waking more than three times during the night. The patients' mental capacity, as measured by Intellectual Quotient and memory tests (Syndrome Kurztest) was to be within normal range for their age.

Exclusion criteria:

Patients presenting contraindications to benzodiazepines or painful conditions, those with a history of drug allergy or chronic alcoholism, those receiving drugs liable to affect metabolism, those refusing to give their consent, those who might have been unable to complete the trial, those already involved in another trial, and those considered unlikely to cooperate were excluded.

Population:	Mear Gene		73.2 years 80% Female	Ethnicity:	NR		
 ervention: Drug name	dos	sage	N=	Duration		Primary outcome	Outcome:
Zopiclone	7.5	mg	36	7 day			sleep onset latency
Nitrazepam	5	mg	36	7 day			quality of sleep
							feeling upon awakening
							duration of sleep
							awakenings during the night
							dreams

Efficacy:

Nitrazepam	
ange from placebo baseline: Score (p vs baseline)	
-15.6 (NS)	P: NS
e from placebo baseline: Score (p vs baseline)	
23.1 (<0.002)	P: NS
change from placebo baseline: Score (p vs baseline)	
6.8 (NS)	P: NS
on day 9 and day 11: Score	
NR	P: <0.02
	ange from placebo baseline: Score (p vs baseline) -15.6 (NS) e from placebo baseline: Score (p vs baseline) 23.1 (<0.002) change from placebo baseline: Score (p vs baseline) 6.8 (NS) on day 9 and day 11: Score

n, 1987		Quality rating: Fair
Spiegel sleep question	aire	
Zopiclone	Nitrazepam	
sleep onset latency: So	core (p vs placebo)	
NR (0.003)	NR (0.009)	P: NS
quality of sleep: Score	(p vs placebo)	
NR (0.003)	NR (0.007)	P: NS
duration of sleep: Score	e (p vs placebo)	
NR (0.003)	NR (0.005)	P: NS
awakenings at night: S	core (p vs placebo)	
NR (0.004)	NR (0.009)	P: NS
dreams: Score (p vs pl	acebo)	
NR (0.003)	NR (0.01)	P: NS
condition in the mornin	g: Score (p vs placebo)	
NR (0.003)	NR (0.002)	P: NS
general evaluation: Sco	ore (p vs placebo)	
NR (0.0004)	NR (0.005)	P: NS
sleep onset latency on	day 12: Score	
NR	better	P: <0.001

Leppik, 1997							Q	Quality rating: Fair			
Design:											
Study design:	RCT	DB	Para	llel	Run-in :	7 days	Se	etting:	Multic	enter	
					Wash out :	4 days	C	ountry:	US		
Sample:	Numbe	er Scre	ened/	Eligible/	Enrolled	Number With	ndrawn/ Los	st to follo	w-up/	Analyz	ed
			NR/	457/	335		40/		0/	3	335
Inclusion crite	ria:										

Enrollment criteria included chronic insomnia of at least 3 months' duration, defined as self-reported sleep duration of 4-6 hours each night and self reported sleep latency of 30 minutes or more; some impairment of daytime functioning related to sleep deprivation; relatively stable mental and physical health; and no evidence of systemic abnormalities or other diseases that would interfere with study drug evaluation. Normal 12-lead electrocardiogram (ÉCG) and clinical laboratory evaluation were required.

Exclusion criteria:

Exclusion criteria included significant and/or unstable medical or psychiatric disorder or mental retardation, use of an investigational drug within 30 days of the start of the study, regular use of medication of a type that could interfere with assessment of a hypnotic; use of a medication that could interfere with absorption or metabolism of a benzodiazepines or other CNS depressants, and previous administration of zolpidem. In addition, patients with a recent history of drug or alcohol abuse, seizure disorder; or symptoms of sleep apnea of myoclonus were excluded. Shift workers and other individuals with changing sleep schedules were also excluded.

Population:	Mean age: Gender:	69 years 63% Female	Ethnicity:	93% white		
Intervention: Drug name	dosage	N=	Duration		Primary outcome	Outcome:
Zolpidem	5 mg	82	28 day		\checkmark	sleep latency
Triazolam	0.12 mg	85	28 day		\checkmark	sleep duration
Temazepam	15 mg	84	28 day			ease of falling asleep
Placebo	NA mg	84	28 day			no. of awakenings
						wake time after sleep onset
						quality of sleep
						morning sleepiness
						ability to concentrate

Efficacy:

...

Zolpidem	Triazolam	Temazepam	Placebo	
leep latency at week 4	: minutes (p vs place	ebo)		
40.5 (<0.05)	47.7 (NS)	38.0 (<0.05)	57.9 (NA)	
leep latency at week 1	and week 3: minute	S		
shorter	multiple data			P: <0.05
leep latency at week 1	and week 3: minute	S		
multiple data	multiple data			P: NS
leep duration at week	4: minutes (p vs plac	ebo)		
362.8 (NS)	359.7 (NS)	375.3 (NS)	363 (NA)	
olerance to treatment:	minutes (p vs placeb	o)		
multiple data (NS)	multiple data (NS)	multiple data (NS)	multiple data (NA)	

k, 1997		Quality rating: Fair
Global Impression of the	erapy	
Zolpidem	Temazepam	
sleep better: Score (p v	s placebo)	
NR, better (<0.05)	NR, better (<0.05)	
sleep latency: Score (p	vs placebo)	
NR, better (<0.05)	NR, better (<0.05)	
medication strength: Sc	core (p vs placebo)	
NR, better (<0.05)	NR, better (<0.05)	
overall feeling: Score (p	o vs placebo)	
NR, better (<0.05)	NR, better (<0.05)	

Roger, 1993								Quality rating: Fair			
Design:											
Study design:	RCT	DB	Para	llel	Run-in :	3 days	Setting:	Multic	enter		
					Wash out :	7 days	Country:	France	е		
Sample:	Number	Scree	ened/	Eligible/	Enrolled	Number Withdrawn/	Lost to follo	w-up/	Analy	zed	
			NR/	NR/	221	16/		0/		205	

Inclusion criteria:

Patients aged 60 to 90 years who had been hospitalized for any reason (except those listed in the exclusion criteria) and who had had insomnia requiring medication for at least 3 weeks were eligible for inclusion if they met at least two of the following criteria: time to fall asleep > 30 minutes; at least two nocturnal awakenings; total nocturnal time awake > 1 hour; total sleep time < 6 hours; or sensation of premature morning awakening.

Exclusion criteria:

Patients were not included if they had concomitant heart or respiratory failure, concurrent malignant or severe disease, history of cerebrovascular accident or transient ischemic accidents, or concurrent requirement for benzodiazepines.

Population:	Mean age: Gender:	81.1 years 74% Female	Ethnicity:	NR		
Intervention: Drug name	dosage	N=	Duration		Primary outcome	Outcome:
Zolpidem	5 mg	70	21 day			sleep onset
Zolpidem	10 mg	74	21 day			total sleep time
Triazolam	0.25 mg	77	21 day			number of nocturnal awakenings
						total duration of nocturnal awakenings
						time of awakening
						feeling of too early awakening
						quality of sleep
						quality of awakening

Efficacy:

questionnaire

Zaleplon 5mg	Zolpidem 10mg	Triazolam	
% of patients falling as	leep well at day 24, ch	ange from baselir	ne: % (p vs baseline)
55.9 (<0.01)	47.9 (<0.01)	51.9 (<0.01)	
% of patients falling as	leep well at day 31, ch	ange from baselir	ne: % (p vs baseline)
34.6 (<0.01)	19.8 (<0.01)	18.6 (<0.01)	
% of patients falling as	leep in <30 minutes at	t day 24, change f	rom baseline: % (p vs baseline)
35 (<0.01)	35 (<0.01)	35 (<0.01)	
mean total sleep time a	at day 24, change from	n baseline: hours (p vs baseline)
1.6 (NR)	1.9 (NR)	1.9 (NR)	
% of patients with >2 a	wakenings per night a	t day 24, change	from baseline: Number (p vs baseline)
-36.8 (<0.001)	-28.8 (<0.001)	-29.8 (<0.001)	
% of patients with a tot	al nocturnal waking tir	ne >1 hours: day	3 (day 24)
55.9 (17.6)	47.9 (11.0)	55.8 (15.6)	
overall sleep quality at	day 24, change from I	baseline (higher s	core=better): Score (p vs baseline)
35.5 (<0.001)	34.4 (<0.001)	33.6 (<0.001)	
% of patients who repo	rted too early awaken	ing at day 24, cha	nge from baseline: % (p vs baseline)
-35 (<0.001)	-38 (<0.001)	-35 (<0.001)	

r, 1993			Quality rating: Fair				
Clinical Global Impressi	on (CGI)						
Zolpidem 5mg	Zolpidem 10mg	Triazolam					
total mean score- safet	y and efficacy: Score						
2.54	2.43	2.51	P: NS				

enter, 1986 Quality rating: Fair									
esign:									
Study design:	RCT	DB	Parallel	Run-in :	7 days		Setting:	Multicente	r
				Wash out :	0 days		Country:	South Afric	са
Sample:	Number	Scre	ened/ Eligib	e/ Enrolled	Numbe	r Withdrawn/	Lost to follo	w-up/ Anal	lyzed
			58/ 4	1/ 41		0/		0/	41
Inclusion crite	ria:								
				5 minutes; 2) mo duration less that			ch night with	out known o	cause, and
				, hepatic, or rena copiclone or triaz					astrointestinai
Population:	Mean ag Gender		76.8 years 76% Female	Ethnicity:	NR				
Population: tervention: Drug name		: 7	-	Ethnicity: Duration	NR	Primary outcome	Outcome		
tervention:	Gender	ie 7	76% Female		NR				ep, 3 points, 1: diff
tervention: Drug name	Gender dosag	: 7 je g	76% Female	Duration	NR			n falling asle	eep, 3 points, 1: diff
tervention: Drug name Zopiclone	Gender dosag	: 7 je g	76% Female N= 20	Duration 17 day	NR		Difficulty in	n falling asle ation (hr)	eep, 3 points, 1: diff
tervention: Drug name Zopiclone	Gender dosag	: 7 je g	76% Female N= 20	Duration 17 day	NR		Difficulty in Sleep dura Sleep qua	n falling asle ation (hr)	
tervention: Drug name Zopiclone	Gender dosag	: 7 je g	76% Female N= 20	Duration 17 day	NR		Difficulty ir Sleep dura Sleep qua Night awa	n falling asle ation (hr) lity kenings (no.	
tervention: Drug name Zopiclone	Gender dosag	: 7 je g	76% Female N= 20	Duration 17 day	NR		Difficulty ir Sleep dura Sleep qua Night awa	n falling asle ation (hr) lity kenings (no. ning awaken	. of times)
tervention: Drug name Zopiclone	Gender dosag	: 7 je g	76% Female N= 20	Duration 17 day	NR		Difficulty ir Sleep dura Sleep qua Night awa Early morr	n falling asle ation (hr) lity kenings (no. ning awaken leep	. of times)
tervention: Drug name Zopiclone	Gender dosag	: 7 je g	76% Female N= 20	Duration	NR		Difficulty in Sleep dura Sleep qua Night awa Early morr Daytime s	n falling asle ation (hr) lity kenings (no. ning awaken leep sfaction	. of times)

Efficacy:

e- and during-treatme	nt questionnaires	
Zopiclone	Triazolam	
Difficulty in falling sleep	o - day 7 (1=none/very littl	; 2=some; 3=a lot): Score
1.21	1.62	P: 0.03
Sleep duration (hr) - da	y 7: No. hours	
7.4	7.5	P: 0.05
Night awakenings - day	7: Frequency	
1	1.7	P: 0.06
Sleep quality, Early mo	rning awakenings, Menta	alertness on rising, Sleep satisfaction- day 7: Score
NR	NR	P: NS
Daytime sleep - day 7,	compare to mean: Minute	
-8	9	P: 0.07
Daytime sleep - day 17	(no. of patients): Number	
2	5	P: NR
Night awakenings - day	17: Frequency	
NR	1	P: 0.06
Daytime sleep - day 17	, compare to mean: Minut	s
-8	4	P: NS

Evidence Table 8. Active controlled trials (Elderly): Rebound

ie, 1990a					Quality	rating: Fa	ir
esign:							
Study design:	RCT D	B Parallel	Run-in :	7 days	Setting:	Multicenter	
			Wash out :	4 days	Country:	Canada	
Sample:	Number S	creened/ Eligib	le/ Enrolled	Number	Withdrawn/ Lost to foll	ow-up/ Analy	zed
		NR/ N	R/ 44		0/	0/	44
Inclusion crite	ria:						
Age betwee	n 60 and 90	years, living in	residential homes	s and suffering f	om chronic insomnia.		
drug abuse	and coffee o	or tea abuse. Pa		e medical condi	disorders, drug hyperse ions, those treated wit		
Population:	Mean age	: 76.0 years	Ethnicity:	NR			
	Gender:	75% Female					
tervention:							
tervention: Drug name	dosage	N=	Duration				
	dosage 5-7. mg	N= 15	Duration 21 day				
Drug name	U						
Drug name Zopiclone	5-7. mg	15	21 day				
Drug name Zopiclone Triazolam	5-7. mg 0.12 mg	15 14	21 day 21 day				
Drug name Zopiclone Triazolam Placebo	5-7. mg 0.12 mg	15 14	21 day 21 day				
Drug name Zopiclone Triazolam Placebo ebound:	5-7. mg 0.12 mg NA mg	15 14 15	21 day 21 day				
Drug name Zopiclone Triazolam Placebo ebound: Post-sleep	5-7. mg 0.12 mg NA mg	15 14 15 ire	21 day 21 day 21 day				
Drug name Zopiclone Triazolam Placebo ebound: Post-sleep	5-7. mg 0.12 mg NA mg	15 14 15	21 day 21 day 21 day				
Drug name Zopiclone Triazolam Placebo ebound: Post-sleep Z	5-7. mg 0.12 mg NA mg questionna	15 14 15 ire Triazola	21 day 21 day 21 day	Number			

Evidence Table 8. Active controlled trials (Elderly): Rebound

Leppik, 1997							Quality	Quality rating: Fair			
Design:											
Study design:	RCT	DB	Para	allel	Run-in :	7 days	Setting:	Multice	nter		
					Wash out :	4 days	Country:	US			
Sample:	Numbe	er Scre	ened/	Eligible/	Enrolled	Number Withdraw	n/ Lost to follo	w-up/ A	nalyzed		
			NR/	457/	335	4	ł0/	0/	335		
Inclusion crite	ria:										

Enrollment criteria included chronic insomnia of at least 3 months' duration, defined as self-reported sleep duration of 4-6 hours each night and self reported sleep latency of 30 minutes or more; some impairment of daytime functioning related to sleep deprivation; relatively stable mental and physical health; and no evidence of systemic abnormalities or other diseases that would interfere with study drug evaluation. Normal 12-lead electrocardiogram (ÉCG) and clinical laboratory evaluation were required.

Exclusion criteria:

Exclusion criteria included significant and/or unstable medical or psychiatric disorder or mental retardation, use of an investigational drug within 30 days of the start of the study, regular use of medication of a type that could interfere with assessment of a hypnotic; use of a medication that could interfere with absorption or metabolism of a benzodiazepines or other CNS depressants, and previous administration of zolpidem. In addition, patients with a recent history of drug or alcohol abuse, seizure disorder; or symptoms of sleep apnea of myoclonus were excluded. Shift workers and other individuals with changing sleep schedules were also excluded.

Population:	Mean age: Gender:	69 years 63% Female	Ethnicity:	93% white
Intervention: Drug name	dosage	N=	Duration	
Zolpidem	5 mg	82	28 day	
Triazolam	0.12 mg	85	28 day	
Temazepam	15 mg	84	28 day	
Placebo	NA mg	84	28 day	

Rebound:

Zolpidem	Triazolam	Temazepam	Placebo
ebound: ease of falling	sleep: Score (p vs l	paseline)	
	worse (<0.05)		
ebound: sleep quality:	Score (p vs baseline	e)	
worse (NR)	worse (NR)	worse (NR)	

Evidence Table 8. Active controlled trials (Elderly): Rebound

jer, 1993				Quality rating: Fair				
sign:							-	
Study design:	RCT DE	Parallel	Run-in: Wash out:	3 days 7 days	Setting Country	: Multicenter /: France		
Sample:	Number Sc	reened/ Eligible NR/ NR	/ Enrolled		er Withdrawn/ Lost to fo 16/			
nclusion crite	ria:							
had had inso criteria: time	omnia requiri to fall asleep	ng medication fo	or at least 3 we at least two no	eks were eligit cturnal awaker	ole for inclusion if they m	the exclusion criteria) and who net at least two of the following e awake > 1 hour; total sleep		
	e not include				/ failure, concurrent mali	gnant or severe disease, for benzodiazepines.		
opulation:	Mean age:	81.1 years	Ethnicity	: NR				
ervention:	Gender:	74% Female						
Drug name	dosage	N=	Duration					
Zolpidem	5 mg	70	21 day					
Zolpidem	10 mg	74	21 day					
Triazolam	0.25 mg	77	21 day					
bound:								
questionnai	iro							
•	eplon 5mg	Zolpidem 10	mg Tria	zolam				
		•	0	ot day 21 obor	nge from baseline: % (p	va baaalina)		
	% of patients 3 (0.001)	28 (<0.001		(0.06)	nge nom basenne. % (p	vs baseline)		
	· · ·	,	,		day 0 (day 01)			
		with a total noc	-		day 3 (day 31)			
	5.9 (13.6)	47.9 (29.6	, ,	8 (26.4)				
rohound	feel well rest	ed in the mornin	a change from	n baseline (higl	her score=better): Score	(n vs triazolam)		
	7.2 (0.05)	23.9 (0.05		5 (NA)		(p vo mazolam)		

ergener, 1989)				Quality rating: Fair				
esign:									
Study design:	RCT	DB	Parallel	Run-in :	4 days	5	Setting:	NR	
				Wash out :	7 days	C	Country:	German	
Sample:	Numb	ber Scr	eened/ Eligib	le/ Enrolled	Number	Withdrawn/ Lo	ost to follo	w-up/ Ana	alyzed
			NR/ N	IR/ 42		NR/		NR/	42
Inclusion crite	ria:								
Patients who the initial pla				14 points on the S	Sleep Disorder i	ntensity Scale	(SDIS) w	ith no impro	ovement during
Exclusion crite									
				predelirium a sev					
endogenous were exclud		osis ar	nd treatment w	vith drugs affecting	g vigilance (rese	erpine and sed	ating anti	histaminics	or barbiturates)
Population:	Mean	age:	NR years	Ethnicity:	NR				
	Gend		86% Female	-					
ntervention:									
Drug name	dos	age	N=	Duration					
			20	21 day					
Zopiclone	7.5	mg	20	•					
Zopiclone Flurazepam		mg mg	22	21 day					
•		0		21 day					
•	30	0		21 day					
Flurazepam	30 ts:	0		21 day					
Flurazepam dverse Even Withdrawal	30 ts:	mg							
Flurazepam dverse Even Withdrawal	30 ts: s copiclor	mg	22 Flurazepa						
Flurazepam dverse Even Withdrawal Z number of p	30 ts: s copiclor	mg	22 Flurazepa ber (%)						P: NS
Flurazepam dverse Even Withdrawal Z number of p	30 ts: s copiclor patients (40)	mg ne s: Num	22 Flurazepa						P: NS

Elie, 1990a			Quality	Quality rating: Fair					
Design:									
Study design:	RCT	DB	Parallel	Run-in :	7 days	Setting:	Multio	center	
				Wash out :	4 days	Country:	Cana	da	
Sample:	Number	Scree	ned/ Eligible/	Enrolled	Number Withdraw	n/ Lost to follo	w-up/	Analyzed	
			NR/ NR/	44		0/	0/	44	
Inclusion crite	ria:								

Age between 60 and 90 years, living in residential homes and suffering from chronic insomnia.

Exclusion criteria:

Psychotic and neurotic patients, history of blood dyscrasia, neurological disorders, drug hypersensitivity, chronic alcoholism, drug abuse and coffee or tea abuse. Patients with severe medical conditions, those treated with CNS drugs and those receiving treatments which could modify drug kinetics were not accepted.

Population:	Mean age: Gender:	76.0 years 75% Female	Ethnicity:	NR
Drug name	dosage	N=	Duration	
Zopiclone	5-7. mg	15	21 day	
Triazolam	0.12 mg	14	21 day	
Placebo	NA mg	15	21 day	

Adverse Events:

reported by patients		
Zopiclone	Triazolam	
reduction of dreams: Nun	nber (p vs placebo)	
5 (<0.02)	3 (NS)	
bitter taste: Number (p vs	s placebo)	
5 (<0.06)	0 (NS)	
withdrawals		
Zopiclone	Trazodone	Placebo
total withdrawals: Numbe	r	
0	0	0
withdrawals due to AEs: I	Number	
0	0	0

Klimm, 1987							Quality rating: Fair			
Design:										
Study design:	RCT	DB	Para	allel	Run-in :	7 days	Setting:	Commu	inity practic	
					Wash out :	7 days	Country:	France		
Sample:	Numbe	r Scree	ened/	Eligible/	Enrolled	Number Withdrawn/	Lost to follo	w-up/ A	nalyzed	
			NR/	NR/	74	2/		2/	72	

Inclusion criteria:

For the purpose of this trial, chronic insomnia was defined as the presence of two of the following criteria: hypnotics taken five times a week for the last 3 months, sleep onset latency > 1 h, total duration of sleep < 6 h, and waking more than three times during the night. The patients' mental capacity, as measured by Intellectual Quotient and memory tests (Syndrome Kurztest) was to be within normal range for their age.

Exclusion criteria:

Patients presenting contraindications to benzodiazepines or painful conditions, those with a history of drug allergy or chronic alcoholism, those receiving drugs liable to affect metabolism, those refusing to give their consent, those who might have been unable to complete the trial, those already involved in another trial, and those considered unlikely to cooperate were excluded.

Population:	Mean age: Gender:	73.2 years 80% Female	Ethnicity:	NR
Drug name	dosage	N=	Duration	
Zopiclone	7.5 mg	36	7 day	
Nitrazepam	5 mg	36	7 day	

Adverse Events:

reported by patients

Zopiclone	Nitrazepam		
bitter taste: Number			
1	0		
dizziness: Number			
1	0		
confusion: Number			
0	1		
fatigue: Number			
0	1		
complaints in answer to	the standarized questi	on on tolerance: Number (p vs baseline)	
less (NS)	more (<0.003)		
withdrawals			
Zopiclone	Nitrazepam		
total withdrawals: Numb	per		
1	1		
withdrawals due to AEs	: Number		
0	1		

Leppik, 1997	.eppik, 1997						Qualit	Quality rating: Fair		
Design:										
Study design:	RCT	DB	Para	allel	Run-in :	7 days	Setting	: Multicen	ter	
					Wash out :	4 days	Countr	y: US		
Sample:	Numbe	er Scre	ened/	Eligible/	Enrolled	Number W	ithdrawn/ Lost to f	ollow-up/ Ar	alyzed	
			NR/	457/	335		40/	0/	335	

Inclusion criteria:

Enrollment criteria included chronic insomnia of at least 3 months' duration, defined as self-reported sleep duration of 4-6 hours each night and self reported sleep latency of 30 minutes or more; some impairment of daytime functioning related to sleep deprivation; relatively stable mental and physical health; and no evidence of systemic abnormalities or other diseases that would interfere with study drug evaluation. Normal 12-lead electrocardiogram (ECG) and clinical laboratory evaluation were required.

Exclusion criteria:

Exclusion criteria included significant and/or unstable medical or psychiatric disorder or mental retardation, use of an investigational drug within 30 days of the start of the study, regular use of medication of a type that could interfere with assessment of a hypnotic; use of a medication that could interfere with absorption or metabolism of a benzodiazepines or other CNS depressants, and previous administration of zolpidem. In addition, patients with a recent history of drug or alcohol abuse, seizure disorder; or symptoms of sleep apnea of myoclonus were excluded. Shift workers and other individuals with changing sleep schedules were also excluded.

Population:	Mean age: Gender:	69 years 63% Female	Ethnicity:	93% white
Intervention: Drug name	dosage	N=	Duration	
Zolpidem	5 mg	82	28 day	
Triazolam	0.12 mg	85	28 day	
Temazepam	15 mg	84	28 day	
Placebo	NA mg	84	28 day	

Adverse Events:

overall adverse events

overall auverse events			
Zolpidem	Triazolam	Temazepam	Placebo
overall incidence rates:	Number (%)		
52 (63)	54 (64)	56 (67)	47 (56)
headache: Number (%)			
15 (18.3)	22 (25.9)	18 (21.4)	16 (19)
drowsiness: Number (%	b)		
4 (4.9)	7 (8.2)	8 (9.5)	3 (3.6)
myalgia: Number (%)			
8 (9.8)	7 (8.2)	8 (9.5)	9 (10.7)
nausea: Number (%)			
6 (7.3)	6 (7.1)	4 (4.8)	6 (7.1)
upper resp infection: Nu	umber (%)		
6 (7.3)	2 (2.4)	7 (8.3)	7 (8.3)
dyspepsia: Number (%))		
5 (6.1)	3 (3.5)	5 (6.0)	7 (8.3)
nervousness: Number ((%)		
2 (2.4)	7 (8.2)	3 (3.6)	4 (4.8)
arthralgia: Number (%)			
4 (4.9)	5 (5.9)	0 (0)	3 (3.6)

oik, 1997				Quality rating: Fair
fatigue: Number (%)				
1 (1.2)	2 (2.4)	5 (6.0)	1 (1.2)	
withdrawals				
Zolpidem	Triazolam	Temazepam	Placebo	
total withdrawals: Num	ber			
6	14	10	10	
withdrawals due to AE	s: Number			
2	5	5	6	

Roger, 1993							Quality	rating:	Fair	
Design:										
Study design:	RCT	DB	Paral	lel	Run-in :	3 days	Setting:	Multice	nter	
					Wash out :	7 days	Country:	France		
Sample:	Numbe	er Scre	ened/	Eligible/	Enrolled	Number Withd	rawn/ Lost to folle	ow-up/ A	nalyzed	
			NR/	NR/	221		16/	0/	205	

Inclusion criteria:

Patients aged 60 to 90 years who had been hospitalized for any reason (except those listed in the exclusion criteria) and who had had insomnia requiring medication for at least 3 weeks were eligible for inclusion if they met at least two of the following criteria: time to fall asleep > 30 minutes; at least two nocturnal awakenings; total nocturnal time awake > 1 hour; total sleep time < 6 hours; or sensation of premature morning awakening.

Exclusion criteria:

Patients were not included if they had concomitant heart or respiratory failure, concurrent malignant or severe disease, history of cerebrovascular accident or transient ischemic accidents, or concurrent requirement for benzodiazepines.

NR

Mean age:	81.1 years	Ethnicity:
Gender:	74% Female	
dosage	N=	Duration
5 mg	70	21 day
10 mg	74	21 day
0.25 mg	77	21 day
	Gender: dosage 5 mg 10 mg	Gender: 74% Female dosage N= 5 mg 70 10 mg 74

Adverse Events:

overall report		
Zolpidem 5mg	Zolpidem 10mg	Triazolam
no. patients experienci	ng adverse events: Nun	nber (%)
11 (16)	8 (11)	16 (21)
nightmares- the most of	ommon adverse effect:	Number
2	3	2
withdrawals		
Zolpidem 5mg	Zolpidem 10mg	Triazolam
total withdrawals: Num	ber	
7	1	5
withdrawals due to AE	s: Number	
0		2

				Quality	rating: Fair
RCT DI	B Parallel	Run-in : Wash out :	7 days 0 days	Setting: Country:	Multicenter South Africa
Number S	-	/ Enrolled		/ithdrawn/ Lost to follo	
ria:					
					nout known cause, and
e excluded ant drugs, wi severe care	th lithium, or if the diac, respiratory,	ey received anx hepatic, or rena	olytic drugs durin I disease, or had	ng the day. They were gastrointestinal diseas	also excluded if they had se or prior gastrointestinal
Mean age	76.8 years	Ethnicity:	NR		
Gender:	76% Female	-			
dosage	N=	Duration			
0.33 mg	20	17 day			
8.25 mg	21	17 day			
ts:					
·					
· · /	()	7 (P: NR
		and day 9: Nu	mber		D 0.040
nore	NR				P: 0.013
y the patien	ts: CNS AEs				
opiclone	Triazolam				
, tearfulness	, drowsiness, diz	ziness, agitatior	i, nightmares, co	nfusion, and disturbed	sleep:
3	7				P: NR
v the patien	ts: Gastrointest	inal AEs			
-					
Number					
6	2				P: NR
y the patien	ts: Other AEs				
opiclone	Triazolam				
ain, andina i	pectoris episodes	. and shortness	of breath: Numb	er	
	Number So ria: n to fall asle alling asleep pria: re excluded ant drugs, wir r severe card bey had know Mean age Gender: dosage 0.33 mg 8.25 mg ts: y the patient copicione er of patient: 7 (35) patient repor more y the patient copicione , tearfulness 3 y the patient copicione Number 6	Number Screened/ Eligible 58/ 41 ria: n to fall asleep longer than 45 alling asleep again; 3) sleep of eria: re excluded if they had a psyce ant drugs, with lithium, or if the r severe cardiac, respiratory, ney had known tolerance to zo Mean age: 76.8 years Gender: 76% Female dosage N= 0.33 mg 20 8.25 mg 21 ts: y the patients copicione Triazolam er of patient: Number (%) 7 7(35) 8 (38) patient reporting AEs on day 1 more NR y the patients: CNS AEs Copicione Triazolam , tearfulness, drowsiness, diz: 3 7 y the patients: Gastrointest Copicione Triazolam , tearfulness, drowsiness, diz: 3 7 y the patients: Gastrointest Copicione Triazolam Number 2 6 2 y the patients: Other AEs	Wash out : Number Screened/ Eligible/ Enrolled 58/ 41/ 41 ria: n to fall asleep longer than 45 minutes; 2) modalling asleep again; 3) sleep duration less that a psychiatric disorder and drugs, with lithium, or if they received anxies revere cardiac, respiratory, hepatic, or renance to zopiclone or triazed. Mean age: 76.8 years Ethnicity: Gender: 76% Female dosage N= Duration 0.33 mg 20 17 day 8.25 mg 21 17 day 8.25 mg 21 17 day st: ythe patients Sopiclone Copiclone Triazolam oatient reporting AEs on day 7 and day 9: Numore NR y the patients: CNS AEs Copiclone Triazolam , tearfulness, drowsiness, dizziness, agitation 3 3 7 y the patients: Gastrointestinal AEs Copiclone Triazolam , tearfulness, drowsiness, dizziness, agitation 3 7 y the patients: Gastrointestinal AEs Copiclone Triazolam Number <td< td=""><td>Wash out: 0 days Number Screened/ Eligible/ Enrolled Number V 58/ 41/ 41 1 ria: n to fall asleep longer than 45 minutes; 2) more than two awalalling asleep again; 3) sleep duration less than six hours a nigeria: re excluded if they had a psychiatric disorder necessitating treat drugs, with lithium, or if they received anxiolytic drugs during reserver cardiac, respiratory, hepatic, or renal disease, or had leey had known tolerance to zopiclone or triazolam, or if they had a gage Mean age: 76.8 years Ethnicity: NR Gender: 76% Female 0.33 mg 20 17 day 8.25 mg 21 17 day 17 day 8.25 mg 21 17 day s.25 mg 8 (38) 0atient reporting AEs on day 7 and day 9: Number or of patients: Number (%) 7 (35) 8 (38) patients: CNS AEs Edicione Triazolam tearfulness, drowsiness, dizziness, agitation, nightmares, cord 3 7 y the patients: Gastrointestinal AEs</td><td>RCT DB Parallel Run-in : 7 days Setting: Wash out : 0 days Country: Number Screened/ Eligible/ Enrolled Number Withdrawn/ Lost to fold 58/ 41/ 41 0/ ria: no fall asleep longer than 45 minutes; 2) more than two awakenings each night with alling asleep again; 3) sleep duration less than six hours a night. 0/ ria: no fall asleep longer than 45 minutes; 2) more than two awakenings each night with alling asleep again; 3) sleep duration less than six hours a night. 0/ ria: no fall asleep longer than 45 minutes; 2) more than two awakenings each night with alling asleep again; 3) sleep duration less than six hours a night. 0/ ria: reackuded if they had a psychiatric disorder necessitating treatment with antipsycho main drugs, with lithium, or if they received anxiolytic drugs during the day. They were resevere cardiac, respiratory, hepatic, or renal disease, or had gastrointestinal diseastey had known tolerance to zopiclone or triazolam, or if they had hypersensitivity to or the days and a gastrointestinal diseastey for the ady as the presensitivity to or the days and a gastrointestinal diseastey for the days and a gastrointestinal diseastey for the patients: Gender: 76% Female dosage N= ts: pute patients: Number (%) 7 (35) 8 (38) patient reporting AEs on day 7</td></td<>	Wash out: 0 days Number Screened/ Eligible/ Enrolled Number V 58/ 41/ 41 1 ria: n to fall asleep longer than 45 minutes; 2) more than two awalalling asleep again; 3) sleep duration less than six hours a nigeria: re excluded if they had a psychiatric disorder necessitating treat drugs, with lithium, or if they received anxiolytic drugs during reserver cardiac, respiratory, hepatic, or renal disease, or had leey had known tolerance to zopiclone or triazolam, or if they had a gage Mean age: 76.8 years Ethnicity: NR Gender: 76% Female 0.33 mg 20 17 day 8.25 mg 21 17 day 17 day 8.25 mg 21 17 day s.25 mg 8 (38) 0atient reporting AEs on day 7 and day 9: Number or of patients: Number (%) 7 (35) 8 (38) patients: CNS AEs Edicione Triazolam tearfulness, drowsiness, dizziness, agitation, nightmares, cord 3 7 y the patients: Gastrointestinal AEs	RCT DB Parallel Run-in : 7 days Setting: Wash out : 0 days Country: Number Screened/ Eligible/ Enrolled Number Withdrawn/ Lost to fold 58/ 41/ 41 0/ ria: no fall asleep longer than 45 minutes; 2) more than two awakenings each night with alling asleep again; 3) sleep duration less than six hours a night. 0/ ria: no fall asleep longer than 45 minutes; 2) more than two awakenings each night with alling asleep again; 3) sleep duration less than six hours a night. 0/ ria: no fall asleep longer than 45 minutes; 2) more than two awakenings each night with alling asleep again; 3) sleep duration less than six hours a night. 0/ ria: reackuded if they had a psychiatric disorder necessitating treatment with antipsycho main drugs, with lithium, or if they received anxiolytic drugs during the day. They were resevere cardiac, respiratory, hepatic, or renal disease, or had gastrointestinal diseastey had known tolerance to zopiclone or triazolam, or if they had hypersensitivity to or the days and a gastrointestinal diseastey for the ady as the presensitivity to or the days and a gastrointestinal diseastey for the days and a gastrointestinal diseastey for the patients: Gender: 76% Female dosage N= ts: pute patients: Number (%) 7 (35) 8 (38) patient reporting AEs on day 7

ter, 1986		Quality rating: Fair
withdrawals		
Zopiclone	Triazolam	
total withdrawals: Numbe	۶r	
0	0	
withdrawals due to AEs:	Number	
0	0	

gnoli, 1989				Su	byroup.	Anxiety		Quality rating: Poor
esign:								
Study design: Sample:		DB ber Sc	reened/ Elig	Wash out ible/ Enrolled	3 day : NR			Setting: NR Country: Rome, Foggia, Italy Lost to follow-up/ Analyzed
			NR/	NR/ 20			0/	0/ 20
concomitant	re ageo t antide gical fa	pressi	ve, anxiolytic		nedicatio	n and abse	ence of som	iety less than 20. Absence of natic, pathophysiological or
		mitant	general illne	ss; renal or hepa	tic failure	e; effective	ness of pla	cebo administration; and pregnancy.
Population:	Mear	n age:	38.2 years	Ethnicit	y: NR			
ntervention:	Gend	ler:	60% Fema	е				
Drug name	dos	age	N=	Duration			Primary outcome	Outcome:
Zopiclone	7.5	mq	12	1 day		-		anxiety levels
Nitrazepam	5	mg	12	1 day				time of sleep induction
		_						hours of sleep
								number of nocturnal arousals
								quality of sleep
								quality of daytime arousal
fficacy: Hamilton R	ating S		f or Anxiety (Nitraze					
Hamilton R	Copiclor	ne 2nd v	Nitraze		e = bette	r): Score		
Hamilton R	Copiclor 1st and lower	ne 2nd v	Nitraze weeks of trea	pam	e = bette	r): Score		P: <0.05
Hamilton R Z after the f	Copiclor 1st and lower	ne 2nd v Attent	Nitraze weeks of trea	pam	e = bette	r): Score		
Hamilton R Z after the T Toulouse-P Z	Copiclor 1st and lower Pieron Copiclor	ne 2nd v Attent	Nitraze weeks of trea - ion Test Nitraze	pam			nber	
Hamilton R Z after the T Toulouse-P Z	Copiclor 1st and lower Pieron Copiclor	ne 2nd v Attent	Nitraze weeks of trea - ion Test Nitraze	pam atment (less scor			nber	
Hamilton R Z after the f Toulouse-P Z reduction	Zopiclor 1st and lower Pieron A Zopiclor of omit more	Attent Attent tted ite	Nitraze weeks of trea ion Test Nitraze ems on the 7	pam atment (less scor	uction=be	etter): Num		P: <0.05
Hamilton R Z after the f Toulouse-P Z reduction	Zopiclor 1st and lower Pieron A Zopiclor of omit more	Attent Attent tted ite	Nitraze weeks of trea ion Test Nitraze ems on the 7	pam atment (less scor pam th day (more red	uction=be	etter): Num		P: <0.05
Hamilton R	Zopiclor 1st and lower Zopiclor of omit more of omit more	Attent Attent ne tted ite	Nitraze weeks of trea ion Test Nitraze ems on the 7 - ems on the 1	pam atment (less scor pam th day (more red	uction=be	etter): Num oetter): Nur	mber	P: <0.05
Hamilton R	Zopiclor 1st and lower Zopiclor of omit more of omit more	Attent Attent ne tted ite	Nitraze weeks of trea ion Test Nitraze ems on the 7 - ems on the 1	pam atment (less scor pam th day (more red 4th day (more red	uction=be	etter): Num oetter): Nur	mber	P: <0.05
Hamilton R Z after the 7 Toulouse-P Z reduction reduction times of e	Zopiclor 1st and lower Pieron A Zopiclor of omir more of omir more of erro more executio	Attent Attent ne tted ite	Nitraze weeks of trea ion Test Nitraze ems on the 7 - ems on the 1	pam atment (less scor pam th day (more red 4th day (more red day (more reduc	uction=be	etter): Num oetter): Nur	mber	P: <0.05 P: <0.01 P: <0.05 P: <0.01
Hamilton R Z after the 7 Toulouse-P Z reduction reduction times of e	2 opicion 1st and lower 2 ieron A 2 opicion of omit more of omit more of erro more	Attent Attent ne tted ite	Nitraze weeks of trea ion Test Nitraze ems on the 7 ems on the 1 - ns on the 7th -	pam atment (less scor pam th day (more red 4th day (more red day (more reduc	uction=be	etter): Num oetter): Nur	mber	P: <0.05 P: <0.01 P: <0.05
Hamilton R	Zopiclor 1st and lower Pieron A Zopiclor of omir more of ormir more of erro more execution shorte d semi	Attent Attent ne tted ite ors iten on (sho r	Nitraze weeks of trea ion Test Nitraze ems on the 7 ems on the 1 ems on the 7 hs on the 7 hs on the 7 hs on the 7 the porter=better):	pam atment (less scor pam th day (more red 4th day (more red day (more reduc Number	uction=be	etter): Num oetter): Nur	mber	P: <0.05 P: <0.01 P: <0.05 P: <0.01
Hamilton R	Zopiclor 1st and lower Pieron A Zopiclor of omit more of omit more of erro more execution shorter d semi Zopiclor	Attent Attent ne tted ite ors iten on (sho r iquant ne	Nitraze weeks of trea ion Test Nitraze ms on the 7 ms on the 1 ms on the 7th orter=better): titative scale Nitraze	pam atment (less scor pam th day (more red 4th day (more red day (more reduc Number pam	uction=be	etter): Num oetter): Nur	mber	P: <0.05 P: <0.01 P: <0.05 P: <0.01
Hamilton R	Zopiclor 1st and lower Pieron A Zopiclor of omir more of ormir more of erro more execution shorter d semi Zopiclor	Attent Attent ne tted ite ors iten on (sho r iquant ne	Nitraze weeks of trea ion Test Nitraze ms on the 7 ms on the 1 ms on the 7th orter=better): titative scale Nitraze	pam atment (less scor pam th day (more red 4th day (more red day (more reduc Number	uction=be	etter): Num oetter): Nur	mber	P: <0.05 P: <0.01 P: <0.05 P: <0.01 P: <0.01
Hamilton R Z after the 7 Toulouse-P Z reduction reduction times of e Time-signe Z time of sle	Zopiclor 1st and lower Pieron A Zopiclor of omit more of omit more of erro more execution shorter d semi Zopiclor eep ind shorter	Attent Attent ne tted ite ors iten on (sho r iquant ne luction r	Nitraze weeks of trea ion Test Nitraze ms on the 7 ms	pam atment (less scor pam th day (more red 4th day (more red day (more reduc Number pam tter): Number	uction=be	etter): Num oetter): Nur	mber	P: <0.05 P: <0.01 P: <0.05 P: <0.01
Hamilton R Z after the 7 Toulouse-P Z reduction reduction times of e Time-signe Z time of sle	Zopiclor 1st and lower Pieron A Zopiclor of omir more of ornir more of erro more execution shorter d semi Zopiclor eep ind shorter daytim	Attent Attent ne tted ite ors iten on (sho r iquant ne luction r e arou	Nitraze weeks of trea ion Test Nitraze ms on the 7 ms on the 1 ms on the 7th orter=better): titative scale Nitraze	pam atment (less scor pam th day (more red 4th day (more red day (more reduc Number pam tter): Number	uction=be	etter): Num oetter): Nur	mber	P: <0.05 P: <0.01 P: <0.05 P: <0.01 P: <0.01 P: <0.01
Hamilton R Z after the f Toulouse-P Z reduction reduction times of e Time-signe Z time of sle quality of	Zopiclor 1st and lower Pieron A Zopiclor of omit more of omit more of erro more execution shorter d semi Zopiclor eep ind shorter daytim better	Attent Attent ne tted ite ors iten on (sho r iquant ne luction r e arou	Nitraze weeks of trea ion Test Nitraze ms on the 7 ms	pam atment (less scor pam th day (more red 4th day (more red day (more reduc Number pam tter): Number	uction=be	etter): Num better): Nur ter): Numb	mber her	P: <0.05 P: <0.01 P: <0.05 P: <0.01 P: <0.01

				Subg	roup:	alcoholism	Quality	rating:	Fair
Design:									
Study design:	RCT	DB	Parallel	Run-in :	2 day	S	Setting:	Multicer	ter
Sample:	Num	ber Sc	reened/ Eligib			Number Withdrawn/	Country: Lost to follo	ow-up/ Ar	
Inclusion criter	ia.		NR/ 5	54/ 52		0/		0/	52
Only insomn years and at	iac pa ble to p	particip				od of at least ten days s those for whom it v			
first time, or benzodiazep were also ex unstable fluc	the for for whe ine ty clude tuatin	iom the pe. Pai d, as w g cond	e existing medie tients having us rell as those su	cation with psych sed high doses o iffering from myas al or physical stre	otropic f hypno sthenia	eated during the stud drugs was being cha tics or with a history gravis, with any dise patients with a sever	anged or tho of drug abus	se using t se before panies by	ranquilizers of the the study period pain, living in an
Population:	Mea	n age:	43.9 years	Ethnicity:	NR				
nton contion.	Gen	der:	33% Female						
ntervention: Drug name	dos	sage	N=	Duration		Primary	Outcome:		
		-		Daration		outcome	••••••		
Zopiclone	7.5	mg	27	5 day					eep Questionnaire)
Zopiclone Lormetazepam							Efficacy (S	Spiegel Sle	eep Questionnaire) on waking up
Lormetazepam	1	mg mg	27 25	5 day 5 day			Efficacy (S Behavior a	Spiegel Sle and mood	
Lormetazepam Efficacy: Efficacy (Sp	1 iegel	mg mg Sleep ne	27 25 Questionnaire Lorazepa	5 day 5 day e)	e to fall		Efficacy (S Behavior a	Spiegel Sle and mood	on waking up
Lormetazepam Efficacy: Efficacy (Sp	1 iegel	mg mg Sleep ne	27 25 Questionnaire Lorazepa	5 day 5 day e)	e to fall		Efficacy (S Behavior a	Spiegel Sle and mood	on waking up
Lormetazepam Efficacy: Efficacy (Sp Zu Improvem	1 iegel opiclo ent fro NS	mg mg Sleep ne	27 25 Questionnaire Lorazepa eline to end of 0.013	5 day 5 day e)		asleep: p-value	Efficacy (S Behavior a	Spiegel Sle and mood	on waking up
Lormetazepam Efficacy: Efficacy (Sp Zu Improvem	1 iegel opiclo ent fro NS	mg mg Sleep ne	27 25 Questionnaire Lorazepa eline to end of 0.013	5 day 5 day e) am treatment on time		asleep: p-value	Efficacy (S Behavior a	Spiegel Sle and mood	on waking up
Lormetazepam Efficacy: Efficacy (Sp Zi Improvem Improvem	1 biegel opiclo ent fro NS ent fro NS	mg mg Sleep ne om bas	27 25 Questionnairo Lorazepa eline to end of 0.013 eline to end of 0.065	5 day 5 day e) am treatment on time	lity of s	asleep: p-value	Efficacy (S Behavior a	Spiegel Sle and mood	on waking up
Lormetazepam Efficacy: Efficacy (Sp Zi Improvem Improvem	1 biegel opiclo ent fro NS ent fro NS	mg mg Sleep ne om bas	27 25 Questionnairo Lorazepa eline to end of 0.013 eline to end of 0.065	5 day 5 day e) am treatment on time treatment on qua	lity of s	asleep: p-value	Efficacy (S Behavior a	Spiegel Sle and mood	on waking up
Lormetazepam Efficacy: Efficacy (Sp Zi Improvem Improvem	1 iegel opiclo ent fro NS ent fro NS ent fro NS ent fro	mg mg Sleep ne om bas	27 25 Questionnaire Lorazepa eline to end of 0.013 eline to end of 0.065 eline to end of NS	5 day 5 day e) am treatment on time treatment on qua treatment on dur	lity of s	asleep: p-value	Efficacy (S Behavior a Overall ev	Spiegel Sle and mood	on waking up
Lormetazepam Efficacy: Efficacy (Sp Zi Improvem Improvem	1 iegel opiclo ent fro NS ent fro NS ent fro NS	mg mg Sleep ne om bas	27 25 Questionnaire Lorazepa reline to end of 0.013 reline to end of 0.065 reline to end of NS	5 day 5 day e) am treatment on time treatment on qua treatment on dur	lity of s	asleep: p-value sleep: p-value	Efficacy (S Behavior a Overall ev	Spiegel Sle and mood	on waking up
Lormetazepam Efficacy: Efficacy (Sp Zr Improvem Improvem Improvem	1 iegel opiclo ent fro NS ent fro NS ent fro NS ent fro NS	mg mg Sleep ne om bas om bas	27 25 Questionnairo Lorazepa eline to end of 0.013 eline to end of NS eline to end of NS eline to end of	5 day 5 day e) am treatment on time treatment on qua treatment on dur	ation o	asleep: p-value sleep: p-value f sleep: p-value awakenings: p-value	Efficacy (S Behavior a Overall ev	Spiegel Sle and mood	on waking up
Lormetazepam Efficacy: Efficacy (Sp Zr Improvem Improvem Improvem	1 iegel opicio ent fro NS ent fro NS ent fro NS ent fro NS ent fro NS	mg mg Sleep ne om bas om bas	27 25 Questionnaire Lorazepa eline to end of 0.013 eline to end of 0.065 eline to end of NS eline to end of NS	5 day 5 day e) am treatment on time treatment on qua treatment on dur treatment on noc	ation o	asleep: p-value sleep: p-value f sleep: p-value awakenings: p-value	Efficacy (S Behavior a Overall ev	Spiegel Sle and mood	on waking up
Lormetazepam Efficacy: Efficacy (Sp Zr Improvem Improvem Improvem Improvem	1 iegel opiclo ent fro NS ent fro NS ent fro NS ent fro NS ent fro NS ent fro NS	mg mg Sleep ne om bas om bas om bas	27 25 Questionnaire Lorazepa eline to end of 0.013 eline to end of NS eline to end of NS eline to end of NS eline to end of	5 day 5 day e) am treatment on time treatment on qua treatment on dur treatment on noc treatment on dre	ation o eturnal a ams: p	asleep: p-value sleep: p-value f sleep: p-value awakenings: p-value	Efficacy (S Behavior a Overall ev	Spiegel Sle and mood	on waking up
Lormetazepam Efficacy: Efficacy (Sp Zr Improvem Improvem Improvem Improvem	1 iiegel ppiclo ent fro NS ent fro NS ent fro NS ent fro NS ent fro NS ent fro NS	mg mg Sleep ne om bas om bas om bas	27 25 Questionnaire Lorazepa eline to end of 0.013 eline to end of 0.065 eline to end of NS eline to end of NS eline to end of NS eline to end of	5 day 5 day e) am treatment on time treatment on qua treatment on dur treatment on noc treatment on dre	ation o eturnal a ams: p	asleep: p-value sleep: p-value f sleep: p-value awakenings: p-value -value	Efficacy (S Behavior a Overall ev	Spiegel Sle and mood	on waking up
Lormetazepam Efficacy: Efficacy (Sp Za Improvem Improvem Improvem Improvem Improvem	1 iegel ppiclo ent fro NS ent fro NS	mg mg Sleep ne om bas om bas om bas om bas	27 25 Questionnaire Lorazepa eline to end of 0.013 eline to end of NS eline to end of NS	5 day 5 day e) am treatment on time treatment on qua treatment on dur treatment on noc treatment on dre treatment on mo	ation o ation o atrinal a ams: p rning d	asleep: p-value sleep: p-value f sleep: p-value awakenings: p-value -value	Efficacy (S Behavior a Overall ev	Spiegel Sle and mood	on waking up

P: NS

zin-Juracic,	1998	6			Subg	roup: sh	iftworker	Quality rating: Fair
sign:								
Study design:	NR	NR	Cross	sover	Run-in :	0 days		Setting: Single Center
					Wash out :	0 days		Country: Croatia
Sample:	Num	ber Sc	reened/	Eligible/	Enrolled	Nu	mber Withdrawn/	Lost to follow-up/ Analyzed
			NR/	32/	29		0/	0/ 29
Inclusion criter	ria:							
A group of w	orkers	s emplo	oyed in a	security	company were	e recruited	to the study as su	ubjects
Exclusion crite	eria:							
Population:	Mear	n age:	NR yea	rs	Ethnicity:	NR		
	Geno	der:	0% Fem	nale	-			
ervention:							Primary	
Drug name	dos	sage	N=		Duration		outcome	Outcome:
Zopiclone	7.5	mg	29		7 day			time in bed
Nitrazepam	5	mg	29		7 day			length of sleep episode
Placebo	NA	mg	29		7 day			total sleep time
								sleep efficacy
								sleep latency
								sleep quality
								no. of awakenings

Efficacy:

Zopiclone	Nitrazepam	Placebo	
an total length of m	ain sleep (estimate fro	m the figure): minutes	
295	285	270	P: NR
an sleep efficacy of	main sleep (estimate	from the figure): %	
88	87	82	P: NR
an sleep efficacy of	all day sleep (estimat	e from the figure): %	
88	87	82	P: NR
items of main sleep	characteristics: Score	9	
NR	NR	NR	P: NS
ems of all day sleep	o characteristics: Scor	e	
NR	NR	NR	P: NS

Fontaine, 1990	⁻ ontaine, 1990					Subgroup: psychiatric			Quality rating: Fair			
Design:												
Study design:	RCT	DB	Para	llel	Run-in :	7 days	Settin	g:	Single Ce	enter		
					Wash out :	21 days	Count	ry:	Canada			
Sample:	Numbe	r Scre	ened/	Eligible/	Enrolled	Number With	ndrawn/ Lost to	follo	w-up/ Ana	alyzed		
			NR/	NR/	75		21/		0/	75		

Inclusion criteria:

Selection criteria required that: (1) patients be aged between 18 & 60 years; 92) patients have a diagnosis of generalized anxiety disorder according to the DSM-III 1978 draft (Diagnostic and Statistical Manual of Mental Disorders, 1978) which specifies that anxiety must be present for a duration of at least 6 months with its onset not associated with a psychosocial stressor (Diagnostic Criteria for GAD are different for the 1980 version); 93) patients have a total score of at least 20 on the Hamilton Anxiety Rating Scale prior to acceptance for participation in the study and; 94) patients with severe insomnia as the target symptom defined as follows. AT least three of the following criteria: sleep latency of 45 min or more, at least two nocturnal awakenings, poor quality of sleep and a total sleep time of less than 6h.

Exclusion criteria:

.....

.....

Exclusion criteria were: patients with specific sleep disorders, physical illnesses, affective or psychotic disorders, organic brain syndrome, mental deficiency (I.Q. below 70), alcoholism or drug addiction).

Population:	Mean age: Gender:	42.9 years 53% Female	Ethnicity:	NR		
Intervention: Drug name	dosage	N=	Duration		Primary outcome	Outcome:
Zopiclone	7.5 mg	30	28 day			sleep induction
Triazolam	0.5 mg	30	28 day			sleep soundness
Placebo	NA mg	15	28 day			duration of sleep
						morning awakening
						hangover effect

Efficacy:

sleep inventory

Zopiclone	Triazolam	
sleep induction time: So	ore (p vs placebo)	
3.5 (<0.01)	3.5 (<0.05)	P: NS
sleep induction cluster:	Score (p vs placebo)	
14.7 (<0.05)	14.1 (NS)	P: NS
duration of sleep: Score	(p vs placebo)	
2.9 (NS)	2.9 (NS)	P: NS
sleep soundness: Score	(p vs placebo)	
11.0 (<0.05)	10.5 (NS)	P: NS
global sleep index: Sco	e (p vs placebo)	
35.7 (NS)	34.6 (NS)	P: NS
morning awakening: Sc	ore (p vs placebo)	
7.3 (NS)	6.7 (NS)	P: NS
hangover: Score (p vs p	lacebo)	
6.8 (NS)	6.3 (NS)	P: NS

		<u> </u>	517 5
aine, 1990		Subgroup: psychiatric	Quality rating: Fair
Hamilton Rating Scale (HAM)		
Zopiclone	Triazolam		
somatic anxiety: Score	(p vs placebo)		
8.8 (NS)	12.0 (NS)		P: <0.01
psychic anxiety: Score	(p vs placebo)		
9.3 (NS)	10.8 (NS)		P: NS
total score: Score (p vs	s placebo)		
18.2 (NS)	22.4 (NS)		P: <0.01
daytime anxiety: Numb	er (%)		
5 (17)	10 (33)		P: 0.16
Clinical Global Impressi	ion (CGI)		
Zopiclone	Triazolam		
overall: Score (p vs pla	icebo)		
NR (sig. better)	NR (sig. better)		P: NR

Pi Shan, 200	4			Sub	group:	Stroke (inpatient)	Quality	rating:	Fair
esign:									
Study design:	RCT D	B Cro	ossover	Run-in : Wash out :	0 day 0 day		Setting: Country:	Single C Canada	enter
Sample:	Number S	creened 44	/ Eligible/ / 27/	Enrolled 18		Number Withdrawn		low-up/ An 0/	alyzed 18
Inclusion crite	ria:								
Each patien	t with a diag	nosis of	either stro	oke or brain ir	jury wa	s consecutively recr	uited for elig	ibility.	
Exclusion crite									
answer ques posttraumat	stions for ar ic amnesia)	iy other i . Subjec	reason (se ts were als	vere aphasia so> 18 years	, blindne of age.	unicate either in Engess, severe cognitive Fhe patients were no a, or restless legs s	e impairment ot excluded i	t, including	patients with
Population:	Mean age	: 56.6 y	years	Ethnicity	: NR				
	Gender:	44%	Female						
tervention: Drug name	dosage	N=		Duration		Primary outcome	e Outcome):	
Zopiclone	3.75 mg	18	eded fo	or 7 day			total time	of sleep	
Lorazepam	0.5- mg	18	eded fo	or 7 day			quality of	sleep	
							depth of s	sleep	
							feeling of	rest	
							daytime c	drowsiness	
							lethargy		
							fatigue		
fficacy:									
recorded by	nurses								
-	opiclone	L	orazepam						
total time	of sleep: ho	ours (SD)						
	23 (0.63)		, 7.49 (0.77)						P: 0.09
	(higher sco		. ,	Pango)					
	(nigher sco 4 (3.5-4)		4 (3.5-4)	nange)					P: 0.6
	· · ·		· · ·	hauta) O					1.0.0
teeling of	•	sned (hię		=better): Sco	e (Ran	je)			D: 0.70
	4 15 17 11		4 (3-4)						P: 0.79
	3.5 (3-4)								
sleep quest									

Zopiclone	Lorazepam	
quality of sleep (higher	score=better): Score (Range)	
8 (5-9)	8.5 (7.5-10)	P: 0.17
depth of sleep (higher	score=better): Score (Range)	
8 (6-10)	8 (7-10)	P: 0.21
feeling of being refresh	ed (higher score=better): Score (Range)	
8 (6.5-10)	8 (6.5-9.5)	P: 0.52
alertness (higher score	=better): Score (Range)	
9 (6.5-10)	9 (8-10)	P: 0.6
tiredness (higher score	=better): Score (Range)	
8 (5.5-8.5)	7.5 (5-10)	P: 0.29

Shan, 2004		Subgroup: Str	roke (inpatient)	Quality rating: Fair	
Mini mental state examin	nation score				
Zopiclone	Lorazepam				
total score: Score (Ran	ge)				
28 (27-30)	27 (25-29)			P: 0.05	4

agot, 1993					Sub	group:	psychia	tric	Quality	rating:	Fair
)esign:											
Study design:	RCT	DB	Paral	el	Run-in :	4 day	/S		Setting:	Multicen	ter
					Wash out :	: 30 da	ays		Country:	France	
Sample:	Numb	oer Scre	ened/	-	Enrolled		Number	Withdrawn/	Lost to follo	ow-up/ An	alyzed
			NR/	NR/	95			33/		0/	62
Inclusion crite						(h					
	-	• •		•	t latency of m stal nocturnal					turnal awa	kenings; total
Exclusion crite		ed sleei	n disord	ers asso	ciated with s	evere n	svchiatric	disorders s	leen annea	sleen-rel:	ated myoclonus, or
insomnia tha hypnotic me women of ch	at had o dication hildbear	develop n or trea ring pot	ed durin atment t ential w	g childh nat could no were	ood, and thos d have had a not taking ad	se who n influe lequate	showed s nce on sle contrace	erious medic eep onset we ptive precau	cal disease ere excluded tions were a	or needed d. Pregnan also exclud	concomitant t women and
					ve an influen						
Population:	Mean	age:	48 years	6	Ethnicity	: NR					
	Gend	er:	61% Fe	male							
ntervention: Drug name	dos	age	N=		Duration			Primary outcome	Outcome	:	
Zolpidem	20	mg	47		86 day				duration o	f sleep	
Triazolam	0.5	mg	48		86 day				number of	nocturnal	awakenings
									time awak	e during th	ne night
									subjective	status on	awakening
									therapeuti	c efficacy	
									anxiety	-	
fficacy:											
therapeutic	efficad	cy by p	atients								
Z	Colpider	n	Tria	azolam							
therapeut	ic effec	ts at da	y 30- go	od and	excellent: Nu	mber (%)				
	32 (75))	32	2 (75)							P: NS
therapeut	ic effec	ts at da	y 60- go	od and	excellent: Nu	mber (9	%)				
	33 (87))	3	1 (84)							P: NS
			y 90- ac	od and	excellent: Nu	mber (9	%)				
	32 (91)			9 (85)			-/				P: NS
quality of											
quality 01	74	uuy O		65							P: NR
quality of		t day 0	0.0/								
quality of		ii day 9	0. %	70							
	81			73							P: NR

overall rating: day 0 (day 90) 38.4 (78.6) 3

28 (44)

36.3 (76.6)

40 (42)

status on awakening and alertness, number of patients: day 4 (day 90)

P: NR

P: NR

ot, 1993		Subgroup: psychiatric	Quality rating: Fair
global assessment by th	ne investigator		
Zolpidem	Triazolam		
sleep latency at day 90	, change from baseli	ne: Score (p vs baseline)	
-1.9 (<0.001)	-1.9 (<0.001)		P: NS
mean sleep time at da	y 90, change from ba	aseline: hours (p vs baseline)	
2.72 (<0.001)	2.26 (<0.001)		P: NS
number of nocturnal av	vakenings at day 60,	change from baseline: Number (p	vs baseline)
-1.7 (0.02)	-1 (0.02)		P: <0.05
duration of nocturnal av	wakenings at day 60:	minutes (p vs baseline)	
18 (0.02)	14 (0.02)		P: <0.05
Hamilton Rating Scale for	or anxiety		
Zolpidem	Triazolam		
total score: Score			
multiple data	multiple data		P: NS

Schwartz, 2004	Ļ			Su	bgroup:	psychiatric (inpatie	Quality	rating: Po	or
Design:									
Study design:	RCT	Оре	Parallel	Run-in : Wash out	NR t: NR		Setting: Country:	Single Cent US	er
Sample:	Number		-	le/ Enrolled R/ 16		Number Withdrawn/ 0/		ow-up/ Analy 0/	zed 16
Inclusion crite inpatient psy		are							
	re exclude ney were u					aking a hypnotic or se or if they had a med			
Population:	Mean ag Gender:		R years % Female	Ethnicit	y: NR				
Intervention: Drug name	dosage	e N	1=	Duration		Primary outcome	Outcome:	:	
Zaleplon	10-2 mg	-	7	AsN			sleepiness	3	
Trazodone	50-1 mg	9	9	AsN			sleep dura	ition	
Efficacy:					n				
Epworth sle	epiness	scale (ESS)						
Ž	Zaleplon		Trazodor	ne					
median at	t study ent	ry-mat	ching: Scor	re					
	7		9					F	P: 0.885
media cha	ange from	baseliı	ne efficacy	and tolerability	/: Score				
	-1		1					F	P: 0.23
inpatient, n	urse-reco	rded s	leep log						
2	Zaleplon		Trazodor	ne					
sleep- me	edian at stu	idy ent	try-matchin	g: hours					
	3		3					F	P: 0.894
sleep- me	edian chan	ge fror	n baseline	efficacy and to	lerability	: hours			

Steens, 1993				Subg	roup: COPD	Quality	Quality rating: Fair		
Design:									
Study design:	RCT	DB Cro	ssover	Run-in :	0 days	Setting:	Multicent	ter	
				Wash out :	0 days	Country:	Canada		
Sample:	Numbe	r Screened/	Eligible/	Enrolled	Number Wit	ndrawn/ Lost to foll	ow-up/ An	alyzed	
		NR/	NR/	24		0/	0/	24	

Inclusion criteria:

Males and nonpregnant females aged between 35 and 69 years with mild to moderate COPD and insomnia were recruited. Insomnia must have been present for at least 6 months and had to be associated with a sleep latency >30 minutes, sleep duration of 4-6 hours and daytime complaints associated with disturbed sleep. COPD must have been present for at least 3 years and objective inclusion criteria were, FEV1 40-80% predicted, FEV1/FVC=40-70% predicted, diffusion capacity (DL CO) >30% predicted, PaCO2=30-48mm Hg and PaO2 > 55mm Hg. Patients were required to be in stable physical health for at least 2 weeks prior to entering the study, and each gave written informed consent.

Exclusion criteria:

Patients were excluded if they had been hospitalized in the previous 4 weeks, if they had right ventricular hypertrophy on the ECG or right heart failure clinically, a hematocrit >55% or if they were on oxygen therapy. They were also excluded if any of the following applied: inability to be withdrawn from hypnotics for the required time (2 nights for triazolam, 7 nights for other short- or intermediate-acting hypnotics and 14 nights for long-acting hypnotics); positive screening for drugs, other than theophylline, know to alter sleep (e.g. benzodiazepines, barbiturates, opiates, amphetamines, cannabinoids and alcohol); medications interfering with the absorption or metabolism of benzodiazepines (e.g. cimetidine); a history suggestive of obstructive sleep apnea or restless legs syndrome/periodic movements during sleep, an adverse effect related to benzodiazepines or CNS depressants, alcohol or drug abuse.

Population:	Mean age: Gender:	58.2 years 38% Female	Ethnicity:	NR	
ntervention: Drug name	dosage	N=	Duration		F
Zolpidem	5 mg	24	1 day		
Zolpidem	10 mg	24	1 day		
Triazolam	0.25 mg	24	1 day		
Placebo	NA mg	24	1 day		
	0				

Primary outcome	Outcome:
	sleep quality
	total wake time
	awakening
	microarousal
	total sleep time
	wake time during sleep period

Efficacy:

overall m	easures		
Z	olpidem 5mg	Zolpidem 10mg	Triazolam
total sle	ep time: minute	s (p vs triazolam)	
3	84.82 (<0.05)	397.12 (NS)	413.79 (NA)
total wa	ake time: minutes	s (p vs triazolam)	
ç	93.09 (<0.05)	82.37 (NS)	66.10 (NA)
sleep e	fficacy: % (p vs t	triazolam)	
7	' 9.74 (<0.05)	82.35 (NS)	85.83 (NA)

ns, 1993		Subgroup: COPD	Quality rating: Fair	
maintenance measures				
Zolpidem 5mg	Zolpidem 10mg	Triazolam		
awakenings (no./hours	of sleep): Number (p	vs triazolam)		
4.70 (<0.05)	4.07 (NS)	3.68 (NA)		
microarousals (no./hou	r of sleep): Number (p	o vs triazolam)		
14.08 (NS)	12.57 (NS)	13.23 (NA)		
Arousals/total sleep tim	ne (no./hour): Number	(p vs triazolam)		
18.69 (NS)	16.46 (NS)	16.72 (NA)		
wake time during sleep	: Number (p vs triazol	am)		
55.57 (NS)	50.69 (NS)	40.47 (NA)		
subjective assessment	of sleep			
Zolpidem 5mg	Zolpidem 10mg	Triazolam		
sleep latency: minutes	(p vs triazolam)			
38.7 (NS)	30.22 (NS)	25.52 (NA)		
ease of falling sleep (lo	ower score=better): Sc	core (p vs triazolam)		
46.48 (<0.05)	30.09 (NS)	20.96 (NA)		
no. of awakenings: mir	utes (p vs triazolam)			
2.74 (NS)	2.17 (NS)	1.61 (NA)		
duration of night waking	g: minutes (p vs triazo	lam)		
103.04 (NS)	16.78 (NS)	43.83 (NA)		
sleep duration: minutes	s (p vs triazolam)			
333.26 (<0.05)	388.22 (NS)	411.17 (NA)		
feeling of sleep (1=exc	ellent, 4=poor): minute	es (p vs triazolam)		
2.61 (<0.05)	2.13 (NS)	1.87 (NA)		
sleepy in the morning (higher score=better):	minutes (p vs triazolam)		
55.04 (NS)	65.44 (NS)	66.52 (NA)		
concentration in the mo	orning (1=excellent, 4=	=poor): minutes (p vs triazolam))	
2.30 (NS)	2.26 (NS)	2.13 (NA)		

Evidence Table 11. Active controlled trials (Other Subgroups): Rebound

agot, 1993					Subg	roup: psychiatric		Quality	rating	: Fa	ir		
Design:													
Study design:	RCT	DB	Paralle	el	Run-in :	4 days		Setting:	Multice	enter			
					Wash out :	30 days		Country:	France	e			
Sample:	Numb	er Scr	eened/ E	ligible/	Enrolled	Number Wit	hdrawn/	_ost to follo	w-up/ /	Analy	zed		
			NR/	NR/	95		33/		0/		62		
Inclusion crite	ria:												
						ore than 30 minutes wake-time of more t			urnal av	vaker	nings	; total	
insomnia tha	at had d	levelop	ped during	g childh	ood, and those	evere psychiatric dis e who showed seric influence on sleep	ous medic	al disease	or neede	ed co	ncon	nitant	is, or
women of ch	nildbear	ing po	tential who	o were	not taking ade	equate contraceptive		ons were a	lso excl	uded,	, as v	vere	
women of ch nursing moth	nildbear ners an	ing po d thos	tential who	o were in who	not taking ade m adequate co			ons were a	lso excl	uded,	, as v	vere	/
women of ch nursing moth	nildbear ners an ng any	ing po d thos treatm	tential who	o were in who ould ha	not taking ade m adequate co	equate contraceptive ompliance could no e on sleep onset.		ons were a	lso excl	uded,	, as v	vere	/
women of ch nursing moth were receivin Population:	nildbear ners an ng any	ing po d thos treatm age:	e patients e patients ent that co	o were in who ould ha	not taking ade m adequate co ve an influenc	equate contraceptive ompliance could no e on sleep onset.		ons were a	lso excl	uded,	, as v	vere	/
women of ch nursing moti were receivin Population: ntervention:	nildbear ners an ng any Mean Gend	ing po d thos treatm age: er:	e patients e patients ent that co 48 years 61% Fem	o were in who ould ha nale	not taking ade m adequate co ve an influenc Ethnicity:	equate contraceptive ompliance could no e on sleep onset.		ons were a	lso excl	uded,	, as v	vere	/
women of ch nursing moth were receivin Population:	nildbear ners an ng any Mean	ing po d thos treatm age: er:	e patients e patients ent that co 48 years	o were in who ould ha nale	not taking ade m adequate co ve an influenc	equate contraceptive ompliance could no e on sleep onset.		ons were a	lso excl	uded,	, as v	vere	/
women of ch nursing moti were receivin Population: ntervention:	hildbear hers an ng any Mean Gendo dosa	ing po d thos treatm age: er:	e patients e patients ent that co 48 years 61% Fem	o were in who ould ha nale	not taking ade m adequate co ve an influenc Ethnicity:	equate contraceptive ompliance could no e on sleep onset.		ons were a	lso excl	uded,	, as v	vere	/
women of ch nursing moti were receivin Population: ntervention: Drug name	hildbear hers an mg any Mean Gend dosa 20	ring po d thos treatm age: er: age mg	e patients e patients eent that co 48 years 61% Ferr N=	o were in who ould ha nale	not taking ade m adequate ca ve an influenc Ethnicity: Duration 86 day	equate contraceptive ompliance could no e on sleep onset.		ons were a	lso excl	uded,	, as v	vere	/
women of ch nursing moth were receivin Population: ntervention: Drug name Zolpidem	hildbear hers an ng any Mean Gend dosa	ring po d thos treatm age: er: age mg	e patients e patients eent that co 48 years 61% Ferr N= 47	o were in who ould ha nale	not taking ade m adequate or ve an influenc Ethnicity: Duration	equate contraceptive ompliance could no e on sleep onset.		ons were a	lso excl	uded,	, as v	vere	/
women of ch nursing moth were receivin Population: ntervention: Drug name Zolpidem	hildbear hers an mg any Mean Gend dosa 20	ring po d thos treatm age: er: age mg	e patients e patients eent that co 48 years 61% Ferr N= 47	o were in who ould ha nale	not taking ade m adequate ca ve an influenc Ethnicity: Duration 86 day	equate contraceptive ompliance could no e on sleep onset.		ons were a	lso excl	uded,	, as v	vere	/
women of ch nursing moth were receivin Population: ntervention: Drug name Zolpidem Triazolam	hildbear hers an ng any Mean Gend dosa 20 0.5	ing po d thos treatm age: er: age mg mg	tential whe e patients nent that co 48 years 61% Ferr N= 47 48	o were in who ould ha nale	not taking ade m adequate ca ve an influenc Ethnicity: Duration 86 day	equate contraceptive ompliance could no e on sleep onset.		ons were a	lso excl	uded,	, as v	vere	/
women of ch nursing motil were receivin Population: Drug name Zolpidem Triazolam Rebound: therapeutic	hildbear hers an ng any Mean Gend dosa 20 0.5	ring po d thos treatm age: er: age mg mg mg	tential whe e patients nent that ca 48 years 61% Ferr N= 47 48 47 48	o were in who ould ha nale	not taking ade m adequate ca ve an influenc Ethnicity: Duration 86 day	equate contraceptive ompliance could no e on sleep onset.		ons were a	lso excl	uded,	, as v	vere	/
vomen of ch nursing moth were receivin Population: ntervention: Drug name Zolpidem Triazolam Rebound: therapeutic	hildbear hers an ng any Mean Gend dosa 20 0.5 efficac	ing po d thos treatm age: er: age mg mg mg	tential whe e patients ent that co 48 years 61% Ferr N= 47 48 47 48 50 50 50 50 50 50 50 50 50 50 50 50 50	o were in who ould ha nale zolam	not taking ade m adequate ca ve an influenc Ethnicity: Duration 86 day 86 day	equate contraceptive ompliance could no ce on sleep onset.	t be expe	ons were a	lso excl	uded,	, as v	vere	/

gnoli, 1989					Subg	roup:	Anxiety	Quality	rating	: Poo	r	
Design:												
Study design:	RCT	DB	Crosso	ver	Run-in : Wash out :	3 day NR	/S	Setting: Country:	NR Rome,	Foggia	, Italy	
Sample:	Num	ber Sc	reened/ El NR/	ligible/ NR/	Enrolled 20		Number Withdrawn	/ Lost to follo		Analyze		
concomitant	re age antide	epressi	ve, anxioly	tic or n		dicatio	n Rating Scale for Ar n and absence of so i insomnia.				of	
Exclusion crite Presence of		omitant	general illr	ness; re	enal or hepatio	; failure	e; effectiveness of pl	acebo admir	nistration	; and pr	egnancy.	
Population:		n age: der:	38.2 year 60% Fem		Ethnicity:	NR						
ntervention: Drug name	do	sage	N=		Duration							
Zopiclone	7.5	mg	12		1 day							
Nitrazepam	5	mg	12		1 day							
Adverse Event epigastralg												
epigastralg		one	Nitraz	zepam								
epigastralg Z	ia Iopiclo		Nitraz	zepam								
epigastralg	ia Iopiclo		Nitraz 1	zepam						P: N	R	
epigastralg Z	ia Copiclo Iumbe 1	er		zepam						P: N	R	
epigastralg Z 1st week: N daytime sec	ia Copiclo Iumbe 1	er N	1	zepam						P: N	R	
epigastralg Z 1st week: N daytime sec	ia Copiclo Jumbe 1 dation Copiclo	er I Dne	1							P: N	R	
epigastralg Z 1st week: N daytime sec Z	ia Copiclo Jumbe 1 dation Copiclo	er I Dne	1							P: N P: N		
epigastralg Z 1st week: N daytime sec Z	ia Copiclo Iumbe 1 dation Copiclo Iumbe 0	er N Dine er	1 Nitraz									
epigastralgi Z 1st week: N daytime sec Z 1st week: N 2dn week: 1	ia Copiclo Iumbe 1 Copiclo Iumbe 0 Numbe 0	er None er	1 Nitraz 6 14	zepam							R	
epigastralgi Z 1st week: N daytime sec Z 1st week: N 2dn week: 1	ia Copiclo Iumbe 1 Copiclo Iumbe 0 Numbe 0	er None er	1 Nitraz 6 14	zepam	en treatment:	Numbe	Đĩ			P: N	R	
epigastralgi Z 1st week: N daytime sec Z 1st week: N 2dn week: 1	ia Copiclo Iumbe 1 Copiclo Iumbe 0 Numbe 0	er None er	1 Nitraz 6 14	zepam	en treatment:	Numbe	Pr			P: N	R	
epigastralgi Z 1st week: N daytime sec Z 1st week: N 2dn week: 1	ia Copiclo Jumbe 1 dation Copiclo Jumbe 0 Numbe 0 nto the 0	er None er	1 Nitraz 6 14 -out period	zepam	en treatment:	Numbe	Đr			P: N P: N	R	
epigastralgi Z 1st week: N daytime sed Z 1st week: N 2dn week: N prolonged in restlessnes	ia Copiclo Jumbe 1 dation Copiclo Jumbe 0 Numbe 0 nto the 0	er one er e wash	1 Nitraz 6 -0ut period 3	zepam	en treatment:	Numbe	er			P: N P: N	R	
epigastralgi Z 1st week: N daytime sed Z 1st week: N 2dn week: N prolonged in restlessnes	ia Copiclo Jumbe 1 dation Copiclo Jumbe 0 Numbe 0 nto the 0 ss	er one er e wash- one	1 Nitraz 6 -0ut period 3	zepam	en treatment:	Numbe	Ðſ			P: N P: N	R	

Ansoms, 1991				Subg	roup: alcoholism	Quality	rating:	Fair	
Design:									
Study design:	RCT	DB Pa	rallel	Run-in :	2 days	Setting:	Multicen	ter	
				Wash out :	NR	Country:	US		
Sample:	Numbe	r Screeneo	/ Eligible/	Enrolled	Number Withdrawr	n/ Lost to follo	w-up/ An	alyzed	
		NF	/ 54/	52	()/	0/	52	

Inclusion criteria:

Only insomniac patients in their postalcoholism withdrawal period of at least ten days, who were aged between 20 and 55 years and able to participate in the trial were included, as well as those for whom it was expected they would need a hypnotic every day because of their withdrawal.

Exclusion criteria:

Patients with the following criteria were excluded: those being treated during the study period with psychotropic drug for the first time, or for whom the existing medication with psychotropic drugs was being changed or those using tranquilizers of the benzodiazepine type. Patients having used high doses of hypnotics or with a history of drug abuse before the study period were also excluded, as well as those suffering from myasthenia gravis, with any disease accompanies by pain, living in an unstable fluctuating condition with mental or physical stress, or patients with a severe liver or kidney disturbance. Shiftworkers were not included in the study

Population:	Mear Geno	-	43.9 years 33% Female	Ethnicity:	NR
Drug name	dos	sage	N=	Duration	
Zopiclone	7.5	mg	27	5 day	
Lormetazepam	1	mg	25	5 day	

Adverse Events:

Overall safety		
Zopiclone	Lormetazepam	
Physician's overall safe	ty assessment ("excellent" or "good"): %	
93	76	P: NR
withdrawals		
Zopiclone	Lorazepam	
total withdrawals: Numb	er	
NR	NR	
withdrawals due to AEs	Number	
NR	NR	
Overall AEs		
Zopiclone	Lormetazepam	
Overall AEs: %		
26	28	P: NS

ozin-Juracic,	1998	•		Sub	ogroup: shiftw	orker	Quality	rating: F	air
Design:									
Study design:	NR	NR	Crossover	Run-in : Wash out	0 days : 0 days		Setting: Country:	Single Ce Croatia	nter
Sample:	Num	ber Sc	reened/ Eligit NR/ 3	ble/ Enrolled 32/ 29	Numb	er Withdrawn/ I 0/	_ost to follo	w-up/ Ana 0/	lyzed 29
Inclusion criter	ria:								
A group of w	orkers	s emplo	oyed in a secu	rity company we	ere recruited to	the study as sul	bjects		
Exclusion crite NR	eria:								
Population:	Mear	n age:	NR years	Ethnicity	y: NR				
_	Geno	der:	0% Female						
ntervention: Drug name	dos	sage	N=	Duration					
Zopiclone	7.5	mg	29	7 day					
Nitrazepam	5	mg	29	7 day					
Placebo	NA	mg	29	7 day					
Adverse Event	ts:								
withdrawals	5								
	opiclo	ne	Nitrazep	am Pl	acebo				
total withdra	awals:	Numb	er						
	0		0		0				
withdrawals	due t	o AEs:	Number						
	0		0		0				

Fontaine, 1990					Subg	roup: psychiatri	c Quality	Quality rating: Fair		
Design:										
Study design:	RCT	DB	Parall	el	Run-in :	7 days	Setting:	Single C	enter	
					Wash out :	21 days	Country:	Canada		
Sample:	Numbe	er Scre	ened/ E	Eligible/	Enrolled	Number W	ithdrawn/ Lost to fol	low-up/ An	alyzed	
			NR/	NR/	75		21/	0/	75	

Inclusion criteria:

Selection criteria required that: (1) patients be aged between 18 & 60 years; 92) patients have a diagnosis of generalized anxiety disorder according to the DSM-III 1978 draft (Diagnostic and Statistical Manual of Mental Disorders, 1978) which specifies that anxiety must be present for a duration of at least 6 months with its onset not associated with a psychosocial stressor (Diagnostic Criteria for GAD are different for the 1980 version); 93) patients have a total score of at least 20 on the Hamilton Anxiety Rating Scale prior to acceptance for participation in the study and; 94) patients with severe insomnia as the target symptom defined as follows. AT least three of the following criteria: sleep latency of 45 min or more, at least two nocturnal awakenings, poor quality of sleep and a total sleep time of less than 6h.

Exclusion criteria:

Exclusion criteria were: patients with specific sleep disorders, physical illnesses, affective or psychotic disorders, organic brain syndrome, mental deficiency (I.Q. below 70), alcoholism or drug addiction).

Population:	Mean age: Gender:	42.9 years 53% Female	Ethnicity:	NR
Intervention: Drug name	dosage	N=	Duration	
Zopiclone	7.5 mg	30	28 day	
Triazolam	0.5 mg	30	28 day	
Placebo	NA mg	15	28 day	

Adverse Events:

Hopkins Symptoms Checklist (SCL-90)

Zopiclone	Triazolam	Placebo	
drowsiness: Number			
3	5	4	P: NS
ataxia: Number			
2	3	1	P: NS
headache: Number			
6	3	3	P: NS
taste perversion: Number	r		
17	3	1	P: <0.001
nausea: Number			
2	3	4	P: NS
dry mouth: Number			
7	1	1	P: <0.05
withdrawals			
Zopiclone	Triazolam	Placebo	
total withdrawals: Numbe	er		
8	8	5	
withdrawals due to AEs:	Number		
4	3	0	

Pi Shan, 200	4			Subg	roup: Stroke (inpatient)	Quality	rating: Fair
esign:							
Study design:	RCT D	B Cro	ossover	Run-in : Wash out :	0 days 0 days	Setting: Country:	Single Center Canada
Sample:	Number S	creened 44	/ Eligible/ / 27/	Enrolled 18	Number Withdraw	n/ Lost to follo 0/	ow-up/ Analyzed 0/ 18
Inclusion crite	ria:						
Each patien	t with a diag	nosis of	either stro	ke or brain inji	ury was consecutively rec	ruited for eligi	bility.
answer ques posttraumat secondary c	stions for an ic amnesia) auses of ins	iy other i . Subjectsomnia s	reason (se ts were als such as dep	vere aphasia, o> 18 years of	communicate either in En blindness, severe cognitiv f age. The patients were r o apnea, or restless legs s	ve impairment not excluded if	, including patients with
Population:	Mean age			Ethnicity:	NR		
tervention:	Gender:	44% I	Female				
Drug name	dosage	N=		Duration			
Zopiclone	3.75 mg	18	eded fo	r 7 day			
Lorazepam	0.5- mg	18	eded fo	r 7 day			
dverse Even	ts:						
withdrawal	s						
Z	opiclone	L	orazepam				
total withdr	awals: Num	ber					
	0		0				
withdrawals	-	s: Numb	-				

Pagot, 1993				Subg	roup: psychiatric	Quality	rating: Fair	
Design:								
Study design:	RCT [B Para		Run-in : Nash out :	4 days 30 days	Setting: Country:	Multicenter France	
Sample:	Number S	creened/	Eligible/ E		-	Irawn/ Lost to follo	w-up/ Analyze	d
		NR/	NR/	95		33/	0/ 6	2
Inclusion crite								
					ore than 30 minutes; r wake-time of more tha		urnal awakening	gs; total
Exclusion crite	eria:							
women of ch	hildbearing those pati	potential w ents in who	no were no om adequa	ot taking ade te complian	influence on sleep or equate contraceptive ce could not be expect sleep onset.	precautions were a	llso excluded, a	s were nursing
Population:	Mean age	: 48 year	S	Ethnicity:	NR			
-	Gender:	61% Fe		,				
Intervention:								
Drug name	dosage	N=	D	uration				
				S. J				
Zolpidem	20 mg	47	86	6 day				
	20 mg 0.5 mg	47 48		o day 6 day				
Zolpidem	0.5 mg							
Zolpidem Triazolam Adverse Even	0.5 mg							
Zolpidem Triazolam Adverse Event withdrawals	0.5 mg	48		5 day				
Zolpidem Triazolam Adverse Event withdrawals Zolp	0.5 mg 	48	86	5 day				
Zolpidem Triazolam Adverse Event withdrawals	0.5 mg ts: s bidem 20mg awals: Num	48 I Triazo	86	5 day				
Zolpidem Triazolam Adverse Even withdrawals Zolp total withdra	0.5 mg ts: s awals: Num 15	48 Triazo ber	86 Diam 0.5mg	5 day				
Zolpidem Triazolam Adverse Event withdrawals Zolp	0.5 mg ts: s awals: Num 15	48 Triazo ber	86 Diam 0.5mg	5 day				

chwartz, 2004	4			Subg	group:	psychiatric (inpatie	Quality	rating: F	' oor
Design:									
Study design:	RCT C	ope Para	allel	Run-in : Wash out :	NR NR		Setting: Country:	Single Ce US	nter
Sample:	Number S	/Screened /NR	0			Number Withdrawn/ 0/	Lost to follo	w-up/ Ana 0/	lyzed 16
Inclusion crite inpatient psy		e							
	ere excluded					aking a hypnotic or se / had a medical contra	0. 7		0
Subjects we	ere excluded	ol or dug	s, if they v		if they	0 11	0. 7		0
Subjects we if they were	ere excluded using alcoh	ol or dug	s, if they v ars	vere manic, or	if they	0 11	0. 7		0
Subjects we if they were Population:	ere excluded using alcoh Mean age	iol or dug: RNR yea 50% F	s, if they v ars	vere manic, or	if they	0 11	0. 7		0
Subjects we if they were Population: Intervention:	ere excluded using alcoh Mean age Gender:	iol or dug: RNR yea 50% F	s, if they v ars remale	vere manic, or Ethnicity:	if they	0 11	0. 7		0

Adverse Events:

Withdrawals: NR

Steens, 1993				Subg	roup: COPD	Qualit	Quality rating: Fair			
Design:										
Study design:	RCT	DB C	rossover	Run-in :	0 days	Setting	Multicen	ter		
				Wash out :	0 days	Country	: Canada			
Sample:	Numbe	er Screene	ed/ Eligible/	Enrolled	Number W	ithdrawn/ Lost to fo	llow-up/ An	alyzed		
		N	R/ NR/	24		0/	0/	24		

Inclusion criteria:

Males and nonpregnant females aged between 35 and 69 years with mild to moderate COPD and insomnia were recruited. Insomnia must have been present for at least 6 months and had to be associated with a sleep latency >30 minutes, sleep duration of 4-6 hours and daytime complaints associated with disturbed sleep. COPD must have been present for at least 3 years and objective inclusion criteria were, FEV1 40-80% predicted, FEV1/FVC=40-70% predicted, diffusion capacity (DL CO) >30% predicted, PaCO2=30-48mm Hg and PaO2 > 55mm Hg. Patients were required to be in stable physical health for at least 2 weeks prior to entering the study, and each gave written informed consent.

Exclusion criteria:

Patients were excluded if they had been hospitalized in the previous 4 weeks, if they had right ventricular hypertrophy on the ECG or right heart failure clinically, a hematocrit >55% or if they were on oxygen therapy. They were also excluded if any of the following applied: inability to be withdrawn from hypnotics for the required time (2 nights for triazolam, 7 nights for other short- or intermediate-acting hypnotics and 14 nights for long-acting hypnotics); positive screening for drugs, other than theophylline, know to alter sleep (e.g. benzodiazepines, barbiturates, opiates, amphetamines, cannabinoids and alcohol); medications interfering with the absorption or metabolism of benzodiazepines (e.g. cimetidine); a history suggestive of obstructive sleep apnea or restless legs syndrome/periodic movements during sleep, an adverse effect related to benzodiazepines or CNS depressants, alcohol or drug abuse.

Population:	Mean Gende	•	58.2 years 38% Female	Ethnicity:	NR
Intervention: Drug name	dosa	age	N=	Duration	
Zolpidem	5 I	mg	24	1 day	
Zolpidem	10 i	mg	24	1 day	
Triazolam	0.25 ו	mg	24	1 day	
Placebo	NA I	mg	24	1 day	

Adverse Events:

withdrawals

Zolpidem 10mg	Triazolam
er	
0	0
Number	
0	0
ents	
Zolpidem 10mg	Triazolam
per	
2	2
er	
•	er 0 Number 0 ents Zolpidem 10mg

lain, 1998								Quality	rating:	Fair
esign:										
Study design:	RCT	DB	Parall	el	Run-in :	3 days		Setting:	Multicen	ter
					Wash out :	3 days		Country:	France	
Sample:	Numb	er Scr	eened/ E	ligible/ l	Enrolled	Numbe	·Withdrawn/	Lost to follo	w-up/ Ar	nalyzed
			NR/	NR/	37		18/		NR/	37
Inclusion crite										
	male vo	luntee	rs over 1	8 years o		ng regularly treations ving out-patient				lowing criteria: am (0.25 to 0.50
										ly or susceptible to eep disorder with
non-complia	ance; shi her thar	ift worl n triazo age:	kers; pati	ents suff 5 mg/day; rs ale	ering from a pregnant of Ethnicity:	n identifiable me r breast feeding	ental disorder women; liver	or treated f	ro their sle	dy or susceptible to eep disorder with myasthenia, or
non-complia hypnotics of epilepsy. Population:	ance; shi her thar Mean	ift worl n triazo age: er:	kers; pati blam 0.25 51.9 yea	ents suff 5 mg/day; rs ale	ering from a ; pregnant of	n identifiable me r breast feeding	ental disorder	or treated f	ro their sle ory failure,	ep disorder with
non-complia hypnotics of epilepsy. Population: tervention:	ince; shi iher thar Mean Gende dosa	ift worl n triazo age: er:	kers; pati blam 0.25 51.9 yea 0% Fem	ents suff 5 mg/day; rs ale [ering from a pregnant of Ethnicity:	n identifiable me r breast feeding	ental disorder women; liver Primary	or treated f or respirato	ro their sle ry failure,	ep disorder with
non-complia hypnotics of epilepsy. Population: tervention: Drug name	ince; shi iher thar Mean Gende dosa	ift worl h triazo age: er: age mg	kers; pati blam 0.25 51.9 yea 0% Fem N=	ents suff i mg/day; rs ale 2	ering from a ; pregnant of Ethnicity: Duration	n identifiable me r breast feeding	ental disorder women; liver Primary	or treated f or respirato Outcome: sleep later	ro their sle bry failure,	ep disorder with
non-complia hypnotics of epilepsy. Population: tervention: Drug name Zolpidem	ance; shi her thar Mean Gende dosa	ift worl h triazo age: er: age mg	kers; pati blam 0.25 51.9 yea 0% Fem N= 18	ents suff i mg/day; rs ale 2	ering from a ; pregnant of Ethnicity: Duration 21 day	n identifiable me r breast feeding	ental disorder women; liver Primary	or treated f or respirato Outcome: sleep later	ro their sle bry failure, c ncy nocturnal	eep disorder with myasthenia, or
non-complia hypnotics of epilepsy. Population: tervention: Drug name Zolpidem	ance; shi her thar Mean Gende dosa	ift worl h triazo age: er: age mg	kers; pati blam 0.25 51.9 yea 0% Fem N= 18	ents suff i mg/day; rs ale 2	ering from a ; pregnant of Ethnicity: Duration 21 day	n identifiable me r breast feeding	ental disorder women; liver Primary	or treated f or respirato Outcome: sleep later number of	ro their sle bry failure, ncy nocturnal time	eep disorder with myasthenia, or
non-complia hypnotics of epilepsy. Population: tervention: Drug name Zolpidem	ance; shi her thar Mean Gende dosa	ift worl h triazo age: er: age mg	kers; pati blam 0.25 51.9 yea 0% Fem N= 18	ents suff i mg/day; rs ale 2	ering from a ; pregnant of Ethnicity: Duration 21 day	n identifiable me r breast feeding	ental disorder women; liver Primary	or treated f or respirato Outcome: sleep later number of total sleep	ro their sle bry failure, ncy nocturnal time ity	eep disorder with myasthenia, or
non-complia hypnotics of epilepsy. Population: tervention: Drug name Zolpidem	ance; shi her thar Mean Gende dosa	ift worl h triazo age: er: age mg	kers; pati blam 0.25 51.9 yea 0% Fem N= 18	ents suff i mg/day; rs ale 2	ering from a ; pregnant of Ethnicity: Duration 21 day	n identifiable me r breast feeding	ental disorder women; liver Primary	or treated f or respirato Outcome: sleep later number of total sleep sleep qual	ro their sle by failure, ncy nocturnal time ity s	eep disorder with myasthenia, or

clinical global impressio	n	
Zolpidem	Placebo	
overall no different exce	pt day 21, where zolpidem was me	re effective, p<0.007: Mean
NR	NR	P: NS
sleep questionnaire		
Zolpidem	Placebo	
daytime alertness: Mea	1	
NR	NR	P: NS
total sleep time (hr) at c	ay 7: Mean	
6.13	6.40	P: NR
total sleep time (hr) at c	ay 28: Mean	
NR	NR	P: NS
less nightmare: %		
93	less	P: <0.04

sleep diary		-
Zolpidem	Placebo	
number of awakenings: c	liary	
better	NR	P: <0.0001
anxiety: diary		
better	NR	P: <0.0003
amount of sleep: diary		
better	NR	P: <0.0001
energy: diary		
better	NR	P: <0.01

Allain, 2001								Quality rating: Fair			
Design:											
Study design:	RCT	DB	Paralle	el	Run-in :	3-7 days	Setting	: Multicen	ter		
					Wash out :	NR	Countr	y: France			
Sample:	Numbe	er Scre	ened/ E	ligible/	Enrolled	Number W	ithdrawn/ Lost to fe	ollow-up/ Ar	alyzed		
			NR/	NR/	245		NR/	NR/	245		

Inclusion criteria:

Patients of either gender (aged 25 to 64 years) with DSM-IV diagnosis of primary insomnia, characterized by sleep disturbance and problems in falling asleep or nocturnal awakenings and resulting in difficulty in performing daytime functions, were eligible for inclusion in the study.

In addition, patients were required to have a score of between 7 and 15 on the Epworth Sleepiness Scale. In order to be included in the double-blind phase of the study, patients must present insomnia as characterized by at least two of the following four criteria: sleep latency > 30 minutes, total sleep time > 3 hours and < 6 hours, number of awakenings > 3 per night and wake-time after sleep onset > 30 minutes per night.

Exclusion criteria:

. .

Patients were excluded from the study if they were pregnant, breast feeding or were of child-bearing potential and not using an adequate method of contraception, or it they had desynchronisationtype sleep-wake rhythm disorders (such as jet-lag), parasomnia (for example somnambulism), anxiety (>4 on the covi scale), symptoms of depression (>6 on the Raskin scale), acute or chronic pain resulting in insomnia, severe psychiatric disturbances, were receiving treatment with psychotropic/sedative drugs, or had a severe medical condition or known hypersensitivity to imidazopyridine. They were also excluded if their lifestyle was expected to change, if they were suspected of drug/alcohol abuse, if they presented with excessive and abnormal daytime drowsiness, or if they were liable to present with known advance sleep apnoea syndrome. Patients who had received benzodiazepines regularly for more than one month, or for more that 15 days in the month prior to inclusion, were also excluded from the study, as were patients who consumed large quantities of caffeine.

Population:	Mear Genc	n age: der:	46.1 years 77% Female	Ethnicity:	NR		
Intervention: Drug name	dos	age	N=	Duration		Primary outcome	Outcome:
Zolpidem	10	mg	124	28 day		\checkmark	sleep duration
Placebo	NA	mg	121	28 day			quality of sleep
							drowsiness during the day
							anxious during the day
							sadness during the day
							duration of daytime sleep
							sleep-onset latency
							number of nocturnal awakenings
							wake time after sleep onset

Efficacy:

sleep diary

Zolpidem	Placebo	
total sleep time (min), c	hange from baseline, all condition: Mean (SD)	
74.6 (77.7)	63.2 (69.9)	P: NS
total sleep time (min), c	hange from baseline, with pill: Mean (SD)	
82.7 (80.1)	62.8 (77.2)	P: <0.05
sleep quality (1=worse;	100=better), change from baseline: Mean (SD)	
14.1 (17.4)	20.6 (22.3)	P: 0.01
daytime drowsiness (1=	worse; 100=better), change from baseline: Mean (SD)	
-1.8 (12.6)	-5.3 (14.9)	P: 0.048

n, 2001		Quality rating: Fair
anxiety during the day (1=worse; 100=better), change from baseline: Mean (SD)	
-1.5 (16.2)	-2.9 (19.7)	P: 0.55
sadness during the day	(1=worse; 100=better), change from baseline: Mean (SD)	
-0.6 (15.4)	-2.8 (17.7)	P: 0.30
vitality in the morning (1	=worse; 100=better), change from baseline: Mean (SD)	
9.1 (16.2)	9.6 (21.3)	P: 0.83
lucidity in the morning (1=worse; 100=better), change from baseline: Mean (SD)	
2.9 (16.2)	2.3 (18.4)	P: 0.77
sleep onset latency (mi	n), change from baseline: Mean (SD)	
-23 (38.7)	-18.8 (35.4)	P: <0.05
wake time after sleep o	nset (min), change from baseline: Mean (SD)	
-32.8 (37.7)	-31.4 (37.1)	P: NR
number of nocturnal aw	vakenings, change from baseline: Mean (SD)	
-1.2 (NR)	-1.2 (NR)	P: <0.05
daytime sleep duration	(min), change from baseline: Mean (SD)	
-2.6 (19.6)	-0.9 (15.1)	P: NR
clinical global impressio	on second s	
Zolpidem	Placebo	
severity of illness- not il	l to mildly ill: Number (%)	
69 (55.6)	46 (38.7)	P: 0.002
global impression- muc	h or very much improved: Number (%)	
67 (54)	29 (24)	P: <0.0001
efficacy index- when eff): Number (%)	ficacy outweighs safety	
108 (87)	84 (71)	P: 0.0004

, 2001		Quality rating: Fair
SF-36 healthy survey		
Zolpidem	Placebo	
physical function, chan	ge from baseline: Mean (SD)	
2.5 (17.3)	2.7 (4.6)	P: NS
role limitations due to p	hysical problem, change from baseline: Mean (SD)	
7.5 (29)	4.9 (32.5)	P: NS
bodily pain, change from	m baseline: Mean (SD)	
4.7 (21)	3.7 (22.4)	P: NS
general health percepti	on, change from baseline: Mean (SD)	
3.4 (12.4)	2.5 (12.5)	P: NS
vitality, change from ba	seline: Mean (SD)	
6.5 (16.6)	5.7 (14)	P: NS
social functioning, char	nge from baseline: Mean (SD)	
6.1 (22.4)	2.8 (21.6)	P: NS
role limitations due to e	motional problems, change from baseline: Mean (SD)	
7.9 (39.1)	-0.3 (33.9)	P: NS
general mental health,	change from baseline: Mean (SD)	
5.9 (16.8)	5.1 (14.5)	P: NS

Chaudoir, 1983	6		Quality rating: Poor			
Design:						
Study design:	RCT	DB C	ossover	Run-in :	NR	Setting: Single Center
				Wash out :	NR	Country: UK
Sample:	Numbe	r Screene	d/ Eligible/	Enrolled		Number Withdrawn/ Lost to follow-up/ Analyzed
		N	R/ 30/	25		5/ 0/ 25
Inclusion crito	rio.					

Inclusion criteria:

The study was carried out in patients of both sexes aged between 35 and 65 years. The admission criterion was at least one of the following complaints--unable to fall asleep within 45 minutes, more than two nocturnal awakenings with difficulty in returning to sleep without known cause, or sleeping less than six hours.

Exclusion criteria:

The exclusion criteria were patients with depression or an anxiety state requiring therapy, mental disability, liver or kidney dysfunction, cardiovascular disease for which medication was being received or with significant symptomatology (chest pains), gastro-intestinal disease, drug addiction or consumption of alcohol which would interfere with the assessment of the drug, or history of hypersensitivity to drugs. Patients receiving medication which was likely to induce sedation, patients requiring regular analgesia for the relief of chronic pain, night-shift workers, pregnant women, nursing mothers and women of child-bearing potential and patients weighing less than 7 stone or more than 14 stone were also excluded.

	Population:	Mean age: Gender:	50 years 72% Female	Ethnicity:	NR		
Int	ervention: Drug name	dosage	N=	Duration		Primary outcome	Outcome:
	Zopiclone	7.5 mg	25	7 day			sleep latency
	Placebo	NA mg	25	7 day			number of awakenings
							sleep quality
							feeling after wakening

Efficacy:

daily sleep questionnaire

Zopiclone	Placebo	
sleep onset latency (min	n): Mean (SD)	
31.1 (4.0)	49.1 (4.5)	P: <0.001
number of night awaker	nings: Mean (SD)	
1.5 (0.2)	2.1 (0.3)	P: <0.05
sleep quality (VAS - mm	n), 0=very badly; 100=very well: Mean (SD)	
67 (4.0)	51 (3.5)	P: <0.05
feelings after wakening	(VAS - mm), 0=very badly; 100=very well: Mean (SD)	
59 (4.4)	59 (4.2)	P: NS

doir, 1983		Quality rating: Poor
weekly assessment		
Zopiclone	Placebo	
sleep onset latency (mi	n): Mean (SD)	
28.6 (3.9)	45.2 (5.5)	P: <0.05
number of night awake	nings: Mean (SD)	
1.6 (0.3)	2.1 (0.3)	P: NS
sleep quality (VAS mm)), 0=very badly; 100=very well: Mean (SD)	
63 (4.8)	48 (5.0)	P: <0.01
feelings after awakenin	g (VAS mm), 0=very badly; 100=very well: Mean (SD)	
67 (4.9)	67 (4.7)	P: NS
percentage of patients	with early awakenings (%): Mean	
44	56	P: NS
mood rating scales (mr	n) - factor I alertness: Mean (SD)	
59 (3.6)	59 (4.2)	P: NS
mood rating scales (mr	n) - factor II contentedness: Mean (SD)	
61 (4.5)	63 (3.9)	P: NS
mood rating scales (mr	n) - factor III calmness: Mean (SD)	
57 (3.7)	59 (4.7)	P: NS

Dockhorn, 1996								Quality	rating	g: Fair	
Design:											
Study design:	RCT	DB	Para	llel	Run-in :	NR		Setting:	Multio	center	
					Wash out :	NR		Country:	US		
Sample:	Numbe	r Scre	ened/	Eligible/	Enrolled		Number Withdrawn/	Lost to follo	w-up/	Analyzed	
			NR/	NR/	138		9/		2/	136	

Inclusion criteria:

Healthy patients who had experienced acute insomnia (3-9 nights) sue to a recent situational stress related to marriage, work, family, or financial matters were randomized. Insomnia was defined as a sleep duration of 4-6 h per night, a sleep latency of 30 min or more, and daytime complaints associated with disturbed sleep (thereby meeting the DSM-III-R definition of acute insomnia)

Exclusion criteria:

None of the patients had any significant psychiatric disorder, a history of insomnia within 2 months of the current episode, depression (criteria adapted from the DSM-III-R Criteria for Major Depression), recurrent thoughts of death or suicide, anxiety requiring treatment with anxiolytics, or a recent history of drug or alcohol abuse; none were regularly taking any medications that could interfere with the assessment of a hypnotics. Patients who normally slept on an unusual schedule (e.g., shift workers) and women who were lactating or at risk on pregnancy were excluded

Population:	Mean age: Gender:	32.7 years 58% Female	Ethnicity:	NR		
Intervention: Drug name	dosage	N=	Duration		Primary outcome	Outcome:
Zolpidem	10 mg	68	7-10 day		\checkmark	sleep latency
Placebo	NA mg	68	7-10 day		\checkmark	total sleep time
						ease of falling asleep
						number of awakenings
						wake time after sleep onset
						quality of sleep
						ability to concentrate in the morning
						morning sleepiness

morning questionnaire		
Zolpidem	Placebo	
sleep latency (min), day	3-10: Mean (SD)	
43.2 (6.9)	64.0 (7.7)	P: 0.001
total sleep time (min), da	ay 3-10: Mean (SD)	
422.2 (11)	389 (10.1)	P: 0.054
ease of falling asleep (0	=very easy; 100= not all easy), day 3-10: Mean (SD)	
34.8 (2.2)	45.2 (2.3)	P: 0.004
number of awakenings,	day 3-10: Mean (SD)	
0.8 (0.1)	1.2 (0.1)	P: 0.014
wake time after sleep or	nset (min), day 3-10: Mean (SD)	
18.1 (3.4)	34.6 (4.8)	P: 0.008
quality of sleep (1=excel	llent; 4=poor), day 3-10: Mean (SD)	
2.2 (0.1)	2.5 (0.01)	P: 0.007
ability to concentrate (1=	excellent; 4=poor), day 3-10: Mean (SD)	
2.3 (0.1)	2.4 (0.1)	P: 0.358

khorn, 1996		Quality rating: Fair
morning sleepiness (0=	very sleepy; 100=not at all sleepy), d	ay 3-10: Mean (SD)
53.6 (2.2)	52.1 (2.3)	P: 0.762
clinical global impressio	on scale	
Zolpidem	Placebo	
quality of sleep- excelle	nt or good: %	
78	42	P: <0.001
change in sleep- improv	ved a lot or somewhat: %	
84	48	P: <0.001
change in time to fall as	sleep: %	
81	42	P: <0.001
change in amount of sle	eep: %	
79	43	P: <0.001
strength of medication-	just right: %	
62	28	P: <0.001
change during posttrea	tment days- much or somewhat bette	r: %
75	40	P: 0.002

Dorsey, 2004 0							Quality rating: Fair			
Design:										
Study design:	RCT	DB Pa	rallel	Run-in :	6-14 days	Setting:	Multio	center		
				Wash out :	NR	Country:	US			
Sample:	Number	Screened	/ Eligible/	Enrolled	Number Withdrawn/	Lost to follo	w-up/	Analyzed		
		242	/ 141/	141	16/		3/	141		
Inclusion crite	ria:	272	, 141,	141	10,		0/	141		

Women aged 39 to 60 years were eligible to participate in the study if they had developed insomnia in temporal conjunction with menopausal symptoms. In addition, they had to have complaints of difficulty maintaining sleep or complaints of nonrestorative sleep for >6 months. Sleep maintenance difficult had to occur an average of >3 night per week and had to be accompanied by >2 nocturnal hot flashes, hot flushes, or night sweats. Participant also had to be in good mental and physical health, as determined by medical and psychiatric history, physical examination, and standard clinical laboratory tests obtained within 2 weeks of study onset.

Exclusion criteria:

Exclusion criteria included the presence of signs or symptoms of clinical depression, as ascertained by clinical interview and a Beck Depression Inventory score of > 10, or any other significant psychiatric disorder, based on DSM-IV criteria; use of any over-the-counter or prescription sleep medication within 7 days or any investigational drug within 30 days before study onset; positive urine screening test for medication that could interfere with the assessment of study medication, including benzodiazepines, barbiturates, opiates, cocaine, phenothiazines, amphetamines, and cannabinoids; a history of drug abuse/dependence or alcoholism; and a history of current symptoms of obstructive sleep apnea or periodic limb movement disorder.

Population:	Mean age: Gender:	50.8 years 100% Female	Ethnicity:	NR		
Intervention: Drug name	dosage	N=	Duration		Primary outcome	Outcome:
Zolpidem	10 mg	68	28 day			sleep latency
Placebo	NA mg	73	28 day			number of awakenings
						wake time after sleep onset
						sleep duration
						quality of sleep

patients g	lobal impressi	on rating	
	Zolpidem	Placebo	
average	summary score	e (lower score=better sleep):	
	5.53	6.71	
number	of patients with	better sleep: %	
	76.8	43.8	P: <0.001

ey, 2004		Quality rating: Fair
sleep questionnaire		
Zolpidem	Placebo	
change in sleep duratio	n (min), 4 weeks average: Mean	
56.5	20.5	P: <0.01
wake after sleep onset	(min), 4 weeks average: Mean	
29.75	52.75	P: <0.05
number of awakenings,	4 weeks average: Mean	
1.4	2	P: <0.05
sleep latency (min), 4 w	veeks average: Mean	
31.25	34.25	P: NS
sleep-related difficulty v	vith daytime functioning: Mean	
2.1	2.2	P: <0.05
quality of life: Mean		
NR	NR	P: NS

Erman, 2006								Quality rating: Fair			
Design:											
Study design:	RCT	DB	Cros	sover	Run-in :	NR	Setting:	Multic	enter		
					Wash out :	5-12 days	Country:	US			
Sample:	Numbe	r Screei	ned/	Eligible/	Enrolled	Number Withdrawn/	Lost to follo	w-up/	Analyzed		
		:	319/	205/	107	4/		0/	103		

Inclusion criteria:

Men and non-pregnant, non-lactating women between the ages of 18 and 64 years who had chronic insomnia were recruited.

All pts met the following criteria: a diagnosis of primary insomnia (DSM-IV-TR) for at least three months, a subjective sleep latency (SSL) greater than 30 min, a subjective total sleep time (sTST) of less than 6.5 h per night, and daytime complaints associated with disturbed sleep; a mean LPS > 20 min for two consecutive PSG screening nights with neither night less than 15 min; a mean wake time after sleep onset (WASO) of at least 60 min for two consecutive PSG screening nights, with neither night less than 45 min; an habitual bedtime between 8:30 p.m. and midnight; and a body weight within 20% of the ideal, according to the Metropolitan Life Tables.

Exclusion criteria:

Pts were excluded from the study if their histories included a potential medical or psychiatric condition that could have confounded the study. Excluded conditions included depression, anxiety, seizure disorders, drug addiction, sleep apnea, nocturnal myoclonus, mental retardation, a history of alcohol abuse within the past two years, tobacco use within the past 90 days, or psychotropic drug use. Other exclusionary criteria included the use of St. John's wort or melatonin, or consumption of grapefruit or grapefruit juice within three weeks prior to the study. Shift workers and patients who had flown across three or more time zones within seven days prior to screening also were excluded, as were those with a history of hypersensitivity to ramelteon or related compounds.

Population:	Mean a Gende		37.7 years 64% Female	Ethnicity:	54.7% Cauca	sian; 22.6 H	ispanic; 21.7% Africa- American; 0.9% Asian
Intervention: Drug name	dosa	ge	N=	Duration		Primary outcome	Outcome:
Ramelteon	4 r	ng	103	2 day		\checkmark	sleep latency
Ramelteon	8 r	ng	103	2 day			sleep duration
Ramelteon	16 r	ng	103	2 day			sleep quality
Ramelteon	32 r	ng	103	2 day			wake after sleep onset
Placebo	NA r	ng	103	2 day			

р	lysomnography				
	Ramelteon 4mg	Ramelteon 8mg	Ramelteon 16mg	Ramelteon 32mg	Placebo
	PSG latency to persister	nt sleep, min: Numb	per (p vs placebo)		
	24.0 (<0.001)	24.3 (<0.001)	24.0 (<0.001)	22.9 (<0.001)	37.7 (NA)
	PSG total sleep time, mi	in: Number (p vs pla	acebo)		
	411.0 (<0.05)	412.9 (<0.01)	411.2 (<0.05)	418.2 (<0.001)	400.2 (NA)
	PSG wake after sleep or	nset (WASO), min:	Number (p vs placeb	o)	
	48.8 (NS)	48.3 (NS)	48.3 (NS)	43.0 (NS)	45.5 (NA)

ın, 2006			Q	uality rating: Fair	
post-sleep questionnaire	9				
Ramelteon 4mg	Ramelteon 8mg	Ramelteon 16mg	Ramelteon 32mg	Placebo	
Subjective sleep latency	y, min: Number (p v	s placebo)			
50.9 (NS)	46.7 (NS)	43.9 (<0.05)	46.5 (NS)	57.0 (NA)	
Subjective total sleep ti	me, min: Number (p	vs placebo)			
364.1 (NS)	370.4 (NS)	370.9 (NS)	372.8 (NS)	360.6 (NA)	
Subjective sleep quality	: Number (p vs plac	ebo)			
3.6 (NS)	3.7 (NS)	3.7 (NS)	3.7 (NS)	3.8 (NA)	
next day, level of alertn	ess: Number (p vs p	olacebo)			
3.5 (NS)	3.6 (NS)	3.5 (NS)	3.6 (NS)	3.6 (NA)	
next day, ability to conc	entrate: Number (p	vs placebo)			
3.5 (NS)	3.5 (NS)	3.5 (NS)	3.6 (NS)	3.6 (NA)	

oldenberg, 19	994							(Quality	rating	: Po	or	
esign:													
Study design:	RCT	DB	Parallel	Rur	-in :	NR		5	Setting:	Multic	enter		
				Was	sh out :	NR		(Country:	UK, Fi	ance		
Sample:	Numbe	Scree	ned/ Elig	gible/ Enro	led		Number Withd	rawn/ L	ost to follo	w-up/	Analyz	ed	
			NR/	NR/ 5	524			NR/		NR/	2	158	
Inclusion crite	ria:												
onset latence							less than 6 hou			st 2 nigi	ntiy aw	akings;	; sieep
Exclusion crite The followin	eria: g exclusi	on crite	ria applie	ed: depress	ion or ot	her ps	ychiatric probler	ms; alcol	hol or drug				rrent
Exclusion crite The followin medication (bereaveme and those p unable to co	eria: g exclusi with CNS nt, divorc erforming omplete th	on crite effects e, uner skilled ie ques	ria applie ; history o nploymer tasks, sh tionnaire	ed: depress of allergy; a nt, etc.) with nift work or or who we	on or ot cute or o nin the p travelling re planni	her ps chronic reviou g frequ ing to g		ms; alco g sleep; ancy or r e also e	hol or drug important isk or preg xcluded fro	negativ nancy. om the s	e life e Nursir study,	events ng moth	iers,
Exclusion crite The followin medication (bereaveme and those p	g exclusi with CNS nt, divorc erforming mplete th Mean a	on crite effects e, uner skilled ie ques ge: Ni	ria applie ; history o nploymer tasks, sh tionnaire R years	ed: depress of allergy; a nt, etc.) with nift work or or who we	on or ot cute or o nin the p travelling	her ps chronic reviou g frequ ing to g	ychiatric probler c illness affectin s month; pregna uently by air wer	ms; alco g sleep; ancy or r e also e	hol or drug important isk or preg xcluded fro	negativ nancy. om the s	e life e Nursir study,	events ng moth	iers,
Exclusion crite The followin medication (bereaveme and those p unable to co	eria: g exclusi with CNS nt, divorc erforming omplete th	on crite effects e, uner skilled ie ques ge: Ni	ria applie ; history o nploymer tasks, sh tionnaire	ed: depress of allergy; a nt, etc.) with nift work or or who we	on or ot cute or o nin the p travelling re planni	her ps chronic reviou g frequ ing to g	ychiatric probler c illness affectin s month; pregna uently by air wer go on holiday wi	ms; alcol ig sleep; ancy or r re also e ithin the	hol or drug important isk or preg xcluded fro	negativ nancy. om the s	e life e Nursir study,	events ng moth	iers,
Exclusion crite The followin medication (bereaveme and those p unable to co Population:	g exclusi with CNS nt, divorc erforming mplete th Mean a	on crite effects e, uner skilled ie ques ge: Ni : %	ria applie ; history o nploymer tasks, sh tionnaire R years	ed: depress of allergy; a nt, etc.) with nift work or or who we	ion or ot cute or o hin the p travelling re planni hnicity:	her ps chronic reviou g frequ ing to g	ychiatric probler c illness affectin s month; pregna uently by air wer go on holiday wi Prin	ms; alcol ig sleep; ancy or r re also e ithin the nary	hol or drug important isk or preg xcluded fro	negativ mancy. om the s he trial.	e life e Nursir study,	events ng moth	iers,
Exclusion crite The followin (bereaveme and those p unable to cc Population:	g exclusi with CNS nt, divorc erforming mplete th Mean a Gender	on crite effects e, uner skilled e ques ge: Ni : % je I	ria applie ; history o nploymer tasks, sh tionnaire R years Female	ed: depress of allergy; a nt, etc.) with ift work or or who we Et	ion or ot cute or in the p travelling re planni hnicity:	her ps chronic reviou g frequ ing to g	ychiatric probler c illness affectin s month; pregna uently by air wer go on holiday wi Prin	ms; alcol g sleep; ancy or r re also e ithin the nary come	hol or drug important isk or preg xcluded fro period of t	negativ nancy. om the s he trial.	e life e Nursir study,	events ng moth	iers,
Exclusion crite The followin (bereaveme and those p unable to cc Population: ntervention: Drug name	g exclusi with CNS nt, divorc erforming omplete th Mean a Gender dosag	on crite effects e, uner skilled ie ques ge: Ni : % je I g 2	ria applie ; history o nploymer tasks, sł tionnaire R years Female N=	ed: depress of allergy; a nt, etc.) with iff work or or who we Et Dura	ion or ot cute or o in the p travelling re planni hnicity: tion	her ps chronic reviou g frequ ing to g	ychiatric probler c illness affectin s month; pregna uently by air wer go on holiday wi Prin	ms; alcoi g sleep; ancy or r re also e ithin the nary come	hol or drug important isk or preg xcluded fro period of t Dutcome:	hegativ nancy. om the s he trial.	e life e Nursir study,	events ng moth	iers,
Exclusion crite The followin medication of (bereaveme and those p unable to co Population: ntervention: Drug name Zopiclone	ria: g exclusi with CNS nt, divorce erforming omplete th Mean a Genden dosag	on crite effects e, uner skilled ie ques ge: Ni : % je I g 2	ria applie ; history o nploymer tasks, sh tionnaire R years Female N= 31	ed: depress of allergy; a nt, etc.) with hift work or or who we Et Dura 48 da	ion or ot cute or o in the p travelling re planni hnicity: tion	her ps chronic reviou g frequ ing to g	ychiatric probler c illness affectin s month; pregna uently by air wer go on holiday wi Prin	ms; alcoi g sleep; ancy or r e also e ithin the nary come	hol or drug important isk or preg xcluded fro period of t Dutcome: quality of s	negativ nancy. om the s he trial.	e life e Nursir study,	events ng moth as were	ers, e those
Exclusion crite The followin medication of (bereaveme and those p unable to co Population: ntervention: Drug name Zopiclone	ria: g exclusi with CNS nt, divorce erforming omplete th Mean a Genden dosag	on crite effects e, uner skilled ie ques ge: Ni : % je I g 2	ria applie ; history o nploymer tasks, sh tionnaire R years Female N= 31	ed: depress of allergy; a nt, etc.) with hift work or or who we Et Dura 48 da	ion or ot cute or o in the p travelling re planni hnicity: tion	her ps chronic reviou g frequ ing to g	ychiatric probler c illness affectin s month; pregna Jently by air wer go on holiday wi	ms; alcol g sleep; ancy or r re also e ithin the nary come (hol or drug important isk or preg xcluded fro period of t Dutcome: quality of s	leep vaking u vell beir	e life e Nursir study,	ng the o	ers, e those

Sleep efficiency at endpoint	
Zoniclone	DI

Zopiclone	Placebo	
quality of sleep: Mean (SD)	
1.9 (1.1)	1.3 (1.2)	P: <0.0001
quality of waking up: Me	ean (SD)	
1.5 (1.2)	1.0 (1.1)	P: <0.0001
feeling of well being dur	ring the day: Mean (SD)	
1.3 (1.1)	0.8 (1.1)	P: <0.0001
physician's overall evalu	uation: average, good or excellent: Number (%)	
187 (92.5)	125 (66.9)	P: <0.0001

lenberg, 1994		Quality rating: Poor
Quality of life - change fr	om baseline	
Zopiclone	Placebo	
PGWBI: Score		
11.8	9.1	P: NS
SEQ: Score		
14.6	2.7	P: <0.0001
Activity: Score		
20	9.9	P: <0.0001
Social: Score		
13.1	5.7	P: <0.01
Profession: Score		
23.3	12.9	P: <0.01
Global: Score		
10.8	5.7	P: NS

dner, 2000							Quality r	aung.	T un	
esign:										
Study design:	RCT	DB	Parallel	Run-in :	7 days		Setting:	Multicer	nter	
				Wash out :	7 days		Country:	Europe		
Sample:	Numl	ber Sci	reened/ Eligibl		Number		Lost to follow	•		
			NR/ NI	R/ 437		22/		NR/	422	
months' dura system (CN American Ps	valuate ation. I S) diso sychiat	nclusic rder. F ric Ass	on to this study Primary insomni sociation, 1994)		dent on the abse eria in the Diagn zed by a sleep la	ence of any s ostic and Sta	significant psy atistical Manu	ychiatric Jal, 4th e		
Exclusion crite			of . 50 on the	Zuna Antistica	D					
				Zung Anxiety or		lies were not	t enrolled.			
Population:			72.5 years	Ethnicity:	NR					
tervention:	Geno	ier:	% Female							
Drug name	dos	age	N=	Duration		Primary outcome	Outcome:			
Zaleplon	5	mg	139	14 day			sleep latend	су		
Zaleplon	10	mg	145	14 day			sleep durati	ion		
Placebo	NA	mg	138	14 day			number of a	awakenir	ngs	
							sleep qualit	v		
ficacy: sleep quest Zal	t ionna i eplon (Zaleplon 10)mg Plac	cebo					
sleep quest Zal	eplon { e sleep	5mg latenc	y (min), week 1	I: Median (p vs p	olacebo)					
sleep quest Zal subjective 43	eplon { e sleep 8 (<0.00	5mg latenc 01)	y (min), week 1 40 (<0.00	1: Median (p vs p 1) 60 (olacebo) (NA)					
sleep quest Zal subjective 43 subjective	eplon { e sleep 3 (<0.00 e sleep	5mg latenc 01) latenc	y (min), week 1 40 (<0.00 y (min), week 2	1: Median (p vs p 1) 60 (2: Median (p vs p	olacebo) (NA) olacebo)					
sleep quest Zal subjective 43 subjective 40	eplon { e sleep 3 (<0.00 e sleep) (<0.00	5mg latenc 01) latenc 01)	y (min), week 1 40 (<0.00 y (min), week 2 37 (<0.00	1: Median (p vs p 1) 60 (2: Median (p vs p 1) 50 (olacebo) (NA) olacebo) (NA)					
sleep quest Zal subjective 43 subjective 40 subjective	eplon { e sleep 3 (<0.00 e sleep 0 (<0.00 e total s	5mg latenc 01) latenc 01) sleep ti	y (min), week 1 40 (<0.00 y (min), week 2 37 (<0.00 me (min), week	1: Median (p vs p 1) 60 (2: Median (p vs p 1) 50 (k 1: Median (p vs	olacebo) (NA) olacebo) (NA) s placebo)					
sleep quest Zal subjective 43 subjective 40 subjective	eplon { e sleep 3 (<0.00 e sleep) (<0.00	5mg latenc 01) latenc 01) sleep ti	y (min), week 1 40 (<0.00 y (min), week 2 37 (<0.00	1: Median (p vs p 1) 60 (2: Median (p vs p 1) 50 (k 1: Median (p vs	olacebo) (NA) olacebo) (NA)					
sleep quest Zal subjective 43 subjective 40 subjective	eplon { e sleep 3 (<0.00 e sleep 0 (<0.00 e total s 342 (NS	5mg latenc 01) latenc 01) sleep ti S)	y (min), week 1 40 (<0.00 y (min), week 2 37 (<0.00 ime (min), week 342.9 (<0.0	1: Median (p vs p 1) 60 (2: Median (p vs p 1) 50 (k 1: Median (p vs	olacebo) (NA) olacebo) (NA) s placebo) I (NA)					
sleep quest Zal subjective 43 subjective 40 subjective 3 subjective	eplon { e sleep 3 (<0.00 e sleep 0 (<0.00 e total s 342 (NS	5mg latenc 01) latenc 01) sleep ti Sleep ti	y (min), week 1 40 (<0.00 y (min), week 2 37 (<0.00 ime (min), week 342.9 (<0.0	1: Median (p vs p 1) 60 (2: Median (p vs p 1) 50 (k 1: Median (p vs 05) 346.1 k 2: Median (p vs	olacebo) (NA) olacebo) (NA) s placebo) I (NA)					
sleep quest Zal subjective 43 subjective 40 subjective 3 subjective 34	eplon { > sleep 3 (<0.00 > sleep 0 (<0.00 > total s 342 (NS > total s 51.7 (N	5mg latenc 01) latenc 01) sleep ti Sleep ti IS)	y (min), week 1 40 (<0.00 y (min), week 2 37 (<0.00 ime (min), week 342.9 (<0.0 ime (min), week 351.4 (NS	1: Median (p vs p 1) 60 (2: Median (p vs p 1) 50 (k 1: Median (p vs 05) 346.1 k 2: Median (p vs	olacebo) (NA) olacebo) (NA) s placebo) I (NA) s placebo) Ø (NA)					
sleep quest Zal subjective 43 subjective 40 subjective 33 subjective 34 subjective	eplon { > sleep 3 (<0.00 > sleep 0 (<0.00 > total s 342 (NS > total s 51.7 (N	5mg latenc 01) latenc 01) sleep ti S) sleep ti IS)	y (min), week 1 40 (<0.00 y (min), week 2 37 (<0.00 ime (min), week 342.9 (<0.0 ime (min), week 351.4 (NS	I: Median (p vs p 1) 60 (2: Median (p vs p 1) 50 (k 1: Median (p vs 05) 346.1 k 2: Median (p vs S) 342.9 ek 1: Median (p	olacebo) (NA) olacebo) (NA) s placebo) I (NA) s placebo) Ø (NA)					
sleep quest Zal subjective 43 subjective 40 subjective 31 subjective	eplon { e sleep 3 (<0.00 e sleep 0 (<0.00 e total s 342 (NS 51.7 (N e numb 2 (NS)	5mg latenc 01) latenc 01) sleep ti S) sleep ti IS) per of a	y (min), week 1 40 (<0.00 y (min), week 2 37 (<0.00 ime (min), week 342.9 (<0.0 ime (min), week 351.4 (NS wakenings, we 2 (<0.05	1: Median (p vs p 1) 60 (2: Median (p vs p 1) 50 (k 1: Median (p vs p 05) 346.1 k 2: Median (p vs p S) 342.9 ek 1: Median (p (p) 2 (f	olacebo) (NA) olacebo) (NA) s placebo) I (NA) s placebo) Ø (NA) vs placebo) NA)					
sleep quest Zal subjective 43 subjective 34 subjective 34 subjective 34 subjective	eplon { e sleep 3 (<0.00 e sleep 0 (<0.00 e total s 342 (NS 51.7 (N e numb 2 (NS)	5mg latenc 01) latenc 01) sleep ti S) sleep ti IS) ver of a	y (min), week 1 40 (<0.00 y (min), week 2 37 (<0.00 ime (min), week 342.9 (<0.0 ime (min), week 351.4 (NS wakenings, we 2 (<0.05	1: Median (p vs p 1) 60 (2: Median (p vs p 1) 50 (k 1: Median (p vs 05) 346.1 k 2: Median (p vs S) 342.9 ek 1: Median (p (p) 2 (f ek 2: Median (p (p) 2 (f	olacebo) (NA) olacebo) (NA) s placebo) I (NA) s placebo) Ø (NA) vs placebo) NA)					
sleep quest Zal subjective 43 subjective 40 subjective 33 subjective subjective	eplon { e sleep 3 (<0.00 e sleep 0 (<0.00 e total s 342 (NS 51.7 (N e numb 2 (NS) e numb 2 (NS)	5mg latenc 01) latenc 01) sleep ti S) sleep ti IS) ber of a ber of a	y (min), week 1 40 (<0.00 y (min), week 2 37 (<0.00 me (min), week 342.9 (<0.0 me (min), week 351.4 (NS wakenings, we 2 (<0.05 wakenings, we 1 (NS)	1: Median (p vs p 1) 60 (2: Median (p vs p 1) 50 (2: Median (p vs p 1) 50 (k 1: Median (p vs 05) 346.1 k 2: Median (p vs 6) 342.9 ek 1: Median (p ') 2 (f ek 2: Median (p 2 (f	olacebo) (NA) olacebo) (NA) s placebo) I (NA) s placebo) O (NA) vs placebo) NA) vs placebo) NA)					
sleep quest Zal subjective 43 subjective 34 subjective 34 subjective subjective subjective	eplon { e sleep 3 (<0.00 e sleep 0 (<0.00 e total s 342 (NS 51.7 (N e numb 2 (NS) e numb 2 (NS)	5mg latenc 01) latenc 01) sleep ti S) sleep ti IS) per of a per of a) quality	y (min), week 1 40 (<0.00 y (min), week 2 37 (<0.00 me (min), week 342.9 (<0.0 me (min), week 351.4 (NS wakenings, we 2 (<0.05 wakenings, we 1 (NS)	1: Median (p vs p 1) 60 (2: Median (p vs p 1) 50 (k 1: Median (p vs 05) 346.1 k 2: Median (p vs S) 342.9 ek 1: Median (p) 2 (f ek 2: Median (p 2 (f e). 1=excellent; 7	olacebo) (NA) olacebo) (NA) s placebo) I (NA) s placebo) O (NA) vs placebo) NA) vs placebo) NA)					
sleep quest Zal Subjective 43 Subjective 34 Subjective 34 Subjective Subjective 34 Subjective 34 Subjective 34 Subjective	eplon { s sleep 3 (<0.00 s sleep 0 (<0.00 s total s 342 (NS) s total s 51.7 (N numb 2 (NS) s numb 2 (NS) s sleep 8 (<0.00 (<0.00 (<0.00 (<0.00 (<0.00 (<0.00 (<0.00 (<0.00 (<0.00 (<0.00 (<0.00 (<0.00 (<0.00 (<0.00 (<0.00 (<0.00 (<0.00 (<0.00 (<0.00 (<0.00 (<0.00 (<0.00 (<0.00 (<0.00 (<0.00 (<0.00 (<0.00 (<0.00 (<0.00 (<0.00 (<0.00 (<0.00 (<0.00 (<0.00 (<0.00 (<0.00 (<0.00 (<0.00 (<0.00 (<0.00 (<0.00 (<0.00 (<0.00 (<0.00 (<0.00 (<0.00 (<0.00 (<0.00 (<0.00 (<0.00 (<0.00 (<0.00 (<0.00 (<0.00 (<0.00 (<0.00 (<0.00 (<0.00 (<0.00 (<0.00 (<0.00 (<0.00 (<0.00 (<0.00 (<0.00 (<0.00 (<0.00 (<0.00 (<0.00 (<0.00 (<0.00 (<0.00 (<0.00 (<0.00 (<0.00 (<0.00 (<0.00 (<0.00 (<0.00 (<0.00 (<0.00 (<0.00 (<0.00 (<0.00 (<0.00 (<0.00 (<0.00 (<0.00 (<0.00 (<0.00 (<0.00 (<0.00 (<0.00 (<0.00 (<0.00 (<0.00 (<0.00 (<0.00 (<0.00 (<0.00 (<0.00 (<0.00 (<0.00 (<0.00 (<0.00 (<0.00 (<0.00 (<0.00 (<0.00 (<0.00 (<0.00 (<0.00) (<0.00 (<0.00 (<0.00) (<0.00 (<0.00) (<0.00) (<0.00) (<0.00) (<0.00) (<0.00) (<0.00) (<0.00) (<0.00) (<0.00) (<0.00) (<0.00) (<0.00) (<0.00) (<0.00) (<0.00) (<0.00) (<0.00) (<0.00) (<0.00) (<0.00) (<0.00) (<0.00) (<0.00) (<0.00) (<0.00) (<0.00) (<0.00) (<0.00) (<0.00) (<0.00) (<0.00) (<0.00) (<0.00) (<0.00) (<0.00) (<0.00) (<0.00) (<0.00) (<0.00) (<0.00) (<0.00) (<0.00) (<0.00) (<0.00) (<0.00) (<0.00) (<0.00) (<0.00) (<0.00) (<0.00) (<0.00) (<0.00) (<0.00) (<0.00) (<0.00) (<0.00) (<0.00) (<0.00) (<0.00) (<0.00) (<0.00) (<0.00) (<0.00) (<0.00) (<0.00) (<0.00) (<0.00) (<0.00) (<0.00) (<0.00) (<0.00) (<0.00) (<0.00) (<0.00) (<0.00) (<0.00) (<0.00) (<0.00) (<0.00) (<0.00) (<0.00) (<0.00) (<0.00) (<0.00) (<0.00) (<0.00) (<0.00) (<0.00) (<0.00) (<0.00) (<0.00) (<0.00) (<0.00) (<0.00) (<0.00) (<0.00) (<0.00) (<0.00) (<0.00) (<0.00) (<0.00) (<0.00) (<0.00) (<0.00) (<0.00) (<0.00) (<0.00) (<0.00) (<0.0)	5mg latenc 01) latenc 01) sleep ti S) sleep ti IS) ver of a) ver of a) quality 01)	y (min), week 1 40 (<0.00 y (min), week 2 37 (<0.00 me (min), week 342.9 (<0.0 me (min), week 351.4 (NS wakenings, we 2 (<0.05 wakenings, we 1 (NS) y, week 1 (scorr 3.8 (<0.0	1: Median (p vs p 1) 60 (2: Median (p vs p 1) 50 (k 1: Median (p vs 05) 346.1 k 2: Median (p vs 6) 342.9 ek 1: Median (p vs 6) 2 (f ek 2: Median (p 1) 2 (f e). 1=excellent; 7 1) 3.9 (f	olacebo) (NA) olacebo) (NA) s placebo) I (NA) s placebo) O (NA) vs placebo) NA) vs placebo) NA) 7=extremely poo (NA)	pr: Mean (p v	/s placebo)			
sleep quest Zal Subjective 43 Subjective 34 Subjective 34 Subjective Subjective 34 Subjective 34 Subjective 35 Subjective	eplon { sleep (<0.00 sleep (<0.00 total s 42 (NS total s 51.7 (N numb 2 (NS) sleep 8 (<0.0 sleep 8 (<0.0 sleep 8 (<0.0 sleep	5mg latenc 01) latenc 01) sleep ti S) sleep ti S) ver of a ver of a ver of a ver of a ver of a	y (min), week 1 40 (<0.00 y (min), week 2 37 (<0.00 me (min), week 342.9 (<0.0 me (min), week 351.4 (NS wakenings, we 2 (<0.05 wakenings, we 1 (NS) y, week 1 (scorr 3.8 (<0.0	I: Median (p vs p 1) 60 (2: Median (p vs p 1) 50 (k 1: Median (p vs 05) 346.1 k 2: Median (p vs S) 342.9 ek 1: Median (p) 2 (f ek 2: Median (p 2 (f e). 1=excellent; 7 1) 3.9 (e). 1=excellent; 7	placebo) (NA) placebo) (NA) s placebo) I (NA) s placebo) Ø (NA) vs placebo) NA) vs placebo) NA) 7=extremely poo (NA) 7=extremely poo	pr: Mean (p v	/s placebo)			
sleep quest Zal subjective 43 subjective 34 subjective 34 subjective 34 subjective subjective 3. subjective 3. subjective 3.	eplon { sleep 3 (<0.00 sleep 0 (<0.00 total s 342 (NS) total s 51.7 (N numb 2 (NS) sleep 8 (<0.0 sleep 8 (<0.0 sleep 7 (<0.0	5mg latenc 01) latenc 01) sleep ti S) sleep ti IS) eer of a) eer of a) quality 01) quality 05)	y (min), week 1 40 (<0.00 y (min), week 2 37 (<0.00 me (min), week 342.9 (<0.0 me (min), week 351.4 (NS wakenings, we 2 (<0.05 wakenings, we 1 (NS) y, week 1 (scorr 3.8 (<0.0 y, week 2 (scorr 3.7 (<0.05	1: Median (p vs p 1) 60 (2: Median (p vs p 1) 50 (2: Median (p vs p 1) 50 (k 1: Median (p vs 05) 346.1 k 2: Median (p vs 6) 342.9 ek 1: Median (p f) 2 (f ek 2: Median (p f 2 (f e). 1=excellent; 7 1) 3.9 (e). 1=excellent; 7 5) 3.8 (placebo) (NA) placebo) (NA) s placebo) I (NA) s placebo) O (NA) vs placebo) NA) vs placebo) NA) 7=extremely poo (NA) 7=extremely poo (NA)	pr: Mean (p v pr: Mean (p v	/s placebo)			
sleep quest Zal Subjective 43 Subjective 34 Subjective 34 Subjective Subjective 35 Subjective 36 Subjective 37 Subjective 38 Subjective 30 Subjective	eplon { sleep (<0.00 sleep (<0.00 total s 42 (NS total s 51.7 (N numb 2 (NS) sleep 8 (<0.0 sleep 7 (<0.0 sleep 7 (<0.0	5mg latenc 01) latenc 01) sleep ti S) eer of a per of a per of a) quality 01) quality 05)	y (min), week 1 40 (<0.00 y (min), week 2 37 (<0.00 ime (min), week 342.9 (<0.0 ime (min), week 351.4 (NS wakenings, we 2 (<0.05 wakenings, we 1 (NS) y, week 1 (score 3.8 (<0.0 y, week 2 (score 3.7 (<0.05 y, improvement	1: Median (p vs p 1) 60 (2: Median (p vs p 1) 50 (2: Median (p vs p 1) 50 (k 1: Median (p vs (b) 346.1 k 2: Median (p vs (c) 342.9 ek 1: Median (p vs (c) 2 (f (c) 2 (f (c) 2 (f (c) 2 (f (c) 1 = excellent; 7 (c) 1 = excellent; 7 (c) 1 = excellent; 7 (c) 3.9 (c) (c) 1 = excellent; 7 (c) 3.8 (c) (c) 1 = excellent; 7	placebo) (NA) placebo) (NA) s placebo) I (NA) s placebo) Ø (NA) vs placebo) NA) vs placebo) NA) 7=extremely poo (NA) 7=extremely poo (NA) 7=extremely poo (NA)	pr: Mean (p v pr: Mean (p v	/s placebo)			
sleep quest Zal subjective 43 subjective 34 subjective 34 subjective 34 subjective 34 subjective 35 subjective 30 subjective 31 subjective 32 subjective 33 subjective 33 subjective	eplon { sleep 3 (<0.00 sleep 0 (<0.00 total s 342 (NS) 2 (NS) 2 (NS) 2 (NS) 2 (NS) 3 sleep 8 (<0.0 2 (NS) 2 (NS)	5mg latenc 01) latenc 01) sleep ti S) sleep ti IS) ber of a) er of a) quality 01) quality 5)	y (min), week 1 40 (<0.00 y (min), week 2 37 (<0.00 me (min), week 342.9 (<0.0 me (min), week 351.4 (NS wakenings, we 2 (<0.05 wakenings, we 1 (NS) y, week 1 (scorr 3.8 (<0.0 y, week 2 (scorr 3.7 (<0.0 y, improvement 55 (<0.000	1: Median (p vs p 1) 60 (2: Median (p vs p 1) 50 (2: Median (p vs p 1) 50 (k 1: Median (p vs (b) 346.1 k 2: Median (p vs (c) 342.9 ek 1: Median (p vs (c) 2 (f (c) 2 (f (c) 2 (f (c) 2 (f (c) 1 = excellent; 7 (c) 1 = excellent; 7 (c) 1 = excellent; 7 (c) 3.9 (c) (c) 1 = excellent; 7 (c) 3.8 (c) (c) 1 = excellent; 7	olacebo) (NA) olacebo) (NA) s placebo) I (NA) s placebo) ∂ (NA) vs placebo) NA) vs placebo) NA) 7=extremely poo (NA) 7=extremely poo (NA) 7=extremely poo (NA)	or: Mean (p v or: Mean (p v s placebo)	/s placebo)			

errmann, 199	3						Quality	rating: Poor
esign:								
Study design:	RCT	DB	Parallel	Run-in : Wash out :	7 days 7 days		Setting: Country:	Single Center France
Sample:	Num	ber Sc	reened/ Eligible NR/ 25		Nur	//mber Withdrawn /NR	Lost to follo	w-up/ Analyzed NR/ 21
Inclusion crite	ria:							
								ria: (i) sleep onset latency of awakenings of at least 5 min
testing and	a were on urin	e drug	screening for a	mphetamines, c	annabinoid	mental disorders, ds, morphine deriv , or shift workers	vatives, barb	
Population:	Mear	age:	NR years	Ethnicity:	NR			
	Genc		43% Female	,				
Drug name	dos	age	N=	Duration		Primary outcome	Outcome:	
Zolpidem	10	mg	11	14 day			sleep effici	iency
Placebo	NA	mg	10	14 day			sleep later	су
							total sleep	time
							number of	awakenings
							wake after	sleep onset
ficacy: polysomno Z	graphy Zolpide		Placebo					
sleep effic	ciency	(%), da	ay 21 treatment:	Mean (SD)				
	86.2 (2)	78.3 (5)					P: <0.05
total sleep	p time ((min), (day 21 treatmen	t: Mean (SD)				
3	81.3 (1	0)	360.3 (23))				P: NS
sleep ons	et later	ncy (m	in), day 21 treat	ment: Mean (SI	D)			
	28 (7)		41.7 (15)					P: NS
time awal	ke (min), day	21 treatment: M	ean (SD)				
	34.7 (7)	60 (12)					P: NS
sleep quest	tionnai	re						
	Zolpide		Placebo					
sleep ons	set later	ncy (m	in), day 15-21 tr	eatment: Mean	(SD)			
2	40.5 (10	D)	72.8 (10)					P: <0.05
total sleep	p time ((min), (day 15-21 treatn	nent: Mean (SD)			
	72.7 (1		327.4 (22)					P: NS
no. of awa	akening	gs, dav	/ 15-21 treatmer	nt: Mean (SD)				
				(-)				

1.8 (0.4)

nulti-data (multi-datanulti-data (multi-data

2.3 (0.4)

calm/restless, fresh/fatigued, relaxed/anxious, lying down during the day: Mean (SD)

P: NS

P: NS

	95							Quality	rating:	I all
sign:										
Study design: Sample:		DE ber Sc	3 Parallel creened/ Eligibl	Run-in : Wash out : e/ Enrolled	NR NR	Number W	/ithdrawn/	Setting: Country: Lost to foll		
			NR/ N	R/ 458			NR/		NR/	458
duration les	ed betw s than (6 hour		suffering from at east 2 nightly aw						
	or othe Iness a	ffectin		s, alcohol or sub ant negative life e						
Population:	Mear	n age:	42.9 years	Ethnicity:	NR					
onvontion	Genc	der:	0% Female							
ervention: Drug name	dos	sage	N=	Duration			Primary outcome	Outcome	:	
Zopiclone	7.5	mg	231	48 day		-		quality of	sleep	
Placebo	NA	mg	227	42 day				quality of	waking up)
								daytime fe	eeling of w	vell being
questionna 2	iire Zolpide	m	Placebo)						
2	Zolpide			x (PGWBI), chan	ge fro	m baseline	, day 14: N	lean		P: NS
psycholog	Zolpider gical ge 11.8 aluation	eneral	well-being inde 9.1 tionnaire (SEQ)		-		-	1ean		
psycholog	Zolpide gical ge 11.8	eneral	well-being inde 9.1	x (PGWBI), chan	-		-	lean		P: NS P: <0.0001
psycholog sleep eva	Zolpider gical ge 11.8 aluation 14.6 thange	eneral n quest	well-being inde 9.1 tionnaire (SEQ) 2.7 paseline, day 14	x (PGWBI), chan , change from ba	-		-	lean		P: <0.0001
psycholog sleep eva activity, c	Zolpide gical ge 11.8 aluation 14.6 change 20	eneral quest	well-being inde 9.1 tionnaire (SEQ) 2.7 paseline, day 14 9.9	x (PGWBI), chan , change from ba I: Mean	-		-	lean		
psycholog sleep eva activity, c	Zolpider gical ge 11.8 aluation 14.6 thange 20 hange fr	eneral quest	well-being inde 9.1 tionnaire (SEQ) 2.7 baseline, day 14 9.9 aseline, day 14:	x (PGWBI), chan , change from ba I: Mean	-		-	lean		P: <0.0001 P: <0.0001
z psycholog sleep eva activity, c social, ch	Zolpider gical ge 11.8 aluation 14.6 hange 20 hange fr 13.4	eneral quest from b rom ba	well-being inde 9.1 tionnaire (SEQ) 2.7 baseline, day 14 9.9 aseline, day 14: 5.7	x (PGWBI), chan , change from ba I: Mean Mean	-		-	lean		P: <0.0001
z psycholog sleep eva activity, c social, ch	Zolpider gical ge 11.8 aluation 14.6 change 20 nange fr 13.4 n, chan	eneral quest from b rom ba	well-being inde 9.1 tionnaire (SEQ) 2.7 baseline, day 14 9.9 aseline, day 14: 5.7 om baseline, day	x (PGWBI), chan , change from ba I: Mean Mean	-		-	lean		P: <0.0001 P: <0.0001 P: <0.01
z psycholog sleep eva activity, c social, ch professio	Zolpider gical ge 11.8 aluation 14.6 thange 20 nange fr 13.4 n, chan 23.3	eneral quest from b rom ba	well-being inde 9.1 tionnaire (SEQ) 2.7 baseline, day 14 5.7 bm baseline, day 12.9	x (PGWBI), chan , change from ba I: Mean Mean y 14: Mean	-		-	lean		P: <0.0001 P: <0.0001
z psycholog sleep eva activity, c social, ch professio	Zolpider gical ge 11.8 aluation 14.6 thange 20 nange fr 13.4 n, chan 23.3	eneral quest from b rom ba	well-being inde 9.1 tionnaire (SEQ) 2.7 baseline, day 14 9.9 aseline, day 14: 5.7 om baseline, day	x (PGWBI), chan , change from ba I: Mean Mean y 14: Mean	-		-	lean		P: <0.0001 P: <0.0001 P: <0.01
z psycholog sleep eva activity, c social, ch professio global, ch	Zolpider gical ge 11.8 aluation 14.6 thange 20 nange fr 13.4 n, chan 23.3 nange fi 10.8	eneral quest from b rom ba	well-being inde 9.1 tionnaire (SEQ) 2.7 baseline, day 14 5.7 om baseline, day 12.9 aseline, day 14 5.7	x (PGWBI), chan , change from ba I: Mean Mean y 14: Mean	seline	e, day 14: M	lean			P: <0.0001 P: <0.0001 P: <0.01 P: <0.01
z psycholog sleep eva activity, c social, ch professio global, ch	Zolpider gical ge 11.8 aluation 14.6 thange 20 nange fr 13.4 n, chan 23.3 nange fi 10.8	eneral quest from b rom ba nge fro rom ba	well-being inde 9.1 tionnaire (SEQ) 2.7 baseline, day 14 5.7 om baseline, day 12.9 aseline, day 14 5.7	x (PGWBI), chan , change from ba I: Mean Mean y 14: Mean	seline	e, day 14: M	lean			P: <0.0001 P: <0.0001 P: <0.01 P: <0.01
psycholog sleep eva activity, c social, ch professio global, ch psycholog	Zolpider gical ge 11.8 aluation 14.6 thange 20 hange fr 13.4 n, chan 23.3 hange fr 10.8 gical ge 15.2	eneral from b rom ba nge fro rom ba	well-being inde 9.1 tionnaire (SEQ) 2.7 baseline, day 14 9.9 aseline, day 14: 5.7 om baseline, day 12.9 aseline, day 14: 5.7 well-being inde 12.9	x (PGWBI), chan , change from ba I: Mean Mean y 14: Mean	seline	e, day 14: M om baseline	ean, endpoint:			P: <0.0001 P: <0.0001 P: <0.01 P: <0.01 P: NS
psycholog sleep eva activity, c social, ch professio global, ch psycholog	Zolpider gical ge 11.8 aluation 14.6 thange 20 hange fr 13.4 n, chan 23.3 hange fr 10.8 gical ge 15.2	eneral from b rom ba nge fro rom ba	well-being inde 9.1 tionnaire (SEQ) 2.7 baseline, day 14 9.9 aseline, day 14: 5.7 om baseline, day 12.9 aseline, day 14: 5.7 well-being inde 12.9	x (PGWBI), chan , change from ba I: Mean Mean y 14: Mean Mean x (PGWBI), chan	seline	e, day 14: M om baseline	ean, endpoint:			P: <0.0001 P: <0.0001 P: <0.01 P: <0.01 P: NS
psycholog sleep eva activity, c social, ch professio global, ch psycholog sleep eva	Zolpider gical ge 11.8 aluation 14.6 thange 20 hange fr 13.4 n, chan 23.3 hange fr 10.8 gical ge 15.2 aluation 20.9	eneral from b rom ba nge fro rom ba eneral	well-being inde 9.1 tionnaire (SEQ) 2.7 baseline, day 14 5.7 om baseline, day 14 5.7 om baseline, day 14 5.7 well-being inde 12.9 tionnaire (SEQ)	x (PGWBI), chan , change from ba I: Mean Mean y 14: Mean Mean x (PGWBI), chan , change from ba	seline	e, day 14: M om baseline	ean, endpoint:			P: <0.0001 P: <0.0001 P: <0.01 P: <0.01 P: NS P: NS
psycholog sleep eva activity, c social, ch professio global, ch psycholog sleep eva	Zolpider gical ge 11.8 aluation 14.6 thange 20 hange fr 13.4 n, chan 23.3 hange fr 10.8 gical ge 15.2 aluation 20.9	eneral from b rom ba nge fro rom ba eneral	well-being inde 9.1 tionnaire (SEQ) 2.7 baseline, day 14 9.9 aseline, day 14: 5.7 om baseline, day 12.9 aseline, day 14: 5.7 well-being inde 12.9 tionnaire (SEQ) 12.5	x (PGWBI), chan , change from ba I: Mean Mean y 14: Mean Mean x (PGWBI), chan , change from ba	seline	e, day 14: M om baseline	ean, endpoint:			P: <0.0001 P: <0.0001 P: <0.01 P: <0.01 P: NS P: NS
z psycholog sleep eva activity, c social, ch professio global, ch psycholog sleep eva activity, c	Zolpider gical ge 11.8 aluation 14.6 thange 20 hange fr 13.4 n, chan 23.3 hange fr 10.8 gical ge 15.2 aluation 20.9 thange 21.6	eneral from b rom ba nge fro rom ba eneral a quest from b	well-being inde 9.1 tionnaire (SEQ) 2.7 baseline, day 14 5.7 om baseline, day 14 5.7 om baseline, day 14 5.7 well-being inde 12.9 tionnaire (SEQ) 12.5 baseline, endpo	x (PGWBI), chan , change from ba I: Mean Mean y 14: Mean Mean x (PGWBI), chan , change from ba int: Mean	seline	e, day 14: M om baseline	ean, endpoint:			P: <0.0001 P: <0.0001 P: <0.01 P: <0.01 P: NS P: NS P: NS P: <0.0001

Hindmarch, 1995		Quality rating: Fair
profession, change fron	n baseline, endpoint: Mean	
24.5	18.7	P: NS
global, change from bas	seline, endpoint: Mean	
13.8	8.9	P: NS
physician's overall evalu	uation of treatment efficacy as "exc	ellent" or "good" at endpoint: %
76.7	51.4	

Design: Study design: RCT DB Parallel Run-in : 14 days Setting: Multicenter Wash out : 14 days Country: US Sample: Number Screened/ Eligible/ Enrolled Number Withdrawn/ Lost to follow-up/ Analy NR/ NR/ NR/ 830 350/ 80/ Inclusion criteria: DSM-IV diagnosis of chronic primary insomnia; Patient-reported average sleep time <= 6.5 hrs/night and/or sleep latency >30 min Exclusion criteria: NR NR Population: Mean age: 45.6 years Ethnicity: Caucasian: 71% Black: 16% Female Black: 16% Outcome: Intervention: dosage N= Duration Sleep latency sleep latency Eszopiclone 3 mg 548 180 day sleep latency sleep maintenance	zed 828
Wash out : 14 days Country: US Sample: Number Screened/ Eligible/ Enrolled Number Withdrawn/ Lost to follow-up/ Analy NR/ NR/ 830 350/ 80/ Inclusion criteria: DSM-IV diagnosis of chronic primary insomnia; 350/ 80/ Patient-reported average sleep time <= 6.5 hrs/night and/or sleep latency >30 min Exclusion criteria: NR NR NR Population: Mean age: 45.6 years Ethnicity: Caucasian: 71% Black: 16% Black: 16% Outcome:	
NR/ NR/ 830 350/ 80/ Inclusion criteria: DSM-IV diagnosis of chronic primary insomnia; 350/ 80/ DSM-IV diagnosis of chronic primary insomnia; Patient-reported average sleep time <= 6.5 hrs/night and/or sleep latency >30 min 80/ Exclusion criteria: NR NR 80/ NR NR 80/ 80/ Population: Mean age: 45.6 years Ethnicity: Caucasian: NR Gender: 61% Female Black: 16% Inclusion criteria: NR NR 9/ Population: Mean age: 45.6 years Ethnicity: Caucasian: Therevention: Gender: 61% Female Black: 16% Primary outcome Outcome: 0/ Eszopiclone 3 mg 548 180 day sleep latency	
DSM-IV diagnosis of chronic primary insomnia; Patient-reported average sleep time <= 6.5 hrs/night and/or sleep latency >30 min Exclusion criteria: NR Population: Mean age: 45.6 years Ethnicity: Caucasian: 71% Gender: 61% Female Black: 16% Ntervention: Drug name dosage N= Duration Qutcome: Eszopiclone 3 mg 548 180 day	
Patient-reported average sleep time <= 6.5 hrs/night and/or sleep latency >30 min Exclusion criteria: NR Population: Mean age: 45.6 years Ethnicity: Caucasian: 71% Gender: 61% Female Duration Eszopiclone 3 mg 548 180 day	
NR Mean age: 45.6 years Ethnicity: Caucasian: 71% Population: Gender: 61% Female Black: 16% Drug name dosage N= Duration Primary outcome Outcome: Eszopiclone 3 mg 548 180 day sleep latency	
Gender: 61% Female Black: 16% Drug name dosage N= Duration Eszopiclone 3 mg 548 180 day	
Drug name dosage N= Duration Primary outcome Outcome: Eszopiclone 3 mg 548 180 day Image: sleep latency	
Placebo NA mg 280 180 day	
sleep duration	
sleep quality	
insomnia severity index	
daytime functioning	
daytime alertness	
well being	
discontinuation effects	

eep efficacy		
Eszopiclone	Placebo	
sleep latency, estimate fr	m figures (data not reported) at month 1, min: median (p vs placebo)	
29 (<0.0001)	53	
sleep latency, estimate fr	m figures (data not reported) at month 6, min: median (p vs placebo)	
25 (<0.0001)	42	
wake time after sleep ons placebo)	et, estimate from figures (data not reported) at month 1, min: median (o vs
18 (<0.0001)	33	
wake time after sleep ons placebo)	et, estimate from figures (data not reported) at month 6, min: median (o vs
15 (<0.0001)	25	
total sleep time, estimate	from figures (data not reported) at month 1, min: median (p vs placebo)
380 (<0.0001)	330	
total sleep time, estimate	from figures (data not reported) at month 6, min: median (p vs placebo)
380 (<0.0001)	330	
number of awakenings, e	timate from figures (data not reported) at month 1: median (p vs place	bo)
1.5 (<0.0005)	2.2	
number of awakenings, e	timate from figures (data not reported) at month 6: median (p vs place	bo)
1.4 (<0.0005)	1.8	

l (poster)		Quality rating: Fair
total severity score with c	inical categories at month 1: mean (p vs	s placebo)
10 (<0.0001)	14	
total severity score with c	linical categories at month 1: mean (p vs	s placebo)
8 (<0.0001)	12	
self report at end of treatm	nent, higher=better	
Eszopiclone	Placebo	
sleep quality: mean (p vs	placebo)	
2.5 (<0.0001)	1.7	
feeling refreshed/rested:	nean (p vs placebo)	
2.3 (<0.0001)	1.8	
daytime fatigue: mean (p	vs placebo)	
1.4 (<0.0001)	2.0	
attention/concentration: m	nean (p vs placebo)	
1.1 (<0.0001)	1.6	
relationship enjoyment: m	ean (p vs placebo)	
0.7 (<0.0001)	1.0	
feeling refreshed/rested:	mean (p vs placebo)	
2.3 (<0.0001)	1.8	
mood disturbance: mean	(p vs placebo)	
0.9 (<0.0001)	1.4	
sleep difficulties (nights/w	k): mean (p vs placebo)	
3.4 (<0.0001)	5.1	
total score =<14: %		
74	46	
total score 0-7: %		
44	14	
total score 8-14: %		
30	32	

Krystal, 2003					Quality	rating: F	air	
Design:								
Study design:	RCT DE	B Parallel	Run-in :	NR	Setting:	Multicente	er	
			Wash out :	5-7 days	Country:	US		
Sample:	Number Sc	reened/ Eligible/	Enrolled	Number V	/ithdrawn/ Lost to follo	w-up/ Ana	llyzed	
		1194/ 791/	788		320/	60/	788	
Inclusion crite	ria:							
Axis I psych (excluded by alcoholic be infect sleep	iatric diagnos y medical his verages per or to be cont	sis other than prin tory); (2) have a h day or more than	nary insomnia, history of substa 14 per week; (e with hypnotic	sexual and gend ance abuse or su 4) use any psych s; (5) use over-th	vided they did not (1) m er-identity disorders, or bstance dependence; otropic, hypnotic, or oth e-counter analgesics th s Wort.	Axis II per (3) consum her medica	sonality disorders e more than 2 tions known to	
Exclusion crite	eria:							
Population:	Mean age:	44 years	Ethnicity:	80% Caucasia	ı			
	Gender:	25% Female	·	13.2% African	American			
Intervention:					Primary			

Drug name	dos	sage	N=	Duration	Primary outcome	Outcome:
Eszopiclone	3	mg	593	180 day		sleep latency
Placebo	NA	mg	195	180 day		wake time after sleep onset
						total sleep time
						number of awakenings
						number of nights during the week
						sleep quality
						daytime ability to function
						daytime alertness
						sense of physical well-being

elephone interview		
Eszopiclone	Placebo	
sleep latency, month 6:	Mean (SD)	
47.0 (50.6)	63.1 (57.9)	P: <0.001
wake after sleep onset,	month 6: Mean (SD)	
44.2 (74.2)	48.2 (59.4)	P: 0.0032
number of awakenings,	month 6: Mean (SD)	
1.9 (1.5)	2.6 (2.7)	P: <0.0001
number of night awake	nings per week, month 6	ean (SD)
3.9 (2.5)	4.7 (2.4)	P: 0.0001
total sleep time, month	6: Mean (SD)	
378.3 (72.3)	339.3 (77.1)	P: <0.001
sleep quality, month 6:	Mean (SD)	
6.4 (1.8)	5.5 (1.8)	P: <0.0001
daytime ability to function	on, month 6: Mean (SD)	
6.8 (1.7)	6.2 (1.8)	P: <0.0001

Krystal, 2003		Quality rating: Fair
daytime alertness, mor	th 6: Mean (SD)	
6.5 (1.7)	5.9 (1.7)	P: <.0001
sense of physical well-l	peing, month 6: Mean (SD)	
6.7 (1.7)	6.1 (1.8)	P: 0.0002

ahmeyer, 199	7							Quality r	ating	j: Fa	air	
Design:												
Study design:	RCT	DB	Para	llel	Run-in :	3 days		Setting:	Multic	enter		
					Wash out :	4 days		Country:	US			
Sample:	Numbe	er Scre	eened/	Eligible/	Enrolled	Numbe	r Withdrawn/	Lost to follow	w-up/	Analy	/zed	
			178/	33/	145		27/		0/		118	
Inclusion crite	ria:											
						of disturbed sl t 30 minutes, a					duratio	n of
Exclusion crite		,	31			· · · · · , · ·		, ,	1			
		uluu s						hotominoo)	norforr	n a d a	t ooroo	nina
other CNS of apnoea; or (were also ex medical and from the stu	lepressa g) had n ccluded. sleep h dy.	acebo ants; (e locturr In ade istory,	o for the e) had b nal myo dition, p physic	first 3 m been an i clonus o batients v al exami	ights of week llicit drug addio r seizures. Pat vith coexisting	1; (d) had a his ct within the pre- ients who were medical or psyo gns, clinical and	tory of exagg vious year; (f shiftworkers chiatric condit) had subjec and women tions (based	nses to tive sy who w on a p	o benz mptor ere bi restuo	zodiaze ms of s reastfe dy eval	epines o leep eding uation o
other CNS of apnoea; or (were also ex medical and	lepressa g) had n kcluded. sleep h dy. Mean	lacebo ants; (e locturr In add istory, age:	o for the e) had t nal myo dition, p physic 44.9 ye	first 3 m been an i clonus o batients v al exami ears	ights of week llicit drug addio r seizures. Pat vith coexisting	1; (d) had a his ct within the pre- ients who were medical or psyc gns, clinical and 92% Caucas	tory of exagg evious year; (f shiftworkers chiatric condit I laboratory te	erated respo i) had subjec and women tions (based	nses to tive sy who w on a p	o benz mptor ere bi restuo	zodiaze ms of s reastfe dy eval	epines o leep eding uation o
other CNS of apnoea; or (were also ex medical and from the stu Population:	lepressa g) had n ccluded. sleep h dy.	lacebo ants; (e locturr In add istory, age:	o for the e) had b nal myo dition, p physic	first 3 m been an i clonus o batients v al exami ears	ights of week llicit drug addiu r seizures. Pat vith coexisting nation, vital sig	1; (d) had a his ct within the pre- ients who were medical or psyc gns, clinical and	tory of exagg evious year; (f shiftworkers chiatric condit I laboratory te	erated respo i) had subjec and women tions (based	nses to tive sy who w on a p	o benz mptor ere bi restuo	zodiaze ms of s reastfe dy eval	epines o leep eding uation o
other CNS of apnoea; or (were also ex medical and from the stu Population:	lepressa g) had n kcluded. sleep h dy. Mean	acebo ants; (e nocturr In add istory, age: er:	o for the e) had t nal myo dition, p physic 44.9 ye	first 3 m been an i clonus o batients v al exami ears	ights of week llicit drug addiu r seizures. Pat vith coexisting nation, vital sig	1; (d) had a his ct within the pre- ients who were medical or psyc gns, clinical and 92% Caucas	tory of exagg evious year; (f shiftworkers chiatric condit I laboratory te	erated respo i) had subjec and women tions (based	nses to tive sy who w on a p	o benz mptor ere bi restuo	zodiaze ms of s reastfe dy eval	epines o leep eding uation o
other CNS of apnoea; or (were also ex medical and from the stu Population: ntervention:	lepressa g) had n ccluded. sleep h dy. Mean Gende dosa	acebo ants; (e nocturr In add istory, age: er:	o for the e) had b nal myo dition, p physic 44.9 ye 56% Fe	first 3 m been an i clonus o batients v al exami ears	ights of week llicit drug addid r seizures. Pat vith coexisting nation, vital sig Ethnicity:	1; (d) had a his ct within the pre- ients who were medical or psyc gns, clinical and 92% Caucas	tory of exagg evious year; (f shiftworkers chiatric condit I laboratory te ian Primary	erated respo) had subjec and women tions (based ests, ECG an	nses to tive sy who w on a p d urina	o benz mptor ere bi restuo	zodiaze ms of s reastfe dy eval	epines o leep eding uation o
other CNS of apnoea; or (were also ex- medical and from the stu Population: ntervention: Drug name	lepressa g) had n ccluded. sleep h dy. Mean Gende dosa	acebc ants; (e nocturr In add istory, age: age	o for the e) had the hal myo dition, p physic 44.9 ye 56% Fe N=	first 3 m been an i clonus o batients v al exami ears	ights of week llicit drug addid r seizures. Pat vith coexisting hation, vital sig Ethnicity: Duration	1; (d) had a his ct within the pre- ients who were medical or psyc gns, clinical and 92% Caucas	tory of exagg evious year; (f shiftworkers chiatric condit l laboratory te sian Primary outcome	erated respo i) had subjec and women tions (based ests, ECG an Outcome:	nses to tive sy who w on a p d urina	o benz mptor ere bi restuo	zodiaze ms of s reastfe dy eval	epines o leep eding uation o

number of awakenings

wake after sleep onset

quality of sleep

morning sleepiness

ability to concentrate

-	g questionnaire - Zolpidem 10mg	4 weeks average Zolpidem 15mg	Placebo
sleep	latency (min), cha	inge from baseline - 4	weeks average: Mea
	-30	-33.5	-9
total s	sleep time (min) - 4	4 weeks average: Mea	n
	379	381	346
numb	er of awakenings	- 4 weeks average: Me	ean
	1.3	1.3	1.9
sleep	quality (1=excelle	nt; 4=poor) - 4 weeks a	average: Mean
	2.4	2.4	2.8

eyer, 1997			Quality rating: Fair
morning questionnaire -	at week 4		
Zolpidem 10mg	Zolpidem 15mg	Placebo	
sleep latency (min), cha	ange from baseline -	at week 4: Mean (p vs place	ebo)
-31 (<0.05)	-31 (NS)	-16 (NA)	
total sleep time (min) -	at week 4: Mean (p v	s placebo)	
390 (NS)	385 (NS)	360 (NA)	
number of awakenings	- at week 4: Mean (p	vs placebo)	
1.4 (NS)	1.2 (NS)	1.7 (NA)	
sleep quality (1=excelle	ent; 4=poor) - at week	4: Mean (p vs placebo)	
2.4 (NS)	2.4 (NS)	2.6 (NA)	
morning questionnaire -	post-treatment		
Zolpidem 10mg	Zolpidem 15mg	Placebo	
sleep latency (min), cha	ange from baseline -	post-treatment: Mean (p vs	placebo)
-10 (NS)	-11 (NS)	-25 (NA)	
total sleep time (min) -	post-treatment: Mear	n (p vs placebo)	
354 (NS)	332 (NS)	359 (NA)	
number of awakenings	- post-treatment: Me	an (p vs placebo)	
1.7 (NS)	1.9 (NS)	1.9 (NA)	
sleep quality (1=excelle	ent; 4=poor) - post-tre	atment: Mean (p vs placeb	o)
2.8 (NS)	2.9 (NS)	2.8 (NA)	
clinical global impressio	on		
Zolpidem 10mg	Zolpidem 15mg	Placebo	
medication helped me	- fall asleep faster: % (p vs placebo)	
84 (<0.05)	78 (<0.05)	51 (NA)	
medication helped me	- sleep longer: % (p vs	placebo)	
78 (<0.05)	76 (NS)	51 (NA)	
medication helped me	- get a better night's sl	eep: % (p vs placebo)	
84 (,0.05)	84 (<0.05)	49 (NA)	
medication strength - to	oo strong: % (p vs plac	ebo)	
0 (NS)	0 (NS)	0 (NA)	
medication strength - s	trong enough: % (p vs	placebo)	
71 (<0.05)	72 (<0.05)	44 (NA)	
medication strength - to	oo weak: % (p vs place	ebo)	
-			

onchesky, 19	86							Quality	rating:	Fair
esign:										
Study design:	RCT	DB	Cross	over	Run-in : Wash out :	7 days 7 days		Setting: Country:	Single C Canada	
Sample:	Numb	er Scr	eened/ E NR/	ligible/ NR/	Enrolled 99	Numbe	er Withdrawn/ 0/	Lost to follo	w-up/ Ai 2/	nalyzed 91
Inclusion crite	ria:									
criteria: (1) s	sleep lat	ency o	of 45 minu	utes or r	more, (2) more	e than three ni	ghtly awakenii	ngs with diffi	culty in fa	wo of the following alling asleep again, than six hours.
abuse or ad	and brea diction;	a histo	ory of seri	ous psy	chiatric, hepa	tic, renal, or m	netabolic disor	ders; epileps	sy; a knov	s; a history of drug wn hypersensitivity osis of sleep apnea
Population:	Mean Gende		NR years 0% Fema		Ethnicity:	NR				
tervention: Drug name	dosa	age	N=		Duration		Primary outcome	Outcome:		
	dos a		N= 91		Duration 7 day			Outcome: sleepiness		ne day
Drug name		mg							during th	ne day
Drug name Zopiclone	7.5	mg	91		7 day			sleepiness	during th	ne day
Drug name Zopiclone	7.5	mg	91		7 day			sleepiness sleep later	during th ncy tion	
Drug name Zopiclone Placebo	7.5	mg	91		7 day		outcome	sleepiness sleep later sleep dura	during th ncy tion	
Drug name Zopiclone	7.5 NA	mg mg	91		7 day		outcome	sleepiness sleep later sleep dura	during th ncy tion	
Drug name Zopiclone Placebo fficacy: sleep quest	7.5 NA	mg mg	91 91	acebo	7 day		outcome	sleepiness sleep later sleep dura	during th ncy tion	
Drug name Zopiclone Placebo fficacy: sleep quest	7.5 NA tionnair	mg mg re	91 91 Pla	acebo	7 day 7 day		outcome	sleepiness sleep later sleep dura	during th ncy tion	
Drug name Zopiclone Placebo fficacy: sleep quest	7.5 NA tionnair	mg mg re	91 91 Pla ay, treatn	acebo	7 day 7 day		outcome	sleepiness sleep later sleep dura	during th ncy tion	
Drug name Zopiclone Placebo fficacy: sleep quest z sleepines	7.5 NA tionnair Colpidem s during 2.3	mg mg re n g the d	91 91 Pla ay, treatn 2	acebo nent day 2.65	7 day 7 day		outcome	sleepiness sleep later sleep dura	during th ncy tion	ngs

duration of sleep (min), treatment day 7: Mean

number of awakenings, treatment day 7: Mean

quality of sleep, treatment day 7: Mean

soundness of sleep, treatment day 7: Mean

morning state of rest, treatment day 7: Mean

307.4

3.5

3.15

2.75

1.95

2.9

119.3

299.5

sleepiness during the day, treatment day 14 (switch): Mean

sleep induction time (min), treatment day 14 (switch): Mean

duration of sleep (min), treatment day 14 (switch): Mean

384.8

1.8

4.15

3.8

2.85

2.3

53.8

376.7

P: NR

Monchesky, 1986		Quality rating: Fair	
number of awakenings,	treatment day 14 (switch): Mean		
2.0	2.45	P: NR	
quality of sleep, treatme	nt day 14 (switch): Mean		
4.35	2.95	P: NR	
soundness of sleep, trea	atment day 14 (switch): Mean		
4.0	2.4	P: NR	
morning state of rest, tre	eatment day 14 (switch): Mean		
2.9	2.15	P: NR	

Design: Study design: RCT DB Parallel Run-in : 2 days Setting: Single Center Sample: Number Screened/ Eligible/ Enrolled NR/ Number Withdrawn/ Lost to follow-up/ Analyzed NR/ NR/ 12 Inclusion criteria: All patients were suffering from at least 2 of the following sleep disturbances: time to fall asleep >30 minutes; total sleep time <6 hours; total nocturnal wake time >20 minutes; number of nocturnal awakenings >3. Exclusion criteria: Pregnant women, women of child-bearing age with inadequate contraception, breastfeeding mothers, patients suffering from organic disease or severe psychiatric disorders, and patients in whom insufficient compliance was to be expected. Alcohol abuse or intake of hypotoics or anxiolytics and/or antidepressants in the seven days prior to the baseline period also led to exclusion. Population: Mean age: 44.25 years Ethnicity: NR Gender: 83% Female Silver for any Outcome: 1 Inclusebo NA mg 27 day sleep latency Placebo NA mg 27 day sleep latency number of awakenings 1 total wake time sleep officiency sleep efficiency sleep efficiency 1 sleep efficiency movement time sleep efficiency sleep fificiency<	onti, 1996							Quality	rating: Fair	
Wash out: 3 days Country: Uruguay Sample: Number Screened/ Eligible/ Enrolled NR/ NR/ 12 Number Withdrawn/ Lost to follow-up/ Analyzed NR/ NR/ 12 Inclusion criteria: All patients were suffering from at least 2 of the following sleep disturbances: time to fall asleep >30 minutes; total sleep time <6 hours,; total nocturnal wake time >20 minutes; number of nocturnal awakenings >3. Exclusion criteria: Pregnant women, women of child-bearing age with inadequate contraception, breastfeeding mothers, patients suffering from organic disease or severe psychiatric disorders, and patients in whom insufficient compliance was to be expected. Alcohol abuse or intake of hypnotics or anxiolytics and/or antidepressants in the seven days prior to the baseline period also led to exclusion. Population: Mean age: 44.25 years Ethnicity: NR Gender: 83% Female Sileep latency Drug name dosage N= Duration Zolpidem 10 mg 6 27 day sleep latency Placebo NA mg 6 27 day uwake time after sleep onset Use of total sleep time sleep time sleep fificiency	esign:									
Sample: Number Screened/ Eligible/ Enrolled NR/ Number Withdrawn/ Lost to follow-up/ Analyzed NR/ Analyzed NR/ Inclusion criteria: All patients were suffering from at least 2 of the following sleep disturbances: time to fall asleep >30 minutes; total sleep time <6 hours,; total nocturnal wake time >20 minutes; number of nocturnal awakenings >3. Exclusion criteria: Pregnant women, women of child-bearing age with inadequate contraception, breastfeeding mothers, patients suffering from organic disease or severe psychiatric disorders, and patients in whom insufficient compliance was to be expected. Alcohol abuse or intake of hypnotics or anxiolytics and/or antidepressants in the seven days prior to the baseline period also led to exclusion. Population: Mean age: 44.25 years Ethnicity: NR Drug name dosage N= Duration Primary outcome Outcome: Zolpidem 10 mg 6 27 day Image: sleep latency Placebo NA mg 6 27 day Image: utal wake time Image: Image: Image: Image: Image: Image: Image: Zolpidem 10 mg 6 27 day Image: Image: Image: Image: Image: Image: Image: Image:	Study design:	RCT	DB	Parallel	Run-in :	2 days		Setting:	Single Center	
NR/ NR/ 12 NR/ NR/ 12 Inclusion criteria: All patients were suffering from at least 2 of the following sleep disturbances: time to fall asleep >30 minutes; total sleep time <5 hours,; total nocturnal wake time >20 minutes; number of nocturnal awakenings >3. Exclusion criteria: Pregnant women, women of child-bearing age with inadequate contraception, breastfeeding mothers, patients suffering from organic disease or severe psychiatric disorders, and patients in whom insufficient compliance was to be expected. Alcohol abuse or intake of hypnotics or anxiolytics and/or antidepressants in the seven days prior to the baseline period also led to exclusion. Population: Mean age: 44.25 years Ethnicity: NR Gender: 83% Female Thervention: Duration Primary outcome Zolpidem 10 mg 6 NR 27 day Placebo NA mg 6 Z7 day Image: data sleep onset Inclusion Induke time Image: data sleep onset Image: data sleep onset					Wash out :	3 days		Country:	Uruguay	
Inclusion criteria: All patients were suffering from at least 2 of the following sleep disturbances: time to fall asleep >30 minutes; total sleep time <6 hours,; total nocturnal wake time >20 minutes; number of nocturnal awakenings >3. Exclusion criteria: Pregnant women, women of child-bearing age with inadequate contraception, breastfeeding mothers, patients suffering from organic disease or severe psychiatric disorders, and patients in whom insufficient compliance was to be expected. Alcohol abuse or intake of hypnotics or anxiolytics and/or antidepressants in the seven days prior to the baseline period also led to exclusion. Population: Mean age: 44.25 years Ethnicity: NR NR Gender: 83% Female Puration Primary outcome Outcome: Zolpidem 10 mg 6 27 day sleep latency sleep latency Placebo NA mg 6 27 day untuber of awake time wake time wake time after sleep onset utal sleep time sleep latency sleep latency sleep litering	Sample:	Numb	er Scr	eened/ Eli	gible/ Enrolled	Number	Withdrawn/	Lost to follo	w-up/ Analyzed	
All patients were suffering from at least 2 of the following sleep disturbances: time to fall asleep >30 minutes; total sleep time <6 hours,; total nocturnal wake time >20 minutes; number of nocturnal awakenings >3. Exclusion criteria: Pregnant women, women of child-bearing age with inadequate contraception, breastfeeding mothers, patients suffering from organic disease or severe psychiatric disorders, and patients in whom insufficient compliance was to be expected. Alcohol abuse or intake of hypnotics or anxiolytics and/or antidepressants in the seven days prior to the baseline period also led to exclusion. Population: Mean age: 44.25 years Gender: 83% Female Tervention: Drug name dosage N= Duration Zolpidem 10 mg 6 27 day Placebo NA mg 6 27 day Placebo NA mg 6 27 day Contact and the seven days prior to the dawakenings Contact and the				NR/	NR/ 12		NR/		NR/ 12	
<6 hours,; total nocturnal wake time >20 minutes; number of nocturnal awakenings >3. Exclusion criteria: Pregnant women, women of child-bearing age with inadequate contraception, breastfeeding mothers, patients suffering from organic disease or severe psychiatric disorders, and patients in whom insufficient compliance was to be expected. Alcohol abuse or intake of hypnotics or anxiolytics and/or antidepressants in the seven days prior to the baseline period also led to exclusion. Population: Mean age: 44.25 years Ethnicity: NR Gender: 83% Female htervention: Drug name dosage N= Duration Zolpidem 10 mg 6 27 day Placebo NA mg 6 27 day Placebo NA mg 6 27 day intotal wake time intotal wake time intotal wake time intotal wake time intotal sleep time isleep efficiency	Inclusion crite	ria:								
Pregnant women, women of child-bearing age with inadequate contraception, breastfeeding mothers, patients suffering from organic disease or severe psychiatric disorders, and patients in whom insufficient compliance was to be expected. Alcohol abuse or intake of hypnotics or anxiolytics and/or antidepressants in the seven days prior to the baseline period also led to exclusion. Population: Mean age: 44.25 years Ethnicity: NR Gender: 83% Female number of dosage N= Duration Primary outcome: Zolpidem 10 mg 6 27 day Placebo NA mg 6 27 day Use of total wake time wake time after sleep onset total sleep time sleep latency Itervention: Itervention: Itervention Drug name dosage N= Duration Vertice Itervention Itervention Itervention Vertice Itervention Itervention									-30 minutes; total sl	eep time
Drug name dosage N= Duration Zolpidem 10 mg 6 27 day Placebo NA mg 6 27 day Image: Solution of the second state of the	abuse or inta exclusion.	ake of h Mean	age:	44.25 yea	olytics and/or antidepoints Ethnicity:	pressants in the				
Drug name dosage N= Duration Zolpidem 10 mg 6 27 day Placebo NA mg 6 27 day Image: State in the sta	tervention:	Gena	er:	83% Fema	ale					
Placebo NA mg 6 27 day Image: constraint of a wakenings Image: constraint of a wakenings Image: constraint of a wakenings Image: constraint of a wakenings Image: constraint of a wakenings Image: constraint of a wakenings Image: constraint of a wakenings Image: constraint of a wakenings Image: constraint of a wakenings Image: constraint of a wakenings Image: constraint of a wakenings Image: constraint of a wakenings Image: constraint of a wakenings Image: constraint of a wakenings Image: constraint of a wakenings Image: constraint of a wakenings Image: constraint of a wakenings Image: constraint of a wakenings Image: constraint of a wakenings Image: constraint of a wakenings Image: constraint of a wakenings Image: constraint of a wakenings Image: constraint of a wakenings Image: constraint of a wakenings Image: constraint of a wakenings Image: constraint of a wakenings Image: constraint of a wakenings Image: constraint of a wakenings Image: constraint of a wakenings Image: constraint of a wakenings Image: constraint of a wakenings Image: constraint of a wakenings Image: constraint of a wakenings Image: constraint of a wakenings Image: constraint of a wakenings Image: constraint of a w	Drug name	dosa					Duine			
total wake time wake time after sleep onset total sleep time sleep efficiency			age	N=	Duration		•	Outcome:		
wake time after sleep onset total sleep time sleep efficiency	Zolpidem	10					•			
total sleep time	•		mg	6	27 day		•	sleep later	ю	
sleep efficiency	•		mg	6	27 day		•	sleep later number of	ncy awakenings	
	•		mg	6	27 day		•	sleep later number of total wake	ncy awakenings time	
movement time	•		mg	6	27 day		•	sleep later number of total wake wake time	ncy awakenings time after sleep onset	
	•		mg	6	27 day		•	sleep later number of total wake wake time total sleep	ncy awakenings time after sleep onset time	

Zolpidem	Placebo	
stage 2 sleep latency (nin), nights 29-30: Mean (SD)	
23.6 (7.1)	35.1 (5.6)	P: NS
total number of awaker	ings, nights 29-30: Mean (SD)	
24.8 (4.3)	25.5 (5.7)	P: NS
total wake time (min), r	ights 29-30: Mean (SD)	
53.8 (6.9)	104.8 (21.8)	P: <0.05
wake time after sleep o	nset (min), nights 29-30: Mean (SD)	
26.3 (7.0)	85.3 (24.2)	P: NS
total sleep time (min), r	ights 29-30: Mean (SD)	
419.3 (7.1)	370.9 (21.2)	P: <0.05
sleep efficiency (%), nig	yhts 29-30: Mean (SD)	
87.3 (1.5)	77.3 (4.4)	P: NS
movement time, nights	29-30: Mean (SD)	
6.9 (2.6)	4.3 (1.2)	P: NS

, 1996	Quality rating: Fair				
questionnaire					
Zolpidem	Placebo				
sleep latency (lower sc	pre indicates more positive response), night 29	-30: Mean (SD)			
2.0 (0.4)	1.8 (0.5)	P: NS			
sleep duration (higher s	core indicates more positive response), night 2	29-30: Mean (SD)			
2.3 (0.3)	2.5 (0.4)	P: NS			
number of awakenings	(lower score indicates more positive response)	, night 29-30: Mean (SD)			
2.6 (0.3)	1.9 (0.3)	P: NS			
disturbed sleep (higher	score indicates more positive response), night	29-30: Mean (SD)			
73.1 (8.7)	48.5 (8.3)	P: <0.01			
daytime alertness (high	er score indicates more positive response), nig	ht 29-30: Mean (SD)			
69.0 (9.5)	44.2 (8.4)	P: NS			

					Quality	rating: F	oor
esign:							
Study design:	RCT I	DB Paralle	Run-in :	3 days	Setting:	Single Ce	nter
			Wash out :	3 days	Country:	Uruguay	
Sample:	Number	Screened/ El	igible/ Enrolled	Number Wit	ndrawn/ Lost to foll	ow-up/ Ana	lyzed
		NR/	NR/ 12		NR/	NR/	12
Inclusion crite	ria:						
Patients age	ed betweer	27 and 59 ye	ears, with chronic pr	imary insomnia acco	rding to the DSM-I	/ participate	d in the study.
pregnant wo Patients with	omen and b h poor heal	reast-feeding	mothers. hronic pain; hepatic	gs or sleep apnea w , renal, respiratory, c ns)>16 were not inclu	ardiac, or neuropsy	chiatric dise	ases [subjects
movements breast-feedi laboratory te benzodiaze	during slee ng mothers ests. Alcoh pine urine s	ep; restless le s, subjects de ol abuse, inta screening also	gs; or sleep apnea emed insufficiently	were excluded from compliant, or those v nxiolytics in the seve	ith clinically signific	ant deviation	cy women, ns in their
movements breast-feedi laboratory te	during slee ng mothers ests. Alcoh pine urine s Mean ag	ep; restless le s, subjects de ol abuse, inta screening also	gs; or sleep apnea emed insufficiently ke of hypnotics or a b led to exclusion.	compliant, or those w nxiolytics in the seve	ith clinically signific	ant deviation	cy women, ns in their
movements breast-feedi laboratory te benzodiaze	during slee ng mothers ests. Alcoh pine urine s	ep; restless le s, subjects de ol abuse, inta screening alse	gs; or sleep apnea emed insufficiently ke of hypnotics or a b led to exclusion. s Ethnicity	compliant, or those w nxiolytics in the seve	ith clinically signific	ant deviation	cy women, ns in their
movements breast-feedi laboratory te benzodiaze	during slee ng mothers ests. Alcoh pine urine s Mean ag	ep; restless le s, subjects de ol abuse, inta screening also e: 51.9 year 100% Fer	gs; or sleep apnea emed insufficiently ke of hypnotics or a b led to exclusion. s Ethnicity	compliant, or those v nxiolytics in the seve : NR P	ith clinically signific	ant deviatio eline period,	cy women, ns in their
movements breast-feedi laboratory te benzodiaze Population: htervention:	during slee ng mothers ests. Alcoh pine urine s Mean ag Gender:	ep; restless le s, subjects de ol abuse, inta screening also e: 51.9 year 100% Fer N=	gs; or sleep apnea emed insufficiently ke of hypnotics or a b led to exclusion. s Ethnicity nale	compliant, or those v nxiolytics in the seve : NR P	rith clinically signific n days prior to base rimary	ant deviatio eline period,	cy women, ns in their
movements breast-feedi laboratory te benzodiaze Population: ntervention: Drug name	during slee ng mothers ests. Alcohi pine urine s Mean ag Gender: dosage	ep; restless les, subjects de ol abuse, inta screening also e: 51.9 year 100% Fer N= 6	gs; or sleep apnea emed insufficiently ke of hypnotics or a b led to exclusion. s Ethnicity nale Duration	compliant, or those v nxiolytics in the seve : NR P	rimary ttcome Outcome sleep late	ant deviatio eline period,	cy women, ns in their or a positive

wake time after sleep onset

total sleep time

sleep efficiency

Efficacy:

Zolpidem	Placebo	
stage 2 sleep latency -	night 4-5: Mean (SD)	
26.1 (4.5)	67.4 (14.9)	P: <0.02
stage 2 sleep latency -	night 17-18: Mean (SD)	
29.2 (6.8)	48.3 (6.9)	P: NS
total number of awaken	ings - night 4-5: Mean (SD)	
29.4 (5.1)	32.2 (3.8)	P: NS
total number of awaken	ings - night 17-18: Mean (SD)	
26.9 (2.2)	26.5 (4.9)	P: NS
waking time after sleep	onset (min) - night 4-5: Mean (SD)	
75.1 (7.9)	137.5 (29.2)	P: <0.03
waking time after sleep	onset (min) - night 17-18: Mean (SD)	
95.7 (23.3)	173.3 (35.4)	P: NS
total sleep time (min) -	night 4-5: Mean (SD)	
378.8 (8.2)	279.3 (24.2)	P: <0.01
total sleep time (min) -	night 17-18: Mean (SD)	
361.2 (25.8)	264.4 (33.3)	P: <0.02

i, 2000		Quality rating: Poor			
sleep efficiency (%) - n	ight 4-5: Mean (SD)				
79.9 (1.6)	61.9 (5)	P: <0.006			
sleep efficiency (%) - n	ight 17-18: Mean (SD)				
75.4 (5.4)	55.1 (6.9)	P: <0.01			
interview					
Zolpidem	Placebo				
sleep latency (min) - nig	ght 4-5: Mean (SD)				
34.6 (8.2)	228.0 (80.8)	P: <0.01			
sleep latency (min) - nig	ght 17-18: Mean (SD)				
49.5 (8.2)	154.0 (52.1)	P: <0.01			
sleep duration (min) - n	ight 4-5: Mean (SD)				
384.0 (29.1)	180.0 (61.3)	P: NS			
sleep duration (min) - n	ight 17-18: Mean (SD)				
342.0 (40.5)	225.0 (55.3)	P: NS			
disturbed sleep - night	4-5 (1=agree; 100=disagree): Mean (SD)				
78.4 (6.2)	46.4 (12.9)	P: NS			
disturbed sleep - night	17-18 (1=agree; 100=disagree): Mean (SD)				
74.6 (8.4)	40.1 (14.8)	P: NS			
alert in the morning - ni	ght 4-5 (1=agree; 100=disagree): Mean (SD)				
20.8 (6.3)	57.5 (16.1)	P: NS			
alert in the morning - ni	ght 17-18 (1=agree; 100=disagree): Mean (SD)				
30.3 (10.6)	65.9 (12.1)	P: NS			

erlis, 2004		Quality rating: Fair							
Design:									
Study design:	RCT	DB F	Parallel	Run-in :	6-14 days	Setting:	Multic	enter	
				Wash out :	NR	Country:	US		
Sample:	Number	r Screene	ed/ Eligible/	Enrolled	Number Withdrawn/	Lost to follo	w-up/	Analyzed	
		32	22/ 277/	199	10/		3/	192	

Patients aged 18 to 64 years were eligible for the study provided they met the DSM-IV criteria for primary insomnia and were deemed to be in good mental and physical health as ascertained by a medical history, physical examination, and standard clinical laboratory tests obtained within 2 weeks of study start.

Exclusion criteria:

Exclusion criteria included presence of any significant psychiatric disorder; use of any over-the-counter or prescription sleep medication within 7 days or any investigational drug within 30 days before study start; positive urine screen for medication that could interfere with the assessment of study medication; history of drug addiction, alcoholism, or drug abuse; and history of or current symptoms compatible with sleep apnea or periodic leg movements during sleep. Additionally, female patients were ineligible if they were breastfeeding, pregnant, or not using double-barrier contraceptive methods.

Population:	Mean age: Gender:	40.8 years 71% Female	Ethnicity:	70% Euro Am	erican	
Intervention: Drug name	dosage	N=	Duration		Primary outcome	Outcome:
Zolpidem	10 mg	98	84 day		\checkmark	sleep latency
Placebo	NA mg	101	84 day		\checkmark	number of awakenings
					\checkmark	wake after sleep onset
					\checkmark	total sleep time

Efficacy:

Zolpidem	Placebo	
sleep latency (min), wit	h pill: Mean (SD)	
38.4 (33.1)	55.1 (52.3)	P: <0.05
sleep latency (min), wit	hout pill: Mean (SD)	
NR (NR)	NR (NR)	P: NS
sleep latency (min), all	condition significant at week 10 only: Mean (SD)	
NR (NR)	NR (NR)	P: NS
number of awakenings,	, with pill: Mean (SD)	
1.03 (0.92)	1.64 (1.33)	P: <0.05
number of awakenings,	, without pill: Mean (SD)	
NR (NR)	NR (NR)	P: NS
number of awakenings,	, all condition, significant at week 2 and 12 only: Mean (SD)	
1.38 (1.00)	1.69 (1.28)	P: NS
wake after sleep onset	(min), with pill: Mean (SD)	
32.6 (43.5)	55.4 (56.1)	P: <0.05
wake after sleep onset	(min), without pill: Mean (SD)	
NR (NR)	NR (NR)	P: NS
wake after sleep onset	(min), all condition, significant at week 2 only: Mean (SD)	
NR (NR)	NR (NR)	P: NS

s, 2004		Quality rating: Fair
total sleep time (min), w	<i>r</i> ith pill: Mean (SD)	
417 (64.4)	359.8 (77.1)	P: <0.05
total sleep time (min), w	/ithout pill: Mean (SD)	
NR (NR)	NR (NR)	P: NS
total sleep time (min), a	all condition: Mean (SD)	
394.1 (60.1)	355.6 (69.6)	P: <0.05
global outcome measure	9	
Zolpidem	Placebo	
IGR scale: Mean (SD)		
6 (0.12)	4.5 (0.14)	P: <0.001

oehrs (poster)	, 2005					Quality rating: Fair				
esign:										
Study design:	RCT	DB	Parallel	Run-in :	no days	Setting:	Multice	nter		
				Wash out	: no days	Country:	US, Ca	nada, Ai	gentina, Germa	any, I
Sample:	Number	Scree	0	ible/ Enrolled	Number Withd	rawn/ Lost to foll		,		
			NR/	NR/ 205		7/	NR/	NR		
Inclusion criter	ia:									
			0		Ilment. A 2-night (screet hours each screening	0,		= 40 mir	nutes (not	
	-									
known to affe respectively.	Axis I ps ect sleep,	or us	e of over-th		history of substance at scription sleep medicat					
Any DSM-IV known to affe	Axis I ps ect sleep, Mean a g	orus je: 7	e of over-th 0.2 years	he-counter or pre		ion within 1 and 2				
Any DSM-IV known to affe respectively. Population:	Axis I ps ect sleep,	orus je: 7	e of over-th	he-counter or pre	scription sleep medicat	ion within 1 and 2				
Any DSM-IV known to affe respectively.	Axis I ps ect sleep, Mean a g	orus ge: 7 5	e of over-th 0.2 years	he-counter or pre	scription sleep medicat r: 95.1% Caucasian; - Prir	ion within 1 and 2	2 weeks pi			
Any DSM-IV known to affe respectively. Population: tervention:	Axis I ps ect sleep, Mean ag Gender dosag	orus je: 7 5 e	e of over-th 0.2 years 7% Female	he-counter or pre Ethnicity e	scription sleep medicat r: 95.1% Caucasian; - Prir	ion within 1 and 2 1.9% other nary come Outcome	2 weeks pi	ior to sc		_
Any DSM-IV known to affe respectively. Population: Itervention: Drug name	Axis I ps ect sleep, Mean ag Gender dosag	orus ge: 7 5 e	e of over-th 0.2 years 7% Female N=	e	scription sleep medicat r: 95.1% Caucasian; - Prir	ion within 1 and 2 4.9% other nary come Outcome wake afte	? weeks p	rior to sc		_
Any DSM-IV known to affe respectively. Population: tervention: Drug name zolpidem exten	Axis I ps ect sleep, Mean ag Gender dosag	orus ge: 7 5 e	e of over-th 0.2 years 7% Female N= 99	e Duration 21 day	scription sleep medicat r: 95.1% Caucasian; - Prir	ion within 1 and 2 4.9% other nary come Outcome wake afte	? weeks pi :: r sleep or f awakeni	rior to sc		_
Any DSM-IV known to affe respectively. Population: tervention: Drug name zolpidem exten	Axis I ps ect sleep, Mean ag Gender dosag	orus ge: 7 5 e	e of over-th 0.2 years 7% Female N= 99	e Duration 21 day	scription sleep medicat r: 95.1% Caucasian; - Prir	ion within 1 and 2 4.9% other nary come Outcome wake afte number o total slee	? weeks pi :: r sleep or f awakeni	rior to sc nset ng		_
Any DSM-IV known to affe respectively. Population: tervention: Drug name zolpidem exten	Axis I ps ect sleep, Mean ag Gender dosag	orus ge: 7 5 e	e of over-th 0.2 years 7% Female N= 99	e Duration 21 day	scription sleep medicat r: 95.1% Caucasian; - Prir	ion within 1 and 2 4.9% other nary come Outcome wake afte number o total slee	e weeks p r sleep or f awakeni o time et latency	rior to sc nset ng		_

Efficacy:

polysomnography		
Zolpidem MR	Placebo	
wake time after sleep on	set (WASO), mean change	seline, Night 1 and 2: Minutes
-32	-6	P: 0.0042
wake time after sleep on	set (WASO), mean change	seline, Night 15 and 16: Minutes
-18	-6	P: <0.001
latency to persistent slee	p (LPS), mean change from	ne, Night 1 and 2: Minutes
-17	-6	P: 0.0001
latency to persistent slee	p (LPS), mean change from	ne, Night 15 and 16: Minutes
-14	-8	P: 0.0255
sleep efficiency (SE), tot	al sleep time/time in bed x1	
10.2	3	P: <0.0001
sleep efficiency (SE), tot	al sleep time/time in bed x1	
5.9	3.5	P: 0.0509
sleep questionnaire		
Zolpidem MR	Placebo	
Patient global impression	and sleep quality, data NR	
better	NR	P: 0.0001
Subjective sleep estimat	e, data NR: %	
better	NR	P: <0.05

Roth, 2006								Quality rating: Fair			
Design:											
Study design:	RCT	DB	Para	allel	Run-in :	7 days	Set	tting:	Multice	enter	
					Wash out :	7 days	Co	ountry:	US		
Sample:	Numbe	r Scre	ened/	Eligible/	Enrolled	Number With	idrawn/ Lost	t to follow	w-up/ /	Analyze	ed
			NR/	NR/	829		128/		NR/	N	IR
In altration online											

Inclusion criteria:

Age 65 years or older with a diagnosis of primary insomnia as defined by the DSM-IV-TR for at least 3 months, a reported sleep latency >=45 minutes, and a total sleep time <=6.5 hours per night for at least 3 nights during the week of the singleblind lead-in period. Body mass index must have been between 18 and 34, inclusive, and habitual bedtime must have been between 8:30 pm and 12:00 am.

Exclusion criteria:

Patients could not have had any significant medical or psychiatric disorder or have used any medications that affected the central nervous system or sleep/wake function within 1 week (or 5 half lives, whichever is longer) prior to the first day of the placebo lead-in period.

Population:	Mea Gen		72.4 years 0% Female	Ethnicity:	Not reported		
Intervention: Drug name		sage	N=	Duration		Primary outcome	Outcome:
Ramelteon	4	mg	281	5 week		\checkmark	Sleep latency
Ramelteon	8	mg	274	5 week			Total sleep time
Placebo	NA	mg	274	5 week			Number of awakenings
							Ease of falling back to sleep
							Sleep quality
							CGI
							Rebound insomnia

Efficacy:

Subjective sleep latency	,			
Ramelteon 4 mg	Ramelteon 8 mg	Placebo		
Sleep latency at week 3	3, minutes (not reported	l if mean or median): N	umber (p vs placebo)	
64.9 (0.142)	60.3 (0.003)	69.3		
Sleep latency at week 1	, minutes (not reported	l if mean or median): N	umber (p vs placebo)	
64.9 (0.142)	60.3 (0.003)	69.3		
Subjective total sleep tir	ne			
Ramelteon 4 mg	Ramelteon 8 mg	Placebo		
Total sleep time at wee	k 1, minutes (not repor	ed if mean or median):	: Number (p vs placebo)	
324.6 (0.004)	321.1 (0.055)	313.9		
Total sleep time at wee	k 3, minutes (not repor	ed if mean or median):	: Number (p vs placebo)	
336.0 (0.007)	332.1 (0.071)	324.3		
Total sleep time at wee	k 5, minutes (not repor	ed if mean or median):	Number (p vs placebo)	
337.5 (0.104)	334.4 (0.347)	330.1		

Scharf, 1994	Quality rating: Fair					rating: Fair		
Design:								
Study design:	RCT	DB	Para	allel	Run-in :	11 days	Setting:	Multicenter
					Wash out :	2 days	Country:	US
Sample:	Numbe	r Scree	ened/	Eligible/	Enrolled	Number Withdrawn/	Lost to follo	w-up/ Analyzed
			178/	75/	75			

Inclusion criteria:

After giving informed consent, outpatient insomniacs, aged 21 to 60 years, were screened to rule out significant medical or psychiatric disorders and to ensure that they were in good health. Patients were not have used any investigational drug within 30 days of the start of the study. In addition, patients were required to have chronic insomnia defined as a history of the following for at least 3 months preceding screening: usual reported sleep duration between 4 and 6 hours, usual reported sleep latency of at least 30 minutes, and daytime complaints associated with disturbed sleep. The first night of placebo screening period served as a laboratory adaptation night and to rule out patients with sleep apnea or periodic limb movements during sleep. During the next 3 nights, patients had to meet the following criteria: total sleep time of 240 to 420 minutes (4 to 7 hours) in a 480-minute recording on at least 2 or the 3 screening nights, and a latency to persistent sleep of > 20 minutes on each of these 2 nights. "Persistent sleep" was defined as the first continuous 20 epochs of a non-wake state.

Exclusion criteria:

Population:	Mean age: Gender:	38 years 64% Female	Ethnicity:	73.3% white 26.7% non-wh	iite	
Intervention: Drug name	dosage	N=	Duration		Primary outcome	Outcome:
Zolpidem	10 mg	26	35 day		\checkmark	sleep latency
Zolpidem	15 mg	25	35 day		\checkmark	sleep efficiency
Placebo	NA mg	24	35 day			total sleep time
						sleep quality
						ease of falling sleep

Efficacy:

polysomnography

Zolpidem 10mg	Zolpidem 15mg	Placebo
sleep latency (min), wee	ek 6: Mean (p vs place	ebo)
25.8 (0.063)	28.1 (p<0.05)	48 (NA)
sleep efficiency (%), we	ek 6: Mean (p vs plac	ebo)
87.9 (0.063)	87.3 (p<0.05)	80.7 (NA)
sleep latency (min), wee	ek 6: Mean (p vs place	ebo)
47.1 (NS)	47.7 (NS)	48.0 (NA)
sleep efficiency (%), we	ek 6: Mean (p vs plac	ebo)
83.1 (NS)	79.9 (NS)	81.9 (NA)

rf, 1994		Quality rating: F	air
morning questionnaire			
Zolpidem 10mg	Zolpidem 15mg	Placebo	
sleep latency (min), we	ek 6: Mean (p vs plac	ebo)	
38.4 (NS)	31.7 (<0.05)	56.6 (NA)	
ease of falling sleep (0=	=very easy; 100=not	asy), week 6: Mean (p vs placebo)	
50.7 (NS)	35.7 (<0.05)	48.4 (NA)	
sleep quality (1=excelle	ent; 4=poor), week 6:	Mean (p vs placebo)	
2.5 (NS)	2.5 (NS)	2.6 (NA)	
total sleep time (min), v	veek 6: Mean (p vs pl	acebo)	
369 (NS)	394 (NS)	356 (NA)	
sleep latency (min), pos	sttreatment: Mean (p	vs placebo)	
62.3 (NS)	78.2 (NS)	47.5 (NA)	
ease of falling sleep (0=	=very easy; 100=not	asy), posttreatment: Mean (p vs placebo)	
63.7 (NS)	64.0 (<0.05)	44.4 (NA)	
sleep quality (1=excelle	ent; 4=poor), posttrea	ment: Mean (p vs placebo)	
2.9 (<0.05)	3.1 (<0.05)	2.6 (NA)	
total sleep time (min), p	osttreatment: Mean	o vs placebo)	
333 (NS)	341 (NS)	333 (NA)	
tolerance assessment,	change from week 2	o week 6: Mean (p vs placebo)	
multi-data (NS)	multi-data (NS)	multi-data (NA)	

Scharf, 2005							Quality rating: Fair			
Design:										
Study design:	RCT	DB P	arallel	Run-in :	3-14 days	Setting:	Multicent	er		
				Wash out :	NR	Country:	US			
Sample:	Numbe	r Screene	d/ Eligible/	Enrolled	Number Withdra	wn/ Lost to follo	ow-up/ Ana	alyzed		
		35	3/ NR/	231		21/	NR/	231		

Inclusion criteria:

Men and women between the ages of 65 and 85 years who met the DSM-IV for primary insomnia and who reported sleeping 6.5 hours per night or less and took more than 30 minutes to fall asleep each night for at least 1 month

Exclusion criteria:

Patients with a prior history of allergies to zopiclone or any sedative hypnotic, history of severe chronic obstructive pulmonary disease, history of any condition that could interfere with the absorption of orally administered medicine, or prior participation in the investigational study less than 30 days prior to screening were excluded.

Population	Ge	an age: nder:	72.3 years 58% Female	Ethnicity:	89.4% Caucasi 2.2% black	ian	
Intervention Drug nam		osage	N=	Duration		Primary outcome	Outcome:
Eszopiclon	ne 1	mg	72	14 day	=	\checkmark	sleep latency
Eszopiclon	ne 2	mg	79	14 day		\checkmark	total sleep time
Placebo	N	A mg	80	14 day			wake time after sleep onset
							number of awakenings
							sleep quality
							sleep depth
							daytime alertness
							ability to function
							sense of physical well-being
							number of naps taken
							length of naps

Efficacy:

morning questionnaire		
Eszopiclone 1mg	Eszopiclone 2mg	Placebo
sleep latency (min) - av	erage: Mean (p vs plac	cebo)
53.6 (<0.05)	50 (0.0034)	85.5 (NA)
total sleep time (min) - a	average: Mean (p vs p	lacebo)
349.8 (NS)	372.3 (0.0003)	328.2 (NA)
wake after sleep onset	(min) - average: Mean	(p vs placebo)
72.6 (NS)	58.5 (0.423)	74.1 (NA)
number of awakenings	- average: Mean (p vs	placebo)
2 (NS)	1.7 (NS)	1.9 (NA)
sleep quality (0=poor; 1	0=excellent) - average	e: Mean (p vs placebo)
6.6 (NS)	7.2 (0.0006)	6.3 (NA)
sleep depth (0=very ligh	nt; 10=very deep) - ave	erage: Mean (p vs placebo)
6.5 (NS)	7.1 (0.0015)	6.2 (NA)

rf, 2005		Quality rating: Fair
evening questionnaire		
Eszopiclone 1mg	Eszopiclone 2mg	Placebo
daytime alertness (0=d	rowsy; 10=alert), avera	age: Mean (p vs placebo)
7.1 (NS)	7.3 (0.0223)	6.8 (NA)
physical well-being (0=	poor; 10=excellent), av	verage: Mean (p vs placebo)
7.5 (NS)	7.7 (0.0474)	7.2 (NA)
morning sleepiness (0=	very sleepy; 10=not at	all sleepy), average: Mean (p vs placebo)
6.9 (NS)	7.2 (0.054)	6.6 (NA)
daily ability to function (0=poor; 10=excellent)	, average: Mean (p vs placebo)
7.4 (NS)	7.6 (0.0579)	7.2 (NA)
number of naps taken,	total: Mean (p vs place	ebo)
5.0 (NS)	4.3 (0.0276)	5.9 (NA)
duration per nap (min),	average: Mean (p vs p	olacebo)
47.7 (<0.05)	52.7 (0.0113)	59.2 (NA)

- :	ster), 2	2005						Quality	rating: Fair
sign:									
Study design:	RCT	DB	Parallel	Run-in : Wash out :	NR NR			Setting: Country:	Multicenter US
Sample:	Numt	ber Scr	reened/ Eligible/ NR/ NR/			Number	/Withdrawn 20/	Lost to follo	w-up/ Analyzed NR/ NR
nclusion crite	ria:								
			nsomnia, WASC er night during th				its per week	during the	preceding month, and time
	/ Axis I fect sle								ubstance with CNS effects weeks prior to screening,
Population:	Mean	ı age:	44.4 years	Ethnicity:	90%	6 Caucasia	in, 10% othe	er	
	Gend	ler:	58% Female						
ervention: Drug name	dos	age	N=	Duration			Primary outcome	Outcome:	
Zolpidem-CR	12.5	mg	102	3 week				wake time	after sleep onset
Placebo	NA	mg	110	3 week				total sleep	time
								latency to	persistent sleep
								number of	awakenings
								sleep qual	ity
								patient glo	bal impression
icacy: polysomno Zo	graphy Ipidem								
welle tim	·		Placebo	and from boool		abt 1 and 1	D. Minuto		
wake time	e after s		onset, mean cha	nge from basel	ine, ni	ght 1 and 2	2: Minute		P: <0.0001
	e after s -33	sleep c	onset, mean cha -10	-		-			P: <0.0001
	e after s -33 e after s	sleep c	onset, mean cha	-		-			P: <0.0001 P: <0.0001
wake time	e after s -33 e after s -30	sleep o sleep o	onset, mean char -10 onset, mean char -13	nge from basel	ine, ni	ght 15 and	16: Minute		
wake time	e after s -33 e after s -30	sleep o sleep o enings	onset, mean chai -10 onset, mean chai	nge from basel	ine, ni	ght 15 and	16: Minute		
wake time number c	e after s -33 e after s -30 of awake -3.0	sleep o sleep o enings	onset, mean char -10 onset, mean char -13 , mean change f -0.9	nge from basel rom baseline, r	ine, ni night 1	ght 15 and and 2: Nu	16: Minute mber		P: <0.0001
wake time number c	e after s -33 e after s -30 of awake -3.0	sleep o sleep o enings	onset, mean chai -10 onset, mean chai -13 , mean change f	nge from basel rom baseline, r	ine, ni night 1	ght 15 and and 2: Nu	16: Minute mber		P: <0.0001
wake tim number c number c	e after s -33 e after s -30 of awako -3.0 of awako -2.7	sleep o sleep o enings, enings,	onset, mean char -10 onset, mean char -13 , mean change f -0.9 , mean change	nge from basel rom baseline, r from baseline,	ine, ni night 1 night ²	ght 15 and and 2: Nu 15 and 16:	16: Minute mber Number		P: <0.0001 P: <0.0001
wake tim number c number c	e after s -33 e after s -30 of awako -3.0 of awako -2.7	sleep o sleep o enings, enings,	onset, mean char -10 onset, mean char -13 , mean change f -0.9 , mean change -0.8	nge from basel rom baseline, r from baseline,	ine, ni night 1 night ²	ght 15 and and 2: Nu 15 and 16:	16: Minute mber Number		P: <0.0001 P: <0.0001
wake time number c number c latency to	e after s -33 e after s -30 of awake -3.0 of awake -2.7 o persis -23	sleep o sleep o enings enings tent sle	onset, mean char -10 onset, mean char -13 , mean change f -0.9 , mean change -0.8 eep, mean change	nge from basel rom baseline, r from baseline, ge from baselin	ine, ni hight 1 night ⁻ e, nig	ght 15 and and 2: Nu 15 and 16: ht 1 and 2:	16: Minute mber Number Minute		P: <0.0001 P: <0.0001 P: <0.0001
wake time number c number c latency to	e after s -33 e after s -30 of awake -3.0 of awake -2.7 o persis -23	sleep o sleep o enings enings tent sle	onset, mean char -10 onset, mean char -13 , mean change f -0.9 , mean change -0.8 eep, mean change -13	nge from basel rom baseline, r from baseline, ge from baselin	ine, ni hight 1 night ⁻ e, nig	ght 15 and and 2: Nu 15 and 16: ht 1 and 2:	16: Minute mber Number Minute		P: <0.0001 P: <0.0001 P: <0.0001
wake time number c number c latency to	e after s -33 e after s -30 of awake -3.0 of awake -2.7 o persis -23 o persis -21	sleep o sleep o enings enings tent slo	onset, mean char -10 onset, mean char -13 , mean change f -0.9 , mean change -0.8 eep, mean charg -13 eep, mean charg	nge from basel rom baseline, r from baseline, ge from baselin ge from baselin	ine, ni night 1 night ² e, nig	ght 15 and and 2: Nu 15 and 16: ht 1 and 2: ht 15 and ²	16: Minute mber Number Minute		P: <0.0001 P: <0.0001 P: <0.0001 P: <0.0001
wake time number c number c latency to	e after s -33 e after s -30 of awake -3.0 of awake -2.7 o persis -23 o persis -21	sleep o sleep o enings enings tent slo	onset, mean chan -10 onset, mean chan -13 , mean change f -0.9 , mean change -0.8 eep, mean chang -13 eep, mean chang -13	nge from basel rom baseline, r from baseline, ge from baselin ge from baselin	ine, ni night 1 night ² e, nig	ght 15 and and 2: Nu 15 and 16: ht 1 and 2: ht 15 and ²	16: Minute mber Number Minute		P: <0.0001 P: <0.0001 P: <0.0001 P: <0.0001
wake time number o number o latency to sleep effi	e after s -33 e after s -30 of awake -3.0 of awake -2.7 o persis -23 o persis -21 ciency, 13	sleep o sleep o enings enings tent sle tent sle total sl	onset, mean char -10 onset, mean char -13 , mean change f -0.9 , mean change -0.8 eep, mean change -13 eep, mean change -13 leep time / time i	nge from basel rom baseline, r from baseline, ge from baselin ge from baselin n bed x100, nig	ine, ni night 1 e, nig e, nig ght 1 a	ght 15 and and 2: Nu 15 and 16: ht 1 and 2: ht 15 and ² and 2: %	16: Minute mber Number Minute		P: <0.0001 P: <0.0001 P: <0.0001 P: <0.0001 P: 0.0338

9.4

6.4

P: 0.0172

Soubrane (poster), 2005		Quality rating: Fair	
sleep questionnaire			
Zolpidem MR	Placebo		
patients global impress	ion and sleep quality, day 2, 15, 22: %		
better	multiple data	P: <0.005	
patients global impress	ion and sleep quality, day 2, 15, 22: %		
better	data NR	P: <0.005	

erzano, 1992						Quality	rating:	Poor
esign:								
Study design:	RCT D	B Parallel	Run-in : Wash out :	14 days NR		Setting: Country:	Single C Italy	Center
Sample:	Number S	creened/ Eligible NR/ NF		Numb	er Withdrawn/ NR/	Lost to follo	ow-up/Ar NR/	nalyzed 12
Inclusion crite	ria:							
		for the diagnosis ficulties in falling						
Exclusion crite patients had		nyoclonus or slee	ep apnea syndro	me				
Population:	Mean age	: 49.6 years	Ethnicity:	NR				
_	Gender:	67% Female	-					
Drug name	dosage	N=	Duration		Primary outcome	Outcome	:	
Zolpidem	10 mg	0	1 day			sleep later	псу	
Placebo	NA mg	0	1 day			wake after	sleep on	set
						total sleep	time	
fficacy:								
polysomno	graphy							
Z	olpidem	Placebo						
sleep late	ncy (min): N	lean (SD)						
	3.1 (7.1)	14.5 (14)						P: NR
wake afte	r sleep onse	et (min): Mean						
	16	41						P: NR
total sleep	time (min):	Mean (SD)						

Walsh, 2000a							Qual	ity rating	: Poor	
Design:										
Study design:	RCT	DB	Parall	el	Run-in :	5-12 days	Settin	g: Multice	enter	
					Wash out :	5-12 days	Count	iry: US		
Sample:	Numbe	er Scre	ened/ E	Eligible/	Enrolled	Number Wit	hdrawn/ Lost to	follow-up/	Analyzed	
			311/	54/	48		NR/	NR/	48	

Inclusion criteria:

Males and female aged 60 to 80 years who reported sleep disturbance of > 3 months' duration with associated daytime impairment were eligible. Historical inclusion criteria included the following occurring three or more times each week: a subjective sleep latency of > 30 minutes and either > 3 awakenings per night (with difficulty returning to sleep) or a total sleep time between 180 and 360 minutes.

Exclusion criteria:

any chronic or recurrent medical illness considered to affect sleep or to potentially require medical attention or medication changes during the study was cause for exclusion. Additionally, patients with a present or past history of a major psychiatric illness [e.g. Diagnostic and Statistical Manual of Mental Disorders (DSM)-IV diagnoses of depressive or psychotic disorders, dementia or mental retardation] that was considered to influence sleep or study outcome were excluded. Additional exclusion criteria included a urine drug screen positive for drugs of abuse or sedative/hypnotic/anxiolytic agents; a history of severe adverse reactions to sedative hypnotics; bodyweight more than 5% below or more than 25% above Metropolitan Life Insurance Company standards; use of any medication with significant CNS effects within the prior 2 weeks (4 weeks for slowly eliminated drugs such as fluoxetine); or a history of drug/alcohol abuse within the past 12 months.

Population:			67.5 years	Ethnicity:	NR		
Intervention:	Gen	der:	35% Female				
Drug name	dos	sage	N=	Duration		Primary outcome	Outcome:
Zaleplon	2	mg	12	2 day		\checkmark	sleep latency
Zaleplon	5	mg	12	2 day		\checkmark	sleep duration
Zaleplon	10	mg	12	2 day		\checkmark	number of awakenings
Placebo	NA	mg	12	2 day			

Efficacy:

polysomnography

peryeeninegraphy			
Zaleplon 2mg	Zaleplon 5mg	Zaleplon 10mg	Placebo
PSG latency to persiste	ent sleep (min): Mea	n (p vs placebo)	
30.4 (0.015)	26.0 (<0.001)	21.8 (<0.001)	47.7 (NA)
PSG total sleep time (r	nin): Mean (p vs plac	cebo)	
359.3 (0.239)	363.9 (0.003)	362.8 (0.03)	351.2 (NA)
PSG no. of awakening	s: Mean (p vs placeb	0)	
21.6 (0.872)	21.9 (0.623)	22.1 (0.969)	21.6 (NA)
questionnaire			
Zaleplon 2mg	Zaleplon 5mg	Zaleplon 10mg	Placebo
subjective sleep latenc	y (min): Mean (p vs p	olacebo)	
55.2 (0.654)	42.0 (0.017)	34.4 (<0.001)	58.3 (NA)
subjective total sleep ti	me (min): Mean (p v	s placebo)	
335.8 (0.776)	343.2 (0.140)	351.6 (0.011)	327.9 (NA)
subjective no. of awake	enings: Mean (p vs p	lacebo)	
3.4 (0.671)	3.1 (0.906)	2.8 (0.045)	3.3 (NA)

alsh, 2000b,	2002					Quality	rating	: Fa	ir	
esign:										
Study design:	RCT DB	Parallel	Run-in :	7 days		Setting:	Multic	enter		
			Wash out :	7 days		Country:	US			
Sample:	Number Sc	reened/ Eligible/	Enrolled	Number V	/ithdrawn/ l	_ost to follo	w-up/	Analy	zed	
		365/ 163/	163		29/		5/		NR	
Inclusion crite	ria:									
and, continu			women or crit	Id-bearing potent					contaition,	or
sleep-relate negative for	ast major psy d items). 7) n any illicit dru on within 7 to er day.	o illicit drug use o g or psychotropic	or excessive alc medication. 9)	nce the study. 6) cohol use or abus no use of a pres , or an investigat	e in the pas cription or n	t 12 month on-prescrip	s. 8) ur tion dru	ine dru ugs tha	ug screen at affect s	uding
sleep-relate negative for wake functio cigarettes po Exclusion crite	ast major psy d items). 7) n any illicit dru on within 7 to er day. eria:	o illicit drug use o g or psychotropic 25 days (depenc	or excessive alo medication. 9) ling on half life)	cohol use or abus no use of a pres , or an investigat	e in the pas cription or n onal drug w	t 12 month on-prescrip	s. 8) ur tion dru	ine dru ugs tha	ug screen at affect s	uding
sleep-relate negative for wake functio cigarettes p Exclusion crite NR	ast major psy d items). 7) n any illicit dru on within 7 to er day. eria:	o illicit drug use o g or psychotropic	or excessive alo medication. 9) ling on half life)	cohol use or abus no use of a pres	e in the pas cription or n onal drug w	t 12 month on-prescrip	s. 8) ur tion dru	ine dru ugs tha	ug screen at affect s	uding
sleep-relate negative for wake functio cigarettes po Exclusion crite NR Population: tervention:	ast major psy d items). 7) n any illicit drug on within 7 to er day. eria: Mean age: Gender:	o illicit drug use o g or psychotropic 25 days (depend 44.1 years 71% Female	or excessive alo medication. 9) ling on half life) Ethnicity:	cohol use of a pres no use of a pres , or an investigat 83.4% Caucas	e in the pas cription or n onal drug w	t 12 month on-prescrip	s. 8) ur tion dru	ine dru ugs tha	ug screen at affect s	uding
sleep-relate negative for wake functio cigarettes p Exclusion crite NR Population:	ast major psy d items). 7) n any illicit drug on within 7 to er day. eria: Mean age:	o illicit drug use o g or psychotropic 25 days (depend 44.1 years	or excessive alo medication. 9) ling on half life)	cohol use of a pres no use of a pres , or an investigat 83.4% Caucas	e in the pas cription or n onal drug w an Primary	t 12 month on-prescrip	s. 8) ur tion dru	ine dru ugs tha	ug screen at affect s	uding
sleep-relate negative for wake functio cigarettes po Exclusion crite NR Population: tervention:	ast major psy d items). 7) n any illicit drug on within 7 to er day. eria: Mean age: Gender:	o illicit drug use o g or psychotropic 25 days (depend 44.1 years 71% Female	or excessive alo medication. 9) ling on half life) Ethnicity:	cohol use of a pres no use of a pres , or an investigat 83.4% Caucas	e in the pas cription or n onal drug w an Primary outcome	t 12 month on-prescrip ithin 30 day	s. 8) ur ition dri /s. 10)	ine dru ugs tha	ug screen at affect s	uding
sleep-relate negative for wake functio cigarettes pr Exclusion crite NR Population: tervention: Drug name	ast major psy d items). 7) n any illicit drug on within 7 to er day. eria: Mean age: Gender: dosage	o illicit drug use o g or psychotropic 25 days (depend 44.1 years 71% Female N=	er excessive alor medication. 9) ling on half life) Ethnicity: Duration	cohol use of a pres no use of a pres , or an investigat 83.4% Caucas	e in the pas cription or n onal drug w an Primary outcome	t 12 month on-prescrip ithin 30 day Outcome:	s. 8) ur ition dru /s. 10)	ine dru ugs tha	ug screen at affect s	uding
sleep-relate negative for wake functio cigarettes p Exclusion crite NR Population: tervention: Drug name Zolpidem	ast major psy d items). 7) n any illicit drug on within 7 to er day. eria: Mean age: Gender: dosage 10 mg	o illicit drug use o g or psychotropic 25 days (depend 44.1 years 71% Female N= 82	ter excessive ald medication. 9) ling on half life) Ethnicity: Duration 56 day	cohol use of a pres no use of a pres , or an investigat 83.4% Caucas	e in the pas cription or n onal drug w an Primary outcome	t 12 month on-prescrip ithin 30 day Outcome: sleep laten	s. 8) ur tion dru /s. 10) cy time	ine dru ugs th smoki	ug screen at affect s	uding

19.55 I, 8 weeks average: Mean 50.4 bill 8 weeks average: Mean	P: NS P: <0.05
50.4	P: <0.05
	P: <0.05
oill, 8 weeks average: Mean	
in, e neene arenager mourr	
364.1	P: <0.05
n pill, 8 weeks average: Mean	
1.8	P: <0.05
4=poor), with pill, 8 weeks average: M	ean
2.5	P: <0.05
Placebo	
multi-data	P: NS
ŀ	h pill, 8 weeks average: Mean 1.8 4=poor), with pill, 8 weeks average: Me 2.5 Placebo

ammit, 2004								Quality	rating:	Fair
esign:										
Study design:	RCT	DB	Parall	el	Run-in : Wash out :	2 days 5-7 days		Setting: Country:	Single (US	Center
Sample:	Num	ber Sci	reened/ E NR/	Eligible/ 669/		-	Withdrawn/ 16/	•		nalyzed 308
Inclusion criter	ria:									
						for primary inso fall asleep eac				ed no more than eligible for
	any u					llness, any peri gs syndrome, c				
Population:			39.8 yea		Ethnicity:	66.2% Cauca 16.6% black	asians			
Population: ntervention: Drug name	Gene		39.8 yea 61% Fer N=	nale	Ethnicity: Duration		Primary	Outcome:		
ntervention:	Gene	der:	61% Fer	male	·			Outcome:		
ntervention: Drug name	Geno dos	der: sage	61% Fer	nale	Duration		Primary		юу	
Drug name Eszopiclone	Geno dos 2	der: sage mg	61% Fer N= 104	nale	Duration 44 day		Primary	sleep later	icy tion	ngs
Drug name Eszopiclone Eszopiclone	Geno dos 2 3	der: sage mg mg	61% Fer N= 104 105	nale	Duration 44 day 44 day		Primary	sleep later sleep dura	icy tion awakenii	0
Drug name Eszopiclone Eszopiclone	Geno dos 2 3	der: sage mg mg	61% Fer N= 104 105	nale	Duration 44 day 44 day		Primary	sleep later sleep dura number of	icy tion awakenii after slee	0
Drug name Eszopiclone Eszopiclone	Geno dos 2 3	der: sage mg mg	61% Fer N= 104 105	nale	Duration 44 day 44 day		Primary	sleep later sleep dura number of wake time	icy tion awakenii after slee leep	0
Drug name Eszopiclone Eszopiclone	Geno dos 2 3	der: sage mg mg	61% Fer N= 104 105	nale	Duration 44 day 44 day		Primary	sleep later sleep dura number of wake time quality of s	icy tion awakenii after slee leep eep	0
Drug name Eszopiclone Eszopiclone	Geno dos 2 3	der: sage mg mg	61% Fer N= 104 105	nale	Duration 44 day 44 day		Primary	sleep later sleep dura number of wake time quality of s depth of sl	icy awakenii after slee leep eep ertness	ep onset

Efficacy:

polysomnography

Eszopiclone 2mg	Eszopiclone 3mg	
sleep latency (minute)	- night 1, 15, 29 avera	ge: Median (p vs placebo)
15 (<0.001)	13.1 (<0.001)	29 (NA)
sleep efficiency (%) - n	ight 1, 15, 29 average	: Median (p vs placebo)
88.1 (<0.01)	90.1 (<0.001)	85.7 (NA)
wake time after sleep o	nset, WASO (min) - n	ight 1, 15, 29 average: Median (p vs placebo)
37.1 (NS)	33.8 (<0.01)	44.1 (NA)
number of awakenings	, NAW - night 1, 15, 29	9 average: Median (p vs placebo)
6.5 (NS)	5.7 (NS)	6.0 (NA)

nit, 2004		Quality rating: Fair	
morning questionnaire			
Eszopiclone 2mg	Eszopiclone 3mg	Placebo	
sleep latency (min): Me	dian (p vs placebo)		
30 (<0.0001)	27.7 (<0.0001)	46 (NA)	
total sleep time (min): N	/ledian (p vs placebo)		
400 (0.0207)	406 (<0.0001)	366 (NA)	
number of awakenings:	Median (p vs placebo)	
2.7 (0.2956)	2.4 (0.1720)	3.0 (NA)	
WASO (min): Median (o vs placebo)		
37.1 (0.6884)	30.2 (0.0204)	45 (NA)	
quality of sleep (0=poor	r; 100=excellent): Medi	ian (p vs placebo)	
54.5 (0.0414)	56.6 (0.0072)	47.7 (NA)	
depth of sleep (0=poor	; 100=excellent): Medi	ian (p vs placebo)	
58.9 (0.0052)	56.7 (0.0457)	51.7 (NA)	
evening questionnaire			
Eszopiclone 2mg	Eszopiclone 3mg	Placebo	
daytime alertness (high	er scores indicate imp	roved function): Mean (p vs placebo)	
6.66 (0.873)	7.02 (0.059)	6.67 (NA)	
daytime ability to function	on (higher scores indi	cate improved function): Mean (p vs placebo)	
6.81 (0.901)	7.15 (0.118)	6.83 (NA)	
morning sleepiness (1=	very sleepy; 100=not a	at all sleepy): Mean (p vs placebo)	
51.3 (0.256)	50.8 (0.344)	48.2 (NA)	

er, 2000							Quality	rating: F	air
sign:									
Study design:	RCT	DB	Parallel	Run-in : Wash out	7 day : 7 day		Setting: Country:	Multicent Europe	er
Sample:	Numl	ber Scr	eened/ Eligibl NR/ N			Number Withdraw 2	vn/ Lost to follo 22/	ow-up/ Ana NR/	alyzed 422
months' dur system (CN American P	evaluate ation. I S) diso sychiat	nclusio order. P tric Ass	n to this study rimary insomn ociation, 1994)	was also depe a, based on cr	ndent or teria in t rized by	65 years old and w h the absence of ar the Diagnostic and a sleep latency of less.	ny significant part statistical Mar	sychiatric o nual, 4th ec	r central nervous lition (DSM-IV;
Exclusion crite Patients with		/ score	of > 50 on the	Zung Anxiety o	r Depre	ssion scales were	not enrolled.		
Population:	Mear	n age:	72.5 years	Ethnicity	: NR				
tervention:	Geno	der:	% Female						
Drug name	dos	sage	N=	Duration					
Zaleplon	5	mg	139	14 day					
Zaleplon	10	mg	145	14 day					
Placebo	NA	mg	138	14 day					
• •	t ionna i eplon (bound insom i Zaleplon 10		acebo				
rebound:	subjec	tive sle	ep latency (mi	n), withdrawal o	lav 1: M	edian			
	45		50	,,	60				
rebound:	subjec	tive tot	al sleep time (r	nin), withdrawa	l day 1:	Median			
	330		300		330				
rebound:	subjec	tive nu	mber of awake	nings, withdrav	val day ²	1: Median			
	2		2		2				
incidence o	of rebo eplon {		somnia Zaleplon 10	ima Pl	acebo				
			•	tency: Number					
Tebound	11 (9)		12 (9)		(%) 7 (5)				
rehound i				ep time: Numb	. ,				
	14 (11		17 (13)	•	6. (70) 6 (5)				
	•			ings: Number (. ,				
	nsomn	iia: num	iber ur awaker						

	3						Quality	rating:	Poo	r
sign:										
Study design:	RCT	DB	Parallel	Run-in : Wash out :	7 days 7 days		Setting: Country:	Single France		
Sample:	Numbe	er Scr	eened/ Eligib NR/ 2			Withdrawn/L NR/	•		nalyze	ed 21
Inclusion crite	ria:									
				to meet two of the f less than 6 h or						
Exclusion crite										
testing and o	on urine	drug	screening for	cal, psychiatric an amphetamines, c vith caffeinism or a	annabinoids, m	orphine deriva	atives, barb	oiturates		ine laborato
Population:	Mean	age:	NR years	Ethnicity:	NR					
-	Gende		43% Female	······································						
ervention: Drug name	dosa	ge	N=	Duration						
Zolpidem	10 r	ng	11	14 day						
Placebo	NA r	ng	10	14 day						
bound: polysomno	graphy									
polysomno Z	olpidem		Placebo		(02)					
polysomno Z sleep effic	Colpidem		y 28 withdraw	al, rebound: Mea	n (SD)					~0.05
polysomno Z sleep effic	Colpidem ciency (% 77.4 (4)	%), da	y 28 withdraw 68.9 (4	val, rebound: Mea)					P:	<0.05
polysomno Z sleep effic total sleep	Colpidem ciency (% 77.4 (4) o time (n	%), da nin), c	y 28 withdraw 68.9 (4 lay 28 withdra	val, rebound: Mea) wal, rebound: Me						
polysomno Z sleep effic total sleep 3	Colpidem ciency (% 77.4 (4) o time (n 41.3 (12	%), da nin), c)	y 28 withdraw 68.9 (4 lay 28 withdra 298.3 (2	ral, rebound: Mea) wal, rebound: Me 1)	an (SD)					<0.05
polysomno Z sleep effic total sleep 3/ sleep ons	Colpidem ciency (% 77.4 (4) o time (n 41.3 (12	%), da nin), c) cy (mi	y 28 withdraw 68.9 (4 lay 28 withdra 298.3 (2	ral, rebound: Mea) wal, rebound: Me 1) hdrawals, rebound	an (SD)				P:	
polysomno Z sleep effic total sleep 3 sleep ons 5	Colpidem Colpidem (% 77.4 (4) o time (n 41.3 (12 et latence 50.7 (11)	%), da nin), c) cy (mi	y 28 withdraw 68.9 (4 day 28 withdra 298.3 (2 n), day 28 with 36.3 (7	ral, rebound: Mea) wal, rebound: Me 1) hdrawals, rebound	an (SD) d: Mean (SD)				P:	<0.05
polysomno Z sleep effic total sleep 3 sleep ons 5 time awak	Colpidem Colpidem (% 77.4 (4) o time (n 41.3 (12 et latence 50.7 (11)	//6), da nin), c) cy (mi , day :	y 28 withdraw 68.9 (4 day 28 withdra 298.3 (2 n), day 28 with 36.3 (7	ral, rebound: Mea) wal, rebound: Me 1) hdrawals, rebound) , rebound: Mean (an (SD) d: Mean (SD)				P: P:	<0.05
polysomno Z sleep effic total sleep 34 sleep ons 5 time awak 5	Colpidem Sciency (% 77.4 (4) o time (n 41.3 (12 et latence 50.7 (11) sce (min), 53.7 (13)	%), da nin), c) cy (mi	y 28 withdraw 68.9 (4 day 28 withdra 298.3 (2 n), day 28 with 36.3 (7 28 withdrawal,	ral, rebound: Mea) wal, rebound: Me 1) hdrawals, rebound) , rebound: Mean (an (SD) d: Mean (SD)				P: P:	<0.05 NS
polysomno Z sleep effic total sleep 34 sleep ons 5 time awak 5 sleep quest	Colpidem Sciency (% 77.4 (4) o time (n 41.3 (12 et latence 50.7 (11) sce (min), 53.7 (13)	%), da nin), c) cy (mi , day : e	y 28 withdraw 68.9 (4 day 28 withdra 298.3 (2 n), day 28 with 36.3 (7 28 withdrawal,	ral, rebound: Mea) wal, rebound: Me 1) hdrawals, rebound) , rebound: Mean (7)	an (SD) d: Mean (SD)				P: P:	<0.05 NS
polysomno Z sleep effic total sleep 3 sleep ons 5 time awak 5 sleep quest Z	Colpidem Sciency (% 77.4 (4) time (n 41.3 (12 et latence 50.7 (11) (50.7 (11) (50.7 (13) (53.7 (13) Colpidem	%), da nin), c) cy (mi , day : e	y 28 withdraw 68.9 (4 298.3 (2 n), day 28 with 36.3 (7 28 withdrawal, 99.3 (17 Placebo	ral, rebound: Mea) wal, rebound: Me 1) hdrawals, rebound) , rebound: Mean (7)	an (SD) d: Mean (SD) SD)				P: P:	<0.05 NS
polysomno Z sleep effic total sleep 3 sleep ons 5 time awak 5 sleep quest Z sleep ons	Colpidem Sciency (% 77.4 (4) time (n 41.3 (12 et latence 50.7 (11) (50.7 (11) (50.7 (13) (53.7 (13) Colpidem	%), da nin), c) cy (mi , day 2 , e	y 28 withdraw 68.9 (4 298.3 (2 n), day 28 with 36.3 (7 28 withdrawal, 99.3 (17 Placebo	ral, rebound: Mea) wal, rebound: Me 1) hdrawals, rebound) , rebound: Mean (7) p withdrawal, rebou	an (SD) d: Mean (SD) SD)				P: P: P:	<0.05 NS
polysomno Z sleep effic total sleep 3 sleep ons 5 time awak 5 sleep quest Z sleep ons 6	Colpidem ciency (% 77.4 (4) time (n 41.3 (12 et latence 50.7 (11) ce (min), 53.7 (13) cionnaire Colpidem et latence 50.8 (14)	%), da nin), c) ccy (mi , day 2 , e 1 1	y 28 withdraw 68.9 (4 298.3 (2 n), day 28 withdra 36.3 (7 28 withdrawal, 99.3 (17 Placebo n), day 22-28 70.8 (10	ral, rebound: Mea) wal, rebound: Me 1) hdrawals, rebound) , rebound: Mean (7) o withdrawal, rebou	an (SD) d: Mean (SD) SD) und: Mean (SD)				P: P: P:	<0.05 NS <0.05
polysomno Z sleep effic total sleep 3 sleep ons 5 time awak 5 sleep quest Z sleep ons 6 total sleep	Colpidem ciency (% 77.4 (4) time (n 41.3 (12 et latence 50.7 (11) ce (min), 53.7 (13) cionnaire Colpidem et latence 50.8 (14)	(%), da nin), c) cy (mi , day 2 , e 1 cy (mi	y 28 withdraw 68.9 (4 298.3 (2 n), day 28 withdra 36.3 (7 28 withdrawal, 99.3 (17 Placebo n), day 22-28 70.8 (10	ral, rebound: Mea) wal, rebound: Me 1) hdrawals, rebound) , rebound: Mean (7) o withdrawal, rebound:)) drawal, rebound:	an (SD) d: Mean (SD) SD) und: Mean (SD)				P: P: P:	<0.05 NS <0.05
polysomno Z sleep effic total sleep 34 sleep ons 5 time awak 5 sleep quest Z sleep ons 6 total sleep 34	Colpidem ciency (% 77.4 (4) to time (n 41.3 (12 et latence 50.7 (11) ce (min), 53.7 (13) cionnaire Colpidem et latence 50.8 (14) to time (n 41.8 (18)	<pre>%), da nin), c)) , day 2 , e , cy (mi , cy (mi , nin), c)</pre>	y 28 withdraw 68.9 (4 298.3 (2 n), day 28 withdra 36.3 (7 28 withdrawal, 99.3 (17 Placebo n), day 22-28 70.8 (10 day 22-28 with 310.9 (2	ral, rebound: Mea) wal, rebound: Me 1) hdrawals, rebound) , rebound: Mean (7) o withdrawal, rebound:)) drawal, rebound:	an (SD) d: Mean (SD) SD) und: Mean (SD) Mean (SD)				P: P: P:	<0.05 NS <0.05

						(Quality	rating:	Fair
Design:									
Study design:	RCT	DB	Parallel	Run-in : Wash out :	2 days 3 days		Setting: Country:	Single C Uruguay	
Sample:	Numbe	er Scr	eened/ Eligible NR/ NF	e/ Enrolled	•	Withdrawn/ Lo NR/	•		
Inclusion crite	ria:								
					sleep disturban er of nocturnal av			30 minut	es; total sleep time
Exclusion crite									
organic dise	ease or s	evere	e psychiatric dis	orders, and pati	ents in whom ins	sufficient com	oliance wa	s to be ex	ients suffering from xpected. Alcohol beriod also led to
Population:	Mean a	age:	44.25 years	Ethnicity:	NR				
nton contion	Gende	er:	83% Female						
ntervention: Drug name	dosa	ae	N=	Duration					
Zolpidem	10 n	ng	6	27 day					
Placebo	NA n	ng	6	27 day					
polysomno	graphy		Disasha						
Z	Zolpidem leep late		Placebo min), nights 31-	33, withdrawal,	rebound: Mean	(SD)			
stage 2 s	•	ncy (r			rebound: Mean	(SD)			P: NS
stage 2 sl	leep late 7.2 (11.1	ncy (r)	min), nights 31- 32.3 (7.9))	rebound: Mean rebound: Mean	. ,			P: NS
stage 2 sl 4 total num	leep late 7.2 (11.1	ncy (r) vaker	min), nights 31- 32.3 (7.9)	-33, withdrawal,		. ,			P: NS P: NS
z stage 2 sl 4 total num 2	leep late 7.2 (11.1 ber of av 28.7 (4.6)	ncy (r) vaker	min), nights 31- 32.3 (7.9) hings, nights 31 26.1 (3.7)	-33, withdrawal,	rebound: Mean	. ,			-
z stage 2 sl 4 total num 2 total wake	leep late 7.2 (11.1 ber of av 28.7 (4.6)	ncy (r) vaker nin), n	min), nights 31- 32.3 (7.9) hings, nights 31 26.1 (3.7)) -33, withdrawal,) thdrawal, rebour	rebound: Mean	. ,			-
z stage 2 sl 4 total num 2 total wake 9	leep late 7.2 (11.1 ber of av 28.7 (4.6) e time (m 7.7 (15.8	ncy (r) vaker hin), n	min), nights 31- 32.3 (7.9) nings, nights 31 26.1 (3.7) nights 31-33, wi 115.9 (18.8)) -33, withdrawal,) thdrawal, rebour 3)	rebound: Mean	(SD)			P: NS
total wake time	leep late 7.2 (11.1 ber of av 28.7 (4.6) e time (m 7.7 (15.8	ncy (r) vaker) nin), n) eep o	min), nights 31- 32.3 (7.9) nings, nights 31 26.1 (3.7) nights 31-33, wi 115.9 (18.8)) -33, withdrawal,) thdrawal, rebour 3) nts 31-33, withdr	rebound: Mean nd: Mean (SD)	(SD)			P: NS
z stage 2 sl 4 total num 2 total wake 9 wake time 5	leep late 7.2 (11.1 ber of av 88.7 (4.6) e time (m 7.7 (15.8 e after sle 4.9 (16.1	ncy (r) vaker hin), n) eep o)	min), nights 31- 32.3 (7.9) nings, nights 31 26.1 (3.7) nights 31-33, wi 115.9 (18.4 onset (min), nigh 92.0 (16.3) -33, withdrawal, thdrawal, rebour 3) hts 31-33, withdr)	rebound: Mean nd: Mean (SD) rawal, rebound: I	(SD)			P: NS P: NS
z stage 2 sl 4 total num 2 total wake 9 wake time 5 total slee	leep late 7.2 (11.1 ber of av 88.7 (4.6) e time (m 7.7 (15.8 e after sle 4.9 (16.1	ncy (r) vaker hin), n) eep o) hin), r	min), nights 31- 32.3 (7.9) nings, nights 31 26.1 (3.7) nights 31-33, wi 115.9 (18.4 onset (min), nigh 92.0 (16.3) -33, withdrawal,) thdrawal, rebour 3) nts 31-33, withdr) thdrawal, rebour	rebound: Mean nd: Mean (SD) rawal, rebound: I	(SD)			P: NS P: NS
z stage 2 sl 4 total num 2 total wake 9 wake time 5 total sleep 37	leep late 7.2 (11.1 ber of av 88.7 (4.6) e time (m 7.7 (15.8 e after sle 4.9 (16.1 p time (m 78.6 (15.3	ncy (r) vaker hin), n) eep o) nin), r 3)	min), nights 31- 32.3 (7.9) nings, nights 31 26.1 (3.7) nights 31-33, wi 115.9 (18.4) onset (min), nigh 92.0 (16.3) nights 31-33, wi 361.2 (17.4)) -33, withdrawal, thdrawal, rebour 3) hts 31-33, withdr) thdrawal, rebour 9)	rebound: Mean nd: Mean (SD) rawal, rebound: I nd: Mean (SD)	(SD)			P: NS P: NS P: NS
z stage 2 sl 4 total num 2 total wake 9 wake time 5 total sleep 37 sleep effe	leep late 7.2 (11.1 ber of av 88.7 (4.6) e time (m 7.7 (15.8 e after sle 4.9 (16.1 p time (m 78.6 (15.3	ncy (r) vaker)) eep o)) hin), r 3)	min), nights 31- 32.3 (7.9) nings, nights 31 26.1 (3.7) nights 31-33, wi 115.9 (18.4) onset (min), nigh 92.0 (16.3) nights 31-33, wi 361.2 (17.4)) -33, withdrawal, thdrawal, rebour 3) nts 31-33, withdr) thdrawal, rebour 9) ndrawal, rebourd	rebound: Mean nd: Mean (SD) rawal, rebound: I nd: Mean (SD)	(SD)			P: NS P: NS P: NS
z stage 2 sl 4 total num 2 total wake 9 wake time 5 total sleep 37 sleep effic 7	leep late 7.2 (11.1 ber of av 8.7 (4.6) e time (m 7.7 (15.8 e after sle 4.9 (16.1 p time (m 7.8.6 (15.3 ciency (% 79.0 (3.7)	ncy (r(r)) nin), n)) eep o)) nin), r 3) (), nių	min), nights 31- 32.3 (7.9) nings, nights 31 26.1 (3.7) nights 31-33, wi 115.9 (18.4) onset (min), nigh 92.0 (16.3) nights 31-33, with 361.2 (17.4) ghts 31-33, with 75.3 (3.7)) -33, withdrawal, thdrawal, rebour 3) nts 31-33, withdr) thdrawal, rebour 9) ndrawal, rebourd	rebound: Mean nd: Mean (SD) rawal, rebound: I nd: Mean (SD) d: Mean (SD)	(SD)			P: NS P: NS P: NS P: NS

ti, 1996		Quality rating: Fair
questionnaire		
Zolpidem	Placebo	
sleep latency (lower sc	ore indicates more positive response), night 31-	33, withdrawal, rebound: Mean (SD)
2.4 (0.4)	1.9 (0.3)	P: NS
sleep duration (higher s	core indicates more positive response), night 3	I-33, withdrawal, rebound: Mean (SD)
2.1 (0.2)	2.4 (0.3)	P: NS
number of awakenings	(lower score indicates more positive response),	night 31-33, withdrawal, rebound: Mean (SD)
2.3 (0.4)	2.6 (0.3)	P: NS
disturbed sleep (higher	score indicates more positive response), night	31-33, withdrawal, rebound: Mean (SD)
64.9 (8.2)	63.7 (6.8)	P: NS
daytime alertness (high	er score indicates more positive response), nigl	t 31-33, withdrawal, rebound: Mean (SD)
73.8 (7.0)	54.1 (7.0)	P: <0.05

Study design: RCT DB Parallel Run-in :: 3 days Setting: Single Center Sample: Number Screened/ Eligible/ Enrolled Number Withdrawn/ Lost to follow-up/ Analyzed Sample: Number Screened/ Eligible/ Enrolled Number Withdrawn/ Lost to follow-up/ Analyzed Patients with poor health, acute or chronic pain, decompensated hepatic, renal or cardiac disease, known drug allergy or abuse, periodic leg movements during sleep, restless legs or sleep apnea were excluded from the study, and so were pregnant women and breast-feeding mothers. Patients with poor health; acute or chronic pain; hepatic, renal, respiratory, cardiac, or neuropsychiatric diseases [subjects emering also led to exclusion. Presst-feeding mothers, subjects deemed insufficiently compliant, or those with clinicant deviations in their laboratory tests. Alcohal abuse, intake of hypnotics or anxiolytics in the seven days prior to baseline period, or a positive berzodiazepine urine screening also led to exclusion. Population: Mean age: 51.9 years Ethnicity: NR Gender: 100% Female Ethnicity: NR Dipidem 10 mg 6 15 day Placebo NA mg 6 15 day Pisot Stage 2 sleep latency - night 19-21, withdrawal, rebound: Mean (SD) 55.7 (15.7) 69.7 (12.	nti, 2000						Qı	uality r	ating: Po	or
Wash out: 3 daysCountry: UruguaySample:Number Screened/ Eligible/ Enrolled NR/Number Withdrawn/ Lost to follow-up/ Analyzed NR/NR/NR/12NR/NR/12Inclusion criteria:Patients aged between 27 and 59 years, with chronic primary insomnia according to the DSM-IV participated in the study.Exclusion criteria:Patients with poor health, acute or chronic pain, decompensated hepatic, renal or cardiac disease, known drug allergy or abuse, periodic leg movements during sleep, restless legs or sleep apnea were excluded from the study, and so were pregnant women and breast-leeding mothers.Patients with poor health; acute or chronic pain; hepatic, renal, respiratory, cardiac, or neuropsychiatric diseases [subjects with a score of HAMAD > 18, or a score of HAMA(14 items)>16 were not included]; known drug allergy or abuse; periodic leg movements during sleep, restless legs or sleep apnea were excluded from the study, as also were pregnancy women, breast-feeding mothers, subjects deemed insufficiently compliant, or those with clinically significant deviations in their laboratority tests. Alcohol abuse, intake of hynontics or anxiolytics in the seven days prior to baseline period, or a positive benzodiazepine urine screening also led to exclusion.PoundementdomentDurationZolpidemPlaceboNADurationStoutZolpidemPlaceboStoutPint 19-21, withdrawal, rebound: Mean (SD)5.7 (15.7)6.9 (8.7	sign:									
NR/NR/12NR/NR/12Inclusion oriteria:Patients aged between 27 and 59 years, with chronic primary insomnia according to the DSM-IV participated in the study.Exclusion oriteria:Patients with poor health, acute or chronic pain, decompensated hepatic, renal or cardiac disease, known drug allergy or abuse, proteidic leg movements during sleep, restless legs or sleep apnea were excluded from the study, and so were pregnant women and breast-feeding mothers.Patients with poor health, acute or chronic pain, hepatic, renal, respiratory, cardiac, or neuropsychiatric diseases [subjects with as ore of HAMA 14 Items)-16 were not included]; known drug allergy or abuse; precidic leg movements during sleep, restless legs or sleep apnea were excluded from the study, as also were pregnancy women, breast-feeding mothers, subjects deemed insufficiently compliant, or those with clinically significant deviations in their laborator types. Alcohol abuse, intake of hyponicis or anxiolytics in the seven days prior to baseline period, or a positive benzodiazepine unine screening also led to exclusion.Population:Mean age: 51.9 yearsEthnicity: NRCender: 100% FemaleEthnicity: NRZolpidem 10 mg 615 dayPaceboZolpidem 10 mg 615 dayPaceboStage 2 sleep latency - night 19-21, withdrawal, rebound: Mean (SD)5.7. (15.7)6.9. (12.5)PrinceZolpidemPlaceboStage 2 s	Study design:	RCT	DB	Parallel				•	0	er
Patients aged between 27 and 59 years, with chronic primary insomnia according to the DSM-IV participated in the study. Exclusion criteria: Patients with poor health, acute or chronic pain, decompensated hepatic, renal or cardiac disease, known drug allergy or abuse, periodic leg movements during sleep, restless legs or sleep apnea were excluded from the study, and so were pregnant women and breast-teeding mothers. Patients with poor health; acute or chronic pain; hepatic, renal, respiratory, cardiac, or neuropsychiatric diseases [subjects with as core of HAMA [14 items]>16 were not included]; known drug allergy or abuse; periodic leg movements during sleep; restless legs; or sleep apnea were excluded from the study, and so were pregnancy women, breast-feeding mothers. Subjects deemed insufficiently compliant, or those with chlinically significant deviations in their laboratory tests. Alcohol abuse, intake of hypnotics or anxiolytics in the seven days prior to baseline period, or a positive benzodiazepine urine screening also led to exclusion. Population: Mean age: 51.9 years Ethnicity: NR Gender: 100% Female tervention: Drug name dosage N= Duration Zolpidem 10 mg 6 15 day Zolpidem Placebo Stage 2 sleep latency - night 19-21, withdrawal, rebound: Mean (SD) 25.4 (3.8) 3.22 (5.9) P: NS total number of awakenings - night 19-21, withdrawal, rebound: Mean (SD) 25.4 (3.8) 32.2 (5.9) P: NS total sleep time (min) - night 19-21, withdrawal, rebound: Mean (SD) 33.4.6 (22) 281.6 (33.2) P: NS	Sample:	Number		-		Number W		t to follov		
Exclusion criteria: Patients with poor health, acute or chronic pain, decompensated hepatic, renal or cardiac disease, known drug allergy or abuse, periodic leg movements during sleep, restless legs or sleep apnea were excluded from the study, and so were pregnant women and breast-feeding mothers. Patients with poor health; acute or chronic pain; hepatic, renal, respiratory, cardiac, or neuropsychiatric diseases [subjects with a score of HAMD > 18, or a score of HAMA(14 items)>16 were not included]; known drug allergy or abuse; periodic leg movements during sleep, restless legs or anxiolytics in the study, as also were pregnancy women, breast-feeding mothers, subjects deemed insufficiently compliant, or those with clinically significant deviations in their laboratory tests. Alcoho labuse, intak of hypontics or anxiolytics in the seven days prior to baseline period, or a positive benzodiazepine urine screening also led to exclusion. Population: Mean age: 51.9 years Ethnicity: NR Gender: 100% Female tervention: Duration Zolpidem 10 mg 6 Zolpidem 10 mg 6 Stage 2 sleep latency - night 19-21, withdrawal, rebound: Mean (SD) 55.7 (15.7) 69.7 (12.5) Stage 2 sleep latency - night 19-21, withdrawal, rebound: Mean (SD) 25.4 (3.8) 32.2 (5.9) P: NS waking time after sleep onset (min) - night 19-21, withdrawal, rebound: Mean (SD) 75.1 (7.9) 137.5 (29.2) P: NS total sleep time (min) - night 19-21, withdrawal, re	Inclusion crite	ria:								
Patients with poor health, acute or chronic pain, decompensated hepatic, renal or cardiac disease, known drug allergy or abuse, periodic leg movements during sleep, restless legs or sleep apnea were excluded from the study, and so were pregnant women and breast-feeding mothers. Patients with poor health; acute or chronic pain; hepatic, renal, respiratory, cardiac, or neuropsychiatric diseases [subjects with a score of HAMD > 18, or a score of HAMA(14 items)>16 were not included]; known drug allergy or abuse; periodic leg movements during sleep; restless legs; or sleep apnea were excluded from the study, as also were pregnancy women, breast-feeding mothers, subjects deemed insufficiently compliant, or those with clinically significant deviations in their laboratory tests. Alcohol abuse, intake of hypototics or anxiolytics in the seven days prior to baseline period, or a positive benzodiazepine urine screening also led to exclusion. Population: Mean age: 51.9 years Ethnicity: NR Gender: 100% Female tervention: Drug name dosage N= Duration Zolpidem 10 mg 6 15 day Placebo NA mg 6 15 day Placebo NA mg 6 15 day Placebo NA mg 6 15 day Placebo Stage 2 sleep latency - night 19-21, withdrawal, rebound: Mean (SD) 55.7 (15.7) 69.7 (12.5) P: NS total number of awakenings - night 19-21, withdrawal, rebound: Mean (SD) 25.4 (3.8) 32.2 (5.9) P: NS waking time after sleep onset (min) - night 19-21, withdrawal, rebound: Mean (SD) 33.4 6 (22) 281.6 (33.2) P: NS sleep efficiency (%) - night 19-21, withdrawal, rebound: Mean (SD) 33.4 6 (22) 281.6 (33.2) P: NS	Patients age	ed betwee	en 27 ar	nd 59 years,	with chronic pri	mary insomnia ac	cording to the I	DSM-IV p	participated i	n the study.
with a score of HAMD > 18, or a score of HAMA(14 items)>16 were not included]; known drug allergy or abuse; periodic leg movements during sleep; restless legs; or sleep apnea were excluded from the study, as also were pregnancy women, breast-feeding mothers, subjects deemed insufficiently compliant, or those with clinically significant deviations in their laboratory tests. Alcohol abuse, intake of hypnotics or anxiolytics in the seven days prior to baseline period, or a positive benzodiazepine urine screening also led to exclusion. Population: Mean age: 51.9 years Ethnicity: NR Gender: 100% Female tervention: Drug name dosage N= Duration Zolpidem 10 mg 6 15 day Placebo NA mg 6 15 day Placebo NA mg 6 15 day bound: polygraphic sleep record Zolpidem Placebo stage 2 sleep latency - night 19-21, withdrawal, rebound: Mean (SD) 55.7 (15.7) 69.7 (12.5) P: NS total number of awakenings - night 19-21, withdrawal, rebound: Mean (SD) Z5.4 (3.8) 32.2 (5.9) P: NS waking time after sleep onset (min) - night 19-21, withdrawal, rebound: Mean (SD) 75.1 (7.9) 137.5 (29.2) P: NS total sleep time (min) - night 19-21, withdrawal, rebound: Mean (SD) 334.6 (22) 281.6 (33.2) P: NS sleep efficiency (%) - night 19-21, withdrawal, rebound: Mean (SD)	Patients with abuse, perio	h poor hea odic leg m	oveme	nts during sl	eep, restless leo					
Gender:100% FemaleDrug namedosageN=DurationZolpidem10mg615 dayPlaceboNAmg615 dayesbound:ZolpidemPlaceboZolpidemPlaceboStage 2 sleep recordStage 2 sleep latency - night 19-21, withdrawal, rebound: Mean (SD)55.7 (15.7)69.7 (12.5)P: NStotal number of awakenings - night 19-21, withdrawal, rebound: Mean (SD)25.4 (3.8)32.2 (5.9)P: NSwaking time after sleep onset (min) - night 19-21, withdrawal, rebound: Mean (SD)75.1 (7.9)137.5 (29.2)P: NStotal sleep time (min) - night 19-21, withdrawal, rebound: Mean (SD)334.6 (22)281.6 (33.2)P: NSsleep efficiency (%) - night 19-21, withdrawal, rebound: Mean (SD)	with a score movements breast-feedi laboratory te	of HAMD during sle ng mothe ests. Alcol) > 18, (eep; res rs, subj hol abu	or a score of stless legs; c jects deeme se, intake of	HAMA(14 item or sleep apnea v d insufficiently c hypnotics or ar	s)>16 were not ind vere excluded from ompliant, or those	luded]; known n the study, as with clinically	drug alle also wer significar	ergy or abuse re pregnancy nt deviations	e; periodic leg v women, in their
Gender:100% FemaleDrug namedosageN=DurationZolpidem10ng615 dayPlaceboNAng615 dayesbound:SolpidemPlaceboZolpidemPlaceboStage 2 sleep recordStage 2 sleep latency - night 19-21, withdrawal, rebound: Mean (SD)55.7 (15.7)69.7 (12.5)P: NStotal number of awakenings - night 19-21, withdrawal, rebound: Mean (SD)25.4 (3.8)32.2 (5.9)P: NSwaking time after sleep onset (min) - night 19-21, withdrawal, rebound: Mean (SD)75.1 (7.9)137.5 (29.2)P: NStotal sleep time (min) - night 19-21, withdrawal, rebound: Mean (SD)334.6 (22)281.6 (33.2)P: NSsleep efficiency (%) - night 19-21, withdrawal, rebound: Mean (SD)	Population:	Mean a	ge: 51	.9 years	Ethnicity:	NR				
Drug namedosageN=DurationZolpidem10mg615 dayPlaceboNAmg615 dayPlaceboZolpidem9 PlaceboZolpidemPlaceboZolpidemPlaceboStage 2 sleep latency - night 19-21, withdrawal, rebound: Mean (SD) 55.7 (15.7)69.7 (12.5)P: NStotal number of awakenings - night 19-21, withdrawal, rebound: Mean (SD) 25.4 (3.8)32.2 (5.9)P: NSvalue after sleep onset (min) - night 19-21, withdrawal, rebound: Mean (SD) 75.1 (7.9)137.5 (29.2)P: NStotal sleep time (min) - night 19-21, withdrawal, rebound: Mean (SD) 334.6 (22)281.6 (33.2)P: NSsleep efficiency (%) - night 19-21, withdrawal, rebound: Mean (SD) 334.6 (22)281.6 (33.2)P: NS										
Zolpidem 10 mg 6 15 day Placebo NA mg 6 15 day ebound: polygraphic sleep record Zolpidem Placebo stage 2 sleep latency - night 19-21, withdrawal, rebound: Mean (SD) 55.7 (15.7) 69.7 (12.5) P: NS total number of awakenings - night 19-21, withdrawal, rebound: Mean (SD) 25.4 (3.8) $32.2 (5.9)$ P: NS waking time after sleep onset (min) - night 19-21, withdrawal, rebound: Mean (SD) 75.1 (7.9) 137.5 (29.2) P: NS total sleep time (min) - night 19-21, withdrawal, rebound: Mean (SD) 334.6 (22) 281.6 (33.2) P: NS sleep efficiency (%) - night 19-21, withdrawal, rebound: Mean (SD)					Demotion					
PlaceboNA mg615 dayebound:polygraphic sleep recordZolpidemPlacebostage 2 sleep latency - night 19-21, withdrawal, rebound: Mean (SD)55.7 (15.7)69.7 (12.5)P: NStotal number of awakenings - night 19-21, withdrawal, rebound: Mean (SD)25.4 (3.8)32.2 (5.9)P: NSwaking time after sleep onset (min) - night 19-21, withdrawal, rebound: Mean (SD)P: NSNStotal sleep time (min) - night 19-21, withdrawal, rebound: Mean (SD)P: NSNSsleep efficiency (%) - night 19-21, withdrawal, rebound: Mean (SD)P: NS	Drug name	dosag	je r	N=	Duration					
abound:polygraphic sleep recordZolpidemPlacebostage 2 sleep latency - night 19-21, withdrawal, rebound: Mean (SD) $55.7 (15.7)$ P: NS69.7 (12.5)P: NStotal number of awakenings - night 19-21, withdrawal, rebound: Mean (SD) $25.4 (3.8)$ 32.2 (5.9)25.4 (3.8)32.2 (5.9)waking time after sleep onset (min) - night 19-21, withdrawal, rebound: Mean (SD) $75.1 (7.9)$ 137.5 (29.2)P: NStotal sleep time (min) - night 19-21, withdrawal, rebound: Mean (SD) $334.6 (22)$ 281.6 (33.2)Sleep efficiency (%) - night 19-21, withdrawal, rebound: Mean (SD)	Zolpidem	10 m	g	6	15 day					
polygraphic sleep recordZolpidemPlacebostage 2 sleep latency - night 19-21, withdrawal, rebound: Mean (SD)55.7 (15.7)69.7 (12.5)P: NS55.7 (15.7)69.7 (12.5)P: NS1000000000000000000000000000000000000	Placebo	NA m	g	6	15 day					
polygraphic sleep recordZolpidemPlacebostage 2 sleep latency - night 19-21, withdrawal, rebound: Mean (SD)55.7 (15.7)69.7 (12.5)P: NS55.7 (15.7)69.7 (12.5)P: NS1000000000000000000000000000000000000	bound:									
stage 2 sleep latency - night 19-21, withdrawal, rebound: Mean (SD) 55.7 (15.7) 69.7 (12.5) P: NS total number of awakenings - night 19-21, withdrawal, rebound: Mean (SD) 25.4 (3.8) 32.2 (5.9) P: NS waking time after sleep onset (min) - night 19-21, withdrawal, rebound: Mean (SD) 75.1 (7.9) 137.5 (29.2) total sleep time (min) - night 19-21, withdrawal, rebound: Mean (SD) 334.6 (22) 281.6 (33.2) sleep efficiency (%) - night 19-21, withdrawal, rebound: Mean (SD) P: NS		c sleep re	ecord							
55.7 (15.7) 69.7 (12.5) P: NS total number of awakenings - night 19-21, withdrawal, rebound: Mean (SD) 25.4 (3.8) 32.2 (5.9) 25.4 (3.8) 32.2 (5.9) P: NS waking time after sleep onset (min) - night 19-21, withdrawal, rebound: Mean (SD) 75.1 (7.9) 137.5 (29.2) Total sleep time (min) - night 19-21, withdrawal, rebound: Mean (SD) 334.6 (22) 281.6 (33.2) Sleep efficiency (%) - night 19-21, withdrawal, rebound: Mean (SD) P: NS	2	Zolpidem		Placebo						
total number of awakenings - night 19-21, withdrawal, rebound: Mean (SD)25.4 (3.8)32.2 (5.9)P: NSwaking time after sleep onset (min) - night 19-21, withdrawal, rebound: Mean (SD)75.1 (7.9)137.5 (29.2)75.1 (7.9)137.5 (29.2)P: NStotal sleep time (min) - night 19-21, withdrawal, rebound: Mean (SD)334.6 (22)281.6 (33.2)Sleep efficiency (%) - night 19-21, withdrawal, rebound: Mean (SD)	stage 2 s	leep laten	cy - nig	ht 19-21, wi	thdrawal, rebou	nd: Mean (SD)				
25.4 (3.8) 32.2 (5.9) P: NS waking time after sleep onset (min) - night 19-21, withdrawal, rebound: Mean (SD) 75.1 (7.9) 137.5 (29.2) 75.1 (7.9) 137.5 (29.2) P: NS total sleep time (min) - night 19-21, withdrawal, rebound: Mean (SD) 334.6 (22) 281.6 (33.2) Sleep efficiency (%) - night 19-21, withdrawal, rebound: Mean (SD) P: NS	5	5.7 (15.7)		69.7 (12.5)				F	P: NS
waking time after sleep onset (min) - night 19-21, withdrawal, rebound: Mean (SD)75.1 (7.9)137.5 (29.2)total sleep time (min) - night 19-21, withdrawal, rebound: Mean (SD)334.6 (22)281.6 (33.2)Sleep efficiency (%) - night 19-21, withdrawal, rebound: Mean (SD)	total num	ber of awa	akening	gs - night 19-	21, withdrawal,	rebound: Mean (S	SD)			
75.1 (7.9) 137.5 (29.2) P: NS total sleep time (min) - night 19-21, withdrawal, rebound: Mean (SD) 334.6 (22) 281.6 (33.2) sleep efficiency (%) - night 19-21, withdrawal, rebound: Mean (SD) P: NS	2	25.4 (3.8)		32.2 (5.9))				F	P: NS
total sleep time (min) - night 19-21, withdrawal, rebound: Mean (SD)P: NS334.6 (22)281.6 (33.2)sleep efficiency (%) - night 19-21, withdrawal, rebound: Mean (SD)	waking tir	me after s	leep on	iset (min) - n	ight 19-21, with	drawal, rebound: l	Mean (SD)			
334.6 (22) 281.6 (33.2) P: NS sleep efficiency (%) - night 19-21, withdrawal, rebound: Mean (SD)	7	75.1 (7.9)		137.5 (29.2	2)				F	P: NS
sleep efficiency (%) - night 19-21, withdrawal, rebound: Mean (SD)	total slee	p time (mi	in) - nig	ht 19-21, wit	hdrawal, rebour	nd: Mean (SD)				
	3	34.6 (22)		281.6 (33.2	2)				F	P: NS
69.7 (4.6) 58.6 (6.9) P: NS	sleep effi	ciency (%) - nigh	t 19-21, with	drawal, rebound	l: Mean (SD)				
	6	07(16)		586(69)					F	2: NS

2000		Quality rating: Poor
nterview		
Zolpidem	Placebo	
sleep latency (min) - nig	ht 19-21, withdrawal, rebound: Mean (SD)	
94.3 (48.5)	118.4 (34.2)	P: NS
sleep duration (min) - n	ght 19-21, withdrawal, rebound: Mean (SD)
342.0 (47.5)	207.4 (70.5)	P: NS
disturbed sleep - night ?	9-21 (1=agree; 100=disagree), withdrawa	, rebound: Mean (SD)
62.7 (11.4)	56.8 (9.3)	P: NS
alert in the morning - nig	ht 19-21 (1=agree; 100=disagree), withdra	wal, rebound: Mean (SD)
37.9 (9.5)	61.5 (9.8)	P: NS

nmmit, 2004						Quality	rating: Fair
esign:							
Study design:	RCT	DB	Parallel	Run-in : Wash out :	2 days 5-7 days	Setting: Country:	Single Center US
Sample:	Num	ber Sci	-	ble/ Enrolled 69/ 308	Number Withd	Irawn/ Lost to follo 16/	ow-up/ Analyzed 0/ 308
Inclusion crite	ria:						
					for primary insomnia, o fall asleep each nigh		ally reported no more than nth, were eligible for
	n any u				illness, any pertinent o egs syndrome, circadi		abnormalities in drug r, or sleep apnea were
Population:	Mear Geno		39.8 years 61% Female	Ethnicity:	66.2% Caucasians 16.6% black		
ntervention: Drug name	dos	age	N=	Duration			
Eszopiclone	2	mg	104	44 day			
Eszopiclone	3	mg	105	44 day			
Placebo	NA	mg	99	44 day			
ebound:							
polysomno	• • •						
Eszc	piclon	e 2mg	Eszopiclon	e 3mg			
sleep late	ency (m	iin), ret	bound insomr	nia, change vs bas	eline: Mean (p vs bas	eline)	
	NR (NS	S)	-8.5 (<0	.05)			
· · · · · · · · · · · · · · · · · · ·		(%), re	bound insom	nia, change vs ba	seline: Mean (p vs bas	seline)	
	ciency			a =)			
sleep effi	ciency .5 (<0.	05)	3.7 (<0.	05)			
sleep effi -2	.5 (<0.	,		,	Mean (p vs baseline)		

lain, 1998							Quality	rating: Fair	
esign:									
Study design:	RCT	DB	Para	llel	Run-in : Wash out :	3 days 3 days	Setting: Country:	Multicenter France	
Sample:	Numl	ber Sci	reened/ NR/	Eligible/ NR/	Enrolled 37	Number With	ndrawn/ Lost to foll 18/	ow-up/Analyzec NR/ 3	
Inclusion crite	ria:								
	volunte	ers ov	er 18 yea			regularly treated w t-patient treatment			
non-complia	e not i nce; sl	hift wo	rkers; pa	tients su	Iffering from an	n criteria applied: re identifiable mental breast feeding wom	disorder or treated	fro their sleep dis	order with
Population:	Mear	n age:	51.9 ye	ars	Ethnicity:	NR			
•	Gend		0% Fer						
itervention: Drug name	dos	age	N=		Duration				
Zolpidem	10	mg	18		21 day				
Placebo	NA	mg	19		21 day				
dverse Even	ts:								
adverse eve	ents								
	ents Zolpide	m	Р	lacebo					
	Colpide								
Z rebound ins	Colpide		(Withdra						
Z rebound ins	Colpide somnia D (0)		(Withdra	awal)					
z rebound ins withdrawals	Colpide somnia D (0)	: Total	(Withdra 15	awal)					
z rebound ins withdrawals	čolpide somnia D (0) s Čolpide	: Total m	(Withdra 15 P	awal) (14)					
Z rebound ins withdrawals Z	čolpide somnia D (0) s Čolpide	: Total m	(Withdra 15 P er	awal) (14)					
Z rebound ins withdrawals Z	Colpide somnia D (0) s Colpide awals: 1	: Total m Numbe	(Withdra 15 P er	awal) (14) lacebo					

Allain, 2001								Quality I	rating:	Fair	
Design:											
Study design:	RCT	DB	Para	llel	Run-in :	3-7 days		Setting:	Multicer	nter	
					Wash out :	NR		Country:	France		
Sample:	Numbe	er Scree	ened/	Eligible/	Enrolled	Num	ber Withdrawn/	Lost to follo	w-up/ A	nalyzed	
			NR/	NR/	245		NR/		NR/	245	

Inclusion criteria:

Patients of either gender (aged 25 to 64 years) with DSM-IV diagnosis of primary insomnia, characterized by sleep disturbance and problems in falling asleep or nocturnal awakenings and resulting in difficulty in performing daytime functions, were eligible for inclusion in the study.

In addition, patients were required to have a score of between 7 and 15 on the Epworth Sleepiness Scale. In order to be included in the double-blind phase of the study, patients must present insomnia as characterized by at least two of the following four criteria: sleep latency > 30 minutes, total sleep time > 3 hours and < 6 hours, number of awakenings > 3 per night and wake-time after sleep onset > 30 minutes per night.

Exclusion criteria:

Patients were excluded from the study if they were pregnant, breast feeding or were of child-bearing potential and not using an adequate method of contraception, or it they had desynchronisationtype sleep-wake rhythm disorders (such as jet-lag), parasomnia (for example somnambulism), anxiety (>4 on the covi scale), symptoms of depression (>6 on the Raskin scale), acute or chronic pain resulting in insomnia, severe psychiatric disturbances, were receiving treatment with psychotropic/sedative drugs, or had a severe medical condition or known hypersensitivity to imidazopyridine. They were also excluded if their lifestyle was expected to change, if they were suspected of drug/alcohol abuse, if they presented with excessive and abnormal daytime drowsiness, or if they were liable to present with known advance sleep apnoea syndrome. Patients who had received benzodiazepines regularly for more than one month, or for more that 15 days in the month prior to inclusion, were also excluded from the study, as were patients who consumed large quantities of caffeine.

Population:	Mean age: Gender:	46.1 years 77% Female	Ethnicity:	NR
Drug name	dosage	N=	Duration	
Zolpidem	10 mg	124	28 day	
Placebo	NA mg	121	28 day	

Adverse Events:

Zolpidem Placebo

Zolpidolli	1 100000	
overall: Number (%)		
23 (19)	18 (15)	P: NS
anxiety: %		
4	0	P: NR
headache: %		
3.2	0	P: NR
rhinitis: %		
0	3.3	P: NR
Vithdrawals		
Zolpidem	Placebo	
otal withdrawals: Numbe		
3	7	
vithdrawals due to AEs: I	lumber	
1	1	

Chaudoir, 1983							Qualit	y rat	ting	: Poor	
Design:											
Study design:	RCT	DB	Cross	sover	Run-in :	NR	Setting	S	ingle	Center	
					Wash out :	NR	Country	/: U	K		
Sample:	Numbe	er Scre	ened/	Eligible/	Enrolled		Number Withdrawn/ Lost to for	llow-	up/ /	Analyzed	
			NR/	30/	25		5/		0/	25	

Inclusion criteria:

The study was carried out in patients of both sexes aged between 35 and 65 years. The admission criterion was at least one of the following complaints--unable to fall asleep within 45 minutes, more than two nocturnal awakenings with difficulty in returning to sleep without known cause, or sleeping less than six hours.

Exclusion criteria:

The exclusion criteria were patients with depression or an anxiety state requiring therapy, mental disability, liver or kidney dysfunction, cardiovascular disease for which medication was being received or with significant symptomatology (chest pains), gastro-intestinal disease, drug addiction or consumption of alcohol which would interfere with the assessment of the drug, or history of hypersensitivity to drugs. Patients receiving medication which was likely to induce sedation, patients requiring regular analgesia for the relief of chronic pain, night-shift workers, pregnant women, nursing mothers and women of childbearing potential and patients weighing less than 7 stone or more than 14 stone were also excluded.

Population:	Mean age: Gender:	50 years 72% Female	Ethnicity:	NR
Drug name	dosage	N=	Duration	
Zopiclone	7.5 mg	25	7 day	
Placebo	NA mg	25	7 day	

Adverse Events:

Zopiclone	Placebo	
Zopicione	Flacebo	
bitter taste (data NR): Nu	nber	
more	less	P: NR
overall adverse event: Nu	mber	
5	2	P: NR
drowsiness/dizziness: Nu	mber	
2	1	P: NR
vithdrawals		
Zopiclone	Placebo	
total withdrawals: Numbe		
2	3	
withdrawals due to AEs: I	lumber	
2	3	

Dockhorn, 199	6						Quality rating: Fair
Design:							
Study design:	RCT	DB	Parall	el	Run-in :	NR	Setting: Multicenter
					Wash out :	NR	Country: US
Sample:	Numbe	er Scre	ened/ E	Eligible/	Enrolled		Number Withdrawn/ Lost to follow-up/ Analyzed
			NR/	NR/	138		9/ 2/ 136

Inclusion criteria:

Healthy patients who had experienced acute insomnia (3-9 nights) sue to a recent situational stress related to marriage, work, family, or financial matters were randomized. Insomnia was defined as a sleep duration of 4-6 h per night, a sleep latency of 30 min or more, and daytime complaints associated with disturbed sleep (thereby meeting the DSM-III-R definition of acute insomnia)

Exclusion criteria:

None of the patients had any significant psychiatric disorder, a history of insomnia within 2 months of the current episode, depression (criteria adapted from the DSM-III-R Criteria for Major Depression), recurrent thoughts of death or suicide, anxiety requiring treatment with anxiolytics, or a recent history of drug or alcohol abuse; none were regularly taking any medications that could interfere with the assessment of a hypnotics. Patients who normally slept on an unusual schedule (e.g., shift workers) and women who were lactating or at risk on pregnancy were excluded

Population:	Mean age: Gender:	32.7 years 58% Female	Ethnicity:	NR
Drug name	dosage	N=	Duration	
Zolpidem	10 mg	68	7-10 day	
Placebo	NA mg	68	7-10 day	

Adverse Events:

adverse events Zolpidem Placebo headache: % 24.6 31.9 drowsiness: % 5.8 1.4 diarrhea: % 0 4.3 dizziness: % 0 4.3 myalgia: % 1.4 4.3 nausea: % 1.4 4.3 withdrawals Zolpidem Placebo total withdrawals: Number 3 6 withdrawals due to AEs: Number 1 2

Dorsey, 2004						Quality	Quality rating: Fair			
Design:										
Study design:	RCT	DB	Para	llel	Run-in :	6-14 days	Setting:	Multice	enter	
					Wash out :	NR	Country	US		
Sample:	Numbe	er Scre	ened/	Eligible/	Enrolled	Number Wi	thdrawn/ Lost to fol	low-up/	Analyzed	
			242/	141/	141		16/	3/	141	

Inclusion criteria:

Women aged 39 to 60 years were eligible to participate in the study if they had developed insomnia in temporal conjunction with menopausal symptoms. In addition, they had to have complaints of difficulty maintaining sleep or complaints of nonrestorative sleep for >6 months. Sleep maintenance difficult had to occur an average of >3 night per week and had to be accompanied by >2 nocturnal hot flashes, hot flushes, or night sweats. Participant also had to be in good mental and physical health, as determined by medical and psychiatric history, physical examination, and standard clinical laboratory tests obtained within 2 weeks of study onset.

Exclusion criteria:

Exclusion criteria included the presence of signs or symptoms of clinical depression, as ascertained by clinical interview and a Beck Depression Inventory score of > 10, or any other significant psychiatric disorder, based on DSM-IV criteria; use of any over-the-counter or prescription sleep medication within 7 days or any investigational drug within 30 days before study onset; positive urine screening test for medication that could interfere with the assessment of study medication, including benzodiazepines, barbiturates, opiates, cocaine, phenothiazines, amphetamines, and cannabinoids; a history of drug abuse/dependence or alcoholism; and a history of current symptoms of obstructive sleep apnea or periodic limb movement disorder.

Population:	Mean age: Gender:	50.8 years 100% Female	Ethnicity:	NR
Drug name	dosage	N=	Duration	
Zolpidem	10 mg	68	28 day	
Placebo	NA mg	73	28 day	

Adverse Events:

overall		
Zolpidem	Placebo	
headache: Number (%)		
36 (52.9)	24 (32.9)	P: 0.08
upper respiratory tract in	fection: Number (%)	
11 (16.2)	5 (6.8)	P: 0.11
drowsiness: Number (%)		
7 (10.3)	1 (4)	P: 0.03
dizziness: Number (%)		
6 (8.8)	0 (0)	P: 0.01
backache: Number (%)		
5 (7.4)	0 (0)	P: 0.02
irritability: Number (%)		
5 (7.4)	2 (2.7)	P: 0.02
withdrawals		
Zolpidem	Placebo	
total withdrawals: Numb	er	
11	5	
withdrawals due to AEs:	Number	
5	2	

Erman, 2006						Quality	rating:	Fair	
Design:									
Study design:	RCT	DB	Crossover	Run-in :	NR	Setting:	Multice	nter	
				Wash out :	5-12 days	Country:	US		
Sample:	Numbe	er Scre	ened/ Eligib	le/ Enrolled	Number Withdrawn	n/ Lost to follo	w-up/ A	nalyzed	
			319/ 20	05/ 107	4	l/	0/	103	

Inclusion criteria:

Men and non-pregnant, non-lactating women between the ages of 18 and 64 years who had chronic insomnia were recruited.

All pts met the following criteria: a diagnosis of primary insomnia (DSM-IV-TR) for at least three months, a subjective sleep latency (SSL) greater than 30 min, a subjective total sleep time (sTST) of less than 6.5 h per night, and daytime complaints associated with disturbed sleep; a mean LPS > 20 min for two consecutive PSG screening nights with neither night less than 15 min; a mean wake time after sleep onset (WASO) of at least 60 min for two consecutive PSG screening nights, with neither night less than 45 min; an habitual bedtime between 8:30 p.m. and midnight; and a body weight within 20% of the ideal, according to the Metropolitan Life Tables.

Exclusion criteria:

Pts were excluded from the study if their histories included a potential medical or psychiatric condition that could have confounded the study. Excluded conditions included depression, anxiety, seizure disorders, drug addiction, sleep apnea, nocturnal myoclonus, mental retardation, a history of alcohol abuse within the past two years, tobacco use within the past 90 days, or psychotropic drug use. Other exclusionary criteria included the use of St. John's wort or melatonin, or consumption of grapefruit or grapefruit juice within three weeks prior to the study. Shift workers and patients who had flown across three or more time zones within seven days prior to screening also were excluded, as were those with a history of hypersensitivity to ramelteon or related compounds.

Population:	Mear Gene		37.7 years 64% Female	Ethnicity:	54.7% Caucasian; 22.6 Hispanic; 21.7% Africa- American; 0.9% Asia
Intervention: Drug name		sage	N=	Duration	
Ramelteon	4	mg	103	2 day	
Ramelteon	8	mg	103	2 day	
Ramelteon	16	mg	103	2 day	
Ramelteon	32	mg	103	2 day	
Placebo	NA	mg	103	2 day	

Adverse Events:

Ramelteon 4mg	Ramelteon 8mg	Ramelteon 16mg	Ramelteon 32mg	Placebo
all adverse events: %				
25.2	18.3	19.6	21.4	19.4
headache, not otherwise	specified: %			
5.8	4.8	4.7	5.8	4.9
somnolence: %				
0.0	1.9	3.7	1.9	1.0
pharyngolaryngeal pain:	%			
3.9	0.0	0.0	3.9	1.0
nasopharyngitis: %				
1.0	0.0	1.9	1.0	2.9
nausea: %				
2.9	1.0	0.9	1.0	1.9
dyspepsia: %				
1.0	0.0	0.9	2.9	0.0

n, 2006				Quality rating: Fair	
influenza: %					
1.0	1.0	0.0	0.0	2.9	
abdominal pain, upper:	: %				
1.0	1.0	0.9	0.0	1.0	
dysmenorrhea: %					
1.9	1.0	0.0	1.0	0.0	
dry mouth: %					
1.9	0.0	0.0	0.0	1.0	
fatigue: %					
0.0	1.0	0.9	1.9	0.0	
Total withdrawals = 4: I	Number				
NR	NR	NR	NR	NR	
Withdrawals due to adv	verse events: Numbe	r			
0	0	0	0	0	

Goldenberg, 1994 Quality							ality rating: Poor			
Design:										
Study design:	RCT	DB	Para	llel	Run-in :	NR	Setting:	Multice	enter	
					Wash out :	NR	Country:	UK, Fr	ance	
Sample:	Numbe	er Scre	ened/	Eligible/	Enrolled		Number Withdrawn/ Lost to foll	ow-up/	Analyzed	b
			NR/	NR/	524		NR/	NR/	45	8

Inclusion criteria:

Patients of either sex aged between 25 and 60 years were recruited to the study if they had suffered at least two of the following symptoms for between 2 to 12 weeks: sleep duration less than 6 hours per night, at least 2 nightly awakings; sleep onset latency of 30 minutes or more, or daily symptoms attributable to disturbed sleep.

Exclusion criteria:

The following exclusion criteria applied: depression or other psychiatric problems; alcohol or drug dependency; concurrent medication with CNS effects; history of allergy; acute or chronic illness affecting sleep; important negative life events (bereavement, divorce, unemployment, etc.) within the previous month; pregnancy or risk or pregnancy. Nursing mothers, and those performing skilled tasks, shift work or travelling frequently by air were also excluded from the study, as were those unable to complete the questionnaire or who were planning to go on holiday within the period of the trial.

Population:	Mean age: Gender:	NR years % Female	Ethnicity:	NR
Drug name	dosage	N=	Duration	
Zopiclone	7.5 mg	231	48 day	
Placebo	NA mg	227	44 day	

Adverse Events:

Adverse events	
Zopiclone	Placebo
overall reported: Number	er (%)
54 (20.6)	30 (11.5)
dry mouth: Number	
10	5
bitter taste: Number	
11	0

withdrawals: NR

Hedner, 2000							Quality	rating:	Fair
Design:									
Study design:	RCT	DB	Parall	el	Run-in :	7 days	Setting:	Multicer	nter
					Wash out :	7 days	Country	Europe	
Sample:	Numbe	er Scre	ened/ E	Eligible/	Enrolled	Number Wi	thdrawn/ Lost to fol	low-up/ A	nalyzed
			NR/	NR/	437		22/	NR/	422

Inclusion criteria:

This study evaluated patients of both sexes who were at least 65 years old and who had a history of insomnia of at least 3 months' duration. Inclusion to this study was also dependent on the absence of any significant psychiatric or central nervous system (CNS) disorder. Primary insomnia, based on criteria in the Diagnostic and Statistical Manual, 4th edition (DSM-IV; American Psychiatric Association, 1994), was characterized by a sleep latency of 30 minutes or more and either three or more awakenings per night or a total sleep time of 6.5 hours or less.

NR

Exclusion criteria:

Patients with a raw score of > 50 on the Zung Anxiety or Depression scales were not enrolled.

Population:	Mean Gend		72.5 years % Female	Ethnicity:
Intervention: Drug name	dos		N=	Duration
Zaleplon	5	mg	139	14 day
Zaleplon	10	mg	145	14 day
Placebo	NA	mg	138	14 day

Adverse Events:

treatment-emergent adverse events

Zaleplon 5mg	Zaleplon 10mg	Placebo	
overall: Number (%)			
68 (48)	59 (40)	74 (51)	P: NS
total withdrawals: Numb	oer (%)		
10 (7)	5 (3)	7 (5)	P: NS
withdrawals due to AEs	: Number		
10	5	7	

errmann, 1993	3						Quality	rating: P	oor
esign:									
Study design:	RCT	DB	Parallel		Run-in : Wash out :	7 days 7 days	Setting: Country:	Single Ce France	nter
Sample:	Numbe	r Scr	eened/ Eli NR/	gible/ 25/	Enrolled 21	Number Wit	hdrawn/ Lost to follo NR/	w-up/ Ana NR/	lyzed 21
Inclusion criter	ia:								
							ysomnographic crite aan 1 h; and (iii) five		
testing and c	a were a on urine	drug	screening f	or amp	hétamines, c	annabinoids, morp	sorders, and normal nine derivatives, bark workers were exclud	piturates and	
Population:	Mean a	ige:	NR years		Ethnicity:	NR			
	Gende	r:	43% Fema	ale					
ntervention: Drug name	dosa	ge	N=	I	Duration				
	dosa 10 n		N=		Duration 4 day				
Drug name		ng		1					
Drug name Zolpidem	10 n NA n	ng	11	1	14 day				
Drug name Zolpidem Placebo	10 n NA n	ng	11	1	14 day				
Drug name Zolpidem Placebo dverse Event adverse eve	10 n NA n	ng	11	1	14 day				
Drug name Zolpidem Placebo dverse Event adverse eve	10 n NA n S: ents olpidem	ng	11 10 Plac	ebo	14 day				
Drug name Zolpidem Placebo dverse Event adverse eve	10 n NA n S: ents olpidem	ng	11 10 Plac	ebo	14 day				
Drug name Zolpidem Placebo dverse Event adverse eve	10 n NA n ents olpidem during tr 3	ng ng reatm	11 10 Plac ment: Numb	ebo	14 day				

withdrawals: NR

indmarch, 199	95				Quality rating: Fair
esign:					
Study design:	RCT D	B Parallel	Run-in : Wash out :	NR NR	Setting: Multicenter Country: UK
Sample:	Number S	creened/ Eligible NR/ NR			Number Withdrawn/ Lost to follow-up/ Analyzed NR/ NR/ 458
Inclusion criter	ria:				
duration less	s than 6 hou		ast 2 nightly aw		two of the following symptoms for two or more weeks: sleep ngs; sleep onset latency of 30 minutes or more; and daily
	or other psy ness affecti				e dependency, concurrent medication with CNS effects, acute s within the previous month, and pregnancy were considered as
Population:	Mean age	2.9 years	Ethnicity:	NR	
_	Gender:	0% Female	-		
ntervention: Drug name	dosage	N=	Duration		
Zopiclone	7.5 mg	231	48 day		
Placebo	NA mg	227	42 day		
dverse Event	s:				
adverse eve	ents				
adverse eve	ents Zaleplon	Placebo			
adverse eve	Zaleplon				
adverse eve Z overall drop	Zaleplon				P: NS
adverse eve Z overall drop	Zaleplon out: Numb (11.5)	er (%)			P: NS
adverse eve Z overall drop 30	Zaleplon out: Numb (11.5)	er (%)			P: NS
adverse eve Z overall drop 30	Zaleplon o out: Numb (11.5) Number 11	er (%) 54 (20.6)			P: NS

withdrawals: NR

Krystal (poster)					Quality	rating	: Fair	
Design:									
Study design:	RCT	DB	Parallel	Run-in: Wash out:	14 days 14 days	Setting: Country:	Multic US	enter	
Sample:	Numb	er Scre	0	ble/ Enrolled NR/ 830	Number Withdrawr 350		w-up/ 80/	Analyze 82	
	orted ave		nic primary i sleep time <		/or sleep latency >30 min				
Patient-repo Exclusion crite NR Population:	orted ave eria:	erage s age:		= 6.5 hrs/night and Ethnicity:	/or sleep latency >30 min Caucasian: 71% Black: 16%				
Patient-repo Exclusion crite NR	orted ave eria: Mean	erage s age: er:	sleep time < 45.6 years	= 6.5 hrs/night and Ethnicity:	Caucasian: 71%				
Patient-repo Exclusion crite NR Population:	rted ave eria: Mean Gende dosa	erage s age: er:	45.6 years 61% Female	= 6.5 hrs/night and Ethnicity:	Caucasian: 71%				

Adverse Events:

Eszopic	lone	Placebo
overall: %		
75.7		58.9
unpleasant taste	: %	
19.7		1.1
infection: %		
16.6		12.1
headache: %		
15.1		15.0
pain: %		
8.8		10.4
somnolence: %		
8.8		3.2
pharyngitis: %		
6.0		3.9
myalgia: %		
6.0		2.9
dyspepsia: %		
6.2		5.4
back pain: %		
5.3		7.1

al (poster)		Quality rating: Fair
CNS adverse events dur	ing washout	
Eszopiclone	Placebo	
hypertonia: %		
0.3	0.7	
insomnia: %		
0.6	0	
confusion: %		
0.3	0	
depression: %		
0.3	0	
dizziness: %		
0.3	0	
hypesthesia: %		
0	0.7	
meningitis: %		
0.3	0	
vertigo: %		
0.3	0	
withdrawals		
Eszopiclone	Placebo	
total withdrawals: Numbe	r (%)	
204 (37.1)	146 (52.1)	
withdrawals due to adver	se events: Number (%)	
48 (8.8)	22 (7.9)	

rystal, 2003						Quality	rating:	Fair	
Design:									
Study design:	RCT	DB Pa	rallel	Run-in :	NR	Setting:	Multicen	ter	
				Wash out :	5-7 days	Country:	US		
Sample:	Number	Screened	/ Eligible/	Enrolled	Number Withdraw	vn/ Lost to follo	ow-up/ An	alyzed	
		1194	/ 791/	788	32	20/	60/	788	

Inclusion criteria:

Patients receiving a DSM IV diagnosis of primary insomnia and/or a usual sleep latency of more than 30 minutes each night for at least 1 month prior to screening were eligible for randomization, provided they did not (1) meet criteria for a DSM-IV Axis I psychiatric diagnosis other than primary insomnia, sexual and gender-identity disorders, or Axis II personality disorders (excluded by medical history); (2) have a history of substance abuse or substance dependence; (3) consume more than 2 alcoholic beverages per day or more than 14 per week; (4) use any psychotropic, hypnotic, or other medications known to infect sleep or to be contraindicated for use with hypnotics; (5) use over-the-counter analgesics that contain caffeine or herbal supplements, including products with herbs, melatonin, or St. John's Wort.

Exclusion criteria:

NR

Population:	Mea Gen		44 years 25% Female	Ethnicity:	80% Caucasian 13.2% African American
Drug name	dos	sage	N=	Duration	
Eszopiclone	3	mg	593	180 day	
Placebo	NA	mg	195	180 day	

Adverse Events:

adverse events

Eszopiclone	Placebo	
overall: %		
81.1	70.8	P: NR
abdominal pain: Number	(%)	
48 (8.1)	11 (5.6)	P: NR
Accidental injury: Numbe	(%)	
43 (7.3)	11 (5.6)	P: NR
asthenia: Number (%)		
26 (4.4)	11 (5.6)	P: NR
back pain: Number (%)		
45 (7.6)	6 (3.1)	P: NR
diarrhea: Number (%)		
45 (7.6)	14 (7.2)	P: NR
dizziness: Number (%)		
58 (9.8)	6 (3.1)	P: NR
dry mouth: Number (%)		
39 (6.6)	3 (1.5)	P: NR
dyspepsia: Number (%)		
41 (6.9)	13 (6.7)	P: NR
headache: Number (%)		
116 (19.6)	37 (19)	P: NR
infection: Number (%)		
94 (15.9)	13 (6.7)	P: NR

al, 2003		Quality rating: Fair
nausea: Number (%)		
67 (11.3)	11 (5.6)	P: NR
pain: Number (%)		
67 (11.3)	12. (6.2)	P: NR
pharyngitis: Number (%)		
59 (9.9)	10 (5.1)	P: NR
rash: Number (%)		
31 (5.2)	6 (3.1)	P: NR
rhinitis: Number (%)		
42 (7.1)	9 (4.6)	P: NR
sinusitis: Number (%)		
25 (4.2)	11 (5.6)	P: NR
somnolence: Number (%))	
54 (9.1)	5 (2.6)	P: NR
unpleasant taste: Numbe	r (%)	
155 (26.1)	11 (5.6)	P: NR
withdrawals		
Eszopiclone	Placebo	
total withdrawals: Numbe	r	
235	85	
withdrawals due to AEs:	Number	
76	14	

ahmeyer, 199	7						Quality	rating:	Fair	
Design:										
Study design:	RCT	DB	Paralle	el	Run-in :	3 days	Setting:	Multice	enter	
					Wash out :	4 days	Country	: US		
Sample:	Number	r Scree	ned/ E	ligible/	Enrolled	Number \	Vithdrawn/ Lost to fo	llow-up/ A	Analyzed	
			178/	33/	145		27/	0/	118	
Inclusion crite	ria:									
							p, characterized by a associated daytime		•	of

Exclusion criteria:

Patients were excluded if they: (a) had used any investigational drug (i.e. a drug still under clinical trial, prior to FDA approval) within 30 days of the start of the study; (b) had used alcohol or a short acting CNS medication within 1q year; (c) had a positive urine drug screen (for benzodiazepines, barbiturates, opiates and amphetamines) performed at screening-patients then took placebo for the first 3 mights of week 1; (d) had a history of exaggerated responses to benzodiazepines or other CNS depressants; (e) had been an illicit drug addict within the previous year; (f) had subjective symptoms of sleep apnoea; or (g) had nocturnal myoclonus or seizures. Patients who were shiftworkers and women who were breastfeeding were also excluded. In addition, patients with coexisting medical or psychiatric conditions (based on a prestudy evaluation of medical and sleep history, physical examination, vital signs, clinical and laboratory tests, ECG and urinalysis) were excluded from the study.

Population:	Mean ag Gender:	e: 44.9 years 56% Female	Ethnicity:	92% Caucasian 6% black
Drug name	dosage	N=	Duration	
Zolpidem	10 mg	45	31 day	
Zolpidem	15 mg	46	31 day	
Placebo	NA mg	54	31 day	

Adverse Events:

overall	adverse	events
---------	---------	--------

Zolpidem 10mg	Zolpidem 15mg	Placebo
drowsiness: %		
11	12	6
dizziness: %		
5	7	4
pharyngitis: %		
2	9	2
rhinitis: %		
0	7	2
lethargy: %		
7	2	0
overall: Number (%)		
25 (57)	30 (70)	56 (43)
CNS related: Number (%))	
19 (28.3)	15 (43.2)	15 (34.8)

hmeyer, 1997			Quality rating: Fair	
withdrawals				
Zolpidem 10mg	Zolpidem 15mg	Placebo		
total withdrawals: Numbe	٢			_
8	9	10		
withdrawals due to AEs:	Number			
4	3	0		

lonchesky, 1986						Quality	rating: Fa	air
Design:								
Study design:	RCT	DB C	rossover	Run-in :	7 days	Setting:	Single Cen	ter
				Wash out :	7 days	Country:	Canada	
Sample:	Number	Screene	d/ Eligible/	Enrolled	Number Withdrawn/	Lost to follo	w-up/ Analy	zed
		Ν	R/ NR/	99	0/		2/	91
Inclusion crite	ria:							

Inclusion criteria:

Adults patients were enrolled who had suffered from insomnia for at least three months and met at least two of the following criteria: (1) sleep latency of 45 minutes or more, (2) more than three nightly awakenings with difficulty in falling asleep again, (3) early final morning awakening, and (4) total sleep time of usually less than five hours and always less than six hours.

Exclusion criteria:

Pregnancy and breast-feeding; concomitant use of neuroleptics, sedatives, analgesics, or antidepressants; a history of drug abuse or addiction; a history of serious psychiatric, hepatic, renal, or metabolic disorders; epilepsy; a known hypersensitivity to hypnotic drugs; abnormal liver or renal function; abnormal hemogram values; and an established diagnosis of sleep apnea

NR

Population:	Mean age:	NR years	Ethnicity:
•	Gender:	0% Female	
Intervention: Drug name	dosage	N=	Duration
Zopiclone	7.5 mg	91	7 day
Placebo	NA mg	91	7 day

Adverse Events:

adverse events	
Zopiclone	Placebo
headache: Number	
11	11
dizziness: Number	
4	6
nausea: Number	
7	4
bad/bitter taste: Number	
4	3
back pain: Number	
1	3
stomach pain: Number	
3	2

lonti, 1996						Quality	rating: Fating: Fating	air	
Design:									
Study design:	RCT	DB Para	llel	Run-in :	2 days	Setting:	Single Cer	nter	
				Wash out :	3 days	Country:	Uruguay		
Sample:	Number	Screened/	Eligible/	Enrolled	Number Wit	ndrawn/ Lost to follo	w-up/ Anal	yzed	
		NR/	NR/	12		NR/	NR/	12	
Inclusion crite	ria:								
						time to fall asleep	>30 minutes	; total sleep tim	е
			ne >20 n	indles; numbe	er of nocturnal awak	enings >3.			
Exclusion crite Pregnant w organic dise	eria: vomen, wor ease or sev	nen of child ere psychia	l-bearing atric diso	age with inad rders, and pati	equate contraceptio	n, breastfeeding mo icient compliance wa en days prior to the l	as to be expe	ected. Alcohol	m
Exclusion crite Pregnant w organic dise abuse or int	eria: vomen, wor ease or sev	nen of child ere psychia notics or an	l-bearing atric diso axiolytics	age with inad rders, and pati	equate contraceptio ients in whom insuff pressants in the sev	n, breastfeeding mo icient compliance wa	as to be expe	ected. Alcohol	m
Exclusion crite Pregnant w organic dise abuse or int exclusion.	eria: romen, wor ease or sev ake of hyp	nen of child ere psychia notics or an e: 44.25 y	d-bearing atric diso nxiolytics rears	age with inad rders, and pati and/or antider	equate contraceptio ients in whom insuff pressants in the sev	n, breastfeeding mo icient compliance wa	as to be expe	ected. Alcohol	m
Exclusion crite Pregnant w organic dise abuse or int exclusion.	eria: romen, wor ease or sev ake of hyp Mean ag	men of chilc ere psychia notics or an e: 44.25 y 83% Fe	d-bearing atric diso nxiolytics rears	age with inad rders, and pati and/or antider	equate contraceptio ients in whom insuff pressants in the sev	n, breastfeeding mo icient compliance wa	as to be expe	ected. Alcohol	m
Exclusion crite Pregnant w organic dise abuse or int exclusion. Population: ntervention:	eria: vomen, woi ease or sev ake of hyp Mean ag Gender:	nen of chilc ere psychia notics or an e: 44.25 y 83% Fe N=	d-bearing atric diso nxiolytics rears	age with inad rders, and pati and/or antidep Ethnicity:	equate contraceptio ients in whom insuff pressants in the sev	n, breastfeeding mo icient compliance wa	as to be expe	ected. Alcohol	m

Adverse Events:

onti, 2000							Quality rating: Poor
esign:							
Study design:	RCT	DB	Paral	lel	Run-in :	3 days	Setting: Single Center
					Wash out :	3 days	Country: Uruguay
Sample:	Numbe	r Scre	ened/	Eligible/	Enrolled	Number Withd	rawn/ Lost to follow-up/ Analyzed
			NR/	NR/	12		NR/ NR/ 12
e		en 27 a	and 59	years, w	ith chronic pri	mary insomnia accord	ing to the DSM-IV participated in the study.
abuse, peric pregnant wo	n poor he dic leg m men and	novem I breas	ents du st-feedii	iring slee ng mothe	ep, restless legers.	gs or sleep apnea wer	or cardiac disease, known drug allergy or e excluded from the study, and so were diac, or neuropsychiatric diseases [subjects
Patients with abuse, peric pregnant wo Patients with with a score movements feeding mot	n poor he dic leg m men and n poor he of HAMI during sl ners, sub ol abuse,	novem d breas alth; a D > 18 leep; re ojects c intake	ents du st-feedin cute or , or a so estless deemed e of hyp	ring slee ng mothe chronic core of H legs; or s l insuffici notics or	p, restless leg pain; hepatic, IAMA(14 item sleep apnea w ently complian	gs or sleep apnea wer renal, respiratory, car s)>16 were not include vere excluded from the nt, or those with clinica	e excluded from the study, and so were

Intervention:	Geno	der:	100% Fer	nale
Drug name	dos	sage	N=	Duration
Zolpidem	10	mg	6	15 day
Placebo	NA	mg	6	15 day

Adverse Events:

erlis, 2004					Quality	rating: Fai	r
esign:							
Study design:	RCT DE	B Parallel	Run-in :	6-14 days	Setting:	Multicenter	
			Wash out :	NR	Country:	US	
Sample:	Number So	reened/ Eligible	e/ Enrolled	Number Wit	ndrawn/ Lost to follo	w-up/ Analyz	ed
		322/ 277	7/ 199		10/	3/ 1	92
Inclusion crite	ria:						
deemed to b	be in good m	ental and physic		certained by a medic	e DSM-IV criteria for al history, physical e		
Exclusion crite	eria:						
could interfe	ere with the a	ssessment of st	udy medication;		udy start; positive uri ction, alcoholism, or		
current sym	ptoms compa hey were bre	atible with sleep	apnea or period gnant, or not usi	history of drug addi dic leg movements d	ction, alcoholism, or uring sleep. Addition ntraceptive methods	drug abuse; a ally, female pa	nd history of or
current sym ineligible if t Population:	ptoms compa hey were bre	atible with sleep astfeeding, preg	apnea or period gnant, or not usi	history of drug addi dic leg movements d ng double-barrier co	ction, alcoholism, or uring sleep. Addition ntraceptive methods	drug abuse; a ally, female pa	nd history of or
current sym ineligible if t Population: ntervention:	ptoms compa hey were bre Mean age: Gender:	atible with sleep astfeeding, preg 40.8 years 71% Female	apnea or perioc gnant, or not usin Ethnicity:	history of drug addi dic leg movements d ng double-barrier co	ction, alcoholism, or uring sleep. Addition ntraceptive methods	drug abuse; a ally, female pa	nd history of or
current sym ineligible if t Population:	ptoms compa hey were bre Mean age:	atible with sleep astfeeding, preg 40.8 years	apnea or period gnant, or not usi	history of drug addi dic leg movements d ng double-barrier co	ction, alcoholism, or uring sleep. Addition ntraceptive methods	drug abuse; a ally, female pa	nd history of or
current sym ineligible if t Population: ntervention:	ptoms compa hey were bre Mean age: Gender:	atible with sleep astfeeding, preg 40.8 years 71% Female	apnea or perioc gnant, or not usin Ethnicity:	history of drug addi dic leg movements d ng double-barrier co	ction, alcoholism, or uring sleep. Addition ntraceptive methods	drug abuse; a ally, female pa	nd history of or
current sym ineligible if t Population: ntervention: Drug name	ptoms compa hey were bre Mean age: Gender: dosage	atible with sleep astfeeding, preg 40.8 years 71% Female N=	apnea or perioc gnant, or not usin Ethnicity: Duration	history of drug addi dic leg movements d ng double-barrier co	ction, alcoholism, or uring sleep. Addition ntraceptive methods	drug abuse; a ally, female pa	nd history of or
current sym ineligible if t Population: ntervention: Drug name Zolpidem	ptoms compa hey were bre Mean age: Gender: dosage 10 mg NA mg	atible with sleep astfeeding, preg 40.8 years 71% Female N= 98	apnea or perioc gnant, or not usin Ethnicity: Duration 84 day	history of drug addi dic leg movements d ng double-barrier co	ction, alcoholism, or uring sleep. Addition ntraceptive methods	drug abuse; a ally, female pa	nd history of or
current sym ineligible if t Population: Drug name Zolpidem Placebo	ptoms compa hey were bre Mean age: Gender: dosage 10 mg NA mg ts:	atible with sleep astfeeding, preg 40.8 years 71% Female N= 98	apnea or perioc gnant, or not usin Ethnicity: Duration 84 day	history of drug addi dic leg movements d ng double-barrier co	ction, alcoholism, or uring sleep. Addition ntraceptive methods	drug abuse; a ally, female pa	nd history of or
current sym ineligible if t Population: Drug name Zolpidem Placebo	ptoms compa hey were bre Mean age: Gender: dosage 10 mg NA mg ts: s	atible with sleep astfeeding, preg 40.8 years 71% Female N= 98 101	apnea or perioc gnant, or not usin Ethnicity: Duration 84 day 84 day	history of drug addi dic leg movements d ng double-barrier co	ction, alcoholism, or uring sleep. Addition ntraceptive methods	drug abuse; a ally, female pa	nd history of or
current sym ineligible if t Population: Drug name Zolpidem Placebo	ptoms compa hey were bre Mean age: Gender: dosage 10 mg NA mg ts:	atible with sleep astfeeding, preg 40.8 years 71% Female N= 98	apnea or perioc gnant, or not usin Ethnicity: Duration 84 day 84 day	history of drug addi dic leg movements d ng double-barrier co	ction, alcoholism, or uring sleep. Addition ntraceptive methods	drug abuse; a ally, female pa	nd history of or
current sym ineligible if t Population: Drug name Zolpidem Placebo dverse Even withdrawal	ptoms compa hey were bre Mean age: Gender: dosage 10 mg NA mg ts: s	atible with sleep astfeeding, prec 40.8 years 71% Female N= 98 101 Placebo	apnea or perioc gnant, or not usin Ethnicity: Duration 84 day 84 day	history of drug addi dic leg movements d ng double-barrier co	ction, alcoholism, or uring sleep. Addition ntraceptive methods	drug abuse; a ally, female pa	nd history of or

withdrawals due to AEs: Number 2

3

cins (poster), 2005				Quality r	rating: Fair
esign:						
Study design:	RCT D	B Parallel	Run-in : Wash out :	no days	Setting:	Multicenter US, Canada, Argentina, Germany,
Sample:	Number S	creened/ Eligible NR/ NR	/ Enrolled	Number Withdrawn/ 7/	•	
bed of 6.5 to	ned primary 9 hours pe	r night for 2 week	s prior to enrollr	ht for at least 3 nights per w nent. A 2-night (screening) iours each screening night v	mean PSG	
	Axis I psyc ect sleep, o			istory of substance abuse, ι cription sleep medication wit		
Population:	Mean age Gender:	70.2 years 57% Female	Ethnicity:	95.1% Caucasian; 4.9% o	ther	
tervention: Drug name	dosage	N=	Duration			
zolpidem exten	6.25 mg	99	21 day			
Placebo	NA mg	106	21 day			
dverse Event	s:					
Treatment e	mergent a	dverse events >=	=5%			
	mergent a bidem MR	dverse events >= Placebo	=5%			
	oidem MR	Placebo	=5%			
Zolj any adverse	oidem MR	Placebo	=5%			
Zolj any adverse 38	e event: Nur (38.4)	Placebo mber (%)	=5%			
Zol any adverse 38 nervous sys	e event: Nur (38.4)	Placebo mber (%) 42 (39.6)	=5%			
Zolj any adverse 38 nervous sys 25	e event: Nur (38.4) (25.3)	Placebo mber (%) 42 (39.6) ers: Number (%) 21 (19.8)	=5%			
Zolj any adverse 38 nervous sys 25 psychiatric o	e event: Nur (38.4) tem disorde (25.3) disorders: N	Placebo mber (%) 42 (39.6) ers: Number (%) 21 (19.8) lumber (%)	=5%			
Zol any adverse 38 nervous sys 25 psychiatric o 7	e event: Nur (38.4) (25.3) disorders: N (7.1)	Placebo mber (%) 42 (39.6) ers: Number (%) 21 (19.8) lumber (%) 7 (6.6)	=5%			
Zol any adverse 38 nervous sys 25 psychiatric o 7 gastrointest	e event: Nur (38.4) (25.3) disorders: N (7.1) inal disorde	Placebo mber (%) 42 (39.6) ers: Number (%) 21 (19.8) lumber (%) 7 (6.6) rs: Number (%)	=5%			
Zol any adverse 38 nervous sys 25 psychiatric o 7 gastrointest 9	e event: Nur (38.4) tem disorde (25.3) disorders: N (7.1) inal disorde (9.1)	Placebo mber (%) 42 (39.6) ers: Number (%) 21 (19.8) lumber (%) 7 (6.6) rs: Number (%) 13 (12.3)		r (%)		
Zol any adverse 38 nervous sys 25 psychiatric o 7 gastrointest 9 musculoske	e event: Nur (38.4) (25.3) disorders: N (7.1) inal disorde (9.1) letal and co	Placebo mber (%) 42 (39.6) ers: Number (%) 21 (19.8) lumber (%) 7 (6.6) rs: Number (%) 13 (12.3) onnective tissue d		r (%)		
Zol any adverse 38 nervous sys 25 psychiatric o 7 gastrointest 9 musculoske 7	e event: Nur (38.4) tem disorde (25.3) disorders: N (7.1) inal disorde (9.1) letal and cc (7.1)	Placebo mber (%) 42 (39.6) ers: Number (%) 21 (19.8) lumber (%) 7 (6.6) rs: Number (%) 13 (12.3) onnective tissue d 7 (6.6)		r (%)		
Zol any adverse 38 nervous sys 25 psychiatric o 7 gastrointest 9 musculoske 7 infections a	e event: Nur (38.4) tem disorder (25.3) disorders: N (7.1) inal disorder (9.1) letal and co (7.1) nd infestation	Placebo mber (%) 42 (39.6) ers: Number (%) 21 (19.8) lumber (%) 7 (6.6) rs: Number (%) 13 (12.3) onnective tissue d 7 (6.6) ons: Number (%)		r (%)		
Zol any adverse 38 nervous sys 25 psychiatric o 7 gastrointest 9 musculoske 7 infections au 9	e event: Nur (38.4) tem disorde (25.3) disorders: N (7.1) inal disorde (9.1) letal and co (7.1) nd infestatio (9.1)	Placebo mber (%) 42 (39.6) ers: Number (%) 21 (19.8) lumber (%) 7 (6.6) rs: Number (%) 13 (12.3) onnective tissue d 7 (6.6) ons: Number (%) 5 (4.7)	lisorder: Numbe			
Zol any adverse 38 nervous sys 25 psychiatric o 7 gastrointest 9 musculoske 7 infections au 9 general disc	e event: Nur (38.4) tem disorde (25.3) disorders: N (7.1) inal disorde (9.1) letal and cc (7.1) nd infestatio (9.1) orders, adm	Placebo mber (%) 42 (39.6) ers: Number (%) 21 (19.8) lumber (%) 7 (6.6) rs: Number (%) 13 (12.3) onnective tissue d 7 (6.6) ons: Number (%) 5 (4.7) inistration site con	lisorder: Numbe			
Zol any adverse 38 nervous sys 25 psychiatric o 7 gastrointest 9 musculoske 7 infections a 9 general disc 7	e event: Nur (38.4) tem disorde (25.3) disorders: N (7.1) inal disorde (9.1) letal and co (7.1) nd infestatio (9.1) orders, adm (7.1)	Placebo mber (%) 42 (39.6) ers: Number (%) 21 (19.8) lumber (%) 7 (6.6) rs: Number (%) 13 (12.3) onnective tissue d 7 (6.6) ons: Number (%) 5 (4.7) inistration site cor 8 (7.5)	lisorder: Numbe			
Zol any adverse 38 nervous sys 25 psychiatric o 7 gastrointest 9 musculoske 7 infections au 9 general disc 7 headache: 1	e event: Nur (38.4) tem disorder (25.3) disorders: N (7.1) inal disorder (9.1) letal and co (7.1) nd infestatio (9.1) orders, adm (7.1) Number (%)	Placebo mber (%) 42 (39.6) ers: Number (%) 21 (19.8) lumber (%) 7 (6.6) rs: Number (%) 13 (12.3) onnective tissue d 7 (6.6) ons: Number (%) 5 (4.7) inistration site con 8 (7.5)	lisorder: Numbe			
Zol any adverse 38 nervous sys 25 psychiatric o 7 gastrointest 9 musculoske 7 infections au 9 general disc 7 headache: 1	e event: Nur (38.4) tem disorder (25.3) disorders: N (7.1) inal disorder (9.1) letal and cc (7.1) nd infestatio (9.1) orders, adm (7.1) Number (%) (14.1)	Placebo mber (%) 42 (39.6) ers: Number (%) 21 (19.8) lumber (%) 7 (6.6) rs: Number (%) 13 (12.3) onnective tissue d 7 (6.6) ons: Number (%) 5 (4.7) inistration site cor 8 (7.5)	lisorder: Numbe			
Zol any adverse 38 nervous sys 25 psychiatric o 7 gastrointest 9 musculoske 7 infections a 9 general disc 7 headache: 1 14 dizziness: N	e event: Nur (38.4) tem disorde (25.3) disorders: N (7.1) inal disorde (9.1) letal and cc (7.1) nd infestatic (9.1) orders, adm (7.1) Number (%) (14.1) lumber (%) (8.1)	Placebo mber (%) 42 (39.6) ers: Number (%) 21 (19.8) lumber (%) 7 (6.6) rs: Number (%) 13 (12.3) onnective tissue d 7 (6.6) ons: Number (%) 5 (4.7) inistration site con 8 (7.5) 12 (11.3) 3 (2.8)	lisorder: Numbe			
Zol any adverse 38 nervous sys 25 psychiatric o 7 gastrointest 9 musculoske 7 infections au 9 general disc 7 headache: 1 14 dizziness: N 8 somnolence	e event: Nur (38.4) tem disorde (25.3) disorders: N (7.1) inal disorde (9.1) letal and cc (7.1) nd infestatic (9.1) orders, adm (7.1) Number (%) (14.1) lumber (%) (8.1) e: Number (%)	Placebo mber (%) 42 (39.6) ers: Number (%) 21 (19.8) lumber (%) 7 (6.6) rs: Number (%) 13 (12.3) onnective tissue d 7 (6.6) ons: Number (%) 5 (4.7) inistration site con 8 (7.5) 12 (11.3) 3 (2.8)	lisorder: Numbe			
Zol any adverse 38 nervous sys 25 psychiatric o 7 gastrointest 9 musculoske 7 infections au 9 general disc 7 headache: 1 14 dizziness: N 8 somnolence	e event: Nur (38.4) tem disorde (25.3) disorders: N (7.1) inal disorde (9.1) letal and cc (7.1) nd infestatic (9.1) orders, adm (7.1) Number (%) (14.1) lumber (%) (8.1) e: Number (%)	Placebo mber (%) 42 (39.6) ers: Number (%) 21 (19.8) lumber (%) 7 (6.6) rs: Number (%) 13 (12.3) onnective tissue d 7 (6.6) ons: Number (%) 5 (4.7) inistration site con 8 (7.5) 12 (11.3) 3 (2.8)	lisorder: Numbe			

ehrs (poster), 2005		Quality rating: Fair
Withdrawals		
Zolpidem MR	Placebo	
total withdrawals: Number		
3	1	
withdrawal due to AEs: Nu	mber	
NR	NR	

Roth, 2006	Quality rating: Fair					
Design:						
Study design:	RCT	DB	Parallel	Run-in :	7 days	Setting: Multicenter
				Wash out :	7 days	Country: US
Sample:	Numbe	er Scre	ened/ Eligible/	Enrolled	Number Withdrawn/	Lost to follow-up/ Analyzed
			NR/ NR/	829	128/	NR/ NR
Inclusion crite	ria:					
• •			s, and a total sle	ep time <=6.5	hours per night for at least	V-TR for at least 3 months, a reported 3 nights during the week of the single-

blind lead-in period. Body mass index must have been between 18 and 34, inclusive, and habitual bedtime must have been between 8:30 pm and 12:00 am.

Exclusion criteria:

Patients could not have had any significant medical or psychiatric disorder or have used any medications that affected the central nervous system or sleep/wake function within 1 week (or 5 half lives, whichever is longer) prior to the first day of the placebo lead-in period.

Population:	Mear Geno	-	72.4 years 0% Female	Ethnicity:	Not reported
Drug name	dos	sage	N=	Duration	
Ramelteon	4	mg	281	5 week	
Ramelteon	8	mg	274	5 week	
Placebo	NA	mg	274	5 week	

Adverse Events:

Total withdrawals

Total withdrawals: Numb	oer (%)		
47 (16.7)	35 (12.5)	46 (16.8)	

Withdrawals due to AEs

2006			Quality rating: Fair
Adverse events			
Ramelteon 4 mg	Ramelteon 8 mg	Placebo	
Any adverse event: Num	ber (%)		
154 (54.8)	159 (58.0)	141 (51.5)	
Dizziness: Number (%)			
19 (6.8)	23 (8.4)	18 (6.6)	
Myalgia: Number (%)			
15 (5.3)	16 (5.8)	7 (2.6)	
Headache: Number (%)			
12 (4.3)	16 (5.8)	12 (4.4)	
Dysgeusia: Number (%)			
8 (2.8)	19 (6.9)	8 (2.9)	
Somnolence: Number (%	6)		
13 (4.6)	13 (4.7)	8 (2.9)	
Depression: Number (%))		
10 (3.6)	11 (4.0)	3 (1.1)	
Insomnia exacerbated: N	lumber (%)		
7 (2.5)	11 (4.0)	11 (4.0)	
Eye pain: Number (%)			
11 (3.9)	7 (2.6)	6 (2.2)	
Fatigue: Number (%)			
3 (1.1)	10 (3.6)	6 (2.2)	
Diarrhea: Number (%)			
3 (1.1)	9 (3.3)	9 (3.3)	

Scharf, 1994							Quality	rating: Fair
Design:								
Study design:	RCT	DB	Para	allel	Run-in :	11 days	Setting:	Multicenter
					Wash out :	2 days	Country:	US
Sample:	Numbe	er Scre	ened/	Eligible/	Enrolled	Number Withdrawn/	Lost to follo	w-up/ Analyzed
			178/	75/	75			

Inclusion criteria:

After giving informed consent, outpatient insomniacs, aged 21 to 60 years, were screened to rule out significant medical or psychiatric disorders and to ensure that they were in good health. Patients were not have used any investigational drug within 30 days of the start of the study. In addition, patients were required to have chronic insomnia defined as a history of the following for at least 3 months preceding screening: usual reported sleep duration between 4 and 6 hours, usual reported sleep latency of at least 30 minutes, and daytime complaints associated with disturbed sleep. The first night of placebo screening period served as a laboratory adaptation night and to rule out patients with sleep apnea or periodic limb movements during sleep. During the next 3 nights, patients had to meet the following criteria: total sleep time of 240 to 420 minutes (4 to 7 hours) in a 480-minute recording on at least 2 or the 3 screening nights, and a latency to persistent sleep of > 20 minutes on each of these 2 nights. "Persistent sleep" was defined as the first continuous 20 epochs of a non-wake state.

Exclusion criteria:

Population:	Mean age: Gender:	38 years 64% Female	Ethnicity:	73.3% white 26.7% non-white
Drug name	dosage	N=	Duration	
Zolpidem	10 mg	26	35 day	
Zolpidem	15 mg	25	35 day	
Placebo	NA mg	24	35 day	

Adverse Events:

adverse events		
Zolpidem 10mg	Zolpidem 15mg	Placebo
dry mouth: Number (%)		
0 (0)	2 (8)	0 (0)
headache: Number (%)		
2 (8)	4 (16)	7 (29)
drowsiness: Number (%)		
3 (12)	5 (20)	2 (8)
dizziness: Number (%)		
3 (12)	4 (16)	0 (0)
lethargy: Number (%)		
2 (8)	1 (4)	1 (4)
drugged: Number (%)		
2 (8)	1 (4)	0 (0)
confusion: Number (%)		
0 (0)	2 (8)	0 (0)
nausea: Number (%)		
1 (4)	3 (12)	1 (4)
dyspepsia: Number (%)		
2 (8)	2 (8)	0 (0)
arthralgia: Number (%)		
1 (4)	0 (0)	2 (8)

rf, 1994			Quality rating: Fair
amnesia: Number (%)			
1 (4)	2 (8)	0 (0)	
rhinitis: Number (%)			
0 (0)	0 (0)	2 (8)	
withdrawals			
Zolpidem 10mg	Zolpidem 15mg	Placebo	
total withdrawals: Numbe	Pr		
4	3	1	
withdrawals due to AEs:	Number		
0	2	0	

Scharf, 2005								Quality	rating	: Fair	
Design:											
Study design:	RCT	DB	Para	llel	Run-in :	3-14	days	Setting:	Multic	enter	
					Wash out :	NR		Country:	US		
Sample:	Numbe	r Scree	ened/	Eligible/	Enrolled		Number Withdrawn/	Lost to follo	w-up/	Analyzed	
			353/	NR/	231		21/		NR/	231	

Inclusion criteria:

Men and women between the ages of 65 and 85 years who met the DSM-IV for primary insomnia and who reported sleeping 6.5 hours per night or less and took more than 30 minutes to fall asleep each night for at least 1 month

Exclusion criteria:

Patients with a prior history of allergies to zopiclone or any sedative hypnotic, history of severe chronic obstructive pulmonary disease, history of any condition that could interfere with the absorption of orally administered medicine, or prior participation in the investigational study less than 30 days prior to screening were excluded.

Population:		in age: ider:	72.3 years 58% Female	Ethnicity:	89.4% Caucasian 2.2% black
Drug name	do	sage	N=	Duration	
Eszopiclone	1	mg	72	14 day	
Eszopiclone	2	mg	79	14 day	

14 day

80

NA mg

Adverse Events:

Placebo

adverse events

Eszopiclone 1m	g Eszopiclone 2mg	Placebo
overall: %		
40	43	40
withdrawals due to adv	verse events: Number (%)
1 (1.4)	2 (2.5)	5 (6.3)
headache: %		
15.3	15.2	15.0
unpleasant taste: %		
8.3	11.4	1.3
somnolence: %		
6.9	3.8	8.8
dyspepsia: %		
5.6	1.3	2.5

ıbrane (pos	ter), 2005				Quality	y ratir	ng: F	air		
sign:										
Study design:	RCT DB	Parallel	Run-in : Wash out :	NR NR	Setting: Country		ticente	r		
Sample:	Number Sc	reened/ Eligible NR/ NR			Number Withdrawn/ Lost to fo 20/			yzed NR		
	ned primary) 1 hour per nig		east 3 nights per week during th				ind time i	'n
	Axis I psych				of substance abuse, use of any n sleep medication within 1 and					
Population:		44.4 years	Ethnicity:	90%	6 Caucasian, 10% other					
ervention:	Gender:	58% Female								
Drug name	dosage	N=	Duration							
Zolpidem-CR	12.5 mg	102	3 week							
Placebo	NA mg	110	3 week							
verse Event	ts:									
	_	verse events >=	=5%							
Treatment e	_	verse events >= Placebo	-5%							
Treatment e	emergent ad	Placebo	-5%							
Treatment e Zol any adverse	emergent ad pidem MR	Placebo	-5%							
Treatment e Zol any adverse 58	emergent ad pidem MR e event: Num (56.8)	Placebo ber (%)	-5%							
Treatment e Zol any adverse 58 nervous sys	emergent ad pidem MR e event: Num (56.8)	Placebo lber (%) 57 (51.8)	:5%							
Treatment e Zol any adverse 58 nervous sys 41	emergent ad pidem MR e event: Num (56.8) stem disorder (40.2)	Placebo ber (%) 57 (51.8) rs: Number (%) 24 (21.8)	:5%							
Treatment of Zol any adverse 58 nervous sys 41 psychiatric	emergent ad pidem MR e event: Num (56.8) stem disorder (40.2) disorders: Nu	Placebo bber (%) 57 (51.8) rs: Number (%) 24 (21.8) umber (%)	-5%							
Treatment e Zol any adverse 58 nervous sys 41 psychiatric 18	e event: Num (56.8) stem disorder (40.2) disorders: Nu (17.6)	Placebo bber (%) 57 (51.8) rs: Number (%) 24 (21.8) umber (%) 11 (10)	-5%							
Treatment of Zol any adverse 58 nervous sys 41 psychiatric 18 gastrointest	emergent ad pidem MR (56.8) stem disorder (40.2) disorders: Nu (17.6) tinal disorders	Placebo bber (%) 57 (51.8) rs: Number (%) 24 (21.8) umber (%) 11 (10) s: Number (%)	:5%							
Treatment of Zol any adverse 58 nervous sys 41 psychiatric 18 gastrointest	e event: Num (56.8) stem disorder (40.2) disorders: Nu (17.6) tinal disorders (11.8)	Placebo bber (%) 57 (51.8) rs: Number (%) 24 (21.8) umber (%) 11 (10) s: Number (%) 14 (12.7)		er (%)						
Treatment e Zol any adverse 58 nervous sys 41 psychiatric 18 gastrointest 12 musculoske	energent ad pidem MR e event: Num (56.8) stem disorder (40.2) disorders: Nu (17.6) tinal disorders (11.8) eletal and cor	Placebo ber (%) 57 (51.8) rs: Number (%) 24 (21.8) umber (%) 11 (10) s: Number (%) 14 (12.7) nnective tissue d		er (%))					
Treatment e Zol any adverse 58 nervous sys 41 psychiatric 18 gastrointest 12 musculoske 11	emergent ad pidem MR e event: Num (56.8) stem disorder (40.2) disorders: Nu (17.6) tinal disorders (11.8) eletal and cor (10.8)	Placebo ber (%) 57 (51.8) rs: Number (%) 24 (21.8) umber (%) 11 (10) s: Number (%) 14 (12.7) nnective tissue d 7 (6.4)		er (%))					
Treatment of Zol any adverse 58 nervous sys 41 psychiatric 18 gastrointest 12 musculoske 11 eye disorde	emergent ad pidem MR e event: Num (56.8) stem disorder (40.2) disorders: Nu (17.6) tinal disorders (11.8) eletal and cor (10.8) ers: Number (Placebo bber (%) 57 (51.8) rs: Number (%) 24 (21.8) umber (%) 11 (10) s: Number (%) 14 (12.7) nnective tissue d 7 (6.4) %)		er (%))					
Treatment e Zol any adverse 58 nervous sys 41 psychiatric 18 gastrointest 12 musculoske 11 eye disorde	emergent ad pidem MR e event: Num (56.8) stem disorder (40.2) disorders: Nu (17.6) tinal disorders (11.8) eletal and cor (10.8) rrs: Number ((7.8)	Placebo bber (%) 57 (51.8) rs: Number (%) 24 (21.8) umber (%) 11 (10) s: Number (%) 14 (12.7) nnective tissue d 7 (6.4) %) 2 (1.8)	isorders: Numb							
Treatment of Zol any adverse 58 nervous sys 41 psychiatric 18 gastrointest 12 musculoske 11 eye disorde 8 general diso	emergent ad pidem MR e event: Num (56.8) stem disorder (40.2) disorders: Nu (17.6) tinal disorders (11.8) eletal and cor (10.8) wrs: Number ((7.8) orders, admir	Placebo ber (%) 57 (51.8) rs: Number (%) 24 (21.8) umber (%) 11 (10) s: Number (%) 14 (12.7) nnective tissue d 7 (6.4) %) 2 (1.8) nistration site cor	isorders: Numb							
Treatment of Zol any adverse 58 nervous sys 41 psychiatric 18 gastrointest 12 musculoske 11 eye disorde 8 general diso	emergent ad pidem MR e event: Num (56.8) stem disorder (40.2) disorders: Nu (17.6) tinal disorders: (11.8) eletal and cor (10.8) trs: Number ((7.8) orders, admir (6.9)	Placebo bber (%) 57 (51.8) rs: Number (%) 24 (21.8) umber (%) 11 (10) s: Number (%) 14 (12.7) nnective tissue d 7 (6.4) %) 2 (1.8)	isorders: Numb							
Treatment of Zol any adverse 58 nervous sys 41 psychiatric 18 gastrointest 12 musculoske 11 eye disorde 8 general diso 7 headache: 1	emergent ad pidem MR e event: Num (56.8) stem disorder (40.2) disorders: Nu (17.6) tinal disorders (11.8) eletal and cor (10.8) ers: Number ((7.8) prders, admir (6.9) Number (%)	Placebo bber (%) 57 (51.8) rs: Number (%) 24 (21.8) umber (%) 11 (10) s: Number (%) 14 (12.7) nective tissue d 7 (6.4) %) 2 (1.8) nistration site cor 7 (6.4)	isorders: Numb							
Treatment e Zol any adverse 58 nervous sys 41 psychiatric e 18 gastrointest 12 musculoske 11 eye disorde 8 general diso 7 headache: 1	emergent ad pidem MR e event: Num (56.8) stem disorder (40.2) disorders: Nu (17.6) tinal disorders (11.8) eletal and cor (10.8) ers: Number ((7.8) orders, admir (6.9) Number (%) (18.6)	Placebo bber (%) 57 (51.8) rs: Number (%) 24 (21.8) umber (%) 11 (10) s: Number (%) 14 (12.7) nective tissue d 7 (6.4) %) 2 (1.8) nistration site cor 7 (6.4) 18 (16.4)	isorders: Numb							
Treatment e Zol any adverse 58 nervous sys 41 psychiatric e 18 gastrointest 12 musculoske 11 eye disorde 8 general diso 7 headache: 1	emergent ad pidem MR e event: Num (56.8) stem disorder (40.2) disorders: Nu (17.6) tinal disorders (11.8) eletal and cor (10.8) ers: Number ((7.8) prders, admir (6.9) Number (%)	Placebo bber (%) 57 (51.8) rs: Number (%) 24 (21.8) umber (%) 11 (10) s: Number (%) 14 (12.7) nective tissue d 7 (6.4) %) 2 (1.8) nistration site cor 7 (6.4) 18 (16.4)	isorders: Numb							
Treatment of Zol any adverse 58 nervous sys 41 psychiatric 18 gastrointest 12 musculoske 11 eye disorde 8 general diso 7 headache: 1 19 somnolence	emergent ad pidem MR e event: Num (56.8) stem disorder (40.2) disorders: Nu (17.6) tinal disorders (11.8) eletal and cor (10.8) ers: Number ((7.8) orders, admir (6.9) Number (%) (18.6)	Placebo bber (%) 57 (51.8) rs: Number (%) 24 (21.8) umber (%) 11 (10) s: Number (%) 14 (12.7) nective tissue d 7 (6.4) %) 2 (1.8) nistration site cor 7 (6.4) 18 (16.4)	isorders: Numb							
Treatment of Zol any adverse 58 nervous sys 41 psychiatric 18 gastrointest 12 musculoske 11 eye disorde 8 general diso 7 headache: 1 19 somnolence	emergent ad pidem MR e event: Num (56.8) stem disorders (40.2) disorders: Nu (17.6) tinal disorders (11.8) eletal and cor (10.8) orders, admir (6.9) Number (%) (18.6) e: Number (%) (14.7)	Placebo bber (%) 57 (51.8) rs: Number (%) 24 (21.8) umber (%) 11 (10) s: Number (%) 14 (12.7) nective tissue d 7 (6.4) %) 2 (1.8) nistration site cor 7 (6.4) 18 (16.4) 5)	isorders: Numb							
Treatment e Zol any adverse 58 nervous sys 41 psychiatric e 18 gastrointest 12 musculoske 11 eye disorde 8 general diso 7 headache: 1 19 somnolence 15 dizziness: N	emergent ad pidem MR e event: Num (56.8) stem disorders (40.2) disorders: Nu (17.6) tinal disorders (11.8) eletal and cor (10.8) orders, admir (6.9) Number (%) (18.6) e: Number (%) (14.7)	Placebo bber (%) 57 (51.8) rs: Number (%) 24 (21.8) umber (%) 11 (10) s: Number (%) 14 (12.7) nective tissue d 7 (6.4) %) 2 (1.8) nistration site cor 7 (6.4) 18 (16.4) 5)	isorders: Numb							
Treatment e Zol any adverse 58 nervous sys 41 psychiatric e 18 gastrointest 12 musculoske 11 eye disorde 8 general diso 7 headache: 1 19 somnolence 15 dizziness: N	emergent ad pidem MR e event: Num (56.8) stem disorder (40.2) disorders: Nu (17.6) tinal disorders: Nu (17.6) tinal disorders (11.8) eletal and cor (10.8) orders, admir (6.9) Number (%) (18.6) e: Number (%) (14.7) Number (%) (11.8)	Placebo bber (%) 57 (51.8) rs: Number (%) 24 (21.8) umber (%) 11 (10) s: Number (%) 14 (12.7) nective tissue d 7 (6.4) %) 2 (1.8) histration site cor 7 (6.4) 18 (16.4) 6) 2 (1.8)	isorders: Numb							

orane (poster), 2005		Quality rating: Fair
Withdrawals		
Zolpidem MR	Placebo	
total withdrawals: Number		
NR	NR	
withdrawal due to AEs: Nu	mber	
6	2	

erzano, 1992							Quality	/ rating:	Poor	
Design:										
Study design:	RCT	DB	Paralle	I	Run-in : Wash out :	14 days NR	Setting: Country	0	Center	
Sample:	Numbe	er Scre	ened/ El NR/	igible/ NR/	Enrolled 12	Number With	drawn/ Lost to fo NR/	low-up/ Ar NR/	nalyzed 12	
following co Exclusion crite	mplaints eria:	: diffic	ulties in fa	alling a	sleep, inadequ	sychophysiological in uate sleep length and ome				ne
following co Exclusion crite patients had Population: ntervention:	mplaints eria: d nocturn Mean a Gende	: diffic al myo age: er:	ulties in fa oclonus or 49.6 years 67% Fem	alling a r sleep s ale	sleep, inadequ apnea syndro Ethnicity:	uate sleep length and		•		ne
following co Exclusion crite patients had Population:	mplaints eria: d nocturn Mean : Gende dosa	: diffic al myo age: er:	ulties in fa oclonus or 49.6 years	alling a r sleep s ale	sleep, inadequ apnea syndro	uate sleep length and		•		he

Adverse Events:

Walsh, 2000a		Quality rating: Poor								
Design:										
Study design:	RCT	DB	Para	allel	Run-in :	5-12 days	Sett	ing:	Multicer	nter
					Wash out :	5-12 days	Cou	ntry:	US	
Sample:	Numbe	r Scre	ened/	Eligible/	Enrolled	Number Witho	drawn/ Lost	to follov	v-up/ Ai	nalyzed
			311/	54/	48		NR/		NR/	48

Inclusion criteria:

Males and female aged 60 to 80 years who reported sleep disturbance of > 3 months' duration with associated daytime impairment were eligible. Historical inclusion criteria included the following occurring three or more times each week: a subjective sleep latency of > 30 minutes and either > 3 awakenings per night (with difficulty returning to sleep) or a total sleep time between 180 and 360 minutes.

Exclusion criteria:

any chronic or recurrent medical illness considered to affect sleep or to potentially require medical attention or medication changes during the study was cause for exclusion. Additionally, patients with a present or past history of a major psychiatric illness [e.g. Diagnostic and Statistical Manual of Mental Disorders (DSM)-IV diagnoses of depressive or psychotic disorders, dementia or mental retardation] that was considered to influence sleep or study outcome were excluded. Additional exclusion criteria included a urine drug screen positive for drugs of abuse or sedative/hypnotic/anxiolytic agents; a history of severe adverse reactions to sedative hypnotics; bodyweight more than 5% below or more than 25% above Metropolitan Life Insurance Company standards; use of any medication with significant CNS effects within the prior 2 weeks (4 weeks for slowly eliminated drugs such as fluoxetine); or a history of drug/alcohol abuse within the past 12 months.

Population:	Mear Gene	n age: der:	67.5 years 35% Female	Ethnicity:	NR
Intervention: Drug name	dos	sage	N=	Duration	
Zaleplon	2	mg	12	2 day	
Zaleplon	5	mg	12	2 day	
Zaleplon	10	mg	12	2 day	
Placebo	NA	mg	12	2 day	

Adverse Events:

alsh, 2000b,	2002				Quality	rating: Fating: Fating	air
esign:							
Study design:	RCT DB	Parallel	Run-in : Wash out :	7 days 7 days	Setting: Country:	Multicente US	r
Sample:	Number Sc	reened/ Eligible 365/ 163		Number Withdrav	wn/ Lost to follo 29/	ow-up/ Anal 5/	yzed NR
Inclusion crite	ria:						
and insomni 9.0 hours; b and, continu current or pa sleep-relate negative for	ia-related day edtime and ri ued contracep ast major psy d items). 7) n any illicit drug on within 7 to er day.	time complaints se time varying l tive measures for chiatric illness w o illicit drug use g or psychotropi	on at least thre by < 3 hours du or women of chi hich may influe or excessive alo c medication. 9)	ep latency (SL) > 45 min e of the seven baseline of ring baseline week. 4) no ld-bearing potential. 5) a noce the study. 6) a Hami cohol use or abuse in the no use of a prescription , or an investigational dr	days 3) nightly egative pregnar absence of a cu ilton Depressior e past 12 month o or non-prescrip	time-in-bed l ncy test, non rrent medica n Scale scor ns. 8) urine c ption drugs t	between 6.5 and breast-feeding al condition, or e < 8 (excluding lrug screen hat affect sleep-
NR							
Population:	Mean age: Gender:	44.1 years 71% Female	Ethnicity:	83.4% Caucasian 16.6% other			
ntervention: Drug name	dosage	N=	Duration				
Zolpidem	10 mg	82	56 day				
Placebo	NA mg	81	56 day				
dverse Even	ts:						
adverse eve	ents						
Z	Zolpidem	Placebo					
overall: Nu	mber						
	1	4				F	2: NS
	s						
withdrawal		Placebo					
	Zolpidem	Пассьо					
2	Zolpidem awals: Numb						
2	•						
total withdr	awals: Numb	er 10					

B Para	allel	Run-in :	2 days	Setting:	Single	Center	
		Wash out :	5-7 days	Country:	US		
creened/	Eligible/	Enrolled	Number Withdrawn/	Lost to follo	w-up/	Analyzed	
NR/	669/	308	16/		0/	308	
	creened/	creened/ Eligible/	Wash out : creened/ Eligible/ Enrolled	Wash out : 5-7 days screened/ Eligible/ Enrolled Number Withdrawn/	Wash out : 5-7 days Country: creened/ Eligible/ Enrolled Number Withdrawn/ Lost to follow	Wash out : 5-7 days Country: US creeened/ Eligible/ Enrolled Number Withdrawn/ Lost to follow-up/	Wash out : 5-7 days Country: US Screened/ Eligible/ Enrolled Number Withdrawn/ Lost to follow-up/ Analyzed

Adults aged 21 years-64 years who met DSM-IV criteria for primary insomnia, and who additionally reported no more than 6.5 h of sleep per night and required more than 30 min to fall asleep each night for at least 1 month, were eligible for screening.

Exclusion criteria:

Patients with any unstable medical abnormality or acute illness, any pertinent drug sensitivities, abnormalities in drug metabolism, periodic limb movement disorder, restless legs syndrome, circadian rhythm disorder, or sleep apnea were excluded.

Population:	Mea Gen	-	39.8 years 61% Female	Ethnicity:	66.2% Caucasians 16.6% black
Drug name	dos	sage	N=	Duration	
Eszopiclone	2	mg	104	44 day	
Eszopiclone	3	mg	105	44 day	
Placebo	NA	mg	99	44 day	

Adverse Events:

adverse events during treatment

Eszopiclone 2mg	Eszopiclone 3mg	Placebo
abnormal dreams: Numb	er (%)	
2 (2)	3 (2.9)	2 (1.9)
nervousness: Number (%	b)	
2 (2)	5 (4.8)	0 (0)
back pain: Number (%)		
2 (2)	1 (1)	4 (3.8)
dizziness: Number (%)		
4 (4)	3 (2.9)	5 (4.8)
dry mouth: Number (%)		
2 (2)	5 (4.8)	6 (5.7)
headache: Number (%)		
8 (8.1)	13 (12.5)	12 (11.4)
somnolence: Number (%)	
3 (3)	8 (7.7)	8 (7.6)
unpleasant taste: Numbe	er (%)	
3 (3)	17 (16.3)	35 (33.3)
adverse events after trea	atment discontinuation	on
Eszopiclone 2mg	Eszopiclone 3mg	Placebo
CNS related: % (p vs place	cebo)	
11.5 (NS)	15.2 (NS)	18.2 (NA)

mmit, 2004			Quality rating: Fair	
withdrawals				
Eszopiclone 2mg	Eszopiclone 3mg	Placebo		
total withdrawals: Number	er			
7	4	5		
withdrawals due to AEs:	Number			
3	0	0		

Evidence Table 16. Quality A	Assessment of efficacy trials
------------------------------	-------------------------------

Internal validity					External validity				
Allain, 1998	Desigr	n: RCT DB	Parallel	Trial type:	Placebo	Quality ratin	g: Fa	air	
1. Randomization adequate?	NR	8. Reporting	of Attrition	No	1. Number Screened/ Eligib	le/ Enrolled:	NR /	NR/	37
2. Allocation adequate?	NR		Crossover	No	3. Run-in/ Wash out (days):		3/	3	
3. Groups similar at baseline?	Yes		Adherence	No	4. Class naive patients only?)	NR (a	all were ta	aking tri
4. Eligibility criteria specified?	Yes		Contaminatio	on No	5. Controlled group standard	of care?	NR		
9. Loss to follow-up, differential?	NR				2. Exclusion criteria reported	!?	Yes		
5. Outcome assessors masked?	Yes				6. Funding: NR				
6. Care provider masked?	Yes								
7. Patients masked?	Yes								
10. Intention-to-treat analysis?	Unab	le to determine	•						
11. Postrandomization exclusior	ns? NR								
Allain, 2001	Desigr	n: RCT DB	Parallel	Trial type:	Placebo	Quality ratin	g: Fa	air	
1. Randomization adequate?	NR	8. Reporting	of Attrition	Yes	1. Number Screened/ Eligib	le/ Enrolled:	NR /	NR /	245
2. Allocation adequate?	NR		Crossover	No	3. Run-in/ Wash out (days):		3-7/	NR	
3. Groups similar at baseline?	Plac		Adherence	Yes	4. Class naive patients only?)	NR		
4. Eligibility criteria specified?	Yes		Contaminatio	on No	5. Controlled group standard	of care?	NR		
9. Loss to follow-up, differential?	Yes				2. Exclusion criteria reported	?	Yes		
5. Outcome assessors masked?	Yes				6. Funding: Sanofi-Synthela	lbo			
6. Care provider masked?	NR								
7. Patients masked?	Yes								
10. Intention-to-treat analysis?	Yes								
11. Postrandomization exclusion	ns? No								
Allain, 2003	Desigr	n: RCT DB	Crossover	Trial type:	H2H	Quality ratin	g: Fa	air	
1. Randomization adequate?	Yes	8. Reporting	of Attrition	Yes	1. Number Screened/ Eligib	le/ Enrolled:	NR /	NR /	53
2. Allocation adequate?	NR		Crossover	Yes	3. Run-in/ Wash out (days):		0/	0	
3. Groups similar at baseline?	Yes		Adherence	Yes	4. Class naive patients only?)	No		
4. Eligibility criteria specified?	Yes		Contaminatio	on No	5. Controlled group standard	of care?	Yes		
9. Loss to follow-up, differential?	No				2. Exclusion criteria reported	1?	Yes		
5. Outcome assessors masked?					6. Funding: Sanofi-Synthela	lbo			
6. Care provider masked?	NR								
7. Patients masked?	Yes								
10. Intention-to-treat analysis?	Yes								
11. Postrandomization exclusion	-0 1								

Internal validity					External validity				
Ancoli-Israel, 1999	Design	:RCT [B Parallel	Trial type:	H2H Quality	Quality rating: Fair			
1. Randomization adequate?	NR	8. Repor	ting of Attrition	Yes	1. Number Screened/ Eligible/ Enrolled:	1224 /	551 /	549	
2. Allocation adequate?	NR		Crossover	No	3. Run-in/ Wash out (days):	7/	7-21		
3. Groups similar at baseline?	Yes		Adherence	No	4. Class naive patients only?	No			
4. Eligibility criteria specified?	Yes		Contaminati	ion No	5. Controlled group standard of care?	Yes			
9. Loss to follow-up, differential?	No				2. Exclusion criteria reported?	Yes			
5. Outcome assessors masked?	Yes				6. Funding: Wyeth-Ayerst				
6. Care provider masked?	NR								
7. Patients masked?	Yes								
10. Intention-to-treat analysis?	No								
11. Postrandomization exclusion	ns? Yes								
Anderson, 1987	Design	RCT E	B Parallel	Trial type:	Active Quality	rating: Fa	air		
1. Randomization adequate?	NR	8. Repor	ting of Attrition	Yes	1. Number Screened/ Eligible/ Enrolled:	NR /	NR /	119	
2. Allocation adequate?	NR		Crossover	No	3. Run-in/ Wash out (days):	7/	7		
3. Groups similar at baseline?	Yes		Adherence	Yes	4. Class naive patients only?	No			
4. Eligibility criteria specified?	Yes		Contaminati	ion No	5. Controlled group standard of care?	Yes			
9. Loss to follow-up, differential?	Yes				2. Exclusion criteria reported?	Yes			
5. Outcome assessors masked?	No				6. Funding: Not reported				
6. Care provider masked?	NR								
7. Patients masked?	Yes								
10. Intention-to-treat analysis?	No								
11. Postrandomization exclusion	ns? Yes								
Autret, 1987	Design	:CT DE	Crossover	Trial type:	e: Active Quality rating: Poor				
1. Randomization adequate?	Not r	8. Repor	ting of Attrition	Yes	1. Number Screened/ Eligible/ Enrolled:	NR /	NR/	121	
2. Allocation adequate?	NR		Crossover	No	3. Run-in/ Wash out (days):	4 /	3		
3. Groups similar at baseline?	NR		Adherence	Yes	4. Class naive patients only?				
4. Eligibility criteria specified?	Yes		Contaminati	ion No	5. Controlled group standard of care?				
9. Loss to follow-up, differential?	No				2. Exclusion criteria reported?	No			
5. Outcome assessors masked?	Yes, b	ut not des	cribed		6. Funding:				
6. Care provider masked?	NR								
7. Patients masked?	Yes, b	ut not des	cribed						
10. Intention-to-treat analysis?	Unable	e to detern	nine						
11. Postrandomization exclusion	ns? Unable	e to detern	nine						

Internal validity					External validity				
Begg, 1992	Design	:RCT SB	Parallel	Trial type:	Active	Quality ra	ating: Po	or	
1. Randomization adequate?	Yes	8. Reporting	of Attrition	Yes	1. Number Screened/ E	Eligible/ Enrolled:	NR /	NR/	88
2. Allocation adequate?	NR		Crossover	No	3. Run-in/ Wash out (da	ays):	2/	2	
3. Groups similar at baseline?	No		Adherence	Yes	4. Class naive patients of	only?	No		
4. Eligibility criteria specified?	Yes		Contaminatio	n No	5. Controlled group star	ndard of care?			
9. Loss to follow-up, differential?	Yes				2. Exclusion criteria repo	orted?	Yes		
5. Outcome assessors masked?	Yes				6. Funding: Roche Proc	ducts (NZ) Ltd.			
6. Care provider masked?	NR								
7. Patients masked?	Yes								
10. Intention-to-treat analysis?	No								
11. Postrandomization exclusion	s? Yes								
Bergener, 1989	Design	RCT DB	Parallel	Trial type:	Active	Quality ra	ating: Fa	lir	
1. Randomization adequate?	NR	8. Reporting	of Attrition	Yes	1. Number Screened/ E	Eligible/ Enrolled:	NR /	NR/	42
2. Allocation adequate?	NR		Crossover	No	3. Run-in/ Wash out (da	ays):	4 /	7	
3. Groups similar at baseline?	NR		Adherence	No	4. Class naive patients of	only?	NR		
4. Eligibility criteria specified?	Yes		Contaminatio	n No	5. Controlled group star	ndard of care?	Yes		
9. Loss to follow-up, differential?	Yes				2. Exclusion criteria repo	orted?	Yes		
5. Outcome assessors masked?	Yes, b	out not describ	ed		6. Funding: Not reporte	ed			
6. Care provider masked?	Yes, b	out not describ	ed						
7. Patients masked?	Yes								
10. Intention-to-treat analysis?	Unable	e to determine	•						
11. Postrandomization exclusion	ns? No								
Chaudoir, 1983	Design	RCT DB	Crossover	Trial type:	Placebo	Quality ra	ating: Po	or	
1. Randomization adequate?	NR	8. Reporting	of Attrition	Yes	1. Number Screened/ E	Eligible/ Enrolled:	NR /	30/	25
2. Allocation adequate?	NR		Crossover	No	3. Run-in/ Wash out (da	ays):	NR /	NR	
3. Groups similar at baseline?	Yes		Adherence	No	4. Class naive patients	only?	No		
4. Eligibility criteria specified?	Yes		Contaminatio	n No	5. Controlled group stan	ndard of care?	NR		
9. Loss to follow-up, differential?	Yes				2. Exclusion criteria repo	orted?	Yes		
5. Outcome assessors masked?	Yes, b	out not describ	ed		6. Funding: NR (May &	Baker provided med	ications and	l placebo)
6. Care provider masked?	NR								
7. Patients masked?	Voc h	out not describ	od						

No (25/30 analyzed)

10. Intention-to-treat analysis?

11. Postrandomization exclusions? No

Internal validity						External validity				
Chaudoir, 1990	Desigr	: RCT	DB F	Parallel	Trial type:	Active	Quality	rating: Fa	air	
1. Randomization adequate?	NR	8. Rep	orting o	f Attrition	Yes	1. Number Screened/	Eligible/ Enrolled:	NR /	NR /	38
2. Allocation adequate?	NR			Crossover	No	3. Run-in/ Wash out (days):	no /	7	
3. Groups similar at baseline?	Yes			Adherence	No	4. Class naive patients	s only?	No		
4. Eligibility criteria specified?	Yes			Contaminatio	on No	5. Controlled group sta	andard of care?	Yes		
9. Loss to follow-up, differential?	No					2. Exclusion criteria re	ported?	Yes		
5. Outcome assessors masked?	Yes, I	out not de	escribe	b		6. Funding: Not report	ted			
6. Care provider masked?	NR									
7. Patients masked?	Yes									
10. Intention-to-treat analysis?	Not cl	ear								
11. Postrandomization exclusion	ns? Unab	e to dete	ermine							
Dockhorn, 1996	Desigr	: RCT	DB F	Parallel	Trial type:	Placebo	Quality	rating: Fa	air	
1. Randomization adequate?	NR	8. Rep	orting o	f Attrition	Yes	1. Number Screened/	Eligible/ Enrolled:	NR /	NR /	138
2. Allocation adequate?	NR			Crossover	No	3. Run-in/ Wash out (days):	NR /	NR	
3. Groups similar at baseline?	Yes			Adherence	No	4. Class naive patients	s only?	NR		
4. Eligibility criteria specified?	Yes			Contaminatio	on No	5. Controlled group sta	andard of care?	NR		
9. Loss to follow-up, differential?	No					2. Exclusion criteria re	ported?	Yes		
5. Outcome assessors masked?	Yes					6. Funding: Lorex Pha	armaceuticals			
6. Care provider masked?	NR									
7. Patients masked?	Yes									
10. Intention-to-treat analysis?	No (1	36/139 a	nalyzec	ł)						
11. Postrandomization exclusion	ns? Yes (1 patient))							
Dorsey, 2004	Desigr	: RCT	DB F	Parallel	Trial type:	Placebo	Quality	rating: Fa	air	
1. Randomization adequate?	NR	8. Rep	orting o	f Attrition	Yes	1. Number Screened/	Eligible/ Enrolled:	242 /	141 /	141
2. Allocation adequate?	NR			Crossover	No	3. Run-in/ Wash out (days):	6-14 /	NR	
3. Groups similar at baseline?	Yes			Adherence	No	4. Class naive patients	s only?	NR		
4. Eligibility criteria specified?	Yes			Contaminatio	on No	5. Controlled group sta	andard of care?	NR		
9. Loss to follow-up, differential?	' No					2. Exclusion criteria re	ported?	Yes		
5. Outcome assessors masked?	Yes, I	out not de	escribe	d		6. Funding: Sanofi-Sy	nthelabo			
6. Care provider masked?	NR									
7. Patients masked?	Yes									
10. Intention-to-treat analysis?	Yes									
11. Postrandomization exclusion	ns? No									

Internal validity					External validity			
Drake (1), 2001	Design	RCT DB	Crossover	Trial type:	Active Qual	ity rating: Fa	air	
1. Randomization adequate?	NR	8. Reporting	of Attrition	Yes	1. Number Screened/ Eligible/ Enrolled	: NR /	NR /	47
2. Allocation adequate?	NR		Crossover	0	3. Run-in/ Wash out (days):	NR /	5-12	
3. Groups similar at baseline?	NR		Adherence	No	4. Class naive patients only?	No		
4. Eligibility criteria specified?	Yes		Contaminatio	on No	5. Controlled group standard of care?	Yes		
9. Loss to follow-up, differential?	No				2. Exclusion criteria reported?	Yes		
5. Outcome assessors masked?	Yes, b	ut not describe	ed		6. Funding: Wyeth-Ayerst Research			
6. Care provider masked?	NR							
7. Patients masked?	Yes							
10. Intention-to-treat analysis?	Unable	e to determine						
11. Postrandomization exclusion	is? No							
Drake (2), 2000	Design	RCT DB	Crossover	Trial type:	Active Qual	ity rating: Fa	air	
1. Randomization adequate?	NR	8. Reporting	of Attrition	Yes	1. Number Screened/ Eligible/ Enrolled	: NR /	NR /	36
2. Allocation adequate?	NR		Crossover	No	3. Run-in/ Wash out (days):	NR /	5-12	
3. Groups similar at baseline?	NR		Adherence	No	4. Class naive patients only?	No		
4. Eligibility criteria specified?	Yes		Contaminatio	on No	5. Controlled group standard of care?	Yes		
9. Loss to follow-up, differential?	No				2. Exclusion criteria reported?	Yes		
5. Outcome assessors masked?	Yes, b	ut not describe	ed		6. Funding: Wyeth-Ayerst Research			
6. Care provider masked?	NR							
7. Patients masked?	Yes							
10. Intention-to-treat analysis?	Unable	e to determine						
11. Postrandomization exclusion	is? No							
Elie, 1990a	Design	RCT DB	Parallel	Trial type:	Active Qual	ity rating: Fa	air	
1. Randomization adequate?	NR	8. Reporting	of Attrition	No	1. Number Screened/ Eligible/ Enrolled	: NR /	NR /	44
2. Allocation adequate?	NR		Crossover	No	3. Run-in/ Wash out (days):	7 /	4	
3. Groups similar at baseline?	NR		Adherence	No	4. Class naive patients only?	No		
4. Eligibility criteria specified?	Yes		Contaminatio	on No	5. Controlled group standard of care?	Yes		
9. Loss to follow-up, differential?	NR				2. Exclusion criteria reported?	Yes		
5. Outcome assessors masked?	Yes, b	ut not describe	ed		6. Funding: Not reported			
6. Care provider masked?	NR							

7. Patients masked?

10. Intention-to-treat analysis?

Yes Yes

11. Postrandomization exclusions? Unable to determine

Internal validity					External validity			
Elie, 1990b	Design	:RCT DB	Parallel	Trial type:	Active Quality	y rating: Fa	air	
1. Randomization adequate?	NR	8. Reporting	of Attrition	No	1. Number Screened/ Eligible/ Enrolled:	NR /	NR /	36
2. Allocation adequate?	NR		Crossover	No	3. Run-in/ Wash out (days):	7/	3	
3. Groups similar at baseline?	NR		Adherence	No	4. Class naive patients only?	No		
4. Eligibility criteria specified?	Yes		Contaminati	on No	5. Controlled group standard of care?	Yes		
9. Loss to follow-up, differential?	NR				2. Exclusion criteria reported?	Yes		
5. Outcome assessors masked?	Yes				6. Funding: Not reported			
6. Care provider masked?	NR							
7. Patients masked?	Yes							
10. Intention-to-treat analysis?	Unabl	e to determine	e					
11. Postrandomization exclusior	ns? Unabl	e to determine	Э					
Elie, 1999	Design	:RCT DB	Parallel	Trial type:	H2H Quality	y rating: Fa	air	
1. Randomization adequate?	NR	8. Reporting	of Attrition	Yes	1. Number Screened/ Eligible/ Enrolled:	NR /	NR /	615
2. Allocation adequate?	NR	-	Crossover	No	3. Run-in/ Wash out (days):	7-21 /	7	
3. Groups similar at baseline?	NR		Adherence	Yes	4. Class naive patients only?	No		
4. Eligibility criteria specified?	Yes		Contaminati	on No	5. Controlled group standard of care?	Yes		
9. Loss to follow-up, differential?	No No				2. Exclusion criteria reported?	Yes		
5. Outcome assessors masked?	Yes				6. Funding: Wyeth-Ayerst			
6. Care provider masked?	NR							
7. Patients masked?	Yes							
10. Intention-to-treat analysis?	No							
11. Postrandomization exclusior	ns? Yes							
Erman, 2006	Design	:RCT DB	Crossover	Trial type:	Placebo Qualit	y rating: Fa	air	
1. Randomization adequate?	Yes	8. Reporting	of Attrition	Yes	1. Number Screened/ Eligible/ Enrolled:	319/	205 /	107
2. Allocation adequate?	NR		Crossover	No	3. Run-in/ Wash out (days):	NR /	5-12	
3. Groups similar at baseline?	Yes		Adherence	No	4. Class naive patients only?	NR		
4. Eligibility criteria specified?	Yes		Contaminati	on No	5. Controlled group standard of care?	Yes		
9. Loss to follow-up, differential?	P No				2. Exclusion criteria reported?	Yes		
5. Outcome assessors masked?	Yes, b	out not describ	ed		6. Funding: Takeda			
6. Care provider masked?	Yes, b	out not describ	ed					
7. Patients masked?	Yes							
10. Intention-to-treat analysis?	No (10)3/107 analyz	ed)					
11. Postrandomization exclusior	ns? Unabl	e to determine	Э					

Internal validity					External validity			
Fleming, 1990	Desigr	RCT DB	Parallel	Trial type:	Active Qua	ality rating: Fa	ir	
1. Randomization adequate?	Yes	8. Reporting	of Attrition	Yes	1. Number Screened/ Eligible/ Enrolle	ed: NR /	NR /	52
2. Allocation adequate?	NR		Crossover	No	3. Run-in/ Wash out (days):	3/	4	
3. Groups similar at baseline?	NR		Adherence	No	4. Class naive patients only?	No		
4. Eligibility criteria specified?	Yes		Contaminatio	on No	5. Controlled group standard of care?	Yes		
9. Loss to follow-up, differential?	' No				2. Exclusion criteria reported?	Yes		
5. Outcome assessors masked?	Yes, I	out not describe	ed		6. Funding: Not reported			
6. Care provider masked?	NR							
7. Patients masked?	Yes							
10. Intention-to-treat analysis?	No (4	8/52 analyzed)						
11. Postrandomization exclusior	ns? Yes							
Fleming, 1995	Desigr	RCT DB	Parallel	Trial type:	Active Qua	ality rating: Fa	ir	
1. Randomization adequate?	NR	8. Reporting	of Attrition	Yes	1. Number Screened/ Eligible/ Enrolle	ed: 222 /	144 /	144
2. Allocation adequate?	NR		Crossover	Yes	3. Run-in/ Wash out (days):	1 /	NR	
3. Groups similar at baseline?	Yes		Adherence	No	4. Class naive patients only?	No		
4. Eligibility criteria specified?	Yes		Contaminatio	on Yes	5. Controlled group standard of care?	Yes		
9. Loss to follow-up, differential?	Yes				2. Exclusion criteria reported?	Yes		
5. Outcome assessors masked?	Yes, I	out not describe	ed		6. Funding: Not reported			
6. Care provider masked?	NR							
7. Patients masked?	Yes							
10. Intention-to-treat analysis?	No							
11. Postrandomization exclusior	ns? Yes							
Fry, 2000	Desigr	RCT DB	Parallel	Trial type:	H2H Qua	ality rating: Fa	ir	
1. Randomization adequate?	NR	8. Reporting	of Attrition	Yes	1. Number Screened/ Eligible/ Enrolle	ed: NR /	830/	595
2. Allocation adequate?	NR		Crossover	No	3. Run-in/ Wash out (days):	7/	0	
3. Groups similar at baseline?	NR		Adherence	No	4. Class naive patients only?	NR		
4. Eligibility criteria specified?	Yes		Contaminatio	on No	5. Controlled group standard of care?	Yes		
9. Loss to follow-up, differential?	P No				2. Exclusion criteria reported?	Yes		
5. Outcome assessors masked?	Yes, I	out not describe	ed		6. Funding: Wyeth-Ayerst			

6. Care provider masked?

10. Intention-to-treat analysis?

11. Postrandomization exclusions? Yes

7. Patients masked?

NR

No

Yes, but not described

Internal validity					External validity			
Goldenberg, 1994	Desigr	n: RCT DE	B Parallel	Trial type:	Placebo C	uality rating: Po	or	
1. Randomization adequate?	NR	8. Reportin	g of Attrition	Yes	1. Number Screened/ Eligible/ En	olled: NR /	NR/	524
2. Allocation adequate?	NR		Crossover	No	3. Run-in/ Wash out (days):	NR /	NR	
3. Groups similar at baseline?	Yes (Adherence	No	4. Class naive patients only?	NR		
4. Eligibility criteria specified?	Yes		Contaminatio	on No	5. Controlled group standard of car	re? NR		
9. Loss to follow-up, differential?	Yes				2. Exclusion criteria reported?	Yes		
5. Outcome assessors masked?	Yes,	but not descri	bed		6. Funding: NR			
6. Care provider masked?	NR							
7. Patients masked?	Yes							
10. Intention-to-treat analysis?	No							
11. Postrandomization exclusion	is? Unab	le to determir	e					
Hajak, 1998, 1995, 1994	Desigr	n: RCT DE	B Parallel	Trial type:	Active C	uality rating: Fa	ir	
1. Randomization adequate?	Yes	8. Reportin	g of Attrition	Yes	1. Number Screened/ Eligible/ En	olled: NR /	NR/	1507
2. Allocation adequate?	NR		Crossover	No	3. Run-in/ Wash out (days):	7/	3	
3. Groups similar at baseline?	Yes		Adherence	Yes	4. Class naive patients only?	No		
4. Eligibility criteria specified?	Yes		Contaminatio	on No	5. Controlled group standard of car	re? Yes		
9. Loss to follow-up, differential?	No				2. Exclusion criteria reported?	Yes		
5. Outcome assessors masked?	Yes,	but not descri	bed		6. Funding: Not reported			
6. Care provider masked?	NR							
7. Patients masked?	Yes							
10. Intention-to-treat analysis?	Yes							
11. Postrandomization exclusion	is? No							
Hayoun, 1989	Desigr	RCT DE	Parallel	Trial type:	Active C	uality rating: Fa	ir	
1. Randomization adequate?	NR	8. Reportin	g of Attrition	Yes	1. Number Screened/ Eligible/ En	olled: NR /	NR/	136
2. Allocation adequate?	NR		Crossover	No	3. Run-in/ Wash out (days):	NR /	NR	
3. Groups similar at baseline?	Yes		Adherence	No	4. Class naive patients only?	No		
4. Eligibility criteria specified?	Yes		Contaminatio	on Yes	5. Controlled group standard of car	re? Yes		
9. Loss to follow-up, differential?	Yes				2. Exclusion criteria reported?	Yes		
5. Outcome assessors masked?	Yes,	but not descri	bed		6. Funding: Not reported (correspo	onding author from Up	ojohn)	
6. Care provider masked?	NR							
7. Patients masked?	Yes							
10. Intention-to-treat analysis?	No							
11. Postrandomization exclusion	s? Yes							

Internal validity					External validity			
Hedner, 2000	Design	RCT DB	Parallel	Trial type:	Placebo Qua	ality rating: Fa	ir	
1. Randomization adequate?	NR	8. Reporting	of Attrition	No	1. Number Screened/ Eligible/ Enroll	ed: NR /	NR /	437
2. Allocation adequate?	NR		Crossover	No	3. Run-in/ Wash out (days):	7/	7	
3. Groups similar at baseline?	Yes f		Adherence	No	4. Class naive patients only?			
4. Eligibility criteria specified?	Yes		Contaminatio	on No	5. Controlled group standard of care?			
9. Loss to follow-up, differential?	NR				2. Exclusion criteria reported?	Yes		
5. Outcome assessors masked?	Yes				6. Funding:			
6. Care provider masked?	NR							
7. Patients masked?	Yes							
10. Intention-to-treat analysis?	No (42	22/437 analyze	ed)					
11. Postrandomization exclusion	is? NR							
Herrmann, 1993	Design	RCT DB	Parallel	Trial type:	Placebo Qua	ality rating: Po	or	
1. Randomization adequate?	NR	8. Reporting	of Attrition	Yes	1. Number Screened/ Eligible/ Enroll	ed: NR /	25/	21
2. Allocation adequate?	NR		Crossover	No	3. Run-in/ Wash out (days):	7/	7	
3. Groups similar at baseline?	NR		Adherence	No	4. Class naive patients only?	NR		
4. Eligibility criteria specified?	Yes		Contaminatio	on No	5. Controlled group standard of care?	NR		
9. Loss to follow-up, differential?	Yes				2. Exclusion criteria reported?	Yes		
5. Outcome assessors masked?	Yes, b	out not describ	ed		6. Funding: NR			
6. Care provider masked?	NR							
7. Patients masked?	Yes							
10. Intention-to-treat analysis?	No (2'	1/25 analyzed))					
11. Postrandomization exclusion	ns? Yes (1	1/25)						
Hindmarch, 1995	Design	RCT DB	Parallel	Trial type:	Placebo Qua	ality rating: Fa	ir	
1. Randomization adequate?	NR	8. Reporting	of Attrition	Yes	1. Number Screened/ Eligible/ Enroll	ed: NR /	NR /	458
2. Allocation adequate?	NR		Crossover	No	3. Run-in/ Wash out (days):	NR /	NR	
3. Groups similar at baseline?	glob		Adherence	No	4. Class naive patients only?			
4. Eligibility criteria specified?	Yes		Contaminatio	on No	5. Controlled group standard of care?			
9. Loss to follow-up, differential?	Yes				2. Exclusion criteria reported?	Yes		
5. Outcome assessors masked?	Yes, b	out not describ	ed		6. Funding:			
6. Care provider masked?	NR							
7. Patients masked?	Yes, b	out not describ	ed					
10. Intention-to-treat analysis?	No							
11. Postrandomization exclusion	s? Unabl	e to determine	•					

Internal validity				External validity				
Klimm, 1987	Design: RCT	DB Parallel	Trial type:	Active	Quality r	ating: Fa	air	
1. Randomization adequate? 2. Allocation adequate? 3. Groups similar at baseline? 4. Eligibility criteria specified? 9. Loss to follow-up, differential? 5. Outcome assessors masked? 6. Care provider masked? 7. Patients masked? 10. Intention-to-treat analysis? 11. Postrandomization exclusion	NR 8. Repo NR Yes Yes Yos Yes, but not de NR Yes No	orting of Attrition Crossover Adherence Contaminatio	Yes No Yes	1. Number Screened/ Eli 3. Run-in/ Wash out (day 4. Class naive patients or 5. Controlled group stand 2. Exclusion criteria repor 6. Funding: Not reported	igible/ Enrolled: /s): hly? lard of care? rted?	NR / 7/ No Yes Yes	NR / 7	74
Krystal (poster)	Design: RCT	DB Parallel	Trial type:	Placebo	Quality r	ating: Fa	air	
 Randomization adequate? Allocation adequate? Groups similar at baseline? Eligibility criteria specified? Loss to follow-up, differential? Outcome assessors masked? Care provider masked? Patients masked? Intention-to-treat analysis? Postrandomization exclusion 	NR Yes (Yes Yes double-blind" I "double-blind" I "double-blind" I No (2 eszopick	orting of Attrition Crossover Adherence Contaminatio out not specified out not specified out not specified out not specified one patients not analy		 Number Screened/ Eli Run-in/ Wash out (day Class naive patients or Controlled group stand Exclusion criteria repor Funding: Sepracor 	rs): hly? lard of care?	NR / 14 / NR NR	NR / 14	830
Krystal, 2003	Design: RCT	DB Parallel	Trial type:	Placebo	Quality r	ating: Fa	air	
 Randomization adequate? Allocation adequate? Groups similar at baseline? Eligibility criteria specified? Loss to follow-up, differential? Outcome assessors masked? Care provider masked? Ratients masked? Intention-to-treat analysis? Postrandomization exclusion 	NR weig Yes No Yes NR Yes Yes	orting of Attrition Crossover Adherence Contaminatio		 Number Screened/ Eli Run-in/ Wash out (day Class naive patients or Controlled group stand Exclusion criteria repor Funding: Sepracor 	vs): hly? lard of care?	1194 / NR / NR NR No	791 / 5-7	788

Internal validity					External validity			
Lahmeyer, 1997	Desigr	RCT DB	Parallel	Trial type:	Placebo Qu	ality rating: Fa	ir	
1. Randomization adequate?	NR	8. Reporting	g of Attrition	Yes	1. Number Screened/ Eligible/Enroll	led: 178 /	33/	145
2. Allocation adequate?	NR		Crossover	No	3. Run-in/ Wash out (days):	3/	4	
3. Groups similar at baseline?	Yes		Adherence	Yes	4. Class naive patients only?	NR		
4. Eligibility criteria specified?	Yes		Contaminatio	n No	5. Controlled group standard of care?	Yes		
9. Loss to follow-up, differential?	Yes				2. Exclusion criteria reported?	Yes		
5. Outcome assessors masked?	Yes				6. Funding: ?orex Pharmaceuticals			
6. Care provider masked?	NR							
7. Patients masked?	Yes							
10. Intention-to-treat analysis?	No							
11. Postrandomization exclusior	ns? No							
Lemoine, 1995	Desigr	: RCT DB	Parallel	Trial type:	H2H Qu	ality rating: Fa	ir	
1. Randomization adequate?	NR	8. Reporting	g of Attrition	Yes	1. Number Screened/ Eligible/ Enroll	led: NR /	NR /	394
2. Allocation adequate?	NR		Crossover	No	3. Run-in/ Wash out (days):	0 /	0	
3. Groups similar at baseline?	Yes		Adherence	No	4. Class naive patients only?	No		
4. Eligibility criteria specified?			Contaminatio	n No	5. Controlled group standard of care?	Yes		
9. Loss to follow-up, differential?	No No				2. Exclusion criteria reported?	Yes		
5. Outcome assessors masked?	Yes				6. Funding: Not reported			
6. Care provider masked?	NR							
7. Patients masked?	Yes							
10. Intention-to-treat analysis?	No							
11. Postrandomization exclusion	ns? No							
Leppik, 1997	Desigr	RCT DB	Parallel	Trial type:	Active Qu	ality rating: Fa	ir	
1. Randomization adequate?	NR	8. Reporting	g of Attrition	Yes	1. Number Screened/ Eligible/ Enroll	led: NR /	457 /	335
2. Allocation adequate?	NR		Crossover	No	3. Run-in/ Wash out (days):	7/	4	
3. Groups similar at baseline?	Yes		Adherence	No	4. Class naive patients only?	No		
4. Eligibility criteria specified?	Yes		Contaminatio	n No	5. Controlled group standard of care?	Yes		
9. Loss to follow-up, differential?	o No				2. Exclusion criteria reported?	Yes		
5. Outcome assessors masked?	Yes, I	out not descrit	bed		6. Funding: Lornex Pharmaceuticals			
6. Care provider masked?	NR							
7. Patients masked?	Yes							
10. Intention-to-treat analysis?	Yes							
11. Postrandomization exclusion								

Internal validity		External vali	dity
Liu, 1997	Design: RCT DB Crosso	over Trial type: Active	Quality rating: Poor
 Randomization adequate? Allocation adequate? Groups similar at baseline? Eligibility criteria specified? Loss to follow-up, differential? Outcome assessors masked? Care provider masked? Patients masked? Intention-to-treat analysis? 	NR 8. Reporting of Attritic NR Crosse NR Adhen Yes Conta Yes Ves Yes, but not described NR Yes, but not described Unable to determine	on Yes 1. Number Scre over No 3. Run-in/ Wash rence Yes 4. Class naive p	ened/ Eligible/ Enrolled: NR / NR / 15 n out (days): 0 / 7 atients only? oup standard of care?
11. Postrandomization exclusion	Design: RCT DB Paralle	el Trial type: Active	Quality rating: Fair
 Randomization adequate? Allocation adequate? Groups similar at baseline? Eligibility criteria specified? Loss to follow-up, differential? Outcome assessors masked? Care provider masked? Patients masked? Intention-to-treat analysis? Postrandomization exclusion 	NR 8. Reporting of Attritic NR Crosse NR Adhen Yes Conta No Yes Yes Unable to determine	on No 1. Number Scre over No 3. Run-in/ Wash rence No 4. Class naive p	ened/ Eligible/ Enrolled: NR / NR / 30 n out (days): 2 / 3 atients only? No oup standard of care? Yes eria reported? Yes
Monchesky, 1986	Design: RCT DB Crosso	over Trial type: Placebo	Quality rating: Fair
 Randomization adequate? Allocation adequate? Groups similar at baseline? Eligibility criteria specified? Loss to follow-up, differential? Outcome assessors masked? Care provider masked? Patients masked? Intention-to-treat analysis? 	Unab	over No 3. Run-in/ Wash ence No 4. Class naive p	atients only? NR oup standard of care? NR eria reported? Yes

11. Postrandomization exclusions? 1/99

Internal validity					External validity			
Monti, 1994	Design	RCT DB	Parallel	Trial type:	Active Qu	ality rating: Fa	ir	
1. Randomization adequate?	NR	8. Reporting	of Attrition	Yes	1. Number Screened/ Eligible/ Enrol	lled: NR /	NR /	24
2. Allocation adequate?	NR		Crossover	Yes	3. Run-in/ Wash out (days):	3/	3	
3. Groups similar at baseline?	Yes		Adherence	Yes	4. Class naive patients only?	No		
4. Eligibility criteria specified?	Yes		Contaminatio	on Yes	5. Controlled group standard of care?	? Yes		
9. Loss to follow-up, differential?	No				2. Exclusion criteria reported?	Yes		
5. Outcome assessors masked?	Yes, b	out not describ	ed		6. Funding: Not reported			
6. Care provider masked?	NR							
7. Patients masked?	Yes							
10. Intention-to-treat analysis?	Yes							
11. Postrandomization exclusion	ns? No							
Monti, 1996	Design	RCT DB	Parallel	Trial type:	Placebo Qu	ality rating: Fa	lir	
1. Randomization adequate?	NR	8. Reporting	of Attrition	No	1. Number Screened/ Eligible/ Enrol	lled: NR /	NR /	12
2. Allocation adequate?	NR		Crossover	No	3. Run-in/ Wash out (days):	2/	3	
3. Groups similar at baseline?	Yes		Adherence	No	4. Class naive patients only?	Yes		
4. Eligibility criteria specified?	Yes		Contaminatio	on No	5. Controlled group standard of care?	? Yes		
9. Loss to follow-up, differential?	No				2. Exclusion criteria reported?	Yes		
5. Outcome assessors masked?	Yes, b	out not describ	ed		6. Funding: NR			
6. Care provider masked?	NR							
7. Patients masked?	Yes							
10. Intention-to-treat analysis?	Yes							
11. Postrandomization exclusion	ns? No							
Monti, 2000	Design	RCT DB	Parallel	Trial type:	Placebo Qu	ality rating: Po	or	
1. Randomization adequate?	No (s	8. Reporting	of Attrition	No	1. Number Screened/ Eligible/ Enrol	lled: NR /	NR /	12
2. Allocation adequate?	No (r		Crossover	No	3. Run-in/ Wash out (days):	3/	3	
3. Groups similar at baseline?	Lowe		Adherence	No	4. Class naive patients only?	No		
4. Eligibility criteria specified?	Yes		Contaminatio	on No	5. Controlled group standard of care?	? NR		
9. Loss to follow-up, differential?	NR				2. Exclusion criteria reported?	Yes		
5. Outcome assessors masked?	Yes				6. Funding: NR			
6. Care provider masked?	NR							
7. Patients masked?	Yes							

Unable to determine

10. Intention-to-treat analysis?

11. Postrandomization exclusions? Unable to determine

Internal validity					External validity			
Nair, 1990	Design	RCT DB	Parallel	Trial type:	Active Quali	ty rating: Fa	air	
1. Randomization adequate?	NR	8. Reporting	g of Attrition	Yes	1. Number Screened/ Eligible/ Enrolled	NR /	NR /	60
2. Allocation adequate?	NR		Crossover	0	3. Run-in/ Wash out (days):	1 /	NR	
3. Groups similar at baseline?	Yes		Adherence	Yes	4. Class naive patients only?	No		
4. Eligibility criteria specified?	Yes		Contaminati	on No	5. Controlled group standard of care?	Yes		
9. Loss to follow-up, differential?	No				2. Exclusion criteria reported?	Yes		
5. Outcome assessors masked?	Yes, b	out not describ	bed		6. Funding: Rhone-Poulenc Pharma			
6. Care provider masked?	NR							
7. Patients masked?	Yes							
10. Intention-to-treat analysis?	No							
11. Postrandomization exclusion	ns? No							
Ngen, 1990	Design	RCT DB	Parallel	Trial type:	Active Quali	ty rating: Fa	air	
1. Randomization adequate?	Yes	8. Reporting	g of Attrition		1. Number Screened/ Eligible/ Enrolled	NR /	NR /	60
2. Allocation adequate?	Yes		Crossover	0	3. Run-in/ Wash out (days):	7/	NR	
3. Groups similar at baseline?			Adherence		4. Class naive patients only?	No		
4. Eligibility criteria specified?			Contaminati	on	5. Controlled group standard of care?	Yes		
9. Loss to follow-up, differential?	Yes				2. Exclusion criteria reported?	Yes		
5. Outcome assessors masked?	Yes				6. Funding: Rhone-Poulenc Pharma			
6. Care provider masked?	NR							
7. Patients masked?	Yes							
10. Intention-to-treat analysis?	No							
11. Postrandomization exclusion	ns? No							
Perlis, 2004	Design	RCT DB	Parallel	Trial type:	Placebo Quali	ty rating: Fa	air	
1. Randomization adequate?	Yes	8. Reporting	g of Attrition	Yes	1. Number Screened/ Eligible/ Enrolled	322 /	277 /	199
2. Allocation adequate?	Yes		Crossover	No	3. Run-in/ Wash out (days):	6-14 /	NR	
3. Groups similar at baseline?	More		Adherence	Yes	4. Class naive patients only?			
4. Eligibility criteria specified?	Yes		Contaminati	on Yes	5. Controlled group standard of care?			
9. Loss to follow-up, differential?	No				2. Exclusion criteria reported?	Yes		
5. Outcome assessors masked?	Yes				6. Funding: Lorex Pharmaceuticals			
6. Care provider masked?	NR							
7. Patients masked?	Yes							
10. Intention-to-treat analysis?	No							
11. Postrandomization exclusion	.							

Evidence Table 16. Quality	Assessment of efficacy trials
----------------------------	-------------------------------

Internal validity					External validity			
Ponciano, 1990	Desigr	RCT DE	B Parallel	Trial type:	Active	Quality rating: F	air	
 Randomization adequate? Allocation adequate? Groups similar at baseline? Eligibility criteria specified? Loss to follow-up, differential? Outcome assessors masked? Care provider masked? Patients masked? Intention-to-treat analysis? Postrandomization exclusion 	? Yes NR Yes Yes	8. Reportir	ng of Attrition Crossover Adherence Contaminatio	Yes No No on No	 Number Screened/ Eligibl Run-in/ Wash out (days): Class naive patients only? Controlled group standard Exclusion criteria reported Funding: Not reported 	7 / No of care? Yes	NR / 7	26
Quadens, 1983	Desigr	n: RCT DE	B Crossover	Trial type:	Active	Quality rating: F	Poor	
 Randomization adequate? Allocation adequate? Groups similar at baseline? Eligibility criteria specified? Loss to follow-up, differential? Outcome assessors masked? Care provider masked? Patients masked? Intention-to-treat analysis? Postrandomization exclusion 	? Yes, I NR Yes Unab	but not descr	ne	No No No on No	 Number Screened/ Eligibl Run-in/ Wash out (days): Class naive patients only? Controlled group standard Exclusion criteria reported Funding: Not reported 	6 / NR of care? Yes	NR / 35	12
Roehrs (poster)	Desigr	RCT DE	3 Parallel	Trial type:	Placebo	Quality rating: F	air	
 Randomization adequate? Allocation adequate? Groups similar at baseline? Eligibility criteria specified? Loss to follow-up, differential? Outcome assessors masked? Care provider masked? Patients masked? Intention-to-treat analysis? 	NR NR Som Yes No Yes, I Yes, I		ng of Attrition Crossover Adherence Contaminatio ibed ibed	Yes No No	 Number Screened/ Eligibli Run-in/ Wash out (days): Class naive patients only? Controlled group standard Exclusion criteria reported Funding: Sanofi-Aventis 	e/ Enrolled: NR / no / NR of care? Yes	NR / no	205

Internal validity					External validity				
Roger, 1993	Design	RCT DB	Parallel	Trial type:	Active	Quality rati	ng: Fa	ir	
1. Randomization adequate?	NR	8. Reporting	of Attrition	Yes	1. Number Screened/ Eligible	le/ Enrolled:	NR /	NR /	221
2. Allocation adequate?	NR		Crossover	No	3. Run-in/ Wash out (days):		3/	7	
3. Groups similar at baseline?	Yes		Adherence	No	4. Class naive patients only?		No		
4. Eligibility criteria specified?	Yes		Contaminatio	on No	5. Controlled group standard	of care?	Yes		
9. Loss to follow-up, differential	? No				2. Exclusion criteria reported	?	Yes		
5. Outcome assessors masked	? Yes, b	out not describ	ed		6. Funding: Not reported				
6. Care provider masked?	Yes, b	out not describ	ed						
7. Patients masked?	Yes								
10. Intention-to-treat analysis?	Unabl	e to determine	;						
11. Postrandomization exclusio	ns? No								
Rosenberg, 1994	Design	RCT DB	Parallel	Trial type:	Active	Quality rati	ng: Po	or	
1. Randomization adequate?	Yes	8. Reporting	of Attrition	Yes	1. Number Screened/ Eligib	le/ Enrolled:	NR /	NR /	178
2. Allocation adequate?	Yes		Crossover	No	3. Run-in/ Wash out (days):		NR /	NR	
3. Groups similar at baseline?	NR		Adherence	No	4. Class naive patients only?		No		
4. Eligibility criteria specified?	Yes		Contaminatio	on No	5. Controlled group standard	of care?	Yes		
9. Loss to follow-up, differential	? Yes				2. Exclusion criteria reported	?	Yes		
5. Outcome assessors masked	? Yes				6. Funding: Synthelabo Sca	ndinavia A/S			
6. Care provider masked?	Yes								
7. Patients masked?	Yes								
10. Intention-to-treat analysis?	No								
11. Postrandomization exclusio	ns? Yes								
Roth	Design	RCT DB	Parallel	Trial type:	Placebo	Quality rati	ng: Fa	lir	
1. Randomization adequate?	NR	8. Reporting	of Attrition	Yes	1. Number Screened/ Eligib	le/ Enrolled:	NR /	NR /	829
2. Allocation adequate?	NR		Crossover	No	3. Run-in/ Wash out (days):		7/	7	
3. Groups similar at baseline?	Yes (Adherence	No	4. Class naive patients only?		NR		
4. Eligibility criteria specified?	Yes		Contaminatio	on No	5. Controlled group standard	of care?	Yes		
9. Loss to follow-up, differential	? NR				2. Exclusion criteria reported	?			
5. Outcome assessors masked	? Yes, b	out not describ	ed		6. Funding: Takeda Pharma	ceuticals			
6. Care provider masked?	Yes, b	out not describ	ed						
7. Patients masked?	Yes, b	out not describ	ed						
10. Intention-to-treat analysis?	Unabl	e to determine)						
11. Postrandomization exclusio									

Internal validity					External validity			
Scharf, 1994	Desigr	: RCT DB	Parallel	Trial type:	Placebo Qua	ality rating: Fa	ir	
1. Randomization adequate?	NR	8. Reporting	of Attrition	Yes	1. Number Screened/ Eligible/ Enroll	ed: 178 /	75/	75
2. Allocation adequate?	NR		Crossover	No	3. Run-in/ Wash out (days):	11 /	2	
3. Groups similar at baseline?	Yes		Adherence	No	4. Class naive patients only?	NR		
4. Eligibility criteria specified?	Yes		Contaminatio	on Yes	5. Controlled group standard of care?	NR NR		
9. Loss to follow-up, differential?	' No				2. Exclusion criteria reported?			
5. Outcome assessors masked?	Yes				6. Funding: NR			
6. Care provider masked?	NR							
7. Patients masked?	Yes							
10. Intention-to-treat analysis?	Unab	le to determine)					
11. Postrandomization exclusion	ns? No							
Scharf, 2005	Desigr	n: RCT DB	Parallel	Trial type:	Placebo Qua	ality rating: Fa	ir	
1. Randomization adequate?	NR	8. Reporting	of Attrition	Yes	1. Number Screened/ Eligible/ Enroll	ed: 353 /	NR/	231
2. Allocation adequate?	NR		Crossover	No	3. Run-in/ Wash out (days):	3-14/	NR	
3. Groups similar at baseline?	Yes		Adherence	No	4. Class naive patients only?	No		
4. Eligibility criteria specified?	Yes		Contaminatio	on No	5. Controlled group standard of care?	NR		
9. Loss to follow-up, differential?	No				2. Exclusion criteria reported?	Yes		
5. Outcome assessors masked?	Yes				6. Funding:			
6. Care provider masked?	NR				-			
7. Patients masked?	Yes							
10. Intention-to-treat analysis?	Yes							
11. Postrandomization exclusion	ns? Unab	le to determine)					
Sepracor Study #190-045	Desigr	RCT DB	Crossover	Trial type:	H2H Qu	ality rating: Fa	ir	
1. Randomization adequate?	NR	8. Reporting	of Attrition	No	1. Number Screened/ Eligible/ Enroll	ed: NR /	NR /	64
2. Allocation adequate?	NR		Crossover	No	3. Run-in/ Wash out (days):	3-7 /	3-7	
3. Groups similar at baseline?	NR		Adherence	No	4. Class naive patients only?	NR		
4. Eligibility criteria specified?	Yes		Contaminatio	on No	5. Controlled group standard of care?	NR		
9. Loss to follow-up, differential?	NR				2. Exclusion criteria reported?	No		
5. Outcome assessors masked?	Yes (l	but concern re	. unpleasant tas	te)	6. Funding: Sepracor			
6. Care provider masked?	NR							
7. Patients masked?	Yes (I	but concern re	. unpleasant tas	te)				
10. Intention-to-treat analysis?	Pts w	ho rec'd at lea	st one dose of m	ne				
11. Postrandomization exclusion	- 0 Ja - b	la ta datarmina						

Internal validity					External validity			
Silvestri, 1996	Desigr	: RCT DB	Parallel	Trial type:	Active Qua	ality rating: Fa	ir	
1. Randomization adequate?	NR	8. Reporting	of Attrition	Yes	1. Number Screened/ Eligible/ Enrolle	ed: NR /	NR /	22
2. Allocation adequate?	NR		Crossover	No	3. Run-in/ Wash out (days):	3/	No	
3. Groups similar at baseline?	Yes		Adherence	No	4. Class naive patients only?	No		
4. Eligibility criteria specified?	Yes		Contaminatio	n No	5. Controlled group standard of care?	Yes		
9. Loss to follow-up, differential?	Yes				2. Exclusion criteria reported?	Yes		
5. Outcome assessors masked?	Yes, t	but not describ	ed		6. Funding: Not reported			
6. Care provider masked?	NR							
7. Patients masked?	Yes, t	out not describ	ed					
10. Intention-to-treat analysis?	No							
11. Postrandomization exclusion	s? Yes							
Singh, 1990	Desigr	RCT DB	Parallel	Trial type:	Active Qua	ality rating: Fa	lir	
1. Randomization adequate?	NR	8. Reporting	of Attrition	Yes	1. Number Screened/ Eligible/ Enrolle	ed: NR /	61/	60
2. Allocation adequate?	NR		Crossover	No	3. Run-in/ Wash out (days):	4 /	NR	
3. Groups similar at baseline?	NR		Adherence	No	4. Class naive patients only?	NR		
4. Eligibility criteria specified?	No		Contaminatio	n No	5. Controlled group standard of care?	Yes		
9. Loss to follow-up, differential?	No				2. Exclusion criteria reported?	Yes		
5. Outcome assessors masked?	Yes, t	but not describ	ed		6. Funding: Rhone-Poulenc Pharma	Inc.		
6. Care provider masked?	NR							
7. Patients masked?	Yes							
10. Intention-to-treat analysis?	Yes							
11. Postrandomization exclusion	is? Yes (1 patient)						
Soubrane (poster)	Desigr	RCT DB	Parallel	Trial type:	Placebo Qua	ality rating: Fa	lir	
1. Randomization adequate?	NR	8. Reporting	of Attrition	Yes	1. Number Screened/ Eligible/ Enrolle	ed: NR /	NR /	212
2. Allocation adequate?	NR		Crossover	No	3. Run-in/ Wash out (days):	/		
3. Groups similar at baseline?	Yes		Adherence	No	4. Class naive patients only?	NR		
4. Eligibility criteria specified?	Yes		Contaminatio	n No	5. Controlled group standard of care?	Yes		
9. Loss to follow-up, differential?	No				2. Exclusion criteria reported?			
5. Outcome assessors masked?	Yes, t	but not describ	ed		6. Funding: Sanofi-Aventis			
6. Care provider masked?	Yes, t	but not describ	ed					
7. Patients masked?	Vaak	out not describ	ام م					

10. Intention-to-treat analysis?

No

11. Postrandomization exclusions? Unable to determine

Internal validity					External validity			
Staner, 2005	Design	RCT DB	Crossover	Trial type:	H2H Quality	rating: Po	oor	
1. Randomization adequate?	Meth	8. Reporting	of Attrition	No	1. Number Screened/ Eligible/ Enrolled:	NR /	NR /	23
2. Allocation adequate?	NR		Crossover	No	3. Run-in/ Wash out (days):	NR /	7	
3. Groups similar at baseline?	NR		Adherence	No	4. Class naive patients only?	No		
4. Eligibility criteria specified?	Yes		Contaminat	ion No	5. Controlled group standard of care?	Yes		
9. Loss to follow-up, differential?	NR				2. Exclusion criteria reported?			
5. Outcome assessors masked?	Yes, b	out not describ	ed		6. Funding: Sanofi-Aventis			
6. Care provider masked?	Yes, b	out not describ	ed					
7. Patients masked?	Yes							
10. Intention-to-treat analysis?	Unabl	e to determine	e					
11. Postrandomization exclusion	is? Unabl	e to determine	e					
Stip, 1999	Design	RCT DB	Parallel	Trial type:	Active Quality	rating: Fa	air	
1. Randomization adequate?	NR	8. Reporting	of Attrition	Yes	1. Number Screened/ Eligible/ Enrolled:	NR /	NR /	60
2. Allocation adequate?	NR		Crossover	No	3. Run-in/ Wash out (days):	7/	7	
3. Groups similar at baseline?	NR		Adherence	No	4. Class naive patients only?	NR		
4. Eligibility criteria specified?	Yes		Contaminat	ion No	5. Controlled group standard of care?	Yes		
9. Loss to follow-up, differential?	Yes				2. Exclusion criteria reported?	No		
5. Outcome assessors masked?	Yes, b	out not describ	ed		6. Funding: Not reported			
6. Care provider masked?	NR							
7. Patients masked?	Yes							
10. Intention-to-treat analysis?	No							
11. Postrandomization exclusion	s? Yes							
Tamminen, 1987	Design	RCT DB	Parallel	Trial type:	Active Quality	rating: Po	oor	
1. Randomization adequate?	NR	8. Reporting	of Attrition	Yes	1. Number Screened/ Eligible/ Enrolled:	NR /	130/	94
2. Allocation adequate?	NR		Crossover	No	3. Run-in/ Wash out (days):	7/	NR	
3. Groups similar at baseline?	NR		Adherence	No	4. Class naive patients only?	No		
4. Eligibility criteria specified?	Yes		Contaminat	ion No	5. Controlled group standard of care?	Yes		
9. Loss to follow-up, differential?	Yes				2. Exclusion criteria reported?	Yes		
5. Outcome assessors masked?	Yes, b	out not describ	ed		6. Funding: Not reported			
6. Care provider masked?	NR							
7. Patients masked?	Yes							
10. Intention-to-treat analysis?	No							
11. Postrandomization exclusion	s? Yes							

Internal validity					External validity			
Terzano, 1992	Desig	n: RCT DB I	Parallel	Trial type:	Placebo Qu	ality rating: Po	oor	
1. Randomization adequate?	NR	8. Reporting of	of Attrition	No	1. Number Screened/ Eligible/ Enrol	lled: NR /	NR /	12
2. Allocation adequate?	NR		Crossover	No	3. Run-in/ Wash out (days):	14 /	NR	
3. Groups similar at baseline?	NR		Adherence	No	4. Class naive patients only?	NR		
4. Eligibility criteria specified?	Yes		Contaminatio	on No	5. Controlled group standard of care	? NR		
9. Loss to follow-up, differential?	? NR				2. Exclusion criteria reported?	Yes		
5. Outcome assessors masked?	? Yes,	but not describe	d		6. Funding: Partially supported by It	alian Ministry of Uni	versity a	nd Scientific
6. Care provider masked?	NR				Research			
7. Patients masked?	Yes,	but not describe	d					
10. Intention-to-treat analysis?	NR							
11. Postrandomization exclusior	ns? NR							
Tsutsui, 2001	Desig	n: RCT DB I	Parallel	Trial type:	H2H Qu	ality rating: Fa	air	
1. Randomization adequate?	NR	8. Reporting of	of Attrition	Yes	1. Number Screened/ Eligible/ Enrol	lled: NR /	NR /	479
2. Allocation adequate?	NR		Crossover	No	3. Run-in/ Wash out (days):	0 /	7	
3. Groups similar at baseline?	NR		Adherence	Yes	4. Class naive patients only?	No		
4. Eligibility criteria specified?	Yes		Contaminatio	on No	5. Controlled group standard of care	? Yes		
9. Loss to follow-up, differential?	? Yes				2. Exclusion criteria reported?	Yes		
5. Outcome assessors masked?	? Yes				6. Funding: Not reported			
6. Care provider masked?	NR							
7. Patients masked?	Yes							
10. Intention-to-treat analysis?	No							
11. Postrandomization exclusior	ns? Yes							
van der Kleijn, 1989	Desig	n:RCT DB	Crossover	Trial type:	Active Qu	ality rating: Fa	air	
1. Randomization adequate?	NR	8. Reporting of	of Attrition	Yes	1. Number Screened/ Eligible/ Enrol	lled: NR /	60 /	55
2. Allocation adequate?	NR		Crossover	No	3. Run-in/ Wash out (days):	2/	7	
3. Groups similar at baseline?	NR		Adherence	No	4. Class naive patients only?	No		
4. Eligibility criteria specified?	Yes		Contaminatio	on No	5. Controlled group standard of care	? Yes		
9. Loss to follow-up, differential?	? No				2. Exclusion criteria reported?	Yes		
5. Outcome assessors masked?	? Yes,	but not describe	d		6. Funding: Rhone-Poulenc Pharma	à		
6. Care provider masked?	NR							
7. Patients masked?	Yes							
10. Intention-to-treat analysis?	No							
11. Postrandomization exclusior	ns? Unab	le to determine						

Internal validity					External validity			
Venter, 1986	Desigr	n: RCT DB	Parallel	Trial type:	Active	Quality rating: Fa	air	
1. Randomization adequate?	NR	8. Reporting	of Attrition	No	1. Number Screened/ Eligible/	Enrolled: 58 /	41/	41
2. Allocation adequate?	NR		Crossover	No	3. Run-in/ Wash out (days):	7/	0	
3. Groups similar at baseline?	Yes		Adherence	No	4. Class naive patients only?	No		
4. Eligibility criteria specified?	Yes		Contaminatio	on No	5. Controlled group standard of	care? Yes		
9. Loss to follow-up, differential?	No No				2. Exclusion criteria reported?	Yes		
5. Outcome assessors masked?	Yes,	but not describ	ed		6. Funding: Not reported			
6. Care provider masked?	Yes,	but not describ	ed					
7. Patients masked?	Yes, I	but not describ	ed					
10. Intention-to-treat analysis?	Yes							
11. Postrandomization exclusior	ns? No							
Voshaar, 2004	Desigr	n: RCT DB	Parallel	Trial type:	Active	Quality rating: Fa	air	
1. Randomization adequate?	NR	8. Reporting	of Attrition	Yes	1. Number Screened/ Eligible/	Enrolled: NR /	NR /	221
2. Allocation adequate?	NR		Crossover	0	3. Run-in/ Wash out (days):	NR /	4	
3. Groups similar at baseline?	Yes		Adherence	No	4. Class naive patients only?	No		
4. Eligibility criteria specified?	Yes		Contaminatio	on No	5. Controlled group standard of	care? Yes		
9. Loss to follow-up, differential?	Yes				2. Exclusion criteria reported?	Yes		
5. Outcome assessors masked?	Yes,	but not describ	ed		6. Funding: Sanfi-Synthelabo			
6. Care provider masked?	NR							
7. Patients masked?	Yes							
10. Intention-to-treat analysis?	No							
11. Postrandomization exclusior	ns? Yes							
Walsh, 1998a	Desigr	n: RCT DB	Parallel	Trial type:	Active	Quality rating: Fa	air	
1. Randomization adequate?	NR	8. Reporting	of Attrition	Yes	1. Number Screened/ Eligible/	Enrolled: NR /	589/	306
2. Allocation adequate?	NR		Crossover	No	3. Run-in/ Wash out (days):	7/	NR	
3. Groups similar at baseline?	Yes		Adherence	No	4. Class naive patients only?	No		
4. Eligibility criteria specified?	Yes		Contaminatio	on No	5. Controlled group standard of	care? Yes		
9. Loss to follow-up, differential?	' No				2. Exclusion criteria reported?	Yes		
5. Outcome assessors masked?	Yes,	but not describ	ed		6. Funding: Lorex Pharmaceuti	cals		
6. Care provider masked?	NR							
7. Patients masked?	Yes							
10. Intention-to-treat analysis?	No							

11. Postrandomization exclusions? Yes

Internal validity				External validity			
Walsh, 1998b	Design:	т	rial type:	Active	Quality rating: G	ood	
1. Randomization adequate?	Yes 8. Repo	rting of Attrition	Yes	1. Number Screened/ Eligible/ E	nrolled: 673 /	456 /	132
2. Allocation adequate?	NR	Crossover	No	3. Run-in/ Wash out (days):	3/	2	
3. Groups similar at baseline?	Yes	Adherence	No	4. Class naive patients only?	No		
4. Eligibility criteria specified?	Yes	Contamination	No	5. Controlled group standard of c	are? Yes		
9. Loss to follow-up, differential?	' No			2. Exclusion criteria reported?	Yes		
5. Outcome assessors masked?	Yes, but not dea	scribed		6. Funding: Wyeth Ayerst			
6. Care provider masked?	NR						
7. Patients masked?	Yes						
10. Intention-to-treat analysis?	Yes						
11. Postrandomization exclusior	ns? No						
Walsh, 2000	Design: RCT	DB Crossover T	rial type:	Active	Quality rating: Po	oor	
1. Randomization adequate?	NR 8. Repo	rting of Attrition	Yes	1. Number Screened/ Eligible/ E	nrolled: 73 /	39 /	30
2. Allocation adequate?	NR	Crossover	0	3. Run-in/ Wash out (days):	NR /	NR	
3. Groups similar at baseline?	NR	Adherence	Yes	4. Class naive patients only?	Yes		
4. Eligibility criteria specified?	Yes	Contamination	No	5. Controlled group standard of c	are? Yes		
9. Loss to follow-up, differential?	Yes			2. Exclusion criteria reported?	Yes		
5. Outcome assessors masked?	Yes, but not dea	scribed		6. Funding: Wyeth-Ayerst Resea	arch		
6. Care provider masked?	NR						
7. Patients masked?	Yes, but not des	scribed					
10. Intention-to-treat analysis?	No						
11. Postrandomization exclusion	ns? Yes						
Walsh, 2000a	Design: RCT	DB Parallel T	rial type:	Placebo	Quality rating: P	oor	
1. Randomization adequate?	Not c 8. Repo	rting of Attrition	Yes	1. Number Screened/ Eligible/ E	nrolled: 311 /	54/	48
2. Allocation adequate?	Not c	Crossover	No	3. Run-in/ Wash out (days):	5-12/	5-12	
3. Groups similar at baseline?	NR	Adherence	No	4. Class naive patients only?			
4. Eligibility criteria specified?	Yes	Contamination	No	5. Controlled group standard of c	are?		
9. Loss to follow-up, differential?	No-			2. Exclusion criteria reported?	Yes		
5. Outcome assessors masked?	Yes, but not dea	scribed		6. Funding:			
6. Care provider masked?	NR						
7. Patients masked?	Yes, but not des	scribed					
10. Intention-to-treat analysis?	No (48/54 analy	zed)					
11. Postrandomization exclusion	· ·	-					

Internal validity					External validity			
Walsh, 2000b, 2002	Design	: RCT DB	Parallel	Trial type:	Placebo Qua	ality rating: Fa	air	
1. Randomization adequate?	Yes	8. Reporting	g of Attrition	Yes	1. Number Screened/ Eligible/ Enrolle	ed: 365 /	163/	163
2. Allocation adequate?	NR		Crossover	No	3. Run-in/ Wash out (days):	7/	7	
3. Groups similar at baseline?	Yes		Adherence	Yes	4. Class naive patients only?	NR		
4. Eligibility criteria specified?	Yes		Contaminatio	n Yes	5. Controlled group standard of care?	Yes		
9. Loss to follow-up, differential?	? Yes				2. Exclusion criteria reported?	No		
5. Outcome assessors masked?	? Yes, t	out not descrit	bed		6. Funding: Lorex Pharmaceuticals			
6. Care provider masked?	NR							
7. Patients masked?	Yes							
10. Intention-to-treat analysis?	No							
11. Postrandomization exclusior	าs? Yes							
Ware, 1997	Design	: RCT DB	Parallel	Trial type:	Active Qua	ality rating: Fa	air	
1. Randomization adequate?	NR	8. Reporting	g of Attrition	Yes	1. Number Screened/ Eligible/ Enrolle	ed: 358 /	NR /	110
2. Allocation adequate?	NR		Crossover	No	3. Run-in/ Wash out (days):	2/	3	
3. Groups similar at baseline?	Yes		Adherence	No	4. Class naive patients only?	Yes		
4. Eligibility criteria specified?	Yes		Contaminatio	n No	5. Controlled group standard of care?	Yes		
9. Loss to follow-up, differential?	? No				2. Exclusion criteria reported?	Yes		
5. Outcome assessors masked?	? Yes, t	out not descrit	bed		6. Funding: Lorex Pharmaceuticals			
6. Care provider masked?	NR							
7. Patients masked?	Yes, t	out not descrit	bed					
10. Intention-to-treat analysis?	No							
11. Postrandomization exclusion	ns? No							
Wheatley, 1985	Design	RCT DB	Crossover	Trial type:	Active Qua	ality rating: Fa	air	
1. Randomization adequate?	NR	8. Reporting	g of Attrition	Yes	1. Number Screened/ Eligible/ Enrolle	ed: NR /	NR /	36
2 Allocation adequate?	NR		Crossover	No	3 Run-in/ Wash out (days):	3/	NR	

Vheatley, 1985	Design: RCT DB	B Crossover	Trial type:	Active Quali	ty rating: Fa	ir	
1. Randomization adequate?	NR 8. Reportin	g of Attrition	Yes	1. Number Screened/ Eligible/ Enrolled	NR /	NR /	36
2. Allocation adequate?	NR	Crossover	No	3. Run-in/ Wash out (days):	3/	NR	
3. Groups similar at baseline?	No	Adherence	No	4. Class naive patients only?	No		
4. Eligibility criteria specified?	No	Contamination	n No	5. Controlled group standard of care?	Yes		
9. Loss to follow-up, differential?	? No			2. Exclusion criteria reported?	No		
5. Outcome assessors masked?	? Yes, but not descri	bed		6. Funding: Not reported			
6. Care provider masked?	NR						
7. Patients masked?	Yes						
10. Intention-to-treat analysis?	Unable to determin	e					
11. Postrandomization exclusior	ns? Unable to determin	ne					

Internal validity					External validity			
Zammit, 2004	Design: RCT DB Parallel		Trial type:	Placebo Q	Quality rating: Fair			
1. Randomization adequate?	NR	8. Reporting	g of Attrition	Yes	1. Number Screened/ Eligible/ Enr	olled: NR /	669 /	308
2. Allocation adequate?	NR		Crossover	No	3. Run-in/ Wash out (days):	2/	5-7	
3. Groups similar at baseline?	Differ		Adherence	No	4. Class naive patients only?	NR		
4. Eligibility criteria specified?	Yes		Contaminatio	on No	5. Controlled group standard of car	re? NR		
9. Loss to follow-up, differential?	No				2. Exclusion criteria reported?	Yes		
5. Outcome assessors masked?	Yes				6. Funding: Sepracor			
6. Care provider masked?	NR							
7. Patients masked?	Yes							
10. Intention-to-treat analysis?	No (30	3/308 at nigl	nt 1; 293/308 at 1	I I				
11. Postrandomization exclusior	ns? No							

Author Year Country	N	Drugs (mean dose); duration of treatment	Duration of treatment	Eligibility Criteria
Allain, 1991 France; Delahaye, France	20,513	Zopiclone 7.5 mg for adults 18-69 years, 3.75 mg to older patients.	3 weeks	Men and women 18 years or older who complained of poor sleep for at least 2 weeks and who were followed as outpatients by general practitioners.

Author Year Country	Other population characteristics	Design	Data sources	Time period of assessment	Adverse events assessment
Allain, 1991 France; Delahaye, France	62.6% women, mean age 52.3 (range 15-99), 58% had concomitant diseases (29% had cardiovascular disorders, 12.3% had anxiety and/or depression	Postmarketing surveillance survey	Case report forms completed by general practitioners	6 months	Reported by the patient

Author Year Country	Results		Funding
France;	Neuropsychiatric adverse events, no. of AEs (%)/ no. of drop-outs Difficulty arising in the morning: 267(1.3%)/ 85	Gastrointestinal adverse events, no. of AEs (%)/ no. of drop-outs	Not reported
Delahaye, France	Sleepiness: 107(0.52%)/ 44 Hypersomnia: 6(0.03%)/ 2 Increased frequency of dreams: 38(0.19%)/ 6 Nightmares: 101(0.49%)/ 59 Headache: 61(0.30%)/ 27 Light headedness/heavy headedness: 11(0.05%)/ 3 Ebrious feeling: 53(0.26%)/ 32 Dizziness: 57(0.28%)/ 24 Fall: 8(0.04%)/ 5 Anxiety: 10(0.05%)/ 5	Bitter taste: 746(3.64%)/ 181 Dysgeusia: 20(0.10%)/ 6 Dry mouth: 325(1.58%)/ 53 Gastric pain: 61(0.30%)/ 33 Nausea: 101(0.49%)/ 49 Vomiting: 101(0.05%)/ 8 Diarrhea: 3(0.01%)/ 2 Constipation: 6(0.03%)/ 1 Various GI disorders: 46(0.22%)/ 23	
	Agitation/ excitation: $56(0.27\%)/41$ Irritability: $17(0.07\%)/8$ Aggressiveness: $4(0.02\%)/2$ Tremor: $12(0.06\%)/9$ Hallucinations: $7(0.03\%)/7$ Confusion: $7(0.03\%)/5$ Difficulty concentrating: $6(0.03\%)/1$ Memory complaints: $15(0.07\%)/2$ Reduced libido: $4(0.02\%)/2$ Various neuropsychiatric disorders: $15(0.07\%)/12$	Somatic adverse events, no. of AEs (%)/ no. of drop-outs Asthenia: 38(0.19%)/ 6 Malaise: 14(0.07%)/ 8 Dyspnea: 8(0.02%)/ 5 Palpitation: 4(0.02%)/ 4 Rash: 8(0.04%)/ 8 Pruritus: 3(0.16%)/ 3 Other: 15(0.07%)/ 7	

Final Report Update 1

Author Year Country	N	Drugs (mean dose); duration of treatment	Duration of treatment	Eligibility Criteria
Ancoli- Israel, 2005 US and Europe	260	Zaleplon 5 mg, increased to 10 mg if needed.	1 year	Primary insomnia defined by DSM-IV criteria. Admission to randomized phase was restricted to those whose symptoms lasted at least 3 months. Inclusion in the extension phase required completion of the double-blind phase and a run-out period of 7 days followed by 7 to 28 treatment-free days without adverse effects, and return to the clinic after the treatment free interval with a minimum of five daily sleep questionnaires to confirm the need for continued sleep therapy.
Bain, 2003 US	4,752 (687 zolpidem, 4,065 temazepam)	Zolpidem or temazepam	Not reported	Patients prescribed zolpidem or temazepam in one hospice practice setting.

discontinuation

Author Year Country	Other population characteristics	Design	Data sources	Time period of assessment	Adverse events assessment
Ancoli- Israel, 2005 US and Europe	Mean age 73.3 years (SD 5.3, range 65-86 years) in the US and 71.8 years (SD 6.8, range 59-95 years) in Europe	Prospective cohort study; open label continuation phase of RCT	Monthly safety assessments which included routine physical exams, laboratory determinations, vital signs including blood pressure, and electrocardiograms.	7 days	Treatment emergent adverse events were defined as any adverse event that first appeared or that intensified after the initiation of open-label treatment. Discontinuation effects.

Bain, 2003 US	Hospice patients	Retrospective database analysis	Database from one practice. ICD-9 codes	6 months	Number of times therapy was
		of prescribing	associated with each		discontinued,
		patterns	treatment modality.		reasons for

Author Year	Results	Funding
Country		
Ancoli- Israel, 2005 US and Europe	Frequency of common Treatment-emergent adverse events (TEAEs) during open-label run-out phase, number(%): Headache- 155(27%) Infection- 73(13%) Backache- 58(10%) Bronchitis/pharyngitis- 65(11%) Rhinitis- 53(9%) Dizziness- 43(7%) The TEAEs most frequently associated with discontinuation, number(%): Pain- 29(5%) Somnolence or dizziness- 23(4%) Gastrointestinal changes- 11(2%) Cardiovascular changes- 8(1%)	Wyeth Research and the Research Service of Veteran Affairs Diego Healthcare System.
Bain, 2003 US	<u>Use temazepam or zolpidem, discontinuation due to adverse events:</u> <u>zolpidem(n=89) vs. temazepam(n=401), (%)</u> adverse drug reaction- 2.2% vs. 4.2%	Not reported
	Discontinuation due to adverse events: [use temazepam and then switch to zolpidem] vs. [use zolpidem and then switch to temazepam], (%) adverse drug reaction or others- 10.6% vs. 7.5%	
	Discontinuation due to adverse events after filtering out "change in dose" as a reason for discontinuation. Among discontinuation except "change in dose": adverse drug reaction- 4.3% vs.10.1%	

Author Year Country	Ν	Drugs (mean dose); duration of treatment	Duration of treatment	Eligibility Criteria
Buckley, 2004 UK	12,063 (10,763 zopiclone, 1,300 zolpidem)	Zolpidem, zopiclone, other sedative hypnotics.	Not reported	Fatal toxicity of anxiolytic and sedative drugs for the years 1983-1999.
Devins, 1995 Canada	274	Zopiclone	Not reported	Women who received zopiclone during pregnancy and consulted the Toronto Motherisk Program Teratogen Information Service).

Author Year Country	Other population characteristics	Design	Data sources	Time period of assessment	Adverse events assessment
Buckley, 2004 UK	Not reported.	Retrospective database analysis	Office for National Statistics (England, Wales), and General Registrar's Office (Scotland)	1983-1999	Total number of deaths/number of prescriptions Zolpidem: 3/1300 Zopiclone: 23/10,763
Devins, 1995 Canada	Indications for drug use: depression (n=10), insomnia (n=3), anxiety depressive disorder (n=3), anxiety (n=2), bipolar disorder (n=2), and schizophrenia (n=2). 16 did not specify and 2 did not know indication.	Prospective cohort study	Mailed patient questionnaire	Not reported	Daytime sleepiness, anxiousness, bad taste, weakness, drowsiness/fatigue, dry mouth, poor memory, poor concentration, Rage/aggression/irr itability, illness intrusiveness, depressive symptoms

Author Year Country	Results	Funding
Buckley,	Fatal toxicity index: total no. of deaths	None
2004	zolpidem vs. zopiclone= 3 vs. 23	
UK	Fatal toxicity index: no. of prescriptions (thousands)	
	zolpidem vs. zopiclone= 1300 vs. 10763	
	Fatal toxicity index: deaths/million prescriptions (95%CI)	
	zolpidem vs. zopiclone= 2.3(0.5-6.7) vs. 2.1 (1.4-3.2)	
Devins,	Adverse events: [zopiclone] vs. [lorazepam] vs. [triazolan] vs. [nitrazepam]	Rhone-Poulen
1995	or flurazepam] vs. [temazepam], no.(%)	Rorer and
Canada	Daytime sleepiness: 5.6(4.71) vs. 6.1(3.91) vs. 6.6(4.28) vs. 6.4(4.3) vs.	Health
	5.5(4.7), p<0.001	Canada.
	Side-effects anxiousness: 45(16.4) vs. 52(19.8) vs. 33(23.15) vs. 22(18.2)	
	vs. 39(21.7)	
	Bad taste: 111(40.5) vs. 35(13.3) vs. 18(12.6) vs. 22(18.2) vs. 37(20.6),	
	p<0.0001	
	Weakness: 24(8.8) vs. 24(9.1) vs. 10(7.0) vs. 12(9.9) vs. 16(8.9)	
	Drowsiness/fatigue: 82(29.9) vs. 80(30.4) vs. 42(29.4) vs. 37(30.6) vs. 60(33.3)	
	Dry mouth: 93(33.9) vs. 85(32.3) vs. 34(23.8) vs. 26(21.5) vs. 60(33.3), p<0.0001	
	Poor memory: 90(32.8) vs. 90(34.2) vs. 43(30.1) vs. 47(38.8) vs. 67(37.2)	
	Poor concentration: 77(28.1) vs. 75(28.5) vs. 39(27.3) vs. 43(35.5) vs.	
	57(31.70)	
	Rage/aggression/irritability: 29(10.6) vs. 39(14.8) vs. 31(21.7) vs. 30(24.8) vs. 39(21.7), p<0.02	
	Illness intrusiveness: 34.7(17.64) vs. 33.7(17.14) vs. 29.6(16.11) vs. 34.4(20.11) vs. 36.1(20.10)	
	Depressive symptoms: 21.8(9.73) vs. 22.2(10.58) vs. 20.3(9.18) vs. 20.7(9.4) vs. 21.81(10.76)	

Author Year Country	N	Drugs (mean dose); duration of treatment	Duration of treatment	Eligibility Criteria
Diav-Citrin, 1999 Canada	40	Zopiclone	Not reported	Women who received zopiclone during pregnancy and consulted the Toronto Motherisk Program Teratogen Information Service).

Author Year Country	Other population characteristics	Design	Data sources	Time period of assessment	Adverse events assessment
Diav-Citrin, 1999 Canada	Indications for drug use: depression (n=10), insomnia (n=3), anxiety depressive disorder (n=3), anxiety (n=2), bipolar disorder (n=2), and schizophrenia (n=2). 16 did not specify and 2 did not know indication.	Prospective cohort study	Followup by telephone interview after the expected date of delivery, using a structured questionnaire.	1993-1997	Pregnancy outcome.

Author Year Country	Results	Funding
Diav-Citrin,	Pregnancy outcome, zopiclone vs. control:	
1999	Pregnancy outcome: NS	
Canada	Birth defects: NS	
	Delivery methods: NS	
	Mean GA (wk): 38.3 <u>+</u> 2.7 vs. 40.0 <u>+</u> 1.6, p=0.002	
	Preterm delivery of <37 wks: NS	
	Mean birth weight (g): 3245.9 <u>+</u> 676 vs. 3624.2 <u>+</u> 536, p=0.01	
	Birth weight by GA: NS	
	Meconium: NS	
	Fetal distress: NS	
	NICU admission: NS	

Author Year Country	Ν	Drugs (mean dose); duration of treatment	Duration of treatment	Eligibility Criteria
Ganzoni, 1994 Switzerland	1,972	Zolpidem 10 mg (5-10 mg in patients over age 65)	Median duration of treatment 29.5 days; range 1- 1,095 days	Men and women aged 15 and above, complaining of insomnia and for whom a hypnotic drug treatment was prescribed by a general practitioner, internist, psychiatrist, or gerontologist.

Author Year Country	Other population characteristics	Design	Data sources	Time period of assessment	Adverse events assessment
Ganzoni, 1994 Switzerland	64.8% male 31.6% elderly mean age=54.6 <u>+</u> 16.5	Postmarketing surveillance survey	Safety data recorded by the prescribing physician on a monitoring form. Codification of adverse events was reviewed by two physicians of the Drug Monitoring Unit.	September 1990- December 1993	CNS-related symptoms Non-CNS-related symptoms.

Author Year Country	Results		Funding
Country Ganzoni, 1994 Switzerland	$\frac{\text{CNS-related adverse events, n=1972: no. of Aes(%)/ no. drop-outs(%)}{\text{Residual daytime sedation: 73(3.7)/ 28(1.4)}{\text{Lack of efficacy: 31(1.6)/ 19(1.0)}}$ $\frac{\text{Confusion, disorientation, obsessive ideas, delirium, psychosis: 19(1.0)/15(0.8)}{\text{Nervousness, internal trembling, nervous feet, restlessness, excitation feeling: 16(0.8)/14(0.7)}{\text{Nightmares: 15(0.8)/11(0.6)}}$ $\frac{\text{Amnesia, memory impaired: 15(0.8)/7(0.4)}{\text{Concentration impaired: 11(0.6)/4(0.2)}}{\text{Amxiety: 11(0.6)/8(0.4)}}{\text{Somnambulism, sleep walking, nocturnal activity, walking activity: 9(0.5)/5(0.3)}{\text{Hallucunation: 6(0.3)/4(0.2)}}{\text{Dreaming increased: 6(0.3)/3(0.2)}}{\text{Blurred vision, diplopia, crying, reading impaired, vision abnormal: 5(0.3)/3(0.2)}}{\text{Agitation, aggressivity: 3(0.2)/2(0.1)}}{\text{Speech disorder: 3(0.2)/2(0.1)}}{\text{Suspicion of drug dependence: 1(0.1)/0(0.0)}}{\text{Drug misuse: 1(0.1)/0(0.0)}}{\text{Total: 228(11.6)/126(6.4)}}$	Non-CNS-related adverse events, n=1972: no. of Aes(%)/ no. drop-outs(%) Gastrointestinal: $33(1.7)/25(1.3)$ Headache, head pressure: $21(1.1)/8(0.4)$ Pruritus, eczema, rash, rash, urticaria, skin papules: $10(0.5)/5(0.3)$ Fall, gait abnormal, coordination impaired, muscle weakness: $9(0.5)/4(0.2)$ Dyspnoea, tachypnoea, respiration regulation impaired: $7(0.4)/6(0.3)$ Palpitation, tachycardia, precordialgia: 6(0.3)/4(0.2) Malaise, weakness: $5(0.3)/5(0.3)$ Eating activity, bulimia: $4(0.2)/2(0.1)$ Dry mouth: $3(0.2)/0(0.0)$ Bone/head contusion, skin wound: $3(0.2)/1(0.1)$ Hypotension: $2(0.1)/1(0.1)$ Polyuria: $2(0.1)/2(0.1)$ Loss of appetite: $1(0.1)/0(0.0)$ Myocardial infarction: $1(0.1)/0(0.0)$ Nasal congestion: $1(0.1)/1(0.1)$ Retching: $1(0.1)/1(0.1)$	Not Reported

Author Year Country	Ν	Drugs (mean dose); duration of treatment	Duration of treatment	Eligibility Criteria
Hajak, 1998 Germany	16,944	Zolpidem 10 mg- 20 mg (5 mg-10 mg in patients over age 65 years)	3 to 4 weeks.	Patients in outpatient practice with difficulties in initiating and/or maintaining sleep.

Author Year Country	Other population characteristics	Design	Data sources	Time period of assessment	Adverse events assessment
Hajak, 1998 Germany	64% women, mean age 58.5 (SD 14.9)	Before-after.	Questionnaire	3-4 weeks	Discontinuation, adverse events.

Author Year	Results	Funding
Country		
Hajak, 1998	3 <u>Tolerance</u> : moderate-1.4%, poor- 0.6%	Synthelabo
Germany	Adverse events:	Arzeimittel
	no. patients /% of 268 AEs/ % of 16944 treated patients/ no. drop-outs	GmbH,
	Total: 268/ 100/ 1.5/ 118	Germany
	Nausea: 36/ 13.4/ 0.2/ 27	
	Dizziness: 35/ 13.1/ 0.2/ 20	
	Malaise: 23/ 8.6/ 0.1/ 10	
	Nightmares: 20/ 7.5/ 0.1/ 15	
	Agitation: 19/ 7.1/ 0.1/ 15	
	Headache: 18/ 6.7/ 0.1/ 13	
	Vomiting: 13/ 4.9/ 0.08/ 11	
	Somnolence: 9/ 3.4/ 0.05/ 4	
	Confusion: 8/ 3.0/ 0.05/ 7	
	Fatigue: 7/ 2.6/ 0.04/ 4	
	Dyspepsia: 7/ 2.6/ 0.04/ 5	
	Abnormal gait: 6/ 2.2/ 0.04/ 4	
	Hallucination: 5/ 1.9/ 0.03/ 4	
	Tremor: 4/ 1.5/ 0.02/ 2	
	Anxiety: 4/ 1.5/ 0.02/ 4	
	Insomnia: 4/ 1.5/ 0.02/ 4	
	Amnesia: 3/ 1.1/ 0.02/ 2	
	Asthenia: 3/ 1.1/ 0.02/ 2	
	Dry mouth: 3/ 1.1/ 0.02/ 3	

Author Year Country	Ν	Drugs (mean dose); duration of treatment	Duration of treatment	Eligibility Criteria
Jaffe, 2003 UK	297	Zolpidem, zopiclone, other sedative hypnotics.	Not reported	Patients admitted to addiction treatment centers.
Maarek, 1992 France	96	Zolpidem 10 mg	1 year (360 days)	Patients were known to be suffering from disorders involving the initiation and/or maintenance of sleep, included in the trial had to be over 40 years of age and show clear evidence of insomnia defined by at least one of the following symptoms: sleep onset latency of more than 30 min; more than two nocturnal awakenings; and total duration of sleep of less than 6 hours.

Author Year Country	Other population characteristics	Design	Data sources	Time period of assessment	Adverse events assessment
Jaffe, 2003 UK	78% male	Before-after.	survey	Not reported	Abuse liability
Maarek, 1992 France	Not reported.	Before-after.	The general practitioner assessed patient compliance by questioning the patients at each visit	6 months-12 months	Any adverse events detected by clinical examination or reported spontaneously by the patient were recorded at each visit.

Author

Results

Funding

Sepracor

	Year Country	
_	Jaffe, 2003	Drug use pattern: zolpidem vs. zopiclone (n=297)
	UK	% subjects use: 5.8 vs. 53.7
		% street purchase: 23.5 vs. 42.0
		% doctor prescribed: 76.5 vs. 79.0
		% not recommend by doctor: 23.5 vs. 30.6
		% took to sleep: 82.3 vs. 88.5
		% took to get high: 23.5 vs. 22.9
		% took to make feel better: 64.7 vs. 56.7
		% like the effects: 41.2 vs. 48.4
		% think they need: 11.8 vs. 28
		% addicted: 0 vs. 5.1
		% might become addicted: 11.8 vs. 19.8
	Maarek,	7(7.3%) of all patients withdrew because of adverse events:
	1992	1(1%) feeling of strangeness
	France	1(1%) feeling of drunkenness
		2(2.1%) anterograde amnesia
		1(1%) nausea
		1(1%) confusional episode
		1(1%) nightmares
		1(1%) malaise
		4(4.2%) vertigo
		2(2.1%) daytime drowsiness
		1(1%) unpleasant awakening

Author Year Country	Ν	Drugs (mean dose); duration of treatment	Duration of treatment	Eligibility Criteria
Morishita, 2000 Japan	31 (13 zopiclone, 18 brotizolam)	Zopiclone 7.5 mg to 10 mg (mean 9.42 mg);	Mean 4.5 years	Elderly patients who had received brotizolam or zopiclone for insomnia in the department of psychiatry at one hospital.
Peeters, 1997 Belgium	1,219	Zolpidem	1 month	Men or women age 50 years or older, suffering from insomnia.

Author Year Country	Other population characteristics	Design	Data sources	Time period of assessment	Adverse events assessment
Morishita, 2000 Japan	Mean age 74.4 years (range 70-86 years). Psychiatric diagnoses: depression (n=23), hypomania (n=1), hypochondriacal neurosis (n=2), paraphrenia (n=1), dementia (n=1), nonorganic insomnia (n=3).	Retrospective chart review.	Medical record review.	Not clear- appears to be 1999-2000	Ataxia, hyperexcitability, daytime anxiety, agitation and confusion, amnesia, affective disturbance, somnambulism, or morning drowsiness.
Peeters, 1997 Belgium	461 males, 751 females, not recorded.	Multicenter, open label postmarketing surveillance study; before-after.	sleep parameters assessed on entry and at the follow-up visit by the investigator.	January 1st to May 31st, 1994	Reported by the patient at the followup visit.

Author Year Country	Results	Funding
Morishita,	All patients reported no adverse events, such as ataxia, hyperexcitability,	Not reported
2000	daytime anxiety, agitation and confusion, amnesia, affective disturbance,	
Japan	somnambulism or morning drowsiness.	

Peeters,	Adverse events reported: All patients (n=1219)/ Patients <65 (n=720)/		
1997	Patients >=65 (n=495)		
Belgium	Autonomic nervous system: 5/ 4/ 1		
	Central/ peripheral nervous system: 27/ 14/ 13		
	Gastro-intestinal system: 4/ 2/ 2		
	Heart rate and rhythm: 3/ 0/ 3		
	Musculoskeletal system: 1/ 0/ 1		
	Neoplasms: 2/ 1/ 1		
	Psychiatric system: 48/ 25/ 23		
	Special senses: 2/ 2/ 0		
	Vision: 1/ 0/ 1		
	Unknown: 5/ 5/ 0		
	Patients with at least one adverse events: 87/46/41		

Author Year Country	N	Drugs (mean dose); duration of treatment	Duration of treatment	Eligibility Criteria
Reith, 2003	946,013	Zopiclone	Not reported	Deaths from sedative and anxiolytic poisonings for New Zealand (NZ) in 2001 were identified from chemical injury cases that are routinely collected for surveillance purposes by Institute of Environmental Science and Research (ESR) from the Coronial Services Office (CSO) in Wellington.

Author Year Country	Other population characteristics	Design	Data sources	Time period of assessment	Adverse events assessment
Reith, 2003	Not reported.	surveillance	The PharmHouse database	January 1, 2001 to December 31, 2001.	Fatal toxicity

Author Results Funding Year Country Reith, 2003 Zopiclone involved in poisoning deaths no. of patients Nitrazepam Not reported <60 vs >=60 years: 8 vs. 4 No. of death: 3 Deaths/100,000 prescriptions: 10.1(2.1-Zopiclone 29.4) No. of dreath:12 Deaths/1.000,000 defined daily doses: Deaths/100,000 prescriptions: 5.4(2.8-9.4) 2.8(0.6-8.2)Deaths/1,000,000 defined daily doses: 1.9(1.0-3.3) No. of primary agent death: 0 Primary agent deaths/100,000 prescription: No. of primary agent death: 3 Primary agent deaths/100,000 prescription: 1.4(0.3-4.0) 0(0-12.4) Primary agent deaths/1,000,000 defined daily doses: 0.5(0.1-1.4) Primary agent deaths/1,000,000 defined daily doses: 0(0-3.4) Lorazepam No. of dreath: 2 Temazepam Deaths/100,000 prescriptions: 2.9(0.3-10.3) No. of death: 5 Deaths/1,000,000 defined daily doses: 1.5(0.2-5.5) Deaths/100,000 prescriptions: 4.4(1.4-10.3) Deaths/1,000,000 defined daily doses: No. of primary agent death: 0 Primary agent deaths/100,000 prescription: 0(0-5.3) 2.1(0.7-4.8)No. of primary agent death: 1 Primary agent deaths/1,000,000 defined daily doses: 0(0-2.8) Primary agent deaths/100,000 prescription: Lormetazepam No. of dreath: 0 0.9(0-4.9)Deaths/100,000 prescriptions: 0(0-138.0) Primary agent deaths/1,000,000 defined Deaths/1,000,000 defined daily doses: 0(0-1379.6) daily doses: 0.4(0-2.2) No. of primary agent death: 0 Triazolam No. of death: 3 Primary agent deaths/100,000 prescription: 0(0-138.0) Primary agent deaths/1,000,000 defined daily doses: 0(0-39.9) Deaths/100,000 prescriptions: 2.7(0.6-8.0) Midazolam Deaths/1,000,000 defined daily doses: No. of dreath: 0 1.0(0.2-2.8) Deaths/100,000 prescriptions: 0(0-35) No. of primary agent death: 1 Deaths/1,000,000 defined daily doses: 0(0-22.2) Primary agent deaths/100,000 prescription: No. of primary agent death: 0 0.9(0-5.1) Primary agent deaths/100,000 prescription: 0(0-35) Primary agent deaths/1,000,000 defined Primary agent deaths/1,000,000 defined daily doses: 0(0-22.2) daily doses: 0.3(0-1.8)

Author Year Country	N	Drugs (mean dose); duration of treatment	Duration of treatment	Eligibility Criteria
Schneeweiss, 2005 US	8,785	Zolpidem benzodiazepine	NR	The study population was restricted to persons living in communities. Of these, the study population was further restricted to Medicare Current Beneficiary Survey respondents aged 65 and older and beneficiaries with at least one medication use in 1999.
Scharf, 1994	233	Zolpidem 15 mg. If adverse events occurred, the investigator could reduce the nightly dose to 10 mg. Patients unable to tolerate 10-mg doses were withdrawn from the study.	3 months	Men and women ages 18 to 60 years, with a history of insomnia of at least 3 months' duration. Patients had to satisfy one or more of the following criteria: usual duration of sleep less than 6 hours, sleep latency of at least 45 minutes on most nights, and the use of a hypnotic drug on most nights.

Final Report Update 1

Author Year Country	Other population characteristics	Design	Data sources	Time period of assessment	Adverse events assessment
Schneeweiss, 2005 US	Mean age = NR 41.7% 65-74 years old 58.2% >=75 years old 41.6% male	Cross-sectional survey data	Medicare Current Beneficiary Survey	1 year	NR
Scharf, 1994	Not reported.	Before-after.	Patient reports Physician assessments	13 weeks	Treatment emergent adverse events.

Author

Results

Funding

NR

Year Country	
Schneeweiss,	Zolpidem (n=62) vs benzodiazepine (n=567) vs none (n=6434)
2005	Patients characteristics:
US	ADL score >=1 point: 54.8% vs 41.3% vs 27.3%
	Cognitive impairment: 16.1% vs 15.2% vs 10.2%
	Rosow-Breslau, impairments: 75.8% vs 69.5% vs 55.9%
	Z vs B; Z vs None; B vs none:
	Quantitative assessment of confounding bias in risk estimates
	<u>ADL score (>1 points): 10.00; 21.48; 9.96</u>
	<u>Cognitive impairment (yes vs no): 1.19; 7.00; 5.78</u>
0.1	$\underline{\text{Rosow-Breslau}} (>=1 \text{ impairments}): 3.43; 10.58; 6.54$
Scharf, 1994	Adverse events: zolpidem 10mg (n=33) vs. zolpidem 15mg (n=229),
	$\frac{\text{no.}(\%)}{1000}$
	Dry mouth: 2(6.1) vs. 14(6.1) Fatigue: 6(18.2) vs. 38(16.6)
	Ataxia: 2(6.1) vs. 7(3.1)
	Confusion: 2(6.1) vs. 5(2.2)
	Dizziness: 2(3.1) vs. 32(14.0)
	Drowsiness: 5(15.2) vs. 60(26.2)
	Drugged: 0(0) vs. 12(5.2)
	Headache: 7(21.2) vs. 65(28.4)
	Lethargy: 1(3.0) vs. 14(6.1)
	Light-headedness: 1(3.0) vs. 24(10.5)
	Abdominal pain: 0(0) vs. 13(5.7)
	Dyspepsia: 1(3.0) vs. 20(8.7)
	Nausea: 1(3.0) vs. 28(12.2)
	Arthralgia: 2(3.1) vs. 7(3.1)
	Amnesia: 1(3.0) vs. 15(6.6)
	Nervousness: 3(9.1) vs. 11(4.8)
	Herpes simplex: 2(6.1) vs. 0(0)
	Pharyngitis: 2(6.1) vs. 6(2.6)
	URI: 4(12.1) vs. 38(16.6)

Author Year Country	Ν	Drugs (mean dose); duration of treatment	Duration of treatment	Eligibility Criteria
Schlich, 1991 France	107	Zolpidem	6 months	Over age 40, clear evidence of insomnia defined as sleep onset latency of more than 30 minutes, number of nocturnal awakenings each night greater than two, and /or total duration of sleep each night less than 6 hours.
Wang, 2001 US	1,222 cases, 4,888 controls	Zolpidem, benzodiazepines, other	6 months	subjects aged >= 65 on July 1, 1993, and have filled one or more claims for a nonprescription service between January 1, 1994 and December 31, 1994 and have filled at least one prescription for any medication through the Medicaid or PAAD programs of New Jersey in each of four consecutive 6-month periods beginning January 1, 1993.

Author Year Country	Other population characteristics	Design	Data sources	Time period of assessment	Adverse events assessment
Schlich, 1991 France	74 females; mean age=63.15+1.10 years 65(60.7%) patients enrolled were aged 60 years or over and only 17(15.9%) were under 50 years of age.	Before-after	clinical examinations	6 months	malaise vertigo anterograde amnesia confusion
Wang, 2001 US	Not reported.	Case Control	New Jersey Medicaid Program New Jersey Pharmaceutical Assistance to the Aged and Disable (PAAD) Program New Jersey Medicare	6 months	NR

Author Year Country	Results	Funding
Schlich,	Tolerance: no evidence	
1991	Adverse events: zolpidem vs. placebo	
France	no. of patients- 24 vs.7	
	no. adverse events- 42 vs. 10	
	Adverse events list:	
	5 malaise	
	5 vertigo (all elderly)	
	5 anterograde amnesia	
	2 confusion (all elderly)	
	Withdrawal effects: 5(7.2%) withdrawal due to adverse events.	
Wang, 200	01 <u>Hip Fracture:</u>	National Institute
US	Adjusted OR (95% CI)- adjusted for age and gender	on drug Abuse
	zolpidem: 1.95 (1.09-3.51)	and the Nationa
	benzodiazepine: 1.46 (1.21-1.76)	Institute on
	antipsychotic medication: 1.61 (1.29-2.01)	Aging.
	antidepression: 1.46 (1.22-1.75)	
	other psychoactive medication: 1.23 (0.90-1.68)	
	thiazide diuretic: 0.85 (0.71-1.02)	

Drug	Subgroup	Adverse Events	Study	Number of cases	Case Characteristics	Effects during treatment	Effects during treatment reduction or discontinuation
Zaleplon	Adult	CNS side effect	(Stillwell, 2003)	1	drug abuse concurrent use of other drugs	CNS depression including slow movements and reactions, poor coordination, lack of balance, and poor attention	not reported
Zaleplon	Adult	hallucination illusions depersonalization	(Bhatia, Arora, & Bhatia, 2001)	1	healthy female nonsmoker, occasional drinker	lightheaded illusion visual hallucinations	not reported
Zaleplon	Pediatrics	somnambulism	(Liskow & Pikalov, 2004)	1	major depressive disorder, moderate no history of sleep deprivation	somnambulism with complex behavior	not reported
Zolpidem	Adult	CNS side effect	(Canaday, 1996)	2	not reported	amnesia	not reported
Zolpidem	Adult	CNS side effect	(Markowitz & Brewerton, 1996)	2	depression no history of drug abuse concurrent use of antidepressants, serotonin-reuptake inhibitors	visual hallucination auditory hallucination confusion difficulties at work and marital	hallucination ceased
Zolpidem	Adult	CNS side effect	(Toner, 1999)	3	motor vehicle accident or psychiatric history	nightmare hallucination visual illusion difficulty in concentration	nightmares, hallucination and visual illusion ceased
Zolpidem	Adult	CNS side effect	(Tripodinakis, 2003)	1	no epileptic seizure nor drug abuse history	the patients increased the dose to 600mg per day epigastric pain, nausea, epileptic seizures and depression	not reported
Zolpidem	Adult	delirium hallucination	(Freudenreich & Menza, 2000)	1	depression	agitated and confused disorganized visual hallucinations	not reported

Drug	Subgroup	Adverse Events	Study	Number of cases	Case Characteristics	Effects during treatment	Effects during treatment reduction or discontinuation
Zolpidem	Adult	dependence	(Aragona, 2000)	1	history of drug abuse seizure history after benzodiazepine discontinuation	the patient increased the dose up to 450-600mg per day for anxiolytic effect. dependence and tolerance	epileptic seizure
Zolpidem	Adult	dependence	(Bottlender, 1996)	1	history of drug abuse	the patient increased the dose up to 140mg per day for well-being and reduction of tremor caused by parkinsonism, and also took five other drugs for Parkinson disease delusion disorder at the same time. dependence and tolerance	disturbed sleep, restlessness, sweating, tachycardia and hypertension.
Zolpidem	Adult	dependence	(Liappas et al., 2002)	1	history of abuse and dependence on cocaine	consumed up to 200-300 mg/day for progressive reduction of his cocaine craving. more excited, hyperactive and euphoric, often exhibiting childish behavior, logorrhea and memory blanks.	not reported
Zolpidem	Adult	dependence	(Liappas, 2003)	3	history of drug abuse	patients increased the dose up to 300-600mg for sedation, reduction of cocaine craving, stimulation, or euphoria. dependence and tolerance childish behavior, confusion, memory blank or amnesia	confusion, amnesia or epileptic seizure
Zolpidem	Adult	dependence	(Ravishankar 1998)	2	depression	the patient increased the dose up to 200mg per day	tachycardia, confusion, anxiety, panic attacks and fear of ongoing outside

Drug	Subgroup	Adverse Events	Study	Number of cases	Case Characteristics	Effects during treatment	Effects during treatment reduction or discontinuation
Zolpidem	Adult	dependence	(Sakkas 1999)	1	depression history of drug abuse	the patient increased the dose up to 300mg per day for stimulation dependence and tolerance depression mood disorders suicidality visual hallucinations	not reported
Zolpidem	Adult	dependence	(Vartzopoulos, Bozikas, Phocas, Karavatos, & Kaprinis, 2000)	4	history of drug abuse patients with borderline personality disorder	patients increased the dose up to 500mg daily to enhance the experienced relieving effect on their dysphoric states. dependence and tolerance Mild to severe withdrawal syndrome after discontinuation.	confusion, anxiety, irritability, nausea, vomiting or psychomotor agitation.
Zolpidem	Adult	dependence tolerance	(Kao, 2004)	1	history of substance abuse	IV administration for stimulant effect and euphoria and increased up to 300-400 mg/day	yawning, rhinorrhea and lacrimation
Zolpidem	Adult	dependence tolerance	(Quaglio et al., 2005)	2	no common characteristics	increasing tolerance	no withdrawal disturbances during detoxification with flumazenil infusion
Zolpidem	Adult	hallucination	(Elko, Burgess, & Robertson, 1998)	5	concurrent use of serotonin-reuptake inhibition depression	hallucination	not reported
Zolpidem	Adult	hallucination	(Ginsberg, 2003), (Huang, 2003)	1	concurrent use of other drugs for hormone replacement, osteoporosis and insomnia	headache spotty memory hallucination visual perception distortion	not reported

Drug	Subgroup	Adverse Events	Study	Number of cases	Case Characteristics	Effects during treatment	Effects during treatment reduction or discontinuation
Zolpidem	Adult	hallucination	(Tsai, 2003)	1	not reported	visual illusions, confusion and hallucination especially reusing after rapid withdrawals.	insomnia
Zolpidem	Adult	hallucination amnesia	(Van Puijenbroek, Egberts, & Krom, 1996)	2	one without history of psychiatric disorders, the other with major depressive disorder for 6 month	hallucination amnesia	not reported
Zolpidem	Adult	hallucination CNS side effect	(Hoyler, Tekell, & Silva, 1996)	1	history of pothyroidism, mild vascular dementia, and auditory hallucinations	agitated and disoriented to time and place hallucination and increased psychomotor activity	regained her orientation, responded to redirection, was able to communicate at her usual level of efficiency, and her bizarre behavior was resolved
Zolpidem	Adult	Hepatic problem	(Clark, 1999)	1	liver transplantation	decline in mentality hepatic encephalopathy abdominal pain awoke in a stupor and was disoriented to place and time	not reported
Zolpidem	Adult	hepatic problem	(Karsenti, Blanc, Bacq, & Melman, 1999)	1	cholecystectomy	abdominal pain hepatotoxicity	not reported
Zolpidem	Adult	others- drug interaction	(Ortega 1996)	1	long term benzodiazepine user no psychiatric history	nervousness, irritability, fainting, asthenia, muscular cramps, excessive hear and sweating occasional febrile episodes, weight loss, and a surprising sweet taste in the mouth	all symptoms disappeared
Zolpidem	Adult	seizure dependence tolerance	(Gericke & Ludolph, 1994)	1	depression no seizure history	consumed 150-280 mg/day for stimulant effect	recurrence of depressive mood with apathy and drug carving

Drug	Subgroup	Adverse Events	Study	Number of cases	Case Characteristics	Effects during treatment	Effects during treatment reduction or discontinuation
Zolpidem	Adult	sensory distortions tolerance	(Pies, 1995)	1	no history of psychosis or substance abuse	sensory distortions	not reported
Zolpidem	Adult	somnambulism	(Harazin & Berigan, 1999)	1	depression	somnambulism	somnambulism stopped
Zolpidem	Adult	somnambulism	(Sattar, Ramaswamy, Bhatia, & Petty, 2003)	1	bipolar disorder history of drug abuse history of alcohol dependence mania taking valproic at the same time	somnambulism difficulty in concentration	insomnia
Zolpidem	Adult	somnambulism	(Yang, 2005)	1	Heavy alcohol consumption with questionable delitium tremens but had stopped drinking alcohol 20 years ago Traumatic head injury	somnambulism agitated and confused but had no psychotic experiences	no additional episodes of sleepwalking
Zolpidem	Adult	tolerance	(Cavallaro, 1993)	2	psychiatric disorders	increase dosage because of tolerance with awakening after 2- 3 h. abstinence phenomena during the day and increased dosage again to control those symptoms.	not reported
Zolpidem	Adult Elderly	CNS side effect	(Logan & Couper, 2001)	29	no common characteristics	driving impairment because of slow movements and reactions visual distortions	not reported

Drug	Subgroup	Adverse Events	Study	Number of cases	Case Characteristics	Effects during treatment	Effects during treatment reduction or discontinuation
Zolpidem	Adult Elderly	dependence	(Liappas, 2003)	8	minor psychiatric disorders	patients increased the dose up to 150-600mg for stimulation, sedation, improving mood, relax, coping or sleep better. dependence and tolerance several traffic accidents memory impairment confusion	4 without withdrawal symptoms 1 with discomfort, irritability, and agitation 1 with epileptic seizure 1 with instability, dizziness and a craving for other psychotropic substances 1 not reported
Zolpidem	Adult Elderly	others	(Morgenthaler & Silber, 2002)	5	no history of eating disorders concurrent use of other drugs	amnestic sleep-related eating disorder restless legs syndrome	no nocturnal eating
Zolpidem	Elderly	CNS side effect	(Brodeur & Stirling, 2001)	1	Extensive medical history	delirium psychosis restless amnesia	not reported
Zolpidem	Elderly	delirium mania	(Hill, Oberstar, & Dunn, 2004)	1	no significant psychiatric history family history of mild depression	no hallucination no suicidal or homicidal ideation mania	not reported
Zolpidem	Elderly	dependence	(Madrak & Rosenberg, 2001)	1	history of alcohol and drug abuse	use up to 100mg/day for the last 1.5 years psychomotor agitation; tremor; facial flushing; anxiety	not reported
Zolpidem	Elderly	hallucination	(Markowitz, Rames, Reeves, & Thomas, 1997)	1	no substance abuse depression	hallucination	no further episodes after discontinuation
Zolpidem	Elderly	hallucination	(Pitner, Gardner, Neville, & Mintzer, 1997)	1	no psychiatric history	hallucination delusion psychomotor agitation irritable and difficult to redirect	not reported

Drug	Subgroup	Adverse Events	Study	Number of cases	Case Characteristics	Effects during treatment	Effects during treatment reduction or discontinuation
Zolpidem	Pediatrics	hallucination	(Andrade, 2002)	1	history of vascular headache	drowsiness, confusion, unsteadiness and hallucination vascular headache and the use of zolpidem in children may increase the hallucination	not reported
Zolpidem	Pediatrics	somnambulism	(Lange, 2005)	1	depressive disorder history of somnambulism family history of somnambulism no epileptiform activity	somnambulism	change to citalopram without incident
Zopiclone	Adult	dependence	(Aranko, Henriksson, Hublin, & Seppalainen, 1991)	1	depression compulsive personality disorder history of drug abuse concurrent use of antidepressants	the patient increase the dose up to 90mg per day for uninterrupted sleep. Memory difficulties cognitive impairments dependence	grand-mal-type convulsion
Zopiclone	Adult	dependence	(Haasen, Mueller- Thomsen, Fink, Bussopulos, & Reimer, 2005)	1	no history of benzodiazepine or other psychotropic substance use and only very in frequently drank a glass of wine	dependence daily dosage of 37.5mg	Remain symptom: dystonia symptoms peaked 8 days after initiating the reduction and 3 days after discontinuation, and then gradually remitted: torticollis such as tremulousness, sympathetic autonomic hyperactivity, including anxiety, arousal, sweating, tachycardia, facial flushing and mild hypertension

Drug	Subgroup	Adverse Events	Study	Number of cases	Case Characteristics	Effects during treatment	Effects during treatment reduction or discontinuation
Zopiclone	Adult	dependence	(Jones, 2005)	4	no common characteristics	dependence	severe anxiety with tachycardia, tremor, sweating, rebound insomnia, flushes, palpitations, and derealization.
Zopiclone	Adult	dependence	(Thakore & Dinan, 1992)	1	depression history of alcohol dependency history of flurazepam addiction take zopiclone more due to anxiety and agoraphobia	dependence	tachycardia hand tremor weakness panic attack
Zopiclone	Adult	global amnesia	(Fava, 1996)	1	no current psychiatric symptomatology no drinking history no other medication	global amnesia	no further episodes of global amnesia were observed during a 6- month period
Zopiclone	Adult	incidence of cancer	(Stebbing et al., 2005)	32	not reported	2 weeks of zopiclone. 32 (5.3%) patients have subsequently been diagnosed with cancer at least 3 months after exposure to zopiclone The label for eszopiclone contains significant warnings regarding carcinogenicity and mutagenesis	not reported
Zopiclone	Elderly	dependence	(Bramness, Arnestad, Karinen, & Hilberg, 2001)	1	smoker respiratory problems anxiety	difficulty in breathing death caused by 337.5mg overdose	not reported

Drug	Subgroup	Adverse Events	Study	Number of cases	Case Characteristics	Effects during treatment	Effects during treatment reduction or discontinuation
Zopiclone	Elderly	dependence	(Kuntze, Bullinger, & Mueller- Spahn, 2002)	1	depressive disorder no use of psychotropic	tolerance to 337.5mg/day dependence	not reported
Zopiclone	Elderly	others- drug interaction	(Alderman, Gebauer, Gilbert, & Condon, 2001)	1	depression concurrent use of antidepressants	morning drowsiness increased plasma concentrations	zopiclone plasma concentrations back to normal after nefazodone discontinuation
Zopiclone	Elderly	respiratory depression	(Vogal, 1998)	1	COPD exsmoker with a history of ethanol abuse	drowsy respiratory acidosis	not reported
Zopiclone	Pediatrics	others	(Sullivan, McBride, & Clee, 1995)	3	history of drug abuse alcohol abuse	no evidence of dependence	not reported

- Alderman, C. P., Gebauer, M. G., Gilbert, A. L., & Condon, J. T. (2001). Possible interaction of zopiclone and nefazodone. *Annals of Pharmacotherapy*, *35*(11), 1378-1380.
- Aragona, M. (2000). Abuse, dependence, and epileptic seizures after zolpidem withdrawal: Review and case report. *Clinical Neuropharmacology*, 23(5), 281-283.
- Aranko, K., Henriksson, M., Hublin, C., & Seppalainen, A. M. (1991). Misuse of zopiclone and convulsions during withdrawal. *Pharmacopsychiatry*, 24(4), 138-140.
- Bhatia, S. C., Arora, M., & Bhatia, S. K. (2001). Perceptual disturbances with zaleplon. Psychiatric Services, 52(1), 109-110.
- Bramness, J. G., Arnestad, M., Karinen, R., & Hilberg, T. (2001). Fatal overdose of zopiclone in an elderly woman with bronchogenic carcinoma. *Journal of Forensic Sciences*, *46*(5), 1247-1249.
- Brodeur, M. R., & Stirling, A. L. (2001). Delirium associated with zolpidem. Annals of Pharmacotherapy, 35(12), 1562-1564.
- Canaday, B. R. (1996). Amnesia possibly associated with zolpidem administration. *Pharmacotherapy*, 16(4), 687-689.
- Clark, A. (1999). Worsening hepatic encephalopathy secondary to zolpidem. Journal of Pharmacy Technology, 15(4), 139-141.
- Elko, C. J., Burgess, J. L., & Robertson, W. O. (1998). Zolpidem-associated hallucinations and serotonin reuptake inhibition: a possible interaction. *Journal of Toxicology Clinical Toxicology*, *36*(3), 195-203.

- Fava, G. A. (1996). Amnestic syndrome induced by zopiclone European Journal of Clinical Pharmacology, 50(6), 509.
- Freudenreich, O., & Menza, M. (2000). Zolpidem-related delirium: A case report Journal of Clinical Psychiatry, 61(6), 449-450.
- Gericke, C. A., & Ludolph, A. C. (1994). Chronic abuse of zolpidem. *Journal of the American Medical Association*, 272(22), 1721-1722.
- Haasen, C., Mueller-Thomsen, T., Fink, T., Bussopulos, A., & Reimer, J. (2005). Zopiclone dependence after insomnia related to torticollis. *International Journal of Neuropsychopharmacology*, 8(2), 309-310.
- Harazin, J., & Berigan, T. R. (1999). Zolpidem tartrate and somnambulism. Military Medicine, 164(9), 669-670.
- Hill, K. P., Oberstar, J. V., & Dunn, E. R. (2004). Zolpidem-Induced Delirium with Mania in an Elderly Woman. *Psychosomatics*, 45(1), 88-89.
- Hoyler, C. L., Tekell, J. L., & Silva, J. A. (1996). Zolpidem-induced agitation and disorganization. *General Hospital Psychiatry*, 18(6), 452-453.
- Karsenti, D., Blanc, P., Bacq, Y., & Melman, E.-H. (1999). Hepatotoxicity associated with zolpidem treatment. *British Medical Journal*, *318*, 1179%N 7192.
- Kuntze, M. F., Bullinger, A. H., & Mueller-Spahn, F. (2002). Excessive use of zopiclone: A case report. *Swiss Medical Weekly*, 132, 35-36.
- Lange, C. L. (2005). Medication-Associated Somnambulism. *Journal of the American Academy of Child & Adolescent Psychiatry*, 44(3), 211-212.
- Liappas, I. A., Malitas, P. N., Dimopoulos, N. P., Gitsa, O. E., Liappas, A. I., Nikolaou, C. H. K., et al. (2002). A zolpidem and cocaine abuse case report. *International Journal of Psychiatry in Clinical Practice*, 6(4), 217-219.
- Liskow, B., & Pikalov, A. (2004). Zaleplon overdose associated with sleepwalking and complex behavior. *Journal of the American Academy of Child and Adolescent Psychiatry*, 43(8), 927-928.
- Logan, B. K., & Couper, F. J. (2001). Zolpidem and driving impairment. Journal of Forensic Sciences, 46(1), 105-110.
- Madrak, L. N., & Rosenberg, M. (2001). Zolpidem abuse American Journal of Psychiatry, 158(8), 1330-1331.
- Markowitz, J. S., & Brewerton, T. D. (1996). Zolpidem-induced psychosis. Annals of Clinical Psychiatry, 8(2), 89-91.
- Markowitz, J. S., Rames, L. J., Reeves, N., & Thomas, S. G. (1997). Zolpidem and hallucinations Annals of Emergency Medicine, 29(2), 300-301.
- Morgenthaler, T. I., & Silber, M. H. (2002). Amnestic sleep-related eating disorder associated with zolpidem. *Sleep Medicine*, *3*(4), 323-327.
- Pitner, J. K., Gardner, M., Neville, M., & Mintzer, J. (1997). Zolpidem-induced psychosis in an older woman *Journal of the American Geriatrics Society*, 45(4), 533-534.

- Quaglio, G., Lugoboni, F., Fornasiero, A., Lechi, A., Gerra, G., & Mezzelani, P. (2005). Dependence on zolpidem: Two case reports of detoxification with flumazenil infusion. *International Clinical Psychopharmacology*, 20(5), 285-287.
- Sattar, S. P., Ramaswamy, S., Bhatia, S. C., & Petty, F. (2003). Somnambulism due to probable interaction of valproic acid and zolpidem. *Annals of Pharmacotherapy*, *37*(10), 1429-1433.
- Stebbing, J., Waters, L., Davies, L., Mandalia, S., Nelson, M., Gazzard, B., et al. (2005). Incidence of cancer in individuals receiving chronic zopiclone or eszopiclone requires prospective study. *Journal of Clinical Oncology*, 23(31), 8134-8136.

Stillwell, M. E. (2003). Zaleplon and driving impairment. Journal of Forensic Sciences, 48(3), 677-679.

- Sullivan, G., McBride, A. J., & Clee, W. B. (1995). Zopiclone abuse in South Wales: Three case reports. *Human Psychopharmacology*, *10*(4), 351-352.
- Thakore, J., & Dinan, T. G. (1992). Physical dependence following zopiclone usage: A case report. *Human Psychopharmacology*, 7(2), 143-145.
- Van Puijenbroek, E. P., Egberts, A. C. G., & Krom, H. J. (1996). Visual hallucinations and amnesia associated with the use of zolpidem *International Journal of Clinical Pharmacology and Therapeutics*, *34*, 318%N 317.
- Vartzopoulos, D., Bozikas, V., Phocas, C., Karavatos, A., & Kaprinis, G. (2000). Dependence on zolpidem in high dose. *International Clinical Psychopharmacology*, 15(3), 181-182.