Author: Allain Trial type: H2H Quality rating: Fair

Year: 2003 Country: France Funding: Sanofi-Synthelabo

Design:

Study design RCT

DB

Crossover

Setting Single Center

Eligibility criteria:

Age between 40 and 65 years; with a clinical examination judged compatible with difficulties falling asleep, with previous history of recurrent episodes of insomnia and justifying the prescription of hypnotic treatment at the time of inclusion.

Comments:

Intervention: Run

Run-in: No Wash out: No

Allow other medication: NR

Age: 52

Range: NR SD: 7

Gender: 26 (49 %) Female

Ethnicity: NR

Number Withdrawn: 0 Lost to fu: 0

Number Screened: NR

Eligible:

Enrolled:

Analyzed: 53

NR

53

Exclusion criteria:

Current episode having lasted more than three weeks; any secondary insomnia resulting from medicl or psychiatric causes; patients who followed a continuous treatment with the same same hypnotic for more than six months; patients who took hypnotic drugs the day before inclusion; patients who took hypnotic drugs the day before inclusion, patients currently treated by zolpidem or zaleplon; night-shift work; current medical treatment including antidepressants, neuroleptics, anxiolytics, H1 antihistamines, barbiturates or hypnotics.

Withdrawals due to AEs/

Drug name	dosage	N=	Duration	Total withdrawal	
Zolpidem	10 mg	52	1 day	0 / 0	
Zaleplon	10 mg	0		/	

Author:	Allain	Trial type:	H2H		Quality rating: Fair
Year:	2003	Country:	France		Funding: Sanofi-Synthelabo
Outcome N	Measurement:			Efficacy	Outcome List:
# Patien	t preference questionnaire			Primary outcome	Outcome:
	analogue scale for day quality				Patient's preference for drug Getting to sleep Quality of sleep (LSEQ) Ease of waking up Behavior following wakefulness Day quality Quality of sleep (VAS) Consciousness Dynamism Drowsiness Anxiety Mood Drowsiness duration (minutes)
Results					
Patient pref	erence				
# Percer drug	ntage of patients preferring a	Zolpidem 62 (Zaleplon) 38	()	() () 0.81
		(%) ()	

Quality rating: Fair Author: Allain Trial type: H2H

Υe nthelabo/

Year:	2003	Country:	Fra	nce	!					Funding:	Sanofi-Syn
LSEQ											
	ng to sleep mean score (lower is	Zolpidem			Zaleplo	on					P value
bette	er)	35.9	(20.0)	45.3	(20.7)	()	() 0.03
		Score	(SD)		l		
	ity of sleep mean score (lower is	Zolpidem			Zaleplo	on					P value
bette	er)	30.6	(18.6)	44.3	(23.2)	()	() <0.0001
		Score	(SD)				
	e of waking up mean score (lower	Zolpidem			Zaleplo	on					P value
is be	tter)	43.6	(22.8)	43.8	(21.8)	()	() 0.27
		Score	(SD)		l		
	avior following wakefulness mean	Zolpidem			Zaleplo	n					P value
score	e (lower is better)	47.4	(23.2)	51.7	(17.2)	()	() 0.31
		Score	(SD	,)		'		ı I

Author: Allain Trial type: H2H Quality rating: Fair

Year: 2003 Country: France Funding: Sanofi-Synthelabo

Year:	2003	Country:	Fran	CE)					Funding:	Sanofi-Synt
VAS for	day quality (0-100, higher is bet	ter <u>)</u>									
# Qu	ality of sleep mean score	Zolpidem			Zaleplo	n					P value
		68.8	(21.8)	50.2	(28.1)	()	() <0.0001
		Score	(SD		!)				
# Co	nsciousness mean score	Zolpidem			Zaleplo	n					P value
		73.9	(21.3)	73.1	(19.7)	()	() 0.18
		Score	(SD)				
# Dy	namism mean score	Zolpidem			Zaleplo	n					P value
		62.6	(26.0)	61.8	(24.9)	()	() 0.47
		Score	(SD)		- II		
# Dro	owsiness mean score	Zolpidem			Zaleplo	n					P value
		28	(27.4)	27.7	(26.5)	()	() 0.53
		Score	(SD		i)				ı
# An	xiety mean score	Zolpidem			Zaleplo	n					P value
		29.3	(30.1)	26.7	(27.7)	()	() 0.34
		Score	(SD)		l l		
# Mo	ood mean score	Zolpidem			Zaleplo	n					P value
		21.6	(25.5)	20.1	(21.6)	()	() 0.92
		Score	(SD)				
# Dro	owsiness duration (minutes)	Zolpidem			Zaleplo	n					P value
		43	(43.8)	38	(21.2)	()	() 0.83
		Number	(SD)		1		

Author: Ancoli-Israel Trial type: H2H Quality rating: Fair

Year: 1999 Country: US Funding: Wyeth-Ayerst

Design:

Study design RCT

DB

Parallel

Setting Multicenter

Eligibility criteria:

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.

Comments:

Elderly

Intervention: Run-in:

Wash out: 7-21

Allow other medication: No

Age: 72

Range: SD: 5 Number Screened: 1224

Eligible: 551

Enrolled: 549

Gender: 318 (58 %) Female

Ethnicity: Number Withdrawn: 2

Lost to fu:

Analyzed: 549

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.

Withdrawals due to AEs/

Drug name	do	sage	N=	Duration	Total withdrawal
Placebo		mg	107	14 day	/
Zaleplon	5	mg	166	2 week	1
Zaleplon	10	mg	165	2 week	1
Zolpidem	5	mg	111	2 week	/

Year:	4000							•	kuanty rat	ing: Fair
	1999	Country:	US					F	unding:	Wyeth-Aye
	Measurement: nt questionnaire				Efficac Primary outcom	e Outcor Sleep la Total sl	ne: atency eep time r of awake			
Results Sleep laten	icv									
				T		1		1		
	n subjective sleep latency tes) at week 1	Zaleplon 5		Zaleplon		Zolpidem	- J			P value
(ITIIITO	do y di wook i		(NS)		(<0.001)		(<0.05)		(
		Number	(p vs plac	ebo)					
	n subjective sleep latency	Zaleplon 5	i mg	Zaleplon	10 mg	Zolpidem	5 mg			P value
(minut	tes) at week 2	39	(<0.001)		(<0.001)		(<0.01)		()
		Number	(p vs plac	ebo)	ļ				
Total sleep	time		(p 10 p.a0		,					
		Zalamlam 5		7-11	10	7-1-1-1	F	Disaska		T
# iviedia week	n subjective total sleep time at 1	Zaleplon 5		Zaleplon		Zolpidem		Placebo	, ,	P value
			(NS)	345	(p<0.05)	360	(<0.00)	318	(
		Number	(p vs plac	ebo)					
	n subjective total sleep time at	Zaleplon 5	i mg	Zaleplon	10 mg	Zolpidem	5 mg	Placebo)	P value
	2		(NS)		(NS)	360	(< 0.01)	326	(1

Score

Author:	Ancoli-Israel	Trial ty	pe: H2H	l				(Quality r	ating: Fai	r
Year:	1999	Countr	y: US					I	Funding	: Wyeth-Ay	ers
Number of	<u>awakenings</u>										
# Numb	er of awakenings at week 1	Zaleplo	n 5 mg	Zaleple	on 10 mg	Zolpid	em 5 mg	Placeb	0	P value	
		1.8	(NS) 1.8	(NS) 1.7	(<0.01)	2.0	(NA)	

(p vs placebo

Number of awakenings at week 2

Number	(pvsp	olace	DO)						
Zaleplon	5 mg		Zalepl	on 10 mg		Zolpid	em 5 mg	Placel	00		P value
1.9	(NS)	1.7	(NS)	1.6	(<0.05)	1.9	(NA)	
	()						

Sleep quality

Median sleep quality at week 1 (1=excellent, 7=extremely poor)

Zaleplo	n 5 mg	Zaleplo	n 10 mg		Zolpid	em 5 mg	Placeb	00		P value
3.83	(NS) 3.67	(< 0.05)	3.50	(<0.00)	4.00	(NA)	
Score	(pvs)	placebo)						

Median sleep quality at week 2 (1=excellent, 7=extremely poor)

Score	(p vs plac	ebo)						
Zaleplon 5	mg	Zaleplon '	10 mg		Zolpidem	5 mg	Placebo			P value
3.75	(NS	3.63	(NS)	3.50	(<0.00)	4.00	(NA)	

Author: Elie Trial type: H2H Quality rating: Fair

Year: 1999 Country: Multinational (Canada and Europe) Funding: Wyeth-Ayerst

Design:

Study design RCT

DB

Parallel

Setting Multicenter

Eligibility 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.

Age: 42.8

Range: NR SD: 12.4

Gender: 394 (64 %) Female

Ethnicity: 99% white

<1% black <1% Asian Number Withdrawn: 41

Number Screened: NR

Eligible:

Enrolled:

NR

615

Lost to fu: NR Analyzed: 574

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 Deepression Scale was >49.

Comments:

Analyzed 574/615 patients randomized. 39 patients excluded from efficacy analysis because of inadequate source documentation. Baseline demographic characteristics given only on 574 patients analyzed, and no statistical analysis of baseline characteristics.

Intervention:

Run-in: Yes Wash out: Yes

Allow other medication :

Withdrawals due to AEs/

Drug name	do	sage	N=	Duration Total withdrawal
Zaleplon	5	mg	113	4 week /
Zaleplon	10	mg	112	4 week /
Zaleplon	20	mg	116	4 week /
Zolpidem	10	mg	0	1
Placebo			118	4 week /

Author:	Elie	Trial typ	e: H	2H						C	luality ra	ting: Fair
Year:	1999	Country	: M	ultin	ationa	I (Canad	la a	nd Eur	ope)	F	unding:	Wyeth-Ayerst
Outcome	Measurement:					Effi	cac	y Outo	come List:			
# Slee	p maintenance and sleep quality	questionnaire			Primary outcome:							
						[/		p latency			
						Ĺ	_		p duration			
						L	_		ber of awake	nings		
						L		Siee	p quality			
Results												
Sleep dura	ation_											
# Medi	ian sleep duration at baseline	Zaleplon	5 mg		Zaleplo	on 10 mg		Zaleplo	n 20 mg	Zolpiden	n 10 mg	P value
(minı	utes)	313	(NS)	331	(NS)	328	(NS)	330	(NS)
		Number	(pvs	place	ebo)					
	ian sleep duration at week 1	Zaleplon	5 mg		Zaleplo	on 10 mg		Zaleplo	n 20 mg	Zolpiden	n 10 mg	P value
(minı	utes)	351	(NS)	370	(NS)	370	(p<0.0)	379	(p<0.00)
		Number	(pvs	place	ebo)	Į.		ļ		1
# Medi	ian sleep duration at week 2	Zaleplon	5 mg		Zaleplo	n 10 mg		Zaleplo	n 20 mg	Zolpiden	n 10 mg	P value
(minu	utes)	359	(NS)	368	(NS)	369	(p<0.0)	387	(p<0.00	
		Number	(p vs	place	ebo)	I	<u> </u>			
# Medi	ian sleep duration at week 3	Zaleplon		1	1	on 10 mg	,	Zalenio	n 20 mg	Zolpiden	n 10 ma	P value
minı		384	(NS)	371	(NS)	374	(NS)	385	(<0.001	
				,		(J	()	200	, 10.001	/
		Number	` '	place	1)	1		1		ĺ
# Medi (minu	ian sleep duration at week 4	Zaleplon	J			n 10 mg		•	n 20 mg	Zolpiden	_	P value
(min)	ui c o <i>j</i>	372	(NS)	384	(NS)	385	(<0.05)	400	(<0.001)
		Number	(pvs	place	ebo)	1		1		

Author:ElieTrial type:H2HQuality rating:FairYear:1999Country:Multinational (Canada and Europe)Funding: Wyeth-Ayerst

Year:	1999	Country	: Mul	tin	ation	al (Canad	a a	nd Europe)			Funding:	Wyeth-Aye
Number of	of awakenings											
	lian number of awakenings at	Zaleplon	5 mg		Zalep	lon 10 mg		Zaleplon 20 mg		Zolpid	lem 10 mg	P value
base	eline	2	(NS)	2	(NS)	2 (NS)	2	(NS)
		Number	(p vs p	lace	bo)	1		1		
	lian number of awakenings at	Zaleplon	5 mg		Zalep	lon 10 mg		Zaleplon 20 mg		Zolpid	lem 10 mg	P value
wee	k 1	2	(NS)	2	(NS)	2 (NS)	2	(NS)
		Number	(pvsp	lace	bo)	I				
	lian number of awakenings at	Zaleplon	5 mg		Zalep	lon 10 mg		Zaleplon 20 mg		Zolpid	lem 10 mg	P value
wee	k 2	2	(NS)	2	(NS)	2 (NS)	2	(NS)
		Number	(pvsp	lace	bo)					
	lian number of awakenings at	Zaleplon	5 mg		Zalep	lon 10 mg		Zaleplon 20 mg		Zolpid	lem 10 mg	P value
wee	k 3	2	(NS)	2	(NS)	1 (NS)	2	(NS)
		Number	(pvsp	lace	bo)	,		1		1 1
	lian number of awakenings at	Zaleplon	5 mg		Zalep	lon 10 mg		Zaleplon 20 mg		Zolpid	lem 10 mg	P value
wee	k 4	2	(NS)	2	(NS)	1 (NS)	2	(NS)
		Number	(pvsp	lace	bo)	1		1		

Author: Elie Trial type: H2H Quality rating: Fair

Year: 1999 Country: Multinational (Canada and Europe) Funding: Wyeth-Ayerst

# Sleep quality mean score at baseline	Zaleplon	5 mg	Zaleple	on 10 mg		Zaleplon 20 mg	Zolpidem	P value	
	4.6	(NS) 4.5	(NS)	4.5 (NS)	4.4	(NS)	
	Score	(p vs pla	icebo)		.1		
# Sleep quality mean score at week 1	Zaleplon	5 mg	Zaleple	on 10 mg		Zaleplon 20 mg	Zolpidem	10 mg	P value
	4.1	(NS) 3.9	(p<0.05)	3.8 (p<0.0)	3.7	(p<0.00)	
	Score	(p vs pla	icebo)		1		1
# Sleep quality mean score at week 2	Zaleplon	5 mg	Zalepl	on 10 mg		Zaleplon 20 mg	Zolpidem	10 mg	P value
	4.0	(NS) 3.9	(NS)	3.8 (NS)	3.6	(p<0.00)	
	Score	(p vs pla	icebo)		1		1
# Sleep quality mean score at week 3	Zaleplon	5 mg	Zalepl	on 10 mg		Zaleplon 20 mg	Zolpidem	10 mg	P value
	3.8	(NS) 3.8	(NS)	3.6 (NS)	3.6	(p<0.05)	
	Score	(p vs pla	icebo)		ı.		1
# Sleep quality mean score at week 4	Zaleplon	5 mg	Zaleple	on 10 mg		Zaleplon 20 mg	Zolpidem	10 mg	P value
	3.8	(NS) 3.7	(NS)	3.6 (NS)	3.4	(p<0.01)	

Author: Elie Trial type: H2H Quality rating: Fair

Year: 1999 Country: Multinational (Canada and Europe) Funding: Wyeth-Ayerst

#	Time to sleep onset at week 1	
	(median, minutes)	

Zaleplon 5	mg	Zaleplon 1	0 mg	Zaleplon 2	20 mg	Zolpidem	10 mg	P value
42	(0.005)	36	(<0.001)	33	(<0.00)	45	(0.47)	
Number	(p vs place	bo)					

Median time to sleep onset at week 2 (median, minutes)

Zaleplor	5 mg		Zalepl	lon 10	mg		Zale	plon	20 mg	Zolpi	idem 1	I0 mg		P value
35	(0.002)	32	(0.001)	31		(<0.00)	37	(0.006)	

Median time to sleep onset at week 3 (median, minutes)

Zaleplon 5 mg		Zaleplon 1	0 mg		Zaleplon 2	20 mg	Zolpidem	P value		
31	(0.004)	30	(0.004)	28	(<0.00)	34	(0.043)	

Number

Number

(p vs placebo

(p vs placebo

Median time to sleep onset at week 4 (median, minutes)

Author: Fry Trial type: H2H Quality rating: Fair

Year: 2000 Country: US Funding: Wyeth-Ayerst

Design:

Study design RCT

DB

Parallel

Setting Multicenter

Eligibility criteria:

Men or non-pregnant women, 18-65 years who met the criteria for primary insomnia or insomnia associated with mild non-psychotic 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 impariment 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.

Comments:

Patients with mild non-psychotic psychiatric disorders. Baseline characteristics reported only for 586/595 randomized (98%) Data on primary outcome (sleep latency) reported graphically only.

Intervention: Run-i

Run-in: 7
Wash out: n

Allow other medication: NF

SD:

Ethnicity: 11% Black

3% Hispanic <1% Native American 1.5% Asian <1% Other 84% White

Gender: 351 (59 %) Female

Age: 42

Range: NR SD: 12

Number Withdrawn: 9

Lost to fu: NR Analyzed: 586

Number Screened: NR

Eligible:

Enrolled:

830

595

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 patietns 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.

Withdrawals due to AEs/

Drug name	dos	sage	N=	Duration	Total withdrawal	
Zaleplon	5	mg	118	4 week	3 / 20	
Zaleplon	10	mg	119	4 week	5 / 18	

Author:	Author: Fry			l type:	H2H		Quality rating: Fair	
Year:	2000		Cou	ıntry:	US			Funding: Wyeth-Ayerst
	Zaleplon	20	mg	116		4 week	10 / 17	
	Zolpidem	10	mg	115		4 week	7 / 20	
	Placebo		mg	118		4 week	4 / 12	

Author:	Fry	Trial type	e: H2	Н				C	Quality r	rati	ng: Fair	
Year:	2000	Country:	US					F	unding): V	Vyeth-Ayerst	
Outcome	Measurement:				Effic	ac	y Outcome List:					
# Patie	ent questionnaire				Prima outco	-						
					✓		Sleep latency					
							Total sleep time					
							Number of awake	enings				
							Sleep quality					
Results												
Sleep late	ency											
# Time	# Time to sleep onset at week 1	Zaleplon 5	5 ma	Zaleplon	10 mg		Zaleplon 20 mg	Zolpider	n 10 ma		Duralina	
	dian, minutes)	45.36	(0.764) 40.71	(0.490	١	35.71 (0.003)	45.71	/ /	١	P value	
			`	' -	`	,	33.71 (0.003)	43.71	(,		
		Number	(pvsz	olpidem 10 m	ng)						
	to sleep onset at week 2	Zaleplon 5	5 mg	Zaleplon	10 mg		Zaleplon 20 mg	Zolpider	n 10 mg		P value	
(med	lian, minutes)	43.57	(0.959) 36.43	(0.183)	31.67 (<0.00)	46.43	()		
		Number	(pvsz	olpidem 10 m	ng)	ļ	I				
# Time	to sleep onset at week 3	Zaleplon 5		Zaleplon			Zaleplon 20 mg	Zolpider	n 10 ma		P value	
	lian, minutes)	40.71	(0.323) 35.71	(0.110)	30.00 (<0.00)	44.29	()	r value	
			`	/		<u>,</u>	(10.00)	11.20	,			
		Number	(pvsz	olpidem 10 m	ng)						
	to sleep onset at week 4	Zaleplon 5	5 mg	Zaleplon	10 mg		Zaleplon 20 mg	Zolpider	n 10 mg		P value	
(med	lian, minutes)	45.63	(0.124) 35.00	(0.988)	30.00 (0.037)	34.29	()		
		Number	(pvsz	olpidem 10 m	ng)	<u>I</u>	1				
					Ŭ	,						

Author:FryTrial type:H2HQuality rating:FairYear:2000Country:USFunding: Wyeth-Ayerst

Year:	2000	Country:	US						F	unding:	Wyeth-Aye
Total sle	ep time										
	al sleep time at week 1 (median,	Zaleplon 5	mg	Zaleplor	n 10 mg		Zaleploi	n 20 mg	Zolpider	n 10 mg	P value
min	nutes)	360.0	(NS)	360.6	(NS)	368.6	(<0.05)	377.1	(<0.001)
		Number	(p vs plac	ebo)	I		I		
# Tot	al sleep time at week 2 (median,	Zaleplon 5	mg	Zaleplor	n 10 mg		Zaleploi	n 20 mg	Zolpider	n 10 mg	P value
min	nutes)	366.4	(NS)	364.3	(NS)	368.6	(NS)	384.4	(<0.05)
		Number	(p vs plac	ebo)					
	al sleep time at week 3 (median,	Zaleplon 5	mg	Zaleplor	n 10 mg		Zaleploi	n 20 mg	Zolpider	n 10 mg	P value
min	nutes)	361.4	(NS)	377.1	(NS)	386.8	(<0.05)	392.1	(<0.01)
		Number	(p vs plac	ebo)					
	al sleep time at week 4 (median,	Zaleplon 5	mg	Zaleplor	n 10 mg		Zaleploi	n 20 mg	Zolpider	n 10 mg	P value
min	minutes)		(NS)	376.3	(NS)	377.5	(NS)	392.9	(<0.05)
		Number	(p vs plac	ebo)	II.		ı		ļ l
Number	of awakenings										
	mber of awakenings at week 1	Zaleplon 5	mg	Zaleplor	n 10 mg		Zaleploi	n 20 mg	Zolpider	n 10 mg	P value
(me	edian)	1.93	(NS)	1.69	(NS)	1.75	(NS)	1.59	(<0.01)
		Number	(p vs plac	ebo)					
	mber of awakenings at week 2	Zaleplon 5	mg	Zaleplor	n 10 mg		Zaleploi	n 20 mg	Zolpider	n 10 g	P value
(me	edian)	1.67	(NS)	1.69	(NS)	1.50	(<0.00)	1.50	(<0.001)
		Number	(p vs plac	ebo)					
# Nur	mber of awakenings at week 3	Zaleplon 5	mg	Zaleplor	n 10 mg		Zaleploi	n 20 mg	Zolpider	n 10 mg	P value
(me	edian)	1.71	(NS)	1.71	(NS)	1.43	(<0.05)	1.71	(NS)
		Number	(p vs plac	ebo)					
	mber of awakenings at week 4	Zaleplon 5	mg	Zaleplor	n 10 mg		Zaleploi	n 20 mg	Zolpider	n 10 mg	P value
(me	edian)	1.71	(NS)	1.57	(NS)	1.60	(NS)	1.67	(NS)
		Number	(p vs plac	ebo)					

Author: Fry Trial type: H2H Quality rating: Fair

Year: 2000 Country: US Funding: Wyeth-Ayerst

Sleep quality (1=excellent, 7=extremely po	<u>oor)</u>										
# Sleep quality at week 1 (median)	Zaleplon 5 mg			Zaleplon 10 mg			Zaleplo	n 20 mg	Zolpide	P value	
	3.43	(NS)	3.57	(NS)	3.43	(<0.01)	3.38	(<0.001)	
	Score	(p vs pla	ace	ebo)			Į.		
# Sleep quality at week 2 (median)	Zaleplor	5 mg		Zaleplo	n 10 mg		Zaleplo	n 20 mg	Zolpide	em 10 mg	P value
	3.43	(NS)	3.57	(NS)	3.43	(NS)	3.29	(<0.05)	
	Score	(p vs pla	ace	ebo)					-11
# Sleep quality at week 3 (median)	Zaleplor	5 mg		Zaleplon 10 mg			Zaleplo	n 20 mg	Zolpide	P value	
	3.43	(NS)	3.43	(NS)	3.29	(NS)	3.29	(<0.05)	
	Score	(p vs pla	ace	ebo)	1		I		1
# Sleep quality at week 4 (median)	Zaleplor	n 5 mg		Zaleplo	n 10 mg		Zaleplo	n 20 mg	Zolpide	em 10 mg	P value
	3.38	(NS)	3.54	(NS)	3.29	(NS)	3.15	(<0.05)	
	Score	(p vs pla	ace	bo)	1		ı		I

Author: Tsutsui Trial type: H2H Quality rating: Fair

Year: 2001 Country: Japan Funding: Not reported

Design:

Study design RCT

DB

Parallel

Setting Multicenter

Age: 42.2

Range: 20-64

12.7

Gender: 277 (58 %) Female

Ethnicity: NR

SD:

Number Withdrawn: 77

Lost to fu: NR Analyzed: 428

NR

NR

479

Number Screened:

Eligible:

Enrolled:

Eligibility criteria:

Patients with chronic primary insomnia (I.e., experincing non-restorative sleep or difficulty for more than a month in initiating or maintaining sleep), experiencing difficulties more than three times a week in sleeping.

Exclusion criteria:

Schizophrenia, depression, manic depression, clinically diagnnosed diseases in the acute or exacerbation phase or with unstable symptoms, organic cerebral disorders (diagnosed or suspected), serious heart, liver, kidney, or blood disorders, severe respiratory dysfunction, myasthenia gravis or acute narrow-angle glaucoma and cognitive disorders or impaired intelligence. Symptoms interfering with sleep (e.g., pain, fever, diarrhea, pollakiuria, cough), hypersensitivity to benzodiazepines and analogous drugs, zopiclone intake within 3 months prior to the study, requirement for hypnotics at a dose exceeding the standard single dose, history of drug dependence, operation of machinery involving risk, pregnancy or likelihood of pregnancy, breastfeeding, participation in other clinical trials within the past 6 months, and inappropriateness for the study according to the investigator's judgment.

Comments:

Baseline demographic data reported only on patients included in efficacy analysis (428/479; 89%).

Additional rebound information: Overall, sleep onset latency, frequency of nocturnal awakenings, sleep duration, daytime mood and daytime physical condition remained significantly improved in both groups relative to baseline (p<0.01, data not reported).

Intervention:

Run-in: no

Wash out: 7

Drug name

Zolpidem

Zopiclone

Allow other medication: No

dosage

10 mg

7.5 mg

N=

209

219

	Withdrawals due to AEs/
Duration	Total withdrawal
2 week	14 / 32
2 week	20 / 45

Author:	Tsutsui	Trial type:	H2H						Quality ra	ting: Fair
Year:	2001	Country:	Japan						Funding:	Not reported
Outcome	Measurement:					Efficacy	Outcome	List:		
# Patie	nt diary					Primary outcome	Outcome:			
							•		ent of sleep disorders on of treatment effic	
Results										
Global imp	provement of sleep disorders									
	nts rated by the investigator as	Zolpidem		Zopiclor	ne					P value
"marl	kedly improved"	18.7 ()	16.4	()	()	() NS
		(%) (1)				
	nts rated by the investigator as	Zolpidem		Zopiclor	ne					P value
"mod	erately improved"	49.3 ()	45.2	()	()	() NS
		(%) ()				
	nts rated by the investigator as	Zolpidem		Zopiclor	ne					P value
"sligh	itly improved"	26.8 ()	31.1	()	()	() NS
		(%) ()				
	nts rated by the investigator as	Zolpidem		Zopiclor	ne					P value
	nanged"	5.3 ()	6.4	()	()	() NS
		(%) (Γ)			<u> </u>	

Author:	Tsutsui	Trial type:	H2H			Quality	rating: Fair
Year:	2001	Country:	Japan			Fundin	g: Not reporte
Patient's in	npression of treatment efficacy						
	nts rating the treatment as	Zolpidem	Zopiclone				P value
"markedly effective"		18.2 () 16.0 ()	()	() NS
		(%)	<u> </u>)		I	
	rating the treatment as	Zolpidem	Zopiclone				P value
	erately effective"	46.4 () 45.2 ()	()	() NS
		(%))		1	
	nts rating the treatment as	Zolpidem	Zopiclone				P value
"sligh	tly effective"	29.7 () 33.3 ()	()	() NS
		(%))		1	
# Patients	nts rating the treatment as	Zolpidem	Zopiclone				P value
	ective"	5.7 () 5.5 ()	()	() NS
		(%)	,)		1	ı

Trial type: H2H Quality rating: Fair Ancoli-Israel Author:

Year: 1999 Country: US **Funding: Wyeth-Ayerst**

Design:

Study design RCT

DB

Parallel

Setting Multicenter Age: 72

> Range: SD: 5

Gender: 31 (58 %) Female

Ethnicity:

Lost to fu:

Number Screened: 1224

Eligible:

Enrolled:

Number Withdrawn: 2

Analyzed: 549

551

549

Eligibility criteria:

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.

Comments:

Elderly

Intervention:

Withdrawals due to AEs/

Drug name	dos	sage	N=	Duration	Total withdrawal
Placebo		mg	107	14 day	/
Zaleplon	5	mg	166	2 week	/
Zaleplon	10	mg	165	2 week	/
Zolpidem	5	mg	111	2 week	/

Rebound:

rebound

rebound insomnia: sleep latency on discontinuation day 1 (minutes, median)

Zaleplon	5mg		Zaleplon 10mg			Zolp	Zolpidem 5mg			0	P value	
30	(NS)	45	(NS)	60	(<0.01)	44	(NA)	
Number	(pvs	pla	cebo)							

Author: **Ancoli-Israel** Trial type: H2H Quality rating: Fair US **Funding: Wyeth-Ayerst** Year: 1999 Country:

> # rebound insomnia: sleep duration, total sleep time on discontinuation day 1 (minutes, median)

(NS 330) 315 Number (p vs placebo

Zaleplon 5mg Zaleplon 10mg Zolpidem 5mg P value Placebo (<0.05) 300 (<0.00) 317.50 (NA

rebound insomnia: number of awakenings on discontinuation day 1 (median)

Zaleplon 5mg			Zaleplon 10mg			Zolpidem 5mg	Placebo			P value	
2	(NS)	2	(NS))	2 (NS)	2	(NA)	

Number (p vs placebo

Author: Elie Trial type: H2H Quality rating: Fair

Year: 1999 Country: Multinational (Canada and Europe) Funding: Wyeth-Ayerst

Design:

Study design RCT

DB

Parallel

Setting Multicenter

Eligibility 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.

Age: 42.8

Range: NR SD: 12.4 Number Screened: NR Eligible: NR Enrolled: 615

Gender: 39 (64 %) Female

Ethnicity: 99% white Number Withdrawn: 41

41% black
41% Asian
Lost to fu: NR
Analyzed: 574

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 Deepression Scale was >49.

Comments:

Analyzed 574/615 patients randomized. 39 patients excluded from efficacy analysis because of inadequate source documentation. Baseline demographic characteristics given only on 574 patients analyzed, and no statistical analysis of baseline characteristics.

Intervention:

Withdrawals due to AEs/

Drug name	do	sage	N=	Duration	Total withdrawal
Zaleplon	5	mg	113	4 week	/
Zaleplon	10	mg	112	4 week	1
Zaleplon	20	mg	116	4 week	1
Zolpidem	10	mg	0		/
Placebo			118	4 week	1

Rebound:

Rebound insomnia

Rebound: Sleep latency on night +1 (median, minutes)

Zaleplon 5mg			Zaleplon 10mg			Zaleplon 20mg			Zolpide	em 10mg	P value
51.7	(NS)	57.6	(NS)	50.4	(NS)	91.6	(<0.00)	

Author:	Elie	Trial type: H	H2H		Qu	Quality rating: Fair				
Year:	1999	Country: M	Multinational (Car	nada and Europe	e) Fu	Funding: Wyeth-Ayerst				
			Number (p vs pla	acebo)						
	#	Rebound: Sleep duration on night +1	Zaleplon 5mg	Zaleplon 10mg	Zaleplon 20mg	Zolpidem 10mg	P value			
		(median, minutes)	344.3 (NS)	349.6 (NS)	339.2 (NS)	324.7 (<0.05)				
			Number (p vs pla	acebo)	ı	-	1			
	#	Rebound: Number of awakenings on	Zaleplon 5mg	Zolpidem 10mg	P value					
		night +1 (median)	2.3 (NS)	2.0 (NS)	1.8 (NS)	2.6 (<0.01)				
			Number (p vs pla	acebo)	1	+	1			

Author: Fry Trial type: H2H Quality rating: Fair

Year: 2000 Country: US Funding: Wyeth-Ayerst

Design:

Study design RCT

DB

Parallel

Setting Multicenter

Eligibility criteria:

Men or non-pregnant women, 18-65 years who met the criteria for primary insomnia or insomnia associated with mild non-psychotic 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 impariment 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.

Comments:

Patients with mild non-psychotic psychiatric disorders. Baseline characteristics reported only for 586/595 randomized (98%) Data on primary outcome (sleep latency) reported graphically only. **Age:** 42

Range: NR SD: 12

Gender: 35 (59 %) Female

Ethnicity: 11% Black

3% Hispanic <1% Native American 1.5% Asian <1% Other 84% White Enrolled:

Number Screened: NR

Eligible:

Number Withdrawn: 9

Lost to fu: NR Analyzed: 586

830

595

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 patietns 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.

Intervention:

Withdrawals due to AEs/

Drug name	do	sage	N=	Duration Total withdrawal
Zaleplon	5	mg	118	4 week 3 / 20
Zaleplon	10	mg	119	4 week 5 / 18
Zaleplon	20	mg	116	4 week 10 / 17
Zolpidem	10	mg	115	4 week 7 / 20
Placebo		mg	118	4 week 4 / 12

Author: Fry Trial type: H2H Quality rating: Fair

Year: 2000 Country: US Funding: Wyeth-Ayerst

Rebound:

Rebound

rebound : Sleep latency on discontinuation night 1 (minutes, median)

rebound : Number of awakenings on discontinuation night 1

rebound : Sleep duration on discontinuation night 1 (median, minutes)

Zaleplon 5mg			Zaleplon 10mg			Zaleplon 20mg			Zolpic	lem 10mg	P value
45	(NS)	40	(NS)	30	(NS)	60	(<0.01)	

Number (p vs placebo

Zaleplon 5mg			Zaleplon 10mg			Zale	plon 20mg		Zolpiden	P value	
2	(NS)	2	(NS)	2	(NS)	2	(<0.05)	

Number (p vs placebo

Zaleplon 5mg			Zaleplon	10mg	Zaleplon 20mg			Zolpidem	P value	
360	(NS)	360	(NS)	360	(NS)	330	(<0.00)	

Number (p vs placebo)

Author: Tsutsui Trial type: H2H Quality rating: Fair

Year: 2001 Country: Japan Funding: Not reported

Design:

Study design RCT

DB

Parallel

Setting Multicenter

Ra

Age:

Range: 20-64 SD: 12.7

Gender: 27 (58 %) Female

42.2

Ethnicity: NR

Number Withdrawn: 77

Number Screened: NR

Eligible:

Enrolled:

Lost to fu: NR

Analyzed: 428

NR

479

Eligibility criteria:

Patients with chronic primary insomnia (I.e., experincing non-restorative sleep or difficulty for more than a month in initiating or maintaining sleep), experiencing difficulties more than three times a week in sleeping.

Exclusion criteria:

Schizophrenia, depression, manic depression, clinically diagnnosed diseases in the acute or exacerbation phase or with unstable symptoms, organic cerebral disorders (diagnosed or suspected), serious heart, liver, kidney, or blood disorders, severe respiratory dysfunction, myasthenia gravis or acute narrow-angle glaucoma and cognitive disorders or impaired intelligence. Symptoms interfering with sleep (e.g., pain, fever, diarrhea, pollakiuria, cough), hypersensitivity to benzodiazepines and analogous drugs, zopiclone intake within 3 months prior to the study, requirement for hypnotics at a dose exceeding the standard single dose, history of drug dependence, operation of machinery involving risk, pregnancy or likelihood of pregnancy, breastfeeding, participation in other clinical trials within the past 6 months, and inappropriateness for the study according to the investigator's judgment.

Comments:

Baseline demographic data reported only on patients included in efficacy analysis (428/479; 89%).

Additional rebound information: Overall, sleep onset latency, frequency of nocturnal awakenings, sleep duration, daytime mood and daytime physical condition remained significantly improved in both groups relative to baseline (p<0.01, data not reported).

Intervention:

Withdrawals due to AEs/

Drug name	dos	sage	N=	Duration	Total withdrawal
Zolpidem	10	mg	209	2 week	14 / 32
Zopiclone	7.5	mg	219	2 week	20 / 45

Rebound:

Rebound insomnia: sleep latency

rebound: patients with an aggravation of sleep onset latency by one grade or more at the end of followup

	Zolpidem			Zopicle	one						P value
,	4.5	()	15.4	()	()	()	0.005
	0/	- (•		١					

Author: Tsutsui Trial type: H2H Quality rating: Fair

Year: 2001 Country: Japan Funding: Not reported

Author: Allain Trial type: H2H Quality rating: Fair

Year: 2003 Country: France Funding: Sanofi-Synthelabo

Age:

52

SD:

Ethnicity: NR

Exclusion criteria:

Range: NR

Gender: 26 (49 %) Female

7

antihistamines, barbiturates or hypnotics.

Design:

Study design RCT

DB

Crossover

Setting Single Center

Eligibility criteria:

Age between 40 and 65 years; with a clinical examination judged compatible with difficulties falling asleep, with previous history of recurrent episodes of insomnia and justifying the prescription of hypnotic treatment at the time of inclusion.

Comments:

Intervention: Run-in: No

Wash out: No

Allow other medication: NR

Withdrawals due to AEs/

Drug name	dosage	N=	Duration	Total withdrawal	
Zolpidem	10 mg	52	1 day	0 / 0	
Zaleplon	10 mg	0		/	

Adverse Events:

Adverse events reported

Any adverse event

Zolpiden	n	Zaleplon						P value:
5.7	(3/53)	7.5	(4/53)	()	()	NR
%	(number)					

Current episode having lasted more than three weeks; any secondary insomnia

resulting from medicl or psychiatric causes; patients who followed a continuous

treatment with the same same hypnotic for more than six months; patients who took

hypnotic drugs the day before inclusion; patients who took hypnotic drugs the day before inclusion, patients currently treated by zolpidem or zaleplon; night-shift work; current medical treatment including antidepressants, neuroleptics, anxiolytics, H1

Number Screened: NR

Number Withdrawn: 0

Eligible:

Enrolled:

Lost to fu: 0 Analyzed: 53

NR

53

Author: Allain Trial type: H2H Quality rating: Fair

Year: 2003 Country: France Funding: Sanofi-Synthelabo

Total withdrawals: none

Withdrawals due to adverse events: none

Author: Ancoli-Israel Trial type: H2H Quality rating: Fair

Year: 1999 Country: US Funding: Wyeth-Ayerst

Design:

Study design RCT

DB

Parallel

Setting Multicenter

Eligibility criteria:

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.

Comments:

Elderly

Intervention: Ru

Run-in:

Wash out: 7-21

Allow other medication: No

Age: 72

Range: SD: 5 Number Screened: 1224
Eligible: 551
Enrolled: 549

Gender: 31 (58 %) Female

Ethnicity: Number Withdrawn: 2

Lost to fu:

Analyzed: 549

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.

Withdrawals due to AEs/

Drug name	do	sage	N=	Duration	Total withdrawal
Placebo		mg	107	14 day	/
Zaleplon	5	mg	166	2 week	/
Zaleplon	10	mg	165	2 week	/
Zolpidem	5	mg	111	2 week	1

Adverse Events:

Adverse events

Frequency of treatment-emergent adverse events

Place	bo		Zalepl	on 5 mg		Zalepl	on 10 mg		Zolpid	em 5 mg		P value:	
56	()	56	()	59	()	63	()	NS	
%	(١								

Author:Ancoli-IsraelTrial type:H2HQuality rating:FairYear:1999Country:USFunding:Wyeth-Ayerst

CNS adverse events

Placebo	Zaleplon 5 mg	Zaleplon 10 mg	Zolpidem 5 mg	P value:
14 ()	NR ()	NR ()	25 (P<0.0)	

% (p vs placebo

Somnolence

Placebo		Zaleplo	n 5 mg	Zaleplon	10 mg	Zolpidem	5 mg	P value:
2	() 4	() NR	(10	(p<0.0)	

% (p vs placebo

Total withdrawals: NR

Withdrawals due to adverse events: NR

Author: Elie Trial type: H2H Quality rating: Fair

Year: 1999 Country: Multinational (Canada and Europe) Funding: Wyeth-Ayerst

Design:

Study design RCT

DB

Parallel

Setting Multicenter

Eligibility 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.

Age: 42.8

Range: NR SD: 12.4

Gender: 39 (64 %) Female

Ethnicity: 99% white

<1% black <1% Asian Number Withdrawn: 41

Number Screened: NR

Eligible:

Enrolled:

NR

615

Lost to fu: NR Analyzed: 574

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 Deepression Scale was >49.

Comments:

Analyzed 574/615 patients randomized. 39 patients excluded from efficacy analysis because of inadequate source documentation. Baseline demographic characteristics given only on 574 patients analyzed, and no statistical analysis of baseline characteristics.

Intervention:

Run-in: Yes

Wash out: Yes

Allow other medication: NR

Drug name	do	sage	N=	Duration	Withdrawals due to AEs/ Total withdrawal
Zaleplon	5	mg	113	4 week	/
Zaleplon	10	mg	112	4 week	/
Zaleplon	20	mg	116	4 week	/
Zolpidem	10	mg	0		/
Placebo			118	4 week	/

Author: Elie Trial type: H2H Quality rating: Fair

Year: 1999 Country: Multinational (Canada and Europe) Funding: Wyeth-Ayerst

Adverse Events:

Withdrawal effects

Incidence of 3 or more new withdrawal symptoms after discontinuation of treatment

Zolpidem 10 mg	Zaleplon 10 mg			P value:
NR (<0.05)	NR (NS)	()	()	

NR (p vs placebo

Adverse events

Patients with treatment-emergent adverse events

Zaleplo	Zaleplon 5 mg		Zaleplon 10 mg		Zalepl	on 20 mg	Zolpid	em 10 mg	P value:	
59	(71)	73	(87) 61	(76) 64	(78)	

% (N)

Total withdrawals NR

Withdrawals due to adverse events

Withdrawals due to adverse events

Zaleplon 5 mg		Zaleplon 10 mg			Zaleplon 20 mg			Zolpidem 10 mg			P value:		
	2	(2)	6	(7)	2	(2)	6	(7)	
	%	(N)							·

Author: Erman Trial type: H2H Quality rating: Poor

Year: NR Country: US Funding:

Design:

Age: Study design

Range: Number Screened:
SD: Eligible:
Enrolled:

Setting Gender: 0 (0 %) Female

Ethnicity: Number Withdrawn:

Lost to fu:

Analyzed:

Eligibility criteria: Exclusion criteria:

Comments:

Poor quality: Information provided in the poster is insufficient to assess quality.

Intervention: Run-in:

Wash out :

Allow other medication:

Adverse Events:

Author: Fry Trial type: H2H Quality rating: Fair

Year: 2000 Country: US Funding: Wyeth-Ayerst

Design:

Study design RCT

DB

Parallel

Setting Multicenter

Eligibility criteria:

Men or non-pregnant women, 18-65 years who met the criteria for primary insomnia or insomnia associated with mild non-psychotic 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 impariment 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.

Comments:

Patients with mild non-psychotic psychiatric disorders. Baseline characteristics reported only for 586/595 randomized (98%) Data on primary outcome (sleep latency) reported graphically only.

Intervention: Run-in:

Wash out: no

Allow other medication: NR

Age: 42

Range: NR SD: 12

Gender: 35 (59 %) Female

Ethnicity: 11% Black

3% Hispanic <1% Native American 1.5% Asian <1% Other 84% White Number Screened: NR

Eligible: 830

Enrolled: 595

Number Withdrawn: 9

Lost to fu: NR Analyzed: 586

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 patietns 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.

Withdrawals due to AEs/

Drug name	do	sage	N=	Duration	Total withdrawal
Zaleplon	5	mg	118	4 week	3 / 20
Zaleplon	10	mg	119	4 week	5 / 18

Author:	Fry	Trial type: H2H		Quality rating: Fair
Year:	2000	Country: US		Funding: Wyeth-Ayerst
	Zaleplon	20 mg 116	4 week 10 / 17	
	Zolpidem	10 mg 115	4 week 7 / 20	
	Placebo	mg 118	4 week 4 / 12	

Adverse Events:

Tolerance: Sleep latency

Tolerance: Number of awakenings

Tolerance: Total sleep time

Total withdrawals

Total withdrawals

Zaleplo	on 5 mg		Zaleplo	on 10 mg		Zalepl	on 20 mg		Zolpide	m 10 m	ng	P value:
16.9	()	15.0	()	14.5	()	17.2	()	NR
%	()							

Withdrawals due to adverse effects

Withdrawals due to adverse effects

Zalep	olon		Zalep	lon		Zalep	lon		Zolpic	lem		P value:
3	()	4	()	9	()	6	()	NR
%	1				١							

Author:LemoineTrial type:H2HQuality rating:FairYear:1995Country:FranceFunding:Not reported

Design:

Study design RCT

DB

Parallel

Setting Multicenter

Age:

Range: SD:

(%) Female

Ethnicity:

Gender:

Number Withdrawn: 15

Number Screened: NR

Eligible:

Enrolled:

Lost to fu: 2 Analyzed: 390

NR

394

Eligibility criteria:

Males and females aged 18 to 65 years who were treated for insomnia for at least 3 months with zopiclone 7.5 mg or zolpidem 10 mg.

Exclusion criteria:

History of depression or other psychiatric disorder, a current depressive episode (total score on the QD2A questionnaire >=7) or any other current psychiatric disorder, severe and evolving physical illness, dementia, alcoholism, drug abuse, or acute pain. Patients were also excluded if they had been taking any psychotropic drug (with the exception of zopiclone or zolpidem) within the previous two weeks. Women were excluded if pregnant or were likely to be or were breast-feeding.

Comments:

Study of withdrawal effects- separate studies of zopiclone and zolpidem; efficacy not assessed. Comparisons were treatment vs withdrawal within drug groups.

Intervention:

Run-in: 0

Wash out: 0

Allow other medication:

Withdrawals due to AEs/

Drug name	dosage	N=	Duration	Total withdrawal	
	mg	100		/	

Adverse Events:

Quality rating: Fair Author: Tsutsui Trial type: H2H

2001 Country: **Funding: Not reported** Year: Japan

Design:

Study design RCT

DB

Parallel

Setting Multicenter Age: 42.2

Range: 20-64

12.7

Gender: 27 (58 %) Female

SD:

Ethnicity: NR

Number Withdrawn: 77

Number Screened: NR

Eligible:

Enrolled:

Lost to fu: NR Analyzed: 428

NR

479

Eligibility criteria:

Patients with chronic primary insomnia (I.e., experincing non-restorative sleep or difficulty for more than a month in initiating or maintaining sleep), experiencing difficulties more than three times a week in sleeping.

Exclusion criteria:

Schizophrenia, depression, manic depression, clinically diagnnosed diseases in the acute or exacerbation phase or with unstable symptoms, organic cerebral disorders (diagnosed or suspected), serious heart, liver, kidney, or blood disorders, severe respiratory dysfunction, myasthenia gravis or acute narrow-angle glaucoma and cognitive disorders or impaired intelligence. Symptoms interfering with sleep (e.g., pain, fever, diarrhea, pollakiuria, cough), hypersensitivity to benzodiazepines and analogous drugs, zopiclone intake within 3 months prior to the study, requirement for hypnotics at a dose exceeding the standard single dose, history of drug dependence, operation of machinery involving risk, pregnancy or likelihood of pregnancy, breastfeeding, participation in other clinical trials within the past 6 months, and inappropriateness for the study according to the investigator's judgment.

Comments:

Baseline demographic data reported only on patients included in efficacy analysis (428/479; 89%).

Additional rebound information: Overall, sleep onset latency, frequency of nocturnal awakenings, sleep duration, daytime mood and daytime physical condition remained significantly improved in both groups relative to baseline (p<0.01, data not reported).

Intervention:

Run-in: 7

Wash out :

Allow other medication: No

Withdrawals due to AEs/

Drug name	dosage	N=	Duration	Total withdrawal
Zolpidem	10 mg	209	2 week	14 / 32
Zopiclone	7.5 mg	219	2 week	20 / 45

Adverse Events:

Total withdrawals

ш		1	I .	1
#	Zolnidem	Zoniclone		D value:

Author:TsutsuiTrial type:H2HQuality rating:FairYear:2001Country:JapanFunding:Not reported

Total withdrawals

Loipiac			Lopion	,, io						ı value.
13.9	()	18.1	()	()	()	NS
%	(1					

Withdrawals due to adverse evects

Withdrawals due to adverse evects

Zolpic	lem		Zopicle	one						P value:
6.1	()	8.1	()	()	()	NR
%	()					

Adverse events

Patients experiencing adverse events "related", "possibly related" or "probably related" to study medication

Zolpic	dem		Zopicl	one						P value:
31	()	45	()	()	()	0.004
0/_	1				١					

Author: Anderson Trial type: Active Quality rating: Fair

Year: 1987 Country: UK Funding: Not reported

Design:

Study design RCT

DB

Parallel

Setting Multicenter

Eligibility criteria:

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

Comments:

Intervention: Run-in: 7

Wash out: 7

Allow other medication: No

Age: NR

Range: 20-69

SD:

Gender: NR (0 %) Female

Ethnicity: NR

Number Withdrawn: 5 Lost to fu: 15

Analyzed: 99

Number Screened: NR

Eligible:

Enrolled:

NR

119

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 ti drugs or continuous use of high doses of a hypnotic for a period in excess of 6 months. Other groups exluded were pregnant women, nursing mothers, women of childbearing potential, and night shift workers.

Drug name	dosage	N=	Duration	Total withdrawal	
Zopiclone	7.5 mg		14 day	1 / 2	
Nitrazepam	5 mg		14 day	1 / 1	
Placebo	NA mg		14 day	1 / 2	

Author:	Anderson	Trial type:	Activ	⁄e				Quality r	rating: I	Fair
Year:	1987	Country:	UK					Funding	: Not rep	orted
Outcome	Measurement:				Efficac	y Outcome L	.ist:			
# Diary # 100-n	nm visual analogue scales				Primary outcome					
# sleep	questionnaire					The time they Sleep duratio No. of times w Wake up earl Sleep latency How much th Slept well - sl Feeling wide	n woke- ier th , ey dr eep (-up en wished eamed quality		
Results	sual analogue scales									
	quality at week 3 (in figure),	Zopiclone		Nitraze	epam	Placebo			P value	e
highe	r score=better		<0.05) 66	(< 0.05)	49 (NA)	()	
		Score	p vs plad	ebo)		ļ			
	to fall asleep at week 3 (in	Zopiclone		Nitraze	epam	Placebo			P value	Э
tigure	e), higher score=better	61	<0.05	63	(<0.05)	44 (NA)	()	
		Score	p vs plad	ebo)				1	
# all sle	eep parameters	Zopiclone		Nitraze	epam				P value	Э
		NR () NR	()	()	() NS	
		Score	,)		,		<u>'</u>	

Author:	Anderson	Trial type	e: Act	ive						Quality	rati	ng: Fair
Year:	1987	Country:	UK							Funding	g: N	lot reporte
sleep ques	tionnaire											
	morning awakenings at week 3	Zopiclone		Nitraze	epam		Placebo					P value
(in figu	ure), higher score=worse	0.38	(< 0.05) 0.35	(<0.05)	0.78	(NA)	()	
		proportion	(p vs pla	acebo)						
# physic	cians global assessment	Zopiclone		Nitraze	epam							P value
		NR	() NR	()		()	()	NS
		Score	()						
# wide-a	awake in the morning	Zopiclone		Nitraze	epam							P value
		better	() -	()		()	()	0.02
		Score	()			,			

Author: Autret Trial type: Active Quality rating: Poor

Year: 1987 Country: France Funding:

Design:

Study design CT

DB

Crossover

Setting Single Center

Age: 46.3

Range:

SD: 11.7

 $\textbf{Gender:} \quad \textbf{85} \quad (\quad \textbf{70} \quad \% \) \ \textbf{Female}$

Ethnicity: NR

Number Withdrawn: NR Lost to fu: 8

Number Screened: NR

Eligible:

Enrolled:

Analyzed: 113

NR

121

Eligibility criteria:

Patients had suffered for more than 3 months from at least two of the following symptoms: subjective period of falling asleep greater than 2 hours; waking up more than twice at night; subjective length of night wakefulness greater than 30 minutes; waking more than 2 hours before the desired time; estimated total sleep time less than 6 hours.

Exclusion criteria:

NR

Comments:

Poor quality: No baseline characteristics reported, not reported if randomized, and unable to determine the number analyzed.

Intervention:

Run-in: 4 Wash out: 3

Allow other medication: NR

Drug name	dosage	N=	Duration	Total withdrawal
Zopiclone	7.5 mg	121	7 day	0 / 8
Triazolam	0.5 mg	121	7 day	0 / 8

Author:	Autret	Trial type:	Ac	tive					Quality	y rati	ing: Poor	
Year:	1987	Country:	Fra	nce					Fundir	ng:		
Outcome	Measurement:				Effic	асу	Outcome Li	st:				
	el and Norris' visual analogue sca by physicians	ale			Prim	nary ome	Outcome: Sleep latency Sleep quality Sleep duration Night waking Dreams Morning state Global evaluat severity of inso	ion omnia				
Results						_	intensity of sid	e-effects				
Spiegel an	d Norris' visual analogue scale											
# Delay	in falling asleep (higher	Zopiclone		Triazol	am						P value	
score	=better)- change from baseline	1.86	(1.35) 1.43	(1.12)	()	()	<0.01	
		Score	(SD)		I				
# qualit	y of sleep (higher score=better)-	Zopiclone		Triazol	am						P value	
chanç	ge from baseline	1.98	(1.25) 1.47	(1.06)	()	()	<0.01	
		Score	(SD)		l .				
# length	n of sleep (higher score=better)-	Zopiclone		Triazol	am						P value	
chanç	ge from baseline	1.47	(1.26) 1.26	(0.97)	()	()	NS	
		Score	(SD	ļ.)		ı			.I I	
# night	waking (higher score=better)-	Zopiclone		Triazol	am						P value	
chanç	ge from baseline	1.64	(1.38) 1.34	(1.11)	()	()	<0.05	
		C	/ CD	ı								

Author: Autret	Trial typ	e: Ac	tive					Quality ra	ating: Poor
Year: 1987	Country	Fra	nce					Funding:	
# dream (higher score=better)- chang	Zopiclone)	Triazol	am					P value
from baseline	0.40	(1.44) 0.32	(1.10)	()	() NS
	Score	(SD	<u> </u>)				
# morning state (higher score=better)	Zopiclone	:	Triazol	am					P value
change from baseline	1.66	(1.46) 1.13	(1.04)	()	() <0.001
	Score	(SD)				
# global evaluation (higher	Zopiclone	;	Triazol	am					P value
score=better)- change from baseline	1.96	(1.40) 1.43	(1.04)	()	() <0.001
	Score	(SD	·)				
rated by physicians									
# therapeutic efficacy- preferences of	Zopiclone)	Temaz	epam					P value
the patients	62	(54.9) 26	(23)	()	() <0.01
	Number	(%	·)				1

Quality rating: Poor Author: Begg Trial type: Active

Year: 1992 Country: NR Funding: Roche Products (NZ) Ltd.

Design:

Study design RCT

SB

Parallel

Setting

Single Center

NR Age:

> Range: >18 SD:

Gender: NR (0 %) Female

Ethnicity: NR

Lost to fu: 33 Analyzed: 51

Number Screened: NR

Eligible:

Enrolled:

Number Withdrawn: 4

NR

88

Eligibility criteria:

Patients were aged 18 years or older and satisfied on or more of the following criteria: a history of taking 30 minutes or more to fall asleep; two or more awakenings during the night; total reported sleep time of less than six hours.

Exclusion criteria:

Patients on medications known to affect sleep or on drugs known to alter drug metabolism during and within two weeks prior to the study were excluded. Alcohol infestion within four hours of retiring or more tna one glass (10 g) alcohol in the previous 24 hours were not permitted.

Comments:

Poor quality: very high withdrawal rate (42%) and no intention-to-treat analysis. No information on baseline characteristics.

Intervention:

Run-in: 2 Wash out: 2

Allow other medication: NR

			1711.1a. a. v. a. c. a.	
Drug name	dosage	N=	Duration Total withdrawal	
Zopiclone	7.5 mg	28	11 day 1 /	
Midazolam	15 mg	23	11 day 3 /	

Author: Begg		Trial type	e: Ac	tive					Quality ra	ating: Poor
Year: 1992		Country:	NR						Funding:	Roche Products (NZ) Ltd.
Outcome Measure	ement:				E	fficacy O	utcome	List:		
# Leeds sleep eva	aluation questionnaire	(LSEQ)								
Results										
LSEQ - pre vs. during	g intervention									
# all 10 items (low	=beneficial effect)	Zopiclone								P value
		Low	()	()	()	() p<0.01
		Score	(<u> </u>)				
# 6 of the 10 items		Midazolar	n							P value
and quality of slo	eep	Low	()	()	()	() p<0.01
		Score	()		\ 		
# all 10 items		Zopiclone		Midazo	olam					P value
		NR	() NR	()	()	() NS
		Score	()				
LSEQ - pre vs. two n	ights after medication	was discontin	ued (reb	ound)						
# 5 of 10 items		Zopiclone								P value
		High	()	()	()	() <0.01
		Score	()		,		
# all 10 items		Midazolar	n							P value
		NR	()	()	()	() NS
		Score	(·)		,		
# all 10 items		Zopiclone		Midazo	olam					P value
		NR	() NR	()	()	() NS
		Score	()				

Quality rating: Fair Author: Chaudoir Trial type: Active

Year: 1990 Country: UK **Funding: Not reported**

Design:

Study design RCT

DB

Parallel

Setting Multicenter

Eligibility criteria:

History of insomnia with at least one of the following symptoms present: time taken to fall asleep longer than 30 minutes, more than two nocturnal awakenings with difficulty in returning to sleep, without known cause, sleep duration of less than 6 hours.

Comments:

Intervention: Run-in: no

7 Wash out :

No medication known to cause drowsiness Allow other medication :

Withdrawals due to AEs/ Total withdrawal Drug name dosage N= Duration Zopiclone 7.5 mg 19 1 week 0 / 1 1 / 3 Triazolam 0.25 mg 19 1 week

50.9 Age:

Range: 30-65

SD:

Gender: 27 (71 %) Female

Ethnicity: 100% caucasian

Number Withdrawn: 4

Lost to fu: NR Analyzed: 38

NR

NR

38

Number Screened:

Eligible:

Enrolled:

Exclusion criteria:

Any serious concomitant disease, psychosis, hypersensitivity, drug addiction, or alxohol consumption that might interfere with assessment; women who were pregnant, nursing, or of child-bearing age intending to become pregnant. No patient was included if taking concomitant medication known to induce drowsiness.

Author:	Chaudoir	Trial type	e: Ac	tive			Quality	rating: Fair	
Year:	1990	Country:	UK				Funding	g: Not reported	
	Measurement:				-	Outcome List	:		
# LSEC					Primary outcome	Outcome:			
# Patie	nt diary					LSEQ: Ease of g	atting to aloop		
						LSEQ: Quality of	-		
						LSEQ: Ease of a			
						LSEQ: Behavior	following wakefulne	ess	
						Global assessme	ent of efficacy		
Results									
	se of getting to sleep								
	score at week 1	Zopiclone		Triazolam				- I	
# IVIEdi	i score at week i	57.91	1) 65.18	/)		(P value) NS (NR)	
) 03.10	()	()	() 143 (1411)	
1.050.0	-Period alarm	Score	()				
LSEQ: Qu	ality of sleep	ı						1	
# Mean	score at week 1	Zopiclone		Triazolam	ı			P value	
		67.13	() 72.13	()	()	() NS (NR)	
		Score	()				
LSEQ Eas	e of awakening								
# Mean	score at week 1	Zopiclone		Triazolam	า			P value	
		68.79	() 53.03	()	()	() NS (NR)	
		Score	()				
LSEQ Beh	avior following wakefulness	200.0	`		,				
	score at week 1	Zopiclone		Triazolam	,		I	T _B	
# iviear	i Score at week 1	58.35) 54.49	/ \	()	1	P value) NS (NR)	
			() 34.49	()	()	() NO (NK)	
		Score	()				

Author:	Chaudoir	Trial type: Acti	ve				Quality	rating: Fair
Year:	1990	Country: UK					Funding	g: Not reporte
Global ass	essment of efficacy							
•	cians' global assessment of	Zopiclone	Triazolam					P value
effica	су	NR, high () NR, high ()	()	() NS
		Score (·)				
# Patie	nts' global assessment of efficacy	Zopiclone	Triazolam					P value
		NR, high () NR, high ()	()	() NS
		Score /		1				

Quality rating: Fair Author: Drake (1) Trial type: Active

2000 Country: US Funding: Wyeth-Ayerst Research Year:

Design:

Study design RCT

DB

Crossover

Setting Multicenter

Eligibility criteria:

Age 21-60, wih 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.

Comments:

Intervention: NR Run-in:

Wash out : 5-12

Allow other medication :

Age: 41.6

Number Screened: NR Range: 21-60 Eligible: SD: 9.5 Enrolled:

Gender: 24 (51 %) Female

Number Withdrawn: 0 Ethnicity: NR Lost to fu: 0

Analyzed: 47

NR

47

Exclusion criteria:

Individuals with medical or psychiatric diagnoses (including any history of alcholism 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.

dosage	N=	Duration	Total withdrawal
10 mg	47	2 day	0 / NR
40 mg	47	2 day	0 / NR
0.25 mg	47	2 day	0 / NR
NA mg	47	2 day	0 / NR
	10 mg 40 mg 0.25 mg	10 mg 47 40 mg 47 0.25 mg 47	10 mg 47 2 day 40 mg 47 2 day 0.25 mg 47 2 day

Author:	Drake (1)	Trial type:	Active			Quality ra	ating: Fa	ir
Year:	2000	Country:	US			Funding:	Wyeth-A	yerst Research
Outcome	Measurement:			Efficacy	/ Outcome List:			
	omnography nt reports			Primary outcome	Outcome:			
					latency to persistent s total sleep time sleep quality ease of falling asleep	leep		
Results								
polysomno	<u>ography</u>							
# latend	cy to persistent sleep	Zaleplon 10	ng Zaler	olon 40mg	Triazolam 0.25mg		P value	
		22.5 (NS) 18.6	(<0.05)	27.5 (NA)	()	
		minutes (p vs triazolam)				
# total s	sleep time	Zaleplon 10	mg Zaler	olon 40mg	Triazolam 0.25mg		P value	
		386.3 (<0.05) 392.6	6 (<0.05)	407.8 (NA)	()	
		minutes (p vs triazolam)				

Quality rating: Fair Author: Drake (1) Trial type: Active

Υe erst Research

Year:	2000	Country:	US					Funding:	Wyeth-Aye
patient re	ports								
# late	ncy to sleep	Zaleplon 10mg	g	Zaleplo	n 40mg		Triazolam 0.25mg		P value
		38.8 (N	IS)	29.3	(NS)	36.4 (NA)	()
		minutes (p	vs triazo	olam)	1		
# total	sleep time	Zaleplon 10mg	g	Zaleplo	n 40mg		Triazolam 0.25mg		P value
		358.1 (N	IS)	375.5	(NS)	386.8 (NA)	()
		minutes (p	vs triazo	olam)	1		
# slee	p quality	Zaleplon 10mg	9	Zaleplo	n 40mg		Triazolam 0.25mg		P value
		2.5 (N	IS)	2.7	(NS)	2.7 (NA)	()
		Score (p	vs triazo	lam)	1		
# ease	e of falling asleep	Zaleplon 10mg	g	Zaleplo	n 40mg		Triazolam 0.25mg		P value
		65.4 (N	IS)	74.1	(NS)	67.3 (NA)	()
		Score (p	vs triazo	olam)			, ,

Author: Drake (2) Trial type: Active Quality rating: Fair

Year: 2000 Country: US Funding: Wyeth-Ayerst Research

Design:

Study design RCT

DB

Crossover

Setting Multicenter

Eligibility criteria:

Age 21-60, wih 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.

Comments:

Intervention: Run-in: NR

Wash out: 5-12

Allow other medication: No

Age: 38.1

Range: 21-60 SD: 11.1 Number Screened: NR Eligible: NR Enrolled: 36

Gender: 14 (39 %) Female

Ethnicity: NR Number Withdrawn: 0
Lost to fu: 0

Analyzed: 36

Exclusion criteria:

Individuals with medical or psychiatric diagnoses (including any history of alcholism 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.

Drug name	dosage	N=	Duration	Total withdrawal
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	1

Author:	Drake (2)	Trial type:	Active			Quality ra	ating: Fa	ir
Year:	2000	Country:	US			Funding:	Wyeth-Ay	yerst Research
Outcome	Measurement:			Efficacy	/ Outcome List:			
	omnography nt reports			Primary outcome	Outcome:			
					latency to persistent s total sleep time sleep quality ease of falling asleep	leep		
Results								
polysomno	<u>ography</u>							
# lateno	cy to persistent sleep	Zaleplon 20	ng Zale _l	olon 60mg	Triazolam 0.25mg		P value	
		30.5	NS) 21.7	(<0.05)	27.6 (NA)	()	
		minutes (p vs triasolam)				
# total s	sleep time	Zaleplon 20	ng Zale _l	olon 60mg	Triazolam 0.25mg		P value	
			<0.05) 404.	7 (<0.05)	422.8 (NA)	()	
		minutes (p vs triasolam)				

Author: Drake (2) Trial type: Active Quality rating: Fair

Year: 20	00	Country	US				Funding:	Wyeth-Ayerst Research
patient reports								
# latency to sl	еер	Zaleplon	20mg	Zaleplon 60mg		Triazolam 0.25mg		P value
		45.5	(NS)	36.6 (NS)	41.9 (NA)	()
		minutes	(p vs triaz	olam)			
# total sleep time		Zaleplon	20mg	Zaleplon 60mg		Triazolam 0.25mg		P value
•	356	(<0.05)	376.3 (NS)	393.5 (NA)	()	
		minutes	(p vs triaz	olam)			
# sleep quality	y (higher score=better)	Zaleplon	20mg	Zaleplon 60mg		Triazolam 0.25mg		P value
		2.3	(<0.05)	2.4 (NS)	2.7 (NA)	()
		Score	(p vs triaz	olam)			
	ng asleep (lower	Zaleplon	20mg	Zaleplon 60mg		Triazolam 0.25mg		P value
score=bette	e=better)	58.8	(NS)	64.5 (NS)	61 (NA)	()
		Score	(p vs triaz	olam)	'		I I

Author: Elie Trial type: Active Quality rating: Fair

Year: 1990b Country: Canada Funding: Not reported

Design:

Study design RCT

DB

Parallel

Setting Single Center

Eligibility 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 askeep, (2) total sleep time less than 6 hours, (3) more than two nocturnal awakenings and (4) poor quality of sleep,

Comments:

Intervention: Run-in: 7

Wash out: 3

Allow other medication: NR

Age: 37.6

Range: SD: 1.84

Gender: 24 (67 %) Female

Ethnicity: NR

Lost to fu: 0 Analyzed: 36

Number Screened: NR

Number Withdrawn: 0

Eligible:

Enrolled:

NR

36

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.

Drug name	dosage	N=	Duration	Total withdrawal	
Zopiclone	7.5 mg	12	28 day	0 / 0	
Flurazepam	30 mg	12	28 day	0 / 0	
Placebo	NA mg	12	28 day	0 / 0	

Author:	Elie	Trial type	: Active)						Quality	rating	: Fair
Year:	1990b	Country:	Canad	a						Funding	g: Not	reported
Outcome N	Measurement:				Effic	асу	Outco	ome L	ist:			
# post-sl	leep questionnaire				Prima outco	•	Outco					
							duratio	y of sleon on of sleon on al awa	еер			
Results												
post-sleep of	<u>quesionnaire</u>											
# rapidity	of sleep onset at week 4	Zopiclone		Fluraz	epam	F	Placebo				Р	value
# rapidity of sleep onset at week 4 (higher score=better)	11.6	(NS)	11.2	(NS) 1	0.5	(NA)	()		
		Score	(p vs place	ebo)			·			
	on of sleep at week 4 (higher	Zopiclone		Fluraz	epam	F	Placebo				Р	value
score=	ebetter)	7.3	(NS)	7.1	(NS) 6	5.5	(NA)	()	
		Score	(p ve place	ebo)			,		ļ	J.
	nal awakenings at week 4	Zopiclone		Fluraz	epam	F	Placebo				Р	value
(highe	r score=worse)	3.5	(<0.01)	3.5	(<0.01) 5	5.5	(NA)	()	
		Score	(p vs place	ebo)			1			

Author: Fleming Trial type: Active Quality rating: Fair

Year: 1995 Country: Canada Funding: Not reported

Design:

Study design RCT

DB

Parallel

Setting Multicenter

Eligibility 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.

Comments:

Intervention: Run-in:

Wash out: NR

Allow other medication: NR

Age: NR

Range: 33-37

SD:

Gender: 69 (48 %) Female

Ethnicity: NR

Number Withdrawn: 7

Lost to fu: 1

Number Screened:

Eligible:

Enrolled:

Analyzed: 141

222

144

144

Exclusion criteria:

Withdrawals due to AEs/

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 medicaiton that would interfere with the assessment, absorbtion 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.

N= Duration **Total withdrawal** Drug name dosage Zolpidem 10 mg 35 3 day 0 / 0 Zolpidem 35 3 day 6 / 7 20 mg 0 / 1 Flurazepam 30 mg 36 3 day Placebo 35 3 day 0 / 0 NA mg

Author:	Fleming	Trial typ	e: Acti	ive					Quality ra	ating: Fair	•	
Year:	1995	Country	: Can	ada					Funding: Not reported			
Outcome	Measurement:				Effica	су О	utcome L	ist:				
# quest	tionnaire				Primar							
# polys	omnography				outcon	ne C	Outcome:					
							leep latency					
							vake time					
							sleep quality sleep efficiend	٠\/				
						3	sieep emolenc	<i>,</i> y				
Results												
polysomno	<u>ography</u>											
# sleep	latency	Zolpidem	Zolpidem 10mg Zolpidem 20mg		m 20mg	Flui	razepam			P value		
		-14.7	(<0.05) -28.4	(<0.05)	-11)	()	_	
		minutes	(n vs flu	ırazepam	١							
# sleen	efficiency	Zolpidem			m 20mg	Flu	razepam	I		P value	7	
# Зісер	Cincicney	NR	(NS) NR	(NS)	NR		`) P value	_	
			•	<i>'</i>	(110)	1	(140	,	('		
		minutes	(p vs pla)	1		10			7	
# wake	time during sleep	Zolpidem			m 20mg		razepam			P value	_	
		NR	(NS) NR	(NS)	NR	(NS)	()		
		minutes	(p vs pla	acebo)						_	
questionna	<u>aire</u>											
# sleep	quality at day 3, (higher	Zolpidem	10mg	Zolpide	m 20mg	Flui	razepam			P value		
	=better)	2.4	(<0.05) 2.5	(<0.05)	1.9	(NA)	() <0.05		
			`	′	, /		(" "	,	`	,	_	
		Score	(p vs flu	ırazepam)							

Author: Fleming_ Trial type: Active Quality rating: Fair

Year: 1990 Country: Canada Funding: Not reported

Design:

Study design RCT

DB

Parallel

Setting Multicenter

r

Age: 45.5

Range: SD:

Gender: NR (%) Female

Ethnicity: NR

Number Withdrawn: 4

Number Screened: NR

Eligible:

Enrolled:

Lost to fu: 0 Analyzed: 48

NR

52

Eligibility 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, analgesis, or antidepressants or with a history of hypersensitivity to one or more hypnotic drugs were excluded. Subjects whose insomnnia was considered secondary to a psychiatric or medical disorder were also excluded as those with a history of alcoholism, drug abuse, or caffeine overuse.

Comments:

Enrolled population characteristics were not reported. Analyzed population characteristics: mean age=45.5 years; 23 (48%) female.

Intervention: Run-in:

Wash out: 4

Allow other medication: No

3

Drug name	dosage	N=	Duration	Total withdrawal
Zopiclone	7.5 mg	24	21 day	2 / 2 10 / 10
Triazolam	0.25 mg	24	21 day	10 / 10

Author: Year:	Fleming_ 1990	Trial type: Country:	Active Canada		Quality rating: Fair Funding: Not reported
i c ai.	1990	Country.	Carraua		Fullding. Not reported
Outcome	Measurement:			Efficacy	Outcome List:
•	sleep questionnaire Iton Anxiety Scale			Primary outcome	Outcome:
					speed and quality of sleep onset duration of sleep perceived quality of sleep no. of awakenings dreaming ease of awakening the time taken to full alertness daytime alertness
Results					
Hamilton A	nxiety Scale				
# total s	score	Zopiclone NR (Triazolar) NR	m ()	() P value NS
		Score ()	

Author: Hajak Trial type: Active Quality rating: Fair

Year: 1998, 1995, 1994 Country: Germany Funding: Not reported

Design:

Study design RCT

DB

Parallel

Setting Multicenter

Eligibility criteria:

Insomnia of at least 4-week duration and the presence of at least two of the following as a mean of 3 days before starting treatment (no-pill baseline): (a) sleep latency >= 45 min, (b) total sleep time <= 6 hours, and © nocturnal awakening >= 3 times.

Age: 51

Range: 18-71 SD: 11

Gender: 940 (62 %) Female

Ethnicity: 99.3% Caucasian 0.9% Others

Lost to fu: 0 Analyzed: 1507

NR

1507

Number Screened: NR

Eligible:

Enrolled:

Number Withdrawn: 0

Exclusion criteria:

Any patients who had taken a single daily dose of a benzodiazepine or any other hypnotic more than three times per week during the 14 days prior to admission, or any patients with psychiatric disorders (e.g., depression, schizophrenia, severe neuroses), or any patients who had contraindications for zopiclone, flunitrazepam, or triazolam were excluded from this study

Comments:

Patients were observed for a further period of 14 days without medication for rebound.

Intervention: Ru

Run-in :

Wash out: 3

Allow other medication: NF

				Withdrawals due to AEs/
Drug name	dosage	N=	Duration	Total withdrawal
Zopiclone	7.5 mg	612	28 day	26 / 190
Triazolam	0.2 mg	307	28 day	11 / 187
Placebo	NA mg	298	28 day	25 / 193

Quality rating: Fair Author: Hajak Trial type: Active

Funding: Not reported Year: 1998, 1995, 1994 Country: Germany

Outcome Measurement:

Visual Analogue Scale for evening (VIS-A)

Visual Analogue Scale for morning (VIS-M)

Efficacy Outcome List:

Primary outcome

Outcome:

~ daytime anxiety **~** total sleep time

~ number of nocturnal awakenings

~ a feeling of being refreshed on awakening i

~ daytime tiredness daytime anxiety

Results

Total response

Improved sleep quality and daytime well-being

well-being- treatment period

# Improved sleep quality and daytime	
well-being- treatment period	

Zopiclone Triazolam 37.4 (<=0.00) 32.2

(NS

Placebo 26.8

(NA)

P value

% (p vs placebo

Zopiclone Triazolam P value 42.3) 36.3) 0.1133

Author: Hayoun Trial type: Active Quality rating: Fair

Year: 1989 Country: France Funding: Not reported (corresponding

Design:

Study design RCT

DB

Parallel

Setting Single Center

Eligibility 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).

Age: 47.9

Range: 18-65

SD:

Gender: 90 (66 %) Female

Ethnicity: NR

Number Withdrawn: 9 Lost to fu: 0

Number Screened:

Eligible:

Enrolled:

Analyzed: 127

NR

NR

136

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; patiens 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.

Comments:

Sleep aid, drug abuse???

More patients on zopiclone had insomnia as a major complaint compared with those on triazolam (70%) vs 55%, respectively; p=0.04). More patients described themselves as tranquil compared with patients on zopiclone.

Intervention:

Run-in: NR

Wash out: NR

Allow other medication :

Drug name	dosage	N=	Duration	Total withdrawal	
Zopiclone	7.5 mg	67	7 day	0 / 0	
Triazolam	0.25 mg	69	7 day	0 / 0	

Author:	Hayoun	Trial type:	Active			Quality rat	ing: Fair
Year:	1989	Country:	France			Funding: I	Not reported (corresponding
Outcome	Measurement:			Efficacy	Outcome List:		
# global	s visual analogue auto-evaluatior I physician's evaluation scale valuation questionnaire	scale		Primary outcome	Outcome: sleep latency sleep duration no. of awakenings sleep soundness awakening without co	ncentration difficul	tie
Results Norris visus	al analogue auto-evaluation scal	<u>e</u>					
# overa	П	Zopiclone NR (Score (Triazolam) NR	()	()	()	P value NS
global phys	sicians' evaluation scale	(,			
# Effica	cy- good or excellent	Zopiclone 73 (% (Triazolam) 69	()	()	()	P value NS

Author:HayounTrial type:ActiveQuality rating:FairYear:1989Country:FranceFunding:Not reported (corresponding)

Year:	1989	Country:	France	9					Funding:	Not reporte
self-e	valuation questionnaire									
# f	alling asleep in less than 30 minutes	Zopiclone		Triazola	am					P value
		63	()	84	()	()	() NS
		%	()				
# 8	sleep more than 7 hours	Zopiclone		Triazola	am					P value
		50	()	69	()	()	() NS
		%	()				
# awakeni	awakening at night once or not at all	Zopiclone		Triazola	am					P value
		64	()	89	()	()	() NS
		%	()				
	sleep heavily while still reporting a	Zopiclone		Triazola	am					P value
Q	good awakening state	55	()	70	()	()	() NS
		%	()				'
# f	eel more rest	Zopiclone		Triazola	am					P value
		80	()	92	()	()	() NS
		%	()				
	awakening with no concentration	Zopiclone		Triazola	am					P value
	difficulties (with a significant nvestigator-by-treatment group	56	()	82	()	()	() 0.04
i	nteraction, p<0.01)	%	()				
# r	medication aided sleep	Zopiclone		Triazola	am					P value
		multiple d	()	multiple	∍d ()	()	() NS
		%	()		·		

Author: Liu Trial type: Active Quality rating: Poor

Year: 1997 Country: Taiwan Funding:

Design:

Age: 40.1 Number Screened: NR Range: 20-58

DB SD: 10.9 Eligible: NR Crossover Enrolled: 15

Setting Single Center Gender: 11 (73 %) Female

Single Center

Sumber Withdrawn: 0

Ethnicity: NR

Lost to fu: 0

Analyzed: 15

Eligibility criteria:

Outpatients who suffered from insomnia for more than 3 months, with at least 3 of the following symptoms: sleep onset greater than 1 hour, total sleep duration of less than 5 hours, more than 2 nocturnal awakenings, and poor subjectively reported sleep quality.

Exclusion criteria:

Patients with psychoses or mood disorders, history of severe physical illness, alcohol abouse or drug abuse.

Comments:

Poor quality- baseline characterisitcs not reported, no information on randomization and allocation concealment methods. Unable to determine if an intention-to-treat analysis was used, and high loss to followup. (8 patients did not complete the trial; unclear if 8 of 15 or 8 of 23).

Intervention:

Run-in: 0 **Wash out**: 7

Allow other medication: No

Drug name	dosage	N=	Duration	Total withdrawal	
Zopiclone	7.5 mg	15	14 day	0 / 0	
Triazolam	0.25 mg	15	14 day	0 / 0	
Placebo	NA mg	15	14 day	0 / 0	

Author:	Liu	Trial type:	Active			Quality rating:	Poor
Year:	1997	Country:	Taiwan			Funding:	
Outcome	Measurement:			Efficacy	Outcome List:		
	gel's sleep questionnaire (SSQ) cal Global Impression Scale (CGI))		Primary outcome	Outcome:		
	lton Anxiety Rating Scale 's sleep evaluation questionnaire	(LSEQ)			therapeutic efficacy delay in falling asleep quality of sleep length of sleep night waking dream morning state global evaluation		
Results	ahal languagian Saala (CCI)						
	obal Impression Scale (CGI)	I	1	ı	I	I	
# thera	peutic efficacy	Zopiclone NR	Triazola (<0.005) NR	m (<0.005)	()	() P v	value G
		Score	(p vs baseline)		l.	

Quality rating: Poor Author: Liu Trial type: Active Year: 1997 Country: Taiwan **Funding:** Spiegel's sleep questionnaire (SSQ) # therapeutic efficacy Zopiclone Triazolam P value NR (<0.005) NR (<0.005)) NS Score (p vs baseline # delay in falling asleep at day 14 Zopiclone Triazolam P value 3.94 (0.70 4.13 (0.64) NS Score (SD # quality of sleep at day 14 Zopiclone Triazolam P value 3.47 4.33 (0.62 (0.64) < 0.05 (SD Score # length of aleep at day 14 Zopiclone Triazolam P value) NS 3.73 (0.70) 3.53 (0.74 Score (SD # night waking at day 14 Zopiclone Triazolam P value 4.20 (0.68 3.33 (0.62) < 0.05 Score (SD # dream at day 14 Zopiclone Triazolam P value 3.93 (0.70 3.73 (1.03) NS (SD Score) # morning state at day 14 Zopiclone Triazolam P value (0.91) NS 3.93 (0.80 3.60 Score (SD) # global evaluation at day 14 Zopiclone Triazolam P value 4.13 (0.92 3.93 (0.96) NS (SD Score

Author: Liu Trial type: Active Quality rating: Poor

Year: 1997 Country: Taiwan Funding:

Leed's sleep evaluation questionnaire (LSEQ)

2 out of 10 items shows more effectiveness in zopiclone: quality of sleep

Zopiclone			Triazolam						P value
NR	()	NR	()	()	() <0.05
Score	()				

Author: Mamelak Trial type: Active Quality rating: Fair

Year: 1987 Country: Canada Funding: Not reported

Design:

Study design RCT

DB

Parallel

Setting Single Center

Single Certier

Eligibility 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 noctunal 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.

Comments:

Ethanol-drug interaction study.

Intervention:

Run-in: 2

Wash out:

Allow other medication :

Age: 50

Range: 32-60

32-60 Eligible:

SD:

Gender: 21 (70 %) Female

Ethnicity: NR

Number Withdrawn: 0 Lost to fu: 0

Number Screened: NR

Enrolled:

Analyzed: 30

NR

30

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.

Drug name	dosage	N=	Duration Total withdrawal	
Zopiclone	7.5 mg	10	12 day 0 / 0	
Flurazepam	30 mg	10	12 day 1 / 1	
Placebo	NA mg	10	12 day 0 / 0	

Author:	Mamelak	Trial type	: Act	ive						Quality	rati	ng: Fair	
Year:	1987	Country:	Can	ada						Funding	g: N	lot reported	
Outcome	Measurement:				Effic	ac	y Outco	me L	st:				
# slee	p questionnaire				Prim outco	•			a				
]]]	sleep la	tency waken	ings	efulness			
Results													
sleep que	<u>estionnaire</u>												
# total	sleep time at day 14, the end of	Zopiclone		Flurazepa	am		Placebo					P value	
trea	tment	417.5	(< 0.05) 410.5	(< 0.05)	328.0	(<0.0	5)	()		
		minutes	(pvsba	aseline)	I		ı				
	p latency at day 14, the end of	Zopiclone		Flurazepa	am		Placebo					P value	
trea	tment	28.8	(< 0.05) 31.5	(<0.05)	69.8	(NS)	()		
		minutes	(pvsba	aseline)	ļ		ı			l l	
	of awakenings at day 14, the end	Zopiclone		Flurazepa	am		Placebo					P value	
of tr	eatment	1.15	(< 0.05) 1.55	(<0.05)	1.65	(<0.0	5)	()		
		Number	(pvsba	aseline)							
	ation of early wakefulness at day	Zopiclone		Flurazepa	am		Placebo					P value	
14, 1	the end of treatment	37.0	(NS) 14.7	(NS)	43.1	(NS)	()		
		minutes	(p vs ba	aseline)	<u> </u>						
# all s	leep itmes at day 14, the end of	Zopiclone		Flurazepa	am							P value	
trea	treatment		() as above	()		()	()	NS	
		minutes	()	<u> </u>						

Quality rating: Fair Author: Monti Trial type: Active

Year: 1994 Country: Uruguay **Funding: Not reported**

Design:

Study design RCT

DB

Parallel

Single Center Setting

Eligibility 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 waketime >20 minutes; number of nocturnal awakenings >3.

Comments:

Intervention: Run-in: 3

Wash out : 3

Allow other medication: NR

47.3 Age:

Range: 21-65

SD:

Gender: 21 (88 %) Female

Ethnicity: NR

Number Withdrawn: 1

Lost to fu: 0 Analyzed: 24

NR

24

Number Screened: NR

Eligible:

Enrolled:

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.

				Williamais due to
Drug name	dosage	N=	Duration	Total withdrawal
Zolpidem	10 mg	8	27 day	0 / 0
Triazolam	0.5 mg	8	27 day	1 / 1
Placebo	NA mg	8	27 day	0 / 0

minutes

Quality rating: Fair **Author:** Monti Trial type: Active Funding: Not reported Year: 1994 Country: Uruguay

Outcome Measurement:

polysomnogram

sleep questionnaire

Efficacy Outcome List:

Primary

outcome Outcome:

~ sleep latency **V** total sleep time

wake time after sleep onset

~ total waketime

number of awakenings

Results

polysomnogram

#	wake time (change from baseline) -
	night 15-16

Zolpidem		Triazolam							P value
-130	(135.9)	-32	(36.10)	()	(()	NR
minutes	(SD)					

wake time (change from baseline) night 29-30

Zolpidem		Triazolan	n					P value
-117	(114.6)	-39	(44.5)	()	()	NR
minutes	(SD)				'

total sleep time (change from baseline) - night 15-16

Zolpidem			Triazolam	1					P value
127	(136.7)	33	(35.8)	()	()	NR
minutes	(SD)				

total sleep time (change from baseline) - night 29-30

Zolpidem		Triazolam						P value
113	(116.2)	41	(44.1)	()	() NR
minutes	(SD		,)				

number of sleep cycles (change from baseline) - night 4-5

Zolpidem			Triazol	am						P value
1.8	(2.1)	0.3	(1.3)	()	()	NR
Number	(SD)					

Author: Monti Trial type: Active Quality rating: Fair 1994 **Funding: Not reported** Year: Country: Uruguay Zolpidem # number of sleep cycles (change from baseline) - night 15-16 Triazolam P value 1.7 (2.0) NR (1 (SD Number # number of sleep cycles (change from baseline) - night 29-30 Zolpidem Triazolam P value 1.2 (1.3) 0.3 (1.5) NR (SD Number

Quality rating: Fair Author: Nair Trial type: Active

Year: 1990 Country: Canada **Funding: Rhone-Poulenc Pharma**

Design:

Study design RCT

DB

Parallel

Single Center Setting

Eligibility criteria:

(a) sleep latentcy 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.

Comments:

Intervention: Run-in:

> Wash out : NR

Allow other medication :

46.9 Age:

> Range: SD: 1.4

Gender: 28 (47 %) Female

Ethnicity: NR

Lost to fu: Analyzed:

Eligible:

Enrolled:

NR

NR

60

Number Screened:

Number Withdrawn:

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.

Drug name	dosage	N=	Duration	Total withdrawal	
Zopiclone	3.75 mg	10	7 day	0 / 0	
Zopiclone	7.5 mg	10	7 day	0 / 0	
Zopiclone	11.2 mg	10	7 day	1 / 1	
Zopiclone	15 mg	10	7 day	1 / 1	
Flurazepam	30 mg	10	7 day	0 / 0	
Placebo	NA mg	10	7 day	1 / 2	

Author:	Nair	Trial type	: Acti	ve				Quality	rating: Fair	
Year:	1990	Country:	Cana	ıda				Fundin	g: Rhone-Poulenc P	harma
Outcome	Measurement:				Efficacy	Outcome L	ist:			
	quesionnaire al global impression (CGI)				Primary outcome	Outcome:				
						sleep induction quality of sleet quality of mor hangover effe	p ning av	vakening		
Results										
sleep ques	sionnaire									
# sleep	induction time	Zopiclone(any dose)	Flurazep	am				P value	
		NR	() NR	()	()	() NS	
		Score	(ı)		ı			
# qualit	y of sleep	Zopiclone(any dose)	Flurazep	am				P value	
		NR	() NR	()	()	() NS	
		Score	(l)		l			
# qualit	y of morning awakening	Zopiclone(any dose)	Flurazep	am				P value	
		NR	() NR	()	()	() NS	
		Score	()					
# hange	over effects (except zopiclone	Zopiclone		Flurazep	am				P value	
3.75n		NR	() NR	()	()	() NS	
		Score	()	•	-			
# hand	over effects (zopiclone 3.75mg	Zopiclone	`	Flurazep	am /				P value	
	(higher score=better)	7	() 5.5	()	()	() <0.05	
		Score	1	*	, ,	`	′	,		

Author:	Nair	Trial type: Active	Quality rating: Fair
Year:	1990	Country: Canada	Funding: Rhone-Poulenc Pharma
<u>CGI</u>			
	rity of illness (except Zopiclone	Zopiclone Flurazepam	P value
3.75m	ng)	NR () NR () ()	() NS
		Score ()	,
	rity of illness (Zopiclone 3.75mg	Zopiclone Flurazepam	P value
only)		NR () better () ()	() NR
		Score ()	
# globa	l improvement	Zopiclone(any dose) Flurazepam	P value
		NR () NR () ()	() NS
		Score ()	

Author: Ngen Trial type: Active Quality rating: Fair

Year: 1990 Country: Malaysia Funding: Rhone-Poulenc Pharma

Age:

Design:

Study design RCT

DB

Parallel

Setting Single Center

Range: SD:

38.4

Gender: 31 (52 %) Female

Ethnicity: NR Number Withdrawn: 16
Lost to fu: 0

Analyzed: 44

NR

NR

60

Number Screened:

Eligible:

Enrolled:

Eligibility criteria:

Subjects must be between 18 and 70 years of age and must have one of the following for at least 2 weeks duration; (a) takes longer than 45 min to fall asleep, (b) more than two nocturnal awakenings each night without known cause and difficulty in returning to sleep, (c) sleep duration of less than 6 hours a night

Comments:

Intervention: Run-in: 7

Wash out: NR

Allow other medication: NR

Exclusion criteria:

(a) serious concomitant disease, (b) likely to require concomitant medication known to cause drwosiness, (c) psychosis, (d) a history of hypersensitivity to benzodiazepines, (e) drug and/or alcohol abuse, (f) pregnant, a nursing mother or intending to become pregnant during the study, (g) working night shifts

Drug name	dosage	N=	Duration	Total withdrawal	
Zopiclone	7.5 mg	20	14 day	2 / 7	
Temazepam	20 mg	20	14 day	0 / 7	
Placebo	NA mg	20	14 day	1 / 10	

Author:	Ngen	Trial type	: Activ	е				Quality r	ating: Fair	
Year:	1990	Country:	Malay	sia				Funding	: Rhone-Pou	ılenc Pharma
Outcome	Measurement:				Efficacy	Outcome	List:			
# sleep	diary				Primary					
# globa	l assessmnet efficacy				outcome	Outcome:				
						sleep latend				
						no. of times		-		
						total duratio	n sleep			
Results										
sleep diary	<u>/</u>									
# total of	duration of sleep at treatment	Zopiclone		Temaz	epam				P value	
week	1	5.97	(<0.01)	5.90	(< 0.05)	()	()	
		hours	(p vs base	eline)					
# total o	duration of sleep at treatment	Zopiclone		Temaz	epam				P value	
week		6.03	(<0.01)	5.62	(NS)	()	()	
		hours	(p vs base	eline)	,	,			
# sleen	latency at treatment week 1	Zopiclone	(p . o o o o	Temaz	enam /				P value	
и стоор	action of at troumont work i	84	(<0.05)	25.9	(<0.05)	()	() r value	
		Minutes	(p vs base		,	· · · · · · · · · · · · · · · · · · ·	,		<u> </u>	
# -1	later are at two atmosphere at the all O		(p vs base	1	,					
# ѕіеер	latency at treatment week 2	Zopiclone 64.5	(<0.05)	Temaz 26.1	(NS)		\		P value	
					(N3)	()	()	
		Minutes	(p vs base	eline)		1			
# no. of	f awakenings at treatment week 1	Zopiclone		Temaz					P value	
		0.77	(NS)	1.2	(<0.05)	()	()	
		Number	(p vs base	eline)				"	
# no. of	f awakenings at treatment week 2	Zopiclone		Temaz	epam				P value	1
		0.62	(<0.05)	1.28	(NS)	()	()	
		Number	(p vs base	eline)					

Author: Ngen Trial type: Active Quality rating: Fair

Year: 1990 Country: Malaysia Funding: Rhone-Poulenc Pharma

global assessmnet efficacy

efficacy- good response

Zopiclone	Temazepam			P value
10 (<0.02)	12 (<0.01)	()	()	NS

Number (p vs placebo)

Author: Ponciano Trial type: Active Quality rating: Fair

Year: 1990 Country: Portugal Funding: Not reported

Design:

Study design RCT

DB

Parallel

Setting Single Center

Age: 30

Range: 18-60 SD: 9

Gender: 12 (46 %) Female

Ethnicity: NR

Number Withdrawn: 2

Number Screened: NR

Eligible:

Enrolled:

Lost to fu: 0 Analyzed: 24

NR

26

Eligibility 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 medicaiton to be used were excluded. Patients with a history of drug use, those with excessive alcohol comsumption (<1 litre of wine/day, or equivalent) pregnant or nursing women and all females of child bearing age without adequate contraception were also excluded.

Comments:

Results were reported in figures only. Therefore, the data reported in the evidence table were estimated from the figures.

Intervention: Rui

Run-in: 7 Wash out: 7

Allow other medication: NR

Drug name	dosage	N=	Duration	Total withdrawal
Zopiclone	7.5 mg	8	21 day	0 / 0
Flurazepam	30 mg	8	21 day	0 / 0
Placebo	NA mg	10	21 day	1 / 2

Author:	Ponciano	Trial type	: Act	ive					Quality	rating:	Fair
Year:	1990	Country:	Por	tugal					Funding	g: Not	reported
Outcome	Measurement:				Efficac	y Outcor	ne Li	ist:			
# visua	s sleep evaluation questionna I analogue rating scale	ire (LSEQ)			Primary outcom		ne:				
# clinica	al interview					the ease quality of ease of integrity mood cl sleep or sleep do	of sleep awake of day hanges	p ening /time l	to sleep behavior		
Results clinical inte	<u>erview</u>										
# sleep	onset latency at day 21	Zopiclone		Flurazepa	m	Placebo				Pv	/alue
		30	(0.02) 28	(0.04)	60	(NA)	()	
			/ n nl			l					
		minutes	(p vs pi	acebo)						
# sleep	duration	Zopiclone	(p vs pi	Flurazepa) m	Placebo				Pv	/alue
# sleep	duration		(p vs pi) m (0.05)		(NA)	(P v	<u>ralue</u>
# sleep	duration	Zopiclone		Flurazepa) 425			(NA)	() P v	ralue
	duration	Zopiclone 393	(NS	Flurazepa) 425			(NA)	() P v	/alue
visual ana		Zopiclone 393	(NS	Flurazepa) 425	(0.05)		(NA)	()	/alue /alue
visual ana	logue rating scale	Zopiclone 393 minutes	(NS	Flurazepa) 425 acebo	(0.05)	410	(NA)	()	/alue

Author: Quadens Trial type: Active Quality rating: Poor

Year: 1983 Country: Belgium Funding: Not reported

Design:

Study design RCT

DB

Crossover

Setting Single Center

Eligibility 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

Comments:

Poor quality- insufficient information to assess quality.

Intervention: Run-in:

Wash out: 35

Allow other medication: No

6

Age: NR

Range: 50-59
SD:

Number Screened: NR
Eligible: NR
Enrolled: 12

Gender: 12 (100%) Female

Ethnicity: NR Number Withdrawn: 0
Lost to fu: 0

Analyzed: 12

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.

Drug name	dosage	N=	Duration	Total withdrawal
Zopiclone	7.5 mg	12	13 day	/
Flurazepam	30 mg	12	13 day	/

Author:	Quadens	Trial type	e: Act	ive					Quality ra	ting: Poo	or .
Year:	1983	Country:	Belg	jium					Funding:	Not report	ted
Outcome	Measurement:				Effica	y Outo	ome L	ist:			
# sleep	questionnaire				Primar outcon		ome:				
						total	f awaker sleep tim o onset la	е			
							efficiend				
Results											
sleep ques	stionnaire .										
# no. of	fawakenings	Zopiclone		Flurazepa	am	Placebo)			P value	
		3.2	(< 0.05) 1.9	(<0.05)	6	(NA)	()	
		Number	(p vs pla	acebo)			,		ı	ı
# total s	sleep time	Zopiclone		Flurazepa	am	Placebo)			P value	
		24903	(< 0.01) 25129	(<0.05)	23225	(NA)	()	
		seconds	(pvspl	acebo)	1		,		ı	ı
# sleep	onset latency	Zopiclone		Flurazepa	am	Placebo	כ			P value	
		1117	(< 0.05) 1174	(<0.1)	1452	(NA)	()	
		seconds	(p vs pla	acebo)						_
# sleep	efficiency index	Zopiclone		Flurazepa	am	Placebo)			P value	
		91.4	(< 0.01) 92.2	(<0.05)	83.6	(NA)	()	
		Score	(p vs pla	acebo)	1					_
	eep items comparing two	Zopiclone		Flurazep	am					P value	
treatn	nent	as above	() as above	()		()	() NS	
		Number	(1)	1					_

Author: Rosenberg Trial type: Active Quality rating: Poor

Year: 1994 Country: Denmark Funding: Synthelabo Scandinavia A/S

Age:

Design:

Study design RCT

DB

Parallel

Setting Multicenter

F

Range: 25-79

SD:

54

Gender: NR (0 %) Female

Ethnicity: NR

Number Withdrawn: 5 Lost to fu: 34

Number Screened:

Eligible:

Enrolled:

Analyzed: 139

NR

NR

178

Eligibility 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

Comments:

Enrolled patients characteristics were not reported. Analyzed patients characteristics were reported instead: mean age=51 years, range 19-79 years; 31% male.

Intervention:

Run-in: NR Wash out: NR

Allow other medication: No

			· · · · · · · · · · · · · · · · · · ·	
Drug name	dosage	N=	Duration ⁻	Total withdrawal
Zolpidem	10 mg	71	14 day	/
Triazolam	0.25 mg	68	14 day	1

Author:	Rosenberg	Trial type:	Active			Qua	lity ra	ting: Po	oor
Year:	1994	Country:	Denmar	k		Fun	ding:	Synthela	abo Scandinavia A/S
Outcome	Measurement:			Efficac	y Outcome Lis	it:			
•	rted by patients Il analogue scales			Primary outcom	duration of slee no. of nocturnal sleep quality				
Results reported b	y patients				day quality				
# total :	sleep times	Zolpidem	Т	riazolam				P value	
			4.8-9.1) 7		() () NS	
		hours (range)		l		ļ	l
# No. o	of awakenings	Zolpidem	Т	riazolam				P value	
		1 (0-4) 1	(0-5)	() () NS	
		Number (range)		ı		I	ı

Score

(Range

Author: **Quality rating: Poor** Rosenberg Trial type: Active Funding: Synthelabo Scandinavia A/S Year: 1994 Country: Denmark visual analogue scales Zolpidem # sleep quality, bad-good Triazolam P value 69 (15-96 69 (18-98)) NS (Range Score # morning feeling, bad-good Zolpidem Triazolam P value 56 (9-98) NS 64 (8-94 (Range Score Zolpidem # daytime alertness. unalert-alert Triazolam P value 65 (6-92 63 (26-92)) NS (Range Score # subjective day feeling Zolpidem Triazolam P value 64 (6-93) 60 (9-92) NS

Author: Silvestri Trial type: Active Quality rating: Fair

Year: 1996 Country: Italy Funding: Not reported

Design:

Study design RCT

DB

Parallel

Setting Multicenter

Eligibility criteria:

Both sexes, age between 18 and 65 years, clinical diagnosis of psychophysiological insomnia (either as a first episode or as a recurrence of short-term situaitonal insomnia) or poor sleepers with subjective reporting of at least two out of these four complaints: time to fall asleep >30 minutes, total sleep duration <6 hours, total wake time >20 minutes, and/or number or awakenings >3. These subjective inclusion criteria had to be confirmed by the objective assessment through polysomnography.

Comments:

Intervention: Run-in: 3

Wash out: No

Allow other medication: No

Age: 33.6

Range: NR SD: 10.4

Gender: 12 (55 %) Female

Ethnicity: NR

Lost to fu: 2 Analyzed: 20

Number Screened: NR

Eligible:

Enrolled:

Number Withdrawn: 0

NR

22

Exclusion criteria:

Pregnant or lactating women; women of child-bearing age withoug adequate contraception; uncooperative patients; severe psychiatric diseases, also screened by means of both Hamilton Rating Scale for Anxiety (total score >16) and Hamilton Rating Scale for Depression (total score >16); neurological diseases (myoclones, kinaesthesis disorders, restless legs syndrome, sleep obstructive apnea of >7 minutes duration); severe internal (heart, renal, liver) diseases; hemocoagulation disorders (Quick's time <70%); intake of any psychotropic durg during 2 weeks preceding the study start as well as a previous with beta blockers or corticosteroids.

Drug name	dosage	N=	Duration	Total withdrawal
Zolpidem	10 mg	10	2 week	0 / 0
Triazolam	0.25 mg	12	2 week	0 / 2

Author:	Silvestri	Trial type	: Acti	ve				Quality ra	ting: Fair	•
Year:	1996	Country:	Italy					Funding:	Not report	:ed
Outcome	Measurement:				Efficacy	Outcome L	_ist:			
# polyse	omnography				Primary					
	analogue scale				outcome	Outcome:				
# quesi	onnaire					total sleep tin				
						sleep onset la	-			
						sleep efficien	•			
						wake time aff	-	n onset		
						REM sleep	.01 01001	5 011001		
						quiet-disturbe	ed sleep)		
						alert-drowsy	awaken	ing		
Results										
polysomno	ography									
		7-1-:-		Triazolar	I		1		1	
	onset latency- change from ine- night 14	Zolpidem -23	/ 24 20			,	,	,	P value) NS	
	-		(21.38) -14.8	(30.92)	()	() NS	
		minutes	(SD)					
	sleep time- change from	Zolpidem		Triazolar					P value	_
basei	ine- night 14	61.1	(43.97) 54.4	(49.70)	()	() NS	
		minutes	(SD	')					_
# sleep	efficiency- change from	Zolpidem		Triazolar	m				P value	
	ine- night 14	14.3	(10.39) 10.7	(7.35)	()	() NS	-
		%	(SD	1	, , ,	•	<i>'</i>	,		
//	Cara afternal and a second about		(3D	T-11	, , , , , , , , , , , , , , , , , , ,					٦
# wake from l	time after sleep onset- change baseline- night 14	Zolpidem	/ 44.00	Triazolar		,	,	,	P value	
	3	-44.9	(44.82) -37	(25.62)	()	() NS	
		minutes	(SD)					

Author: Silvestri	Trial type:	: Acti	ve					Quality r	rating: Fair
/ear: 1996	Country:	Italy						Funding	: Not reporte
# no. of awakenings- change from	Zolpidem		Triazola	am					P value
baseline- night 14	-2.2	(3.51) -3.5	(2.45)	()	() NS
	Number	(SD	·)		\ 		
quesionnaire									
# time to fall asleep- change from	Zolpidem		Triazola	am					P value
baseline- night 14	-41.8	(32.51) -19.9	(36.83)	()	() NS
	minutes	(SD)				
# total sleep time- change from	Zolpidem		Triazola	am					P value
baseline- night 14	66.9	(44.53) 81.4	(46.9)	()	() NS
	minutes	(SD)				
# total wake time- change from	Zolpidem		Triazola	am					P value
baseline- night 14	-12.1	(9.88) -11.4	(8.53)	()	() NS
	minutes	(SD)		1		
# no. of nocturnal awakenings- change	Zolpidem		Triazola	am					P value
from baseline- night 14	-1.4	(0.75) -1.2	(1.63)	()	() NS
	Number	(SD	')				
<u>visual analogue scale</u>									
# sleep quality- change from baseline-	Zolpidem		Triazola	am					P value
night 14	-22.8	(17.90) -31.8	(20.66)	()	() NS
	Score	(SD	1)				
# awakening quality- change from	Zolpidem		Triazola	am					P value
baseline- night 14	-16.3	(18.14) -26.9	(23.32)	()	() NS
	Score	(SD	ı)		ļ		I I

Author: Singh Trial type: Active Quality rating: Fair

Year: 1990 Country: Canada Funding: Rhone-Poulenc Pharma Inc.

Design:

Study design RCT

DB

Parallel

r aranor

Setting Single Center

Eligibility criteria:

NR

Age: 39.6

Range: 19-64 SD: 1.5

Gender: 32 (53 %) Female

Ethnicity: NR

ty: NR

Lost to fu: 0 Analyzed: 57

61

60

Number Screened: NR

Number Withdrawn: 3

Eligible:

Enrolled:

Exclusion criteria:

Psychotic and neurotic patients were excluded as well as those with a history of mental retardation, chronic alcoholism, drug abuse, coffee or tea abuse, neurolpgical disorders, established sleep apnoea and drug hypersensitivity. Patients with any significant medical condition interfering with sleep, those treatment which could modify drug kinetics were also excluded. Finally, pregnancy, lactation, and child-bearing potential not controlled by a recognized contraceptive programme precluded entry in the study.

Comments:

Two patients were taking a benzodiazepine hypnotic medication at time of recrutment and they both fulfilled the inclusion criteria after a 4-day minimun washout period. The study did not report patient number for each treatment groups, and the analyzed results were the mean from parts of the patients as well. (?!)

Intervention:

Run-in: 4

Wash out: NR

Allow other medication: NR

Drug name	dosage	N=	Duration	Total withdrawal	
Zopiclone	7.5 mg		24 day	0 / 0	
Zopiclone	11.2 mg		24 day	1 / 2	
Flurazepam	30 mg		24 day	0 / 1	

Author:	Singh	Trial type	: Acti	ve			Quality rat	ing: Fair
Year:	1990	Country:	Cana	ada			Funding:	Rhone-Poulenc Pharma Inc.
# post-	Measurement: -sleep quesionnaire cal global impression (CGI)				Efficac Primary outcom		÷	
Results								
post-sleep	o quesionnaire							
# durat	tion of sleep onset at week 4	Zopiclone	7.5mg	Zopiclone	e 11.25mg	Flurazepam 30mg		P value
		6.7	(< 0.01) 6.9	(<0.01)	7.5 (<0.01)	(
		Score	(p vs pla	cebo)			
# sleep	soundness at week 4	Zopiclone	7.5mg	Zopiclone	e 11.25mg	Flurazepam 30mg		P value
		6.7	(< 0.01) 6.6	(<0.01)	7.5 (<0.01)	(
		Score	(p vs pla	acebo)			
# quali	ty of sleep at week 4	Zopiclone	7.5mg	Zopiclone	e 11.25mg	Flurazepam 30mg		P value
		11.2	(<0.01) 11.0	(<0.01)	12.2 (<0.01)	(
		Score	(p vs pla	acebo)			
	tion of sleep onset, sleep	Zopiclone	7.5mg	Zopiclone	e 11.25mg	Flurazepam 30mg		P value
soun	dness, quality of sleep at week 4	as above	(NS) as above	(NS)	as above (NA)	(
		Score	(p vs flu	eazepam)	1		
<u>CGI</u>								
# thera	apeutic index (less score=worse)	Zopiclone	7.5mg		e 11.25mg	Flurazepam 30mg		P value
at We	5GN 1	3.2	() 3	()	2.5 ()	() <0.05
		Score	(-)			

Author: Stip Trial type: Active Quality rating: Fair
Year: 1999 Country: Canada Funding: Not reported

Design:

Study design RCT

DB

Parallel

Setting Single Center

Age: 42.6

Range: SD:

Gender: NR (%) Female

Ethnicity: NR

Number Withdrawn: 2

Number Screened:

Eligible:

Enrolled:

Lost to fu: 8 Analyzed: 50

NR

NR

60

Eligibility criteria:

Patients with either primary insomnia or insomnia associated with mild non-psychotic psychiatrc disroders (DSM III-R). Daytime fatigability, diminished power of concentration at work and at least two of the following symptoms: falling asleep time greater than 30 min, sleep duration less than 5 hours, more than two awakenings per night and early wake up in the morning.

Exclusion criteria:

NR

Comments:

Participants who had been taking hypnotic drugs with a long half-life received lorazepam for one week, prior to a week placebo. Patients who had been taking benzodiazepines with a short or intermediate half-life were put only on placebo for one week.

Enrolled population characteristic were not reported. Analyzed population characteristics: mean age=42.6 years; 21 (42%) female

Intervention: Run-in: 7

Wash out: 7

Allow other medication: NF

Drug name	dosage	N=	Duration	Total withdrawal
Zopiclone	7.5 mg	19	21 day	0 / 0
Temazepam	30 mg	16	21 day	0 / 1
Placebo	NA mg	15	21 day	0 / 1

Author:	Stip	Trial type:	Activ	е					Quality rat	ing: Fair	
Year:	1999	Country:	Canad	da					Funding: I	Not reported	
Outcome Measurement: # Hamilton scale for anxiety # Self-rating questionnaire for sleep # auditory and visual span test					Efficac Primar outcon	anxiet quality sleep sleep	ome: by y of sle onset depth	ер	attention		
Results											
Hamilton se	cale for anxiety										
# anxiet	ty	Zopiclone		Temazepa	m	Placebo				P value	
		NR (()	NR	()	NR	()	()	NS	
Self-rating	questionnaire for sleep	Score	()						
# sleep	onset at treatment week 1	Zopiclone		Temazepa	m					P value	
		NR ((<0.01)	NR	(<0.01)		()	()		
		Score	(p vs plac	ebo)						
# sleep	depth at treatment week 1	Zopiclone		Temazepa	m					P value	
·	•		(<0.01)	•	(<0.01)		()	()	1 Value	
		Score	(p vs plac	eho	· · · · · · · · · · · · · · · · · · ·		•		<u> </u>		
auditory an	nd visual span test	000.0	(p re plac		,						
# alertn	ess over all 5 weeks	Zopiclone		Nitrazepan	n	Placebo				P value	
" dioitii	oss s. s. an o moone	multiple d (()	multiple d		multiple	()	()	NS	
		Score	(<u> </u>)	<u> </u>	`	,	` '		

Quality rating: Poor Tamminen Author: Trial type: Active

1987 Country: **Funding: Not reported** Year: Finland

Design:

Study design RCT

DB

Parallel

Setting Multicenter Age: 47

Range: 26-71

SD:

Gender: 72 (77 %) Female

Ethnicity: NR

Number Withdrawn: 0

Number Screened: NR

Eligible:

Enrolled:

Lost to fu: 0

Analyzed: 94

130

94

Eligibility 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, noctural awakenings >2 per night, time to fall asleep after at least one noctural awakening >30min, awakening >2hour before scheduled time.

Exclusion criteria:

Known hypersensitivity to benzodiazepines, major psychiatric disorders, somatic disorders directly causeing 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.

Comments:

Poor quality: no baseline demographic characteristics, high and differential loss to followup and no intention to treat analysis

Intervention: Run-in: 7

> NR Wash out :

Allow other medication :

Drug name	dos	age	N=	Duration	Total withdrawal
Zopiclone	7.5	mg	52	42 day	3 / 3
Nitrazepam	5	mg	46	42 day	1 / 1

Author: Year:	Tamminen 1987	Trial type Country:	: Active Finland					•	rating: Poor g: Not reporte
Outcome I # diary	Measurement:				Efficacy Primary	Outcome L	_ist:		
,	questionnaire				outcome	Outcome:			
# global	evaluation Mood Rating					sleep onset la sleep quality night awaken duration of sl	nings		
Results									
<u>diary</u>									
# sleep	onset latency, mean score	Zopiclone	Ni	trazepam					P value
		32.6	() 33	3.1 ()	()	() NS
		Score	()		·		! !
# quality	y of sleep, mean score	Zopiclone	Ni	trazepam					P value
		34	() 30).2 ()	()	()
		Score	()		Ņ		ı ı
global eval	<u>uation</u>								
# efficad	cy (1=poor; 5=excellent)	Zopiclone	Ni	trazepam					P value
		3.2	() 3.	1 ()	()	() NS
		Score	()		I		

Author: Tamminen	Trial type: Ac	tive				Quality	rating:	Poor
/ear: 1987	Country: Fin	land				Fundin	g: Not r	eported
sleep questionnaire								
# latency of sleep onset >30 min	Zopiclone	Nitrazepam					P va	alue
	38 () 44.4 ()	()	() 0.07	7
	% (<u> </u>)					
# duration of sleep <6.5 hours	Zopiclone	Nitrazepam					P va	alue
	37.5 () 37.7 ()	()	() NS	
	% (·)					
# >2 night awakenings	Zopiclone	Nitrazepam					P va	alue
	18.4 () 24.4 ()	()	() NS	
	% ()					
# time to fall askeep after a nught	Zopiclone	Nitrazepam					P va	alue
awakenings >30 min	14.6 () 22.2 ()	()	() NS	
	% ()		·		"	<u>'</u>
# awakening at least 2 hours before	Zopiclone	Nitrazepam					P va	alue
expected time	20.4 () 20 ()	()	() NS	
	% ()					
Norris Mood Rating								
# overall	Zopiclone	Nitrazepam					P va	alue
	- () better ()	()	() <0.0)5
	Score ()				*	

Author: van der Kleijn Trial type: Active Quality rating: Fair

Year: 1989 Country: Nijmegen Funding: Rhone-Poulenc Pharma

Design:

Study design RCT

DB

Crossover

Setting NR

Eligibility criteria:

1. latency of sleep onset exceeding 30 min

2. waking up too early

3. waking up several times at night and difficulty in falling asleep afterwards

4. being bothered duting the day by unsatisfactory sleep

Comments:

Intervention: Run-in: 2
Wash out: 7

wasii out . '

Drug name

Zopiclone

Temazepam

Allow other medication: N

dosage

7.5 mg

20 mg

N=

53

53

Age: 53

Range: 28-69 SD:

Eligible: 60 Enrolled: 55

Gender: 39 (71 %) Female

Ethnicity: NR Number Withdrawn: 2
Lost to fu: 0

Analyzed: 53

Number Screened: NR

Exclusion criteria:

1. Patients taking a non-benzodiazapine hypnotic prior to the studym those who received another psychotropic drug for the first time, or patients whose psychotropic medicine was changed during the study period.

2. Patients who took benzodiazapine tranquillizers or hypnotics in doses at least twice that recommended before the study.

3. Patients suffering from painful disorder

4. Patients unable to fill in a sleep questionnaire, those with a history of alcohol and/or drug abuse, who lived in psychiatric or physical stress situations likely to fluctuate during the study, with liver or kidney disorders, myasthenia gravis, shift-workers

5. Women pregnant or likely to become pregnant

	Withdrawals due to AEs/
Duration	Total withdrawal
5 day	1 / 1
5 day	1 / 1

Author: van der Kleijn Trial type: Active Quality rating: Fair

Funding: Rhone-Poulenc Pharma Year: 1989 Country: Nijmegen

Outcome Measurement:

Efficacy Outcome List:

Questionnaire

Primary outcome Outcome:

V Sleep quality

V Latency of sleep onset **✓** Status after awaking

Results

Questionnaire in the morning about sleep

# Sleep quality - average score	Zopiclon	e		Temaz	epam						P value
	3.9	(0.2)	3.9	(0.21)	()	()	0.096
	Score	(SD)		ı			1
# Sleep quality - average score	Zopiclon	е		Placeb	0						P value
	3.9	(0.2)	3.4	(0.21)	()	()	<0.001
	Score	(SD)		,			I
# Latency of sleep onset - average score	Zopiclon	е		Temaz	epam					٠	P value
	3.8	(0.2)	3.7	(0.2)	()	()	0.106
	Score	(SD		ı)		ı			I
# Latency of sleep onset - average score	Zopiclon	е		Placeb	0						P value
	3.8	(0.2)	3.1	(0.22)	()	()	<0.01
	Score	(SD)		I			
# Status after awaking - average score	Zopiclon	е		Temaz	epam						P value
	3.5	(0.19)	3.4	(0.18)	()	()	0.45
	Score	(SD)		,			I
# Status after awaking - average score	Zopiclon	е		Placeb	0						P value
	3.5	(0.19)	3.2	(0.19)	()	()	<0.01
	Score	(SD		1)					1

Author: van der Kleijn Trial type: Active Quality rating: Fair Nijmegen **Funding: Rhone-Poulenc Pharma** Year: 1989 Country: **Preference** # Sleep better Zopiclone Temazepam Placebo Z and T P value 16) 2) 10) 6) NR Number Zopiclone Placebo Z and T # Better status during the day Temazepam P value) 0 29) 23) NR 0 Number Zopiclone Z and T # Preferred drug to continue Temazepam Placebo P value) 5) 2) NR

Author: Voshaar Trial type: Active Quality rating: Fair

Year: 2004 Country: Netherlands Funding: Sanfi-Synthelabo

Design:

Age: 46.1 Number Screened: NR Range:

DB SD: Eligible: NR Parallel 221

Parallel Enrolled: 2

Setting Multicenter Gender: NR (0 %) Female

Setting Multicenter Number Withdrawn: 9
Ethnicity: NR Lost to fu: 5

Analyzed: 159

Eligibility criteria:

Patients were included in the study if they were diagnosed with primary insomnia according to DSM-III-R and were aged between 18 and 65 years.

Exclusion criteria:

Patients with other axis I disorders, severe somatic disorders, pregnancy, current use of psychotropic medication, complaints of a jet lag in the 2 weeks preceding the study or occupation requiring shift work

Comments:

Enrolled population characteristics were not reported. Only analyzed population characteristics were reported:

Intervention: Run-in: NR

Wash out: 4

Allow other medication: NF

			Withdrawals	due to AEs/
Drug name	dosage	N=	Duration Total withdr	awal
Zolpidem	10 mg	74	28 day N / N	R
Temazepam	20 mg	85	28 day N / N	R
•				

Author:	Voshaar	Trial type:	: Ac	tive				Quality	rati	ng: Fair	
Year:	2004	Country:	Net	therlands				Funding	g: S	Sanfi-Synthelabo	
Outcome	Measurement:				Efficacy	Outcome	List:				
	o/wake diary L self-report questionnaire	ae			Primary outcome	Outcome:					
	r-Trait-Anxiety-Inventory vo				y y	Total sleep	latency (after sleep		D)		
Results											
Sleep/wak	<u>ke diaries</u>										
# total	sleep time	Zolpidem		Temazepa	am					P value	
		413	(78) 386	(82)	()	()	NS	
		minutes	(SD	,)		'			1	
# sleep	onset latency	Zolpidem		Temazepa	am					P value	
		46	(33) 46	(34)	()	()	NS	
		minutes	(SD	")		'			1	
# wake	time after sleep	Zolpidem		Temazepa	am					P value	
		40	(36) 39	(38)	()	()	NS	
		minutes	(SD	U.)						
# time	in bed	Zolpidem		Temazepa	am					P value	
		530	(77) 508	(58)	()	()	NS	
		minutes	(SD	1)						
# SWE	L total score	Zolpidem		Temazepa	am					P value	
		35.7	(7.7) 35.8	(9.2)	()	()	NS	
		Score	(SD	I)		<u> </u>			1	

Author:	Voshaar	Trial type: Activ	/e	Quality rating: Fair Funding: Sanfi-Synthelabo				
Year:	2004	Country: Netho	erlands					
# STAI-DY-1 sum score		Zolpidem	Temazepam			P value		
		41.6 (12) 39 (10.7)	()	() NS		
		Score (SD)					

Quality rating: Fair **Author:** Walsh Trial type: Active

Year: 1998a Country: US **Funding: Lorex Pharmaceuticals**

Design:

Study design RCT

DB

Parallel

Setting Multicenter

NR Age:

Range: 21-65

SD:

Gender: NR (0 %) Female

Ethnicity: NR

Number Withdrawn: 28 Lost to fu: 0

Number Screened:

Eligible:

Enrolled:

Analyzed: 278

NR

589

306

Eligibility 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 seld-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.

Comments:

Enrolled population characteristics were not reported. Instead, analyzed population characteristics were reported: 63% female; 84% Caucasian.

Intervention:

Run-in:

Wash out : NR

Allow other medication :

			Withdrawals due to AEs/
Drug name	dosage	N=	Duration Total withdrawal
Zolpidem	10 mg	102	14 day 5 / 11
Trazodone	50 mg	100	14 day 5 / 10
Placebo	NA mg	104	14 day 2 / 7

Author:	Walsh	Trial type	e: Ac	tive			Quality rating: Fair					
Year:	1998a	Country:	US						Funding	: Lorex	Pharmaceuticals	
# mornir # patient	Measurement: ng questionnaire ts global impressions ian Disability Scale m visual analog scales				Effica Prima outco	ary ome	Outcome: sleep latency sleep duratio ease of falling number of av wake time aff quality of slee morning slee ability to cond disruption ca social life or f	y g asle vaken ter sle ep pines centra used	ings eep onset s ate in the morning by insomnia			
Results	estionnaire and 100mm visua	l analog scales										
	atency at week 1	Zolpidem 48.2	(2.7	Trazoo	done (4.0)	()	(P valu		
# sleep l	latency at week 2	minutes Zolpidem 48.1 minutes	(SD (3.1 (SD	Trazoo	done (4.1)	()	(P valu	ie	
# sleep o	duration at week 1	Zolpidem 378.8 minutes	(5.3 (SD	Trazoo) 366.4	done (6.4)	()	(P valu	ie	
# sleep o	duration at week 2	Zolpidem NR minutes	(NR (SD	Trazoo) NR	done (NR)	()	(P valu	ue	

Author:	Walsh	Trial type	e: Acti	ve	•					Quality	rati	ng: Fair
Year:	1998a	Country:	US							Funding	g: L	orex Pharmaceutical
# ease o	f falling asleep at week 2	Zolpidem			Trazodone							P value
		44.3	(1.8)	44.0 (2.3)		()	()	NS
		Score	(SD)			I			
# number of awakenings at week 2		Zolpidem			Trazodone							P value
		1.5	(0.2)	1.4 (0.1)		()	()	NS
		minutes	(SD)	ı		I			
# subjective waking time after sleep onset at week 2		Zolpidem			Trazodone							P value
		39.5	(3.6)	42.1 (4.3)		()	()	NS
		minutes	(SD)			l l			
# sleep quality at week 2		Zolpidem			Trazodone							P value
		2.45	(0.05)	2.43 (0.07)		()	()	NS
		minutes	(SD)			ļ.			1
patients glo	bal impressions											
# sleep s	status (excellent and good) at	Zolpidem			Trazodone							P value
week 2	2	49	(53.8)	47 (52.2)		()	()	NS
		Number	(%)						
# sleep i	mprovement (a lot and	Zolpidem	<u> </u>		Trazodone							P value
somew	vhat) at week 2	60	(66)	62 (68.8)		()	()	NS
		Number	(%)						
# time to	fall asleep (shortened a lot and	Zolpidem	•		Trazodone							P value
	ned somewhat) at week 2	56	(61.5)	50 (55.5)		()	()	NS
		 Number	(%)	l		´			
# sleep t	ime (increased a lot and	Zolpidem	`		Trazodone	,						P value
	sed somewhat) at week 2	56	(61.5)	61 (67.8)		()	()	NS
		Number	(%)		•	<u> </u>			

Author: Walsh Trial type: Active Quality rating: Fair

Year: 1998a Country: US Funding: Lorex Pharmaceuticals

Sheehan Disability Scale

overall

Zolpider	m		Trazoo	done						P value
NR	()	NR	()	()	()	NS
_										

Score (

Author: Walsh_ Trial type: Active Quality rating: Good

Year: 1998b Country: US Funding: Wyeth Ayerst

Design:

Study design

DB

Parallel

Setting

Eligibility criteria:

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).

Comments:

day 1-3 placebo; day 4-17 treatment; day 18-19 placebo

Intervention: Run-in: 3

Wash out: 2

Allow other medication: NF

Age: 40.3

Range: 18-60

SD:

Gender: 77 (58 %) Female

Ethnicity: NR

Number Withdrawn: 7 Lost to fu: 0

Number Screened: 673

Eligible:

Enrolled:

Analyzed: 125

456

132

Exclusion criteria:

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

				Withdrawals due to AEs/
Drug name	dosage	N=	Duration	Total withdrawal
Zaleplon	5 mg	34	14 day	1 / 3
Zaleplon	10 mg	33	33 day	0 / 1
Triazolam	0.25 mg	31	14 day	0 / 0
Placebo	NA mg	34	14 day	0 / 3

Author:	Walsh_	Trial typ	e: Activ	/e					Q	uality rat	ing: Good	
Year:	1998b	Country	: US						F	unding: \	Wyeth Ayers	t
Outcome	Measurement:				Effica	су	Outcon	ne List	:			
# Polys	somnography				Prima	•						
# Sleep	questionnaire				outcor	ne						
							Total sle					
		☐ Sleep duration ☐ No. of awakenings										
								-		n each slee	n et	
							70 OI 1010	ai oloop ti	то ороти	11 64611 5166	p 3t	
Results												
Polysomno	<u>ography</u>											
	# Total sleep time day 4-5 and day 16-	Zaleplon	5mg	Zaleplor	n 10mg	F	Placebo				P value	
17, minutes	ninutes	413.6	(18) 402	(396.8) 4	100	(411.3)		() NS	
		during	(after	ı	Y)			I			
# Total	sleep time- day 4-5	Zaleplon	` 5ma	Zaleplor	n 10mg	1	Friazolam	0.25mg	Placebo		P value	
	,	413.6	(<0.001		(0.014	-		(NA)	400	(< 0.001		
		Minute	(p vs tria:	´ ∣ zolam	,) 		,				
# Total	sleep time- day 16-17	Zaleplon		Zaleplor	10mg	, 	Triazolam	0.25ma	Placebo		D l	
# 101a1	sleep line- day 10-17	418	(0.63) 396.8	(0.22	-		(NA)	411.3	(0.35	P value	
				<u> </u>	(0.22		720	(14/4)	711.0	(0.55	,	
		Minute	(p vs tria:		,)			1			
# Later	ncy to persistent sleep- day 4-5	Zaleplon		Zaleplor		-	Triazolam		Placebo		P value	
		17	(0.019) 19.25	(0.039) 1	18.5	(NR)	25.38	(NA)	
		Minute	(p vs plad	cebo)					_	
# Later	ncy to persistent sleep- day 16-17	Zaleplon	5mg	Zaleplor	n 10mg	1	Friazolam (0.25mg	Placebo		P value	
-,		18	(0.019) 16.75	(0.039) 2	23.75	(NR)	20.5	(NA)	
			(p vs plac	cebo))			1			

Author:	Walsh_	Trial type	: Acti	ve						Q	uality ra	ting: Good	
Year:	Country:	Country: US							Funding: Wyeth Ayerst				
	awakenings- day 4-5 and day	Zaleplon 5mg Zaleplon 10mg			on 10mg		Triazola	m 0.25m	g	Placebo		P value	
16-17		NR	() NR	()	NR	()	NR	() NS	
		Number	()	I						
	tal sleep time spent in each	Zaleplon 5	mg	Zaleplo	on 10mg		Triazola	m 0.25m	g	Placebo		P value	
sleep st	tage- day 4-5 and day 16-17	NR	() NR	()	NR	()	NR	() NS	
		Number	()							
# Latency to persistent sleep- day 16-17		Zaleplon 5	mg	Zaleplo	n 10mg		Triazola	m 0.25m	g	Placebo		P value	
		416.5	(NS) 400	(NS)	406.75	(NS)	408.5	(NA) NS	
		Minute	(p vs pla	icebo)							

Author:Walsh_Trial type:ActiveQuality rating:GoodYear:1998bCountry:USFunding:Wyeth Ayerst

Year:	1998b	Country:	US					Funding:	W	yeth Ayers
Sleep qu	uestionnaire									
# Sub	ojective sleep latency- day 4-5,	Zaleplon 5	mg	Zaleplor	10mg		Triazolam 0.25mg	Placebo		P value
sco	ore	shorter	(0.003) shorter	(0.056)	shorter (0.015)	NR (NA)	
		vs placebo	(p vs plac	ebo)				
# Sub	# Subjective sleep latency- day 6-14,		mg	Zaleplor	10mg		Triazolam 0.25mg	Placebo		P value
sco	pre	shorter	(0.67) shorter	(0.03)	shorter (0.168)	NR (NA)	
		vs placebo	(p vs plac	ebo)	1	1		
	ojective total sleep time- day 1-2,	Zaleplon 5	mg	Zaleplor	10mg		Triazolam 0.25mg	Placebo		P value
sco	ore	NR	(NS) NR	(NS)	NR (<0.00)	NR (NA)	
		vs placebo	(p vs plac	ebo)	1	1		
# Sub	ojective total sleep time- day 3-19,	Zaleplon 5	mg	Zaleplor	10mg		Triazolam 0.25mg	Placebo		P value
sco	ore	NR	(NS) NR	(NS)	NR (NS)	NR (NA)	
		vs placebo	(p vs plac	ebo)	ı		1	II.
	ojective no. of awakenings- day 6-	Zaleplon 5	mg	Zaleplor	10mg		Triazolam 0.25mg	Placebo		P value
14,	number	NR	(NS) NR	(NS)	NR (0.046)	NR (NA)	
		vs placebo	(p vs plac	ebo)	1		1	
	ojective sleep latency after	Zaleplon 5	mg	Zaleplor	10mg		Triazolam 0.25mg	Placebo		P value
disc	continuation night, score	NR	(NS) NR	(NS)	longer (0.036)	NR (NA)	
		vs placebo	(p vs plac	ebo)	I.	-	·	
	ojective total sleep time after	Zaleplon 5	mg	Zaleplor	Zaleplon 10mg		Triazolam 0.25mg	Placebo		P value
disc	continuation night, score	NR	(NS) NR	(NS)	shorter (0.022)	NR (NA)	
		vs placebo	(p vs plac	cebo)	1	1		

Author: Walsh__ Trial type: Active Quality rating: Poor

Year: 2000 Country: US Funding: Wyeth-Ayerst Research

Design:

Age: 42 Number Screened: 73 Range: 22-49

DB SD: Eligible: 39
Crossover Enrolled: 30

Crossover Enrolled: 30

Gender: NR (%) Female

Setting Single Center Number Withdrawn: 2

Ethnicity: NR Lost to fu: 0

Analyzed: 22

Eligibility criteria:

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, comsumption 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 absorbtion or metabolism of the study drugs.

Comments:

The population characteristics of enrolled subjects were not reported. Only the characteristics for analyzed subjects were reported. 22 subjects were analyzed, 11 men; mean age, 42 y; range, 22-49.

Intervention: Run

Run-in: NR Wash out: NR

Allow other medication :

Withdrawals due to AEs/

Drug name	dosage	N=	Duration	Total withdrawal
Zaleplon	10 mg	22	2 day	/
Flurazepam	30 mg	22	2 day	/
Placebo	NA mg	22	2 day	/

Author:	Walsh	Trial type:	Active	Quality rating:	Poor
		7 1			

Year: 2000 Country: US Funding: Wyeth-Ayerst Research

Primary

Outcome Measurement:

sleep latency testing

sleep questionnaire

outcome Outcome:

✓ Sleep latency

Efficacy Outcome List:

✓ Number of minutes sleep

Results

Sleep latency testing

# 5 hourrs after drug administration,	Zaleplon	1							P value
score	16.6	(20.0)	()	()	()	0.071
	Mean	(Median)					_
# 5 hourrs after drug administration,	Flurazep	oam							P value
score	6.8	(5.5)	()	()	()	<0.001
	Mean	(Median)					
# 5 hourrs after drug administration,	Flurazep	oam							P value
score	6.8	(5.5)	()	()	()	<0.001
	Mean	(Median)					
# 6.5 hourrs after drug administration,	Zaleplon	ı							P value
score	14.7	(15.5)	()	()	()	0.111
	Mean	(Median)					
# 6.5 hourrs after drug administration,	Flurazep	oam							P value
score	5.6	(4.3)	()	()	()	<0.001
	Mean	(Median)		,			,
# 6.5 hourrs after drug administration,	Flurazep	oam							P value
score	5.6	(4.3)	()	()	()	<0.001
	Mean	(Median)		,		-	

Median

Author: **Quality rating: Poor** Walsh__ Trial type: Active Country: US **Funding: Wyeth-Ayerst Research** Year: 2000 sleep questionnaire Zaleplon Flurazepam # time to sleep (minute) P value 27.5) 22.5) NR Median # number of minutes sleep Zaleplon P value 195) NR Median Flurazepam # number of minutes sleep P value) < 0.01 206.3 Median # number of minutes sleep Flurazepam P value 206.3) < 0.05

Author: Ware Trial type: Active Quality rating: Fair

Year: 1997 Country: US Funding: Lorex Pharmaceuticals

Design:

Study design RCT

DB

Parallel

Setting Multicenter

Eligibility 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.

Age: NR

Range: 21-55

SD:

Gender: 64 (58 %) Female

Ethnicity: 69% white

Number Withdrawn: 11 Lost to fu: NR

Eligible:

Enrolled:

Number Screened:

Analyzed: 99

358

NR

110

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.

Comments:

No baseline demographic data provided, but states groups did not differ significantly in gender, age, race, height, and weight.

Intervention:

Run-in: 2

Wash out: 3

Allow other medication: NR

Withdrawals due to AEs/

Drug name	dos	age	N=	Duration	Total w	ithdrawal	
Zolpidem	10	mg	37	28 day	3	/ NR	
Triazolam	0.5	mg	30	28 day	4	/ NR	
Placebo	NA	mg	35	28 day	0	/ NR	

Author:	Ware	Trial type	: Acti	ve				Quality rat	ing: Fair
Year:	1997	Country:	US					Funding: I	Lorex Pharmaceuticals
Outcome	e Measurement:					-	ome List:		
# ever	rsomnography ning questionnaire g effects questionnaire				Primar outcon	Sleep Sleep no. of waking wake % of ti quality mornii	Latency Efficiency awakenings g time during s time after slee	p EM and deep sleep	
Results									
polysomn	nography								
# later 28	ncy to persistent sleep- nigtht 27 &	Zolpidem -7	(NS	Triazo	lam (NS)	Placebo -15	(<0.05)	()	P value
		minutes	(p vs ba	seline)	1			
# slee	ep efficiency- nigtht 27 & 28	Zolpidem		Triazo	lam	Placebo			P value
		1	(NS) 3	(<0.05)	5	(<0.05)	()	
		%	(p vs ba	seline)		·		
# no. 0	of awakenings- night 27 & 28	Zolpidem		Triazo	lam	Placebo			P value
		1	(NS) -2	(<0.05)	-1	(NS)	()	
		Number	(p vs ba	seline)	-1	l.		
# wak	ing time during sleep	Zolpidem		Triazo	lam	Placebo			P value
		0	(NS) -20	(<0.05)	2	(NS)	()	
		minutes	(p vs ba	seline)	1	l I		

Author: Wheatley Trial type: Active Quality rating: Fair
Year: 1985 Country: NR Funding: Not reported

Design:

Study design RCT

DB

Crossover

Setting NR

Age: 53.2

Range: 25-82 SD: 2.1

Gender: 22 (61 %) Female

Ethnicity: NR

Number Withdrawn: 2 Lost to fu: 0 Analyzed: 36

Number Screened: NR

Eligible:

Enrolled:

NR

36

_ . .

Eligibility criteria:
Patients aged 18 years and over suffering from difficulty in sleeping,

provided that symptoms had been present for at least one week.

Exclusion criteria:

NR

Comments:

zopiclone first group had a higher proportion of patients previously responding well to hypnotics and more heavy smokers.

Intervention:

Run-in: 3

Wash out: NR

Allow other medication: NR

				Withdrawals due to AEs/
Drug name	dosage	N=	Duration	Total withdrawal
Zopiclone	7.5 mg	36	7 day	2 / 2
Temazepam	20 mg	36	7 day	0 / 0

Author:	Wheatley	Trial type	: Act	ive					Quality	ratir	ng: Fair
Year:	1985	Country:	NR						Fundin	g: N	ot report
Outcome I	Measurement:				Effic	асу	Outcome Li	st:			
# Patien	t Questionnaires				Prim outc		Outcome:				
]]]	Sleep latency No. time wakir Quality of slee Duration of sle	p			
					✓		Dreaming State on wakir	ıg			
Results Patient Que	estionnaires										
# Sleep	latency	Zopiclone		Placeb	0						P value
		30.8	(<0.01) 29.1	(<0.01)	()	()	
		Minutes	(p vs ba	seline)					
# No. tin	ne waking	Zopiclone		Temaz							P value
		0.75	(<0.01) 0.66	(<0.01)	()	()	
		Number	(p vs ba	seline)					
# Quality	of sleep (0-4)	Zopiclone		Temaz							P value
		0.93	(<0.01) 0.87	(<0.01)	()	()	
		Score	(p vs ba	seline)					
# Duration	on of sleep	Zopiclone		Temaz	epam						P value
		6.6	(< 0.01) 6.6	(<0.01)	()	()	
		Hours	(p vs ba	seline)					
# Dream	ning (0-4)	Zopiclone		Temaz	epam						P value
		0.46	(NS) 0.46	(NS)	()	()	
		Score	(p vs ba	seline)					

Author: Wheatley	Trial type: Active Quality rating: Fair
Year: 1985	Country: NR Funding: Not reported
# State on waking (0-3)	Zopiclone Temazepam P value
	0.39 (NS) 0.38 (NS) () ()
	Score (p vs baseline)
# At work (0-3)	Zopiclone Temazepam P value
	0.51 (<0.05) 0.54 (NS) () ()
	Score (p vs baseline)
# With others (0-3)	Zopiclone Temazepam P value
	0.63 (NS) 0.67 (NS) () ()
	Score (p vs baseline)
# Driving (0-3)	Zopiclone Temazepam P value
	0.35 (NS) 0.57 (NS) () ()
	Score (p vs baseline)
# All measures	Zopiclone Temazepam P value
	as above () as above () () NS

Quality rating: Fair Author: Elie Trial type: Active

Year: 1990b Country: Canada **Funding: Not reported**

Design:

Study design RCT

DB

Parallel

Setting Single Center Age: 37.6

Range:

SD: 1.84

Gender: 24 (67 %) Female

Ethnicity: NR

Lost to fu: 0

Number Screened:

Eligible:

Enrolled:

Number Withdrawn: 0

Analyzed: 36

NR

NR

36

Eligibility 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 askeep, (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.

Comments:

Intervention:

Withdrawals due to AEs/

Drug name	dosage	N=	Duration	Total withdrawal	
Zopiclone	7.5 mg	12	28 day	0 / 0	
Flurazepam	30 mg	12	28 day	0 / 0	
Placebo	NA mg	12	28 day	0 / 0	

Rebound:

post-sleep quesionnaire

rebound: rapidity of sleep onset at day 29 (higher score=better)

Zopiclone Flurazepam Placebo P value 5.8 (NS) 7.3 (NS 10 (<0.01)Score (p vs baseline

rebound: duration of sleep at day 29 (higher score=better)

Zopiclone Flurazepam Placebo P value 3.6 (NS) 6.2) 7.3 (<0.05)(NS

Score (p vs baseline

Author:ElieTrial type:ActiveQuality rating:FairYear:1990bCountry:CanadaFunding:Not reported

rebound: nocturnal awakenings at day 29 (higher score=worse)

Zopiclon	ne		Fluraz	epam		Place	bo				P value
5.0	(NS)	6.3	(NS)	8.0	(NS)	()	
Score	(p vs	ba	seline)	•					1

 Author:
 Fleming_
 Trial type:
 Active
 Quality rating:
 Fair

 Year:
 1990
 Country:
 Canada
 Funding:
 Not reported

Design:

Study design RCT

DB

Parallel

Setting Multicenter

Age: 45.5

Ethnicity: NR

Range:

SD:

Gender: NR (%) Female

remale

Number Withdrawn: 4

Number Screened: NR

Eligible:

Enrolled:

Lost to fu: 0 Analyzed: 48

NR

52

Eligibility 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, analgesis, or antidepressants or with a history of hypersensitivity to one or more hypnotic drugs were excluded. Subjects whose insomnnia was considered secondary to a psychiatric or medical disorder were also excluded as those with a history of alcoholism, drug abuse, or caffeine overuse.

Comments:

Enrolled population characteristics were not reported. Analyzed population characteristics: mean age=45.5 years; 23 (48%) female.

Intervention:

Withdrawals due to AEs/

Drug name	dosage	N=	Duration	Total withdrawal
Zopiclone	7.5 mg	24	21 day	2 / 2
Triazolam	0.25 mg	24	21 day	10 / 10

Rebound:

post-sleep quesionnaire

rebound: sleep duration at the last withdrawal day

rebound: sleep induction at the last withdrawal day

Zopiclor	ie		Triazo	lam						P value
4.3	()	5.9	()	()		()	<0.05
Score	()			l .		
Zoniclor			Triazo	lam						P value

Score	(•)		,				-
Zopiclon	е		Triazo	olam						P value	
4.7	()	6.1	()	()	()	NS	
Score	()					•	•

Author:	Fleming_	Trial type:	Active						Quality	rating:	Fair			
Year:	1990	Country:	Canada	Canada						Funding: Not reported				
		ep soundness at the las	t Zopiclor	ne	Triazolam						P value			
	withdrawal da	ay	7.4	() 8.6	()	()	()	NS		
			Score	()							
	withdrawal effects													
	# rebound insomnia		Zopiclor	ne	Tria	zolam						P value		
			73	() 71	()	()	()	NS		
			%	(•)							
	# rebound: slee	ound: sleep induction, duration	Zopiclor	ne	Tria	zolam						P value		
	and soundne nights	ess at the first withdrawa	NR NR	(NS) NR,	wor (<0	.05)	()	()			
	9		Score	(pv	s baseline))							
	# rebound: slee	ep soundness	Zopiclor	ne	Tria	zolam						P value		
			NR	() NR,	bett ()	()	()	<0.05		
)		+					
	# rebound: with	ndrawal symptoms	Zopiclor	ne	Tria	zolam						P value		
			3	() 2	()	()	()	NS		
			Numbe	r ()		+					

Trial type: Active Quality rating: Fair Author: Hajak

Year: 1998, 1995, 1994 Country: **Funding: Not reported** Germany

Design:

Study design RCT

DB

Parallel

Setting Multicenter Age: 51

> Range: 18-71 SD: 11

Gender: 940 (62 %) Female

Ethnicity: 99.3% Caucasian

0.9% Others

Number Screened: NR

Eligible: NR

Enrolled: 1507

Number Withdrawn: 0 Lost to fu: 0

Analyzed: 1507

P value

0.00126

Eligibility criteria:

Insomnia of at least 4-week duration and the presence of at least two of the following as a mean of 3 days before starting treatment (no-pill baseline): (a) sleep latency >= 45 min, (b) total sleep time <= 6 hours, and © nocturnal awakening >= 3 times.

Exclusion criteria:

Any patients who had taken a single daily dose of a benzodiazepine or any other hypnotic more than three times per week during the 14 days prior to admission, or any patients with psychiatric disorders (e.g., depression, schizophrenia, severe neuroses), or any patients who had contraindications for zopiclone, flunitrazepam, or triazolam were excluded from this study

Comments:

Patients were observed for a further period of 14 days without medication for rebound.

Intervention:

Withdrawals due to AEs/

Drug name	dosage	N=	Duration	Total withdrawal	
Zopiclone	7.5 mg	612	28 day	26 / 190	
Triazolam	0.2 mg	307	28 day	11 / 187	
Placebo	NA mg	298	28 day	25 / 193	

Rebound:

Total response

rebound: Improved sleep quality and daytime well-being

Zopiclo	ne	Triazo	lam				
27.0	() 18.8	()	()	(
%	(,)		ı	

Rebound rates in treatment respnders

overall rebound

Zopiclone	Triazolam			P value
46.07 (1.42)	46.63 (1.93)	()	()	NS

(SD

Author:	Hajak	Trial type:	Active						Quality	rating: F	air
ear:	1998, 1995, 1994	Country:	Germany	,					Fundin	g: Not rep	oorted
	# Rebound: over	all rebound	Zopiclor	ne	Placebo	0					P value
			46.07	(1.42	48.56	(3.28)	()	() <=0.01
			%	(SD)		+		
	# Rebound: Resp	oonder	Zopiclor	ne	Triazola	am					P value
			9.05	(1.16	7.70	(0.88)	()	() <=0.01
			%	(SD)				"
	# Rebound: Resp	oonder	Zopiclor	ne	Placebo)					P value
			9.05	(1.16	4.92	(1.20)	()	() <=0.01
			%	(SD	•)				·
	# Rebound: Nonr	esponder	Zopiclor	ne	Triazola	am					P value
			36.02	(1.35	38.93	(1.45)	()	() <=0.01
			%	(SD)		•		·
	Rebound rates for items	s of sleep quality									
	# Rebound: sleep	o quality - 1 item	Zopiclor	ne	Triazola	am					P value
			14.33	(1.11	16.32	(1.33)	()	() <0.001
			(%)	(SD)				
	# Rebound: sleep	o quality - 2 items	Zopiclor	ne	Triazola	am					P value
			6.76	(0.83	8.27	(1.04)	()	() <=0.05
			(%)	(SD)				
	# Rebound: sleep	o quality - 3 items	Zopiclor	ne	Triazola	am					P value
			2.36	(0.47	2.39	(0.85)	()	() NS
			(%)	(SD)				
	Rebound rates for items	s of daytime well-bei	ing		i						ı
	# Rebound: dayti	me well-being - 1 ite	em Zopiclor	ie	Triazola	am					P value
			18.52	(1.44	19.04	(2.00)	()	() NS
			%	(SD)				

Author:	Hajak	Trial type:	Active			Q	Quality rating: Fair					
Year:	1998, 1995, 1994	Country:	Germany					F	Funding: Not reported			
	# Rebound: daytir	me well-being - 2	Zopiclone	е	Triazo	am						P value
	items		14.09	(1.11)	13.10	(1.91)		()	()	NS
			%	(SD)						
	# Rebound: daytir	me well-being - 3	Zopiclone	е	Triazo	am						P value
	items		7.89	(0.82)	7.73	(1.33)		()	()	NS
			%	(SD	I)	1		+			

Trial type: Active **Quality rating: Poor** Author: Liu Year: 1997 Country: Taiwan **Funding:** Design: Age: 40.1 Number Screened: NR Study design RCT Range: 20-58 NR

DB SD: 10.9 Eligible: Crossover Enrolled:

Setting Single Center Gender: 11 (73 %) Female

Number Withdrawn: 0

Ethnicity: NR Lost to fu: 0
Analyzed: 15

15

Eligibility criteria:

Outpatients who suffered from insomnia for more than 3 months, with at least 3 of the following symptoms: sleep onset greater than 1 hour, total sleep duration of less than 5 hours, more than 2 nocturnal awakenings, and poor subjectively reported sleep quality.

Exclusion criteria:

Patients with psychoses or mood disorders, history of severe physical illness, alcohol abouse or drug abuse.

Comments:

Poor quality- baseline characterisitcs not reported, no information on randomization and allocation concealment methods. Unable to determine if an intention-to-treat analysis was used, and high loss to followup. (8 patients did not complete the trial; unclear if 8 of 15 or 8 of 23).

Intervention:

Withdrawals due to AEs/

Drug name	dosage	N=	Duration	Total withdrawal	
Zopiclone	7.5 mg	15	14 day	0 / 0	
Triazolam	0.25 mg	15	14 day	0 / 0	
Placebo	NA mg	15	14 day	0 / 0	

Score

Rebound:

Spiegel's sleep questionnaire (SSQ)

#	rebound: 6 out of 7 items shows less	Zopiclone	Triazolam					P value
	rebound effects in Zopiclone	mulitple d ()	multiple ()	()	()	<0.05
		Score ()		,			

Leed's sleep evaluation questionnaire (LSEQ)

rebound: 9/10 items show more withdrawal sleep distrubance of triazolam

Zopiclone			Triazol	am						P value
NR	()	NR	()	()	()	<0.05

Quality rating: Fair Author: Mamelak Trial type: Active

Year: 1987 Country: Canada **Funding: Not reported**

Design:

Study design RCT

DB

Parallel

Setting Single Center Age: 50

Range: 32-60

Number Screened: NR

Eligible: NR

30

Enrolled:

Gender: 21 (70 %) Female

SD:

Number Withdrawn: 0 Ethnicity: NR

Lost to fu: 0 Analyzed: 30

Eligibility 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 noctunal 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.

Comments:

Ethanol-drug interaction study.

Intervention:

Withdrawals due to AEs/

Drug name	dosage	N=	Duration	Total withdrawal
Zopiclone	7.5 mg	10	12 day	0 / 0
Flurazepam	30 mg	10	12 day	1 / 1
Placebo	NA mg	10	12 day	0 / 0

Rebound:

sleep questionnaire

rebound: total sleep time at day 15

Zopiclone	Flurazepam	Placebo		P value
313.5 (NS)	356.5 (NS)	313.5 (NS)	()	

minutes (p vs baseline

rebound: sleep latency at day 15

Zopiclone	Э	Fluraze	pam	Placebo)				P value
105.0	(<0.05)	39.7	(<0.05)	75.5	(NS)	()	

minutes (p vs baseline

Author: Mamelak Trial type: Active Quality rating: Fair Year: 1987 Country: Canada **Funding: Not reported** Flurazepam Placebo # rebound: no. of awakenings at day 15 Zopiclone P value 2.10 (NS 2.05 (<0.05) 1.70 (<0.05)(p vs baseline minutes P value # rebound: duration of early Zopiclone Flurazepam Placebo wakefulness at day 15 41.5 (NS 27.8 (NS 46.9 (NS (p vs baseline minutes Zopiclone Flurazepam # rebound: sleep latency at day 15 P value <0.05 105.0 39.7 minutes Flurazepam P value # rebound: no. of awakenings at day 17 Zopiclone < 0.05 2.05 3.15 Number (Flurazepam # other rebounds P value Zopiclone NS multiple d (multiple (number

Trial type: Active Quality rating: Fair Author: Monti

Year: 1994 Country: Uruguay **Funding: Not reported**

Design:

Study design RCT

DB

Parallel

Setting Single Center Age: 47.3

Range: 21-65

SD:

Gender: 21 (88 %) Female

Ethnicity: NR

Number Withdrawn: 1

Number Screened: NR

Eligible:

Enrolled:

Lost to fu: 0 Analyzed: 24

NR

24

Eligibility 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 waketime >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.

Comments:

Intervention:

			Withdraw	als due to AEs/
Drug name	dosage	N=	Duration Total with	drawal
Zolpidem	10 mg	8	27 day 0 /	0
Triazolam	0.5 mg	8	27 day 1 /	1
Placebo	NA mg	8	27 day 0 /	0

Rebound:

polysomnogram

rebound: mean wake time (change from baseline)

#	rebound: mean total sleep time
	(change from baseline)

Zolpidem			Triazo	olam						P value
-80	(118)	43	(47.4)	()	()	NR
minutes	(SD)					
1			ii							I.

i	•			•	i.				
Zolpidem		Triazola	m						P value
80	(118.5)	-40	(52.2)	()	()	NR
minutes	(SD	•)					

Author:	Monti	Trial type:	Active						Qua	lity ra	ating:	Fair	•	
Year:	1994	Country:	Uruguay							Funding: Not reported				
	#	rebound: mean number of sleep	Zolpidem	Zolpidem		Triazolam							P value	
		cycles (change from baseline)	1.3	(1.5) -0.7	(0.7)	()		()	NR	
			Number	(SD	<u> </u>)	1						
	sleep o	<u>questionnaire</u>												
	#	rebound: increased number of	Zolpidem		Triazo	olam		Placebo					P value	
	#	awakenings- day 32	3	(37.5) 5	(62.5)	0 (0)		()	NR	
			Number	(%)							
	#	rebound: decreased sleep duration-	Zolpidem		Triazo	olam		Placebo					P value	
		day 32	3	(37.5) 6	(75)	2 (25)		()	NR	
			Number	(%)							
	#	rebound: increased time to fall sleep	- Zolpidem		Triazo	olam		Placebo					P value	
		day 32	3	(37.5) 8	(100)	0 (0)		()	NR	
			Number	(%	*)						•	

Author:QuadensTrial type:ActiveQuality rating:PoorYear:1983Country:BelgiumFunding:Not reported

Design:

Study design RCT

DB

Crossover

Setting Single Center

Age: NR

Range: 50-59

Number Screened: NR

Eligible: NR Enrolled: 12

SD:

Gender: 12 (100 %) Female

Number Withdrawn: 0

Lost to fu: 0

Analyzed: 12

Eligibility 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:

Ethnicity: NR

(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.

Comments:

Poor quality- insufficient information to assess quality.

Intervention:

Withdrawals due to AEs/

Drug name	dosage	N=	Duration	Total withdrawal
Zopiclone	7.5 mg	12	13 day	/
Flurazepam	30 mg	12	13 day	1

Rebound:

sleep questionnaire

rebound: no. of awakenings

Zopiclor	ne	Fluraze	epam					P value
5.5	(<0.05)	6.1	(<0.01)	()	()	

Number (p vs treatment data

Zopiclone	Flurazepam			P value
23490 (<0.05)	23184 (<0.05)	()	()	

seconds (p vs treatment data

rebound: total sleep time

Author:	Quadens	Trial type:	Active					Qua	lity ratir	ng:	Poo	r
Year:	1983	Country:	Belgium				Funding: Not reported					
	# rebound:	sleep onset latency	Zopiclone		Fluraz	epam						P value
			1255 (NS)	1042	(NR)	()		()	
			seconds (pv	s tre	atment	data)						1
	# rebound:	sleep efficiency index	Zopiclone		Fluraz	epam						P value
			86.9 (NS)	84.9	(<0.01)	()		()	
			Score (pv	s tre	atment	data)		+				II.

Author: Silvestri Trial type: Active Quality rating: Fair

Year: 1996 Country: Italy Funding: Not reported

Design:

Study design RCT

DB

Parallel

Setting Multicenter

Age: 33.6

Range: NR SD: 10.4

Gender: 12 (55 %) Female

Ethnicity: NR

Number Withdrawn: 0

Number Screened:

Eligible:

Enrolled:

Lost to fu: 2 Analyzed: 20

NR

NR

22

Exclusion criteria:

Eligibility criteria:

Both sexes, age between 18 and 65 years, clinical diagnosis of psychophysiological insomnia (either as a first episode or as a recurrence of short-term situaitonal insomnia) or poor sleepers with subjective reporting of at least two out of these four complaints: time to fall asleep >30 minutes, total sleep duration <6 hours, total wake time >20 minutes, and/or number or awakenings >3. These subjective inclusion criteria had to be confirmed by the objective assessment through polysomnography.

Pregnant or lactating women; women of child-bearing age withoug adequate contraception; uncooperative patients; severe psychiatric diseases, also screened by means of both Hamilton Rating Scale for Anxiety (total score >16) and Hamilton Rating Scale for Depression (total score >16); neurological diseases (myoclones, kinaesthesis disorders, restless legs syndrome, sleep obstructive apnea of >7 minutes duration); severe internal (heart, renal, liver) diseases; hemocoagulation disorders (Quick's time <70%); intake of any psychotropic durg during 2 weeks preceding the study start as well as a previous with beta blockers or corticosteroids.

Comments:

Intervention:

Withdrawals due to AEs/ Drug name N= Duration Total withdrawal dosage Zolpidem 10 mg 10 2 week 0 / 0 Triazolam 0.25 mg 12 2 week 0 / 2

Rebound:

polysomnography

- # rebound: sleep onset latencychange from baseline- night 15
- # rebound: total sleep time- change from baseline- night 15

Zolpidem		Triazolam						P value
-11.6	(31.98)	7.1 (30.73)	()	()	NS
minutes	(SD	ı)					

Zolpidem	Triazolam			P value
43.8 (62.54)	-34.5 (50.24)	()	()	<0.01

minutes (SD

Author: 'ear:	Silvestr 1996	7 1	ctive aly					-	y rating: Fai	
		<u> </u>			1				.g	
	#	rebound: sleep efficiency- change from baseline- night 15	Zolpidem		Triazo					P value
		nom baseline mgm to	9.9	(13.63)	-6.3	(8.55)	()	(<0.01
			%	(SD)				
	#	rebound: wake time after sleep	Zolpidem		Triazo	am				P value
		onset- change from baseline- night 15	9.9-37.5	(49.01)	17.3	(31.89)	()	(<0.01
			minutes	(SD)		•		
	#	rebound: no. of awakenings- change	Zolpidem		Triazo	am				P value
		from baseline- night 15	-1.9	(7.16)	-1.2	(4.67)	()	() NS
			Number	(SD	1)		4		
	quesion	naire								
	#	rebound: time to fall asleep- change	Zolpidem		Triazo	am				P value
		from baseline- night 15	-20.8	(28.23)	8.6	(31.65)	()	(<0.05
			minutes	(SD	-)				
	#	rebound: total sleep time- change	Zolpidem		Triazo	am				P value
		from baseline- night 15	51.9	(45.4)	-35.6	(127.9)	()	() <0.01
			minutes	(SD	1)				
	#	rebound: total wake time- change	Zolpidem		Triazo	am				P value
		from baseline- night 15	-2.2	(12.96)	13.2	(38.71)	()	() NS
			minutes	(SD	-)				
	#	rebound: no. nocturnal awakenings-	Zolpidem		Triazo	am				P value
		change from baseline- night 15	-0.3	(2.32)	0.4	(0.86)	()	() NS
			Number	(SD	1)				
	visual a	nalogue scale		•		,				
		rebound: sleep quality- change from	Zolpidem		Triazo	am				P value
		baseline- night 15	-12.9	(20.59)	0.8	(22.88)	()	() NS
			Score	(SD	1)	`			·

Author: Silvestri Trial type: Active Quality rating: Fair
Year: 1996 Country: Italy Funding: Not reported

rebound: awakening quality- change from baseline- night 15

Zolpidem	1	Triazol	am					P value
-12.9	(21.34)	-1.5	(21.36)	()	()	NS
Score	(SD)			1		

sleep depth after discontinuation-

rebound

Quality rating: Fair Author: Stip Trial type: Active Year: 1999 Country: Canada **Funding: Not reported** Design: Age: 42.6 Number Screened: NR Study design RCT Range: Eligible: NR DB SD: Enrolled: 60 Parallel Gender: NR (%) Female Setting Single Center Number Withdrawn: 2 Ethnicity: NR Lost to fu: 8 Analyzed: 50 Eligibility criteria: **Exclusion criteria:** Patients with either primary insomnia or insomnia associated with mild NR non-psychotic psychiatrc disroders (DSM III-R). Daytime fatigability, diminished power of concentration at work and at least two of the following symptoms: falling asleep time greater than 30 min, sleep duration less than 5 hours, more than two awakenings per night and early wake up in the morning. Comments: Participants who had been taking hypnotic drugs with a long half-life received lorazepam for one week, prior to a week placebo. Patients who had been taking benzodiazepines with a short or intermediate half-life were put only on placebo for one week. Enrolled population characteristic were not reported. Analyzed population characteristics: mean age=42.6 years; 21 (42%) female Intervention: Withdrawals due to AEs/ Drug name dosage N= Duration Total withdrawal Zopiclone 7.5 mg 19 21 day 0 / 0 30 mg 0 / 1 Temazepam 16 21 day Placebo 0 / 1 NA mg 15 21 day Rebound: Self-rating questionnaire for sleep # sleep onset after discontinuation -Zopiclone Temazepam P value rebound NR (NS NR, wor (<0.05) Score (p vs placebo

Temazepam

NR, wors (<0.01) NR, wor (<0.01)

(p vs placebo

P value

Zopiclone

Score

Author: Voshaar Trial type: Active Quality rating: Fair

Year: 2004 Country: Netherlands Funding: Sanfi-Synthelabo

Design:

Study design RCT

DB

Parallel

Setting Multicenter

Age: 46.1

Range: SD:

3D.

Gender: NR (0 %) Female

Ethnicity: NR

Lost to fu: 5 Analyzed: 159

Number Screened: NR

Eligible:

Enrolled:

Number Withdrawn: 9

NR

221

Eligibility criteria:

Patients were included in the study if they were diagnosed with primary insomnia according to DSM-III-R and were aged between 18 and 65 years.

Exclusion criteria:

Patients with other axis I disorders, severe somatic disorders, pregnancy, current use of psychotropic medication, complaints of a jet lag in the 2 weeks preceding the study or occupation requiring shift work

Comments:

Enrolled population characteristics were not reported. Only analyzed population characteristics were reported:

Intervention:

Withdrawals due to AEs/

Drug name	dos	age	N=	Duration	Total withdrawal
Zolpidem	10	mg	74	28 day	N / NR
Temazepam	20	mg	85	28 day	N / NR

Rebound:

rebound

rebound- mean total sleep time

Zolpidem			Temaz	zepam						P value
370	(84)	352	(89)	()	()	NS
minutes	(SD)			•		

rebound- prevalence rebound insomnia (TST)

rebound- sleep onset latency

		P value
27 () 25.9 () ()	() NS

% ()

Zolpidem	Temazepam			P value
60 (51)	73 (53)	()	()	NS

minutes (SD

Author: Voshaar Trial type: Active Quality rating: Fair 2004 Year: Country: Netherlands Funding: Sanfi-Synthelabo # rebound- prevalence rebound insomnia (SOL) Zolpidem P value Temazepam NS 53.4) 58.3

Trial type: Active Quality rating: Fair Author: Ware

Year: 1997 Country: US **Funding: Lorex Pharmaceuticals**

Design:

Study design RCT

DB

Parallel

Setting Multicenter Age: NR

Range: 21-55

Number Screened:

358 Eligible: NR

110

Gender: 64 (58 %) Female

Ethnicity: 69% white

Lost to fu: NR

Enrolled:

Number Withdrawn: 11

Analyzed: 99

Eligibility 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:

SD:

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.

Comments:

No baseline demographic data provided, but states groups did not differ significantly in gender, age, race, height, and weight.

Intervention:

Withdrawals due to AEs/

Drug name	dosage	N=	Duration	Total withdrawal	
Zolpidem	10 mg	37	28 day	3 / NR	
Triazolam	0.5 mg	30	28 day	4 / NR	
Placebo	NA mg	35	28 day	0 / NR	

Rebound:

polysomnography

rebound: latency to persistent sleepdiscontinuation nigtht 1

Zolpidem			Triazo	am	Placeb	00			P value
6	(NS)	47	(<0.05)	-11	(NS)	()	

rebound: latency to persistent sleepdiscontinuation nigtht 1

Zolpidem	Triazolam	Placebo		P value
6 (NS)	47 (<0.05)	-11 (NS)	()	

(p vs baseline minutes

minutes (p vs baseline

Author:	Ware	Trial type: A	Active				Quality	/ rating: F	Fair	
ear:	1997	Country: L	JS				Fundir	ng: Lorex	Phar	maceutio
	#	rebound: sleep efficiency-	Zolpiden	1	Triazo	lam	Placebo			P value
		discontinuation nigtht 1	-3	(NS)	-15	(<0.05)	5 (<0.05)	()	
			%	(p vs ba	seline)				
	<u>reboun</u>	d questionnaire- discontinuation night 1	<u>-</u> ,							
	#	rebound: sleep latency	Zolpiden	า	Triazo	lam	Placebo			P value
			14	(NS)	72	(<0.05)	-16 ()	()	
			minutes	(p vs ba	seline)	•			
	#	rebound: total sleep time	Zolpiden	า	Triazo	lam	Placebo			P value
			-4	(NS)	-63	(<0.05)	49 (0.05)	()	
			minutes	(p vs ba	seline)				
	#	rebound: no. of awakenings	Zolpiden	า	Triazo	lam	Placebo			P value
			1	(NS)	1	(NS)	-1 (<0.05)	()	
			Number	(p vs ba	seline)	<u>'</u>		,	
	#	rebound: wake min during sleep	Zolpidem	า	Triazo	lam	Placebo			P value
			-4	(NS)	48	(<0.05)	-29 (<0.05)	()	
			minutes	(p vs ba	seline)	<u>'</u>		,	
	#	rebound: quality lantency	Zolpidem	า	Triazo	lam	Placebo			P value
			0.3	(NS)	0.8	(<0.05)	-0.4 (<0.05)	()	
			Score	(p vs ba	seline)	-			
	#	rebound: morning sleepiness	Zolpiden	า	Triazo	lam	Placebo			P value
			-5	(NS)	-6.7	(NS)	4.5 (NS)	()	
			Score	(p vs ba	seline)	1			
	#	rebound: ability to concentrate	Zolpiden	า	Triazo	lam	Placebo			P value
		·	0.2	(<0.05)	0.1	(NS)	-0.1 (NS)	()	
			Score	(p vs ba	seline)	· · ·			

Evidence Table 5. Active controlled trials (Adults): Rebound Insomnia

Author: Ware Trial type: Active Quality rating: Fair

Year: 1997 Country: US Funding: Lorex Pharmaceuticals

rebound: over all repounds

Zolpidem			Triaz	olam		Place	ebo				P value
15	()	43	()	11	()	()	
%	- (,						•

Author: Anderson Trial type: Active Quality rating: Fair

Year: 1987 Country: UK Funding: Not reported

Design:

Study design RCT

DB

Parallel

Setting Multicenter

Eligibility criteria:

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

Comments:

Intervention: Run-in: 7

Wash out: 7

Allow other medication: No

Age: NR

Range: 20-69

SD:

Gender: NR (0 %) Female

Ethnicity: NR

NR Number Withdrawn: 5
Lost to fu: 15

Analyzed: 99

Number Screened: NR

Eligible:

Enrolled:

NR

119

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 ti drugs or continuous use of high doses of a hypnotic for a period in excess of 6 months. Other groups exluded were pregnant women, nursing mothers, women of childbearing potential, and night shift workers.

Drug name	dosage	N=	Duration	Total withdrawal	
Zopiclone	7.5 mg		14 day	1 / 2	
Nitrazepam	5 mg		14 day	1 / 1	
Placebo	NA mg		14 day	1 / 2	

Author: Anderson Trial type: Active Quality rating: Fair

Year: 1987 Country: UK Funding: Not reported

Adverse Events:

bitter tastes

no, of patients

Zopiclone	Nitrazepam			P value:
9 (24.3)	NR (NR)	()	()	

Number (%

withdrawals

total withdrawals

Zopicl	one		Nitraz	zepam		Plac	ebo				P value:
2	()	1	()	2	()	()	

Number (

withdrawals due to AEs

Zopicl	one		Nitraz	epam		Place	ebo				P value:
1	()	1	()	1	()	()	

Number (

Author: Autret Trial type: Active Quality rating: Poor

Year: 1987 Country: France Funding:

Design:

Study design CT

DB

Crossover

Setting Single Center

Age: 46.3

Range: SD: 11.7

Gender: 85 (70 %) Female

Ethnicity: NR

Number Withdrawn: NR

Number Screened: NR

Eligible:

Enrolled:

Lost to fu: 8 Analyzed: 113

NR

121

Eligibility criteria:

Patients had suffered for more than 3 months from at least two of the following symptoms: subjective period of falling asleep greater than 2 hours; waking up more than twice at night; subjective length of night wakefulness greater than 30 minutes; waking more than 2 hours before the desired time; estimated total sleep time less than 6 hours.

Exclusion criteria:

NR

Comments:

Poor quality: No baseline characteristics reported, not reported if randomized, and unable to determine the number analyzed.

Intervention:

Run-in: 4 Wash out: 3

Allow other medication: NR

				Withdrawals due to AEs/
Drug name	dosage	N=	Duration	Total withdrawal
Zopiclone	7.5 mg	121	7 day	0 / 8
Triazolam	0.5 mg	121	7 day	0 / 8

Author: Autret Trial type: Active Quality rating: Poor

Year: 1987 Country: France Funding:

Adverse Events:

Guelfi side-effects check list

12 out of 18 items shows favour Zopiclone

Zopiclone	Triazolam	1				P value:
NR, bett ()	NR	()	(()	<0.05

Score (

Quality rating: Poor Author: Begg Trial type: Active

Year: 1992 Country: NR Funding: Roche Products (NZ) Ltd.

Design:

Study design RCT

SB

Parallel

Single Center Setting

NR Age:

> Range: >18 SD:

Gender: NR (0 %) Female

Ethnicity: NR

Lost to fu: 33 Analyzed: 51

Number Screened: NR

Eligible:

Enrolled:

Number Withdrawn: 4

NR

88

Eligibility criteria:

Patients were aged 18 years or older and satisfied on or more of the following criteria: a history of taking 30 minutes or more to fall asleep; two or more awakenings during the night; total reported sleep time of less than six hours.

Exclusion criteria:

Patients on medications known to affect sleep or on drugs known to alter drug metabolism during and within two weeks prior to the study were excluded. Alcohol infestion within four hours of retiring or more tna one glass (10 g) alcohol in the previous 24 hours were not permitted.

Comments:

Poor quality: very high withdrawal rate (42%) and no intention-to-treat analysis. No information on baseline characteristics.

Intervention: Run-in:

Wash out : 2

Allow other medication :

Drug name	dosage	N=	Duration	Total withdrawal	
Zopiclone	7.5 mg	28	11 day	1 /	
Midazolam	15 mg	23	11 day	3 /	

Author: Begg Trial type: Active **Quality rating: Poor**

Year: 1992 Country: NR Funding: Roche Products (NZ) Ltd.

Adverse Events:

#	No. of patients experiencing AEs (overall)	Zopiclor	ne	Midazo	olam						P value	
	(overall)	15	(31)	16	(40)	()	()	>0.05
		Number	(%)		·			
#	No. of AEs	Zopiclor	ne		Midazo	olam						P value
		21	()	28	()	()	()	>0.05
		Number	()		·			
#	No. of patients ecperiencing AEs - Daytime tiredness	Zopiclor	ne		Midazo	olam						P value
	Dayune mediess	6	(12.5)	6	(15)	()	()	NR
		Number	(%)					
#	No. of patients ecperiencing AEs - Taste disturbance	Zopiclor	ne		Midazo	olam						P value
	raste disturbance	6	(12.5)	0	(0)	()	()	NR
		Number	(%)		·			
#	No. of patients ecperiencing AEs -	Zopiclor	ne		Midazo	olam						P value
	Dry mouth	2	(4.2)	3	(7.5)	()	()	NR
		Number	(%)					
#	No. of patients ecperiencing AEs -	Zopiclor	ne		Midazo	olam						P value
	Indigestion/nousea/vomiting	1	(2.1)	5	(12.	5)	()	()	NR
		Number	(%)					•
#	No. of patients ecperiencing AEs -	Zopiclor	ne		Midazo	olam						P value
	Clumsiness	0	(0		4	(10		,	١.	,)	NR

Author:	Begg	Trial type: Ad	Trial type: Active					
Year:	1992	Country: NR		Funding: Roche Products (NZ) Ltd.				
		# No. of patients ecperiencing AEs -	Zopiclone Midazolam	P value:				
		Disturbed sleep pattern	2 (4.2) 5 (12.5)	() () NR				
			Number (%)					
		# No. of patients ecperiencing AEs -	Zopiclone Midazolam	P value:				
		Others	4 (8.3) 5 (12.5)	() () NR				
			Number ()	1				

Author: Chaudoir Trial type: Active Quality rating: Fair

Year: 1990 Country: UK Funding: Not reported

Design:

Study design RCT

Eligibility criteria:

DB

Parallel

Setting Multicenter

Age: 50.9

Range: 30-65

SD:

Gender: 27 (71 %) Female

Ethnicity: 100% caucasian

Number Withdrawn: 4

Number Screened: NR

Eligible:

Enrolled:

Lost to fu: NR Analyzed: 38

NR

38

.

Exclusion criteria:

Any serious concomitant disease, psychosis, hypersensitivity, drug addiction, or alxohol consumption that might interfere with assessment; women who were pregnant, nursing, or of child-bearing age intending to become pregnant. No patient was included if taking concomitant medication known to induce drowsiness.

History of insomnia with at least one of the following symptoms present: time taken to fall asleep longer than 30 minutes, more than two nocturnal awakenings with difficulty in returning to sleep, without known cause, sleep duration of less than 6 hours.

Comments:

Intervention:

Run-in: no Wash out: 7

Allow other medication: No medication known to cause drowsiness

				Withdrawals due to AEs/
Drug name	dosage	N=	Duration	Total withdrawal
Zopiclone	7.5 mg	19	1 week	0 / 1
Triazolam	0.25 mg	19	1 week	1 / 3

Chaudoir Quality rating: Fair Author: Trial type: Active Country: UK **Funding: Not reported** Year: 1990 **Adverse Events:** reported by patients # no. of patients ecpereincing severe Zopiclone Triazolam P value: side effect) 1) Number (withdrawals # total withdrawals Zopiclone P value: Triazolam) 3 Number (# withdrawals due to Aes Zopiclone Triazolam P value:

Number (

Author: Drake (1) Trial type: Active Quality rating: Fair

Year: 2000 Country: US Funding: Wyeth-Ayerst Research

Design:

Study design RCT

DB

Crossover

Setting Multicenter

Eligibility criteria:

Age 21-60, wih 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.

Comments:

Intervention: Run-in: NR

Wash out: 5-12

Allow other medication: No

Age: 41.6

Range: 21-60 SD: 9.5

Gender: 24 (51 %) Female

Ethnicity: NR Number Withdrawn: 0
Lost to fu: 0

Analyzed: 47

NR

NR

47

Number Screened:

Eligible:

Enrolled:

Exclusion criteria:

Individuals with medical or psychiatric diagnoses (including any history of alcholism 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.

Drug name	dosage	N=	Duration	Withdrawals due to AEs/ Total withdrawal
Zaleplon	10 mg	47	2 day	0 / NR
Zaleplon	40 mg	47	2 day	0 / NR
Triazolam	0.25 mg	47	2 day	0 / NR
Placebo	NA mg	47	2 day	0 / NR

Author: Drake (1) Trial type: Active Quality rating: Fair

Year: 2000 Country: US Funding: Wyeth-Ayerst Research

Adverse Events:

reported by patients

no. of patients experiencing AEs

Zaleplor	10mg		Zaleplo	n 40mg		Triaz	olam				P value:
9	()	18	()	8	()	()	
Number	1				١						

withdrawals

total withdrawals

Zaleplon 10mg		Zaleplon 40mg		Triazo	lam 0.25	mg			P value:
NR ()	NR ()	NR	()	()	

withdrawals due to AEs

Zalep	lon 10mg		Zalep	lon 40mg	Triazo	olam 0.2	5mg			P value:
0	()	0	() 0	()	()	
	(١					

Author: Drake (2) Trial type: Active Quality rating: Fair

Year: 2000 Country: US Funding: Wyeth-Ayerst Research

Design:

Study design RCT

DB

Crossover

Setting Multicenter

Eligibility criteria:

Age 21-60, wih 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.

Comments:

Intervention: Run-in: NR

Wash out: 5-12

Allow other medication: No

Age: 38.1

Range: 21-60 SD: 11.1

Gender: 14 (39 %) Female

Ethnicity: NR Number Withdrawn: 0
Lost to fu: 0

Analyzed: 36

NR

NR

36

Number Screened:

Eligible:

Enrolled:

Exclusion criteria:

Individuals with medical or psychiatric diagnoses (including any history of alcholism 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.

				Withdrawals due to AEs/
Drug name	dosage	N=	Duration	Total withdrawal
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	/

Author: Drake (2) Trial type: Active Quality rating: Fair

Year: 2000 Country: US Funding: Wyeth-Ayerst Research

Adverse Events:

reported by patients

no. of patients experiencing AEs

Zaleplo	n 20mg		Zalepl	on 60mg	Triazo	olam				P value:
6	()	17	() 8	()	()	
Number	()					

withdrawals

total withdrawals

Zaleplon 2	20mg	Zaleplon 60n	ng	Triazo	lam				P value:
NR ()	NR ()	NR	()	()	

Number (

withdrawals due to AEs

Zaleplo	n 20mg		Zalep	lon 60mg		Triaz	olam				P value:
0	()	1	()	0	()	()	

Number (

Quality rating: Fair Author: Elie Trial type: Active

Year: 1990b Country: Canada **Funding: Not reported**

Design:

Study design RCT

DB

Parallel

Setting Single Center

Eligibility 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 askeep, (2) total sleep time less than 6 hours, (3) more than two nocturnal awakenings and (4) poor quality of sleep.

Comments:

Intervention: Run-in: 7

Wash out :

Allow other medication :

37.6 Age:

> Range: SD: 1.84

Gender: 24 (67 %) Female

Ethnicity: NR

Number Withdrawn: 0 Lost to fu: 0 Analyzed: 36

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.

Number Screened: NR

Eligible:

Enrolled:

NR

36

Drug name	dosage	N=	Duration	Total withdrawal
Zopiclone	7.5 mg	12	28 day	0 / 0
Flurazepam	30 mg	12	28 day	0 / 0
Placebo	NA mg	12	28 day	0 / 0

Author:ElieTrial type:ActiveQuality rating:FairYear:1990bCountry:CanadaFunding:Not reported

Adverse Events:

# s	somnolence	Zopicl	one		Fluraz	epam		Place	00				P value:
		11	()	12	()	9	()	()	NS
		Numbe	er ()						
# 10	oss of concentration	Zopicl	one		Fluraz	epam		Place	00				P value:
		8	()	8	()	5	()	()	NS
		Numbe	er ()			·			
# e	excitation	Zopic	one		Fluraz	epam		Place	00				P value:
		10	()	2	()	7	()	()	NS
		Numbe	er ()						
# te	ension	Zopicl	one		Fluraz	epam		Place	00				P value:
		10	()	7	()	9	()	()	NS
		Numbe	er ()						
# ta	aste disturbance	Zopicl	one		Fluraz	epam		Place	00				P value:
		10	()	10	()	4	()	()	<0.05
		Numbe	er ()						
# tı	ry mouth	Zopicl	one		Fluraz	epam		Place	00				P value:
		11	()	7	()	8	()	()	NS
		Numbe	er ()			•			•
# tl	hick tongue	Zopic	one		Fluraz	epam		Place	00				P value:
		9	()	7	()	5	()	()	NS

Author:ElieTrial type:ActiveQuality rating:FairYear:1990bCountry:CanadaFunding:Not reported

withdrawals

total withdrawals

withdrawals due to Aes

Zopiclo	ne		Flu	razepan	า	Pla	cebo						P value:
0	()	0	()	0		()	()	(

Number (

 Zopiclone
 Flurazepam
 Placebo
 P value:

 0
 (
)
 0
 (
)
 (
)

Number (

Author: Fleming Trial type: Active Quality rating: Fair

Year: 1995 Country: Canada Funding: Not reported

Design:

Study design RCT

DB

Parallel

Setting Multicenter

Eligibility 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.

Comments:

Intervention: Run-in:

Wash out: NR

Allow other medication: NF

Withdrawals due to AEs/ Total withdrawal Duration Drug name dosage N= Zolpidem 35 3 day 0 / 0 10 mg 6 / 7 Zolpidem 20 mg 35 3 day 0 / 1 Flurazepam 30 mg 36 3 day Placebo NA mg 35 3 day 0 / 0

Age: NR

Range: 33-37

SD:

Gender: 69 (48 %) Female

Ethnicity: NR

Number Withdrawn: 7
Lost to fu: 1

Number Screened:

Eligible:

Enrolled:

Analyzed: 141

222

144

144

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 medicaiton that would interfere with the assessment, absorbtion 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.

Quality rating: Fair Author: Fleming Trial type: Active

Year: 1995 Country: Canada Funding: Not reported

Adverse Events:

any event		Zolpide	em 10mg		Zolpidem 20mg		Flurazepam 30mg	I	Placebo			P value:
		14	(40)	23 (6537)	15 (41.7) ·	15 (4	2.9)	<0.05
		Number	r (%		1)						1.
dry mouth		Zolpide	em 10mg		Zolpidem 20mg		Flurazepam 30mg	ı	Placebo			P value:
		0	(0)	1 (2.9)	2 (5.6) (0 (0)	
		Number	r (%)						
back pain		Zolpide	em 10mg		Zolpidem 20mg		Flurazepam 30mg	ı	Placebo			P value:
		0	(0)	2 (5.7)	0 (0) (0 (0)	
		Number	r (%)						
fatigue		Zolpide	em 10mg		Zolpidem 20mg		Flurazepam 30mg		Placebo			P value:
		3	(8.6)	2 (5.7)	0 (0)	1 (2	.9)	
		Number	r (%)						
t ataxia		Zolpide	em 10mg		Zolpidem 20mg		Flurazepam 30mg	I	Placebo			P value:
		1	(2.9)	3 (8.6)	0 (0)	1 (2	.9)	
		Number	r (%)						
confusion		Zolpide	em 10mg		Zolpidem 20mg		Flurazepam 30mg	ı	Placebo			P value:
		0	(0)	2 (5.7)	0 (0) (0 (0)	
		Number	r (%)						
difficulty co	ncentrating	Zolpide	em 10mg		Zolpidem 20mg		Flurazepam 30mg		Placebo			P value:
		0	(0)	0 (0)	1 (2.8) :	2 (5	.7)	

Author:	Fleming	Trial type:	Active					Quality ra	ting: F	air	•
Year:	1995	Country:	Canada					Funding:	Not rep	ort	ted
	# dizzines	ss	Zolpid	lem 10mg	Zolpic	lem 20mg	Flu	razepam 30mg Placeb	00		P value:
			0	(0) 3	(8.6) 1	(2.8) 0	(0)	
			Numbe	er (%)				
	# drugged	feeling	Zolpid	lem 10mg	Zolpic	lem 20mg	Flu	razepam 30mg Placeb	00		P value:
			0	(0) 2	(5.7) 1	(2.8)0	(0)	
			Numbe	er (%)	1			
	# dysarth	ria	Zolpid	lem 10mg	Zolpic	lem 20mg	Flu	razepam 30mg Placeb	00		P value:
			1	(2.9) 3	(8.6) 0	(0)0	(0)	
			Numbe	er (%)				
	# headacl	ne	Zolpid	lem 10mg	Zolpic	lem 20mg	Flu	razepam 30mg Placeb	00		P value:
			4	(11.4) 2	(5.7) 4	(11.1) 3	(8.6)	
			Numbe	er (%)				
	# light-hea	adedness	Zolpid	lem 10mg	Zolpic	lem 20mg	Flu	razepam 30mg Placeb	00		P value:
			0	(0) 0	(0) 2	(5.6)0	(0)	
			Numbe	er (%)				
	# vomiting		Zolpid	lem 10mg	Zolpic	lem 20mg	Flu	razepam 30mg Placeb	00		P value:
			0	(0) 3	(8.6) 0	(0) 0	(0)	
			Numbe	er (%)				_
	# myalgia		Zolpid	lem 10mg	Zolpic	lem 20mg	Flu	razepam 30mg Placeb	00		P value:
			0	(0) 2	(5.7) 1	(2.8) 1	(2.9)	
			Numbe	er (%	ı)	1			1
	# amnesia	a	Zolpid	lem 10mg	Zolpic	lem 20mg	Flu	razepam 30mg Placeb	00		P value:
			1	(2.9) 3	(8.6) 1	(2.8) 0	(0)	
			Numbe	er (%	,)	<u>'</u>			

Author:	Fleming		Trial type:	Active					Qua	lity ra	ating:	Fair	
Year:	1995		Country:	Canada					Fund	ding:	Not re	port	ed
-	#	nervousness		Zolpi	dem 10mg		Zolpidem 20mg		Flurazepam 30mg	Place	ebo		P value:
				1	(2.9)	2 (5.7)) 1 (2.8)	0	(0)	
				Numb	er (%))	<u> </u>			
	#	pharyngitis		Zolpi	dem 10mg		Zolpidem 20mg		Flurazepam 30mg	Place	ebo		P value:
				2	(5.7)	0 (0)) 1 (2.8)	0	(0)	
				Numb	er (%))				1
	#	abnormal vision	า	Zolpi	dem 10mg		Zolpidem 20mg		Flurazepam 30mg	Place	ebo		P value:
				0	(0)	2 (5.7)	0 (0)	0	(0)	
				Numb	er (%		1))				'
	withdr	awals											
	#	total withdrawa	ls	Zolpi	dem 10mg		Zolpidem 20mg		Flurazepam 30mg	Place	ebo		P value:
				0	()	7 ()) 1 ()	0	()	NR
					())				1
	#	withdrawal due	to AEs	Zolpi	dem 10mg		Zolpidem 20mg		Flurazepam 30mg	Place	ebo		P value:
				0	()	6 ()	0 (0	()	NR
					())	•			

Author: Fleming_ Trial type: Active Quality rating: Fair

Year: 1990 Country: Canada Funding: Not reported

Design:

Study design RCT

DB

Parallel

Setting Multicenter

Eligibility 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.

Age: 45.5

Range: SD:

Gender: NR (%) Female

Ethnicity: NR

Number Withdrawn: 4

Number Screened: NR

Eligible:

Enrolled:

Lost to fu: 0

NR

52

Analyzed: 48

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, analgesis, or antidepressants or with a history of hypersensitivity to one or more hypnotic drugs were excluded. Subjects whose insomnnia was considered secondary to a psychiatric or medical disorder were also excluded as those with a history of alcoholism, drug abuse, or caffeine overuse.

Comments:

Enrolled population characteristics were not reported. Analyzed population characteristics: mean age=45.5 years; 23 (48%) female.

Intervention:

Run-in: 3 Wash out: 4

Allow other medication: No

Drug name	dosage	N=	Duration	Total withdrawal
Zopiclone	7.5 mg	24	21 day	2 / 2
Triazolam	0.25 mg	24	21 day	10 / 10

 Author:
 Fleming_
 Trial type:
 Active
 Quality rating:
 Fair

 Year:
 1990
 Country:
 Canada
 Funding:
 Not reported

Adverse Events:

overall report

no. of patients experiencing adverse effect

Zopiclon	ie		Triazolan	า					P value:
18	(75)	20	(83.3))	()	()	NS
Number	(%			Y)				

taste percersion

Zo	Zopiclone			Triazolam						P value:
NI	R	()	NR, mor ()	()	()	<0.05

Number (

moderate or severe adverse effects reported

Zopic	lone		Triazo	lam						P value:
18	()	42	()	()	()	<0.05
%	()					

Quality rating: Fair Hajak Trial type: Active Author:

Year: 1998, 1995, 1994 Country: **Funding: Not reported** Germany

Design:

Study design RCT

DB

Parallel

Setting Multicenter

Eligibility criteria:

Insomnia of at least 4-week duration and the presence of at least two of

the following as a mean of 3 days before starting treatment (no-pill baseline): (a) sleep latency >= 45 min, (b) total sleep time <= 6 hours, and © nocturnal awakening >= 3 times.

Comments: Patients were observed for a further period of 14 days without medication for rebound.

Intervention:

7 Run-in: Wash out :

Allow other medication: NR

Age: 51

Range: 18-71 SD: 11

Gender: 940 (62 %) Female

Ethnicity: 99.3% Caucasian

0.9% Others

Number Screened: NR

Eligible: NR

Enrolled: 1507

Number Withdrawn: 0

Lost to fu: 0

Analyzed: 1507

Exclusion criteria:

Any patients who had taken a single daily dose of a benzodiazepine or any other hypnotic more than three times per week during the 14 days prior to admission, or any patients with psychiatric disorders (e.g., depression, schizophrenia, severe neuroses), or any patients who had contraindications for zopiclone, flunitrazepam, or triazolam were excluded from this study

Drug name	dosage	N=	Duration	Total withdrawal
Zopiclone	7.5 mg	612	28 day	26 / 190
Triazolam	0.2 mg	307	28 day	11 / 187
Placebo	NA mg	298	28 day	25 / 193

Author: Hajak Trial type: Active Quality rating: Fair

Year: 1998, 1995, 1994 Country: Germany Funding: Not reported

Adverse Events:

withdrawals

total withdrawals

withdrawals due to Aes

Zopiclone	Triazolam	Placebo		P value:
190 ()	187 ()	193 ()	()	

Number (

 Zopiclone
 Triazolam
 Placebo
 P value:

 26
 ()
 11
 ()
 25
 ()
 ()

Number (

Author: Hayoun Trial type: Active Quality rating: Fair

Year: 1989 Country: France Funding: Not reported (corresponding

Design:

Study design RCT

DB

Parallel

Setting Single Center

Eligibility 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).

Age: 47.9

Range: 18-65

SD:

Gender: 90 (66 %) Female

Ethnicity: NR

Number Withdrawn: 9 Lost to fu: 0

Number Screened:

Eligible:

Enrolled:

Analyzed: 127

NR

NR

136

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; patiens 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.

Comments:

Sleep aid, drug abuse???

More patients on zopiclone had insomnia as a major complaint compared with those on triazolam (70%) vs 55%, respectively; p=0.04). More patients described themselves as tranquil compared with patients on zopiclone.

Intervention:

Run-in: NR Wash out: NR

Allow other medication: No

Withdrawals due to AEs/
Total withdrawal

 Drug name
 dosage
 N=
 Duration
 Total withdow

 Zopiclone
 7.5 mg
 67
 7 day
 0 / 0

 Triazolam
 0.25 mg
 69
 7 day
 0 / 0

Author: Hayoun Trial type: Active Quality rating: Fair

Year: 1989 Country: France Funding: Not reported (corresponding

Adverse Events:

reported by patients

overall sife effects

Zopicl	one		Zalepl	on						P value:
NR	()	NR	()	()	()	NS
%	()					

global evaluation

safety- good or excellent

Zopiclone	Triazolam			P value:
86 ()	82 ()	()	()	NS

Author: Liu Trial type: Active Quality rating: Poor

Year: 1997 Country: Taiwan Funding:

Design:

Study design RCT

DB

Crossover

Setting Single Center

Age: 40.1

Range: 20-58 SD: 10.9

Gender: 11 (73 %) Female

Ethnicity: NR

Number Withdrawn: 0

Number Screened:

Lost to fu: 0

NR

NR

15

Analyzed: 15

Eligible:

Enrolled:

Eligibility criteria:

Outpatients who suffered from insomnia for more than 3 months, with at least 3 of the following symptoms: sleep onset greater than 1 hour, total sleep duration of less than 5 hours, more than 2 nocturnal awakenings, and poor subjectively reported sleep quality.

Exclusion criteria:

Patients with psychoses or mood disorders, history of severe physical illness, alcohol abouse or drug abuse.

Comments:

Poor quality- baseline characterisities not reported, no information on randomization and allocation concealment methods. Unable to determine if an intention-to-treat analysis was used, and high loss to followup. (8 patients did not complete the trial; unclear if 8 of 15 or 8 of 23).

Intervention:

Run-in: 0 Wash out: 7

Allow other medication: No

			Withdrawais due to ALS/
Drug name	dosage	N=	Duration Total withdrawal
Zopiclone	7.5 mg	15	14 day 0 / 0
Triazolam	0.25 mg	15	14 day 0 / 0
Placebo	NA mg	15	14 day 0 / 0

Author:	Liu	Trial type: Ac	ctive					(Quality i	rating:	Poo	r
Year:	1997	Country: Tai	iwan					F	unding	:		
Adverse E	Events:											
	rebo	und insomnia										
		# rebound insomnia- mild degree of	Zopiclon	е	Triaz	olam						P value:
		poor sleep	6	(40) 1	(6.7)	()	()	
			Number	(%	·)		<u>.</u>			
		# rebound insomnia- moderate degree of poor sleep	Zopiclon	е	Triaz	olam						P value:
		degree of poor sleep	6	(40) 4	(26.7)	()	()	
			Number	(%	·)					
		# rebound insomnia- severe degree of poor sleep	Zopiclon	е	Triaz	olam						P value:
		or poor sieep	3	(20) 10	(67.6)	()	()	
			Number	(%)					
	over	all AEs										
		# number of events reported	Zopiclon	е	Triaz	olam						P value:
			10	() 16	()	()	()	
			Number	(1)		1			II.

Author: Mamelak Trial type: Active Quality rating: Fair

Year: 1987 Country: Canada Funding: Not reported

Design:

Study design RCT

DB

Parallel

Setting Single Center

origic defice

Eligibility 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 noctunal 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.

Comments:

Ethanol-drug interaction study.

Intervention: Run-in:

Wash out: 3

Allow other medication: NR

Age: 50

Range: 32-60

SD:

Gender: 21 (70 %) Female

Ethnicity: NR

Number Withdrawn: 0

Lost to fu: 0 Analyzed: 30

NR

30

Number Screened: NR

Eligible:

Enrolled:

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.

Drug name	dosage	N=	Duration	Total withdrawal	
Zopiclone	7.5 mg	10	12 day	0 / 0	
Flurazepam	30 mg	10	12 day	1 / 1	
Placebo	NA mg	10	12 day	0 / 0	

Author: Mamelak Trial type: Active Quality rating: Fair

Year: 1987 Country: Canada Funding: Not reported

Adverse Events:

withdrawals

total withdrawals

withdrawals due to AEs

Zopiclone		Flurazepam		Placebo			P value:
0	()	1	()	0	()	()	

Number (

 Zopiclone
 Flurazepam
 Placebo
 P value:

 0
 (
)
 1
 (
)
 0
 (
)
 (
)

Number (

Author: Monti Trial type: Active Quality rating: Fair

Year: 1994 Country: Uruguay Funding: Not reported

Design:

Study design RCT

DB

Parallel

Setting Single Center

Eligibility 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 waketime >20 minutes; number of nocturnal awakenings >3.

Comments:

Intervention: Run-in: 3

Wash out: 3

Allow other medication: NR

Age: 47.3

Range: 21-65

SD:

Gender: 21 (88 %) Female

Ethnicity: NR

Number Withdrawn: 1 Lost to fu: 0

Number Screened: NR

Eligible:

Enrolled:

NR

24

Analyzed: 24

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.

Drug name	dosage	N=	Duration	Total withdrawal	
Zolpidem	10 mg	8	27 day	0 / 0	
Triazolam	0.5 mg	8	27 day	1 / 1	
Placebo	NA mg	8	27 day	0 / 0	

Quality rating: Fair Author: Trial type: Active Monti Year: 1994 Country: Uruguay **Funding: Not reported Adverse Events:** overall AEs # Emergent adverse events Zolpidem Triazolam Placebo P value:) 10 13) 16 NR Number (AEs with significant differences # rebound: pessimist Zolpidem Triazolam P value:) higher (0.096 lower Number (# rebound: tense Zolpidem Triazolam P value: higher 0.061 lower Number (# rebound: pessimist Triazolam P value: Zolpidem 0.040 lower) higher Number (withdrawals # total withdrawals Placebo Zolpidem Triazolam P value:) 0 Number (# withdrawals due to AEs Zolpidem Triazolam Placebo P value:) 0) Number (

Author: Nair Trial type: Active Quality rating: Fair

Year: 1990 Country: Canada Funding: Rhone-Poulenc Pharma

Design:

Study design RCT

DB

Parallel

Setting Single Center

Eligibility criteria:

(a) sleep latentcy 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.

Comments:

Intervention: Run-in: 1

Wash out: NR

Allow other medication: NR

Age: 46.9

Range: SD: 1.4

Gender: 28 (47 %) Female

Ethnicity: NR

Number Withdrawn: Lost to fu:

Analyzed:

Number Screened: NR

Eligible:

Enrolled:

NR

60

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.

Drug name	dosage	N=	Duration	Total withdrawal
Zopiclone	3.75 mg	10	7 day	0 / 0
Zopiclone	7.5 mg	10	7 day	0 / 0
Zopiclone	11.2 mg	10	7 day	1 / 1
Zopiclone	15 mg	10	7 day	1 / 1
Flurazepam	30 mg	10	7 day	0 / 0
Placebo	NA mg	10	7 day	1 / 2

Quality rating: Fair Author: Nair Trial type: Active **Funding: Rhone-Poulenc Pharma** Year: 1990 Country: Canada **Adverse Events:** overall AEs # Total number of patients Zopiclone 11.25mg Zopiclone 15mg Zopiclone 3.75 Zopiclone 7.5mg P value:) 11) 5 Number (# Total number of patients Flurazepam Placebo P value: 10) 5 Number (withdrawals # total withdrawals Zopiclone 3.75mg | Zopiclone 7.5mg Zopiclone 11.5mg Zopiclone 15mg P value: Number (# total withdrawals Flurazepam Placebo P value:) 2 Number (# withdrawals due to AEs Zopiclone 11.5mg Zopiclone 3.75mg Zopiclone 7.5mg Zopiclone 15mg P value: Number (# withdrawals due to AEs Flurazepam Placebo P value: Number (

Author: Ngen Trial type: Active Quality rating: Fair

Year: 1990 Country: Malaysia Funding: Rhone-Poulenc Pharma

Design:

Study design RCT

DB

Parallel

Setting Single Center

Eligibility criteria:

Subjects must be between 18 and 70 years of age and must have one of the following for at least 2 weeks duration; (a) takes longer than 45 min to fall asleep, (b) more than two nocturnal awakenings each night without known cause and difficulty in returning to sleep, (c) sleep duration of less than 6 hours a night

Comments:

Intervention: Run-in:

Wash out: NR

Allow other medication: N

Age: 38.4

Range: SD:

Gender: 31 (52 %) Female

Ethnicity: NR

Number Withdrawn: 16

Number Screened:

Eligible:

Enrolled:

Lost to fu: 0 Analyzed: 44

NR

NR

60

Exclusion criteria:

(a) serious concomitant disease, (b) likely to require concomitant medication known to cause drwosiness, (c) psychosis, (d) a history of hypersensitivity to benzodiazepines, (e) drug and/or alcohol abuse, (f) pregnant, a nursing mother or intending to become pregnant during the study, (g) working night shifts

Drug name	dosage	N=	Duration	Total withdrawal
Zopiclone	7.5 mg	20	14 day	2 / 7
Temazepam	20 mg	20	14 day	0 / 7
Placebo	NA mg	20	14 day	1 / 10

Author: Ngen Trial type: Active Quality rating: Fair

Year: 1990 Country: Malaysia Funding: Rhone-Poulenc Pharma

Adverse Events:

reported by patients

excessive sedation

Zopiclone			Tema	zepam	Place	bo				P value:
2	()	0	() 1	()	()	
Numb	er ()					

withdrawals

total withdrawals

Zopicle	one		Tema	azepam		Plac	ebo					P value:
7	()	7	()	10	()		()	

Number (

withdrawals due to AEs

Zopiclone			Temazepam			Placebo					P value:
2	()	0	()	1	()	()	

Author: Ponciano Trial type: Active Quality rating: Fair

Year: 1990 Country: Portugal Funding: Not reported

Design:

Study design RCT

DB

Parallel

Setting Single Center

Age: 30

Range: 18-60 SD: 9

Gender: 12 (46 %) Female

Ethnicity: NR

Lost to fu: 0 Analyzed: 24

Number Screened: NR

Eligible:

Enrolled:

Number Withdrawn: 2

NR

26

Eligibility 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 medicaiton to be used were excluded. Patients with a history of drug use, those with excessive alcohol comsumption (<1 litre of wine/day, or equivalent) pregnant or nursing women and all females of child bearing age without adequate contraception were also excluded.

Comments:

Results were reported in figures only. Therefore, the data reported in the evidence table were estimated from the figures.

Intervention:

Run-in:

Wash out: 7

Allow other medication: NF

				Withdrawais due to ALS
Drug name	dosage	N=	Duration	Total withdrawal
Zopiclone	7.5 mg	8	21 day	0 / 0
Flurazepam	30 mg	8	21 day	0 / 0
Placebo	NA mg	10	21 day	1 / 2

Author: Ponciano Trial type: Active Quality rating: Fair

Year: 1990 Country: Portugal Funding: Not reported

Adverse Events:

withdrawals

total withdrawals

withdrawals due to AEs

Zopiclone		Flurazepa	am	Placebo			P value:	
0 ()	0	()	2	()	()	

Number (

 Zopiclone
 Flurazepam
 Placebo
 P value:

 0
 (
)
 0
 (
)
 (
)

Quality rating: Poor Trial type: Active Author: Quadens

1983 Country: Belgium **Funding: Not reported** Year:

Design:

Study design RCT

DB

Crossover

Setting Single Center

Eligibility 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

Comments:

Poor quality- insufficient information to assess quality.

Intervention:

Run-in: 6 35 Wash out :

Allow other medication :

Age: NR

Number Screened: NR Range: 50-59 Eligible: SD:

Gender: 12 (100%) Female

Number Withdrawn: 0 Ethnicity: NR Lost to fu: 0

Analyzed: 12

Enrolled:

NR

12

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.

Drug name	dosage	N=	Duration	Total withdrawal
Zopiclone	7.5 mg	12	13 day	/
Flurazepam	30 mg	12	13 day	1

Quality rating: Poor Author: Quadens Trial type: Active Country: Funding: Not reported Year: 1983 Belgium

Adverse Events:

N

<u>Norris</u>	<u>quesionnaire</u>										
#	clear headed-muzzy	Zopiclor	ne	Fluraz	epam						P value:
		28.1	(9.3)	34.6	(13.4)	()		()	<0.05
		Score	(SD	<u>.</u>)					
#	energic-lethargic	Zopiclor	ne	Fluraz	epam						P value:
		29.2	(12.7)	34.9	(10.1)	()		()	<0.05
		Score	Score (SD)								
#	tranquil-troubled	Zopiclor	ne	Fluraz	epam						P value:
		19.8	(11.2)	24.7	(9.4)	()		()	<0.05
		Score	(SD)					
#	relaxed-tense	Zopiclor	ne	Fluraz	epam						P value:
		21.4	(11.7)	25.9	(10.8)	()		()	<0.05
		Score	(SD)					
#	elated-depressed	Zopiclor	ne	Fluraz	epam						P value:
		48.1	(15.3)	50.5	(14.0)	()		()	<0.05
		Score	(SD)					
#	sociable-introverted	Zopiclor	ne	Fluraz	epam						P value:
		53.6	(15.3)	52.3	(13.4)	()		()	<0.05
		Score	(SD	<u>.</u>)					
#	other 12 items show no difference	Zopiclor	ne	Fluraz	epam						P value:
		multiple	()	multipl	е ()	()		()	NS
		Score	()		•			

Author:	Quadens	Trial type:	Active	Active Quality rating: Poor								
Year:	1983	Country:	Belgium				Funding: Not reported					
	<u>withdrawals</u>											
	# total		Zopiclone		Fluraz	epam						P value:
			0 ()	0	()	()	()	NR
			Number (·)		·			1
	# due to AEs		Zopiclone		Fluraz	epam						P value:
			0 ()	0	()	()	()	NR
			Number ()		'			

Quality rating: Poor Author: Rosenberg Trial type: Active

1994 Denmark Funding: Synthelabo Scandinavia A/S Year: Country:

Design:

Study design RCT

DB

Parallel

Setting Multicenter

Eligibility 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.

Age: 54

Range: 25-79

SD:

Gender: NR (0 %) Female

Ethnicity: NR

Lost to fu: Analyzed: 139

NR

NR

178

Number Screened:

Eligible:

Enrolled:

Number Withdrawn: 5

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

Comments:

Enrolled patients characteristics were not reported. Analyzed patients characteristics were reported instead: mean age=51 years, range 19-79 years; 31% male.

Intervention:

Run-in: NR

NR Wash out :

Drug name

Zolpidem

Triazolam

Allow other medication :

Withdrawals due to AEs/ N= Duration **Total withdrawal** dosage 10 mg 71 14 day 0.25 mg 68 14 day

Author: Rosenberg Trial type: Active Quality rating: Poor

Year: 1994 Country: Denmark Funding: Synthelabo Scandinavia A/S

Zolpidem

Adverse Events:

Overall AEs

CNS-related adverse events

 Number (%
)

 Zolpidem
 Triazolam
 P value:

 () 2 (2.8) 3 (4.4)
 () NS

Triazolam

(14.7)

(11.3)10

P value:

NS

GI-related adverse events

Number (%

) 8

other adverse events

| Zolpidem | Triazolam | P value: | () | 5 | (7) | 2 | (2.9) | () | NS |

Number (%

total

	Zolpidem	Triazolam		P value:
()	15 (21.1)	15 (22)	()	NS

Author: Silvestri Trial type: Active Quality rating: Fair

Year: 1996 Country: Italy Funding: Not reported

Design:

Study design RCT

DB

Parallel

Setting Multicenter

Gender: 12 (55 %) Female

enter Ethi

Ethnicity: NR

Age:

Number Withdrawn: 0 Lost to fu: 2

Number Screened: NR

Eligible:

Enrolled:

Analyzed: 20

NR

22

Eligibility criteria:

Both sexes, age between 18 and 65 years, clinical diagnosis of psychophysiological insomnia (either as a first episode or as a recurrence of short-term situaitonal insomnia) or poor sleepers with subjective reporting of at least two out of these four complaints: time to fall asleep >30 minutes, total sleep duration <6 hours, total wake time >20 minutes, and/or number or awakenings >3. These subjective inclusion criteria had to be confirmed by the objective assessment through polysomnography.

Comments:

Intervention: Run-in: 3

Wash out: No

Allow other medication: No

Exclusion criteria:

33.6

SD:

Range: NR

10.4

Pregnant or lactating women; women of child-bearing age withoug adequate contraception; uncooperative patients; severe psychiatric diseases, also screened by means of both Hamilton Rating Scale for Anxiety (total score >16) and Hamilton Rating Scale for Depression (total score >16); neurological diseases (myoclones, kinaesthesis disorders, restless legs syndrome, sleep obstructive apnea of >7 minutes duration); severe internal (heart, renal, liver) diseases; hemocoagulation disorders (Quick's time <70%); intake of any psychotropic durg during 2 weeks preceding the study start as well as a previous with beta blockers or corticosteroids.

Drug name	dosage	N=	Duration	Total withdrawal
Zolpidem	10 mg	10	2 week	0 / 0
Triazolam	0.25 mg	12	2 week	0 / 2

Author: Silvestri Trial type: Active Quality rating: Fair

Year: 1996 Country: Italy Funding: Not reported

Adverse Events:

withdrawals

total withdrawals

Zolpi	dem	Triazo	olam					P value:
0	(0) 2	(16.7)	()	()	

Number (%

withdrawals due to AEs

Zolpidem	Triazolam			P value:
0 ()	0 ()	()	()	

Number (

overall AEs

no. of adverse events reported by patients

Zolpidem	า		Triazola	am						P value:
1	()	1	()	()	()	NR

Author: Singh Trial type: Active Quality rating: Fair

Year: 1990 Country: Canada Funding: Rhone-Poulenc Pharma Inc.

Design:

Study design RCT

DB

Parallel

Setting Single Center

Eligibility criteria:

NR

Age: 39.6

Range: 19-64 SD: 1.5

Gender: 32 (53 %) Female

Ethnicity: NR

Lost to fu: 0 Analyzed: 57

Number Screened: NR

Eligible:

Enrolled:

Number Withdrawn: 3

61

60

Exclusion criteria:

Psychotic and neurotic patients were excluded as well as those with a history of mental retardation, chronic alcoholism, drug abuse, coffee or tea abuse, neurolpgical disorders, established sleep apnoea and drug hypersensitivity. Patients with any significant medical condition interfering with sleep, those treatment which could modify drug kinetics were also excluded. Finally, pregnancy, lactation, and child-bearing potential not controlled by a recognized contraceptive programme precluded entry in the study.

Comments:

Two patients were taking a benzodiazepine hypnotic medication at time of recrutment and they both fulfilled the inclusion criteria after a 4-day minimun washout period. The study did not report patient number for each treatment groups, and the analyzed results were the mean from parts of the patients as well. (?!)

Intervention:

Run-in: 4

Wash out: NR

Allow other medication: NR

				Withdrawals due to AEs/
Drug name	dosage	N=	Duration	Total withdrawal
Zopiclone	7.5 mg		24 day	0 / 0
Zopiclone	11.2 mg		24 day	1 / 2
Flurazepam	30 mg		24 day	0 / 1

Quality rating: Fair Author: Singh Trial type: Active Year: 1990 Country: Canada Funding: Rhone-Poulenc Pharma Inc. **Adverse Events:** withdrawals # total Zopiclone 7.5mg Zopiclone 11.25mg Flurazepam 30mg P value: 0) 2 Number (# due to AEs Zopiclone 11.25mg Flurazepam 30mg Zopiclone 7.5mg P value:) 0 Number (overall AEs # taste perversion Zopiclone 7.5mg Zopiclone 11.25mg Flurazepam 30mg P value: NR Number (# drowsiness Zopiclone 11.25mg Flurazepam 30mg Zopiclone 7.5mg P value:) 9 < 0.05 Number (# headache Zopiclone 11.25mg Flurazepam 30mg P value: Zopiclone 7.5mg 0 5 NS Number (# taste perversion- moderate and Zopiclone 7.5mg Zopiclone 11.25mg Flurazepam 30mg P value: severe) 0

Author: Stip Trial type: Active Quality rating: Fair
Year: 1999 Country: Canada Funding: Not reported

Design:

Study design RCT

DB

Parallel

Setting Single Center

Age: 42.6

Range: SD:

Gender: NR (%) Female

Ethnicity: NR

Number Withdrawn: 2 Lost to fu: 8

Analyzed: 50

Number Screened: NR

Eligible:

Enrolled:

NR

60

Eligibility criteria:

Patients with either primary insomnia or insomnia associated with mild non-psychotic psychiatrc disroders (DSM III-R). Daytime fatigability, diminished power of concentration at work and at least two of the following symptoms: falling asleep time greater than 30 min, sleep duration less than 5 hours, more than two awakenings per night and early wake up in the morning.

Exclusion criteria:

NR

Comments:

Participants who had been taking hypnotic drugs with a long half-life received lorazepam for one week, prior to a week placebo. Patients who had been taking benzodiazepines with a short or intermediate half-life were put only on placebo for one week.

Enrolled population characteristic were not reported. Analyzed population characteristics: mean age=42.6 years; 21 (42%) female

Intervention:

Run-in: 7 Wash out: 7

Allow other medication: N

Drug name	dosage	N=	Duration	Total withdrawal	
Zopiclone	7.5 mg	19	21 day	0 / 0	
Temazepam	30 mg	16	21 day	0 / 1	
Placebo	NA mg	15	21 day	0 / 1	

Author: Stip Trial type: Active Quality rating: Fair

Year: 1999 Country: Canada Funding: Not reported

Adverse Events:

withdrawals

total withdrawals

withdrawals due to AEs

Zopiclone		Temazep	am	Placebo				P value:
0 ()	1	()	1	()	()	

Number (

 Zopiclone
 Temazepam
 Placebo
 P value:

 0
 (
)
 0
 (
)
 (
)

Quality rating: Poor Tamminen Author: Trial type: Active

1987 Country: **Finland Funding: Not reported** Year:

Design:

Study design RCT

DB

Parallel

Setting Multicenter Age: 47

Range: 26-71

SD:

Gender: 72 (77 %) Female

Number Withdrawn: 0 Ethnicity: NR Lost to fu: 0

Analyzed: 94

130

94

Number Screened: NR

Eligible:

Enrolled:

Eligibility 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, noctural awakenings >2 per night, time to fall asleep after at least one noctural awakening >30min, awakening >2hour before scheduled time.

Exclusion criteria:

Known hypersensitivity to benzodiazepines, major psychiatric disorders, somatic disorders directly causeing 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.

Comments:

Poor quality: no baseline demographic characteristics, high and differential loss to followup and no intention to treat analysis

Intervention:

Run-in: NR Wash out :

Allow other medication : NR

Drug name	dosage	N=	Duration	Total withdrawal
Zopiclone	7.5 mg	52	42 day	3 / 3
Nitrazepam	5 mg	46	42 day	1 / 1

Author:TamminenTrial type:ActiveQuality rating:PoorYear:1987Country:FinlandFunding:Not reported

Adverse Events:

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

# anxiety	Zopiclone	Nitrazepam			P value:
	3.8 (<0.06) -6.8 (<0.00)	()	()	<0.05
	Score (pvs	paseline)	·		
# sweating	Zopiclone	Nitrazepam			P value:
	5.7 (<0.00) -7.1 (<0.05)	()	()	NS
	Score (pvsl	paseline)			
# nausea	Zopiclone	Nitrazepam			P value:
	4.3 (NS) -3.2 (NS)	()	()	<0.05
	Score (pvsl	paseline)			
# loss of appetite	Zopiclone	Nitrazepam			P value:
	0 (NS) -6.5 (<0.05)	()	()	NS
	Score (pvsl	paseline)			
# restlessness	Zopiclone	Nitrazepam			P value:
	2.2 (NS) -5.9 (<0.05)	()	()	NS
	Score (pvsl	paseline)			
# physical tiredness	Zopiclone	Nitrazepam			P value:
	-3.5 (<0.00) -10.3 (<0.00)	()	()	NS
	Score (pvsl	paseline)			
# dizziness	Zopiclone	Nitrazepam			P value:
	3.5 (NS) -7.8 (<0.00)	()	()	<0.05
	Score (pvsl	aseline)			

Author:	Tamminen	Trial type:	Active					Quality	rating:	Poo	r		
ear:	1987	Country:	Finland				Funding: Not reported						
	# indigesti	on	Zopiclor	ne	Nitraze	oam					P value:		
			8.8	(<0.05)	-10	(< 0.01)	()	()	<0.05		
			Score	(p vs bas	eline)							
	reported by pati	<u>ents</u>											
	# number	of events reported	Zopiclor	ne	Nitraze	oam					P value:		
			24	()	13	()	()	()			
			Number	()							
		of patients experiencing	Zopiclor	ne	Nitraze	oam					P value:		
	unwante	ed effects	52	()	46	()	()	()			
			Number	()		,					
	global evaluatio	<u>n</u>											
	# safety so	core (1=poor; 5=exceller	t) Zopiclor	ne	Nitraze	oam					P value:		
			3.4	()	3.5	()	()	()	NS		
			Score	()					1		

Author: van der Kleijn Trial type: Active Quality rating: Fair

Year: 1989 Country: Nijmegen Funding: Rhone-Poulenc Pharma

Design:

Study design RCT

DB

Crossover

Setting NR

Eligibility criteria:

1. latency of sleep onset exceeding 30 min

2. waking up too early

3. waking up several times at night and difficulty in falling asleep afterwards

4. being bothered duting the day by unsatisfactory sleep

Comments:

Intervention: Run-in: 2

Wash out: 7

Allow other medication: No

Age: 53

Range: 28-69 SD: Number Screened: NR Eligible: 60

Enrolled: 55

Gender: 39 (71 %) Female

Ethnicity: NR Number Withdrawn: 2

Lost to fu: 0 Analyzed: 53

Exclusion criteria:

1. Patients taking a non-benzodiazapine hypnotic prior to the studym those who received another psychotropic drug for the first time, or patients whose psychotropic medicine was changed during the study period.

- 2. Patients who took benzodiazapine tranquillizers or hypnotics in doses at least twice that recommended before the study.
- 3. Patients suffering from painful disorder
- 4. Patients unable to fill in a sleep questionnaire, those with a history of alcohol and/or drug abuse, who lived in psychiatric or physical stress situations likely to fluctuate during the study, with liver or kidney disorders, myasthenia gravis, shift-workers
- 5. Women pregnant or likely to become pregnant

Drug name	dosage	N=	Duration	Total withdrawal	
Zopiclone	7.5 mg	53	5 day	1 / 1	
Temazepam	20 mg	53	5 day	1 / 1	

Author: van der Kleijn Trial type: Active Quality rating: Fair

Year: 1989 Country: Nijmegen Funding: Rhone-Poulenc Pharma

Adverse Events:

Reported by patinets

Bad headache

	Zopiclone	Э		Temaze	pam	ı	Placebo				P value:
	8	()	12	()	14	()	()	NR
_											

% (

Very severe perspiration

Zopic	lone		Tema	zepam		Place	bo				P value:
8	()	18	()	10	()	()	NR
%	()						

Quality rating: Fair Author: van der Kleijn Trial type: Active

Year:	1989	Country:	Nijmegen						Fu	ınding	g: Rhone	e-Po	ulenc Pharm
	<u>Oponic</u>	on of the patient about day-time	status										
	#	Well/normal	Zopiclo	ne		Temaz	epam	Placel	00				P value:
			30	(57)	35	(66) 27	(51)	()	NR
			Number	(%		ı)		l			
	#	Sleepy/dull/tired	Zopiclo	ne		Temaz	epam	Placel	00				P value:
			7	(13)	6	(11) 12	(23)	()	NR
			Number	(%)		l			
	#	Headache	Zopiclo	ne		Temaz	epam	Placel	00				P value:
			3	(6)	3	(6) 1	(2)	()	NR
			Number	(%)		l			
	#	Irritable/unstable	Zopiclo	ne		Temaz	epam	Placel	00				P value:
			4	(8)	4	(8) 6	(11)	()	NR
			Number	(%		ı)		l			
	#	Trembling/palpitation	Zopiclo	ne		Temaz	epam	Placel	00				P value:
			2	(4)	4	(8) 2	(4)	()	NR
			Number	(%)		l			
	#	Difficulties to concentrate	Zopiclo	ne		Temaz	epam	Placel	00				P value:
			2	(4)	0	(0) 0	(0)	()	NR
			Number	(%)					
	#	Depressive	Zopiclo	ne		Temaz	epam	Placel	00				P value:
			3	(6)	1	(2) 2	(4)	()	
			%	(ı)		ı			
	#	Unknown	Zopiclo	ne		Temaz	epam	Placel	00				P value:
			2	(4)	0	(0) 3	(6)	()	
			%	1		1)					ı

Author:	van der Kleijn	Trial type:	Active						Quality	rating:	Fair	
Year:	1989	Country:	Nijmegen Funding: Rhone-Poulenc Pha							ulenc Pharma		
	withdrawals											
	# Total withdr	rawals	Zopiclone)	Tema	zepam						P value:
			1	()	1	()	()	()	NR
			Number	()		·			<u>. </u>
	# withdrawals	due to Aes	Zopiclone)	Tema	zepam						P value:
			1	()	1	()	()	()	NR
			Number	()		·			<u>. </u>

Author: Voshaar Trial type: Active Quality rating: Fair

Year: 2004 Country: Netherlands Funding: Sanfi-Synthelabo

Design:

Age: 46.1 Number Screened: NR Range:

DB SD: Eligible: NR Parallel 221

Parallel Enrolled: 22'

Gender: NR (0 %) Female

Setting Multicenter Number Withdrawn: 9
Ethnicity: NR Lost to fu: 5

Analyzed: 159

Eligibility criteria:

Patients were included in the study if they were diagnosed with primary insomnia according to DSM-III-R and were aged between 18 and 65 years.

Exclusion criteria:

Patients with other axis I disorders, severe somatic disorders, pregnancy, current use of psychotropic medication, complaints of a jet lag in the 2 weeks preceding the study or occupation requiring shift work

Comments:

Enrolled population characteristics were not reported. Only analyzed population characteristics were reported:

Intervention: Run-in:

Wash out: 4

Allow other medication: NR

NR

Drug name	dosage	N=	Duration	Total withdrawal	
Zolpidem	10 mg	74	28 day	N / NR	
Temazepam	20 mg	85	28 day	N / NR	

Author: Voshaar Trial type: Active Quality rating: Fair

Year: 2004 Country: Netherlands Funding: Sanfi-Synthelabo

Adverse Events:

withdrawals

total withdrawals- not reported

								P value:
()	()	()	()	
1			١					

withdrawals due to AEs- not reported

								P value:	
()	()	()	()		
()						

Author: Walsh Trial type: Active Quality rating: Fair

Year: 1998a Country: US Funding: Lorex Pharmaceuticals

Age:

Design:

Study design RCT

DB

Parallel

Setting Multicenter

Gen

Gender: NR (0 %) Female

Range: 21-65

NR

SD:

Ethnicity: NR

Number Withdrawn: 28 Lost to fu: 0

Eligible:

Enrolled:

Number Screened:

Analyzed: 278

NR

589

306

Eligibility 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 seld-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.

Comments:

Enrolled population characteristics were not reported. Instead, analyzed population characteristics were reported: 63% female; 84% Caucasian.

Intervention:

Run-in: 7

Wash out: NR

Allow other medication: NR

Drug name	dosage	N=	Duration	Total withdrawal
Zolpidem	10 mg	102	14 day	5 / 11
Trazodone	50 mg	100	14 day	5 / 10
Placebo	NA mg	104	14 day	2 / 7

Author: Walsh Trial type: Active Quality rating: Fair

Year: 1998a Country: US Funding: Lorex Pharmaceuticals

Adverse Events:

reported by patients

total number of events

Zolpidem Trazodone		done						P value:		
78	(76.5)	75	(75)	()	()	NS
Number	(%)					

headache (highest incidence)

Zolpidem	Trazodone	Placebo		P value:
24 () 30 ()	19 ()	()	

.

somnolence (highest incidence)

Zolpic	dem		Trazo	done		Place	bo				P value:
16	()	23	()	8	()	()	
	,										

(

withdrawals

total withdrawals

Zolpide	em		Trazo	done		Place	ebo				P value:
11	()	10	()	7	()	()	
	,				١.						

withdrawals due to AEs

Zolp	oidem	Trazo	done	Place	bo				P value:
5	(5	() 2	()	()	
	,			\					

Author: Walsh_ Trial type: Active Quality rating: Good

Year: 1998b Country: US Funding: Wyeth Ayerst

Design:

Study design

DB

Parallel

Setting

Eligibility criteria:

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).

Comments:

day 1-3 placebo; day 4-17 treatment; day 18-19 placebo

Intervention: Ru

Run-in: 3 Wash out: 2

Allow other medication: NR

Age: 40.3

Range: 18-60

Gender: 77 (58 %) Female

SD:

Ethnicity: NR

Number Withdrawn: 7
Lost to fu: 0

Analyzed: 125

456

132

Number Screened: 673

Eligible:

Enrolled:

Exclusion criteria:

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

Drug name	dosage	N=	Duration	Total withdrawal
Zaleplon	5 mg	34	14 day	1 / 3
Zaleplon	10 mg	33	33 day	0 / 1
Triazolam	0.25 mg	31	14 day	0 / 0
Placebo	NA mg	34	14 day	0 / 3

Quality rating: Good Author: Trial type: Active Walsh Year: 1998b Country: US **Funding: Wyeth Ayerst Adverse Events:** Treatmet emergent adverse effects # Overall number of reports Placebo Zaleplon 5mg Zaleplon 10mg Triazolam P value: (35) 14) 17 13 (38) 12 (42 (55 NS Number (% # Nausea Placebo Zaleplon 5mg Zaleplon 10mg Triazolam P value: (<0.04) (<0.04)1(NR (NA) Number (p vs triazolam # headache- the most common Zaleplon 10mg P value: Placebo Zaleplon 5mg Triazolam adverse event (15 (15) 6 (18 (23 Number (% withdrawals # total withdrawals Placebo P value: Zaleplon 5mg Zaleplon 10mg Triazolam) 0) 3 Number (# withdrawals due to AEs Zaleplon 5mg Zaleplon 10mg Triazolam Placebo P value:) 0) 0) 0

Quality rating: Poor Author: Walsh Trial type: Active

Year: 2000 Country: US Funding: Wyeth-Ayerst Research

Design:

Study design RCT

DB

Crossover

Single Center Setting

Age:

%) Female Gender: NR (

Range: 22-49

42

SD:

Ethnicity: NR

Lost to fu: 0 Analyzed: 22

39

30

Number Screened: 73

Number Withdrawn: 2

Eligible:

Enrolled:

Eligibility criteria:

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, comsumption of 20 cigarettes per day or >21 ounces of ethanol per week, currently pregnant or breastfeeding, 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 absorbtion or metabolism of the study drugs.

Comments:

The population characteristics of enrolled subjects were not reported. Only the characteristics for analyzed subjects were reported. 22 subjects were analyzed, 11 men; mean age, 42 y; range, 22-49.

Intervention:

Run-in: NR

NR Wash out :

Allow other medication :

Drug name	dosage	N=	Duration	Total withdrawal
Zaleplon	10 mg	22	2 day	/
Flurazepam	30 mg	22	2 day	/
Placebo	NA mg	22	2 day	/

Author: Walsh__ Trial type: Active Quality rating: Poor

Year: 2000 Country: US Funding: Wyeth-Ayerst Research

Adverse Events:

Author: Ware Trial type: Active Quality rating: Fair

Year: 1997 Country: US Funding: Lorex Pharmaceuticals

Design:

Study design RCT

DB

Parallel

Setting Multicenter

Eligibility 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.

Age: NR

Range: 21-55

SD:

Gender: 64 (58 %) Female

Ethnicity: 69% white

Number Withdrawn: 11 Lost to fu: NR

Eligible:

Enrolled:

Number Screened:

Analyzed: 99

358

NR

110

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.

Comments:

No baseline demographic data provided, but states groups did not differ significantly in gender, age, race, height, and weight.

Intervention:

Run-in: 2 Wash out: 3

Allow other medication: NR

Drug name	dosage	N=	Duration	Total withdrawal	
Zolpidem	10 mg	37	28 day	3 / NR	
Triazolam	0.5 mg	30	28 day	4 / NR	
Placebo	NA mg	35	28 day	0 / NR	

Author: Ware Trial type: Active Quality rating: Fair

Year: 1997 Country: US Funding: Lorex Pharmaceuticals

Adverse Events:

withdrawals

withdrawals due to Aes

total withdrawals

Zolpidem	Triazolam	Placebo		P value:
3 (8.1)	4 (11.1)	0 (0)	()	

Number (%

 Zolpidem
 Triazolam
 Placebo
 P value:

 NR
 ()
 NR
 ()
 ()

Author: Wheatley Trial type: Active Quality rating: Fair
Year: 1985 Country: NR Funding: Not reported

Design:

Study design RCT

DB

Crossover

Setting NR

Age: 53.2

Range: 25-82 SD: 2.1

Gender: 22 (61 %) Female

Ethnicity: NR

Number Withdrawn: 2 Lost to fu: 0

Number Screened: NR

Eligible:

Enrolled:

Analyzed: 36

NR

36

Eligibility criteria:

Patients aged 18 years and over suffering from difficulty in sleeping, provided that symptoms had been present for at least one week.

Exclusion criteria:

NR

Comments:

zopiclone first group had a higher proportion of patients previously responding well to hypnotics and more heavy smokers.

Intervention:

Run-in: 3 Wash out: NR

Allow other medication: NR

			Withdrawals due to AEs/
Drug name	dosage	N=	Duration Total withdrawal
Zopiclone	7.5 mg	36	7 day 2 / 2
Temazepam	20 mg	36	7 day 0 / 0

Quality rating: Fair Author: Wheatley Trial type: Active 1985 NR **Funding: Not reported** Year: Country: **Adverse Events:** Reported by patients # Overall AEs, no. of patients Zopiclone Temazepam P value: (28 (25 10) 9 NR Number (% # Daytime drowsiness Zopiclone Temazepam P value:) 2) NR Number (withdrawals # total withdrawals Zopiclone P value: Temazepam Number (# withdrawals due to Aes Zopiclone P value: Temazepam) 0

Evidence Table 7. Active controlled trials (Elderly): Efficacy

Quality rating: Fair **Author:** Bergener Trial type: Active

Year: 1989 Country: German **Funding: Not reported**

Design:

Study design RCT

DB

Parallel

Setting NR

Eligibility criteria:

Patients who have a minimun score of 14 points on the Sleep Disorder intensity Scale (SDIS) with no improvement during the initial placebo period of 4 days.

Comments:

Intervention: Run-in:

Wash out: 7

Allow other medication :

4

NR Age:

Range: 64-80

SD:

Gender: 36 (86 %) Female

Ethnicity: NR

Number Withdrawn: NR

Number Screened: NR

Eligible:

Enrolled:

Lost to fu: NR Analyzed: 42

NR

42

Exclusion criteria:

Patients with a history of a delirium or a predelitiumm a severe disease of the heart, liver, or kidney, seizure disorder, endogenous psychosis and treatment with drugs affecting vigilance (reserpine and sedating antihistaminics or barbiturates) were excluded

Withdrawals due to AEs/ Total withdrawal

Drug name dosage N= Duration 20 Zopiclone 7.5 mg 21 day 2 / 8 22 21 day 5 / 8 Flurazepam 30 mg

Evidence Table 7. Active controlled trials (Elderly): Efficacy

Author:BergenerTrial type:ActiveQuality rating:FairYear:1989Country:GermanFunding:Not reported

Outcome Measurement:

Efficacy Outcome List:

Sleep Disorder Intensity Scale (SDIS)

Visual Analogue Self-rating scales afternoon - VIS-A

Visual Analogue Self-rating scales morning - VIS-M

Primary

outcome Outcome:

Sleep Disorder Intensity Scale (SDIS)

Results

SDIS (6=best sleep; 30=worst sleep)

Day 33

Zopiclone Flurazepam							P value	
NR (17)	NR	(10)	()	()	<0.1

Score (astimate from the figure

Evidence Table 7. Active controlled trials (Elderly): Efficacy

Quality rating: Fair **Author:** Elie Trial type: Active

Year: 1990a Country: Canada **Funding: Not reported**

Design:

Study design RCT

DB

Parallel

Multicenter Setting

Eligibility criteria:

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

Comments:

Elderly patients living in nursing homes.

Intervention:

Run-in: 7 Wash out :

Allow other medication: NR

76.0 Age:

> Range: 60-90 SD: 1.3

Gender: 33 (75 %) Female

Ethnicity: NR

Lost to fu: 0 Analyzed: 44

Number Screened: NR

Eligible:

Enrolled:

Number Withdrawn: 0

NR

44

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.

dosage	N-	Duration	Withdrawals due to AEs/ Total withdrawal
uosaye	14-	Duration	i Otal Withdrawai
5-7. mg	15	21 day	0 / 0
0.12 mg	14	21 day	0 / 0
NA mg	15	21 day	0 / 0
	0.12 mg	5-7. mg 15 0.12 mg 14	5-7. mg 15 21 day 0.12 mg 14 21 day

Elie_	Trial type:	Activ	⁄e				Quality ra	ting: Fair
1990a	Country:	Cana	da				Funding:	Not reported
Measurement:				Efficacy	Outcome	List:		
sleep questionnaire, administer	ed by a research	nurse		Primary outcome	Outcome:			
					Sleep sound Sleep quality Status of wa	ness	ess upon arising	
					Ü			
questionnaire								
latency, mean score	Zopiclone		Triazola	am				P value
	6.7 (<0.05	6.8	(<0.05)	()	()
	Score (p vs plac	ebo)				
soundness, mean score	Zopiclone		Triazola	am				P value
	6.8 (<0.01	6.4	(<0.08)	()	()
	Score (p vs plac	ebo)				
y of sleep, mean score	Zopiclone		Triazola	am				P value
	10.8 (<0.08) 11.0	(<0.08)	()	() NS
	Score (p vs plac	ebo)				
ing wake-up, mean score	Zopiclone		Triazola	am				P value
	10.5 (NS	10.5	(NS)	()	() NS
	Score (p vs plac	ebo)				
over, mean score	Zopiclone		Triazola	am				P value
	16.6 (NS	16.7	(NS)	()	() NS
	Score (p vs plac	ebo)				
	Measurement: sleep questionnaire, administer questionnaire latency, mean score soundness, mean score y of sleep, mean score ing wake-up, mean score	Measurement: sleep questionnaire, administered by a research Questionnaire latency, mean score Score Score Zopiclone 6.8 (Score (Zopiclone 10.8 (Score (Zopiclone 10.8 (Score (Zopiclone 10.8 (Score (Zopiclone 10.8 (Score (Zopiclone 10.5 (Score (Zopiclone 10.6 (Score (Zopiclone 10.6) (Score (Score (Zopiclone 10.6) (Score	Measurement: sleep questionnaire latency, mean score Score (p vs place) soundness, mean score Zopiclone 6.8 (<0.01) Score (p vs place) y of sleep, mean score Zopiclone 10.8 (<0.08) Score (p vs place) In gwake-up, mean score Zopiclone 10.8 (<0.08) Score (p vs place) In gwake-up, mean score Zopiclone 10.5 (NS) Score (p vs place) In gwake-up, mean score Zopiclone 10.5 (NS) Score (p vs place) In gwake-up, mean score	Measurement: sleep questionnaire latency, mean score Score (p vs placebo Zopiclone Triazola 6.7 (<0.05) 6.8 Score (p vs placebo Zopiclone Triazola 6.8 (<0.01) 6.4 Score (p vs placebo Zopiclone Triazola 10.8 (<0.08) 11.0 Score (p vs placebo Zopiclone Triazola 10.8 (<0.08) 11.0 Score (p vs placebo Zopiclone Triazola 10.8 (<0.08) 11.0 Score (p vs placebo Zopiclone Triazola 10.5 (NS) 10.5 Score (p vs placebo Zopiclone Triazola 10.5 (NS) 10.5 Score (p vs placebo Zopiclone Triazola 10.5 (NS) 10.5 Score (p vs placebo Zopiclone Triazola 10.5 (NS) 10.5 Score (p vs placebo Zopiclone Triazola 10.5 (NS) 10.5 Score (p vs placebo	Measurement: Efficacy Primary outcome	Measurement: Sleep questionnaire, administered by a research nurse	Measurement: sleep questionnaire, administered by a research nurse Primary outcome Sleep latency Sleep soundness Sleep quality Status of wakefuln Hangover	Neasurement: Sleep questionnaire, administered by a research nurse Primary outcome Sleep questionnaire, administered by a research nurse Primary outcome Sleep quality Status of wakefulness upon arising Hangover

Author: Klimm Trial type: Active Quality rating: Fair

Year: 1987 Country: France Funding: Not reported

Design:

Study design RCT

DB

Parallel

Setting Community practic

Age: 73.2

Range: >65 SD: 1.54

Gender: 59 (80 %) Female

Ethnicity: NR

Number Withdrawn: 2

Number Screened: NR

Eligible:

Enrolled:

Lost to fu: 2

Analyzed: 72

NR

74

Eligibility 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 (Syndrom Kurztest) was to be within normal range for their age.

Exclusion criteria:

Patients presenting contraindictions 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.

Comments:

no psychotropic or centrally active drugs were allowed, but medication for concomitant disease were continued, including antihypertensices, non-steroidal anti-inflammatory drugs, hypoglycemic agents, uricosuric agents, anti-anginal agents, and hypolipidaemic agents.

Intervention:

Run-in: 7 Wash out: 7

rusii out : 7

Allow other medication: medication for concomitant disease were continued

Withdrawals due to AEs/

Drug name	dos	age	N=	Duration	Total withdrawal
Zopiclone	7.5	mg	36	7 day	0 / 1
Nitrazepam	5	mg	36	7 day	1 / 1

Author:	Klimm	Trial type	: Activ	е						Quality ra	ting:	Fair
Year:	1987	Country:	Franc	е						Funding:	Not re	eported
Outcome	Measurement:				Effica	асу	Outcome L	ist:				
-	analogue scales gel sleep questionnaire				Prima outco		sleep onset la		y			
							quality of sleet feeling upon a duration of sle awakenings of dreams	awak eep		ght		
Results												
diary: anal	ogue scales											
# sleep place	onset latency- change from bo baseline	Zopiclone -18.2	(< 0.04)	Nitraze	epam (NS)	()		(P val	ue
		Score	(p vs base	eline	`)	,	,		,	<u> </u>	
	y of sleep- change from placebo	Zopiclone		Nitraze	pam						P val	ue
basel	ine	24	(<0.006)	23.1	(< 0.002)	()		() NS	
		Score	(p vs base	eline)						
# feelin	g on awakening- change from	Zopiclone		Nitraze	pam						P val	ue
place	bo baseline	-5.7	(NS)	6.8	(NS)	()		() NS	
		Score	(p vs base	eline)					1	
	g on awakening- on day 9 and	Zopiclone		Nitraze	pam						P val	ue
day 1	1	better	()	NR	()	()		() <0.02	
		Score	()						

Quality rating: Fair **Author: Klimm** Trial type: Active Year: 1987 Country: France Funding: Not reported Spiegel sleep questionnaire # sleep onset latency Zopiclone Nitrazepam P value NR) NR (0.009) NS (0.003 Score (p vs placebo Zopiclone # quality of sleep Nitrazepam P value NR (0.003) NR (0.007)) NS Score (p vs placebo Zopiclone # duration of sleep Nitrazepam P value NR (0.003) NR (0.005)) NS Score (p vs placebo # awakenings at night Zopiclone Nitrazepam P value NR) NS (0.004) NR (0.009 Score (p vs placebo # dreams Zopiclone Nitrazepam P value NR (0.003) NR (0.01) NS Score (p vs placebo # condition in the morning Zopiclone Nitrazepam P value NR (0.003) NR (0.002) NS Score (p vs placebo # general evaluation Zopiclone Nitrazepam P value NR (0.0004) NR (0.005)) NS (p vs placebo Score) Zopiclone # sleep onset latency on day 12 Nitrazepam P value NR) < 0.001 better Score

Author: Leppik Trial type: Active Quality rating: Fair

Year: 1997 Country: US Funding: Lornex Pharmaceuticals

Design:

Study design RCT

DB

Parallel

Setting Multicenter

Eligibility 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 repored 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.

Comments:

Intervention: Run-in:

Wash out: 4

Allow other medication: NR

Age: 69

Range: 59-85

SD:

Gender: 211 (63 %) Female

Ethnicity: 93% white

Number Withdrawn: 40 Lost to fu: 0

Eligible:

Enrolled:

Number Screened:

Analyzed: 335

NR

457

335

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 addtion, 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.

Withdrawals due to AEs/

Drug name	dosage	N=	Duration Total withdrawal
Zolpidem	5 mg	82	28 day 2 / 6
Triazolam	0.12 mg	85	28 day 5 / 14
Temazepam	15 mg	84	28 day 5 / 10
Placebo	NA mg	84	28 day 6 / 10

Author:	Leppik	Trial type	: Acti	ve					Q	uality ra	iting:	Fair
Year:	1997	Country:	US						F	unding:	Lorne	ex Pharmaceuticals
Outcome	Measurement:				Efficac	y Outco	ome Li	st:				
# morni	ng questionnaire al Impression of therapy				Primary outcom	sleep sleep ease no. of wake quality morni	latency duration of falling awaken	asl ings r sl	eep s eep onset	t		
Results	uestionnaire											
		İ		I		1			Т		ĺ	
# sleep	latency at week 4	Zolpidem 40.5	(<0.05	Triazolam) 47.7	(NS)	Temaze 38.0	pam (<0.0	5)	Placebo 57.9	(NA	P valu	ue
		minutes	(p vs pla	icebo)	1						
# sleep	latency at week 1 and week 3	Zolpidem		Triazolam							P valu	ue
		shorter	() multiple d	()		()		() <0.05	j
		minutes	(<u> </u>)	1						
# sleep	latency at week 1 and week 3	Zolpidem		Temazepa	am						P valu	ue
		multiple d	() multiple d	()		()		() NS	
		minutes	(ļ)	I					.1	
# sleep	duration at week 4	Zolpidem		Triazolam	<u> </u>	Temaze	pam		Placebo		P valu	ue
·		362.8	(NS) 359.7	(NS)	375.3	(NS)	363	(NA)	
		minutes	(p vs pla	icebo)	П						

Author:	Leppik	Trial type: Activ	е					Q	uality r	ratir	ng: Fair
Year:	1997	Country: US						Fu	unding	: Lo	ornex Pharmaceuti
# tolera	nce to treatment	Zolpidem	Triazolam		Temazep	am		Placebo			P value
		multiple d (NS)	multiple d (NS)	multiple	(NS)	multiple	(NA)	
		minutes (p vs plac	ebo)				1			
Global Imp	ression of therapy										
# sleep	better	Zolpidem	Temazepam								P value
		NR, better (<0.05)	NR, bette (<0.05)		()		()	
		Score (p vs plac	ebo)				1			
# sleep	latency	Zolpidem	Temazepam								P value
		NR, better (<0.05)	NR, bette (<0.05)		()		()	
		Score (p vs plac	ebo)				1			
# medic	cation strength	Zolpidem	Temazepam								P value
		NR, better (<0.05)	NR, bette (<0.05)		()		()	
		Score (p vs plac	ebo)				1			
# overa	II feeling	Zolpidem	Temazepam							1	P value
		NR, better (<0.05)	NR, bette (<0.05)		()		()	
		Score (p vs plac	ebo)							

Quality rating: Fair **Author:** Roger Trial type: Active

Year: 1993 Country: **France Funding: Not reported**

Design:

Study design RCT

DB

Parallel

Setting Multicenter Age: 81.1

Range: 58-98

SD:

Gender: 164 (74 %) Female

Ethnicity: NR

Number Withdrawn: 16

Number Screened: NR

Eligible:

Enrolled:

Lost to fu: 0 Analyzed: 205

NR

221

Eligibility 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 inlcusion 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.

Comments:

Inpatients at geriatric wards.

Intervention: Run-in: 3

Wash out: 7

Allow other medication: a rescure hypnotic (nitrazepam 5mg) was given at night by the attending nurse on specific patient request in cases of inefficiency

Withdrawals due to AEs/

Drug name	dosage	N=	Duration	Total withdrawal
Zolpidem	5 mg	70	21 day	0 / 7
Zolpidem	10 mg	74	21 day	0 / 1
Triazolam	0.25 mg	77	21 day	2 / 5

Author:	Roger	Trial type:	Activ	'e				Quality ra	ting: Fair	
Year:	1993	Country:	Franc	e				Funding:	Not report	ed
Outcome	Measurement:				Efficad	cy Outo	come List:			
# quest	tionnaire				Primar	y				
# Clinic	cal Global Impression (CGI)				outcon	ne Outo	come:			
							p onset			
							sleep time			
								nal awakenings		
								octurnal awakenings		
							of awakening			
							ng of too earl _! ity of sleep	y awakening		
							ity of sleep ity of awaken	ina		
						quai	ity of awarron	mig		
Results										
questionna	<u>aire</u>									
# % of	patients falling asleep well at day	Zolpidem 5	ma	Zolpide	m 10mg	Triazol	am		P value	
	nange from baseline		(<0.01		(<0.01)	51.9	(<0.01)	()	
							('0.01)	\	/]
			(p vs bas	1)	1		1]
	patients falling asleep well at day hange from baseline	Zolpidem 5		- ·	m 10mg	Triazol			P value	
01, 0	lange nom basemie	34.6	(<0.01	19.8	(<0.01)	18.6	(<0.01)	()	
		%	(p vs bas	eline)					•
# % of	patients falling asleep in <30	Zolpidem 5ı	ng	Zolpide	m 10mg	Triazol	am		P value	
minut basel	tes at day 24, change from	35	(<0.01	35	(<0.01)	35	(< 0.01)	()	
Dasei	ine	%	p vs bas	olino	,		,			
	total alaga tina at day 04			1	/	T		1]
# mean	n total sleep time at day 24, ge from baseline	Zolpidem 5	-		m 10mg	Triazol		,	P value	
on an	go 2000mio	1.6	(NR	1.9	(NR)	1.9	(NR)	()	
		hours	(p vs bas	eline)					

Author: Roger	Trial type: Act	ive		Quality rating: Fair				
Year: 1993	Country: Fran	nce		Funding: N	lot reported			
# % of patients with >2 awakenings per	Zolpidem 5mg	Zolpidem 10mg	Friazolam		P value			
night at day 24, change from baseline	-36.8 (<0.001) -28.8 (<0.001) -	29.8 (<0.00)	()				
	Number (p vs ba	aseline)						
# % of patients with a total nocturnal	Zolpidem 5mg	Zolpidem 10mg	Friazolam		P value			
waking time >1 hours	55.9 (17.6) 47.9 (11.0) 5	55.8 (15.6)	()				
	day 3 (day 24)	'	-				
# overall sleep quality at day 24, change	Zolpidem 5mg	Zolpidem 10mg	Triazolam		P value			
from baseline (higher score=better)	35.5 (<0.001) 34.4 (<0.001) 3	33.6 (<0.00)	()				
	Score (p vs ba	aseline)	·					
# % of patients who reported too early	Zolpidem 5mg	Zolpidem 10mg	Γriazolam		P value			
awakening at day 24, chagne from baseline	-35 (<0.001) -38 (<0.001) -	35 (<0.00)	()				
	% (pvsba	aseline)	·	. '	! !			
Clinical Global Impression (CGI)								
# total mean score- safety and efficacy	Zolpidem 5mg	Zolpidem 10mg	Γriazolam		P value			
	2.54 () 2.43 () 2	2.51 ()	()	NS			
	Score ()	l					

Quality rating: Fair Author: Venter Trial type: Active

1986 Country: **South Africa Funding: Not reported** Year:

Design:

Study design RCT

DB

Setting

Parallel Multicenter

Ethnicity: NR

Lost to fu: 0 Analyzed: 41

Number Screened: 58

Number Withdrawn: 0

Eligible:

Enrolled:

41

41

Eligibility criteria:

1) time taken to fall asleep longer than 45 minutes; 2) more than two awakenings each night without known cause, and difficulty in falling asleep again; 3) sleep duration less than six hours a night.

Exclusion criteria:

76.8

SD:

Range: 60-96

Gender: 31 (76 %) Female

Patients were excluded if they had a psychiatric disorder necessitating treatment with antipsychotic antidepressive, or anticonvulsant drugs, with lithium, or if they received anxiolytic drugs during the day. They were also excluded if they had acute and/or severe cardiac, respiratory, hepatic, or renal disease, or had gastrointestinal disease or prior gastrointestinal surgery, if they had known tolerance to zopiclone or triazolam, or if they had hypersensitivity to drugs.

Comments:

22 patients were already receiving another hypnotic drug; the investigators decided a wahout period in these patients would be undesirable. It was therefore decided that this group of patients should discontunue their previous hypnotic therapy and immediately start the trial medicine, without a washout phase. Day 7 of the treatment was recorded as the first day of baseline assessment for this study.

Age:

Zopiclone-2(10%) and Triazolam-7(33.3%) patients increased the dosage twice after day 8.

Intervention:

Run-in: Wash out: 0

Allow other medication :

Withdrawals due to AEs/

Drug name	dosage	N=	Duration	Total withdrawal	
Zopiclone	0.33 mg	20	17 day	0 / 0	
Triazolam	8.25 mg	21	17 day	0 / 0	

Author:	Venter	Trial type:	Active					Quality	/ rati	ng: Fair
Year:	1986	Country:	South Af	rica				Fundin	ng: N	lot reported
Outcome	Measurement:				Efficacy	Outcome	List:			
# Pre- a	and during-treatment questionnai	res			Primary outcome	Outcome:				
						Difficulty in Sleep durate	_	eep, 3 points,	, 1: dif	f
						Sleep quali				
						Night awak	enings (no	o. of times)		
						-	-	nings (no. of t	times)	
						Daytime sle				
						Sleep satis Daytime sle				
						Dayline sie	Бер			
Results										
Pre- and d	uring-treatment questionnaires									
# Diffice	ulty in falling sleep - day 7	Zopiclone	Tr	azolam						P value
(1=nc	one/very little; 2=some; 3=a lot)	1.21	() 1.0	62 ()	()	()	0.03
		Score)					
# Sleep	duration (hr) - day 7	Zopiclone	Tr	azolam						P value
		7.4	() 7.	5 ()	()	()	0.05
		No. hours	()		"			
# Night	awakenings - day 7	Zopiclone	Tr	azolam						P value
		1	() 1.	7 ()	()	()	0.06
		Frequency	()		ı		٠	I I
# Sleep	quality, Early morning	Zopiclone	Tr	azolam						P value
	enings, Mental alertness on , Sleep satisfaction- day 7	NR	() NF	₹ ()	()	()	NS
_	•		()		,			

Author:	Venter	Trial typ	e:	Acti	ve					Quality	rating: Fair			
Year:	1986	Country: South Africa							Funding: Not reported					
	sleep - day 7, compare to	Zopiclon	е		Triaz	olam					P value			
mean		-8	() 9	()	()	() 0.07			
		Minutes	()							
# Daytime sleep - day 17 (no. of		Zopiclon	е		Triaz	olam					P value			
patients)	2	() 5	()	()	() NR				
		Number	()		, ,					
# Night aw	akenings - day 17	Zopiclon	е		Triaz	olam					P value			
		NR	() 1	()	()	() 0.06			
		Frequenc	y (,)		<u> </u>					
# Daytime sleep - day 17, compare to mean	Zopiclon	е		Triaz	olam					P value				
		-8	() 4	()	()	() NS			
		Minutes	()		ı		, I			

Author: Elie_ Trial type: Active Quality rating: Fair

Year: 1990a Country: Canada Funding: Not reported

Design:

Study design RCT

DB

Parallel

Setting Multicenter

Ra

Age:

Range: 60-90 SD: 1.3

Gender: 33 (75 %) Female

76.0

Ethnicity: NR

Number Withdrawn: 0

Number Screened: NR

Eligible:

Enrolled:

Lost to fu: 0 Analyzed: 44

NR

44

Eligibility criteria:

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.

Comments:

Elderly patients living in nursing homes.

Intervention:

Withdrawals due to AEs/

Drug name	dosage	N=	Duration	Total withdrawal
Zopiclone	5-7. mg	15	21 day	0 / 0
Triazolam	0.12 mg	14	21 day	0 / 0
Placebo	NA mg	15	21 day	0 / 0

Rebound:

Post-sleep questionnaire

rebound: no. of items above show withdrawal effects

Zopiclone Triazolam						P value			
0	()	3	()	()	()	
Number	(ļ.		١				,

Trial type: Active Quality rating: Fair Author: Leppik

Year: 1997 Country: US **Funding: Lornex Pharmaceuticals**

Design:

Study design RCT

DB

Parallel

Setting Multicenter

Age: 69

Range: 59-85

SD:

Gender: 211 (63 %) Female

Ethnicity: 93% white

Number Withdrawn: 40

Number Screened:

Eligible:

Enrolled:

Lost to fu: 0 Analyzed: 335

NR

457

335

Eligibility 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 repored 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 addtion, 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.

Comments:

Intervention:

				Withdrawals due to AEs/
Drug name	dosage	N=	Duration	Total withdrawal
Zolpidem	5 mg	82	28 day	2 / 6
Triazolam	0.12 mg	85	28 day	5 / 14
Temazepam	15 mg	84	28 day	5 / 10
Placebo	NA mg	84	28 day	6 / 10

Rebound:

morning questionnaire

rebound: ease of falling sleep

Triazola	m							P value
worse	(<0.05)	(()	()	()	

Score (p vs baseline

Author: Leppik Trial type: Active Quality rating: Fair

Year: 1997 Country: US Funding: Lornex Pharmaceuticals

rebound: sleep quality

Zolpidem	Triazolam	Temazepam		P value
worse (NR) worse (NR)	worse (NR)	()	

Score (p vs baseline

Quality rating: Fair Author: Trial type: Active Roger

Year: 1993 Country: **France Funding: Not reported**

Design:

Study design RCT

DB

Parallel

Setting Multicenter Age: 81.1

Ethnicity: NR

Range: 58-98

Number Screened: NR

Enrolled:

Eligible: NR

221

SD:

Gender: 164 (74 %) Female

Number Withdrawn: 16

Lost to fu: 0

Analyzed: 205

Eligibility 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 inlcusion 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.

Comments:

Inpatients at geriatric wards.

Intervention:

Withdrawals due to AEs/

Drug name	dosage	N=	Duration	Total withdrawal
Zolpidem	5 mg	70	21 day	0 / 7
Zolpidem	10 mg	74	21 day	0 / 1
Triazolam	0.25 mg	77	21 day	2 / 5

Rebound:

questionnaire

rebound: % of patients falling asleep in <30 minutes at day 31, change from baseline

> % (p vs baseline

18

Zolpidem 5mg Zolpidem 10mg (0.001) 28 (<0.00)

Triazolam (0.06 P value

rebound: % of patients with a total nocturnal waking time >1 hours

Zolpidem 5mg	Zolpidem 10mg	Triazolam		P value
55.9 (13.6)	47.9 (29.6)	55.8 (26.4)	()	

(day 31 day 3

Author: Roger Trial type: Active Quality rating: Fair
Year: 1993 Country: France Funding: Not reported

rebound: feel well rested in the morning, chage from baseline (higher score=better)

Zaleplor	5mg		Zolpidem 10mg Tria:		Triazo	riazolam					P value	
17.2	(0.05)	23.9	(0.05)	10.5	(NA)		()	
Score	(pvs	tria	zolam)	•			ı			

Quality rating: Fair **Author:** Bergener Trial type: Active

Year: 1989 Country: German **Funding: Not reported**

Design:

Study design RCT

DB

Parallel

NR

Setting

Ethnicity: NR

Age:

Gender: 36 (86 %) Female

Range: 64-80

NR

SD:

Number Withdrawn: NR Lost to fu: NR

Analyzed: 42

NR

42

Number Screened: NR

Eligible:

Enrolled:

Eligibility criteria:

Patients who have a minimun score of 14 points on the Sleep Disorder intensity Scale (SDIS) with no improvement during the initial placebo period of 4 days.

Comments:

Intervention:

Run-in:

Wash out: 7

Allow other medication :

Exclusion criteria:

Patients with a history of a delirium or a predelitiumm a severe disease of the heart, liver, or kidney, seizure disorder, endogenous psychosis and treatment with drugs affecting vigilance (reserpine and sedating antihistaminics or barbiturates) were excluded

Withdrawals due to AEs/

				Withdrawals due to ALS
Drug name	dosage	N=	Duration	Total withdrawal
Zopiclone	7.5 mg	20	21 day	2 / 8
Flurazepam	30 mg	22	21 day	5 / 8

Adverse Events:

Withdrawals

number of patients

Zopiclone Flurazepam				P value:
8 (40)	8 (36.3)	()	()	NS

Number (%

Author:BergenerTrial type:ActiveQuality rating:FairYear:1989Country:GermanFunding: Not reported

withdrawals due to AEs

Zopic	Zopiclone Flurazepam						P value:	
2	(10) 5	(22.7)	()	()	NS

Number (%

Author: Elie_ Trial type: Active Quality rating: Fair

Year: 1990a Country: Canada Funding: Not reported

Design:

Study design RCT

DB

Parallel

Setting Multicenter

Ra

Age:

Range: 60-90 SD: 1.3

Gender: 33 (75 %) Female

76.0

Ethnicity: NR

Number Withdrawn: 0 Lost to fu: 0

Number Screened: NR

Eligible:

Enrolled:

Analyzed: 44

NR

44

Eligibility criteria:

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.

Comments:

Elderly patients living in nursing homes.

Intervention:

Run-in: 7 Wash out: 4

Allow other medication: NR

Withdrawals due to AEs/

Drug name	dosage	N=	Duration	Total withdrawal	
Zopiclone	5-7. mg	15	21 day	0 / 0	
Triazolam	0.12 mg	14	21 day	0 / 0	
Placebo	NA mg	15	21 day	0 / 0	

Adverse Events:

reported by patients

reduction of dreams

2	Zopiclone		Triazolam	ı				P value:
į	5 ((<0.02)	3	(NS)	()	()	

Number (p vs placebo

Author:	Elie_	Trial type:	Active					C	Quality	rating:	Fair	
Year:	1990a	Country:	Canada					F	unding	: Not re	∍port	ed
	# bitter t	aste	Zopiclone		Triazolam							P value:
			5	(<0.06)	0	(NS)	()	()	
			Numbe	r (pvspla	cebo)		·			<u> </u>
	withdrawals											
	# total w	ithdrawals	Zopicl	one	Trazodo	ne	Placebo					P value:
			0	()	0	() 0	()	()	
			Numbe	er ()					
	# withdra	awals due to AEs	Zopicl	one	Trazodo	ne	Placebo					P value:
			0	()	0	() 0	()	()	
			Numbe	er ()					

Author:KlimmTrial type:ActiveQuality rating:FairYear:1987Country:FranceFunding:Not reported

Design:

Study design RCT

DB

Parallel

Setting Community practic

Age: 73.2

Range: >65 SD: 1.54

Gender: 59 (80 %) Female

Ethnicity: NR

Number Withdrawn: 2 Lost to fu: 2

Number Screened: NR

Eligible:

Enrolled:

Analyzed: 72

NR

74

Eligibility 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 (Syndrom Kurztest) was to be within normal range for their age.

Exclusion criteria:

Patients presenting contraindictions 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.

Comments:

no psychotropic or centrally active drugs were allowed, but medication for concomitant disease were continued, including antihypertensices, non-steroidal anti-inflammatory drugs, hypoglycemic agents, uricosuric agents, anti-anginal agents, and hypolipidaemic agents.

Intervention:

Run-in: 7
Wash out: 7

Allow other medication :

medication for concomitant disease were continued

Withdrawals due to AEs/

Drug name	dos	age	N=	Duration	Total withdrawal
Zopiclone	7.5	mg	36	7 day	0 / 1
Nitrazepam	5	mg	36	7 day	1 / 1

Adverse Events:

reported by patients

bitter taste

Zopiclone Nitrazepam		P value:
1 () 0 () (()	

Number ()

Author: Year:	Klimm 1987		ctive ance		Quality rating: Fai Funding: Not repor	
	#	dizziness	Zopiclone	Nitrazepam		P value:
			1 ()	0 ()	() ()	T value.
			Number ()	, ,	
	#	confusion	Zopiclone	Nitrazepam		P value:
			0 ()	1 ()	() ()	1 10110101
			Number ()		
	#	fatigue	Zopiclone	Nitrazepam		P value:
			0 ()	1 ()	() ()	
			Number ()	<u>.</u>	
	#	complaints in answer to the standarized question on tolerance	Zopiclone	Nitrazepam		P value:
		standarized question on tolerance	less (NS)	more (<0.00)	()	
			Number (p vs bas	eline)	·	
	<u>withd</u>	<u>rawals</u>				
	#	total withdrawals	Zopiclone	Nitrazepam		P value:
			1 ()	1 ()	()	
			Number ()		
	#	withdrawals due to AEs	Zopiclone	Nitrazepam		P value:
			0 ()	1 ()	() ()	
			Number ()		

Quality rating: Fair Author: Leppik Trial type: Active

1997 Country: US **Funding: Lornex Pharmaceuticals** Year:

Design:

Study design RCT

DB

Parallel

Setting Multicenter

Eligibility 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 repored 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.

Comments:

Intervention: Run-in:

Wash out :

Allow other medication: NR

Age: 69

Range: 59-85

Number Screened: Eligible:

SD:

Gender: 211 (63 %) Female

Ethnicity: 93% white

Number Withdrawn: 40

Lost to fu: 0

Enrolled:

Analyzed: 335

NR

457

335

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 addtion, 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.

Withdrawals due to AEs/

Drug name	dosage	N=	Duration	Total withdrawal
Zolpidem	5 mg	82	28 day	2 / 6
Triazolam	0.12 mg	85	28 day	5 / 14
Temazepam	15 mg	84	28 day	5 / 10
Placebo	NA mg	84	28 day	6 / 10

Adverse Events:

overall adverse events

overall incidence rates

Zolpide	em		Triazo	olam		Tema	zepam		Placebo)		P value:
52	(63)	54	(64)	56	(67)	47	(56)	

Author: Leppik Trial type: Active Quality rating: Fair

Year: 1997 Country: US Funding: Lornex Pharmaceuticals

Year:	1997	Country: US						Fu	naing: L	ornex	۲h	armaceutic
			Number	(%)					
	#	t headache	Zolpider	m		Triazolam		Temazepam	Placebo			P value:
			15	(18.3))	22 (25.9)	18 (21.4) 16	(19)	
			Number	(%)		·			
	#	drowsiness	Zolpider	m		Triazolam		Temazepam	Placebo			P value:
			4	(4.9))	7 (8.2)	8 (9.5) 3	(3.6)	
			Number	(%)					
	#	t myalgia	Zolpider	m		Triazolam		Temazepam	Placebo			P value:
			8	(9.8))	7 (8.2)	8 (9.5) 9	(10.7)	
			Number	(%	1)		ı			1
	#	t nausea	Zolpider	m	1	Triazolam		Temazepam	Placebo			P value:
			6	(7.3)	,	6 (7.1)	4 (4.8) 6	(7.1)	
			Number	(%)					
	#	upper resp infection	Zolpider	m		Triazolam		Temazepam	Placebo			P value:
			6	(7.3)	,	2 (2.4)	7 (8.3) 7	(8.3)	
			Number	(%)					
	#	dyspepsia	Zolpider	m	I	Triazolam		Temazepam	Placebo			P value:
			5	(6.1)	,	3 (3.5)	5 (6.0) 7	(8.3)	
			Number	(%	ı)		ı			1
	#	nervousness	Zolpider	n		Triazolam		Temazepam	Placebo			P value:
			2	(2.4))	7 (8.2)	3 (3.6) 4	(4.8)	
			Number	(%)		L			

Author:	Leppik	Trial type:	Active					Qual	ity ı	rating: Fa	air	
Year:	1997	Country:	US					Fund	ding	: Lornex I	Ph	armaceutio
	# arthralgia		Zolpidem			Triazolam		emazepam	Placebo			P value:
			4	(4.9)) :	5 (5.9) 0	(0)	3	(3.6)	
			Numbe	er (%)					
	# fatigue		Zolpid	em		Triazolam	T	emazepam	Plac	ebo		P value:
			1	(1.2))	2 (2.4) 5	(6.0)	1	(1.2)	
			Numbe	er (%)					
	withdrawals											
	# total withdra	awals	Zolpid	em	1	Triazolam	Т	emazepam	Plac	ebo		P value:
			6	())	14 () 10	0 ()	10	()	
			Numbe	er (1)		'			I
	# withdrawals	due to AEs	Zolpid	em	ŀ	Triazolam	T	emazepam	Plac	ebo		P value:
			2	())	5 () 5	()	6	()	
			Numbe	er ()					

Quality rating: Fair **Author:** Roger Trial type: Active

1993 **France Funding: Not reported** Year: Country:

Design:

Study design RCT

DB

Parallel

Setting Multicenter Age: 81.1

Ethnicity: NR

Range: 58-98

Number Screened:

Eligible: NR Enrolled: 221

NR

SD:

Gender: 164 (74 %) Female

Number Withdrawn: 16

Lost to fu: 0

Analyzed: 205

Eligibility 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 inlcusion 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.

Comments:

Inpatients at geriatric wards.

Intervention: Run-in: 3

Wash out: 7

Allow other medication: a rescure hypnotic (nitrazepam 5mg) was given at night by the

attending nurse on specific patient request in cases of inefficiency

Withdrawals due to AEs/

Drug name	dosage	N=	Duration	Total withdrawal	
Zolpidem	5 mg	70	21 day	0 / 7	
Zolpidem	10 mg	74	21 day	0 / 1	
Triazolam	0.25 mg	77	21 day	2 / 5	

Adverse Events:

overall report

no. patients experiencing adverse events

Zolpide	m 5mg		Zolpic	lenm 10mg	Triazo	olam				P value:
11	(16)	8	(11) 16	(21)	()	
Number	(%)					

Author:	Roger	Trial type:	Active					Quality	rating:	Fair	
Year:	1993	Country:	France					Funding	g: Not re	port	ed
		nightmares- the most common	Zolpidem 5mg			g Zolpidenm 10mg					P value:
	,	adverse effect	2	()	3 () 2	()	()	
			Numbe	r (,)	<u> </u>			1
	withdray	<u>vals</u>									
	#	total withdrawals	Zolpide	em 5mg		Zolpidem 10mg	Triazolam				P value:
			7	()	1 () 5	()	()	
			Numbe	r (,)	·			1
	#	withdrawals dur to Aes	Zolpide	em 5mg		Zolpidem 10mg	Triazolam				P value:
			0	()	0 () 2	()	()	
			Numbe	r (,)	ļ.			1

Quality rating: Fair Author: Venter Trial type: Active

1986 **South Africa Funding: Not reported** Year: Country:

Design:

Study design RCT

DB

Parallel

Setting Multicenter

Age:

Gender: 31 (76 %) Female Ethnicity: NR

76.8

SD:

Range: 60-96

Lost to fu: 0

Number Withdrawn: 0

Number Screened: 58

Eligible:

Enrolled:

41

41

Analyzed: 41

Eligibility criteria:

1) time taken to fall asleep longer than 45 minutes; 2) more than two awakenings each night without known cause, and difficulty in falling asleep again; 3) sleep duration less than six hours a night.

Exclusion criteria:

Patients were excluded if they had a psychiatric disorder necessitating treatment with antipsychotic antidepressive, or anticonvulsant drugs, with lithium, or if they received anxiolytic drugs during the day. They were also excluded if they had acute and/or severe cardiac, respiratory, hepatic, or renal disease, or had gastrointestinal disease or prior gastrointestinal surgery, if they had known tolerance to zopiclone or triazolam, or if they had hypersensitivity to drugs.

Comments:

22 patients were already receiving another hypnotic drug; the investigators decided a wahout period in these patients would be undesirable. It was therefore decided that this group of patients should discontunue their previous hypnotic therapy and immediately start the trial medicine, without a washout phase. Day 7 of the treatment was recorded as the first day of baseline assessment for this study.

Zopiclone-2(10%) and Triazolam-7(33.3%) patients increased the dosage twice after day 8.

Intervention:

Run-in:

Wash out: 0

Allow other medication :

Withdrawals due to AEs/

Drug name	dosage	N=	Duration	Total withdrawal	
Zopiclone	0.33 mg	20	17 day	0 / 0	
Triazolam	8.25 mg	21	17 day	0 / 0	

Adverse Events:

Reported by the patients

total number of patient

Zopiclone	Triazolam			P value:
7 (35)	8 (38)	()	()	NR

Number (%

Author:	Venter	Trial type: Ac	tive	Quality rating: Fair								
ear:	1986	Country: So	South Africa Funding: Not reported									
		nber of patient reporting AEs on	Zopiclone		Triazolam						P value:	
	uay	7 and day 9	more ()	NR ()	()	()	0.013	
			Number ()						
	Reported by	y the patients: CNS AEs										
		ression, tearfulness,	Zopiclone		Triazolam						P value:	
		wsiness, dizziness, agitation, ntmares, confusion, and	3 ()	7 ()	()	()	NR	
		urbed sleep	Number ()						
	Reported b	y the patients: Gastrointestinal AE	` <u>:s</u>			,						
	# Bad	I taste	Zopiclone		Triazolam						P value:	
			6 ()	2 ()	()	()	NR	
			Number (,	`	\ \	,		`	,		
	Papartad b	y the patients: Other AEs	radilibei (,						
	· · · · · · · · · · · · · · · · · · ·	scular pain, angina pectoris			1							
		sodes, and shortness of breath	Zopiclone		Triazolam			\			P value:	
			3 ()	1 ()	()	()	NR	
			Number ()						
	withdrawals	<u> </u>										
	# tota	l withdrawals	Zopiclone		Triazolam						P value:	
			0 ()	0 ()	()	()		
			Number ()		ľ				
	# with	drawals due to AEs	Zopiclone		Triazolam						P value:	
			0 ()	0 ()	()	()	. vaido.	
			Number (- (<u>' </u>	`	,	`			

Subgroup: Anxiety **Quality rating: Poor Author:** Agnoli Trial type: Active Year: 1989 Country: Rome, Foggia, Italy **Funding: Not reported**

Design:

Study design RCT

DB

Crossover

Setting

NR

38.2 Age:

> Range: SD: 2.1

Gender: 12 (60 %) Female

Ethnicity: NR

Number Withdrawn: 0 Lost to fu: 0

Number Screened: NR

Eligible:

Enrolled:

NR

20

Analyzed: 20

Eligibility criteria:

Patients were aged 20-50 years with total score of the Hamilton Rating Scale for Anxiety less than 20. Absence of concomitant antidepressive, anxiolytic or neuroleptic medication and absence of somatic, pathophysiological or pharmacological factors related to the onset and persistence of insomnia.

Comments:

Poor quality: insufficient information to assess. Patients with generalized anxiety disorder.

Intervention:

Run-in: 3

Wash out: NR

Allow other medication: NR

Exclusion criteria:

Presence of concomitant general illness; renal or hepatic failure; effectiveness of placevo administration; and pregnancy.

Withdrawals due to AEs/

Drug name	dosage	N=	Duration	Total withdrawal	
Zopiclone	7.5 mg	12	1 day	/	
Nitrazepam	5 mg	12	1 day	1	

Author:	Agnoli	Trial type:	Active	Subgroup:	Anxiety	Quality rating	Poor		
Year:	1989	Country:	Rome, Fogg	ia, Italy	Funding: Not reported				
Outcome	Measurement:			Efficacy	Outcome List:				
# Toulo	Iton Rating Scale for Anxiety (HR buse-Pieron Attention Test (TPAT) signed semiquantitative scale	,		Primary outcome	Outcome: anxiety levels time of sleep induction hours of sleep number of nocturnal quality of sleep quality of daytime ar	arousals			
# after t	Rating Scale for Anxiety (HRSA) the 1st and 2nd weeks of nent (less score = better)	Nitrazepam - (Score ()	()	()		value .05		

Author: Agnoli	Trial type:	Active	Subgrou	ıp:	Anxiety		Quality ra	ating: Poor
Year: 1989	Country:	Rome, F	oggia, Italy				Funding:	Not reporte
Toulouse-Pieron Attention Test								
# reduction of omitted items on the 7th	Nitrazepam							P value
day (more reduction=better)	- ()	()	()	() <0.01
	Number (<u>"</u>)		1		
# reduction of omitted items on the 14th	Nitrazepam							P value
day (more reduction=better)	- ()	()	()	() <0.05
	Number (<u>'</u>)				
# reduction of errors items on the 7th	Nitrazepam							P value
day (more reduction=better)	- ()	()	()	() <0.01
	Number (I)		I		
# times of excution (shorter=better)	Nitrazepam					ĺ		P value
	- ()	()	()	() <0.01
	Number (ı)		,		l l
Time-signed semiquantitative scale								
# time of sleep induction (shorter=better)	Nitrazepam							P value
	- ()	()	()	() <0.001
	Number (<u> </u>)				
# quality of daytime arousal	Nitrazepam							P value
	- ()	()	()	() <0.01
	Number (<u> </u>)				
# number of nocturnal arousals, the	Nitrazepam							P value
quality of sleep, the duration of sleep	NR ()	()	()	() NS
	Number (l)				

Author: Ansoms Trial type: Active Subgroup: alcoholism Quality rating: Fair
Year: 1991 Country: US Funding: Not reported

Design:

Study design RCT

DB

Parallel

Setting Multicenter

Eligibility 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.

Comments:

Intervention: Run-in: 2

Wash out: NR

Allow other medication: No

Age: 43.9

Range: 20-55

SD:

Gender: 17 (33 %) Female

Ethnicity: NR

Number Withdrawn: 0 Lost to fu: 0

Number Screened: NR

Eligible:

Enrolled:

Analyzed: 52

54

52

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 flucuating condition with mental or physical stress, or patients with a severe liver or kidney disturbance. Shiftworkers were not included in the study

Withdrawals due to AEs/

Drug name	dos	sage	N=	Duration	Total withdrawal
Zopiclone	7.5	mg	27	5 day	0 / 0
Lormetazepam	1	mg	25	5 day	0 / 0

Vear: 1991 Country: US Funding: Not reported	Author:	Ansoms	Trial type:	Activ	'e	Subg	group:	alcoholisr	n	Quality ra	ating:	Fair
# Spiegel Sleep Questionnaire # Visual Analogue Scale # Investigator-completed scale (1=excellent, 2=good, 3=fair, 4=poor) Fificacy (Spiegel Sleep Questionnaire)	Year:	1991	Country:	US						Funding:	Not re	eported
# Visual Analogue Scale # Investigator-completed scale (1=excellent, 2=good, 3=fair, 4=poor) Efficacy (Spiegel Sleep Questionnaire) Behavior and mood on waking up Overall evaluation of efficacy and tolerabilit Palue Palu	Outcome	Measurement:				Ei	fficacy	Outcome	List:			
# Investigator-completed scale (1=excellent, 2=good, 3=fair, 4=poor) Behavior and mood on waking up Overall evaluation of efficacy and tolerabilit Fificacy (Spiegel Sleep Questionnaire)	# Spieg	gel Sleep Questionnaire				P	Primary					
Results Efficacy (Spiegel Sleep Questionnaire) # Improvement from baseline to end of treatment on quality of sleep # Improvement from baseline to end of treatment on duration of sleep # Improvement from baseline to end of treatment on nocturnal awakenings # Improvement from baseline to end of treatment on nocturnal awakenings # Improvement from baseline to end of treatment on duration of sleep # Improvement from baseline to end of treatment on duration of sleep # Improvement from baseline to end of treatment on nocturnal awakenings # Improvement from baseline to end of treatment on duration of sleep # Improvement from baseline to end of treatment on dreams # Improvement	# Visua	al Analogue Scale				0	utcome	Outcome:				
Results Efficacy (Spiegel Sleep Questionnaire) # Improvement from baseline to end of treatment on quality of sleep MS () 0.013 () () () P value p-value () p-value () p-value () # Improvement from baseline to end of treatment on duration of sleep MS () 0.065 () () () () P value P value # Improvement from baseline to end of treatment on duration of sleep MS () NS () NS () () () () # Improvement from baseline to end of treatment on nocturnal awakenings # Improvement from baseline to end of treatment on dreams # Improvement from baseline to end of treatment on dreams # Improvement from baseline to end of treatment on dreams # Improvement from baseline to end of treatment on dreams Depoil one Lormetazepam P value P val	# Inves	tigator-completed scale (1=excell	ent, 2=good, 3=	=fair, 4=po	or)				-		e)	
Efficacy (Spiegel Sleep Questionnaire) # Improvement from baseline to end of treatment on time to fall asleep # Improvement from baseline to end of treatment on quality of sleep # Improvement from baseline to end of treatment on duration of sleep # Improvement from baseline to end of treatment on duration of sleep # Improvement from baseline to end of treatment on nocturnal awakenings # Improvement from baseline to end of treatment on nocturnal awakenings # Improvement from baseline to end of treatment on dreams # Improvement from baseline to end of treatme										• .		
# Improvement from baseline to end of treatment on time to fall asleep # Improvement from baseline to end of treatment on time to fall asleep # Improvement from baseline to end of treatment on quality of sleep # Improvement from baseline to end of treatment on duration of sleep # Improvement from baseline to end of treatment on nocturnal awakenings # Improvement from baseline to end of treatment on nocturnal awakenings # Improvement from baseline to end of treatment on dreams # Improvement from baseline to end of treatment on dreams # Improvement from baseline to end of treatment on dreams # Improvement from baseline to end of treatment on dreams # Improvement from baseline to end of treatment on dreams # Improvement from baseline to end of treatment on dreams # Improvement from baseline to end of treatment on dreams # Improvement from baseline to end of treatment on dreams # Improvement from baseline to end of treatment on dreams # Improvement from baseline to end of treatment on dreams # Improvement from baseline to end of treatment from baseline to end of treatment on dreams # Improvement from baseline to end of treatment from baseline from baseline from the from								Overall eval	uation	or efficacy and tole	radilit	
# Improvement from baseline to end of treatment on time to fall asleep Description Results												
# Improvement from baseline to end of treatment on duration of sleep # Improvement from baseline to end of treatment on duration of sleep # Improvement from baseline to end of treatment on nocturnal awakenings # Improvement from baseline to end of treatment on nocturnal awakenings # Improvement from baseline to end of treatment on nocturnal awakenings # Improvement from baseline to end of treatment on nocturnal awakenings # Improvement from baseline to end of treatment on dreams # Improvement from baseline to end of treatment on dreams # Improvement from baseline to end of treatment on dreams NS	Efficacy (S	Spiegel Sleep Questionnaire)										
# Improvement from baseline to end of treatment on duration of sleep # Improvement from baseline to end of treatment on quality of sleep # Improvement from baseline to end of treatment on duration of sleep # Improvement from baseline to end of treatment on nocturnal awakenings # Improvement from baseline to end of treatment on nocturnal awakenings # Improvement from baseline to end of treatment on order from baseline to end of treatment on dreams # Improvement from baseline to end of treatment from baseline to end of treatment on dreams # Improvement from baseline to end of treatment on dreams NS			Zopiclone		Lormeta	azepam					P val	ue
# Improvement from baseline to end of treatment on quality of sleep Zopiclone NS	treatn	ment on time to fall asleep	NS (()	0.013	()	()	()	
treatment on quality of sleep NS			p-value (r	I)					
treatment on quality of sleep NS	# Impro	ovement from baseline to end of	Zopiclone	<u> </u>	Lormeta	zepam	'		ĺ		P val	III E
# Improvement from baseline to end of treatment on duration of sleep # Improvement from baseline to end of treatment on nocturnal awakenings # Improvement from baseline to end of treatment on nocturnal awakenings # Improvement from baseline to end of treatment on dreams #				·)		()	()	() ' ' ' '	uc
# Improvement from baseline to end of treatment on duration of sleep Description			`	,		`	<u> </u>	`	,	`	'	
treatment on duration of sleep NS () NS () () () () p-value () # Improvement from baseline to end of treatment on nocturnal awakenings # Improvement from baseline to end of treatment on dreams NS () NS () () () () # Improvement from baseline to end of treatment on dreams Description Desc	4 1		i `				,		ĺ		1	
# Improvement from baseline to end of treatment on nocturnal awakenings # Improvement from baseline to end of treatment on dreams # Improvement from baseline to end of treatment on dreams # Improvement from baseline to end of treatment on dreams # Improvement from baseline to end of treatment on dreams # Improvement from baseline to end of treatment on dreams # Improvement from baseline to end of treatment on dreams # Improvement from baseline to end of treatment on powering disposition # Improvement from baseline to end of treatment on powering disposition # Improvement from baseline to end of treatment on powering disposition # Improvement from baseline to end of treatment on powering disposition # Improvement from baseline to end of treatment on powering disposition # Improvement from baseline to end of treatment on powering disposition # Improvement from baseline to end of treatment on powering disposition # Improvement from baseline to end of treatment on powering disposition # Improvement from baseline to end of treatment on powering disposition # Improvement from baseline to end of treatment on powering disposition # Improvement from baseline to end of treatment on powering disposition # Improvement from baseline to end of treatment on powering disposition # Improvement from baseline to end of treatment on powering disposition # Improvement from baseline to end of treatment on powering disposition # Improvement from baseline to end of treatment on powering disposition # Improvement from baseline to end of treatment on powering disposition # Improvement from baseline to end of treatment on powering disposition # Improvement from baseline to end of treatment on powering disposition # Improvement from baseline to end of treatment on powering disposition # Improvement from baseline to end of treatment on powering disposition # Improvement from baseline to end of treatment on trea				, ,		azepam '	``		`		P val	ue
# Improvement from baseline to end of treatment on nocturnal awakenings Xopiclone			,	.)	INS	()	()	(,	
treatment on nocturnal awakenings NS					1)					
# Improvement from baseline to end of treatment on dreams Topiclone Lormetazepam P value						azepam					P val	ue
# Improvement from baseline to end of treatment on dreams Zopiclone	пеаш	nent on noctumal awakeriings	NS (()	NS	()	()	()	
treatment on dreams NS () NS () () () () p-value () # Improvement from baseline to end of treatment on marriar disposition. Zopiclone Lormetazepam P value			p-value (,)				•	
# Improvement from baseline to end of treatment or married disposition. Value Val			Zopiclone		Lormeta	azepam					P val	ue
# Improvement from baseline to end of Zopiclone Lormetazepam P value	treatment on dreams	NS (()	NS	()	()	()	_	
treatment on marriag disposition			p-value (ı)		ļ		I	1
treatment on marriag disposition	# Impro	ovement from baseline to end of	Zopiclone		Lormeta	azepam					P val	ue
			NS (()	NS	()	()	()	
p-value (n-value (·	1	•	,	`	,	•	*	

Author:	Ansoms	Trial type	e: Ac	tive	Subg	roup:	alcoholisr	n	Quality	rating: Fair
Year:	1991	Country	US						Fundin	g: Not reporte
	ement from baseline to end of	Zopiclone		Lorme	tazepam					P value
treatment on general evaluation		NS	() NS	()	()	()
		p-value	(<u>"</u>)		II.		
Overall eval	uation of efficacy and tolerability	•								
	an's overall efficacy	Zopiclone		Lorme	tazepam					P value
	ment after treatment lent or good")	44	() 48	()	()	() NS
		(%)	()				
Behavior an	d mood on waking up									
# No differences between treatments		0								P value
any of 18 items based on Norris rating scale			()	()	()	()
			()				

Author: Bozin-Juracic Trial type: Active Subgroup: shiftworker Quality rating: Fair

Year: 1995 Country: Croatia Funding: May and Becker and Rhone-

Design:

Study design NR

NR

Crossover

Setting Single Center

Age: NR

Range: 24-58

SD:

Gender: NR (0 %) Female

Ethnicity: NR

Number Withdrawn: 0 Lost to fu: 0

Analyzed: 29

Number Screened: NR

Eligible:

Enrolled:

32

29

Eligibility criteria:

A group of workers employed in a security company were recruited to the study as subjects

Exclusion criteria: NR

Comments:

Not clear if randomized.

Intervention:

Run-in: 0 **Wash out**: 0

Wash out: 0
Allow other medication: NR

2

Withdrawals due to AEs/

Drug name	dosage	N=	Duration	Total withdrawal
Zopiclone	7.5 mg	29	7 day	0 / 0
Nitrazepam	5 mg	29	7 day	0 / 0
Placebo	NA mg	29	7 day	0 / 0

Author:	Bozin-Juracic	Trial type:	Activ	е 🤄	Subgroup:	shiftv	vorke	er	Quality ra	ting:	Fair
Year:	1995	Country:	Croati	ia					Funding:	May a	and Becker and Rhone-
Outcome	Measurement:				Efficacy	/ Outco	ome I	_ist:			
# sleep	questionnaire using visual-analog	ue scale			Primary outcome	Outco					
							of slee	ep episod ne	le		
						sleep of sleep of sleep of no. of	atency quality	,			
						sponta	aneous	final awa	akenings		
Results											
sleep ques	stionnaire using visual-analogue so	ale									
	total length of main sleep nate from the figure)	Zopiclone 295	()	Nitrazepar 285		Placebo 270	()	(P va	ılue
		minutes	()						
# mean	sleep efficacy of main sleep	Zopiclone		Nitrazepar	m	Placebo				P va	alue
(estin	nate from the figure)	88	()	87	()	82	()	() NR	
		%	()			I			
# mean	sleep efficacy of all day sleep	Zopiclone		Nitrazepar	m	Placebo				P va	llue
(estimate from the figure)	nate from the figure)	88	()	87	()	82	()	() NR	
		%	()			,		. 1	
# 10 ite	ms of main sleep characteristics	Zopiclone		Nitrazepar	m	Placebo				P va	llue
		NR	()	NR	()	NR	()	() NS	
		Score	()			1			

Author:	Bozin-Juracic	Trial type:	Active	Subgroup:	shiftworker	Quality rat	ting: Fair
Year:	1995	Country:	Croatia			Funding:	May and Becker and Rhone-
# 5 item	s of all day sleep characteristics	Zopiclone	N	Vitrazepam	Placebo		P value
		NR () N	NR ()	NR ()	() NS
		Scoro (١		•	

Author: Fontaine Trial type: Active Subgroup: psychiatric Quality rating: Fair

Year: 1990 Country: Canada Funding: Rhone-Poulenc Pharma

Design:

Study design RCT

DB

Parallel

Setting Single Center

Eligibility 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.

Comments:

Subgroup: generalized anxiety disorder

Intervention:

Run-in:

Wash out: 21

Allow other medication: no psychotopic medications

Age: 42.9

Range: 26-58 SD: 1.1

Gender: 40 (53 %) Female

Ethnicity: NR

Number Withdrawn: 21 Lost to fu: 0

Number Screened: NR

Eligible:

Enrolled:

Analyzed: 75

NR

75

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).

				Withdrawals due to AEs/
Drug name	dosage	N=	Duration	Total withdrawal
Zopiclone	7.5 mg	30	28 day	4 / 8
Triazolam	0.5 mg	30	28 day	3 / 8
Placebo	NA mg	15	28 day	0 / 5

Author:	Fontaine	Trial type	: Activ	/e	Subgroup:	psychiatric	Quality	rating:	Fair
Year:	1990	Country:	Cana	da			Funding	g: Rhone	-Poulenc Pharma
# sleep # Hamil	Measurement: inventory Iton Rating Scale (HAM) cal Global Impression (CGI)				Efficacy Primary outcome	Outcome: sleep induction sleep soundness duration of sleep morning awakeni hangover effect			
Results									
sleep inver	ntory								
# sleep induction time	Zopiclone		Triazola	ım			P valu	ie	
	3.5	(<0.01) 3.5	(<0.05)	()	() NS		
		Score	(p vs plad	cebo)		1		
# sleep	induction cluster	Zopiclone		Triazola	ım			P valu	ie
		14.7	(< 0.05) 14.1	(NS)	()	() NS	
		Score	(p vs plad	cebo)		11		
# durati	ion of sleep	Zopiclone		Triazola	ım			P valu	ie
		2.9	(NS) 2.9	(NS)	()	() NS	
		Score	(p vs plac	cebo)				
# sleep	soundness	Zopiclone		Triazola	ım			P valu	ie
		11.0	(< 0.05) 10.5	(NS)	()	() NS	
		Score	(p vs plac	cebo)		1		
# globa	ıl sleep index	Zopiclone		Triazola	ım			P valu	ıe
		35.7	(NS) 34.6	(NS)	()	() NS	
		Score	(p vs plac	cebo)		1	1	

core (Zopiclone 5.8 (core (Zopiclone 3.8 (p vs place NS) p vs place NS)	Triazolar 6.7 ebo Triazolar 6.3	(NS m (NS)	()	()	P value NS P value NS
7.3 (core (Zopiclone 6.8 (core (Copiclone 8.8 (p vs place NS) p vs place NS)	6.7 Ebo Triazolar 6.3 Ebo Triazolar	(NS m (NS)	()	()	P value NS
core (Zopiclone 5.8 (core (Zopiclone 3.8 (p vs place NS) p vs place NS)	Triazolar 6.3 Ebo Triazolar	m (NS)))	()	()	P value NS
Zopiclone 6.8 (core (Zopiclone 8.8 (NS) p vs place	Triazolar 6.3 ebo	(NS)	()	()	NS
core (Copiclone 3.8 (p vs place	6.3 ebo Triazolar	(NS)	()	()	NS
core (Zopiclone 3.8 (p vs place	ebo	m)	()	()	
Zopiclone 3.8 (NS)	Triazolar)					
3.8 (· · · · · · · · · · · · · · · · · · ·								
3.8 (· · · · · · · · · · · · · · · · · · ·								
•	· · · · · · · · · · · · · · · · · · ·	12.0	/ 1.10						P value
core ((NS)	()	()	<0.01
0010 (p vs place	ebo)					
Zopiclone		Triazolar	m						P value
9.3 (NS)	10.8	(NS)	()	()	NS
core (p vs place	ebo)					
Zopiclone		Triazolar	m	1					P value
	NS)	22.4	(NS)	()	()	<0.01
core (p vs place	ebo							
Zopiclone		1	m						P value
	17)	10	(33)	()	()	0.16
umber (%					,	·		
(, ,,			,					
opiclone		Triazolar	m						P value
•	sig. bet)			et)	()	()	NR
NK (Į.	(- 3)	`	<i>'</i>	`	,	
- -	mber ((17) Imber (% Impictone R (sig. bet)	(17) 10 mber (% Triazolar R (sig. bet) NR	(17) 10 (33 mber (% ppiclone Triazolam R (sig. bet) NR (sig. bet)	(17) 10 (33) mber (%) ppiclone Triazolam R (sig. bet) NR (sig. bet)	(17) 10 (33) (Imber (%) Opiclone Triazolam R (sig. bet) NR (sig. bet) ((17) 10 (33) () Imber (%) Opiclone Triazolam R (sig. bet) NR (sig. bet) ()	(17) 10 (33) () () (mber (%)) () (pipiclone Triazolam R (sig. bet) NR (sig. bet) () ()	(17) 10 (33) () () mber (%) ppiclone

Author: Li Pi Shan Trial type: Active Subgroup: Stroke (inpatient) Quality rating: Fair
Year: 2004 Country: Canada Funding: Not reported

Design:

Study design RCT

DB

Crossover

Setting Single Cen

Single Center

Range: 20-78

Age:

SD:

56.6

Gender: 8 (44 %) Female

Ethnicity: NR

Number Withdrawn: 0 Lost to fu: 0

Number Screened: 44

Eligible:

Enrolled:

Analyzed: 18

27

18

Eligibility criteria:

Each patient with a diagnosis of either stroke or brain injury was consecutively recruited for eligibility.

Exclusion criteria:

Patients were excluded if they were acutely ill, unable to communicate either in English or French, or unable to ead and answer questions for any other reason (severe aphasia, blindness, severe cognitive impairment, including patients with posttraumatic amnesia). Subjects were also> 18 years of age. The patients were not excluded if they experienced any secondary causes of insomnia such as depression, sleep apnea, or restless legs syndrome.

Comments:

Although there was no formal washout period between weeks 1 and 2, the questionnaire was not administered on any of the first 3 days to allow for a washout of the medication taken during week 1.

Any additional medications the patients were receiving were maintained constant throughout the trial. Those whose medications changed over the course of the study were excluded.

Intervention:

Run-in: 0 **Wash out**: 0

Allow other medication :

Concomitatnt use of medication were maintained throughout the trial

Withdrawals due to AEs/

Drug name	dosage	N=	Duration	Total withdrawal
Zopiclone	3.75 mg	18	As needed for 7 day	0 / 0
Lorazepam	0.5- mg	18	As needed for 7 day	0 / 0

Author:	Li Pi Shan	Trial type:	Activ	е	Subgroup:	Stroke (inpatient)	Quality ratin	g: Fair
Year:	2004	Country:	Canad	da			Funding: No	ot reported
Outcome	Measurement:				Efficacy	Outcome List:		
	ded by nurses questionnaire				Primary outcome	Outcome:		
# Mini r	nentalstate examination score					total time of sleep quality of sleep depth of sleep feeling of rest daytime drowsiness lethargy fatigue		
Results								
recorded b	y nurses							
# total t	ime of sleep	Zopiclone		Lorazepa	am			P value
		7.23 (0.63)	7.49	(0.77)	()	()	0.09
		hours (SD	1)	l		
# alertn	ess (higer score=better)	Zopiclone		Lorazepa	am		1	P value
		4 (3.5-4	4	(3.5-4)	()		0.6
		Score (Range)			
	g of being refreshed (higer	Zopiclone		Lorazepa	am			P value
score	=better)	3.5 (3-4)	4	(3-4)	()	()	0.79
		Score (Range	I)	l l		

Author:	Li Pi Shan 2004	Trial type			Subgroup:	Stroke (ir	npatient			_
Year:	2004	Country:	Canad	ıa				rundin	ıg: N	lot reporte
sleep quest	tionnaire									
# quality	of sleep (higher score=better)	Zopiclone		Loraze	pam					P value
		8	(5-9)	8.5	(7.5-10)	()	()	0.17
		Score	(Range)					
# depth of sleep (higher score=better)		Zopiclone		Loraze	pam					P value
		8	(6-10)	8	(7-10)	()	()	0.21
		Score	(Range)					
<pre># feeling of being refreshed (higher score=better)</pre>		Zopiclone		Loraze	pam					P value
		8	(6.5-10)	8	(6.5-9.5)	()	()	0.52
		Score	(Range)		I			
# alertne	ess (higher score=better)	Zopiclone		Loraze	pam					P value
		9	(6.5-10)	9	(8-10)	()	()	0.6
		Score	(Range	•)		,			I I
# tiredne	ess (higher score=better)	Zopiclone		Loraze	pam					P value
		8	(5.5-8.5)	7.5	(5-10)	()	()	0.29
		Score	(Range)		"			
Mini menta	Istate examination score									
# total s	core	Zopiclone		Loraze	pam					P value
		28	(27-30)	27	(25-29)	()	()	0.054
		Score	(Range)		l			

Author:	Pagot	Trial type: Active	Subgroup: psychiatric	Quality rating: Fair
Year:	1993	Country: France		Funding: Not reported

Design:

Study design RCT

DB

Parallel

Setting Multicenter

Eligibility criteria:

two of the following symptoms: sleep onset latency of more than 30 minutes; more than two nocturnal awakenings; total duration of sleep of less than 6 hours; or total nocturnal wake-time of more than 20 minutes.

Comments:

Intervention: Run-in: 4

Wash out: 30

Allow other medication: no other hypnotic drugs

Withdrawals due to AEs/

Drug name	dosage	N=	Duration	Total withdrawal
Zolpidem	20 mg	47	86 day	1 / 15
Triazolam	0.5 mg	48	86 day	2 / 18

Age: 48

Range: Number Screened: NR SD: Screened: NR Eligible: NR Enrolled: 95

Gender: 58 (61 %) Female

Ethnicity: NR Number Withdrawn: 33
Lost to fu: 0

Analyzed: 62

Exclusion criteria:

Patients who showed sleep disorders associated with severe psychiatric disorders, sleep apnea, sleep-related myoclonus, or insomnia that had developed during childhood, and those who showed serious medical disease or needed concomitant hypnotic medication or treatment that could have had an influence on sleep onset were excluded. Pregnant women and women of childbearing potential who were not taking adequate contraceptive precautions were also excluded, as were nursing mothers and those patients in whom adequate compliance could not be expected. Patients were excluded if they were receiving any treatment that could have an influence on sleep onset.

Author:	Pagot	Trial type	: Activ	/e	Subgroup):	psychiatric	;	Quality rati	ing:	Fair
Year:	1993	Country:	Franc	e					Funding: 1	Not re	eported
Outcome	Measurement:				Efficac	су (Outcome L	ist:			
# thera	al assessment by the investigator apeutic efficacy by patients iilton Rating Scale for anxiety				Primar outcom		Outcome: duration of sle number of noo time awake du	cturr	nal awakenings		
							subjective sta therapeutic ef anxiety	tus (on awakening		
Results											
therapeuti	ic efficacy by patients										
# thera	apeutic effects at day 30- good excellent	Zolpidem 32	(75	Triazolar	m (75)		()	()	P val	ue
		Number	(%	I)				I	ļ	
	apeutic effects at day 60- good excellent	Zolpidem 33	(87	Triazolar	m (84)		()	()	P val	ue
		Number	(%)						
# thera	apeutic effects at day 90- good	Zolpidem	`	Triazolar						P val	IIE.
	excellent	32	(91) 29	(85)		()	()	NS	
		Number	(%)						
# quali	ity of sleep at day 60	Zolpidem	•	Triazolar						P val	ue
		74	() 65	()		()	()	NR	
		%	(I)				<u>I</u>		
# quali	ity of sleep at day 90	Zolpidem		Triazolar	m					P val	ue
		81	() 73	()		()	()	NR	
		%	(u .)	-			I	1	

Author: Pagot	Trial type	: Activ	ve :	Subgro	up:	psychiatric	;	Quality	rating:	Fair
/ear: 1993	Country:	Franc	се					Funding	g: Not	reported
# overall rating	Zolpidem		Triazolam	1					P va	alue
	38.4	(78.6) 36.3	(76.6)	()	() NR	
	day 0	(day 90	l)					
# status on awakening and alertness,	Zolpidem		Triazolam	1					Pva	alue
number of patients	28	(44) 40	(42)	()	() NR	
	day 4	(day 90	I)		I			
global assessment by the investigator										
# sleep latency at day 90, change from	Zolpidem		Triazolam)					Pva	alue
baseline	-1.9	(< 0.001) -1.9	(<0.001)	()	() NS	
	Score	(p vs bas	seline)					
# mean sleep time at day 90, change	Zolpidem		Triazolam	1					Pva	alue
from baseline	2.72	(< 0.001) 2.26	(<0.001)	()	() NS	
	hours	(p vs bas	seline)		l l			
# number of nocturnal awakenings at	Zolpidem		Triazolam	1					Pva	alue
day 60, change from baseline	-1.7	(0.02) -1	(0.02)	()	() <0.0	05
	Number	(p vs bas	seline)		I			
# duration of nocturnal awakenings at	Zolpidem		Triazolam	l					Pva	alue
day 60	18	(0.02) 14	(0.02)	()	() <0.0	05
	minutes	(p vs bas	seline)					
Hamilton Rating Scale for anxiety										
# total score	Zolpidem		Triazolam	l					Pva	alue
	multiple d	() multiple d	()	()	() NS	
	Score	(•)		1		ı	ı

Subgroup: psychiatric (inpati Quality rating: Poor **Author: Schwartz** Trial type: Active Year: 2004 Country: US **Funding: Not reported**

Design:

Study design RCT

Open

Parallel

Setting Single Center

Eligibility criteria:

inpatient psychiatric care

Comments:

Psychiatric inpatients

Intervention:

Run-in: NR NR Wash out :

Allow other medication :

Age: NR

Range: 18-65

SD:

Gender: 8 (50 %) Female

Ethnicity: NR

Lost to fu: 0 Analyzed: 16

NR

16

Number Screened: NR

Eligible:

Enrolled:

Number Withdrawn: 0

Exclusion criteria:

Subjects were excluded from the study if they were presently taking a hypnotic or sedating psychotropic agent in the evening, if they were using alcohol or dugs, if they were manic, or if they had a medical contraindication to the study medications.

				Withdrawals due to AEs/
Drug name	dosage	N=	Duration	Total withdrawal
Zaleplon	10-2 mg	7	AsN	1 / 1
Trazadone	50-1 mg	9	AsN	1 / 1

Author:	Schwartz	Trial type	: Activ	ve	Subg	roup:	psychiatri	c (inp	ati Quality	rating: Poo	r	
Year:	2004	Country:	US	US					Funding	j: Not report	ported	
Outcome	Measurement:				Ef	ficacy	Outcome I	_ist:				
# analo	rth sleepiness scale (ESS) gue sleep quality scale ent, nurse-recorded sleep log					rimary utcome	Outcome: sleepiness sleep duration	n				
Results												
Epworth sle	eepiness scale (ESS)											
# media	n at study entry-matching	Zaleplon		Trazo	done					P value		
		7	() 9	()	()	() 0.885		
		Score	(!)		l.			_	
	change from baseline efficacy	Zaleplon		Trazo	done					P value		
and to	blerability	-1	() 1	()	()	() 0.23		
		Score	()		I			_	
inpatient, n	urse-recorded sleep log											
# sleep-	- median at study entry-matching	Zaleplon		Trazo	done					P value		
		3	() 3	()	()	() 0.894		
			(<u> </u>)					_	
	- median change from baseline	Zaleplon		Trazo	done					P value		
efficad	cy and tolerability	0	() 3	()	()	() 0.181		
		hours	(<u> </u>)					_	

Author: Steens Trial type: Active Subgroup: COPD Quality rating: Fair

Year: 1993 Country: Canada Funding: Lorex Pharmaceuticals

Design:

Study design RCT

DB

Crossover

Setting Multicenter

Eligibility 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.

Age: 58.2

Range: SD: 5.5

Gender: 9 (38 %) Female

Ethnicity: NR

Number Withdrawn: 0 Lost to fu: 0

Eligible:

Enrolled:

Number Screened:

Analyzed: 24

NR

NR

24

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 th 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.

Comments:

One of 24 patients designated an outlier and excluded from group analysis, but results reported separately.

Intervention:

Run-in: 0 **Wash out**: 0

Allow other medication: no other hypnotics

Withdrawals due to AEs/

Drug name	dosage	N=	Duration	Total withdrawal	
Zolpidem	5 mg	24	1 day	0 / 0	
Zolpidem	10 mg	24	1 day	0 / 0	
Triazolam	0.25 mg	24	1 day	0 / 0	
Placebo	NA mg	24	1 day	0 / 0	

Author:	Steens	Trial type:	Active	Subgroup	: COPD	Quality rating: Fair		
Year:	1993	Country:	Canada			Funding:	Lorex Pharmaceuticals	
Outcome	Measurement:			Efficac	y Outcome List:			
	ng questionnaire omnography			Primary outcom				
# morni	ng questionnaire				sleep quality total wake time awakening microarousal total sleep time wake time during sle	ep period		
Results								
overall mea	<u>asures</u>							
# total s	sleep time	Zolpidem 5m	g Zolp	oidem 10mg	Triazolam		P value	
		384.82 (<0.05) 397	.12 (NS)	413.79 (NA)	(
		minutes (p vs triazolam)	'			
# total v	vake time	Zolpidem 5m	g Zolp	oidem 10mg	Triazolam		P value	
		93.09 (<0.05) 82.3	37 (NS)	66.10 (NA)	(
		minutes (p vs triazolam)	1			
# sleep	efficacy	Zolpidem 5m	g Zolp	oidem 10mg	Triazolam		P value	
		79.74 (<0.05) 82.3	35 (NS)	85.83 (NA)	(
		% (p vs triazolam)	1			

Subgroup: COPD Quality rating: Fair Author: Trial type: Active **Steens** Year: 1993 Country: Canada **Funding: Lorex Pharmaceuticals** maintenance measures # awakenings (no./hours of sleep) Zolpidem 5mg Zolpidem 10mg Triazolam P value 4.70 (<0.05) 4.07 (NS 3.68 (NA) (p vs triazolam Number # microarousals (no./hour of sleep) Zolpidem 5mg Zolpidem 10mg Triazolam P value (NA) 14.08 (NS 12.57 (NS 13.23 Number (p vs triazolam # Arousals/total sleep time (no./hour) Zolpidem 5mg Zolpidem 10mg Triazolam P value 18.69 (NS 16.46 (NS 16.72 (NA) Number (p vs triazolam # wake time during sleep Zolpidem 5mg Zolpidem 10mg Triazolam P value 55.57 (NS (NS (NA)) 50.69) 40.47 Number (p vs triazolam

Author:	Steens	Trial type	e: Activ	/e	Subgre	oup	: COP	D		Quality	/ rati	ng: Fair
Year:	1993	Country:	Cana	da						Fundin	ng: L	orex Pharmaceuticals
subjective a	ssessment of sleep											
# sleep la	atency	Zolpidem	5mg	Zolpide	m 10mg		Triazola	m				P value
		38.7	(NS) 30.22	(NS)	25.52	(NA)	()	
		minutes	(p vs triaz	zolam)	1					
	f falling sleep (lower	Zolpidem	5mg	Zolpide	m 10mg		Triazola	m				P value
score=	better)	46.48	(< 0.05) 30.09	(NS)	20.96	(NA)	()	
		Score	(p vs triaz	zolam)	1					
# no. of a	awakenings	Zolpidem	5mg	Zolpide	m 10mg		Triazola	m				P value
		2.74	(NS) 2.17	(NS)	1.61	(NA)	()	
		minutes	(p vs triaz	zolam)	<u> </u>					
# duratio	n of night waking	Zolpidem	5mg	Zolpide	m 10mg		Triazola	m				P value
		103.04	(NS) 16.78	(NS)	43.83	(NA)	()	
		minutes	(p vs triaz	zolam)	I		ı			
# sleep o	duration	Zolpidem	5mg	Zolpide	m 10mg		Triazola	m				P value
		333.26	(< 0.05) 388.22	(NS)	411.17	(NA)	()	
		minutes	(p vs triaz	zolam)						
# feeling	of sleep (1=excellent, 4=poor)	Zolpidem	5mg	Zolpide	m 10mg		Triazola	m				P value
		2.61	(< 0.05) 2.13	(NS)	1.87	(NA)	()	
		minutes	(p vs triaz	zolam)						
# sleepy	in the morning (higher	Zolpidem	5mg	Zolpidei	m 10mg		Triazola	m				P value
score=	better)	55.04	(NS) 65.44	(NS)	66.52	(NA)	()	
		minutes	(p vs triaz	zolam)	1					
# concer	ntration in the morning	Zolpidem	 5mg	Zolpide	m 10mg		Triazola	m				P value
	ellent, 4=poor)	2.30	(NS) 2.26	(NS)	2.13	(NA)	()	
		minutes	(p vs triaz	zolam)	1					

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

Trial type: Active Subgroup: psychiatric Author: **Pagot** Quality rating: Fair Year: 1993 Country: **France Funding: Not reported**

Design:

Study design RCT

DB

Parallel

Setting Multicenter Age: 48

> Range: SD:

Gender: 58 (61 %) Female

Ethnicity: NR

Number Withdrawn: 33

Number Screened: NR

Eligible:

Enrolled:

Lost to fu: 0 Analyzed: 62

NR

95

Eligibility criteria:

two of the following symptoms: sleep onset latency of more than 30 minutes; more than two nocturnal awakenings; total duration of sleep of less than 6 hours; or total nocturnal wake-time of more than 20 minutes.

Exclusion criteria:

Patients who showed sleep disorders associated with severe psychiatric disorders, sleep apnea, sleep-related myoclonus, or insomnia that had developed during childhood, and those who showed serious medical disease or needed concomitant hypnotic medication or treatment that could have had an influence on sleep onset were excluded. Pregnant women and women of childbearing potential who were not taking adequate contraceptive precautions were also excluded, as were nursing mothers and those patients in whom adequate compliance could not be expected. Patients were excluded if they were receiving any treatment that could have an influence on sleep onset.

Comments:

Intervention:

				Withdrawals due to AEs/
Drug name	dosage	N=	Duration	Total withdrawal
Zolpidem	20 mg	47	86 day	1 / 15
Triazolam	0.5 mg	48	86 day	2 / 18

Rebound:

therapeutic efficacy by patients

rebound: therapeutic effects at day 120- good and excellent

Zolpidem			Triazo	olam						P value	
33	(89)	34	(83)	()	()	NS	
Number	(%		Į.)					'	

Subgroup: Anxiety **Quality rating: Poor Author:** Agnoli Trial type: Active Year: 1989 Country: Rome, Foggia, Italy **Funding: Not reported**

Design:

Study design RCT

DB

Crossover

NR Setting

Eligibility criteria:

Patients were aged 20-50 years with total score of the Hamilton Rating Scale for Anxiety less than 20. Absence of concomitant antidepressive, anxiolytic or neuroleptic medication and absence of somatic, pathophysiological or pharmacological factors related to the onset and persistence of insomnia.

Comments:

Poor quality: insufficient information to assess. Patients with generalized anxiety disorder.

Intervention:

Run-in: 3 Wash out: NR

Allow other medication: NR

38.2 Age:

Range: SD: 2.1

Gender: 12 (60 %) Female

Ethnicity: NR

Number Withdrawn: 0 Lost to fu: 0 Analyzed: 20

Number Screened: NR

Eligible:

Enrolled:

NR

20

Exclusion criteria:

Presence of concomitant general illness; renal or hepatic failure; effectiveness of placevo administration; and pregnancy.

Withdrawals due to AEs/

Drug name	dosage	N=	Duration Total withdrawal
Zopiclone	7.5 mg	12	1 day /
Nitrazepam	5 mg	12	1 day /

Adverse Events:

epigestralgia

1st week

Zopiclone		Nitraz	epam						P value:
1 ()	1	()	()	()	NR

Number (

Author:	Agnoli	Trial type:	Active	Su	bgroup	Anxie	ety	(Quality	rating:	Poo	r		
Year:	1989	Country: F	Rome, Fog	me, Foggia, Italy					Funding: Not reported					
	daytime seda													
	# 1st we	eek	Zopiclo	ne	Nitra	epam						P value:		
			0	() 6	()	()	()	NR		
			Number	(")					1		
	# 2dn w	reek	Zopiclo	ne	Nitra	epam						P value:		
			0	() 14	()	()	()	NR		
			Number	(,)		,					
		nged into the wash-out period en treatment	Zopiclo	ne	Nitra	epam						P value:		
	Detwe	en treatment	0	() 3	()	()	()	NR		
			Number	()		·					
	restlessness													
	# 1st we	eek	Zopiclo	ne	Nitra	epam						P value:		
			0	() 1	()	()	()	NR		
			Number	()		,					

Subgroup: alcoholism Quality rating: Fair Author: Trial type: Active **Ansoms** 1991 Country: US **Funding: Not reported** Year:

Design:

Study design RCT

DB

Parallel

Setting Multicenter

Eligibility 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.

Comments:

Intervention: Run-in: 2

NR Wash out :

Allow other medication: No.

Age: 43.9

Range: 20-55

SD:

Gender: 17 (33 %) Female

Number Withdrawn: 0 Ethnicity: NR Lost to fu: 0 Analyzed: 52

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 flucuating condition with mental or physical stress, or patients with a severe liver or kidney disturbance. Shiftworkers were not included in the study

Number Screened: NR

Eligible:

Enrolled:

54

52

Withdrawals due to AEs/

Drug name	dos	sage	N=	Duration	Total withdrawal	
Zopiclone	7.5	mg	27	5 day	0 / 0	
Lormetazepam	1	mg	25	5 day	0 / 0	

Adverse Events:

Overall safety

Physician's overall safety assessment ("excellent" or "good")

		Zopicl	one		Lorm	etazepam				P value:
()	93	()	76	()	()	NR

%

Author:	Ansoms	Trial type:	Active	S	ubgr	oup:	alcoh	olism		Quality	rating:	Fair	
Year:	1991	Country:	US							Funding	g: Not re	port	ed
	withdrawa	als_											
	# to	tal withdrawals not reported											P value:
				()		()	()	()	
				()					
	# wi	thdrawals due to AEs not repor	ted										P value:
				()		()	()	()	
				()					
	Overall Al	<u>Es</u>											
	# O	verall AEs				Zopiclo	ne	Lori	metazepa	m			P value:
				()	26	() 28	()	()	NS
			%	(·)		·			•

Subgroup: shiftworker Quality rating: Fair **Author: Bozin-Juracic** Trial type: Active

Year: 1995 Country: Croatia Funding: May and Becker and Rhone-

Design:

Study design NR

NR

Crossover

Setting Single Center Age: NR

Range: 24-58

SD:

Gender: NR (0 %) Female

Ethnicity: NR

Number Withdrawn: 0 Lost to fu: 0

Number Screened: NR

Eligible:

Enrolled:

Analyzed: 29

32

29

Eligibility criteria:

A group of workers employed in a security company were recruited to the study as subjects

Exclusion criteria: NR

Comments:

Not clear if randomized.

Intervention: Run-in:

Wash out : 0

Allow other medication : NR

0

Withdrawals due to AEs/

Drug name	dosage	N=	Duration	Total withdrawal	
Zopiclone	7.5 mg	29	7 day	0 / 0	
Nitrazepam	5 mg	29	7 day	0 / 0	
Placebo	NA mg	29	7 day	0 / 0	

Adverse Events:

withdrawals

total withdrawals

Zopicl	one		Nitra	zepam		Plac	ebo				P value:
0	()	0	()	0	()	()	

Number (

Nitrazepam Placebo Zopiclone P value:) 0 0) 0)

Number (

withdrawals due to AEs

Author: Fontaine Trial type: Active Subgroup: psychiatric Quality rating: Fair

Year: 1990 Country: Canada Funding: Rhone-Poulenc Pharma

Design:

Study design RCT

DB

Parallel

Setting Single Center

Eligibility 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.

Comments:

Subgroup: generalized anxiety disorder

Intervention:

Run-in:

Wash out: 21

Allow other medication: no psychotopic medications

chotopic medications

				Withdrawals due to AEs/
Drug name	dosage	N=	Duration	Total withdrawal
Zopiclone	7.5 mg	30	28 day	4 / 8
Triazolam	0.5 mg	30	28 day	3 / 8
Placebo	NA mg	15	28 day	0 / 5

Adverse Events:

Hopkins Symptoms Checklist (SCL-90)

Age: 42.9

Range: 26-58 SD: 1.1

Gender: 40 (53 %) Female

Ethnicity: NR

Number Withdrawn: 21 Lost to fu: 0

Analyzed: 75

Number Screened: NR

Eligible:

Enrolled:

NR

75

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).

Author: Year:	Fontaine 1990	Trial type: Country:	Active Canada	Subgrou	o: psych	niatric	-	rating: Fair g: Rhone-Po	r oulenc Pharma
	# drowsiness	5	Zopiclone	e Tria	zolam	Placebo			P value:
			3	() 5	() 4	()	()	NS
			Number	()	1		
	# ataxia		Zopiclone	e Tria	zolam	Placebo			P value:
			2	() 3	() 1	()	()	NS
			Number	()	1		
	# headache		Zopiclone	Tria	zolam	Placebo			P value:
			6	() 3	() 3	()	()	NS
			Number	()	1		
	# taste perve	ersion	Zopiclone	Tria	zolam	Placebo			P value:
			17	() 3	() 1	()	()	<0.001
			Number	()	1		
	# nausea		Zopiclone	Tria	zolam	Placebo			P value:
			2	() 3	() 4	()	()	NS
			Number	()	1		
	# dry mouth		Zopiclone	e Tria	zolam	Placebo			P value:
			7	() 1	() 1	()	()	<0.05
			Number	()	I		

Author:	Fontaine	Trial type:	Active	Subgroup: p	sychiatric	Quality r	rating:	Fair	
Year:	1990	Country:	Canada			Funding	: Rhone	e-Poulenc Phar	rma
	withdrawals								
	# total withdra	awals	Zopiclone	Triazolar	n Placeb	00		P value:	
			8 () 8	() 5	()	()	Ī
			Number ()	·			_
	# withdrawals	s due to AEs	Zopiclone	Triazolar	n Placet	00		P value:	
			4 () 3	() 0	()	()	Ī
			Number ()			1	_

Li Pi Shan Subgroup: Stroke (inpatient) Quality rating: Fair Author: Trial type: Active

2004 **Funding: Not reported** Year: Country: Canada

Design:

Study design RCT

DB

Crossover

Setting

Single Center

Gender: 8 (44 %) Female

Range: 20-78

56.6

SD:

Ethnicity: NR

Age:

Number Withdrawn: 0

Number Screened: 44

Eligible:

Enrolled:

Lost to fu: 0 Analyzed: 18

27

18

Eligibility criteria:

Each patient with a diagnosis of either stroke or brain injury was consecutively recruited for eligibility.

Exclusion criteria:

Patients were excluded if they were acutely ill, unable to communicate either in English or French, or unable to ead and answer questions for any other reason (severe aphasia, blindness, severe cognitive impairment, including patients with posttraumatic amnesia). Subjects were also > 18 years of age. The patients were not excluded if they experienced any secondary causes of insomnia such as depression, sleep apnea, or restless legs syndrome.

Comments:

Although there was no formal washout period between weeks 1 and 2, the questionnaire was not administered on any of the first 3 days to allow for a washout of the medication taken during week 1.

Any additional medications the patients were receiving were maintained constant throughout the trial. Those whose medications changed over the course of the study were excluded.

Intervention:

Run-in: 0

0 Wash out :

Allow other medication : Concomitatnt use of medication were maintained throughout the trial

Withdrawals due to AEs/

Drug name	dosage	N=	Duration	Total withdrawal
Zopiclone	3.75 mg	18	As needed for 7 day	0 / 0
Lorazepam	0.5- mg	18	As needed for 7 day	0 / 0

Adverse Events:

withdrawals

total withdrawals

Zopiclo	ne		Loraz	epam						P value:
0	()	0	()	()	()	

Number (

Author: Li Pi Shan Trial type: Active Subgroup: Stroke (inpatient) Quality rating: Fair
Year: 2004 Country: Canada Funding: Not reported

withdrawals due to AEs

Zopiclone		Lorazepa	am					P value:
0 ()	0	()	()	()	

Number (

Author: Pagot Trial type: Active Subgroup: psychiatric Quality rating: Fair
Year: 1993 Country: France Funding: Not reported

Design:

Study design RCT

DB

Parallel

Setting Multicenter

Eligibility criteria:

two of the following symptoms: sleep onset latency of more than 30 minutes; more than two nocturnal awakenings; total duration of sleep of less than 6 hours; or total nocturnal wake-time of more than 20 minutes.

Comments:

Intervention: Run-in: 4

Wash out: 30

Allow other medication: no other hypnotic drugs

Withdrawals due to AEs/

Drug name	dosage	N=	Duration	Total withdrawal
Zolpidem	20 mg	47	86 day	1 / 15
Triazolam	0.5 mg	48	86 day	2 / 18

Adverse Events:

withdrawals

total withdrawals

Zolpidem 20mg			Triazolam 0.5mg						P value:
15	()	18	()	()	()	

Number (

Age: 48

Range: SD:

Gender: 58 (61 %) Female

Ethnicity: NR

Number Withdrawn: 33 Lost to fu: 0

Number Screened: NR

Eligible:

Enrolled:

Analyzed: 62

NR

95

Exclusion criteria:

Patients who showed sleep disorders associated with severe psychiatric disorders, sleep apnea, sleep-related myoclonus, or insomnia that had developed during childhood, and those who showed serious medical disease or needed concomitant hypnotic medication or treatment that could have had an influence on sleep onset were excluded. Pregnant women and women of childbearing potential who were not taking adequate contraceptive precautions were also excluded, as were nursing mothers and those patients in whom adequate compliance could not be expected. Patients were excluded if they were receiving any treatment that could have an influence on sleep onset.

Author: Pagot Trial type: Active Subgroup: psychiatric Quality rating: Fair

Year: 1993 Country: France Funding: Not reported

withdrawals due to AEs

Zolpidem 20mg		g	Triazolam 0.5mg							P value:
1	()	2	()	()	()	

Number ()

Subgroup: psychiatric (inpati Quality rating: Poor **Author: Schwartz** Trial type: Active Year: 2004 Country: US **Funding: Not reported**

Design:

Study design RCT

Open

Parallel

Single Center Setting

Eligibility criteria:

inpatient psychiatric care

Comments:

Psychiatric inpatients

Intervention:

Run-in: NR

NR Wash out :

Allow other medication : NR Age: NR

Range: 18-65

SD:

Gender: 8 (50 %) Female

Ethnicity: NR

Exclusion criteria:

Number Withdrawn: 0 Lost to fu: 0

Number Screened: NR

Eligible:

Enrolled:

Analyzed: 16

NR

16

Subjects were excluded from the study if they were presently taking a hypnotic or sedating psychotropic agent in the evening, if they were using alcohol or dugs, if they were manic, or if they had a medical contraindication to the study medications.

Withdrawals due to AEs/ Drug name dosage N= Duration Total withdrawal 7 Zaleplon 10-2 mg AsN 1 / 1 Trazadone 50-1 mg 9 AsN 1 / 1

Adverse Events:

Author:	Steens	Trial type:	Active	Sul	bg	roup:	COPD		(Quality I	rating:	Fair	
Year:	1993	Country:	Canada		Funding: Lorex Pha					rmaceuticals			
	# total wi	thdrawals	Zolpid	lem 5mg		Zolpidem 10mg		Triazolam					P value:
			0	()	0	() 0	()	()	
			Numbe	er (")		ч			
	# withdra	wals due to AEs	Zolpid	em 5mg		Zolpide	m 10mg	Triazo	lam				P value:
			0	()	0	() 0	()	()	
			Numbe	er ()		·			<u> </u>
	Lab data- resp	iratory events											
	# reduction	on of SaO2	Zolpid	em 5mg		Zolpide	m 10mg	Triazo	lam				P value:
			0	()	2	() 2	()	()	
			Numbe	er (,)		"			
	# apnea-hypopnea		Zolpid	em 5mg		Zolpide	m 10mg	Triazo	lam				P value:
			1	()	2	() 1	()	()	
			Numbe	er ()					

Author: Steens Trial type: Active Subgroup: COPD Quality rating: Fair

Year: 1993 Country: Canada Funding: Lorex Pharmaceuticals

Design:

Study design RCT

DB

Crossover

Setting Multicenter

Eligibility 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.

Age: 58.2

Range: SD: 5.5

Gender: 9 (38 %) Female

Ethnicity: NR

Mithelesurals due to AEs/

Lost to fu: 0 Analyzed: 24

NR

NR

24

Number Screened:

Eligible:

Enrolled:

Number Withdrawn: 0

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 th 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.

Comments:

One of 24 patients designated an outlier and excluded from group analysis, but results reported separately.

Intervention:

Run-in: 0 **Wash out**: 0

Allow other medication :

no other hypnotics

			withdrawais due to AES/
Drug name	dosage	N=	Duration Total withdrawal
Zolpidem	5 mg	24	1 day 0 / 0
Zolpidem	10 mg	24	1 day 0 / 0
Triazolam	0.25 mg	24	1 day 0 / 0
Placebo	NA mg	24	1 day 0 / 0

Adverse Events:

withdrawals

Evidence Table 13. Placebo controlled trials: Efficacy

Author: Allain Trial type: Placebo Quality rating: Fair

Year: 1998 Country: France Funding: NR

Design:

Study design RCT

DB

Parallel

Setting Multicenter

Age: 51.9

Range: 32-84 SD: 16.7

Gender: NR (0 %) Female

Ethnicity: NR

Number Withdrawn: 18 Lost to fu: NR

Number Screened: NR

Eligible:

Enrolled:

Analyzed: 37

NR

37

Eligibility criteria:

The subjects were suffering from chronic insomnia, being regularly treated with triazolam. They met the following criteria: male and female volunteers over 18 years of age; receiving out-patient treatment from a GP; taking triazolam (0.25 to 0.50 mg/day) for longer than one month.

Exclusion criteria:

Patients were not included if any of the following exclusion criteria applied: refusal to participate in the study or susceptiable to non-compliance; shift workers; patients suffering from an identifiable mental disorder or treated fro their sleep disorder with hypnotics other than triazolam 0.25 mg/day; pregnant or breast feeding woemn; liver or respiratory failure, myasthenia, or epilepsy.

Comments:

Intervention: Run-in: 3

Wash out: 3

Allow other medication: NR

Withdrawals due to AEs/

Drug name	dosage	N=	Duration	Total withdrawal
Zolpidem	10 mg	18	21 day	1 / 1
Placebo	NA mg	19	21 day	17 / 17

Author: Allain	Trial type:	Placebo		Quality rating: Fair Funding: NR							
Year: 1998	Country:	France									
Outcome Measurement:			Efficacy	Outcome List:							
# clinical global impression # sleep quesionnaire			Primary outcome	Outcome:							
# sleep diary				sleep latency number of nocturnal total sleep time sleep quality nightmares wakefulness daytime alertness anxity mood energy	awakenings						
Results clinical global impression											
# overall no different except day 21, where zolpidem was more effective,	Zolpidem NR (Placebo				P value					
p<0.007	Mean () NR	()	()	() 143					

Quality rating: Fair Author: Allain Trial type: Placebo Funding: NR Year: 1998 Country: France sleep quesionnaire # daytime alertness Zolpidem Placebo P value NR) NR) NS Mean # total sleep time (hr) at day 7 Zolpidem Placebo P value 6.13) 6.40) NR Mean # total sleep time (hr) at day 28 Zolpidem Placebo P value NR) NR) NS Mean Placebo # less nightmare Zolpidem P value 93) < 0.04) less % sleep diary Zolpidem # number of awakenings Placebo P value) NR) < 0.0001 better Zolpidem Placebo # anxiety P value) NR better) < 0.0003 Placebo # amount of sleep Zolpidem P value better) NR) < 0.0001 Zolpidem Placebo # energy P value) NR) < 0.01 better

Author: Allain_ Trial type: Placebo Quality rating: Fair

Year: 2001 Country: France Funding: Sanofi-Synthelabo

Design:

Study design RCT

DB

Parallel

Setting Multicenter

Eligibility criteria:

Patients of either gender (aged 25 to 64 years) with DSM-IV diagnosis of primary insomnia, characterised 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 characterised 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.

Comments:

Zolpidem was administrated as needed, not every night.

Intervention: Run-in:

Wash out: NR

Allow other medication: NF

3-7

Age: 46.1

Range: 25-64 SD: 10.5

Gender: 188 (77 %) Female

Ethnicity: NR

Number Withdrawn: NR

Eligible:

Enrolled:

Lost to fu:

Number Screened:

Analyzed: 245

NR

NR

245

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), anziety (>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 imidazopyridines. 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 abnoea syndrom. Patients who had received benzodiazepines regularly for more than one month, or for more thatn 15 days in the month prior to inclusion, were also excluded from the study, as were patients who consumed large quantities of caffeine.

Withdrawals due to AEs/ Drug name N= Duration Total withdrawal dosage 1 / 3 28 day Zolpidem 10 mg 124 Placebo NA mg 121 28 day 1 / 7

Author:	Allain_	Trial type:	Place	bo		Quality rating: Fair							
Year:	2001	Country:	France	е		Funding: Sanofi-Synthelabo							
Outcome	Measurement:				Efficac	y Outcom	ne Lis	st:					
	al global impression				Primary outcom		e:						
# SF-36	6 healthy survey					sleep dui quality of drowsine anxious of sadness duration sleep-ons number of wake tim	f sleep ess dur during during of day set late of noct	the dathe dathe dathe the	ay lay leep awakenings				
Results sleep diary	Ĺ												
	sleep time (min), change from line, all condition	Zolpidem 74.6	(77.7)	Placebo 63.2	(69.9)	()	(P value) NS			
		Mean	(SD)	1					J		
	sleep time (min), change from	Zolpidem		Placebo						P value			
basel	line, with pill	82.7	(80.1)	62.8	(77.2)	()	() <0.05			
		Mean	(SD	1)	1					J		
# sleep	quality (1=worse; 100=better),	Zolpidem		Placebo						P value			
chan	ge from baseline	14.1	(17.4)	20.6	(22.3)	()	() 0.01			
		Mean	(SD)								
# daytir	me drowsiness (1=worse;	Zolpidem		Placebo	,					P value			
	better), change from baseline		(12.6)	-5.3	(14.9)	()	() 0.048	•		
		Mean	(SD	I)	<u> </u>							

-2.6

Mean

uthor:	Allain_	Trial type: Placebo										Quality rating: Fair			
'ear:	2001	Country:	Fra	nc	е						Funding	g: \$	Sanofi-Synthelab		
	ty during the day (1=worse;	Zolpidem			Placebo								P value		
100=k	petter), change from baseline	-1.5	(16.2)	-2.9	(19.7)		()	()	0.55		
		Mean	(SD		·)			,					
	ess during the day (1=worse;	Zolpidem			Placebo								P value		
100=b	petter), change from baseline	-0.6	(15.4)	-2.8	(17.7)		()	()	0.30		
		Mean	(SD)			ı					
# vitality in the morning (1=worse;		Zolpidem			Placebo								P value		
100=k	petter), change from baseline	9.1	(16.2)	9.6	(21.3)		()	()	0.83		
		Mean	(SD		11)	ı		I					
	ty in the morning (1=worse;	Zolpidem			Placebo								P value		
100=k	petter), change from baseline	2.9	(16.2)	2.3	(18.4)		()	()	0.77		
		Mean	(SD		į)	Į.				٠	1		
	onset latency (min), change	Zolpidem			Placebo								P value		
from b	paseline	-23	(38.7)	-18.8	(35.4)		()	()	<0.05		
		Mean	(SD)								
	time after sleep onset (min),	Zolpidem			Placebo								P value		
chang	ge from baseline	-32.8	(37.7)	-31.4	(37.1)		()	()	NR		
		Mean	(SD)			1					
	er of nocturnal awakenings,	Zolpidem			Placebo								P value		
chang	ge from baseline	-1.2	(NR)	-1.2	(NR)		()	()	<0.05		
		Mean	(SD)	ı		1					
	ne sleep duration (min), change	Zolpidem			Placebo								P value		
from b	paseline	-2.6	(19.6)	-0.9	(15.1)		(١	()	NR		

) -0.9

(15.1

(19.6

(SD

) NR

Author: Allain_ Trial type: Placebo Quality rating: Fair

(%

Number

Funding: Sanofi-Synthelabo Year: 2001 Country: France

clinica	global	impression

# severity of illness- not ill to mildly ill	Zolpidem			Placebo					P value
	69	(55.6)	46	(38.7)	()	()	0.002
	Number	(%)			
# global impression- much or very much	Zolpidem			Placebo					P value
improved	67	(54)	29	(24)	()	()	<0.0001
	Number	(%)			
# efficacy index- when efficacy	Zolpidem			Placebo					P value
outseighs safety)	108	(87)	84	(71)	()	()	0.0004

Quality rating: Fair Author: Allain_ Trial type: Placebo

Υe nthelabo/

Year:	2001	Country:	Frai	nce	e					Funding:	Sanofi-Syn
<u>SF-36 h</u>	ealthy survey										
	ysical function, change from	Zolpidem			Placebo)					P value
bas	seline	2.5	(17.3)	2.7	(4.6)	()	() NS
		Mean	(SD		1)		·		
	e limitations due to physical	Zolpidem			Placebo	0					P value
pro	bblem, change from baseline	7.5	(29)	4.9	(32.5)	()	() NS
		Mean	(SD		· ·)		l l		
# boo	dily pain, change from baseline	Zolpidem			Placebo)					P value
		4.7	(21)	3.7	(22.4)	()	() NS
		Mean	(SD		ı)		I		
# ger	neral health perception, change	Zolpidem			Placebo)					P value
froi	m baseline	3.4	(12.4)	2.5	(12.5)	()	() NS
		Mean	(SD		ı)		,		ı
# vita	ality, change from baseline	Zolpidem			Placebo)					P value
		6.5	(16.6)	5.7	(14)	()	() NS
		Mean	(SD		ı)		I		
	cial functioning, change from	Zolpidem			Placebo)					P value
bas	seline	6.1	(22.4)	2.8	(21.6)	()	() NS
		Mean	(SD		ı)		I		
	e limitations due to emotional	Zolpidem			Placebo)					P value
pro	blems, change from baseline	7.9	(39.1)	-0.3	(33.9)	()	() NS
		Mean	(SD		ı)		I		
	neral mental health, change from	Zolpidem			Placebo)					P value
bas	seline	5.9	(16.8)	5.1	(14.5)	()	() NS
		Mean	(SD)				

Author: Chaudoir Trial type: Placebo Quality rating: Poor

Year: 1983 Country: UK Funding: NR (May & Baker provided m

Design:

Study design RCT

DB

Crossover

Setting Single Center

Eligibility 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 difficultry in returning to sleep without known cause, or sleeping less than six hours.

Age: 50

Range: 35-65 SD: NR

Gender: 18 (72 %) Female

Ethnicity: NR

Lost to fu: 0 Analyzed: 25

30

25

Number Screened: NR

Number Withdrawn: 5

Eligible:

Enrolled:

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.

Comments:

Crossover design, but the results combined placebo outcomes and treatment outcomes from two groups.

Intervention:

Run-in: NR

Wash out: NR

Allow other medication: NR

Withdrawals due to AEs/

Drug name	dosage	N=	Duration	Total withdrawal	
Zopiclone	7.5 mg	25	7 day	2 / 2	
Placebo	NA mg	25	7 day	3 / 3	

Author:	Chaudoir	Trial type	e: Pla	cebo					Quality ra	ating:	Poo	r
Year:	1983	Country:	UK						Funding:	NR (May &	Baker provided m
Outcome	Measurement:				Effi	icacy	Outcome l	List:				
	questionnaire					mary	Outcomo					
# interv	riew by investigator				out	tcome	Outcome:					
					l [sleep latency number of a	•				
					[sleep quality	J				
					[feeling after					
Results												
	augationnaira											
<u>ually sleep</u>	<u>questionnaire</u>					0.						
	gs after wakening (VAS - mm), ry badly; 100=very well	Zopiclone		Placebo						_	alue	_
U=ve	ry badiy, 100=very well	59	(4.4) 59	(4.2)	()	() NS		
		Mean	(SD)		"				1
# sleep	onset latency (min)	Zopiclone		Placebo						Pva	alue	
		31.1	(4.0) 49.1	(4.5)	()	() <0.0	001	
		Mean	(SD	I)		I		I		
# numb	per of night awakenings	Zopiclone		Placebo						Pva	alue	
		1.5	(0.2) 2.1	(0.3)	()	() <0.0	05	-
		Mean	(SD)						_
# sleep	quality (VAS - mm), 0=very	Zopiclone		Placebo						Pv	alue	
	; 100=very well	67	(4.0) 51	(3.5)	()	() <0.0		-
		Mean	(SD)	•	*				_
			,			,						

Author: Chaudoir Trial type: Placebo Quality rating: Poor

Year: 1983 Country: UK Funding: NR (May & Baker provided m

ear:	1983	Country:	UK						Funding	: NR (May
weekly a	ssessment									
# slee	ep onset latency (min)	Zopiclone		Place	ebo					P value
		28.6	(3.9) 45.2	(5.5)	()	() <0.05
		Mean	(SD)				
# num	nber of night awakenings	Zopiclone		Place	ebo					P value
		1.6	(0.3) 2.1	(0.3)	()	() NS
		Mean	(SD)				
	ep quality (VAS mm), 0=very badly;	Zopiclone		Place	ebo					P value
100	=very well	63	(4.8) 48	(5.0)	()	() <0.01
		Mean	(SD)				
	ings after awakening (VAS mm),	Zopiclone		Place	ebo					P value
0=v	ery badly; 100=very well	67	(4.9) 67	(4.7)	()	() NS
		Mean	(SD	')		ļ		ı
	centage of patients with early	Zopiclone		Place	ebo					P value
awa	kenings (%)	44	() 56	()	()	() NS
		Mean	()				
	od rating scales (mm) - factor I	Zopiclone		Place	ebo					P value
aler	tness	59	(3.6) 59	(4.2)	()	() NS
		Mean	(SD)				
	od rating scales (mm) - factor II	Zopiclone		Place	ebo					P value
con	tentedness	61	(4.5) 63	(3.9)	()	() NS
		Mean	(SD)				
	od rating scales (mm) - factor III	Zopiclone		Place	ebo					P value
caln	nness	57	(3.7) 59	(4.7)	()	() NS
		Mean	(SD	1)				

Author: Dockhorn Trial type: Placebo Quality rating: Fair

Year: 1996 Country: US Funding: Lorex Pharmaceuticals

Design:

Study design RCT

DB

Parallel

Setting Multicenter

Eligibility 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. Insomia 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)

Comments:

Intervention: Run-in: NR

Wash out: NR

Allow other medication: NR

Age: 32.7

Range: 20-55 SD: NR

Gender: 80 (58 %) Female

Ethnicity: NR

Lost to fu: 2 Analyzed: 136

NR

NR

138

Number Screened:

Eligible:

Enrolled:

Number Withdrawn: 9

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 alcohop 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

Withdrawals due to AEs/

Drug name	dosage	N=	Duration	Total withdrawal	
Zolpidem	10 mg	68	7-10 day	1 / 3	
Placebo	NA mg	68	7-10 day	2 / 6	

Author:	Dockhorn	Trial type	e: Pla	cebo					Quality ra	ting: I	Fair
Year:	1996	Country:	US						Funding:	Lorex I	Pharmaceuticals
Outcome I	Measurement:				Effic	асу	Outcome I	_ist:			
# mornii	ng questionnaire				Prim						
# clinica	Il global impression scale				outc		Outcome:				
					✓		sleep latency total sleep tir				
]	ease of fallin		:D		
							number og a	-			
							wake time af		p onset		
]]	quality of sle		. to the constant		
							morning slee		e in the morning		
						_	morning siec	ритооо			
Results											
morning qu	<u>estionnaire</u>										
# sleep	latency (min), day 3-10	Zolpidem		Placebo						P value	Э
		43.2	(6.9) 64.0	(7.7)	()	() 0.001	
		Mean	(SD)		·			
# total s	leep time (min), day 3-10	Zolpidem		Placebo						P value	Э
		422.2	(11) 389	(10.1)	()	() 0.054	
		Mean	(SD)				'	
# ease	of falling asleep (0=very easy;	Zolpidem		Placebo						P value	e
100= 1	not all easy), day 3-10	34.8	(2.2) 45.2	(2.3)	()	() 0.004	
		Mean	(SD	')		,		. I	l e e e e e e e e e e e e e e e e e e e
# numbe	er of awakenings, day 3-10	Zolpidem		Placebo						P value	Э
		0.8	(0.1) 1.2	(0.1)	()	() 0.014	
		Mean	(SD	1)		<u> </u>		I .	

Author:	Dockhorn	Trial type	e: Pl	acebo	Quality	Quality rating: Fair						
Year:	1996 time after sleep onset (min), day	Country	US	1					Funding: Lorex Pharmaceutical			
		Zolpidem		Placeb	0					P value		
3-10		18.1	(3.4) 34.6	(4.8)	()	() 0.008		
		Mean	(SD)					J	
# quality of sleep (1=excellent; 4=poor)		Zolpidem		Placeb	0					P value		
day 3	3-10	2.2	(0.1) 2.5	(0.01)	()	() 0.007		
		Mean	(SD	·)		\ 		-	1	
	y to concentrate (1=excellent;	Zolpidem		Placeb	0					P value		
4=po	or), day 3-10	2.3	(0.1) 2.4	(0.1)	()	() 0.358		
		Mean	(SD)						
	ing sleepiness (0=very sleepy;	Zolpidem		Placeb	0					P value		
	at at all cloopy), day 3 10	53.6	(2.2) 52.1	(2.3)	()	() 0.762		
		Mean	(SD			١				. 1	1	

Quality rating: Fair Author: Dockhorn Trial type: Placebo

armaceuticals

Year:	1996	Country	: US							Funding	: L	orex Phar
clinical gl	obal impression scale											
# qual	lity of sleep- excellent or good	Zolpidem		F	Placeb	0						P value
		78	() 4	42	()	()	()	<0.001
		%	()					
	nge in sleep- improved a lot or	Zolpidem		F	Placeb	0					ļ	P value
som	newhat	84	() 4	48	()	()	()	<0.001
		%	()					
# char	nge in time to fall asleep	Zolpidem		F	Placeb	0						P value
		81	() 4	42	()	()	()	<0.001
		%	()					
# char	nge in amount of sleep	Zolpidem		F	Placeb	0						P value
		79	() 4	43	()	()	()	<0.001
		%	(,)		1		I.	l I
# strei	ngth of medication- just right	Zolpidem		F	Placeb	0						P value
		62	() 2	28	()	()	()	<0.001
		%	()		<u> </u>			
	nge during posttreatment days-	Zolpidem		F	Placeb	0						P value
muc	ch or somewhat better	75	() 4	40	()	()	()	0.002
		%	()					

Author: Dorsey Trial type: Placebo Quality rating: Fair

Year: 2004 Country: US Funding: Sanofi-Synthelabo

Design:

Study design RCT

DB

Parallel

Setting Multicenter

Eligibility criteria:

Women aged 39 to 60 years were eligible to participate in the study if they had developed insomnia in temportal conjuction 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.

Comments:

Intervention: Run-in: 6-14

Wash out: NR

Allow other medication: NR

Age: 50.8

Range: 39-60
SD: 4.5

Number Screened:
Eligible:
Enrolled:

Gender: 141 (100 %) Female

Ethnicity: NR Number Withdrawn: 16
Lost to fu: 3

Analyzed: 141

242

141

141

Exclusion criteria:

Exclusion criteria included the presence of signs or symptoms of clinical depression, as ascertained by clinical interview and a Beck Depression Inventory socre 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; postive urinte screening test for medication that could interfere with the assessment of study medication, including benzodiazepines, barbituates, 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.

				Withdrawals due to AEs/
Drug name	dosage	N=	Duration	Total withdrawal
Zolpidem	10 mg	68	28 day	5 / 11
Placebo	NA mg	73	28 day	2 / 5
-				

Author:	Dorsey	Trial type:	Place	bo				Quality	rating:	Fair
Year:	2004	Country:	US					Fundin	ıg: Sanof	fi-Synthelabo
Outcome	Measurement:				Efficacy	Outcome	List:			
	nts global impression rating questionnaire				Primary outcome	Outcome: sleep latenc number of a wake time a sleep duration quality of sleep	wakenings fter sleep on			
Results										
patients glo	obal impression rating									
	ige summary score (lower	Zolpidem		Placebo					P val	ue
score	=better sleep)	5.53 ()	6.71	()	()	()	
		Mean (, ,	11)					
# numb	er of patients with better sleep	Zolpidem		Placebo					P val	ue
		76.8	()	43.8	()	()	() <0.00	
		% (,	П)		<u> </u>			

Author: Dorsey Trial type: Placebo Quality rating: Fair

Year: 2004 Country: US Funding: Sanofi-Synthelabo

Year:	2004	Country:	US						Fundin	ig: Sanofi-Sy
sleep c	<u>juestionnaire</u>									
	nange in sleep duration (min), 4	Zolpidem		Placebo)					P value
We	eeks average	56.5	()	20.5	()	()	() <0.01
		Mean	()				
# wa	ake after sleep onset (min), 4 weeks	Zolpidem		Placebo)					P value
av	verage	29.75	()	52.75	()	()	() <0.05
		Mean	()				
	umber of awakenings, 4 weeks	Zolpidem		Placebo)					P value
av	verage	1.4	()	2	()	()	() <0.05
		Mean	(<u>"</u>)		I		II.
# slo	eep latency (min), 4 weeks average	Zolpidem		Placebo)					P value
		31.25	()	34.25	()	()	() NS
		Mean	(')		ı		l
	eep-related difficulty with daytime	Zolpidem		Placebo)					P value
fu	nctioning	2.1	()	2.2	()	()	() <0.05
		Mean	()				
# qı	uality of life	Zolpidem		Placebo)					P value
		NR	()	NR	()	()	() NS
		Mean	(*)		, <u> </u>		1

Quality rating: Poor Trial type: Placebo Goldenberg Author:

Year: 1994 Country: **UK, France** Funding: NR

Design:

Study design RCT

DB

Parallel

Setting Multicenter Gender: NR (

Age:

Ethnicity: NR

Number Screened: NR

> Eligible: NR

Enrolled: 524

Number Withdrawn: NR

Lost to fu:

Analyzed: 458

Eligibility 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 wakings; sleep onset latency of 30 minutes or more, or daily symptoms attributable to disturbed sleep.

Exclusion criteria:

NR

SD:

Range: 25-60

NR

%) Female

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, shiftwork or travelling frequently by air were also excluded from the study, as were those unable to complete the questionnarire or who were planning to go on holibday within the period of the trial.

Comments:

Only analyzed population characteristics were reported: Mean age=42.9 years; 36.4% male; Ethnicity NR.

Intervention: Run-in: NR

NR Wash out :

Allow other medication: NR

Withdrawals due to AEs/

Drug name	dosage	N=	Duration	Total withdrawal	
Zopiclone	7.5 mg	231	48 day	N / NR	
Placebo	NA mg	227	44 day	N / NR	

Author:	Goldenberg	Trial type	e: Pla	acebo					Quality	rating: Poor
Year:	1994	Country	UK	, France					Funding	g: NR
Outcome	Measurement:				Effic	асу	Outcome I	_ist:		
# psyho	ological general well being index	(PGWBI)			Prim	•	. .			
	eveluation questionnaire (SEQ)				outc	ome	Outcome:			
# leeds	sleep evaluation questionnaire ((LSEQ)]	quality of sle			
] 	quality of wal	•	•	
]	physician's o		g during the day	
							priysicians o	verali	evaluation	
Results										
Sleep effic	iancy at endpoint									
# quality	y of sleep	Zopiclone		Placebo						P value
		1.9	(1.1) 1.3	(1.2)	()	() <0.0001
		Mean	(SD)	`	1		
# qualit	y of waking up	Zopiclone	,	Placebo		,		ĺ		
# quality	y or waking up				/ 4 4	`		,		P value
		1.5	(1.2) 1.0	(1.1)	()	() <0.0001
		Mean	(SD)				
# feeling	g of well being during the day	Zopiclone		Placebo						P value
		1.3	(1.1) 0.8	(1.1)	()	() <0.0001
		Mean	(SD	<u> </u>)				
# physic	cian's overall evaluation:	Zopiclone		Placebo						P value
avera	ge, good or excellent	187	(92.5) 125	(66.9)	()	() <0.0001
		Number	(%			\	•	,	-	
		Nullibel	(/0			,				

Author:	Goldenberg	Trial type	e: P	lacebo					Quality	rating: Poo
rear:	1994	Country	U	K, France					Funding	g: NR
Quality of	life - change from baseline									
# PGW	ВІ	Zopiclone		Placebo)					P value
		11.8	() 9.1	()	()	() NS
		Score	(ı)				
# SEQ		Zolpidem		Placebo)					P value
		14.6	() 2.7	()	()	() <0.0001
		Score	(')		I		
# Activi	ty	Zopiclone		Placebo)					P value
		20	() 9.9	()	()	() <0.0001
		Score	(')		I		
# Socia	ıl	Zolpidem		Placebo)					P value
		13.1	() 5.7	()	()	() <0.01
		Score	(')		'		l .
# Profe	ssion	Zopiclone		Placebo)					P value
		23.3	() 12.9	()	()	() <0.01
		Score	()		1		
# Globa	al	Zopiclone		Placebo)					P value
		10.8	() 5.7	()	()	() NS
		Score	()		1		I

Author: Hedner Trial type: Placebo Quality rating: Fair

Year: 2000 Country: Europe Funding:

Design:

Study design RCT

DB

Parallel

Setting Multicenter

Age: 72.5

Range: 59-95

SD: NR

Gender: NR (%) Female
Ethnicity: NR

Number Withdrawn: 22

Number Screened:

Lost to fu: NR

Eligible:

Enrolled:

Analyzed: 422

NR

NR

437

Eligibility 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 Maunal, 4th edition (DSM-IV; American Psychiatric Association, 1994), was characterised 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.

Exclusion criteria:

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

Comments:

Only analyzed population characteristics were reported: Mean age=72.5 years; 32.3% male; 99% white, 1% black.

Intervention: Run-in: 7

Wash out: 7

Allow other medication: NR

Withdrawals due to AEs/

Drug name	dos	sage	N=	Duration	Total withdrawal
Zaleplon	5	mg	139	14 day	10 / 10
Zaleplon	10	mg	145	14 day	5 / 5
Placebo	NA	mg	138	14 day	7 / 7

Author:	Hedner	Trial type	: Place	ebo					Quality r	ating: Fair	
Year:	2000	Country:	Europ	ре					Funding	:	
	Measurement: o questionnaire				Efficac Primary outcom	sleep sleep numbe			gs		
Results											
sleep ques	stionnaire										
# subje	ective sleep latency (min), week 1	Zaleplon 5	mg	Zaleplo	n 10mg	Placebo				P value	
		43	(<0.001)	40	(<0.001)	60	(NA)	()	
		Median	(p vs plac	ebo)	ļ		ļ		ļ	I
# subje	ective sleep latency (min), week 2	Zaleplon 5	mg	Zaleplo	n 10mg	Placebo				P value	
		40	(<0.001)	37	(<0.001)	50	(NA)	()	
		Median	(p vs plac	ebo)	I		ı		ļ	I
# subje	ective total sleep time (min), week	Zaleplon 5	mg	Zaleplo	n 10mg	Placebo				P value	
1		342	(NS	342.9	(<0.05)	346.1	(NA)	()	
		Median	(p vs plac	ebo)						J
	ective total sleep time (min), week	Zaleplon 5	mg	Zaleplo	n 10mg	Placebo				P value	
2		351.7	(NS	351.4	(NS)	342.9	(NA)	()	
		Median	(p vs plac	ebo)						J
	ective number of awakenings,	Zaleplon 5	mg	Zaleplo	n 10mg	Placebo				P value	
week	:1	2	(NS	2	(<0.05)	2	(NA)	()	
		Median	(p vs plac	ebo)	<u>I</u>		1			I

author: Hedner	Trial typ	e: Pla	ce	bo					Quality rat	ing: Fair
'ear: 2000	Country	: Euro	ope	e					Funding:	
# subjective number of awakenings,	Zaleplon	5mg		Zaleplon 10mg		Placebo				P value
week 2	2	(NS)	1 (NS)	2	(NA)	()
	Median	(p vs pl	ace	ebo)					1
# subjective sleep quality, week 1	Zaleplon	5mg		Zaleplon 10mg		Placebo				P value
(score). 1=excellent; 7=extremely poo	3.8	(<0.01)	3.8 (<0.01)	3.9	(NA)	()
	Mean	(p vs pl	ace	ebo)					
# subjective sleep quality, week 2	Zaleplon	5mg		Zaleplon 10mg		Placebo				P value
(score). 1=excellent; 7=extremely poo	3.7	(< 0.05)	3.7 (<0.05)	3.8	(NA)	()
	Mean	(p vs pl	ace	ebo)					
# subjective sleep quality, improvement	Zaleplon	5mg		Zaleplon 10mg		Placebo				P value
in sleep quality- week 1	48	(NS)	55 (<0.000)	36	(NA)	()
	%	(p vs pl	ace	ebo)					
# subjective sleep quality, improvement	Zaleplon	5mg		Zaleplon 10mg		Placebo				P value
in sleep quality- week 2	53	(NS)	63 (<0.000)	36	(NA)	()
	%	(p vs pl	ace	ebo)			ı		-1

Author: Herrmann Trial type: Placebo Quality rating: Poor

Year: 1993 Country: France Funding: NR

Design:

Study design RCT

DB

Parallel

Setting Single Center

Age: NR

Range: 25-65 SD: NR

Gender: 9 (43 %) Female

Ethnicity: NR

Number Withdrawn: NR

Number Screened: NR

Eligible:

Enrolled:

Lost to fu: NR Analyzed: 21

25

21

Eligibility criteria:

For inclusion in the study, patients had to meet two of the following three polysomnographic criteria: (i) sleep onset latency of more than 30 min; (ii) total sleep time of less than 6 h or time awake more than 1 h; and (iii) five awakenings of at least 5 min each.

Comments:

Intervention: Run-in:

Wash out: 7

Allow other medication: NR

7

Exclusion criteria:

Other criteria were an absence of medical, psychiatric and organic mental disorders, and normal results on routine laboratory testing and on urine drug screeing for amphetaines, cannabinoids, morphine derivatives, barbiturates and benzodiazepines. Patients presenting with caffeinism or alcoholism, or shift workers were excluded.

Withdrawals due to AEs/ Total withdrawal Drug name dosage N= Duration Zolpidem 10 mg 11 14 day N / NR Placebo NA mg 10 14 day N / NR

Author:	Herrmann	Trial type:	Pla	cebo)					Qual	ity rati	ng: Poo
Year:	1993	Country:	Fran	nce						Fund	ling: N	IR
Outcome	Measurement:					Eff	icacy	Outcome	List:			
	omnography questionnaire						imary tcome	Outcome: sleep efficie	ncv			
								sleep latend total sleep t number of a wake after s	y ime wakenir	-		
Results												
polysomno	ography .											
# sleep	efficiency (%), day 21 treatment	Zolpidem		Р	lacebo							P value
		86.2	(2) 7	3.3	(5)	()	()	<0.05
		Mean	(SD)					
	sleep time (min), day 21	Zolpidem		Р	lacebo							P value
treatn	nent	381.3	(10) 3	60.3	(23)	()	()	NS
		Mean	(SD	·)					I
	onset latency (min), day 21	Zolpidem		Р	lacebo							P value
treatn	nent	28	(7) 4	1.7	(15)	()	()	NS
		Mean	(SD)		1			<u>I</u>
# time a	awake (min), day 21 treatment	Zolpidem		Р	lacebo							P value
		34.7	(7) 6	ס	(12)	()	()	NS
		Mean	(SD	I)					I

Author: Herri	mann	Trial type	: Plac	cebo					Quality r	ating: Poo
Year: 1993		Country:	Fran	ice					Funding	: NR
sleep questionnaire										
	ency (min), day 15-21	Zolpidem		Placebo)					P value
treatment	treatment		(10) 72.8	(10)	()	() <0.05
		Mean	(SD)				
# total sleep time (min), day 15-21		Zolpidem		Placebo)					P value
treatment		372.7	(12) 327.4	(22)	()	() NS
		Mean	(SD)				l l
# no. of awakenir	ngs, day 15-21	Zolpidem		Placebo)					P value
treatment		1.8	(0.4) 2.3	(0.4)	()	() NS
		Mean	(SD)				l l
# calm/restless, f		Zolpidem		Placebo)					P value
relaxed/anxious day	s, lying down during the	multi-data	(multi-d) multi-da	ita (multi-	d)	()	() NS
•		Mean	(SD)		'		ı

Author: Hindmarch Trial type: Placebo Quality rating: Fair

Year: 1995 Country: UK Funding:

Design:

Study design RCT

DB

Parallel

Setting Multicenter

Age: 42.9

Range: 25-60 SD: 8.9

Gender: NR (0 %) Female

Military and the Arts

Ethnicity: NR

Number Withdrawn: NR Lost to fu: NR

Eligible:

Enrolled:

Number Screened:

Analyzed: 458

NR

NR

458

Eligibility criteria:

patients aged between 25 and 60 years suffering from at least two of the following symptoms for two or more weeks: sleep duration less than 6 hours per night; at least 2 nightly awakenings; sleep onset latency of 30 minutes or more; and daily symptoms attributable to sleep disorders.

Comments:

Intervention: Run-in: NR

Wash out: NR

Allow other medication: NR

Exclusion criteria:

Depression or other psychiatric disorders, alcohol or substance dependency, concurrent medication with CNS effects, acute or chronic illness affecting sleep, important negative life events within the previous month, and pregnancy were considered as exclusion criteria.

				Withdrawals due to AES/	
Drug name	dosage	N=	Duration	Total withdrawal	
Zopiclone	7.5 mg	231	48 day	N / NR	
Placebo	NA mg	227	42 day	N / NR	

Author:	Hindmarch	Trial type:	Place	ebo					Quality i	ating: Fair	
Year:	1995	Country:	UK						Funding	:	
Outcome	Measurement:				Efficac	y Outco	me L	ist:			
# quest	ionnaire				Primary outcome	e Outcor quality quality	of slee of wak	ing up	rell being		
Results											
questionna	aire										
# psych	nological general well-bing index	Zolpidem		Placebo						P value	
(PGW 14	VBI), change from baseline, day	11.8 (9.1	()		()	() NS	
)			·			
	# sleep evaluation questionnaire (SEQ), change from baseline, day 14			Placebo						P value	
chanç	ge from baseline, day 14	14.6 () 2.7	()		()	() <0.0001	
		Mean (·)	ı		,		! !	
# activit	ty, change from baseline, day 14	Zolpidem		Placebo						P value	
		20 (9.9	()		()	() <0.0001	
		Mean ()	I					
# socia	I, change from baseline, day 14	Zolpidem		Placebo						P value	
		13.4 () 5.7	()		()	() <0.01	
		Mean (<u> </u>)						
# profes	ssion, change from baseline, day	Zolpidem		Placebo						P value	
14		23.3 () 12.9	()		()	() <0.01	
		Mean (1)	l					
# globa	I, change from baseline, day 14	Zolpidem		Placebo						P value	
0		10.8 () 5.7	()		()	() NS	
		Mean (1)		-	-			

Author:	Hindmarch	Trial type	e: Pla	се	bo					Quality	/ rati	ng: Fair
Year:	1995	Country:	UK							Fundir	ng:	
	ogical general well-bing index	Zolpidem			Placebo							P value
(PGWB endpoir	I), change from baseline, nt	15.2	()	12.9	()	()	()	NS
		Mean	()					
	valuation questionnaire (SEQ),	Zolpidem			Placebo							P value
change	from baseline, endpoint	20.9	()	12.5	()	()	()	<0.0001
		Mean	()					
	change from baseline,	Zolpidem			Placebo							P value
endpoint		21.6	()	14.2	()	()	()	<0.0001
		Mean	()					
# social, change from baseline, endpo		Zolpidem			Placebo							P value
		14.9	()	9.1	()	()	()	<0.01
		Mean	()		ļ.		٠	I I
# profess	ion, change from baseline,	Zolpidem			Placebo							P value
endpoir	nt	24.5	()	18.7	()	()	()	NS
		Mean	()		I			
# global,	change from baseline, endpoint	Zolpidem			Placebo							P value
		13.8	()	8.9	()	()	()	NS
		Mean	(1)					
	an's oveall evaluation of	Zolpidem			Placebo							P value
treatme	ent efficacy as "excellent" or at endpoint	76.7	()	51.4	()	()	()	
-		%	()					

Author: Krystal Trial type: Placebo Quality rating: Fair

Year: 2003 Country: US Funding: Sepracor

Design:

Study design RCT

DB

Parallel

Setting Multicenter

Eligibility 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.

Comments:

Intervention: Run-in: NR

Wash out: 5-7

Allow other medication: NR

Withdrawals due to AEs/

Drug name	dos	age	N=	Duration	Total withdrawal	
Eszopiclone	3	mg	593	180 day	76 / 235	
Placebo	NA	mg	195	180 day	14 / 85	

Age: 44

Range: 21-69 SD: 11.3

Gender: 195 (25 %) Female

Ethnicity: 80% caucasian

13.2% african american 7.9% other

Exclusion criteria:

NR

Number Screened: 1194

Eligible: 791 Enrolled: 788

Number Withdrawn: 320 Lost to fu: 60

Analyzed: 788

Author:	Krystal	Trial typ	e: Pla	acebo		Quality rating: Fair						
Year:	2003	Country	: US					Funding:	Sepracor			
Outcome	Measurement:				Efficacy	Outcome Li	st:					
# telepl	none interview				Primary outcome	Outcome:						
						sleep latency wake time afte total sleep time number of awa number of nigh sleep quality daytime ability daytime alertne sense of physi	e ikenii its du to fu ess	ngs uring the week nction				
Results telephone	<u>interview</u>											
# sleep	latency, month 6	Eszopicko 47.0	one (50.6	Placebo) 63.1	(57.9)	()	(P value) <0.001			
		Mean	(SD	<u> </u>)							
# wake	after sleep onset, month 6	Eszopiclo	ne	Placebo					P value			
		44.2	(74.2) 48.2	(59.4)	()	() 0.0032			
		Mean	(SD	ļ)							
# numb	er of awakenings, month 6	Eszopiclo	ne	Placebo					P value			
	•	1.9	(1.5) 2.6	(2.7)	()	() <0.0001			
		Mean	(SD)							
# numb	er of night awakenings per	Eszopick	,	Placebo	,				P value			
week	, month 6	3.9	(2.5) 4.7	(2.4)	()	() 0.0001			
		Mean	(SD)							

Author:	Krystal	Trial typ	e: Pla	acebo						Quality rat	ing: Fai
Year:	2003	Country	: US							Funding:	Sepracor
# total sl	leep time, month 6	Eszopicle	one	Placebo)						P value
		378.3	(72.3) 339.3	(77.1)	()		(<0.001
		Mean	(SD	<u>'</u>)			II .		
# sleep	quality, month 6	Eszopick	one	Placebo)						P value
		6.4	(1.8) 5.5	(1.8)	()		(<0.0001
		Mean	(SD)					-
# daytim	ne ability to function, month 6	Eszopick	one	Placebo)						P value
		6.8	(1.7) 6.2	(1.8)	()		(<0.0001
		Mean	(SD)					
# daytim	ne alertness, month 6	Eszopicle	one	Placebo)						P value
		6.5	(1.7) 5.9	(1.7)	()		(<.0001
		Mean	(SD)					
# sense	of physical well-being, month 6	Eszopick	one	Placebo)						P value
		6.7	(1.7) 6.1	(1.8)	()		(0.0002
		Mean	(SD)					·

Author: Lahmeyer Trial type: Placebo Quality rating: Fair

Year: 1997 Country: US Funding: ?orex Pharmaceuticals

Design:

Study design RCT

DB

Parallel

Setting Multicenter

Eligibility criteria:

Patients had to have a history of a minimum of 3 months of disturbed sleep, characterised by a typical sleep duration of between 4 and 6 hours, a typical sleep latency of at least 30 minutes, and associated daytime complaints.

Comments:

Intervention: Run-in: 3
Wash out: 4

Allow other medication: NR

Age: 44.9

Range: 19-61 SD: 11.6

Gender: 81 (56 %) Female

Ethnicity: 92% caucasian

6% black <1% hispanic 1% asian Number Screened: 178

Eligible: 33

Enrolled: 145

Number Withdrawn: 27

Lost to fu: 0 Analyzed: 118

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 shortacting 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 yar; (f) had subjective symptons 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.

				Withdrawals due to AEs/
Drug name	dosage	N=	Duration	Total withdrawal
Zolpidem	10 mg	45	31 day	4 / 8
Zolpidem	15 mg	46	31 day	3 / 9
Placebo	NA mg	54	31 day	0 / 10

Author:	Lahmeyer	Trial type	e: Plac	ebo						Quality ra	ting:	Fair
Year:	1997	Country:	US							Funding:	?orex	Pharmaceuticals
# morni	Measurement: ing questionnaire al global impression				Prin outo	nary	sleep of sle	duration datency of fallinger of avalenter sland of sleeping sleeping sleeping	n , g asleep vakenin eep ons ep	gs et		
Results												
morning qu	uestionnaire - 4 weeks average											
	latency (min), change from ine - 4 weeks average	Zolpidem -30	10mg (Zolpiden) -33.5	n 15mg ()	Placebo -9	()	(P valu	le
		Mean	()			<u> </u>			
# total s avera	sleep time (min) - 4 weeks lae	Zolpidem	10mg	Zolpiden	n 15mg		Placebo				P valu	<u>ie</u>
		379	() 381	()	346	()	()	
		Mean	()						
# numb avera	per of awakenings - 4 weeks	Zolpidem	10mg	Zolpiden	n 15mg		Placebo				P valu	<u>ie</u>
avera	ige	1.3	() 1.3	()	1.9	()	()	
		Mean	()						·
	quality (1=excellent; 4=poor) - 4 s average	Zolpidem 2.4	10mg (Zolpiden) 2.4	n 15mg ()	Placebo 2.8	()	(P valu	ie
		Mean	(<u> </u>)						

Author: Lahmeyer Trial type: Placebo Quality rating: Fair

Year: 1997 Country: US Funding: ?orex Pharmaceuticals

Year:	1997	Country:	US							Funding:	?orex Phari
morning	g questionnaire - at week 4										
	eep latency (min), change from	Zolpidem	10mg	Zolpide	m 15mg		Placebo				P value
ba	seline - at week 4	-31	(<0.05)	-31	(NS)	-16	(NA)	()
		Mean	(p vs plac	ebo)	II		l .		
# tot	tal sleep time (min) - at week 4	Zolpidem	10mg	Zolpide	m 15mg		Placebo				P value
		390	(NS)	385	(NS)	360	(NA)	()
		Mean	(p vs plac	ebo)			1		
# nu	ımber of awakenings - at week 4	Zolpidem	10mg	Zolpide	m 15mg		Placebo				P value
		1.4	(NS)	1.2	(NS)	1.7	(NA)	()
		Mean	(p vs plac	ebo)			1		
	eep quality (1=excellent; 4=poor) -	Zolpidem	10mg	Zolpide	m 15mg		Placebo				P value
at	week 4	2.4	(NS)	2.4	(NS)	2.6	(NA)	()
		Mean	(p vs plac	ebo)	1		'		!!!
morning	g questionnaire - post-treatment										
	eep latency (min), change from	Zolpidem	10mg	Zolpide	m 15mg		Placebo				P value
ba	seline - post-treatment	-10	(NS)	-11	(NS)	-25	(NA)	()
		Mean	(p vs plac	ebo)			1		
# tot	tal sleep time (min) - post-treatment	Zolpidem	10mg	Zolpide	m 15mg		Placebo				P value
		354	(NS)	332	(NS)	359	(NA)	()
		Mean	(p vs plac	ebo)	"				
	ımber of awakenings - post-	Zolpidem	10mg	Zolpide	m 15mg		Placebo				P value
tre	eatment	1.7	(NS)	1.9	(NS)	1.9	(NA)	()
		Mean	(p vs plac	ebo)			1		
	eep quality (1=excellent; 4=poor) -	Zolpidem	10mg	Zolpide	m 15mg		Placebo				P value
po	est-treatment	2.8	(NS)	2.9	(NS)	2.8	(NA)	()
		Mean	(p vs plac	ebo)	1				,

Quality rating: Fair Author: Lahmeyer Trial type: Placebo

armaceuticals

Year:	1997	Country:	US					Funding:	?orex Phar
clinical g	lobal impression								
	dication helped me - fall asleep	Zolpidem ²	10mg	Zolpid	em 15mg		Placebo		P value
fast	er	84	(< 0.05) 78	(<0.05)	51 (NA)	()
		%	(p vs plad	cebo)			
# med	dication helped me - sleep longer	Zolpidem ²	10mg	Zolpid	em 15mg		Placebo		P value
		78	(< 0.05) 76	(NS)	51 (NA)	()
		%	(p vs plad	cebo)	1		
	dication helped me - get a better	Zolpidem ²	10mg	Zolpid	em 15mg		Placebo		P value
nigh	nt's sleep	84	(,0.05) 84	(<0.05)	49 (NA)	()
		%	(p vs plad	cebo)	1		
# med	dication strength - too strong	Zolpidem 1	10mg	Zolpid	em 15mg		Placebo		P value
		0	(NS) 0	(NS)	0 (NA)	()
		%	(p vs plad	cebo)			ı
# med	dication strength - strong enough	Zolpidem ²	10mg	Zolpid	em 15mg		Placebo		P value
		71	(< 0.05) 72	(< 0.05)	44 (NA)	()
		%	(p vs plad	cebo)	'		
# med	dication strength - too weak	Zolpidem ²	10mg	Zolpid	em 15mg		Placebo		P value
		29	(NS) 28	(NS)	56 (NA)	()
		%	(p vs plac	cebo)	1		

Quality rating: Fair Trial type: Placebo Author: Monchesky

Year: 1986 Country: Canada Funding: NR

Design:

Study design RCT

DB

Crossover

Setting Single Center

NR Age:

> Range: 23-69 SD: NR

Gender: NR (0 %) Female

Ethnicity: NR

Number Withdrawn: 0 Lost to fu: 2

Analyzed: 91

NR

99

Number Screened: NR

Eligible:

Enrolled:

Eligibility 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

Comments:

Zopiclone 7.5mg for run-in and wash-out periods.

Only analyzed population characteristics were reported: Mean age=46.8; 28.6% male; Ethnicity NR.

Intervention:

Run-in:

7 Wash out :

Allow other medication: No use of neuroleptics, sedatives, analgesics, or antidepressants

Withdrawals due to AEs/

Drug name	dosage	N=	Duration	Total withdrawal
Zopiclone	7.5 mg	91	7 day	N / NR
Placebo	NA mg	91	7 day	N / NR

Author:	Monchesky	Trial type:	Place	bo				Quality i	rating: Fair
Year:	1986	Country:	Canad	la				y: NR	
	Measurement:				Efficacy Primary	/ Outcome I	List:		
# Sieep	questionnaire				outcome	Outcome:			
						sleepiness d sleep latency sleep duratio number of av	/ on	·	
Results									
sleep ques	stionnaire								
# durat	ion of sleep (min), treatment day	Zolpidem		Placebo					P value
7		384.8	()	307.4	()	()	() NR
		Mean	(1)		I		
# numb	per of awakenings, treatment	Zolpidem		Placebo					P value
day 7	•	1.8	()	3.5	()	()	() NR
		Mean	(ı)		I		
# qualit	y of sleep, treatment day 7	Zolpidem		Placebo					P value
		4.15	()	3.15	()	()	() NR
		Mean	()				
# sound	dness of sleep, treatment day 7	Zolpidem		Placebo					P value
		3.8	()	2.75	()	()	() NR
		Mean	(<u> </u>)				
# morn	ing state of rest, treatment day 7	Zolpidem		Placebo					P value
		2.85	()	1.95	()	()	() NR
		Mean	(1)				

uthor: Monchesky	Trial type:	Plac	ebo					Quality	rating: Fair
ear: 1986	Country:	Cana	ıda					Funding	g: NR
# sleepiness during the day, treatment	Zolpidem		Placebo						P value
day 14 (switch)	2.3	() 2.9	()	()	() NR
	Mean	()		I		
# sleep induction time (min), treatment	Zolpidem		Placebo						P value
day 14 (switch)	53.8	() 119.3	()	()	() NR
	Mean	()				
# duration of sleep (min), treatment day	Zolpidem		Placebo						P value
14 (switch)	376.7	() 299.5	()	()	() NR
	Mean	()				
# number of awakenings, treatment	Zolpidem		Placebo						P value
day 14 (switch)	2.0	() 2.45	()	()	() NR
	Mean	(')		ı		.1 1
# quality of sleep, treatment day 14	Zolpidem		Placebo						P value
(switch)	4.35	() 2.95	()	()	() NR
	Mean	()		<u> </u>		
# soundness of sleep, treatment day 14	Zolpidem		Placebo						P value
(switch)	4.0	() 2.4	()	()	() NR
	Mean	()				
# morning state of rest, treatment day	Zolpidem		Placebo						P value
14 (switch)	2.9	() 2.15	()	()	() NR
	Mean	(ı)				
# sleepiness during the day, treatment	Zolpidem		Placebo						P value
day 7	2.3	() 2.65	()	()	() NR
	Mean	(I)				

Author: Monchesky	Trial type:	Placebo			Quality r	ating: Fair
Year: 1986	Country:	Canada			Funding	: NR
# sleep induction time (min), treatment	Zolpidem	Placebo				P value
day 7	51.85 () 89.9	()	()	() NR
	Mean (·)		I.	"

Author: Monti Trial type: Placebo Quality rating: Fair

Year: 1996 Country: Uruguay Funding: NR

Design:

Study design RCT

DB

Parallel

Setting Single Center

Eligibility 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 waketime >20 minutes; number of nocturnal awakenings >3.

Comments:

Intervention: Run-in: 2

Wash out: 3

Allow other medication: No

Age: 44.25

Range: NR SD: 4.8

Gender: 10 (83 %) Female

Ethnicity: NR

Lost to fu: NR

Analyzed: 12

NR

12

Number Screened: NR

Eligible:

Enrolled:

Number Withdrawn: NR

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.

				Withdrawals due to AEs/
Drug name	dosage	N=	Duration	Total withdrawal
Zolpidem	10 mg	6	27 day	N / NR
Placebo	NA mg	6	27 day	N / NR

Author:	Monti	Trial type	: Plac	cebo					Quality	ratir	ng: Fair
Year:	1996	Country:	Urug	guay					Funding	g: N	R
# polyso	Measurement: omnography ionnaire				Pri out [[[[icacy mary come	Outcome: sleep latency number of av total wake tim wake time ad total sleep tii sleep efficiel movement ti	/ wakenii me fter slee me			
Results											
polysomno	graphy										
	2 sleep latency (min), nights 29-	Zolpidem		Placebo	١						P value
30		23.6	(7.1) 35.1	(5.6)	()	()	NS
		Mean	(SD)					
# total n	number of awakenings, nights 29-	Zolpidem		Placebo)						P value
30		24.8	(4.3) 25.5	(5.7)	()	(NS
		Mean	(SD)					
# total w	vake time (min), nights 29-30	Zolpidem		Placebo)						P value
	-	53.8	(6.9) 104.8	(21.8)	()	(<0.05
		Mean	(SD	<u> </u>)					
# wake	time after sleep onset (min),	Zolpidem	`	Placebo)	, 					P value
	29-30	26.3	(7.0) 85.3	(24.2)	()	(NS
		Mean	(SD	- 1	•)			•		
# total e	sleep time (min), nights 29-30	Zolpidem	(05	Placebo	<u> </u>	,					Divolus
# 10tal 5	ncop une (min), mgma 29-30	419.3	(7.1) 370.9	(21.2))			P value <0.05
				, 010.3	(21.2		(,	,		10.00
		Mean	(SD)					

author: Monti	Trial typ	e: Pla	cebo					Quality	/ rating: Fair
'ear: 1996	Country	: Uru	guay					Fundin	ng: NR
# sleep efficiency (%), nights 29-30	Zolpidem	1	Placebo)					P value
	87.3	(1.5) 77.3	(4.4)	()	() NS
	Mean	(SD	!)		 		
# movement time, nights 29-30	Zolpidem	1	Placebo)					P value
	6.9	(2.6) 4.3	(1.2)	()	() NS
	Mean	(SD)				
questionnaire									
# sleep latency (lower score indicates	Zolpidem	1	Placebo)					P value
more positive response), night 29-30	2.0	(0.4) 1.8	(0.5)	()	() NS
	Mean	(SD)		<u> </u>		<u> </u>
# sleep duration (higher score indicates	Zolpidem	1	Placebo)					P value
more positive response), night 29-30	2.3	(0.3) 2.5	(0.4)	()	() NS
	Mean	(SD	·)		"		
# number of awakenings (lower score	Zolpidem	1	Placebo)					P value
indicates more positive response), night 29-30	2.6	(0.3) 1.9	(0.3)	()	() NS
	Mean	(SD)				,
# disturbed sleep (higher score	Zolpidem	1	Placebo)					P value
indicates more positive response), night 29-30	73.1	(8.7) 48.5	(8.3)	()	() <0.01
	Mean	(SD)		•		,
# daytime alertness (higher score	Zolpidem	1	Placebo)					P value
indicates more positive response), night 29-30	69.0	(9.5) 44.2	(8.4)	()	() NS
	Mean	(SD)				'

Author: Monti_ Trial type: Placebo Quality rating: Poor

Year: 2000 Country: Uruguay Funding: NR

Design:

Study design RCT

DB

Parallel

Setting Single Center

Ra

Age:

Range: NR SD: 3.6

Gender: 12 (100 %) Female

51.9

Ethnicity: NR

Number Withdrawn: NR Lost to fu: NR

Number Screened:

Eligible:

Enrolled:

Analyzed: 12

NR

NR

12

Eligibility criteria:

Patients aged between 27 and 59 years, with chronic primary insomina 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-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 swere pregnanct women, breast-feeding mothers, subjects deemed insufficiently compliant, or those with clinically significant diviations 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.

Comments:

Intervention: Run-in: 3

Wash out: 3

Allow other medication: NR

				Withdrawals due to AEs/
Drug name	dosage	N=	Duration	Total withdrawal
Zolpidem	10 mg	6	15 day	N / NR
Placebo	NA mg	6	15 day	N / NR

Author:	Monti_	Trial type	: Pla	cebo				Quality	rating: Poor
Year:	2000	Country:	Uru	iguay				Funding	g: NR
Outcome	Measurement:				Efficacy	Outcome L	.ist:		
# Interv	riew raphic sleep record				Primary outcome	Outcome:			
# polyg	тарпіс меер гесого					sleep latency number of av wake time af total sleep tir sleep efficien	vakeninç er sleep ne		
Results						·	,		
	c sleep record								
# total s	sleep time (min) - night 17-18	Zolpidem		Placebo					P value
		361.2	(25.8) 264.4	(33.3)	()	() <0.02
		Mean	(SD	<u> </u>)				
# sleep	efficiency (%) - night 4-5	Zolpidem		Placebo					P value
		79.9	(1.6) 61.9	(5)	()	() <0.006
		Mean	(SD	· · · · · · · · · · · · · · · · · · ·)				
# sleep	efficiency (%) - night 17-18	Zolpidem		Placebo					P value
		75.4	(5.4) 55.1	(6.9)	()	() <0.01
		Mean	(SD)		·		
# stage	2 sleep latency - night 4-5	Zolpidem		Placebo					P value
		26.1	(4.5) 67.4	(14.9)	()	() <0.02
		Mean	(SD	1)				
# stage	2 sleep latency - night 17-18	Zolpidem		Placebo					P value
		29.2	(6.8) 48.3	(6.9)	()	() NS
		Mean	(SD)				

Author: Monti_	Trial typ	e: Pl	acebo					Quality	rating: Poo
Year: 2000	Country	: Uru	uguay					Funding	g: NR
# total number of awakenings - night 4-5	Zolpidem		Placebo						P value
	29.4	(5.1) 32.2	(3.8)	()	() NS
	Mean	(SD	·)				
# total number of awakenings - night 17-	Zolpidem		Placebo						P value
18	26.9	(2.2) 26.5	(4.9)	()	() NS
	Mean	(SD)		·		<u>'</u>
# waking time after sleep onset (min) -	Zolpidem		Placebo						P value
night 4-5	75.1	(7.9) 137.5	(29.2)	()	() <0.03
	Mean	(SD)		·		<u>'</u>
# waking time after sleep onset (min) -	Zolpidem	l	Placebo						P value
night 17-18	95.7	(23.3) 173.3	(35.4)	()	() NS
	Mean	(SD	·)		,		.!
# total sleep time (min) - night 4-5	Zolpidem		Placebo						P value
	378.8	(8.2) 279.3	(24.2)	()	() <0.01
	Mean	(SD	<u>. </u>)		ı		ı

Trial type: Placebo Quality rating: Poor Author: Monti Funding: NR Year: 2000 Country: Uruguay interview # sleep latency (min) - night 4-5 Zolpidem Placebo P value 34.6) < 0.01 (8.2 228.0 8.08 Mean (SD # sleep latency (min) - night 17-18 Zolpidem Placebo P value 49.5 (8.2 154.0 (52.1) < 0.01 Mean (SD Zolpidem # sleep duration (min) - night 4-5 Placebo P value 384.0 (29.1 180.0 (61.3) NS (SD Mean Zolpidem # sleep duration (min) - night 17-18 Placebo P value (55.3 342.0 (40.5) 225.0) NS Mean (SD # disturbed sleep - night 4-5 (1=agree; Zolpidem Placebo P value 100=disagree) 78.4 (6.2 46.4 (12.9) NS Mean (SD # disturbed sleep - night 17-18 Zolpidem Placebo P value (1=agree; 100=disagree) 74.6 (8.4 40.1 (14.8) NS

P value

P value

) NS

) NS

(SD

(6.3

(SD

(10.6

(SD

Placebo

Placebo

(16.1

(12.1

)

57.5

65.9

Mean

20.8

Mean

30.3

Mean

Zolpidem

Zolpidem

alert in the morning - night 4-5

alert in the morning - night 17-18

(1=agree; 100=disagree)

(1=agree; 100=disagree)

Author: Perlis Trial type: Placebo Quality rating: Fair

Year: 2004 Country: US Funding: Lorex Pharmaceuticals

Design:

Study design RCT

DB

Parallel

Setting Multicenter

Eligibility criteria:

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. **Age:** 40.8

Range: 18-64 SD: 12.7

Gender: 141 (71 %) Female

Ethnicity: 70% euro-american

Number Withdrawn: 10 Lost to fu: 3

Eligible:

Enrolled:

Number Screened:

Analyzed: 192

322

277

199

Exclusion criteria:

Exclusion criteria included presene 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; postiive urine screen for medication that could interfere with the assessment of study medication; history of drug addiciton, alcoholism, or drug abuse; and histroy 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.

Comments:

Patients were instructed to "take the medication when you think you need it, at bedtime, for a total of between 3 and 5 capsules per week". They were also told to take only 1 pill per night and not to use the study medication to treat early awakenings.

Intervention:

Run-in: 6-14
Wash out: NR

Allow other medication: NR

Withdrawals due to AEs/

Drug name	dosage	N=	Duration	Total withdrawal	
Zolpidem	10 mg	98	84 day	7 / 7	
Placebo	NA mg	101	84 day	3 / 3	

Author: Perlis Trial type: Placebo Quality rating: Fair

Year: 2004 Country: US Funding: Lorex Pharmaceuticals

Outcome Measurement:

sleep diaries

global outcome measure

Efficacy Outcome List:

Primary

outcome Outcome:

✓ sleep latency

number of awakenings
wake after sleep onset

✓ total sleep time

Results

sleep diaries

# sleep latency (min), without pill	Zolpidem			Placebo						P value
	NR	(NR)	NR (NR)		()	() NS
	Mean	(SD		1)			(1)		1 1
# sleep latency (min), all condition	Zolpidem			Placebo						P value
significant at week 10 only	NR	(NR)	NR (NR)		()	() NS
	Mean	(SD)	1		į		1 1
# number of awakenings, with pill	Zolpidem			Placebo						P value
	1.03	(0.92)	1.64 (1.33)		()	() <0.05
	Mean	(SD)					
# number of awakenings, without pill	Zolpidem			Placebo						P value
	NR	(NR)	NR (NR)		()	() NS
	Mean	(SD		1)					
# number of awakenings, all condition,	Zolpidem			Placebo				ĺ		P value
significant at week 2 and 12 only	1.38	(1.00)	1.69 (1.28)		()	() NS
	Mean	(SD)					

Author:	Perlis	Trial type	e: Pla	се	bo					Quality r	ati	ng: Fair
Year:	2004	Country	US							Funding	: L	orex Pharmaceuticals
# wake a	ifter sleep onset (min), with pill	Zolpidem			Placebo							P value
		32.6	(43.5)	55.4	(56.1)	()	()	<0.05
		Mean	(SD		1)		Į.			
	ifter sleep onset (min), without	Zolpidem			Placebo							P value
pill		NR	(NR)	NR	(NR)	()	()	NS
		Mean	(SD		1)		·			
# wake a	ifter sleep onset (min), all	Zolpidem			Placebo							P value
conditi	on, significant at week 2 only	NR	(NR)	NR	(NR)	()	()	NS
		Mean	(SD		1)		·			
# total sl	eep time (min), with pill	Zolpidem			Placebo							P value
		417	(64.4)	359.8	(77.1)	()	()	<0.05
		Mean	(SD)		II.		٠	l I
# total sl	eep time (min), without pill	Zolpidem			Placebo							P value
		NR	(NR)	NR	(NR)	()	()	NS
		Mean	(SD		1)		·			
# total sl	eep time (min), all condition	Zolpidem			Placebo							P value
		394.1	(60.1)	355.6	(69.6)	()	()	<0.05
		Mean	(SD)					
# sleep l	atency (min), with pill	Zolpidem			Placebo							P value
		38.4	(33.1)	55.1	(52.3)	()	()	<0.05
		Mean	(SD)		ı			
global outco	me measure											
# IGR so	ale	Zolpidem			Placebo							P value
		6	(0.12)	4.5	(0.14)	()	()	<0.001
		Mean	(SD		ı)					

Author: Scharf Trial type: Placebo Quality rating: Fair

Year: 2005 Country: US Funding:

Design:

Study design RCT

DB

Parallel

Setting Multicenter

Eligibility criteria:

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

Comments:

Intervention: Run-in: 3-14

Wash out: NR

Allow other medication: NR

Age: 72.3

Gender: 133 (58 %) Female

Ethnicity: 89.4% caucasian
2.2% black

Number Withdrawn: 21
Lost to fu: NR

2.2% black Lost to tt. 14K 1.3% hispanic Analyzed: 231

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.

				Withdrawals due to AEs/
Drug name	dosage	N=	Duration	Total withdrawal
Eszopiclone	1 mg	72	14 day	1 / NR
Eszopiclone	2 mg	79	14 day	2 / NR
Placebo	NA mg	80	14 day	5 / NR

Author:	Scharf	Trial type:	Plac	ebo					Quality ra	ıting: Fai	r
Year:	2005	Country:	US						Funding:		
# morni	Measurement: ing questionnaire ng questionnaire				Efficac Primary outcome	e Outc		ist:			
						total : wake numb sleep sleep daytii ability sense	sleep tim time after per of away quality depth me alertn y to funct	er sle aker ess ion ical	well-being		
Results											
morning qu	<u>uestionnaire</u>										
# numb	er of awakenings - average	Eszopiclone	1mg	Eszopi	clone 2mg	Placebo)			P value	
		2 (NS) 1.7	(NS)	1.9	(NA)	()	
		Mean (p vs pla	cebo)						_
	quality (0=poor; 10=excellent) -	Eszopiclone	1mg	Eszopi	clone 2mg	Placebo)			P value	
avera	ige	6.6 (NS) 7.2	(0.0006)	6.3	(NA)	()	
		Mean (p vs pla	cebo)						_
	depth (0=very light; 10=very	Eszopiclone	1mg	Eszopi	clone 2mg	Placebo)			P value	
deep)) - average	6.5 (NS	7.1	(0.0015)	6.2	(NA)	()	
		Mean (p vs pla	cebo)			!	l	I	I

Author:	Scharf	Trial type	: Plac	ebo				Qu	ality rati	ng: Fair
Year:	2005	Country:	US	Fui	Funding:					
# sleep la	tency (min) - average	Eszopiclor	ne 1mg	Eszopio	clone 2mg	Placebo				P value
		53.6	(< 0.05) 50	(0.0034)	85.5	(NA)	(()	
		Mean	(p vs pla	cebo)			1		1
# total sle	ep time (min) - average	Eszopiclor	ne 1mg	Eszopio	clone 2mg	Placebo				P value
		349.8	(NS) 372.3	(0.0003)	328.2	(NA)	(()	
		Mean	(p vs pla	cebo)			1		
# wake af	ter sleep onset (min) - average	Eszopiclor	ne 1mg	Eszopio	clone 2mg	Placebo				P value
		72.6	(NS) 58.5	(0.423)	74.1	(NA)	(()	
		Mean	(p vs pla	cebo)					

Trial type: Placebo Quality rating: Fair **Author: Scharf** Year: 2005 Country: US **Funding:** evening questionnaire # daytime alertness (0=drowsy; Eszopiclone 1mg Eszopiclone 2mg Placebo P value 10=alert), average 7.1 (NS) 7.3 (0.0223)6.8 (NA) Mean (p vs placebo # physical well-being (0=poor; Eszopiclone 1mg Eszopiclone 2mg Placebo P value 10=excellent), average 7.5 (NS) 7.7 (0.0474)7.2 (NA) Mean (p vs placebo # morning sleepiness (0=very sleepy; Eszopiclone 1mg Eszopiclone 2mg Placebo P value 10=not at all sleepy), average) 7.2 6.9 (NS (0.054 6.6 (NA) Mean (p vs placebo # daily ability to function (0=poor; Eszopiclone 1mg Eszopiclone 2mg Placebo P value 10=excellent), average 7.4 (NS) 7.6 (0.0579) 7.2 (NA) Mean (p vs placebo Eszopiclone 1mg # number of naps taken, total Eszopiclone 2mg Placebo P value 5.0 (NS) 4.3 (0.0276)5.9 (NA)

Eszopiclone 2mg

Placebo

(NA)

(0.0113) 59.2

P value

duration per nap (min), average

(<0.05 Mean (p vs placebo

(p vs placebo

) 52.7

Mean

47.7

Eszopiclone 1mg

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 nightns, patients had to meet the following criteria: total sleep time of 240 to 420 minutes (4 to 7 hours) in a 480-

Quality rating: Fair Author: Trial type: Placebo Scharf

Year: 1994 Country: US Funding: NR

Design:

Study design RCT

Eligibility criteria:

DB

Parallel

Setting

Multicenter

Age: 38

Range: 22-60 SD: NR

Gender: 48 (64 %) Female

Ethnicity: 73.3% white

26.7% non-white

Exclusion criteria:

Number Screened: 178

Eligible: 75 Enrolled: 75

Number Withdrawn:

Lost to fu: Analyzed:

minute recording on at least 2 or the 3 screening nights, and a latency to persistant 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.

Comments:

Intervention: Run-in: 11

Wash out: 2

Allow other medication: NR

Withdrawals due to AEs/

Drug name	dosage	N=	Duration	Total withdrawal	
Zolpidem	10 mg	26	35 day	0 / 4	
Zolpidem	15 mg	25	35 day	2 / 3	
Placebo	NA mg	24	35 day	0 / 1	

Author:	Scharf_	Trial type	e: Plac	ebo				Quality	rating: Fair	ſ
Year:	1994	Country:	US					Funding	g: NR	
	Measurement:				Efficac Primary	y Outcome Li	st:			
	ing questionnaire				outcom V C		•			
Results										
polysomno	ography									
# sleep	latency (min), week 6	Zolpidem	10mg	Zolpide	m 15mg	Placebo			P value	
										-1
		25.8	(0.063) 28.1	(p<0.05)	48 (NA)	()	
		25.8 Mean	(0.063	<u> </u>	(p<0.05)	48 (NA)	()	
# sleep	efficiency (%), week 6		(p vs pla	acebo	(p<0.05) m 15mg	48 (NA Placebo)	() P value]
# sleep	efficiency (%), week 6	Mean	(p vs pla	acebo)	,)	(P value	_
# sleep	efficiency (%), week 6	Mean Zolpidem	(p vs pla	Zolpide) 87.3) m 15mg	Placebo)	(P value	_
·	efficiency (%), week 6 latency (min), week 6	Mean Zolpidem 87.9	(p vs pla 10mg (0.063 (p vs pla	Zolpide) 87.3) m 15mg	Placebo)	()	
·		Mean Zolpidem 87.9 Mean	(p vs pla 10mg (0.063 (p vs pla	Zolpide) 87.3) m 15mg (p<0.05)	Placebo 80.7 (NA)	(P value) P value)	
·		Mean Zolpidem 87.9 Mean Zolpidem	(p vs pla 10mg (0.063 (p vs pla 10mg	zolpide Zolpide S7.3 acebo Zolpide Zolpide Ar.7) m 15mg (p<0.05)) m 15mg	Placebo 80.7 (NA)	()	
# sleep		Mean Zolpidem 87.9 Mean Zolpidem 47.1	(p vs pla 10mg (0.063 (p vs pla 10mg (NS (p vs pla	Zolpide) 87.3 acebo Zolpide) 20lpide) 47.7 acebo) m 15mg (p<0.05)) m 15mg	Placebo 80.7 (NA)	()	

Author: Scharf_ Trial type: Placebo Quality rating: Fair

'ear:	1994	Country:	US					Fundin	g: N	I R
morning	<u>questionnaire</u>									
# slee	ep latency (min), week 6	Zolpidem ²	10mg	Zolpide	em 15mg		Placebo			P value
		38.4	(NS) 31.7	(<0.05)	56.6 (NA)	()	
		Mean	(p vs plac	cebo)				
	e of falling sleep (0=very easy;	Zolpidem ²	10mg	Zolpide	em 15mg		Placebo			P value
100	=not easy), week 6	50.7	(NS) 35.7	(<0.05)	48.4 (NA)	()	
		Mean	(p vs plac	cebo)				
	ep quality (1=excellent; 4=poor),	Zolpidem ²	10mg	Zolpide	em 15mg		Placebo			P value
wee	ek 6	2.5	(NS) 2.5	(NS)	2.6 (NA)	()	
		Mean	(p vs plac	cebo)				
# tota	I sleep time (min), week 6	Zolpidem ²	10mg	Zolpide	em 15mg		Placebo			P value
		369	(NS) 394	(NS)	356 (NA)	()	
		Mean	(p vs plac	cebo)	1			ļ
# slee	ep latency (min), posttreatment	Zolpidem ²	10mg	Zolpide	em 15mg		Placebo			P value
		62.3	(NS	78.2	(NS)	47.5 (NA)	()	
		Mean	(p vs plac	cebo)				
	e of falling sleep (0=very easy;	Zolpidem ²	10mg	Zolpide	em 15mg		Placebo			P value
100	=not easy), posttreatment	63.7	(NS) 64.0	(<0.05)	44.4 (NA)	()	
		Mean	(p vs plac	cebo)	1			I.
	ep quality (1=excellent; 4=poor),	Zolpidem ²	10mg	Zolpide	em 15mg		Placebo			P value
pos	ttreatment	2.9	(< 0.05	3.1	(< 0.05)	2.6 (NA)	()	
		Mean	(p vs plac	cebo)	1			
# tota	I sleep time (min), posttreatment	Zolpidem ²	10mg	Zolpide	em 15mg		Placebo			P value
		333	(NS) 341	(NS)	333 (NA)	()	
		Mean	(p vs plac	cebo)				1

Author: Scharf_ Trial type: Placebo Quality rating: Fair

Year: 1994 Country: US Funding: NR

tolerance assessment, change from week 2 to week 6

Zolpidem 10mg	Zolpidem 15mg	Placebo		P value
multi-data (NS)	multi-data (NS)	multi-dat (NA)	()	

Mean (p vs placebo

Author: Terzano Trial type: Placebo Quality rating: Poor

Year: 1992 Country: Italy Funding: Partially supported by Italian

Age:

Design:

Study design RCT

DB

Parallel

Setting Single Center

SD: 5.1

49.6

Gender: 8 (67 %) Female

Range: 40-60

Ethnicity: NR

Number Withdrawn: NR Lost to fu: NR

Number Screened: NR

Eligible:

Enrolled:

Analyzed: 12

NR

12

Eligibility criteria:

patients met the criteria for the diagnosis of persistent psychophysiological insomnia and self-reported at least two of the following complaints: difficulties in falling asleep, inadequate sleep length and frequent nocturnal awakenings.

Comments:

Intervention: Run-in: 14

Wash out: NR

Allow other medication: NR

Exclusion criteria:

patients had nocturnal myoclonus or sleep apnea syndrome

Withdrawals due to AEs/ Drug name dosage N= Duration Total withdrawal Zolpidem 10 mg 0 1 day N / NA Placebo NA mg 0 1 day N / NA

Author:	Terzano	Trial type	: Pla	cebo			Quality ra	ting: Poor
Year:	1992	Country:	Italy	1			Funding:	Partially supported by Italian
Outcome	Measurement:				Efficacy	/ Outcome List:		
# polyso	omnography				Primary outcome			
						sleep latency wake after sleep onse total sleep time	et	
Results								
polysomno	<u>graphy</u>							
# sleep	latency (min)	Zolpidem		Placebo				P value
		8.1	(7.1) 14.5	(14)	()	() NR
		Mean	(SD)	 		
# wake	after sleep onset (min)	Zolpidem		Placebo				P value
		16	() 41	()	()	() NR
		Mean	(II.)			
# total s	sleep time (min)	Zolpidem		Placebo				P value
		420	(49.7) 402	(37.9)	()	() NR
		Mean	(SD	ı)			

Quality rating: Poor Walsh Trial type: Placebo Author:

2000a Country: US **Funding:** Year:

Design:

Study design RCT

DB

Parallel

Setting Multicenter

Eligibility 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 tiem between 180 and 360 minutes.

Comments:

Intervention: Run-in: 5-12

Wash out : 5-12

Allow other medication: NR

Age: 67.5

Number Screened: 311 Range: 60-79 Eligible: NR SD: Enrolled:

Gender: 17 (35 %) Female

Number Withdrawn: NR Ethnicity: NR Lost to fu: NR

Analyzed: 48

54

48

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 medicaiton with significant CNS effects within the prior 2 weeks (4 weeks for slowly eliminated drugs such as fluoxtetine); or a history of drug/alcohol abuse within the past 12 months.

				Withdrawals due to AEs/
Drug name	dosage	N=	Duration	Total withdrawal
Zaleplon	2 mg	12	2 day	N / NR
Zaleplon	5 mg	12	2 day	N / NR
Zaleplon	10 mg	12	2 day	N / NR
Placebo	NA mg	12	2 day	N / NR

Author: Walsh Trial type: Placebo Quality rating: Poor

Year: 2000a Country: US Funding:

Outcome Measurement:

polysomnography

questionnaire

Efficacy Outcome List:

Primary

outcome Outcome:

sleep latency
sleep duration

number of awakenings

Results

polysomnography

PSG latency to persistent sleep (min)

PSG total sleep time (min)

PSG no. of awakenings

Zaleplon 2mg	Zaleplon 5mg	Zaleplon 10mg	Placebo	P value
30.4 (0.015)	26.0 (<0.001)	21.8 (<0.00)	47.7 (NA)	

Mean (p vs placebo

 Zaleplon 2mg
 Zaleplon 5mg
 Zaleplon 10mg
 Placebo
 P value

 359.3
 (0.239)
 363.9
 (0.003)
 362.8
 (0.03)
 351.2
 (NA)

Mean (p vs placebo)

 Zaleplon 2mg
 Zaleplon 5mg
 Zaleplon 10mg
 Placebo
 P value

 21.6
 (0.872)
 21.9
 (0.623)
 22.1
 (0.969)
 21.6
 (NA)

Mean (p vs placebo)

335.8

subjective no. of awakenings

Author:	Walsh	Trial type		Quality rating: Poor								
Year:	2000a	Country:	Country: US				Funding:					
questionna	<u>ire</u>											
# subject	ctive sleep latency (min)	Zaleplon 2mg		Zaleplon 5mg		Zaleplon 10mg		Placebo		P value		
		55.2	(0.654)	42.0 (0	017	34.4	(<0.00)	58.3 (NA)		
		Mean	(p vs plac	ebo	,			1				
# subject	ctive total sleep time (min)	Zaleplon 2	mg	Zaleplon 5mg		Zaleplo	on 10mg	Placebo		P value		

(0.140)

(0.776) 343.2 (p vs placebo Mean

> Zaleplon 2mg Zaleplon 5mg Zaleplon 10mg Placebo P value (0.045) 3.3 3.4 (0.671) 3.1 (0.906) 2.8 (NA

351.6

(0.011) 327.9 (NA

(p vs placebo Mean

Author: Walsh_ Trial type: Placebo Quality rating: Fair

Year: 2000b, 2002 Country: US Funding: Lorex Pharmaceuticals

Design:

Study design RCT

DB

Parallel

Setting Multicenter

lticenter

Ethnic

Eligibility criteria:

1) DSM-IV diagnosis of primary insomnia 2) reported sleep latency (SL) > 45 minutes, or totla sleep time (TST) < 6.5 hours, and insomina-related daytime complaints on at least three of the seven baseline days 3) nightly time-in-bed between 6.5 and 9.0 hours; betime and risetime varying by < 3 hours during baseline week. 4) negative pregnancy test, non breast-feeding and, continued contraceptive measures for women of child-bearing potential. 5) absence of a current medical condition, or current or past major psychiatric illness which may influence the study. 6) a Hamilton Depression Scale score < 8 (excluding sleep-related items). 7) no illicit drug use or excessive alcohol use or abuse in the past 12 months. 8) urine drug screen negative for any illicit drug or psychotropic medication. 9) no use of a prescription or non-prescription drugs that affect sleep-wake fucntion within 7 to 25 days (depending on half life), or an investigational drug within 30 days. 10) smoking < 10 cigarettes per day.

Age: 44.1

Range: 21-65 SD: 1.2

Gender: 115 (71 %) Female

Ethnicity: 83.4% caucasian

16.6% other

Exclusion criteria:

NR

Number Screened: 365

Eligible: 163 Enrolled: 163

Number Withdrawn: 29

Lost to fu: 5 Analyzed: NR

Comments:

Patients were instructed to "take the medication when you thini you need it, at bed time, between three and five nights per week".

Intervention:

Run-in: 7 Wash out: 7

Allow other medication: NR

Withdrawals due to AEs/

Drug name	dosage	N=	Duration Total withdrawal
Zolpidem	10 mg	82	56 day 4 / 18
Placebo	NA mg	81	56 day 1 / 10

Author:	Walsh_	Trial type	: Pla	cebo			Quality ra	ating: Fair	
Year:	2000b, 2002	Country:	US				Funding:	Lorex Pharmaceuticals	maceuticals
Outcome	Measurement:				Efficacy	Outcome List:			
# morn	ing quesionnaire				Primary				
# SF-3	6				outcome				
						sleep latency			
						total sleep time number of awakening	9		
						sleep quality	•		
5 4									
Results morning questionniare # sleep latency (min), all condition weeks average # sleep latency (min), with pill, 8 average									
		Zolpidem		Placebo				P value P value o < 0.05 P value o < 0.05	
WEEK	as average	12.39	() 19.55	()	()	() NS	
		Mean	()				
		Zolpidem		Placebo				P value	
avera	age	36.7	() 50.4	()	()	() <0.05	
		Mean	(ı)	I		l l	
# total	sleep time (min), with pill, 8	Zolpidem		Placebo				P value	
week	ks average	415.4	() 364.1	()	()	(
		Mean	(l)				
# numb	per of awakenings, with pill, 8	Zolpidem	`	Placebo				P value	
	s average	1.1	() 1.8	()	()	() <0.05	
		Mean	()				
# sleer	quality (1=excellent; 4=poor),	Zolpidem	`	Placebo	,			P value	
	pill, 8 weeks average	2.1	() 2.5	()	()	() <0.05	
			(, 2.0	\ /	()	'	, 10.00	
		Mean	()				

Author: Walsh_ Trial type: Placebo Quality rating: Fair

Year: 2000b, 2002 Country: US Funding: Lorex Pharmaceuticals

SF-36

quality of life

Zolpidem	Placebo			P value
multi-data ()	multi-data ()	()	()	NS

Mean (

Author: Zammit Trial type: Placebo Quality rating: Fair

Year: 2004 Country: US Funding: Sepracor

Design:

Study design RCT

DB

Parallel

Setting Single Center

Eligibility criteria:

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.

Comments:

Intervention: Run-in: 2

Wash out: 5-7

Allow other medication: NR

Age: 39.8

Range: 21-64 SD: 11.7

Gender: 189 (61 %) Female

Ethnicity: 66.2% caucasians

16.6% black 13% hispanic 4.2% other

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.

Number Screened: NR

Eligible:

Enrolled:

Lost to fu: 0

Analyzed: 308

Number Withdrawn: 16

669

308

Withdrawals due to AEs/

Drug name	dos	age	N=	Duration	Total withdrawal
Eszopiclone	2	mg	104	44 day	3 / 7
Eszopiclone	3	mg	105	44 day	0 / 4
Placebo	NA	mg	99	44 day	0 / 5

Author:	Zammit	Trial type:	Place	ebo					Quality	ratii	ng: Fair	
Year:	2004	Country:	US						Funding	g: S	epracor	
# polys	Measurement:				Prima			ist:				
	ing questionnaire ing questionnaire				outcor	sleep sleep numbe wake quality depth daytin daytin	latency duratior er of aw	akeni er sle p ess	ep onset			
Results polysomne	ograph <u>y</u>											
	o latency (minute) - night 1, 15, verage	Eszopiclone	e 2mg (<0.001)		lone 3mg (<0.001	Placebo 29	(NA)	()	P value	
			(p vs plac		,)				,		1
# sleep avera	o efficiency (%) - night 1, 15, 29	Eszopiclone			lone 3mg	Placebo					P value	
aveid	age	88.1 ((<0.01)	90.1	(<0.001	85.7	(NA)	()		
		Median ((p vs plac	ebo	,)						
	e time after sleep onset, WASO	Eszopiclone	2mg	Eszopic	lone 3mg	Placebo					P value	
(min)	- night 1, 15, 29 average	37.1 ((NS)	33.8	(<0.01	44.1	(NA)	()		
		Median ((p vs plac	ebo)						1
# numb	per of awakenings, NAW - night	Eszopiclone	2mg	Eszopic	lone 3mg	Placebo					P value	
	, 29 average		(NS)	5.7	(NS	6.0	(NA)	()		
		Median ((p vs plac	ebo	,)		ı				

Author:ZammitTrial type:PlaceboQuality rating:FairYear:2004Country:USFunding:Sepracor

Year: 2004	Country: US	Funding: Sepracor
morning questionnaire		
# sleep latency (min)	Eszopiclone 2mg Eszopiclone 3mg Placebo	P value
	30 (<0.000) 27.7 (<0.000) 46 (NA)	()
	Median (p vs placebo)	
# total sleep time (min)	Eszopiclone 2mg Eszopiclone 3mg Placebo	P value
	400 (0.0207) 406 (<0.000) 366 (NA)	()
	Median (p vs placebo)	
# number of awakenings	Eszopiclone 2mg Eszopiclone 3mg Placebo	P value
	2.7 (0.2956) 2.4 (0.1720) 3.0 (NA)	()
	Median (p vs placebo)	
# WASO (min)	Eszopiclone 2mg Eszopiclone 3mg Placebo	P value
	37.1 (0.6884) 30.2 (0.0204) 45 (NA)	()
	Median (p vs placebo)	ı
# quality of sleep (0=poor;	Eszopiclone 2mg Eszopiclone 3mg Placebo	P value
100=excellent)	54.5 (0.0414) 56.6 (0.0072) 47.7 (NA)	()
	Median (p vs placebo)	
# depth of sleep (0=poor;	Eszopiclone 2mg Eszopiclone 3mg Placebo	P value
100=excellent)	58.9 (0.0052) 56.7 (0.0457) 51.7 (NA)	()
	Median (p vs placebo)	

Author:	Zammit	Trial typ	e: Plac	ebo						(Quality	ratin	ng: Fai			
Year:	2004	Country: US									Funding: Sepracor					
evening qu	uestionnaire															
# daytime alertness (higher scores indicate improved function)		Eszopick	one 2mg	Eszopio	clone 3mg		Placebo	Placebo					P value			
		6.66	(0.873) 7.02	(0.059)	6.67	(NA)		()				
		Mean	(p vs pla	cebo)										
	ne ability to function (higher	Eszopick	one 2mg	Eszopio	clone 3mg		Placebo						P value			
score	scores indicate improved function)	6.81	(0.901) 7.15	(0.118)	6.83	(NA)		()				
		Mean)													
	ng sleepiness (1=very sleepy;	Eszopick	one 2mg	Eszopio	clone 3mg		Placebo						P value			
100=r	100=not at all sleepy)		(0.256) 50.8	(0.344)	48.2	(NA)		()				

Evidence Table 14. Placebo controlled trials: Rebound Insomnia

Author: Hedner Trial type: Placebo Quality rating: Fair
Year: 2000 Country: Europe Funding:

Design:

Study design RCT

DB

Parallel

Setting Multicenter

Age: 72.5

Range: 59-95 SD: NR

Gender: NR (%) Female

Ethnicity: NR

Enrolled: 437

Number Screened:

Number Withdrawn: 22 Lost to fu: NR

Eligible:

Analyzed: 422

NR

NR

Eligibility 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 Maunal, 4th edition (DSM-IV; American Psychiatric Association, 1994), was characterised 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.

Exclusion criteria:

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

Comments:

Only analyzed population characteristics were reported: Mean age=72.5 years; 32.3% male; 99% white, 1% black.

Intervention:

Withdrawals due to AEs/

Drug name	dosaç	ge N=	Duration	Total withdrawal	
Zaleplon	5 m	ng 139	14 day	10 / 10	
Zaleplon	10 m	ng 145	14 day	5 / 5	
Placebo	NA m	ng 138	14 day	7 / 7	

Rebound:

sleep questionnaire - rebound insomnia

rebound: subjective sleep latency (min), withdrawal day 1

rebound: subjective total sleep time (min), withdrawal day 1

Zaleplon 5	ōmg		Zaleplor	n 10mg	Placel	00				P value
45	()	50	()	60	()	()	
Median	()						

 Zaleplon 5mg
 Zaleplon 10mg
 Placebo
 P value

 330
 () 300
 () 330
 ())
 ())

Median (

Evidence Table 14. Placebo controlled trials: Rebound Insomnia

Author:	Hedner	Trial type:	Placebo				Quali	ty rating:	Fair	•				
Year:	2000	Country:	Europe							Fund	ing:			
	#	rebound: subjective number of	Zaleplon 5mg		Zaleplon 10mg			Place	ebo				P value	
		awakenings, withdrawal day 1	2	() 2	()	2	()	()		
			Median	()			1				
	inciden	ce of rebound insomnia												
	#	rebound insomnia: subjective sleep	Zaleplon	5mg	Zale	eplon 10m	9	Place	ebo				P value	
		latency	11	(9) 12	(9)	7	(5)	()		
			Number	(%)			*				
	#	rebound insomnia: subjective total	Zaleplon	5mg	Zale	plon 10m	9	Place	ebo				P value	
		sleep time	14	(11) 17	(13)	6	(5)	()		
			Number	(%	.)			*				
	#	rebound insomnia: number of	Zaleplon	5mg	Zale	eplon 10m	9	Place	ebo				P value	
		awakenings	7	(6) 4	(3)	7	(6)	()		
			Number	(%)							

Author: Herrmann Trial type: Placebo Quality rating: Poor

Year: 1993 Country: France Funding: NR

Design:

Study design RCT

DB

Parallel

Setting Single Center

Age: NR

Range: 25-65

SD: NR

Gender: 9 (43 %) Female

Ethnicity: NR

Number Withdrawn: NR Lost to fu: NR

Number Screened: NR

Eligible:

Enrolled:

Analyzed: 21

25

21

Eligibility criteria:

For inclusion in the study, patients had to meet two of the following three polysomnographic criteria: (i) sleep onset latency of more than 30 min; (ii) total sleep time of less than 6 h or time awake more than 1 h; and (iii) five awakenings of at least 5 min each.

Exclusion criteria:

Other criteria were an absence of medical, psychiatric and organic mental disorders, and normal results on routine laboratory testing and on urine drug screeing for amphetaines, cannabinoids, morphine derivatives, barbiturates and benzodiazepines. Patients presenting with caffeinism or alcoholism, or shift workers were excluded.

Comments:

Intervention:

Withdrawals due to AEs/ Drug name N= Duration Total withdrawal dosage Zolpidem 14 day N / NR 10 mg 11 N / NR Placebo NA mg 10 14 day

Rebound:

polysomnography

- # sleep efficiency (%), day 28 wistrawal, rebound
- # total sleep time (min), day 28 wistrawal, rebound
- # sleep onset latency (min), day 28 wistrawal, rebound

Zolpider	n	Place	bo						P value
77.4	(4) 68.9	(4)	()	()	<0.05
Mean	(SD			١			1		,

341.3 (12) 298.3 (21) () () <0.05	Zolpidem		Placebo)						P value
	341.3 (12)	298.3	(21)	()	()	<0.05

Mean	(SD	·)

Zolpidem	Placebo			P value
50.7 (11)	36.3 (7)	()	()	NS

Mean (SD

Author:	Herrma	nn Trial type:	Placebo						Quality	rating:	Poo	r
ear:	1993	Country:	France						Funding: NR			
	#	time awake (min), day 28 wistrawal,	Zolpiden	า	Place	00						P value
		rebound	53.7	(13) 99.3	(17)	()	()	<0.05
			Mean	(SD)		1			
	sleep q	<u>uestionnaire</u>										
	#		Zolpiden	ı	Place	00						P value
			60.8	(14) 70.8	(10)	()	()	NS
			Mean	(SD	•)		•			
	#	total sleep time (min), day 22-28	Zolpidem	า	Place	00						P value
		withdrawal, rebound	341.8	(18) 310.9	(21)	()	()	NS
			Mean	(SD	•)		•			
	#	withdrawal robound	Zolpiden	า	Place	00						P value
			2.4	(0.5) 2.5	(0)	()	()	NS
			Mean	(SD)		-1			

Author: Monti Trial type: Placebo Quality rating: Fair

Year: 1996 Country: Uruguay Funding: NR

Design:

Study design RCT

DB

Parallel

Setting Single Center

Age: 44.25

Range: NR SD: 4.8

Gender: 10 (83 %) Female

Ethnicity: NR

Number Withdrawn: NR

Number Screened:

Eligible:

Enrolled:

Lost to fu: NR Analyzed: 12

NR

NR

12

Eligibility 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 waketime >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.

Comments:

Intervention:

Withdrawals due to AEs/ Drug name N= Duration Total withdrawal dosage Zolpidem 6 27 day N / NR 10 mg N / NR Placebo NA mg 6 27 day

Rebound:

polysomnography

- # stage 2 sleep latency (min), nights 31-33, withdrawal, rebound
- # total number of awakenings, nights 31-33, withdrawal, rebound
- # total wake time (min), nights 31-33, withdrawal, rebound

Zolpidem			Placebo	1						P value	
47.2	(11.1)	32.3	(7.9)	()	()	NS	
Mean	(SD)						

 Zolpidem
 Placebo
 P value

 28.7
 (4.6)
 26.1
 (3.7)
 ()
 ()
 NS

 Zolpidem
 Placebo
 P value

 97.7
 (15.8)
 115.9
 (18.8)
 ()
 ()
 NS

Mean (SD)

(SD

Mean

Author:	Monti	• •	Placebo						-	rating: Fa	air
ear:	1996	Country:	Uruguay						Fundin	g: NK	
	#	wake time after sleep onset (min),	Zolpider	n	Placeb	00					P value
		nights 31-33, withdrawal, rebound	54.9	(16.1	92.0	(16.3)	()	() NS
			Mean	(SD)		-		
	#		Zolpider	n	Placeb	00					P value
		withdrawal, rebound	378.6	(15.3	361.2	(17.9)	()	() NS
			Mean	(SD)		-		<u> </u>
	#	sleep efficiency (%), nights 31-33,	Zolpider	n	Placeb	00					P value
		withdrawal, rebound	79.0	(3.7	75.3	(3.7)	()	() NS
			Mean	(SD	*)		*		
	#	movement time, nights 31-33, withdrawal, rebound	Zolpider	n	Placeb	00					P value
			3.7	(0.8	2.9	(0.7)	()	() NS
			Mean	(SD)		+		
	questic	<u>onnaire</u>									
	#	sleep latency (lower score indicates	Zolpider	n	Placeb	00					P value
		more positive response), night 31-33 withdrawal, rebound	2.4	(0.4	1.9	(0.3)	()	() NS
		•	Mean	(SD)				
	#			n	Placeb	00					P value
		more positive response), night 31-33 withdrawal, rebound	2.1	(0.2	2.4	(0.3)	()	() NS
			Mean	(SD	*)		•		
	#		Zolpider	n	Placeb	00					P value
		indicates mars positive responses	2.3	(0.4	2.6	(0.3)	()	() NS
		3 ,	Mean	(SD)		-		
	#		Zolpider	n	Placeb	00					P value
		indicates more positive response), night 31-33, withdrawal, rebound	64.9	(8.2	63.7	(6.8)	()	() NS
			Mean	(SD	•)		+		

Author:	Monti	Trial type: Placebo	Quality rating: Fair
Year:	1996	Country: Uruguay	Funding: NR

[#] daytime alertness (higher score indicates more positive response), night 31-33, withdrawal, rebound

Zolpiden	n		Placeb	00						P value
73.8	(7.0)	54.1	(7.0)	()	()	<0.05
Mean	(SD)			1		

Trial type: Placebo Author: Monti Quality rating: Poor

Year: 2000 Country: Funding: NR Uruguay

Design:

Study design RCT

DB

Parallel

Setting

Single Center

Age: 51.9

Range: NR SD: 3.6

Gender: 12 (100%) Female

Ethnicity: NR

Number Withdrawn: NR Lost to fu: NR

Number Screened: NR

Eligible:

Enrolled:

Analyzed: 12

NR

12

Eligibility criteria:

Patients aged between 27 and 59 years, with chronic primary insomina 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-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 swere pregnanct women, breast-feeding mothers, subjects deemed insufficiently compliant, or those with clinically significant diviations 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.

Comments:

Intervention:

Withdrawals due to AEs/

Drug name	dos	age	N=	Duration	Total withdrawal
Zolpidem	10	mg	6	15 day	N / NR
Placebo	NA	mg	6	15 day	N / NR

Rebound:

polygraphic sleep record

total sleep time (min) - night 19-21, withdrawal, rebound

Zolpidem	Placebo			P value
334.6 (22)	281.6 (33.2)	()	()	NS

Mean (SD

uthor:	Monti_	Trial type: P	lacebo						Qual	ity rating:	Poo	r	
ear:	2000	Country: U	Jruguay							Funding: NR			
	#	sleep efficiency (%) - night 19-21,	Zolpidem	1	Placeb	0						P value	
		withdrawal, rebound	69.7	(4.6)	58.6	(6.9)	()	()	NS	
			Mean	(SD)		1				
	#	stage 2 sleep latency - night 19-21,	Zolpidem	1	Placeb	0						P value	
		withdrawal, rebound	55.7	(15.7)	69.7	(12.5)	()	()	NS	
			Mean	(SD	')						
	#	total number of awakenings - night	Zolpidem	1	Placeb	0						P value	
		19-21, withdrawal, rebound	25.4	(3.8)	32.2	(5.9)	()	()	NS	
			Mean	(SD)					1	
	#	waking time after sleep onset (min) night 19-21, withdrawal, rebound	Zolpidem	1	Placeb	0						P value	
		night 19-21, withdrawal, rebound	75.1	(7.9)	137.5	(29.2)	()	()	NS	
			Mean	(SD)		1				
	intervie	<u>w</u>											
	#	sleep latency (min) - night 19-21,	Zolpidem	1	Placeb	0						P value	
		withdrawal, rebound	94.3	(48.5)	118.4	(34.2)	()	()	NS	
			Mean	(SD	•)						
	#	sleep duration (min) - night 19-21,	Zolpidem	1	Placeb	0						P value	
		withdrawal, rebound	342.0	(47.5)	207.4	(70.5)	()	()	NS	
			Mean	(SD	*)		1				
	#	disturbed sleep - night 19-21	Zolpidem	1	Placeb	0						P value	
		(1=agree; 100=disagree), withdrawal, rebound	62.7	(11.4)	56.8	(9.3)	()	()	NS	
			Mean	(SD	1)		-				
	#	alert in the morning - night 19-21	Zolpidem	1	Placeb	0						P value	
		(1=agree; 100=disagree), withdrawal, rebound	37.9	(9.5)	61.5	(9.8)	()	()	NS	
			Mean	(SD	•)						

Trial type: Placebo Quality rating: Fair Author: Zammit **Funding: Sepracor** Year: 2004 Country: US

Design:

Study design RCT

DB

Parallel

Single Center Setting

39.8 Age:

> Range: 21-64 SD: 11.7

Gender: 189 (61 %) Female

Ethnicity: 66.2% caucasians

16.6% black 13% hispanic Number Withdrawn: 16

Number Screened: NR

Eligible:

Enrolled:

Lost to fu: 0 Analyzed: 308

P value

669

308

4.2% other

Eligibility criteria:

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.

Comments:

Intervention:

Withdrawals due to AEs/

Drug name	dos	age	N=	Duration	Total withdrawal	
Eszopiclone	2	mg	104	44 day	3 / 7	
Eszopiclone	3	mg	105	44 day	0 / 4	
Placebo	NA	mg	99	44 day	0 / 5	

Rebound:

polysomnography

sleep latency (min), rebound insomnia, change vs baseline

NR (NS -8.5 (<0.05)Mean (p vs baseline

Eszopiclone 3mg

sleep efficiency (%), rebound insomnia, change vs baseline Eszopiclone 2mg P value Eszopiclone 3mg -2.5 (<0.05) 3.7 (<0.05)

Mean (p vs baseline

Eszopiclone 2mg

Author:ZammitTrial type:PlaceboQuality rating:FairYear:2004Country:USFunding:Sepracor

WASO (min), rebound insomnia, change vs baseline

Eszopio	lone 2mg	e 2mg Eszopiclone 3mg						P value	
7	(<0.05)	NR	(NS)	()	()	
Mean	(p vs bas	seline)			H		

Quality rating: Fair **Author:** Allain Trial type: Placebo

Year: 1998 Country: **France** Funding: NR

Design:

Study design RCT

DB

Parallel

Setting

Multicenter

Eligibility criteria:

The subjects were suffering from chronic insomnia, being regularly treated with triazolam. They met the following criteria: male and female volunteers over 18 years of age; receiving out-patient treatment from a GP; taking triazolam (0.25 to 0.50 mg/day) for longer than one month.

Comments:

Intervention: Run-in: 3

Wash out : 3

Allow other medication: NR

51.9 Age:

> Range: 32-84 SD: 16.7

Gender: NR (0 %) Female

Ethnicity: NR

Exclusion criteria:

Patients were not included if any of the following exclusion criteria applied: refusal to participate in the study or susceptiable to non-compliance; shift workers; patients suffering from an identifiable mental disorder or treated fro their sleep disorder with hypnotics other than triazolam 0.25 mg/day; pregnant or breast feeding woemn; liver or respiratory failure, myasthenia, or epilepsy.

Number Screened: NR

Eligible:

Enrolled:

Lost to fu: NR Analyzed: 37

Number Withdrawn: 18

NR

37

				Withdrawals due to AEs/
Drug name	dosage	N=	Duration	Total withdrawal
Zolpidem	10 mg	18	21 day	1 / 1
Placebo	NA mg	19	21 day	17 / 17

Author: Allain Trial type: Placebo Quality rating: Fair

Year: 1998 Country: France Funding: NR

Adverse Events:

adverse events

rebound insomnia

Zolpidem	Placebo			P value:
0 (0)	15 (14)	()	()	

Total (Withdrawal

Author: Allain_ Trial type: Placebo Quality rating: Fair

Year: 2001 Country: France Funding: Sanofi-Synthelabo

Design:

Study design RCT

DB

Parallel

Setting Multicenter

Eligibility criteria:

Patients of either gender (aged 25 to 64 years) with DSM-IV diagnosis of primary insomnia, characterised 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 characterised 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.

Comments:

Zolpidem was administrated as needed, not every night.

Intervention: Run-in: 3-7

Wash out: NR

Allow other medication: NR

Age: 46.1

Range: 25-64 SD: 10.5

Gender: 188 (77 %) Female

Ethnicity: NR

Number Withdrawn: NR

Eligible:

Enrolled:

Lost to fu:

Number Screened:

Analyzed: 245

NR

NR

245

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), anziety (>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 imidazopyridines. 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 abnoea syndrom. Patients who had received benzodiazepines regularly for more than one month, or for more thatn 15 days in the month prior to inclusion, were also excluded from the study, as were patients who consumed large quantities of caffeine.

			Withdrawals due to AEs/
Drug name	dosage N=	Duration	Total withdrawal
Zolpidem	10 mg 124	28 day	1 / 3
Placebo	NA mg 121	28 day	1 / 7

Author: Allain_ Trial type: Placebo Quality rating: Fair

Year: 2001 Country: France Funding: Sanofi-Synthelabo

Adverse Events:

treatment-emergent adverse events

overall

23 (19) 18 (15) Number (%

Placebo

anxiety

 Zolpidem
 Placebo
 P value:

 4
 ()
 0
 ()
 ()
 NR

P value:

NS

% (

Zolpidem

headache

 Zolpidem
 Placebo
 P value:

 3.2
 () 0
 ())
 () NR

% (

rhinitis

 Zolpidem
 Placebo
 P value:

 0
 ()
 3.3
 ()
 ()
 NR

% (

Author: Chaudoir Trial type: Placebo Quality rating: Poor

Year: 1983 Country: UK Funding: NR (May & Baker provided m

Design:

Study design RCT

DB

Crossover

Setting Single Center

Eligibility 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 difficultry in returning to sleep without known cause, or sleeping less than six hours.

Age: 50

Range: 35-65 SD: NR

Gender: 18 (72 %) Female

Ethnicity: NR

Lost to fu: 0 Analyzed: 25

30

25

Number Screened: NR

Number Withdrawn: 5

Eligible:

Enrolled:

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.

Comments:

Crossover design, but the results combined placebo outcomes and treatment outcomes from two groups.

Intervention:

Run-in: NR

Wash out: NR

Allow other medication : N

Withdrawals due to AEs/

Drug name	dosage	N=	Duration	Total withdrawal	
Zopiclone	7.5 mg	25	7 day	2 / 2	
Placebo	NA mg	25	7 day	3 / 3	

Author: Chaudoir Trial type: Placebo Quality rating: Poor

Year: 1983 Country: UK Funding: NR (May & Baker provided m

Adverse Events:

40-item symptom check-list

bitter taste (data NR)

Zopiclone	Placebo							P value:
more () less	()	()	()	NR
Number ()					

overall adverse event

Zopiclo	one		Placel	bo						P value:
5	()	2	()	()	()	NR

Number (

drowsiness/dizziness

Zopiclor	ne		Placebo							P value:
2	()	1	()	()	()	NR

Number (

Author: Dockhorn Trial type: Placebo Quality rating: Fair

Year: 1996 Country: US Funding: Lorex Pharmaceuticals

Design:

Study design RCT

DB

Parallel

Setting Multicenter

Eligibility 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. Insomia 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)

Comments:

Intervention: Run-in: NR

Wash out: NR

Allow other medication: NR

Rar

Age:

Range: 20-55 SD: NR

Gender: 80 (58 %) Female

Ethnicity: NR

32.7

Lost to fu: 2 Analyzed: 136

NR

NR

138

Number Screened:

Eligible:

Enrolled:

Number Withdrawn: 9

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 alcohop 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

				Withdrawals due to AEs/
Drug name	dosage	N=	Duration	Total withdrawal
Zolpidem	10 mg	68	7-10 day	1 / 3
Placebo	NA mg	68	7-10 day	2 / 6

Quality rating: Fair Author: Dockhorn Trial type: Placebo

Funding: Lorex Pharmaceuticals Year: 1996 Country: US

Adverse Events:

verse events		1			
# headache	Zolpidem	Placebo			P value:
	31.9 ()	24.6 ()	()	()	
	% ()			
# drowsiness	Zolpidem	Placebo			P value:
	5.8 ()	1.4 ()	()	()	
	% ()			
# diarrhea	Zolpidem	Placebo			P value:
	4.3 ()	0 ()	()	()	
	% ()			
# dizziness	Zolpidem	Placebo			P value:
	4.3 ()	0 ()	()	()	
	% ()			
# myalgia	Zolpidem	Placebo			P value:
	1.4 ()	4.3 ()	()	()	
	% ()			
# nausea	Zolpidem	Placebo			P value:
	1.4 ()	4.3 ()	()	()	
	% (1			

Author: Dorsey Trial type: Placebo Quality rating: Fair

Year: 2004 Country: US Funding: Sanofi-Synthelabo

Design:

Study design RCT

DB

Parallel

Setting Multicenter

Eligibility criteria:

Women aged 39 to 60 years were eligible to participate in the study if they had developed insomnia in temportal conjuction 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.

Comments:

Intervention: Run-in: 6-14

Wash out: NR

Allow other medication: NR

Age: 50.8

Range: 39-60 SD: 4.5

Gender: 141 (100 %) Female

Ethnicity: NR

Lost to fu: 3 Analyzed: 141

Number Screened: 242

Eligible:

Enrolled:

Number Withdrawn: 16

141

141

Exclusion criteria:

Exclusion criteria included the presence of signs or symptoms of clinical depression, as ascertained by clinical interview and a Beck Depression Inventory socre 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; postive urinte screening test for medication that could interfere with the assessment of study medication, including benzodiazepines, barbituates, 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.

Withdrawals due to AEs/

Drug name	dosage	N=	Duration	Total withdrawal
Zolpidem	10 mg	68	28 day	5 / 11
Placebo	NA mg	73	28 day	2 / 5

Quality rating: Fair Author: Dorsey Trial type: Placebo

Year: 2004 Country: US Funding: Sanofi-Synthelabo

Adverse Events:

verall												
#	headache	Zolpide	m		Placebo							P value:
		36	(52.9)	24	(32.9)	()	()	0.08
		Number	(%)					
#	upper respiratory tract infection	Zolpide	m		Placebo							P value:
		11	(16.2)	5	(6.8)	()	()	0.11
		Number	(%)					
#	drowsiness	Zolpide	m		Placebo							P value:
		7	(10.3)	1	(4)	()	()	0.03
		Number	(%)					
#	dizziness	Zolpide	m		Placebo							P value:
		6	(8.8)	0	(0)	()	()	0.01
		Number	(%)					
#	backache	Zolpide	m		Placebo							P value:
		5	(7.4)	0	(0)	()	()	0.02
		Number	(%		•)					
#	irritability	Zolpide	m		Placebo							P value:
		5	(7.4)	2	(2.7)	()	()	0.02
		Number	(%)		•			•

Author: Goldenberg Trial type: Placebo Quality rating: Poor

Year: 1994 Country: UK, France Funding: NR

Design:

Study design RCT

DB

Parallel

Setting Multicenter

Eligibility 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 wakings; sleep onset latency of 30 minutes or more, or daily symptoms attributable to disturbed sleep.

Age: NR

Range: 25-60 SD: NR

Gender: NR (%) Female

Ethnicity: NR

Number Withdrawn: NR

Number Screened:

Eligible:

Enrolled:

Lost to fu: NR Analyzed: 458

NR

NR

524

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, shiftwork or travelling frequently by air were also excluded from the study, as were those unable to complete the questionnarire or who were planning to go on holibday within the period of the trial.

Comments:

Only analyzed population characteristics were reported: Mean age=42.9 years; 36.4% male; Ethnicity NR.

Intervention:

Run-in: NR

Wash out: NR

Allow other medication :

Withdrawals due to AEs/

Drug name	dosage	N=	Duration	Total withdrawal
Zopiclone	7.5 mg	231	48 day	N / NR
Placebo	NA mg	227	44 day	N / NR

Author: Goldenberg Trial type: Placebo Quality rating: Poor

Year: 1994 Country: UK, France Funding: NR

Adverse Events:

Adverse events

overall reported

dry mouth

bitter taste

 Zopiclone
 Placebo
 P value:

 54
 (20.6)
 30
 (11.5)
 ()
 ()

Number (%

 Zopiclone
 Placebo
 P value:

 10
 ()
 ()
 ()

Number (

 Zopiclone
 Placebo
 P value:

 11 () 0 () ()
 () ()

Number (

Author: Hedner Trial type: Placebo Quality rating: Fair

Year: 2000 Country: Europe Funding:

Design:

Study design RCT

DB

Parallel

Setting Multicenter

Age: 72.5

Range: 59-95 SD: NR

Gender: NR (%) Female

Ethnicity: NR

Number Withdrawn: 22

Eligible:

Enrolled:

Number Screened:

Lost to fu: NR

NR

NR

437

Analyzed: 422

Eligibility 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 Maunal, 4th edition (DSM-IV; American Psychiatric Association, 1994), was characterised 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.

Exclusion criteria:

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

Comments:

Only analyzed population characteristics were reported: Mean age=72.5 years; 32.3% male; 99% white, 1% black.

Intervention:

Run-in: 7

Wash out: 7

Allow other medication: Ni

				Withdrawals due to AEs/
Drug name	dosage	N=	Duration	Total withdrawal
Zaleplon	5 mg	139	14 day	10 / 10
Zaleplon	10 mg	145	14 day	5 / 5
Placebo	NA mg	138	14 day	7 / 7

Author: Hedner Trial type: Placebo Quality rating: Fair

Year: 2000 Country: Europe Funding:

Adverse Events:

treatment-emergent adverse events

overall

withdrawals

Zaleplon	5mg		Zaleplo	n 10mg		Placebo					P value:
68	(48)	59	(40)	74	(51)	()	NS

Number (%

Zaleplo	n 5mg		Zaleplor	n 10mg		Placebo					P value:
10	(7)	5	(3)	7	(5)	()	NS

Number (%

Quality rating: Poor Author: Herrmann Trial type: Placebo

Year: 1993 Country: France Funding: NR

Design:

Study design RCT

DB

Parallel

Single Center Setting

NR Age:

Range: 25-65 SD: NR

Gender: 9 (43 %) Female

Number Withdrawn: NR Ethnicity: NR Lost to fu: NR

Analyzed: 21

25

21

Number Screened: NR

Eligible:

Enrolled:

Eligibility criteria:

For inclusion in the study, patients had to meet two of the following three polysomnographic criteria: (i) sleep onset latency of more than 30 min; (ii) total sleep time of less than 6 h or time awake more than 1 h; and (iii) five awakenings of at least 5 min each.

Comments:

Intervention: Run-in:

Wash out :

Allow other medication :

7

Exclusion criteria:

Other criteria were an absence of medical, psychiatric and organic mental disorders, and normal results on routine laboratory testing and on urine drug screeing for amphetaines, cannabinoids, morphine derivatives, barbiturates and benzodiazepines. Patients presenting with caffeinism or alcoholism, or shift workers were excluded.

				Withdrawals due to AEs/
Drug name	dosage	N=	Duration	Total withdrawal
Zolpidem	10 mg	11	14 day	N / NR
Placebo	NA mg	10	14 day	N / NR

Author: Herrmann Trial type: Placebo Quality rating: Poor

Year: 1993 Country: France Funding: NR

Adverse Events:

adverse events

headache - during treatment

Zolpic	dem		Place	bo						P value:
3	()	4	()	()	()	
Numbe	er ()					

headache - withdrawal

Zolpid	dem		Place	bo						P value:
2	()	1	()	()	()	

Number (

Author: Hindmarch Trial type: Placebo Quality rating: Fair

Year: 1995 Country: UK Funding:

Design:

Study design RCT

DB

Parallel

Setting Multicente

Multicenter

Eligibility criteria:

patients aged between 25 and 60 years suffering from at least two of the following symptoms for two or more weeks: sleep duration less than 6 hours per night; at least 2 nightly awakenings; sleep onset latency of 30 minutes or more; and daily symptoms attributable to sleep disorders.

Comments:

Intervention: Run-in: NR

Wash out: NR

Allow other medication: NI

Age: 42.9

Range: 25-60 SD: 8.9

Gender: NR (0 %) Female

Ethnicity: NR

ty: NR Lost to fu:

Analyzed: 458

NR

458

Number Screened: NR

Eligible:

Enrolled:

Number Withdrawn: NR

Exclusion criteria:

Depression or other psychiatric disorders, alcohol or substance dependency, concurrent medication with CNS effects, acute or chronic illness affecting sleep, important negative life events within the previous month, and pregnancy were considered as exclusion criteria.

				Withdrawals due to AEs/
Drug name	dosage	N=	Duration	Total withdrawal
Zopiclone	7.5 mg	231	48 day	N / NR
Placebo	NA mg	227	42 day	N / NR

Author: Hindmarch Trial type: Placebo Quality rating: Fair

Year: 1995 Country: UK Funding:

Adverse Events:

adverse events

overall drop out

bitter taste

dry mouth

Zolpiden	n	Placebo					P value:
30	(11.5)	54	(20.6)	()	()	NS

Number (%

Zolpide	m		Place	ebo						P value:
11	()	0	()	()	()	

Number (

 Zaleplon
 Placebo
 P value:

 10
 ()
 ()
 ()

Number ()

Author: Krystal Trial type: Placebo Quality rating: Fair

Year: 2003 Country: US Funding: Sepracor

Design:

Study design RCT

DB

Parallel

Setting Multicenter

Eligibility 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.

Comments:

Intervention: Run-in: NR

Wash out: 5-7

Allow other medication: NI

Age: 44

Range: 21-69 SD: 11.3

Gender: 195 (25 %) Female

Ethnicity: 80% caucasian

13.2% african american 7.9% other

Exclusion criteria:

NR

Number Screened: 1194

Eligible: 791 Enrolled: 788

Number Withdrawn: 320 Lost to fu: 60

Analyzed: 788

Withdrawals due to AEs/

Drug name N= Duration Total withdrawal dosage 593 180 day 76 / 235 Eszopiclone 3 mg NA mg 14 / 85 Placebo 195 180 day

Quality rating: Fair Author: **Krystal** Trial type: Placebo US Year: 2003 Country: **Funding: Sepracor Adverse Events:** adverse events # overall Placebo P value: Eszopiclone 81.1 70.8 NR % (# abdominal pain Eszopiclone Placebo P value: (8.1) 11 (5.6 NR Number (% # Accidental injury Eszopiclone P value: Placebo (7.3) 11 (5.6 NR Number (% # asthenia Placebo Eszopiclone P value: (5.6 NR (4.4 11 Number (% # back pain P value: Eszopiclone Placebo (7.6 (3.1 NR Number (% # diarrhea Eszopiclone Placebo P value: 14 (7.2 NR (7.6 Number (% # dizziness Eszopiclone Placebo P value: 58 (9.8) 6 (3.1 NR)

Number (%

Author:	Krystal	Trial type:	Placebo					(Quality i	rating:	Fair	
rear:	2003	Country:	US					F	unding	: Sepra	cor	
	# dry mouth		Eszopio	clone	Placel	00						P value:
			39	(6.6)	3	(1.5)	()	()	NR
			Number	(%	<u> </u>)		·			
	# dyspepsia		Eszopio	clone	Placel	00						P value:
			41	(6.9)	13	(6.7)	()	()	NR
			Number	(%)		·			
	# headache		Eszopio	clone	Placel	00						P value:
			116	(19.6)	37	(19)	()	()	NR
			Number	(%)		Ш			
	# infection		Eszopio	clone	Placel	00						P value:
			94	(15.9)	13	(6.7)	()	()	NR
			Number	(%)		·			<u> </u>
	# nausea		Eszopio	clone	Placel	00						P value:
			67	(11.3)	11	(5.6)	()	()	NR
			Number	(%)					
	# pain		Eszopio	clone	Placel	00						P value:
			67	(11.3)	12.	(6.2)	()	()	NR
			Number	(%)		·			<u> </u>
	# pharyngitis		Eszopio	clone	Placel	00						P value:
			59	(9.9)	10	(5.1)	()	()	NR
			Number	(%)					
	# rash		Eszopio	clone	Placel	00						P value:
			31	(5.2)	6	(3.1)	()	()	NR
			Number	(%	•)					

Author:	Krystal	Trial type:	Placebo					G	uality	rating:	Fair	
Year:	2003	Country:	US							Funding: Sepracor		
	# rhinitis	3	Eszopio	lone	Pla	acebo						P value:
			42	(7.1) 9	(4.6)	()	()	NR
			Number	(%	·)		,			1
	# sinusi	tis	Eszopio	lone	Pla	acebo						P value:
			25	(4.2) 11	(5.6)	()	()	NR
			Number	(%	1)		<u>'</u>			
	# somno	olence	Eszopio	lone	Pla	acebo						P value:
			54	(9.1) 5	(2.6)	()	()	NR
			Number	(%)					1
	# unplea	asant taste	Eszopio	lone	Pla	acebo						P value:
			155	(26.1) 11	(5.6)	()	()	NR
			Number	(%)					П

Quality rating: Fair Trial type: Placebo Author: Lahmeyer

1997 Country: US **Funding: ?orex Pharmaceuticals** Year:

Design:

Study design RCT

DB

Parallel

Setting Multicenter

Eligibility criteria:

Patients had to have a history of a minimum of 3 months of disturbed sleep, characterised by a typical sleep duration of between 4 and 6 hours, a typical sleep latency of at least 30 minutes, and associated daytime complaints.

Comments:

Intervention: Run-in: 3 Wash out:

Allow other medication :

Age: 44.9

Number Screened: 178 Range: 19-61 Eligible: SD: 11.6 Enrolled:

Gender: 81 (56 %) Female

Ethnicity: 92% caucasian

Lost to fu: 0 6% black <1% hispanic Analyzed: 118

33

145

Number Withdrawn: 27

1% asian

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 shortacting CNS medication within 1g 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 yar; (f) had subjective symptons of sleep apnoea; or (g) had nocturnal myoclonus or seizures. Patients who were shiftworkers and women who were breastfeeding were also excluded. In addtion, 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.

Withdrawals due to AEs/

Drug name	dosag	e N=	Duration	Total withdrawal	
Zolpidem	10 m	g 45	31 day	4 / 8	
Zolpidem	15 m	g 46	31 day	3 / 9	
Placebo	NA m	g 54	31 day	0 / 10	

Quality rating: Fair Author: Lahmeyer Trial type: Placebo

Year: 1997 Country: US **Funding: ?orex Pharmaceuticals**

Adverse Events:

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

Author: Monchesky Trial type: Placebo Quality rating: Fair

Year: 1986 Country: Canada Funding: NR

Design:

Study design RCT

DB

Crossover

Setting Single Center

Age: NR

Range: 23-69 SD: NR

Gender: NR (0 %) Female

Ethnicity: NR

Number Withdrawn: 0

Number Screened: NR

Eligible:

Enrolled:

Lost to fu: 2 Analyzed: 91

NR

99

Eligibility 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

Comments:

Zopiclone 7.5mg for run-in and wash-out periods.

Only analyzed population characteristics were reported: Mean age=46.8; 28.6% male; Ethnicity NR.

Intervention:

Run-in: 7 Wash out: 7

Allow other medication :

No use of neuroleptics, sedatives, analgesics, or antidepressants

Withdrawals due to AEs/

Drug name	dosage	N=	Duration	Total withdrawal	
Zopiclone	7.5 mg	91	7 day	N / NR	
Placebo	NA mg	91	7 day	N / NR	

Trial type: Placebo Quality rating: Fair Author: Monchesky Funding: NR Year: 1986 Country: Canada **Adverse Events:** adverse events # headache Zopiclone Placebo P value: 11) 11 Number (# dizziness Zopiclone Placebo P value:) 6 Number (# nausea Zopiclone Placebo P value: Number (# bad/bitter taste Placebo Zopiclone P value: Number (# back pain Zopiclone Placebo P value: Number (# stomach pain P value: Zopiclone Placebo) 2 Number (

Author: Scharf Trial type: Placebo Quality rating: Fair

Year: 2005 Country: US Funding:

Design:

Study design RCT

DB

Parallel

Setting Multicenter

Eligibility criteria:

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

Comments:

Intervention: Run-in: 3-14

Wash out: NR

Allow other medication: NR

Age: 72.3

Gender: 133 (58 %) Female

Ethnicity: 89.4% caucasian

2.2% black

Lost to fu: NR

2.2% black Lost to fu: NR 1.3% hispanic Analyzed: 231

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.

					Withdrawals due to AEs/
Drug name	dos	sage	N=	Duration	Total withdrawal
Eszopiclone	1	mg	72	14 day	1 / NR
Eszopiclone	2	mg	79	14 day	2 / NR
Placebo	NA	mg	80	14 day	5 / NR

Quality rating: Fair Author: Scharf Trial type: Placebo US **Funding:** Year: 2005 Country: **Adverse Events:** adverse events # overall Eszopiclone 1mg Eszopiclone 2mg Placebo P value: 40 43) 40 % # withdrawals due to adverse events Eszopiclone 1mg Eszopiclone 2mg Placebo P value: 1.4 2.5) 6.3 # headache Placebo P value: Eszopiclone 1mg Eszopiclone 2mg 15.3 15.2) 15.0 # unpleasant taste Eszopiclone 1mg Eszopiclone 2mg Placebo P value: 8.3) 1.3 11.4 # somnolence Placebo P value: Eszopiclone 1mg Eszopiclone 2mg 6.9 3.8 8.8 % # dyspepsia Placebo Eszopiclone 1mg Eszopiclone 2mg P value: 5.6) 1.3) 2.5

Author: Scharf_ Trial type: Placebo Quality rating: Fair

Year: 1994 Country: US Funding: NR

Design:

Study design RCT

DB

Parallel

Setting Multicenter

Age: 38

Range: 22-60 SD: NR

Gender: 48 (64 %) Female

Ethnicity: 73.3% white

Exclusion criteria:

26.7% non-white

Number Withdrawn:

Lost to fu: Analyzed:

Number Screened: 178

Eligible:

Enrolled:

75

75

Eligibility 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 nightns, 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 persistant 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.

Comments:

Intervention: Run-in:

Wash out: 2

Allow other medication: NR

11

Withdrawals due to AEs/

Drug name	dosage	N=	Duration	Total withdrawal
Zolpidem	10 mg	26	35 day	0 / 4
Zolpidem	15 mg	25	35 day	2 / 3
Placebo	NA mg	24	35 day	0 / 1

Quality rating: Fair Author: Scharf_ Trial type: Placebo

Funding: NR Year: 1994 Country: US

Adverse Events:

vers	<u>e events</u>					
#	dry mouth	Zolpidem 10mg	Zolpidem 15mg	Placebo		P value:
		0 (0)	2 (8)	0 (0)	()	
		Number (%))		
#	headache	Zolpidem 10mg	Zolpidem 15mg	Placebo		P value:
		2 (8)	4 (16)	7 (29)	()	
		Number (%))		
#	drowsiness	Zolpidem 10mg	Zolpidem 15mg	Placebo		P value:
		3 (12)	5 (20)	2 (8)	()	
		Number (%))		1
#	dizziness	Zolpidem 10mg	Zolpidem 15mg	Placebo		P value:
		3 (12)	4 (16	0 (0)	()	
		Number (%))		1
#	lethargy	Zolpidem 10mg	Zolpidem 15mg	Placebo		P value:
		2 (8)	1 (4) 1 (4)	()	
		Number (%))		1
#	drugged	Zolpidem 10mg	Zolpidem 15mg	Placebo		P value:
		2 (8)	1 (4)	0 (0)	()	
		Number (%))		1
#	confusion	Zolpidem 10mg	Zolpidem 15mg	Placebo		P value:
		0 (0)	2 (8	0 (0)	()	

Number (%

Trial type: Placebo Quality rating: Fair Author: Scharf US Funding: NR Year: 1994 Country: # nausea Zolpidem 10mg Zolpidem 15mg Placebo P value: (4 (12 (4 Number (% # dyspepsia Zolpidem 10mg Zolpidem 15mg Placebo P value: 8) (8) 0 (0 Number (% # arthralgia Zolpidem 10mg Zolpidem 15mg Placebo P value:) 2 (8 (4 (0) Number (% # amnesia Placebo Zolpidem 10mg Zolpidem 15mg P value:) 0 (4) 2 (8 (0) Number (% # rhinitis Zolpidem 10mg Zolpidem 15mg Placebo P value:) 2 (8 (0 (0) Number (%

Author: Walsh_ Trial type: Placebo Quality rating: Fair

Year: 2000b, 2002 Country: US Funding: Lorex Pharmaceuticals

Design:

Study design RCT

DB

Parallel

Setting Multicenter

Age: 44.1

Range: 21-65 SD: 1.2

Gender: 115 (71 %) Female

Ethnicity: 83.4% caucasian

16.6% other

Number Withdrawn: 29 Lost to fu: 5

Number Screened:

Eligible:

Enrolled:

Analyzed: NR

365

163

163

Eligibility criteria:

1) DSM-IV diagnosis of primary insomnia 2) reported sleep latency (SL) > 45 minutes, or totla sleep time (TST) < 6.5 hours, and insomina-related daytime complaints on at least three of the seven baseline days 3) nightly time-in-bed between 6.5 and 9.0 hours; betime and risetime varying by < 3 hours during baseline week. 4) negative pregnancy test, non breast-feeding and, continued contraceptive measures for women of child-bearing potential. 5) absence of a current medical condition, or current or past major psychiatric illness which may influence the study. 6) a Hamilton Depression Scale score < 8 (excluding sleep-related items). 7) no illicit drug use or excessive alcohol use or abuse in the past 12 months. 8) urine drug screen negative for any illicit drug or psychotropic medication. 9) no use of a prescription or non-prescription drugs that affect sleep-wake fucntion within 7 to 25 days (depending on half life), or an investigational drug within 30 days. 10) smoking < 10 cigarettes per day.

Exclusion criteria:

NR

Comments:

Patients were instructed to "take the medication when you thini you need it, at bed time, between three and five nights per week".

Intervention:

Run-in: 7 Wash out: 7

Allow other medication: NR

Withdrawals due to AEs/

Drug name	dosage	N=	Duration	Total withdrawal
Zolpidem	10 mg	82	56 day	4 / 18
Placebo	NA mg	81	56 day	1 / 10

Author: Walsh_ Trial type: Placebo Quality rating: Fair

Year: 2000b, 2002 Country: US Funding: Lorex Pharmaceuticals

Adverse Events:

adverse events

overall

Zolpide	em		Placeb	00						P value:
1	()	4	()	()	()	NS

Number (

Author: Zammit Trial type: Placebo Quality rating: Fair

Year: 2004 Country: US Funding: Sepracor

Design:

Study design RCT

DB

Parallel

Setting Single Center

Eligibility criteria:

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.

Comments:

Intervention: Run-in: 2

Wash out: 5-7

Allow other medication: NR

Age: 39.8

Range: 21-64 SD: 11.7

Gender: 189 (61 %) Female

Ethnicity: 66.2% caucasians

16.6% black 13% hispanic 4.2% other

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.

Number Screened: NR

Eligible:

Number Withdrawn: 16

Enrolled:

Lost to fu: 0

Analyzed: 308

669

308

Drug name	dosage	N=	Duration	Withdrawals due to AEs/ Total withdrawal
Eszopiclone	2 mg	104	44 day	3 / 7
Eszopiclone	3 mg	105	44 day	0 / 4
Placebo	NA mg	99	44 day	0 / 5

Quality rating: Fair Author: Zammit Trial type: Placebo

Year: 2004 Country: US Funding: Sepracor

Adverse Events:

erse events during treatment					
# abnormal dreams	Eszopiclone 2mg	Eszopiclone 3mg	Placebo		P value:
	2 (2)	3 (2.9	2 (1.9)	()	
	Number (%)		
# nervousness	Eszopiclone 2mg	Eszopiclone 3mg	Placebo		P value:
	2 (2)	5 (4.8	0 (0)	()	
	Number (%)		
# back pain	Eszopiclone 2mg	Eszopiclone 3mg	Placebo		P value:
	2 (2)	1 (1) 4 (3.8)	()	
	Number (%)		
# dizziness	Eszopiclone 2mg	Eszopiclone 3mg	Placebo		P value:
	4 (4)	3 (2.9) 5 (4.8)	()	
	Number (%)		
# dry mouth	Eszopiclone 2mg	Eszopiclone 3mg	Placebo		P value:
	2 (2)	5 (4.8) 6 (5.7)	()	
	Number (%)		
# headache	Eszopiclone 2mg	Eszopiclone 3mg	Placebo		P value:
	8 (8.1)	13 (12.5) 12 (11.4)	()	
	Number (%	1)		1
# somnolence	Eszopiclone 2mg	Eszopiclone 3mg	Placebo		P value:
	3 (3)	8 (7.7) 8 (7.6)	()	

Number (%

Author:	Zammit	Trial type:	Placebo			Quality	rating: Fa	ir
Year:	2004	Country:	US			Funding	g: Sepraco	r
	# unplea	asant taste	Eszop	piclone 2mg	Eszopiclone 3mg	Placebo		P value:
			3	(3)	17 (16.3) 35 (33.3)	()
			Numbe	er (%)		
	adverse even	ts after treatment discontin	<u>uation</u>					
	# CNS r	related	Eszop	oiclone 2mg	Eszopiclone 3mg	Placebo		P value:
			11.5	(NS)	15.2 (NS) 18.2 (NA)	()
			%	(p vs pla	cebo)		

Author: Agnoli Trial type: Active Quality rating: Poor

Year: 1989 Country: Rome, Foggia, Italy Funding: Not reported

Internal valididy

Randomization adequate?
 Allocation adequate?
 NR

3. Groups similar at baseline: NR

4. Eligibility criteria specified Yes5. Outcome assessors masked Yes

5. Outcome assessors masked Yes6. Care provider masked NR

7. Patients masked Yes

8. Reporting of Attrition No Crossover No

Adherence No

Contamination No

9. Loss to follow-up

differential/ high No

If Yes, please report:

External valididy

1. Number Screened: NR

Eligible: NR Enrolled: 20

2. Exclusion criteria:

Presence of concomitant general illness; renal or hepatic failure; effectiveness of

placevo administration; and pregnancy.

3. Run-in: 3
Wash out: NR

4. Class naive patients only Yes

5. Controlled group standard of care: Yes

6. Funding: Not reported

10. Intention-to-treat analysis: Unable to determine

11. Postramdomization exclusions: Unable to determine

12. Quality rating: Poor

7. Relevance:

patients with gener

Comment: Poor quality: insufficient information to assess.

Patients with generalized anxiety disorder.

Quality rating: Fair Author: Allain Trial type: Placebo

Year: 1998 Country: **France** Funding: NR

Internal valididy

1. Randomization adequate? NR 2. Allocation adequate? NR 3. Groups similar at baseline: Yes 4. Eligibility criteria specified Yes 5. Outcome assessors masked Yes 6. Care provider masked Yes 7. Patients masked Yes 8. Reporting of Attrition No

Crossover No Adherence No Contamination No

9. Loss to follow-up

differential/ high NR

If Yes, please report:

External valididy

1. Number Screened: NR

> Eligible: NR Enrolled: 37

2. Exclusion criteria:

Patients were not included if any of the following exclusion criteria applied: refusal to participate in the study or susceptiable to non-compliance; shift workers; patients suffering from an identifiable mental disorder or treated fro their sleep disorder with hypnotics other than triazolam 0.25 mg/day; pregnant or breast feeding woemn; liver or respiratory failure, myasthenia, or epilepsy.

3. Run-in: 3 Wash out: 3

4. Class naive patients only NR (all were 5. Controlled group standard of care: NR

6. Funding: NR

10. Intention-to-treat analysis: Unable to determine

11. Postramdomization exclusions: NR

12. Quality rating: Fair Patients discontinui 7. Relevance:

Author:	Allain	Trial type: Placebo	Quality rating: Fair
Year:	1998	Country: France	Funding: NR

r:	1998	Country:	France	Funding: NK					
Inte	ernal valididy		External valididy						
	1. Randomization adequate?	Yes	1. Number Screened:	NR					
	2. Allocation adequate?	NR	Eligible:	NR					
	3. Groups similar at baseline:	Yes	Enrolled:	53					
	4. Eligibility criteria specified	Yes	2. Exclusion criteria:						
	5. Outcome assessors masked	Yes	Current ep	sode having lasted more than three weeks; any secondary insomnia					
	6. Care provider masked	NR		resulting from medicl or psychiatric causes; patients who followed a continuous treatment with the same same hypnotic for more than six months; patients who took hypnotic drugs the day before inclusion; patients who took hypnotic drugs the					
	7. Patients masked	Yes							
	8. Reporting of Attrition	Yes		inclusion, patients currently treated by zolpidem or zaleplon; night-shift					
	Crossover	Yes		nt medical treatment including antidepressants, neuroleptics, anxiolytics,					
	Adherence	Yes	H1 antihist	amines, barbiturates or hypnotics.					
	Contamination	No							
	9. Loss to follow-up differential/ high	No							
	If Yes, please report:								
			3. Run-in:	No					
			Wash out:	No					
			4. Class naive patients	only No					
			5. Controlled group sta	ndard of care: Yes					
			6. Funding: Sanofi-Sy	nthelabo					
	10. Intention-to-treat analysis:	Yes							
	11. Postramdomization exclusions	s: No							
	12. Quality rating:	Fair	7. Relevance:	No (single dose)					

Author: Allain_ Trial type: Placebo Quality rating: Fair

Year: 2001 Country: France Funding: Sanofi-Synthelabo

Internal valididy

Randomization adequate? Allocation adequate? NR

3. Groups similar at baseline: Placebo group lower

4. Eligibility criteria specified Yes
5. Outcome assessors masked Yes
6. Care provider masked NR
7. Patients masked Yes
8. Reporting of Attrition Yes

Crossover No Adherence Yes Contamination No

9. Loss to follow-up

differential/ high Yes

If Yes, please report:

7 placebo and 3 zolpidem withdrew, but report ITT results

10. Intention-to-treat analysis: Yes11. Postramdomization exclusions: No

12. Quality rating: Fair

External valididy

1. Number Screened: NR

Eligible: NR Enrolled: 245

2. 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), anziety (>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 imidazopyridines. 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 abnoea syndrom. Patients who had received benzodiazepines regularly for more than one month, or for more thatn 15 days in the month prior to inclusion, were also excluded from the study, as were patients

3. Run-in: 3-7
Wash out: NR

4. Class naive patients only NR

5. Controlled group standard of care: NR

6. Funding: Sanofi-Synthelabo

7. Relevance: Yes

Comment: Zolpidem was administrated as needed, not every night.

Author: Ancoli-Israel Trial type: H2H Quality rating: Fair

Year: 1999 Country: US Funding: Wyeth-Ayerst

Internal valididy

1. Randomization adequate? NR 2. Allocation adequate? NR 3. Groups similar at baseline: Yes 4. Eligibility criteria specified Yes 5. Outcome assessors masked Yes 6. Care provider masked NR 7. Patients masked Yes 8. Reporting of Attrition Yes

> Crossover No Adherence No Contamination No

9. Loss to follow-up

differential/ high No

If Yes, please report:

External valididy

1. Number Screened: 1224

Eligible: 551 Enrolled: 549

2. 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.

3. Run-in: 7
Wash out: 7-21

4. Class naive patients only No

5. Controlled group standard of care: Yes

6. Funding: Wyeth-Ayerst

10. Intention-to-treat analysis: No11. Postramdomization exclusions: Yes

12. Quality rating: Fair

7. Relevance: Yes

Comment: Elderly

Author: Anderson Trial type: Active Quality rating: Fair

Year: 1987 Country: UK Funding: Not reported

Internal valididy

1. Randomization adequate? NR 2. Allocation adequate? NR 3. Groups similar at baseline: Yes 4. Eligibility criteria specified Yes 5. Outcome assessors masked No 6. Care provider masked NR 7. Patients masked Yes 8. Reporting of Attrition Yes Crossover No

Adherence Yes
Contamination No

Contamination

9. Loss to follow-up

differential/ high Yes

If Yes, please report:

17% who withdrew before taking medication or did not comply excluded from analysis.

External valididy

1. Number Screened: NR

Eligible: NR Enrolled: 119

2. 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 ti drugs or continuous use of high doses of a hypnotic for a period in excess of 6 months. Other groups exluded were pregnant women, nursing mothers, women of childbearing potential, and night shift workers.

3. Run-in: 7
Wash out: 7

4. Class naive patients only No

5. Controlled group standard of care: Yes

6. Funding: Not reported

10. Intention-to-treat analysis: No11. Postramdomization exclusions: Yes

12. Quality rating: Fair 7. Relev

7. Relevance: Yes

Author: Ansoms Trial type: Active Quality rating: Fair

Year: 1991 Country: US Funding: Not reported

Internal valididy

Randomization adequate? Allocation adequate? NR

3. Groups similar at baseline: Yes4. Eligibility criteria specified Yes

5. Outcome assessors masked Yes, but not describe

6. Care provider masked NR

7. Patients masked Yes, but not describe

8. Reporting of Attrition Yes

Crossover No
Adherence No
Contamination No

9. Loss to follow-up

differential/ high Yes

If Yes, please report:

54 enrolled, 27 zopiclone and 25 lormetazepam evaluable, but numbers

randomized not reported.

10. Intention-to-treat analysis: No11. Postramdomization exclusions: Yes

12. Quality rating: Fair

External valididy

1. Number Screened: NR

Eligible: 54 Enrolled: 52

2. 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 flucuating condition with mental or physical stress, or patients with a severe liver or kidney disturbance. Shiftworkers were not included in the study

3. Run-in: 2 Wash out: NR

4. Class naive patients only No

5. Controlled group standard of care: Yes

6. Funding: Not reported

7. Relevance: alcoholism

Quality rating: Poor **Author:** Trial type: Autret Active

Year: 1987 Country: France **Funding:**

Internal valididy **External valididy**

1. Randomization adequate? 1. Number Screened: Not randomized NR 2. Allocation adequate? NR Eligible: NR

3. Groups similar at baseline: NR Enrolled: 121

4. Eligibility criteria specified 2. Exclusion criteria: Yes NR

5. Outcome assessors masked Yes, but not describe

6. Care provider masked NR

7. Patients masked Yes, but not describe

8. Reporting of Attrition Yes

> Crossover No Adherence Yes No

Contamination

9. Loss to follow-up

differential/ high No

If Yes, please report:

3. Run-in:

Wash out: 3

4. Class naive patients only

5. Controlled group standard of care:

6. Funding:

10. Intention-to-treat analysis: Unable to determine

11. Postramdomization exclusions: Unable to determine

12. Quality rating: Poor 7. Relevance:

Poor quality: No baseline characteristics reported, not reported if randomized, and unable to determine the number analyzed.

Author: Begg Trial type: Active Quality rating: Poor

Year: 1992 Country: NR Funding: Roche Products (NZ) Ltd.

Internal valididy

Randomization adequate?
 Allocation adequate?
 Roroups similar at baseline:

4. Eligibility criteria specified Yes5. Outcome assessors masked Yes

6. Care provider masked NR7. Patients masked Yes

8. Reporting of Attrition Yes

Crossover No Adherence Yes Contamination No

9. Loss to follow-up

differential/ high Yes

If Yes, please report:

42% withdrew, but not differential.

External valididy

1. Number Screened: NR

Eligible: NR Enrolled: 88

2. Exclusion criteria:

Patients on medications known to affect sleep or on drugs known to alter drug metabolism during and within two weeks prior to the study were excluded. Alcohol infestion within four hours of retiring or more tna one glass (10 g) alcohol in the previous 24 hours were not permitted.

3. Run-in: 2 Wash out: 2

4. Class naive patients only No5. Controlled group standard of care:6. Funding: Roche Products (NZ) Ltd.

10. Intention-to-treat analysis: No11. Postramdomization exclusions: Yes

12. Quality rating: Poor

7. Relevance:

Comment: Poor quality: very high withdrawal rate (42%) and no intention-to-treat analysis. No information on baseline characteristics.

Author: Bergener Trial type: Active Quality rating: Fair

Year: 1989 Country: German Funding: Not reported

Internal valididy

Randomization adequate?
 Allocation adequate?
 NR

3. Groups similar at baseline: NR

4. Eligibility criteria specified

5. Outcome assessors masked Yes, but not describe6. Care provider masked Yes, but not describe

Yes

7. Patients masked Yes8. Reporting of Attrition Yes

Crossover No Adherence No Contamination No

9. Loss to follow-up

differential/ high Yes

If Yes, please report:

16 of 42 patients (38%) dropped out, but not differential (8 in each group) and

information provided on reasons for dropout.

External valididy

1. Number Screened: NR

Eligible: NR Enrolled: 42

2. Exclusion criteria:

Patients with a history of a delirium or a predelitiumm a severe disease of the heart, liver, or kidney, seizure disorder, endogenous psychosis and treatment with drugs affecting vigilance (reserpine and sedating antihistaminics or barbiturates) were

excluded

3. Run-in: 4
Wash out: 7

4. Class naive patients only NR

5. Controlled group standard of care: Yes

6. Funding: Not reported

10. Intention-to-treat analysis: Unable to determine

11. Postramdomization exclusions: No

12. Quality rating: Fair

7. Relevance:

elderly inpatients

Quality rating: Fair **Author: Bozin-Juracic** Trial type: Active

Year: 1995 Country: Croatia Funding: May and Becker and Rhone-

Internal valididy **External valididy**

Yes

No

1. Number Screened: NR NR NR

Eligible: 32

Enrolled: 29

2. Exclusion criteria:

NR

5. Outcome assessors masked Yes

1. Randomization adequate?

3. Groups similar at baseline:

4. Eligibility criteria specified

2. Allocation adequate?

6. Care provider masked NR 7. Patients masked Yes

8. Reporting of Attrition No

> Crossover No Adherence No

> Contamination No

9. Loss to follow-up

differential/ high No

If Yes, please report:

3. Run-in: 0 Wash out: 0

4. Class naive patients only NR

5. Controlled group standard of care: Yes

6. Funding: May and Becker and Rhone-Poulenc Sante

10. Intention-to-treat analysis: Unable to determine

11. Postramdomization exclusions: Yes

12. Quality rating: Fair Shiftworkers 7. Relevance:

Comment: Not clear if randomized.

Quality rating: Poor Chaudoir Author: Trial type: Placebo

Funding: NR (May & Baker provided m 1983 Country: UK Year:

Internal valididy

External valididy

1. Randomization adequate? NR 1. Number Screened: 2. Allocation adequate? NR Eligible:

Yes

Enrolled: 25

NR 30

4. Eligibility criteria specified Yes

3. Groups similar at baseline:

2. Exclusion criteria:

5. Outcome assessors masked Yes, but not describe

NR 6. Care provider masked

7. Patients masked Yes, but not describe

8. Reporting of Attrition Yes

> Crossover No Adherence No No

Contamination

9. Loss to follow-up

differential/ high Yes

If Yes, please report:

High (16.7%, 2 zopiclone, 3 placebo)

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 analogsia 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.

3. Run-in: NR Wash out: NR

4. Class naive patients only No

placebo)

5. Controlled group standard of care: NR

6. Funding: NR (May & Baker provided medications and

10. Intention-to-treat analysis: No (25/30 analyzed)

11. Postramdomization exclusions: No

12. Quality rating: Poor 7. Relevance: Yes

Crossover design, but the results combined placebo outcomes and treatment outcomes from two groups.

Author:	Chaudoir	Trial type: Placebo	Quality rating: Poor
Year:	1983	Country: UK	Funding: NR (May & Baker provided m

	303	Country. On			I dilding. Wit (way & baker provided in
Internal v	/alididy		External valididy		
1. Rand	lomization adequate?	NR	1. Number Screened:	NR	
2. Alloc	ation adequate?	NR	Eligible:	NR	
3. Grou	ps similar at baseline:	Yes	Enrolled:	38	
4. Eligik	oility criteria specified	Yes	2. Exclusion criteria:		
5. Outco	ome assessors masked	Yes, but not describe	Any seriou	s concomitant disease,	psychosis, hypersensitivity, drug addiction, or
6. Care	provider masked	NR		terfere with assessment; women who were	
7. Patie	nts masked	Yes			ring age intending to become pregnant. No comitant medication known to induce drowsiness.
8. Repo	orting of Attrition	Yes	pationt was	inoladed in taking cont	somitant medication known to induce drowsiness.
	Crossover	No			
	Adherence	No			
	Contamination	No			
9. Loss	to follow-up differential/ high	No			
	If Yes, please report:				
			3. Run-in:	no	
			Wash out:	7	
			4. Class naive patients	only No	
			Controlled group sta	ndard of care: Yes	
			6. Funding: Not report	ed	
10. Inte	ntion-to-treat analysis:	Not clear			
11. Pos	tramdomization exclusion	s: Unable to determine			
12. Qua	ality rating:	Fair	7. Relevance:	Yes	

Author: Dockhorn Trial type: Placebo Quality rating: Fair

Year: 1996 Country: US Funding: Lorex Pharmaceuticals

Internal valididy

1. Randomization adequate? NR 2. Allocation adequate? NR 3. Groups similar at baseline: Yes 4. Eligibility criteria specified Yes 5. Outcome assessors masked Yes 6. Care provider masked NR 7. Patients masked Yes 8. Reporting of Attrition Yes

Crossover No
Adherence No
Contamination No

9. Loss to follow-up

differential/ high No

If Yes, please report:

External valididy

1. Number Screened: NR

Eligible: NR Enrolled: 138

2. 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 alcohop 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

3. Run-in: NR Wash out: NR

4. Class naive patients only NR

5. Controlled group standard of care: NR

6. Funding: Lorex Pharmaceuticals

10. Intention-to-treat analysis: No (136/139 analyzed

11. Postramdomization exclusions: Yes (1 patient)

12. Quality rating: Fair 7. Relevance: Acute insomnia

Author: Dorsey Trial type: Placebo Quality rating: Fair

Year: 2004 Country: US Funding: Sanofi-Synthelabo

Internal valididy

Randomization adequate? Allocation adequate? Groups similar at baseline: Yes

4. Eligibility criteria specified Yes

5. Outcome assessors masked Yes, but not describe

6. Care provider masked NR7. Patients masked Yes8. Reporting of Attrition Yes

Crossover No
Adherence No
Contamination No

9. Loss to follow-up

differential/ high No

If Yes, please report:

External valididy

1. Number Screened: 242

Eligible: 141 Enrolled: 141

2. Exclusion criteria:

Exclusion criteria included the presence of signs or symptoms of clinical depression, as ascertained by clinical interview and a Beck Depression Inventory socre 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; postive urinte screening test for medication that could interfere with the assessment of study medication, including benzodiazepines, barbituates, 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.

3. Run-in: 6-14 Wash out: NR

4. Class naive patients only NR

5. Controlled group standard of care: NR

6. Funding: Sanofi-Synthelabo

10. Intention-to-treat analysis: Yes11. Postramdomization exclusions: No

12. Quality rating: Fair

Relevance:

Women

Author: Drake (1) Trial type: Active Quality rating: Fair

Year: 2000 Country: US Funding: Wyeth-Ayerst Research

Internal valididy

Randomization adequate? Allocation adequate? Groups similar at baseline: NR

4. Eligibility criteria specified Yes

5. Outcome assessors masked Yes, but not describe

6. Care provider masked NR
7. Patients masked Yes
8. Reporting of Attrition Yes

Crossover 0 Adherence No Contamination No

9. Loss to follow-up

differential/ high No

If Yes, please report:

External valididy

1. Number Screened: NR

Eligible: NR Enrolled: 47

2. Exclusion criteria:

Individuals with medical or psychiatric diagnoses (including any history of alcholism 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.

3. Run-in: NR
Wash out: 5-124. Class naive patients only

5. Controlled group standard of care: Ye

6. Funding: Wyeth-Ayerst Research

10. Intention-to-treat analysis: Unable to determine

11. Postramdomization exclusions: No

12. Quality rating: Fair 7. Relevance: Yes

Author: Drake (2) Trial type: Active Quality rating: Fair

Year: 2000 Country: US Funding: Wyeth-Ayerst Research

Internal valididy

Randomization adequate? Allocation adequate? RR Groups similar at baseline: NR

4. Eligibility criteria specified Yes

5. Outcome assessors masked Yes, but not describe

6. Care provider masked NR7. Patients masked Yes8. Reporting of Attrition Yes

Crossover No Adherence No Contamination No

9. Loss to follow-up

differential/ high No

If Yes, please report:

External valididy

1. Number Screened: NR

Eligible: NR Enrolled: 36

2. Exclusion criteria:

Individuals with medical or psychiatric diagnoses (including any history of alcholism 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.

3. Run-in: NR
Wash out: 5-12

4. Class naive patients only No

5. Controlled group standard of care: Yes6. Funding: Wyeth-Ayerst Research

10. Intention-to-treat analysis: Unable to determine

11. Postramdomization exclusions: No

12. Quality rating: Fair 7. Relevance: Yes

Author: Elie Trial type: Active Quality rating: Fair

Year: 1990b Country: Canada Funding: Not reported

Internal valididy

1. Randomization adequate? NR 2. Allocation adequate? NR 3. Groups similar at baseline: NR 4. Eligibility criteria specified Yes 5. Outcome assessors masked Yes 6. Care provider masked NR 7. Patients masked Yes 8. Reporting of Attrition No

Crossover No Adherence No Contamination No

9. Loss to follow-up

differential/ high NR

If Yes, please report:

External valididy

1. Number Screened: NR

Eligible: NR Enrolled: 36

2. 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.

3. Run-in: 7
Wash out: 3

4. Class naive patients only No.

5. Controlled group standard of care: Yes

6. Funding: Not reported

10. Intention-to-treat analysis: Unable to determine11. Postramdomization exclusions: Unable to determine

12. Quality rating: Fair

Relevance:

rance: Yes

Author:ElieTrial type:ActiveQuality rating:FairYear:1990bCountry:CanadaFunding:Not reported

ai.	13300	Country.	Janada	r unumg. Not reported
Int	ernal valididy		External valididy	
	1. Randomization adequate?	NR	1. Number Screened:	NR
	2. Allocation adequate?	NR	Eligible:	NR
	3. Groups similar at baseline:	NR	Enrolled:	44
	4. Eligibility criteria specified	Yes	2. Exclusion criteria:	
	5. Outcome assessors masked	Yes, but not descri		nd neurotic patients, history of blood dyscrasia, neurological disorders,
	6. Care provider masked	NR		ensitivity, chronic alcoholism, drug abuse and coffee or tea abuse.
	7. Patients masked	Yes		h severe medical conditions, those treated with CNS drugs and those eatments which could modify drug kinetics were not accepted.
	8. Reporting of Attrition	No	receiving the	samone who recall meany arag landing were not accepted.
	Crossover	No		
	Adherence	No		
	Contamination	No		
	9. Loss to follow-up differential/ high	NR		
	If Yes, please report:			
			3. Run-in:	7
			Wash out:	4
			4. Class naive patients	only No
			Controlled group star	ndard of care: Yes
			6. Funding: Not reporte	ed
	10. Intention-to-treat analysis:	Yes		
	11. Postramdomization exclusion	s: Unable to determin	e	
	12. Quality rating:	Fair	7. Relevance:	elderly residents of

Comment: Elderly patients living in nursing homes.

Author:	Elie	Trial type:	Active		Quality rating: Fair	
ear:	1990b	Country:	Canada		Funding: Not reported	
Intern	al valididy		External v	alididy		
1. R	Randomization adequate?	NR	1. Numbe	r Screened:	NR	
2. A	Allocation adequate?	NR		Eligible:	NR	
3. G	Groups similar at baseline:	NR		Enrolled:	615	
4. E	Eligibility criteria specified	Yes	2. Exclusi	on criteria:		
5. Outcome assessors masked6. Care provider masked7. Patients masked		Yes		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		
		NR				
		Yes			vith a history or current manifestations of sleep apnea, restless legs e, or a major psychiatric disorder and patients whose raw score on either	
8. R	Reporting of Attrition	Yes			Self-Rating Anxiety Scale or the Zung Self-Rating Deepression Scale was	
	Crossover	No		>49.		
	Adherence	Yes				
	Contamination	No				
9. L	oss to follow-up	No				
	If Yes, please report:					
			3. Run-in:		Yes	
			Wash	out:	Yes	
			4. Class r	naive patients	s only No	
			5. Contro	lled group sta	andard of care: Yes	
			6. Fundin	g: Wyeth-Aye	yerst	
10.	Intention-to-treat analysis:	No				
	Postramdomization exclusion	s: Yes				
12.	Quality rating:	Fair	7. Releva	nce:	Yes	

Comment: Analyzed 574/615 patients randomized. 39 patients excluded from efficacy analysis because of inadequate source documentation. Baseline demographic characteristics given only on 574 patients analyzed, and no statistical analysis of baseline characteristics.

Quality rating: Fair Erman (FDA #190-0 **Author:** Trial type: H2H

Year: NR Country: US **Funding: Sepracor**

Internal valididy

External valididy

1. Randomization adequate? NR 2. Allocation adequate? NR

3. Groups similar at baseline: NR 4. Eligibility criteria specified Yes

5. Outcome assessors masked Yes (but concern re.

6. Care provider masked NR

7. Patients masked Yes (but concern re.

8. Reporting of Attrition No

> Crossover No Adherence No Contamination No

9. Loss to follow-up

differential/ high NR

If Yes, please report:

1. Number Screened:

Eligible:

Enrolled:

2. Exclusion criteria:

NR

3. Run-in:

Wash out:

4. Class naive patients only NR

5. Controlled group standard of care: NR

6. Funding: Sepracor

10. Intention-to-treat analysis: Pts who rec'd at least

11. Postramdomization exclusions: Unable to determine

12. Quality rating: Fair 7. Relevance:

Yes

Author: Fleming Trial type: Active Quality rating: Fair

Year: 1990 Country: Canada Funding: Not reported

Internal valididy

3. Groups similar at baseline:

External valididy

Randomization adequate?
 Allocation adequate?
 NR
 Eligible:
 NR

Enrolled: 52

4. Eligibility criteria specified Yes

Exclusion criteria:

5. Outcome assessors masked Yes, but not describe

NR

6. Care provider masked NR
7. Patients masked Yes
8. Reporting of Attrition Yes

Crossover No Adherence No

Contamination No

9. Loss to follow-up

differential/ high No

If Yes, please report:

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, analgesis, or antidepressants or with a history of hypersensitivity to one or more hypnotic drugs were excluded. Subjects whose insomnnia was considered secondary to a psychiatric or medical disorder were also excluded as those with a history of alcoholism, drug abuse, or caffeine overuse.

3. Run-in: 3
Wash out: 4

4. Class naive patients only No

5. Controlled group standard of care: Yes

6. Funding: Not reported

10. Intention-to-treat analysis: No (48/52 analyzed)

11. Postramdomization exclusions: Yes

12. Quality rating: Fair 7. Relevance: Yes

Comment: Enrolled population characterisics were not reported. Analyzed population characteristics: mean age=45.5 years; 23 (48%) female.

Author:FlemingTrial type:ActiveQuality rating:FairYear:1990Country:CanadaFunding:Not reported

ar:	1990	Country: C	anada Funding: Not reported				
Inte	ernal valididy		External valididy				
	Randomization adequate?	NR	1. Number Screened: 222				
	2. Allocation adequate?	NR	Eligible: 144				
	3. Groups similar at baseline:	Yes	Enrolled: 144				
	4. Eligibility criteria specified	Yes	2. Exclusion criteria:				
	5. Outcome assessors masked	Yes, but not describ	Any significant medical or psychiatric disorder or mental retardation; use of any				
	6. Care provider masked	NR	other investigational drug within 30 days prior to the start of the study; use of				
	7. Patients masked	Yes	flurazepam within 30 days of the first sleep laboratory night; regular use of any medicaiton that would interfere with the assessment, absorbtion or metabolism of				
8. Reporting of Attrition		Yes	the study hypnotic; use of alcohol or short-acting central nervous system				
	Crossover	Yes	medication within 12 hours of any study night; use of triazolam within 4 nights, other				
	Adherence	No	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				
	Contamination	Yes					
9. Loss to follow-up differential/ high		Yes	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				
	If Yes, please report:		initiation.				
	7 (10%) zolpidem vs 1	(3%) flurazepam					
	discontinued		3. Run-in: 1				
			Wash out: NR				
			4. Class naive patients only No				
			5. Controlled group standard of care: Yes				
			6. Funding: Not reported				
	10. Intention-to-treat analysis:	No					
	11. Postramdomization exclusions:	Yes					
	12. Quality rating:	Fair	7. Relevance: Yes				

Quality rating: Fair Author: **Fontaine** Trial type: Active

Year: 1990 Country: Canada **Funding: Rhone-Poulenc Pharma**

Internal valididy

External valididy

1. Randomization adequate? 1. Number Screened: NR 2. Allocation adequate? NR Eligible: NR

Enrolled:

3. Groups similar at baseline: Yes 4. Eligibility criteria specified Yes

5. Outcome assessors masked Yes, but not describe

6. Care provider masked NR 7. Patients masked Yes 8. Reporting of Attrition

Yes Crossover No

Adherence No Contamination No

9. Loss to follow-up

differential/ high No

If Yes, please report:

NR

75

2. 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).

3. Run-in: 7 Wash out: 21

4. Class naive patients only

5. Controlled group standard of care: Yes

Yes

6. Funding: Rhone-Poulenc Pharma

10. Intention-to-treat analysis: Yes

11. Postramdomization exclusions: No

12. Quality rating: Fair 7. Relevance:

Comment: Subgroup: generalized anxiety disorder

Quality rating: Fair Author: Fry Trial type: H2H

Year: 2000 Country: US **Funding: Wyeth-Ayerst**

Internal valididy **External valididy**

1. Randomization adequate? 1. Number Screened: NR NR 2. Allocation adequate? NR Eligible: 830

3. Groups similar at baseline: Enrolled: 595 NR

4. Eligibility criteria specified 2. Exclusion criteria: Yes Patients excluded if they experienced transient insomnia, situational insomnia, or

5. Outcome assessors masked Yes, but not describe

No

No

insomnia associated with sleep-wake schedules (e.g., shift-work) or the use of 6. Care provider masked NR alcohol or drugs. Also excluded were patietns with a history or current

7. Patients masked Yes, but not describe manifestations of sleep apnea, restless legs syndrome, or a major psychiatric 8. Reporting of Attrition Yes

disorder, and patients whose raw score on either the Zung anxiety or depression self-rating scales was 50 or greater. Crossover

No Adherence No

3. Run-in: 7

> Wash out: no

4. Class naive patients only NR 5. Controlled group standard of care:

6. Funding: Wyeth-Ayerst

10. Intention-to-treat analysis: No

Contamination

differential/ high

If Yes, please report:

9. Loss to follow-up

11. Postramdomization exclusions: Yes

12. Quality rating: Fair 7. Relevance: Yes

Patients with mild non-psychotic psychiatric disorders. Comment:

> Baseline characteristics reported only for 586/595 randomized (98%) Data on primary outcome (sleep latency) reported graphically only.

Author: Goldenberg Trial type: Placebo Quality rating: Poor

Year: 1994 Country: UK, France Funding: NR

Internal valididy

Randomization adequate?
 Allocation adequate?
 NR

3. Groups similar at baseline: Yes (for analyzed pop

4. Eligibility criteria specified Yes

5. Outcome assessors masked Yes, but not describe

6. Care provider masked NR
 7. Patients masked Yes
 8. Reporting of Attrition Yes
 Crossover No

Adherence No Contamination No

9. Loss to follow-up

differential/ high Yes

If Yes, please report:

High: 36.8% dropped out; groups not

specified

External valididy

1. Number Screened: NR

Eligible: NR Enrolled: 524

2. 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, shiftwork or travelling frequently by air were also excluded from the study, as were those unable to complete the questionnarire or who were planning to go on holibday within the period of the trial.

3. Run-in: NR Wash out: NR

4. Class naive patients only NR

5. Controlled group standard of care: NR

6. Funding: NR

10. Intention-to-treat analysis: No

11. Postramdomization exclusions: Unable to determine

12. Quality rating: Poor 7. Relevance: Yes

Comment: Only analyzed population characteristics were reported: Mean age=42.9 years; 36.4% male; Ethnicity NR.

Quality rating: Fair **Author:** Hajak Trial type: Active

Year: 1998, 1995, 1994 Country: **Funding: Not reported** Germany

Internal valididy

External valididy

1. Randomization adequate? Yes 2. Allocation adequate? NR

3. Groups similar at baseline: Yes

4. Eligibility criteria specified

5. Outcome assessors masked Yes, but not describe

Yes

6. Care provider masked NR 7. Patients masked Yes 8. Reporting of Attrition Yes

> Crossover No Adherence Yes Contamination No

9. Loss to follow-up

differential/ high No

If Yes, please report:

1. Number Screened: NR

> Eligible: NR Enrolled: 1507

2. Exclusion criteria:

Any patients who had taken a single daily dose of a benzodiazepine or any other hypnotic more than three times per week during the 14 days prior to admission, or any patients with psychiatric disorders (e.g., depression, schizophrenia, severe neuroses), or any patients who had contraindications for zopiclone, flunitrazepam,

or triazolam were excluded from this study

3. Run-in: 7 Wash out: 3

4. Class naive patients only

5. Controlled group standard of care:

6. Funding: Not reported

10. Intention-to-treat analysis: Yes 11. Postramdomization exclusions: No

12. Quality rating: Fair

7. Relevance: Yes

Patients were observed for a further period of 14 days without medication for rebound.

Quality rating: Fair Author: Hayoun Trial type: Active

1989 Funding: Not reported (corresponding Year: Country: France

Internal valididy

External valididy

1. Randomization adequate? NR 1. Number Screened: 2. Allocation adequate? NR

Enrolled:

4. Eligibility criteria specified Yes

Yes

5. Outcome assessors masked Yes, but not describe

NR 6. Care provider masked 7. Patients masked Yes 8. Reporting of Attrition Yes

3. Groups similar at baseline:

Crossover No Adherence No Contamination Yes

9. Loss to follow-up

differential/ high Yes

If Yes, please report:

2 of 68 (3%) triazolam vs 5 of 66 (8%) zopiclone patients discontinued and not

included in analysis.

NR

NR Eligible: 136

2. 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; patiens 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.

3. Run-in: NR Wash out: NR

4. Class naive patients only No

5. Controlled group standard of care:

6. Funding: Not reported (corresponding author from Upjohn)

10. Intention-to-treat analysis: No 11. Postramdomization exclusions: Yes

12. Quality rating: Fair 7. Relevance: Yes

Sleep aid, drug abuse??? Comment:

More patients on zopiclone had insomnia as a major complaint compared with those on triazolam (70%) vs 55%, respectively; p=0.04).

More patients described themselves as tranquil compared with patients on zopiclone.

Author: Hedner Trial type: Placebo Quality rating: Fair

Year: 2000 Country: Europe Funding:

Internal valididy

Randomization adequate?
 Allocation adequate?
 NR

3. Groups similar at baseline: Yes for analyzed pop

4. Eligibility criteria specified Yes

5. Outcome assessors masked Yes6. Care provider masked NR

7. Patients masked Yes8. Reporting of Attrition No

Crossover No Adherence No Contamination No

9. Loss to follow-up

differential/ high NR

If Yes, please report:

External valididy

1. Number Screened: NR

Eligible: NR Enrolled: 437

2. Exclusion criteria:

Patients with a raw score of > 50 on the Zung Anxiety or Depression scales were

not enrolled

3. Run-in: 7Wash out: 74. Class naive patients only

5. Controlled group standard of care:

6. Funding:

10. Intention-to-treat analysis: No (422/437 analyzed

11. Postramdomization exclusions: NR

12. Quality rating: Fair 7. Relevance: Older adults

Comment: Only analyzed population characteristics were reported: Mean age=72.5 years; 32.3% male; 99% white, 1% black.

Quality rating: Poor Author: Trial type: Placebo Herrmann

Year: 1993 Country: **France** Funding: NR

Internal valididy

1. Randomization adequate? NR

2. Allocation adequate? NR 3. Groups similar at baseline: NR

4. Eligibility criteria specified Yes

5. Outcome assessors masked

Yes, but not describe

6. Care provider masked NR 7. Patients masked Yes 8. Reporting of Attrition Yes

> Crossover No Adherence No Contamination No

9. Loss to follow-up

differential/ high Yes

If Yes, please report: 16% not analyzed

External valididy

1. Number Screened: NR

> Eligible: 25 Enrolled: 21

2. Exclusion criteria:

Other criteria were an absence of medical, psychiatric and organic mental disorders, and normal results on routine laboratory testing and on urine drug screeing for amphetaines, cannabinoids, morphine derivatives, barbiturates and benzodiazepines. Patients presenting with caffeinism or alcoholism, or shift workers

were excluded.

3. Run-in: Wash out: 7

4. Class naive patients only NR

5. Controlled group standard of care: NR

6. Funding: NR

10. Intention-to-treat analysis: No (21/25 analyzed)

11. Postramdomization exclusions: Yes (1/25)

12. Quality rating: Poor

7. Relevance: Yes

Author: Hindmarch Trial type: Placebo Quality rating: Fair

Year: 1995 Country: UK Funding:

Internal valididy

Randomization adequate?
 Allocation adequate?
 NR

3. Groups similar at baseline: global QOL score hig

4. Eligibility criteria specified Yes

5. Outcome assessors masked Yes, but not describe

6. Care provider masked NR

7. Patients masked Yes, but not describe

8. Reporting of Attrition Yes

Crossover No Adherence No Contamination No

9. Loss to follow-up

differential/ high Yes

If Yes, please report:

High- 36.8%; groups not specified

External valididy

1. Number Screened: NR

Eligible: NR Enrolled: 458

2. Exclusion criteria:

Depression or other psychiatric disorders, alcohol or substance dependency, concurrent medication with CNS effects, acute or chronic illness affecting sleep, important negative life events within the previous month, and pregnancy were considered as exclusion criteria.

3. Run-in: NR
Wash out: NR4. Class naive patients only

5. Controlled group standard of care:

6. Funding:

10. Intention-to-treat analysis: No

11. Postramdomization exclusions: Unable to determine

12. Quality rating: Fair

7. Relevance:

Author: Klimm Trial type: Active Quality rating: Fair

Year: 1987 Country: France Funding: Not reported

Internal valididy

Randomization adequate? Allocation adequate? NR

3. Groups similar at baseline: Yes

4. Eligibility criteria specified Yes

5. Outcome assessors masked Yes, but not describe

6. Care provider masked NR
7. Patients masked Yes
8. Reporting of Attrition Yes

Crossover No Adherence Yes Contamination No

9. Loss to follow-up

differential/ high No

If Yes, please report:

External valididy

1. Number Screened: NR

Eligible: NR Enrolled: 74

2. Exclusion criteria:

Patients presenting contraindictions 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.

3. Run-in: 7
Wash out: 7

4. Class naive patients only No

5. Controlled group standard of care: Yes

6. Funding: Not reported

10. Intention-to-treat analysis: No11. Postramdomization exclusions: No

12. Quality rating: Fair

Relevance:

elderly patients

Comment:

no psychotropic or centrally active drugs were allowed, but medication for concomitant disease were continued, including antihypertensices, non-steroidal anti-inflammatory drugs, hypoglycemic agents, uricosuric agents, anti-anginal agents, and hypolipidaemic agents.

Quality rating: Fair **Author: Krystal** Trial type: Placebo

Year: 2003 Country: US **Funding: Sepracor**

Internal valididy

External valididy

1. Randomization adequate? 1. Number Screened: NR 1194 2. Allocation adequate? NR

3. Groups similar at baseline: weight and BMI > in e Enrolled:

4. Eligibility criteria specified Yes 2. Exclusion criteria:

5. Outcome assessors masked Yes 6. Care provider masked NR

7. Patients masked Yes 8. Reporting of Attrition Yes

Crossover No Adherence No

Contamination No

9. Loss to follow-up

differential/ high No

If Yes, please report:

Eligible: 791 788

NR

3. Run-in: NR Wash out: 5-7

4. Class naive patients only NR

5. Controlled group standard of care: NR

6. Funding: Sepracor

10. Intention-to-treat analysis: Yes

11. Postramdomization exclusions: 3 patients discontinue

12. Quality rating: Fair 7. Relevance: Yes

Author: Lahmeyer Trial type: Placebo Quality rating: Fair

Year: 1997 Country: US Funding: ?orex Pharmaceuticals

Internal valididy

1. Randomization adequate? NR 2. Allocation adequate? NR 3. Groups similar at baseline: Yes 4. Eligibility criteria specified Yes 5. Outcome assessors masked Yes 6. Care provider masked NR 7. Patients masked Yes 8. Reporting of Attrition Yes Crossover No Adherence Yes Contamination No

9. Loss to follow-up

differential/ high Yes

If Yes, please report:

High- 19% discontinued; not differential

10. Intention-to-treat analysis: No11. Postramdomization exclusions: No

12. Quality rating: Fair

External valididy

1. Number Screened: 178

Eligible: 33 Enrolled: 145

2. 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 shortacting 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 yar; (f) had subjective symptons 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.

3. Run-in: 3 Wash out: 4

4. Class naive patients only NR

5. Controlled group standard of care: Yes

6. Funding: ?orex Pharmaceuticals

7. Relevance: Yes

Author: Lemoine Trial type: H2H Quality rating: Fair

Year: 1995 Country: France Funding: Not reported

Internal valididy

Randomization adequate? Allocation adequate? Groups similar at baseline:

4. Eligibility criteria specified

5. Outcome assessors masked Yes
 6. Care provider masked NR
 7. Patients masked Yes
 8. Reporting of Attrition Yes

Crossover No Adherence No

Contamination No

9. Loss to follow-up

differential/ high No

If Yes, please report:

External valididy

1. Number Screened: NR

Eligible: NR Enrolled: 394

2. Exclusion criteria:

History of depression or other psychiatric disorder, a current depressive episode (total score on the QD2A questionnaire >=7) or any other current psychiatric disorder, severe and evolving physical illness, dementia, alcoholism, drug abuse, or acute pain. Patients were also excluded if they had been taking any psychotropic drug (with the exception of zopiclone or zolpidem) within the previous two weeks. Women were excluded if pregnant or were likely to be or were breast-feeding.

3. Run-in: 0
Wash out: 0

4. Class naive patients only No

5. Controlled group standard of care: Yes

Yes

6. Funding: Not reported

10. Intention-to-treat analysis: No11. Postramdomization exclusions: No

12. Quality rating: Fair 7. Relevance:

Comment: Study of withdrawal effects- separate studies of zopiclone and zolpidem; efficacy not assessed. Comparisons were treatment vs withdrawal within drug groups.

Quality rating: Fair **Author:** Leppik Trial type: Active

Year: 1997 Country: US **Funding: Lornex Pharmaceuticals**

Internal valididy

1. Randomization adequate? NR 2. Allocation adequate? NR 3. Groups similar at baseline: Yes 4. Eligibility criteria specified Yes

5. Outcome assessors masked

Yes, but not describe

6. Care provider masked NR 7. Patients masked Yes 8. Reporting of Attrition Yes Crossover No

Adherence No Contamination No

9. Loss to follow-up

differential/ high No

If Yes, please report:

External valididy

1. Number Screened: NR

> Eligible: 457 Enrolled: 335

2. 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 addtion, 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.

3. Run-in: 7 Wash out:

4. Class naive patients only

5. Controlled group standard of care:

6. Funding: Lornex Pharmaceuticals

10. Intention-to-treat analysis: Yes 11. Postramdomization exclusions: No

12. Quality rating: Fair 7. Relevance: Elderly

Author: Li Pi Shan Trial type: Active Quality rating: Fair

Year: 2004 Country: Canada Funding: Not reported

Internal valididy

Randomization adequate? Allocation adequate? Roroups similar at baseline:

4. Eligibility criteria specified Yes

5. Outcome assessors masked Yes6. Care provider masked Yes

7. Patients masked Yes8. Reporting of Attrition Yes

Crossover No

Adherence No Contamination No

9. Loss to follow-up

differential/ high No

If Yes, please report:

External valididy

1. Number Screened: 44

Eligible: 27 Enrolled: 18

2. Exclusion criteria:

Patients were excluded if they were acutely ill, unable to communicate either in English or French, or unable to ead and answer questions for any other reason (severe aphasia, blindness, severe cognitive impairment, including patients with posttraumatic amnesia). Subjects were also> 18 years of age. The patients were not excluded if they experienced any secondary causes of insomnia such as depression, sleep apnea, or restless legs syndrome.

3. Run-in: 0
Wash out: 0

4. Class naive patients only No

5. Controlled group standard of care: Yes

6. Funding: Not reported

10. Intention-to-treat analysis: No11. Postramdomization exclusions: No

12. Quality rating: Fair 7. Relevance: Inpatients with stro

Comment:

Although there was no formal washout period between weeks 1 and 2, the questionnaire was not administered on any of the first 3 days to allow for a washout of the medication taken during week 1.

Any additional medications the patients were receiving were maintained constant throughout the trial. Those whose medications changed over the course of the study were excluded.

Quality rating: Poor Author: Liu Trial type: Active

Year: 1997 Country: Taiwan **Funding:**

Internal valididy **External valididy**

1. Randomization adequate? 1. Number Screened: NR NR NR

2. Allocation adequate? NR Eligible: 3. Groups similar at baseline: NR Enrolled:

4. Eligibility criteria specified 2. Exclusion criteria: Yes

5. Outcome assessors masked Yes, but not describe Patients with psychoses or mood disorders, history of severe physical illness,

15

alcohol abouse or drug abuse. 6. Care provider masked NR

7. Patients masked Yes, but not describe

8. Reporting of Attrition Yes

> Crossover No Adherence Yes No

Contamination

9. Loss to follow-up

differential/ high Yes

If Yes, please report:

8 patients did not finish the trial due to lack

of compliance.

3. Run-in: 0 Wash out: 7

4. Class naive patients only

5. Controlled group standard of care:

6. Funding:

10. Intention-to-treat analysis: Unable to determine

11. Postramdomization exclusions: Unable to determine

12. Quality rating: Poor 7. Relevance:

Poor quality- baseline characterisitis not reported, no information on randomization and allocation concealment methods. Unable to determine if an Comment: intention-to-treat analysis was used, and high loss to followup. (8 patients did not complete the trial; unclear if 8 of 15 or 8 of 23).

Author: Mamelak Trial type: Active Quality rating: Fair

Year: 1987 Country: Canada Funding: Not reported

Internal valididy

Randomization adequate?
 NR
 Allocation adequate?
 NR
 Groups similar at baseline:
 NR
 Fligibility criteria specified.

4. Eligibility criteria specified Yes5. Outcome assessors masked Yes

6. Care provider masked NR7. Patients masked Yes

8. Reporting of Attrition No Crossover No

Adherence No Contamination No

9. Loss to follow-up

differential/ high No

If Yes, please report:

External valididy

1. Number Screened: NR

Eligible: NR Enrolled: 30

2. 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.

3. Run-in: 2 Wash out: 3

4. Class naive patients only No.

5. Controlled group standard of care: Yes

6. Funding: Not reported

10. Intention-to-treat analysis: Unable to determine

11. Postramdomization exclusions: Unable to determine

12. Quality rating: Fair

7. Relevance:

assessments perfo

Comment: Ethanol-drug interaction study.

Author: Monchesky Trial type: Placebo Quality rating: Fair

Year: 1986 Country: Canada Funding: NR

Internal valididy

External valididy

Randomization adequate?
 Allocation adequate?
 NR

1. Number Screened: NR Eligible: NR

3. Groups similar at baseline: Yes (for 91/99 analyz

NR

Enrolled: 99

4. Eligibility criteria specified Yes

Exclusion criteria:

5. Outcome assessors masked Yes, but not describe

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

7. Patients masked Yes8. Reporting of Attrition Yes

hemogram values; and an established diagnosis of sleep apnea

Crossover No Adherence No Contamination No

9. Loss to follow-up

6. Care provider masked

differential/ high

Unable to determine

If Yes, please report:

3. Run-in: 7
Wash out: 7

4. Class naive patients only NR

5. Controlled group standard of care: NR

6. Funding: NR

10. Intention-to-treat analysis: No (91/99 analyzed)

11. Postramdomization exclusions: 1/99

12. Quality rating: Fair 7. Relevance: Yes

Comment: Zopiclone 7.5mg for run-in and wash-out periods.

Only analyzed population characteristics were reported: Mean age=46.8; 28.6% male; Ethnicity NR.

Author: Monti Trial type: Active Quality rating: Fair

Year: 1994 Country: Uruguay Funding: Not reported

Internal valididy

_,

Randomization adequate?
 Allocation adequate?
 Roroups similar at baseline:

Yes Yes

Yes, but not describe

4. Eligibility criteria specified

5. Outcome assessors masked

6. Care provider masked NR

7. Patients masked Yes8. Reporting of Attrition Yes

Crossover Yes Adherence Yes

Contamination Yes

9. Loss to follow-up

differential/ high No

If Yes, please report:

External valididy

1. Number Screened: NR

Eligible: NR Enrolled: 24

2. 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.

3. Run-in: 3 Wash out: 3

4. Class naive patients only No

5. Controlled group standard of care: Yes

6. Funding: Not reported

10. Intention-to-treat analysis: Yes11. Postramdomization exclusions: No

12. Quality rating: Fair

7. Relevance:

e: Yes

Author: Monti Trial type: Active Quality rating: Fair
Year: 1994 Country: Uruguay Funding: Not reported

r: 1994	Country: Uru	iguay Funding: Not reported
Internal valididy		External valididy
1. Randomization adequate?	NR	1. Number Screened: NR
2. Allocation adequate?	NR	Eligible: NR
3. Groups similar at baseline:	Yes	Enrolled: 12
4. Eligibility criteria specified	Yes	2. Exclusion criteria:
5. Outcome assessors masked	Yes, but not describe	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.
6. Care provider masked	NR	
7. Patients masked	Yes	
8. Reporting of Attrition	No	
Crossover	No	
Adherence	No	
Contamination	No	
9. Loss to follow-up differential/ high If Yes, please report:	No	
		3. Run-in: 2
		Wash out: 3
		4. Class naive patients only Yes
		5. Controlled group standard of care: Yes
		6. Funding: NR
10. Intention-to-treat analysis:	Yes	·
11. Postramdomization exclusion		
12. Quality rating:	Fair	7. Relevance: Yes
12. Quality fating.	ı ail	7. Notovariot. 165

Quality rating: Poor Author: Monti Trial type: Placebo

2000 Country: Funding: NR Year: Uruguay

Internal valididy

1. Randomization adequate? No (sequential order) No (randomized in se 2. Allocation adequate?

3. Groups similar at baseline: Lower weight in zolpid

4. Eligibility criteria specified Yes 5. Outcome assessors masked Yes 6. Care provider masked NR 7. Patients masked Yes 8. Reporting of Attrition No

> Crossover No Adherence No Contamination No

9. Loss to follow-up

differential/ high NR

If Yes, please report:

External valididy

1. Number Screened: NR

> NR Eligible: Enrolled: 12

2. 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 sleep apnea were excluded from the study, as also swere pregnanct women, breast-feeding mothers, subjects deemed insufficiently compliant, or those with clinically significant diviations 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

3. Run-in: Wash out: 3

4. Class naive patients only

5. Controlled group standard of care: NR

6. Funding: NR

10. Intention-to-treat analysis: Unable to determine

11. Postramdomization exclusions: Unable to determine

12. Quality rating: Poor 7. Relevance: Women

Author: Nair Trial type: Active Quality rating: Fair

Year: 1990 Country: Canada Funding: Rhone-Poulenc Pharma

Internal valididy

Randomization adequate? Allocation adequate? Groups similar at baseline: Eligibility criteria specified

5. Outcome assessors masked Yes, but not describe

6. Care provider masked NR
7. Patients masked Yes
8. Reporting of Attrition Yes
Crossover 0

Adherence Yes
Contamination No

9. Loss to follow-up

differential/ high No

If Yes, please report:

External valididy

1. Number Screened: NR

Eligible: NR Enrolled: 60

2. 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.

3. Run-in: 1
Wash out: NR

4. Class naive patients only No

5. Controlled group standard of care: Yes

6. Funding: Rhone-Poulenc Pharma

10. Intention-to-treat analysis: No11. Postramdomization exclusions: No

12. Quality rating: Fair 7.

7. Relevance:

Author: Ngen Trial type: Active Quality rating: Fair

Year: 1990 Country: Malaysia Funding: Rhone-Poulenc Pharma

Internal valididy

1. Randomization adequate? Yes2. Allocation adequate? Yes

3. Groups similar at baseline:

4. Eligibility criteria specified

5. Outcome assessors masked Yes6. Care provider masked NR7. Patients masked Yes

8. Reporting of Attrition

Crossover 0 Adherence

Contamination

9. Loss to follow-up

differential/ high Yes

If Yes, please report:

27% discontinued, but not differential (7 placebo, 5 zopiclone, 4 temazepan)

External valididy

1. Number Screened: NR

Eligible: NR Enrolled: 60

2. Exclusion criteria:

(a) serious concomitant disease, (b) likely to require concomitant medication known

to cause drwosiness, (c) psychosis, (d) a history of hypersensitivity to

benzodiazepines, (e) drug and/or alcohol abuse, (f) pregnant, a nursing mother or

intending to become pregnant during the study, (g) working night shifts

3. Run-in: 7
Wash out: NR

4. Class naive patients only No

5. Controlled group standard of care: Yes

6. Funding: Rhone-Poulenc Pharma

10. Intention-to-treat analysis: No11. Postramdomization exclusions: No

12. Quality rating: Fair

7. Relevance: Yes

Quality rating: Fair Author: **Pagot** Trial type: Active

1993 Country: **France Funding: Not reported** Year:

Internal valididy

1. Randomization adequate? NR 2. Allocation adequate? NR 3. Groups similar at baseline: Yes 4. Eligibility criteria specified Yes

5. Outcome assessors masked Yes, but not describe

6. Care provider masked NR 7. Patients masked Yes 8. Reporting of Attrition Yes Crossover No

Adherence No Contamination No

9. Loss to follow-up

differential/ high Yes

If Yes, please report:

32% zolpidem and 38% triazolam dropped

out

External valididy

1. Number Screened: NR

> Eligible: NR Enrolled: 95

2. Exclusion criteria:

Patients who showed sleep disorders associated with severe psychiatric disorders, sleep apnea, sleep-related myoclonus, or insomnia that had developed during childhood, and those who showed serious medical disease or needed concomitant hypnotic medication or treatment that could have had an influence on sleep onset were excluded. Pregnant women and women of childbearing potential who were not taking adequate contraceptive precautions were also excluded, as were nursing mothers and those patients in whom adequate compliance could not be expected. Patients were excluded if they were receiving any treatment that could have an

influence on sleep onset.

3. Run-in: 4 Wash out: 30

4. Class naive patients only

5. Controlled group standard of care:

6. Funding: Not reported

10. Intention-to-treat analysis: No 11. Postramdomization exclusions: No

12. Quality rating: Fair

7. Relevance:

patients with anxiet

Quality rating: Fair Author: **Perlis** Trial type: Placebo

2004 Country: US **Funding: Lorex Pharmaceuticals** Year:

Internal valididy

External valididy

1. Randomization adequate? Yes 2. Allocation adequate? Yes

Enrolled: 3. Groups similar at baseline: More women in place

4. Eligibility criteria specified Yes 5. Outcome assessors masked Yes 6. Care provider masked NR 7. Patients masked Yes 8. Reporting of Attrition Yes

> Crossover No Adherence Yes Contamination Yes

9. Loss to follow-up

Comment:

differential/ high No

If Yes, please report:

1. Number Screened: 322

277 Eligible:

199

2. Exclusion criteria:

Exclusion criteria included presene 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; postiive urine screen for medication that could interfere with the assessment of study medication; history of drug addiciton, alcoholism, or drug abuse; and histroy 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.

3. Run-in: 6-14 Wash out: NR

4. Class naive patients only

5. Controlled group standard of care: 6. Funding: Lorex Pharmaceuticals

10. Intention-to-treat analysis: No 11. Postramdomization exclusions: No

12. Quality rating: Fair 7. Relevance:

Patients were instructed to "take the medication when you think you need it, at bedtime, for a total of between 3 and 5 capsules per week". They were also told to take only 1 pill per night and not to use the study medication to treat early awakenings.

Author: Ponciano Trial type: Active Quality rating: Fair

Year: 1990 Country: Portugal Funding: Not reported

Internal valididy

Randomization adequate? Allocation adequate? Groups similar at baseline: Eligibility criteria specified

5. Outcome assessors masked Yes6. Care provider masked NR

7. Patients masked Yes8. Reporting of Attrition Yes

Crossover No Adherence No Contamination No

9. Loss to follow-up

differential/ high No

If Yes, please report:

External valididy

1. Number Screened: NR

Eligible: NR Enrolled: 26

2. 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 medicaiton to be used were excluded. Patients with a history of drug use, those with excessive alcohol comsumption (<1 litre of wine/day, or equivalent) pregnant or nursing women and all females of child bearing age without adequate contraception were also excluded.

3. Run-in: 7
Wash out: 7

4. Class naive patients only No

5. Controlled group standard of care: Yes

6. Funding: Not reported

10. Intention-to-treat analysis: Yes11. Postramdomization exclusions: No

12. Quality rating: Fair

7. Relevance: Yes

Comment: Results were reported in figures only. Therefore, the data reported in the evidence table were estimated from the figures.

Author: Quadens Trial type: Active Quality rating: Poor

Year: 1983 Country: Belgium Funding: Not reported

Internal valididy External valididy

1. Randomization adequate? NR 1. Number Screened: NR 2. Allocation adequate? NR Eligible: NR

3. Groups similar at baseline: NR Enrolled:

4. Eligibility criteria specified Yes 2. Exclusion criteria:

5. Outcome assessors masked Yes, but not describe (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

8. Reporting of Attrition
No
Crossover
No

the absorption, metabolism, or excretion of the drugs and susceptible to alter the evaluation of the hypnotic effects.

12

Adherence No

differential/ high NR
If Yes, please report:

No

3. Run-in: 6 Wash out: 35

4. Class naive patients only NR

5. Controlled group standard of care: Yes

6. Funding: Not reported

10. Intention-to-treat analysis: Unable to determine

11. Postramdomization exclusions: Unable to determine

Contamination

9. Loss to follow-up

12. Quality rating: Poor 7. Relevance: postmenopausal w

Comment: Poor quality- insufficient information to assess quality.

Author: Roger Trial type: Active Quality rating: Fair

Year: 1993 Country: France Funding: Not reported

Internal valididy

External valididy

1. Randomization adequate?NR1. Number Screened:NR2. Allocation adequate?NREligible:NR

3. Groups similar at baseline: Yes Enrolled:4. Eligibility criteria specified Yes 2. Exclusion criteria:

4. Eligibility criteria specified
 5. Outcome assessors masked
 Yes
 Exclusion criteria:
 Patients were not included if they had concomitant heart or respiratory failure,

6. Care provider masked

Yes, but not describe

concurrent malignant or severe disease, history of cerebrovascular accident or transient ischemic accidents, or concurrent requirement for benzodiazepines.

7. Patients masked Yes
8. Reporting of Attrition Yes

Crossover No Adherence No

Contamination No

9. Loss to follow-up

differential/ high No

If Yes, please report:

3. Run-in: 3
Wash out: 7

4. Class naive patients only No

5. Controlled group standard of care: Yes

221

6. Funding: Not reported

10. Intention-to-treat analysis: Unable to determine

11. Postramdomization exclusions: No

12. Quality rating: Fair 7. Relevance: Elderly inpatients

Comment: Inpatients at geriatric wards.

Quality rating: Poor Author: Rosenberg Trial type: Active

1994 Country: Funding: Synthelabo Scandinavia A/S Year: Denmark

Internal valididy

1. Randomization adequate? Yes 2. Allocation adequate? Yes 3. Groups similar at baseline: NR 4. Eligibility criteria specified Yes 5. Outcome assessors masked Yes 6. Care provider masked Yes 7. Patients masked Yes

> Crossover No Adherence No Contamination No

Yes

9. Loss to follow-up

8. Reporting of Attrition

differential/ high Yes

If Yes, please report:

19% excluded due to lack of data or protocol violations (16 zolpidem, 23 triazolzam, number randomized not

reported by group)

10. Intention-to-treat analysis: No 11. Postramdomization exclusions: Yes

12. Quality rating: Poor

External valididy

1. Number Screened: NR

> Eligible: NR Enrolled: 178

2. 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

3. Run-in: NR Wash out: NR

4. Class naive patients only No

5. Controlled group standard of care:

Yes

6. Funding: Synthelabo Scandinavia A/S

Enrolled patients characteristics were not reported. Analyzed patients characteristics were reported instead: mean age=51 years, range 19-79 years; Comment: 31% male.

7. Relevance:

Quality rating: Fair Author: **Scharf** Trial type: Placebo

Year: 2005 Country: US **Funding:**

Internal valididy

1. Randomization adequate? NR 2. Allocation adequate? NR 3. Groups similar at baseline: Yes 4. Eligibility criteria specified Yes 5. Outcome assessors masked Yes 6. Care provider masked NR 7. Patients masked Yes 8. Reporting of Attrition Yes

> Crossover No Adherence No No

Contamination

9. Loss to follow-up

differential/ high No

If Yes, please report:

External valididy

1. Number Screened: 353

> Eligible: NR Enrolled: 231

2. 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.

3-14 3. Run-in: Wash out: NR

4. Class naive patients only

5. Controlled group standard of care: NR

6. Funding:

10. Intention-to-treat analysis: Yes

11. Postramdomization exclusions: Unable to determine

12. Quality rating: Fair 7. Relevance:

Older adults

Quality rating: Fair **Author:** Scharf Trial type: Placebo

Funding: NR Year: 1994 Country: US

Internal valididy

3. Groups similar at baseline:

External valididy

1. Randomization adequate? 1. Number Screened: NR 178 2. Allocation adequate? NR

Enrolled:

2. Exclusion criteria: 4. Eligibility criteria specified Yes

Yes

5. Outcome assessors masked Yes 6. Care provider masked NR

7. Patients masked Yes 8. Reporting of Attrition Yes

Crossover No

Adherence No

Contamination Yes

9. Loss to follow-up

differential/ high No

If Yes, please report:

Eligible: 75

75

3. Run-in: 11 Wash out: 2

4. Class naive patients only NR

5. Controlled group standard of care: NR

6. Funding: NR

10. Intention-to-treat analysis: Unable to determine

11. Postramdomization exclusions: No

12. Quality rating: Fair 7. Relevance: Yes

Author: Schwartz Trial type: Active Quality rating: Poor

Year: 2004 Country: US Funding: Not reported

Internal valididy

Randomization adequate?
 Allocation adequate?
 No- open

3. Groups similar at baseline: NR
4. Eligibility criteria specified No
5. Outcome assessors masked No
6. Care provider masked No

7. Patients masked No 8. Reporting of Attrition Yes

> Crossover No Adherence No Contamination No

9. Loss to follow-up

differential/ high No

If Yes, please report:

External valididy

1. Number Screened: NR

Eligible: NR Enrolled: 16

2. Exclusion criteria:

Subjects were excluded from the study if they were presently taking a hypnotic or sedating psychotropic agent in the evening, if they were using alcohol or dugs, if they were manic, or if they had a medical contraindication to the study medications.

3. Run-in: NR Wash out: NR

4. Class naive patients only No

5. Controlled group standard of care: Yes

6. Funding: Not reported

10. Intention-to-treat analysis: Yes11. Postramdomization exclusions: No

12. Quality rating: Poor

7. Relevance:

psychiatric inpatien

Comment: Psychiatric inpatients

Quality rating: Fair Silvestri Author: Trial type: Active

Year: 1996 Country: Italy **Funding: Not reported**

Internal valididy

1. Randomization adequate? NR 2. Allocation adequate? NR 3. Groups similar at baseline: Yes

4. Eligibility criteria specified Yes

5. Outcome assessors masked Yes, but not describe

6. Care provider masked NR

7. Patients masked Yes, but not describe

8. Reporting of Attrition Yes

Crossover No Adherence No Contamination No

9. Loss to follow-up

differential/ high Yes

If Yes, please report:

2/12 triazolam (10%) patients vs 0/10

zolpidem patients lost to f/u

3. Run-in: 3 Wash out: No

4. Class naive patients only

5. Controlled group standard of care:

Yes

6. Funding: Not reported

7. Relevance:

10. Intention-to-treat analysis: No 11. Postramdomization exclusions: Yes

12. Quality rating: Fair

External valididy

1. Number Screened: NR

> Eligible: NR Enrolled: 22

2. Exclusion criteria:

Pregnant or lactating women; women of child-bearing age withoug adequate contraception; uncooperative patients; severe psychiatric diseases, also screened by means of both Hamilton Rating Scale for Anxiety (total score >16) and Hamilton Rating Scale for Depression (total score >16); neurological diseases (myoclones, kinaesthesis disorders, restless legs syndrome, sleep obstructive apnea of >7 minutes duration); severe internal (heart, renal, liver) diseases; hemocoagulation disorders (Quick's time <70%); intake of any psychotropic durg during 2 weeks preceding the study start as well as a previous with beta blockers or corticosteroids.

Quality rating: Fair Author: Singh Trial type: Active

Funding: Rhone-Poulenc Pharma Inc. 1990 Country: Canada Year:

Internal valididy

1. Randomization adequate? NR 1. Number Screened: 2. Allocation adequate? NR

Enrolled: 3. Groups similar at baseline: NR

4. Eligibility criteria specified No 5. Outcome assessors masked Yes, but not describe

6. Care provider masked NR 7. Patients masked Yes 8. Reporting of Attrition Yes

> Crossover No Adherence No

Contamination No

9. Loss to follow-up

differential/ high No

If Yes, please report:

External valididy

NR

Eligible: 61 60

2. Exclusion criteria:

Psychotic and neurotic patients were excluded as well as those with a history of mental retardation, chronic alcoholism, drug abuse, coffee or tea abuse, neurological disorders, established sleep apnoea and drug hypersensitivity. Patients with any significant medical condition interfering with sleep, those

treatment which could modify drug kinetics were also excluded. Finally, pregnancy, lactation, and child-bearing potential not controlled by a recognized contraceptive

programme precluded entry in the study.

3. Run-in: Wash out: NR

4. Class naive patients only NR

5. Controlled group standard of care:

6. Funding: Rhone-Poulenc Pharma Inc.

10. Intention-to-treat analysis: Yes

11. Postramdomization exclusions: Yes (1 patient)

12. Quality rating: Fair 7. Relevance: Yes

Comment:

Two patients were taking a benzodiazepine hypnotic medication at time of recrutment and they both fulfilled the inclusion criteria after a 4-day minimum washout period.

The study did not report patient number for each treatment groups, and the analyzed results were the mean from parts of the patients as well. (?!)

Quality rating: Fair Author: Steens Trial type: Active

1993 Country: **Funding: Lorex Pharmaceuticals** Year: Canada

Internal valididy **External valididy**

1. Randomization adequate? NR 1. Number Screened: NR 2. Allocation adequate? NR

Enrolled: 3. Groups similar at baseline: NR

Yes, but not describe

4. Eligibility criteria specified Yes

NR 6. Care provider masked 7. Patients masked Yes 8. Reporting of Attrition No

5. Outcome assessors masked

Crossover No Adherence No Contamination No

9. Loss to follow-up

differential/ high No

If Yes, please report:

NR Eligible: 24

2. 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 th 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.

3. Run-in: 0 Wash out: 0

4. Class naive patients only

5. Controlled group standard of care:

6. Funding: Lorex Pharmaceuticals

10. Intention-to-treat analysis: Yes 11. Postramdomization exclusions: No

Patients with COP 12. Quality rating: Fair 7. Relevance:

Comment: One of 24 patients designated an outlier and excluded from group analysis, but results reported separately.

Author: Stip Trial type: Active Quality rating: Fair

Year: 1999 Country: Canada Funding: Not reported

Internal valididy External valididy

1. Randomization adequate? NR 1. Number Screened: NR 2. Allocation adequate? NR Eligible: NR

2. Allocation adequate? NR3. Groups similar at baseline: NREligible: NREnrolled: 60

4. Eligibility criteria specified Yes 2. Exclusion criteria:

5. Outcome assessors masked Yes, but not describe NR

6. Care provider masked NR
7. Patients masked Yes

8. Reporting of Attrition Yes
Crossover No

Adherence No

Contamination No

9. Loss to follow-up

differential/ high Yes

If Yes, please report:

17% excluded from analysis

3. Run-in: 7
Wash out: 7

4. Class naive patients only NR

5. Controlled group standard of care: Yes

6. Funding: Not reported

10. Intention-to-treat analysis: No

11. Postramdomization exclusions: Yes

12. Quality rating: Fair 7. Relevance: Yes

Comment:

Participants who had been taking hypnotic drugs with a long half-life received lorazepam for one week, prior to a week placebo. Patients who had been taking benzodiazepines with a short or intermediate half-life were put only on placebo for one week.

Enrolled population characteristic were not reported. Analyzed population characteristics: mean age=42.6 years; 21 (42%) female

Quality rating: Poor Author: **Tamminen** Trial type: Active

Year: 1987 Country: **Finland Funding: Not reported**

Internal valididy

External valididy

1. Number Screened: 1. Randomization adequate? NR NR 2. Allocation adequate? NR

Enrolled: 94

4. Eligibility criteria specified Yes

5. Outcome assessors masked Yes, but not describe

NR

6. Care provider masked NR 7. Patients masked Yes 8. Reporting of Attrition Yes

3. Groups similar at baseline:

Crossover No Adherence No Contamination No

9. Loss to follow-up

differential/ high Yes

If Yes, please report:

28% not included in the analysis (10 zopiclone, 16 nitrazepam excluded)

3. Run-in: Wash out: NR

> 4. Class naive patients only No

5. Controlled group standard of care:

Yes

6. Funding: Not reported

10. Intention-to-treat analysis: No 11. Postramdomization exclusions: Yes

12. Quality rating: Poor 7. Relevance:

Eligible: 130

2. Exclusion criteria:

Known hypersensitivity to benzodiazepines, major psychiatric disorders, somatic disorders directly causeing 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.

Poor quality: no baseline demographic characteristics, high and differential loss to followup and no intention to treat analysis

Quality rating: Poor **Author: Terzano** Trial type: Placebo

Year: 1992 Country: Italy Funding: Partially supported by Italian

Internal valididy **External valididy**

1. Randomization adequate? 1. Number Screened: NR NR 2. Allocation adequate? NR

3. Groups similar at baseline: NR Enrolled:

4. Eligibility criteria specified 2. Exclusion criteria: Yes

5. Outcome assessors masked Yes, but not describe

6. Care provider masked NR

7. Patients masked Yes, but not describe

8. Reporting of Attrition No

> Crossover No Adherence No Contamination No

9. Loss to follow-up

differential/ high NR

If Yes, please report:

Eligible: NR 12

patients had nocturnal myoclonus or sleep apnea syndrome

3. Run-in: 14 Wash out: NR

4. Class naive patients only NR 5. Controlled group standard of care:

6. Funding: Partially supported by Italian Ministry of University

and Scientific Research

10. Intention-to-treat analysis: NR 11. Postramdomization exclusions: NR

12. Quality rating: Poor 7. Relevance: Yes

Author: Tsutsui Trial type: H2H Quality rating: Fair

Year: 2001 Country: Japan Funding: Not reported

Internal valididy

1. Randomization adequate? NR 2. Allocation adequate? NR 3. Groups similar at baseline: NR 4. Eligibility criteria specified Yes 5. Outcome assessors masked Yes NR 6. Care provider masked 7. Patients masked Yes 8. Reporting of Attrition Yes Crossover No

Crossover No
Adherence Yes
Contamination No

9. Loss to follow-up

differential/ high Yes

If Yes, please report:

13.9% zolpidem vs 18.1% zopiclone

withdrew (p=NS)

10. Intention-to-treat analysis: No11. Postramdomization exclusions: Yes

12. Quality rating: Fair

External valididy

1. Number Screened: NR

Eligible: NR Enrolled: 479

2. Exclusion criteria:

Schizophrenia, depression, manic depression, clinically diagnnosed diseases in the acute or exacerbation phase or with unstable symptoms, organic cerebral disorders (diagnosed or suspected), serious heart, liver, kidney, or blood disorders, severe respiratory dysfunction, myasthenia gravis or acute narrow-angle glaucoma and cognitive disorders or impaired intelligence. Symptoms interfering with sleep (e.g., pain, fever, diarrhea, pollakiuria, cough), hypersensitivity to benzodiazepines and analogous drugs, zopiclone intake within 3 months prior to the study, requirement for hypnotics at a dose exceeding the standard single dose, history of drug dependence, operation of machinery involving risk, pregnancy or likelihood of pregnancy, breastfeeding, participation in other clinical trials within the past 6 months, and inappropriateness for the study according to the investigator's judgment.

3. Run-in: no Wash out: 7

4. Class naive patients only No

5. Controlled group standard of care: Yes

6. Funding: Not reported

7. Relevance: Yes

Comment: Baseline demographic data reported only on patients included in efficacy analysis (428/479; 89%).

Additional rebound information: Overall, sleep onset latency, frequency of nocturnal awakenings, sleep duration, daytime mood and daytime physical condition remained significantly improved in both groups relative to baseline (p<0.01, data not reported).

Author: van der Kleijn Trial type: Active Quality rating: Fair

Year: 1989 Country: Nijmegen Funding: Rhone-Poulenc Pharma

Internal valididy

Randomization adequate? Allocation adequate? Groups similar at baseline:

4. Eligibility criteria specified Yes

5. Outcome assessors masked Yes, but not describe

6. Care provider masked NR
7. Patients masked Yes
8. Reporting of Attrition Yes

Crossover No
Adherence No
Contamination No

9. Loss to follow-up

differential/ high No

If Yes, please report:

External valididy

1. Number Screened: NR

Eligible: 60 Enrolled: 55

2. Exclusion criteria:

 Patients taking a non-benzodiazapine hypnotic prior to the studym those who received another psychotropic drug for the first time, or patients whose psychotropic medicine was changed during the study period.

2. Patients who took benzodiazapine tranquillizers or hypnotics in doses at least twice that recommended before the study.

3. Patients suffering from painful disorder

4. Patients unable to fill in a sleep questionnaire, those with a history of alcohol and/or drug abuse, who lived in psychiatric or physical stress situations likely to fluctuate during the study, with liver or kidney disorders, myasthenia gravis, shiftworkers

5. Women pregnant or likely to become pregnant

3. Run-in: 2 Wash out: 7

Class naive patients onlyNo

5. Controlled group standard of care: Yes

Yes

6. Funding: Rhone-Poulenc Pharma

10. Intention-to-treat analysis: No

11. Postramdomization exclusions: Unable to determine

12. Quality rating: Fair

7. Relevance:

Author: Venter Trial type: Active Quality rating: Fair

Year: 1986 Country: South Africa Funding: Not reported

Internal valididy

External valididy

Randomization adequate?
 Allocation adequate?
 NR
 Screened: 58
 Allocation adequate?
 NR
 Eligible: 41

3. Groups similar at baseline: Yes Enrolled:

4. Eligibility criteria specified Yes 2. Exclusion criteria:

No

No

5. Outcome assessors masked
4. Care provider masked
5. Care provider masked
4. Care provider masked
5. Care provider masked
4. Care provider masked
5. Care provider masked
5. Care provider masked
5. Care provider masked
5. Care provider masked
6. Care provider masked
6. Care provider masked
6. Care provider masked
6. Care provider masked
7. Patients were excluded if they had a psychiatric disorder necessitating treatment with antipsychotic antidepressive, or anticonvulsant drugs, with lithium, or if they received anxiolytic drugs during the day. They were also excluded if they had acute and/or severe cardiac, respiratory, hepatic, or renal disease, or had gastrointestinal

8. Reporting of Attrition No disease or prior gastrointestinal surgery, if they had known tolerance to zopiclone or

41

Crossover No triazolam, or if they had hypersensitivity to drugs.

9. Loss to follow-up

differential/ high No

If Yes, please report:

Adherence

Contamination

3. Run-in: 7
Wash out: 0

4. Class naive patients only No

5. Controlled group standard of care: Yes

6. Funding: Not reported

10. Intention-to-treat analysis: Yes

11. Postramdomization exclusions: No12. Quality rating: Fai

. Quality rating: Fair 7. Relevance: elderly residents of

Comment:

22 patients were already receiving another hypnotic drug; the investigators decided a wahout period in these patients would be undesirable. It was therefore decided that this group of patients should discontunue their previous hypnotic therapy and immediately start the trial medicine, without a washout phase. Day 7 of the treatment was recorded as the first day of baseline assessment for this study. Zopiclone-2(10%) and Triazolam-7(33.3%) patients increased the dosage twice after day 8.

Author: Voshaar Trial type: Active Quality rating: Fair

Year: 2004 Country: Netherlands Funding: Sanfi-Synthelabo

Internal valididy

External valididy NP. 1 Number Screen

1. Randomization adequate?NR1. Number Screened:2. Allocation adequate?NREligible:

3. Groups similar at baseline: Yes Enrolled: 221

4. Eligibility criteria specified
 5. Outcome assessors masked
 Yes
 Yes
 Exclusion criteria:
 Patients with other axis I diso

5. Outcome assessors masked

Yes, but not describe

Patients with other axis I disorders, severe somatic disorders, pregnancy, current use of psychotropic medication, complaints of a jet lag in the 2 weeks preceding the study or occupation requiring shift work

NR

NR

7. Patients masked Yes

8. Reporting of Attrition Yes
Crossover 0

Adherence No Contamination No

9. Loss to follow-up

differential/ high Yes

If Yes, please report:

More zolpidem patients dropped out (24 vs

12, p<0.05)

3. Run-in: NR Wash out: 4

4. Class naive patients only No

5. Controlled group standard of care: Yes

6. Funding: Sanfi-Synthelabo

10. Intention-to-treat analysis: No

11. Postramdomization exclusions: Yes

12. Quality rating: Fair 7. Relevance: Yes

Comment: Enrolled population characteristics were not reported. Only analyzed population characteristics were reported:

Author: Walsh Trial type: Placebo Quality rating: Poor

Year: 2000a Country: US Funding:

Internal valididy

Randomization adequate?
 Allocation adequate?
 Not clear (allocation s
 Not clear (allocation s

3. Groups similar at baseline: NR4. Eligibility criteria specified Yes

5. Outcome assessors masked Yes, but not describe

6. Care provider masked NR

7. Patients masked Yes, but not describe

8. Reporting of Attrition Yes

Crossover No Adherence No Contamination No

No- unclear if different

9. Loss to follow-up

differential/ high

If Yes, please report:

External valididy

1. Number Screened: 311

Eligible: 54 Enrolled: 48

2. Exclusion criteria:

Significant medical and psychiatric illnesses were ruled out by clinical interview, physical and neurological examinations, ECG, and clinical laboratory tests (haematology, chemistry and urine analysis). Specifically, 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

3. Run-in: 5-12Wash out: 5-124. Class naive patients only

5. Controlled group standard of care:

6. Funding:

10. Intention-to-treat analysis: No (48/54 analyzed)

11. Postramdomization exclusions: Yes

12. Quality rating: Poor

Relevance:

Older adults

Comment:

Trial type: Placebo

Author:

Walsh

10. Intention-to-treat analysis:

12. Quality rating:

11. Postramdomization exclusions: Yes

No

Fair

0		
Country: US		Funding:
	External valididy	
NR	1. Number Screened: NF	R
NR	Eligible: 58	9
Yes	Enrolled: 30	6
Yes	2. Exclusion criteria:	
Yes, but not describe NR Yes Yes No No No No	by a physician) disorder, smoki 25% from desir	medical or psychiatric disorder (as determined by clinical interview, a history suggestive of sleep apnea or periodic limb movement ng of more than 10 cigarettes per day, weight varying by more than able weight based on the Metro-politan Life Insurance Table, sk of becoming pregnant, and lactation.
	3. Run-in: 7	
	Wash out: NF	₹
	4. Class naive patients only	, No
	NR Yes Yes, but not describe NR Yes Yes Yes No No	RR NR Seligible: 58 Yes Yes Yes, but not describe NR Yes Yes Yes NR Yes NR Yes NR Yes NR Yes Yes NR Yes Yes Any significant by a physician), disorder, smoki 25% from desir pregnancy or risorder. NO

5. Controlled group standard of care: Yes6. Funding: Lorex Pharmaceuticals

Yes

Quality rating: Poor

Comment: Enrolled population characteristics were not reported. Instead, analyzed population characteristics were reported: 63% female; 84% Caucasian.

7. Relevance:

Author:	Walsh	Trial type: Placebo	Quality rating: Poor
Year:	2000a	Country: US	Funding:

ear:	2000a	Country:	US	Funding:
Inte	ernal valididy			External valididy
	1. Randomization adequate?	Yes		1. Number Screened: 673
	2. Allocation adequate?	NR		Eligible: 456
	3. Groups similar at baseline:	Yes		Enrolled: 132
	4. Eligibility criteria specified	Yes		2. Exclusion criteria:
	5. Outcome assessors masked	Yes, but not desc	ribe	Individuals with significant medical or psychiatric illness, as determined by history
	6. Care provider masked	NR		and physical examination, clinical laboratory tests, the Zung Anxiety and
	7. Patients masked	Yes		Depressopm scales (scores >40) were exlcuded, as were those using CNS active medication. Individuals with prior exposure to zaleplone, or sensitivity to
	8. Reporting of Attrition	Yes		benzodiazepines or other psychotropic drugs, were exluded.
	Crossover	No		
	Adherence	No		
	Contamination	No		
	9. Loss to follow-up differential/ high	No		
	If Yes, please report:			
				3. Run-in: 3
				Wash out: 2
				4. Class naive patients only No
				5. Controlled group standard of care: Yes
				6. Funding: Wyeth Ayerst
	10. Intention-to-treat analysis:	Yes		
	11. Postramdomization exclusion	s: No		
	12. Quality rating:	Good		7. Relevance: Yes

Comment: day 1-3 placebo; day 4-17 treatment; day 18-19 placebo

Quality rating: Poor Trial type: Placebo Author: Walsh

Year: 2000a Country: US **Funding:**

Internal valididy **External valididy**

1. Randomization adequate? NR 1. Number Screened: 2. Allocation adequate? NR Eligible: 3. Groups similar at baseline: Enrolled: NR 4. Eligibility criteria specified Yes 2. Exclusion criteria:

5. Outcome assessors masked Yes, but not describe

NR 6. Care provider masked

7. Patients masked Yes, but not describe

8. Reporting of Attrition Yes

Crossover 0 Adherence Yes Contamination No

9. Loss to follow-up

differential/ high Yes

If Yes, please report:

8 of 30 (27%) randomized were excluded from analysis; groups not specified.

NR 3. Run-in: Wash out: NR

4. Class naive patients only Yes

5. Controlled group standard of care: Yes

73

39

30

metabolism of the study drugs.

individuals for any of the following: >120% of ideal body weight, comsumption 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

the past week, or use of medications that would interfere with the absorbtion or

investigational drug, psychotropic medication, tryptophan, or melatoantihistamine in

10. Intention-to-treat analysis: No 11. Postramdomization exclusions: Yes

12. Quality rating: Poor

6. Funding: Wyeth-Ayerst Research

7. Relevance: No- very stringent e

The population characteristics of enrolled subjects were not reported. Only the characteristics for analyzed subjects were reported. 22 subjects were Comment: analyzed, 11 men; mean age, 42 y; range, 22-49.

Quality rating: Fair **Author:** Walsh Trial type: Placebo

Year: 2000b, 2002 Country: US **Funding: Lorex Pharmaceuticals**

Internal valididy **External valididy**

1. Randomization adequate? 1. Number Screened: Yes 365 2. Allocation adequate? NR Eligible: 163

3. Groups similar at baseline: Enrolled: Yes 163

4. Eligibility criteria specified 2. Exclusion criteria: Yes

5. Outcome assessors masked Yes, but not describe NR

6. Care provider masked NR 7. Patients masked Yes

8. Reporting of Attrition Yes Crossover No

Adherence Yes Yes

Contamination

9. Loss to follow-up

differential/ high Yes

If Yes, please report:

18% withdrew:12.3% placebo, 30%

zolpidem

Wash out:

3. Run-in:

4. Class naive patients only NR

5. Controlled group standard of care:

7

7

6. Funding: Lorex Pharmaceuticals

10. Intention-to-treat analysis: No

11. Postramdomization exclusions: Yes

12. Quality rating: Fair 7. Relevance: Yes

Patients were instructed to "take the medication when you thini you need it, at bed time, between three and five nights per week".

Quality rating: Fair Author: Ware Trial type: Active

1997 Country: US **Funding: Lorex Pharmaceuticals** Year:

Internal valididy

1. Number Screened: 1. Randomization adequate? NR 2. Allocation adequate? Eligible: NR

Enrolled: 3. Groups similar at baseline: Yes

4. Eligibility criteria specified Yes

5. Outcome assessors masked Yes, but not describe 6. Care provider masked NR

7. Patients masked Yes, but not describe

8. Reporting of Attrition Yes

> Crossover No Adherence No

> Contamination No

9. Loss to follow-up

differential/ high No

If Yes, please report:

External valididy

358

NR 110

2. 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.

3. Run-in: 2 Wash out: 3

4. Class naive patients only 5. Controlled group standard of care:

6. Funding: Lorex Pharmaceuticals

10. Intention-to-treat analysis: No 11. Postramdomization exclusions: No

12. Quality rating: Fair 7. Relevance: Yes

No baseline demographic data provided, but states groups did not differ significantly in gender, age, race, height, and weight.

Author: Wheatley Trial type: Active Quality rating: Fair

Year: 1985 Country: NR Funding: Not reported

Internal valididy External valididy

1. Randomization adequate? NR 1. Number Screened: NR 2. Allocation adequate? NR Eligible: NR

2. Allocation adequate?NRBligible:NR3. Groups similar at baseline:NoEnrolled:36

4. Eligibility criteria specified No 2. Exclusion criteria:

5. Outcome assessors masked Yes, but not describe NR

6. Care provider masked NR7. Patients masked Yes8. Reporting of Attrition Yes

Crossover No

Adherence No Contamination No

9. Loss to follow-up

differential/ high No

If Yes, please report:

3. Run-in: 3
Wash out: NR

4. Class naive patients only No

5. Controlled group standard of care: Yes

6. Funding: Not reported

10. Intention-to-treat analysis: Unable to determine

11. Postramdomization exclusions: Unable to determine

12. Quality rating: Fair 7. Relevance: Yes

Comment: zopiclone first group had a higher proportion of patients previously responding well to hypnotics and more heavy smokers.

Author: Zammit Trial type: Placebo Quality rating: Fair

Year: 2004 Country: US Funding: Sepracor

Internal valididy

Randomization adequate? Allocation adequate? NR

3. Groups similar at baseline: Differences in gener a

4. Eligibility criteria specified Yes5. Outcome assessors masked Yes6. Care provider masked NR

7. Patients masked Yes

8. Reporting of Attrition Yes
Crossover No

Adherence No Contamination No

9. Loss to follow-up

differential/ high No

If Yes, please report:

External valididy

1. Number Screened: NR

Eligible: 669 Enrolled: 308

Lillolled.

2. 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.

3. Run-in: 2 Wash out: 5-7

4. Class naive patients only NR

5. Controlled group standard of care: NR

6. Funding: Sepracor

10. Intention-to-treat analysis: No (303/308 at night

11. Postramdomization exclusions: No

12. Quality rating: Fair 7. Relevance: Yes

Comment:

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
Allain, 1991 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,	Sleepiness: 107(0.52%)/ 44	Bitter taste: 746(3.64%)/ 181	
France	Hypersomnia: 6(0.03%)/ 2	Dysgeusia: 20(0.10%)/ 6	
	Increased frequency of dreams: 38(0.19%)/ 6	Dry mouth: 325(1.58%)/ 53	
	Nightmares: 101(0.49%)/ 59	Gastric pain: 61(0.30%)/ 33	
	Headache: 61(0.30%)/ 27	Nausea: 101(0.49%)/ 49	
	Light headedness/heavy headedness: 11(0.05%)/3	Vomiting: 101(0.05%)/ 8	
	Ebrious feeling: 53(0.26%)/ 32	Diarrhea: 3(0.01%)/ 2	
	Dizziness: 57(0.28%)/ 24	Constipation: 6(0.03%)/ 1	
	Fall: 8(0.04%)/ 5 Anxiety: 10(0.05%)/ 5	Various GI disorders: 46(0.22%)/ 23	
	Angitation/ excitation: 56(0.27%)/ 41	Somatic adverse events, no. of AEs	
	Irritability: 17(0.07%)/ 8	(%)/ no. of drop-outs	
	Aggressiveness: 4(0.02%)/ 2	Asthenia: 38(0.19%)/ 6	
	Tremor: 12(0.06%)/ 9	Malaise: 14(0.07%)/ 8	
	Hallucinations: 7(0.03%)/ 7	Dyspnea: 8(0.02%)/ 5	
	Confusion: 7(0.03%)/ 5	Palpitation: 4(0.02%)/ 4	
	Difficulty concentrating: 6(0.03%)/ 1	Rash: 8(0.04%)/ 8	
	Memory complaints: 15(0.07%)/ 2	Pruritus: 3(0.16%)/ 3	
	Reduced libido: 4(0.02%)/ 2 Various neuropsychiatric disorders: 15(0.07%)/ 12	Other: 15(0.07%)/ 7	

Evidence Table 17: Observational Studies

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 folowed by 7 to 28 treatment-free days without adverse effects, and return to the clinic after the treatmentfree 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.

Evidence Table 17: Observational Studies

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; openlabel continuation phase of RCT	Monthly safety assessments which included routine physical exams, laborator determinations, vital signs including blood pressure, and electrocardiograms.	7 days	Treatment emergent adverseevents 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 of prescribing patterns	Database from one practice. ICD-9 codes associated with each treatment modality.	6 months	Number of times therapy was discontinued, reasons for discontinuation

Author Year Country	Results	Funding
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	Use temazepam or zolpidem, discontinuation due to adverse events: zolpidem(n=89) vs. temazepam(n=401), (%) adverse drug reaction- 2.2% vs. 4.2% Discontinuation due to adverse events: [use temazepam and then swith to zolpidem] vs. [use zolpidem and then switch to temazepam], (%) adverse drug reaction or others- 10.6% vs. 7.5%	Not reported
	Discontinuation due to adverse events after filtering out "change in dose" as a reason for discontinuation. Among discontinuation except "change in dose": adverse drug reation-4.3% vs.10.1%	

Evidence Table 17: Observational Studies

Author Year Country	N	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).

Evidence Table 17: Observational Studies

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), anxietydepressive 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	Results	Funding	
Country			
Buckley, 2004	Fatal toxicity index: total no. of deaths	None	
UK	zolpidem vs. zopiclone= 3 vs. 23		
	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, 1995	Adverse events: [zopiclone] vs. [lorazepam] vs. [triazolan] vs. [nitrazepam]	Rhone-Poulenc	
Canada	or flurazepam] vs. [temazepam], no.(%)	Rorer and	
	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)		

Evidence Table 17: Observational Studies

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).

Evidence Table 17: Observational Studies

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), anxietydepressive 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	Results	Funding
Year		
Country		

Diav-Citrin, 1999 Pregnancy outcome, zopiclone vs. control:

Canada Preganancy outcome: NS

Birth defects: NS Delivery methods: NS

Mean GA (wk): 38.3±2.7 vs. 40.0±1.6, p=0.002

Preterm delivery of <37 wks: NS

Mean birth weight (g): 3245.9±676 vs. 3624.2±536, p=0.01

Birth weight by GA: NS

Meconium: NS Fetal distress: NS NICU admission: NS

Evidence Table 17: Observational Studies

Author Year Country	N	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.

Evidence Table 17: Observational Studies

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
Ganzoni, 1994 Switzerland	CNS-related adverse events, n=1972: no. of Aes(%)/ no. drop-outs(%) Residual daytime sedation: 73(3.7)/ 28(1.4) Lack of efficacy: 31(1.6)/ 19(1.0) Confusion, disorientation, obsessive ideas, delirium, psychosis: 19(1.0)/ 15(0.8) Nervousness, internal trembling, nervous feet, restlessness, excitation feeling: 16(0.8)/ 14(0.7) Nightmares: 15(0.8)/ 11(0.6) Amnesia, memory impaired: 15(0.8)/ 7(0.4) Concentration impaired: 11(0.6)/ 4(0.2) Anxiety: 11(0.6)/ 8(0.4) Somnambulism, sleep walking, nocturnal activity, walking activity: 9(0.5)/ 5(0.3) Hallucunation: 6(0.3)/ 4(0.2) Dreaming increased: 6(0.3)/ 3(0.2) Blurred vision, diplopia, crying, reading impaired, vision abnormal: 5(0.3)/ 3(0.2) Agitation, aggressivity: 3(0.2)/ 2(0.1) Speech disorder: 3(0.2)/ 2(0.1) Tremor: 2(0.1)/ 0(0.0) Benzodiazepine withdrawal: 1(0.1)/ 1(0.1) Suspicion of drug dependence: 1(0.1)/ 0(0.0) Drug misuse: 1(0.1)/ 0(0.0) Total: 228(11.6)/ 126(6.4)	Non-CNS-related adverse events, n=1972: no. of Aes(%)/ no. dropouts(%) 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)/ 1(0.1) Retching: 1(0.1)/ 1(0.1) Total: 115(5.8)/ 69(3.5)	Not Reported

Evidence Table 17: Observational Studies

Author Year Country	N	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 initating 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	Results	Funding	
Year Country			
Hajak, 1998	Tolerance: 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		

Evidence Table 17: Observational Studies

Author Year Country	N	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

Any adverse events Maarek, 1992 Not reported. Before-after. The general practitioner 6 months-12 assessed patient detected by clinical France months compliance by questioning examination or the patients at each visit reported spontaneously by the patient were recorded at each visit.

Author	Results	Funding
Year		
Country		
Jaffe, 2003	Drug use pattern: zolpidem vs. zopiclone (n=297)	Sepracor
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, 1992	7(7.3%) of all patients withdrew because of adverse events:	
France	1(1%) feeling of strangeness	
	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	

Evidence Table 17: Observational Studies

Author Year Country	N	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 insomnnia 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.

Evidence Table 17: Observational Studies

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), paraphrenie (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 bisit by the investigator.	January 1st to May 31st, 1994	Reported by the patient at the followup visit.

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

Peeters, 1997 Adverse events reported: All patients (n=1219)/ Patients <65 (n=720)/

Belgium Patients >=65 (n=495)

Autonomic nervousd 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 Unknon: 5/ 5/ 0

Patients with at least one adverse events: 87/46/41

Evidence Table 17: Observational Studies

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

Evidence Table 17: Observational Studies

Author Year Country	N	Drugs (mean dose); duration of treatment	Duration of treatment	Eligibility Criteria
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.

Author Year Country	Other population characteristics	Design	Data sources	Time period of assessment	Adverse events assessment
Scharf, 1994	Not reported.	Before-after.	Patient reports Physician assessments	13 weeks	Treatmentemergent adverse events.

Author Year	Results	Funding
Country		
Scharf, 1994	Adverse events: zolpidem 10mg (n=33) vs. zolpidem 15mg (n=229),	
	<u>no.(%)</u>	
	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)	

Evidence Table 17: Observational Studies

Author Year Country	N	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 clains for a nonprescription service between January 1, 1994 and December 31, 1994 and have filled at least one prescription for any meducation through the Medicaid or PAAD programs of New Jersey in each of four consecutive 6-month periods beginning

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	Results	Funding					
Country							
Schlich, 1991	Tolerance: no evidence						
France	Adverse events: zolpidem vs. placebo						
	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, 2001	Hip Fracture:	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)	Institue on					
	antipsychotic medication: 1.61 (1.29-2.01)	Aging.					
	antidepression: 1.46 (1.22-1.75)	3 3					
	other psychoactive medication: 1.23 (0.90-1.68)						
	thiazide diuretic: 0.85 (0.71-1.02)						

Evidence Table 18. Case Reports

Drug	Study	Number of cases	Group	Case Characteristics	Effects during treatment	Effects during treatment reduction or discontinuation
Zolpidem	(Vartzopoulos, Bozikas, Phocas, Karavatos, & Kaprinis, 2000)	4	dependence	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	(I. A. Liappas et al., 2003)	3	dependence	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	(I.A. Liappas et al., 2003)	8	dependence	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 discomfortable, irritability, abd agitation 1 with epileptic seizure 1 with instability, duzzubess and a craving for other psychotropic substances 1 not reported

Zolpidem	(Bottlender, Schutz, Moller, & Soyka)	1	dependence	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	(Aragona, 2000)	1	dependence	history of drug abuseseizure history after benzodiazepine discontinuation	the patient increased the dose up to 450-600mg per day for anxiolytic effect.dependence and tolerance	epileptic seizure
Zolpidem	(Sakkas, Psarros, Masdrakis, Liappas, & Christodoulou)	1	dependence	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	(Ravishankar & Carnwath)	2	dependence	depression	the patient increased the dose up to 200mg per day	tachycardia, confusion, anxiety, panic attacks and fear of ogoing outside
Zolpidem	(Sattar, Ramaswamy, Bhatia, & Petty, 2003)	1	somnambulism	bipolar disorder history of drug abuse history of alcohol dependence mania taking valproic at the same time	somnambulism difficulty in concentration	insomnia

Zolpidem	(Harazin & Berigan, 1999)	1	somnambulism	depression	somnambulism	somnambulism stopped
Zolpidem	(Clark, 1999)	1	Hepatic problem	liver transplantation	decline in mentality hepatic encephalopathy abdominal pain awoke in a stupor and was disoriented to place and time	not reported
Zolpidem	(Karsenti, Blanc, Bacq, & Melman, 1999)	1	Hepatic problem	cholecystectomy	abdominal pain hepatotoxicity	not reported
Zolpidem	(Tsai, Huang, & Wu, 2003)	1	hallucination	not reported	visual illusions, confusion and hallucination especially reusing after rapid withdrawals.	insomnia
Zolpidem	(Elko, Burgess, & Robertson, 1998)	5	hallucination	concurrent use of serotonin-reuptake inhibition depression	hallucination	not reported
Zolpidem	(Ginsberg, 2003), (Huang, Chang, Hung, & Lin, 2003)	1	hallucination	concurrent use of other drugs for hormone replacement, osteoporosis and insomnia	headache spotty memory hallucination visual perception distortion	not reported
Zolpidem	(Toner, Tsambiras, Catalano, Catalano, & Cooper, 2000)	3	CNS side effect	motor vehicle accident or psychiatric history	nightmare hallucination visual illusion difficulty in concentration	nightmares, hallucination and visual illusion ceased
Zolpidem	(Tripodianakis, Potagas, Papageorgiou, Lazaridou, & Matikas, 2003)	1	CNS side effect	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	(Markowitz & Brewerton, 1996)	2	CNS side effect	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	(Ortega, Iruela, Ibanez- Rojo, & Baca)	1	others- drug interaction	long term benzodiazepine user no psychiatric history	nervousness, irritability, fainting, asthenia, muscular cramps, excessive hear and sweatingm occasional febrile episodes, weight loss, and a surprising sweet taste in the mouth	all symptoms disappeared
Zolpidem	(Morgenthaler & Silber, 2002)	5	others	no history of eating disorders concurrent use of other drugs	amnestic sleep-related eating disorder restless legs syndrome	no nocturnal eating
Zolpidem	(Logan & Couper, 2001)	29	CNS side effect	no common characteristics	driving impairment because of slow movements and reactionsvisual distortions	not reported
Zolpidem	(Canaday, 1996)	2	CNS side effect	not reported	amnesia	not reported
Zolpidem	(Brodeur & Stirling, 2001)	1	CNS side effect	Extensive medical history	delirium psychosis restless amnesia	not reported
Zopiclone	(Alderman, Gebauer, Gilbert, & Condon, 2001)	1	others- drug interaction	depression concurrent use of antidepressants	morning drowsiness increased plasma concentrations	zopiclone plasma concentrations back to normal after nefazodone discontinuation

Zopiclone	(Aranko, Henriksson, Hublin, & Seppalainen, 1991)	1	dependence	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	(Bramness, Arnestad, Karinen, & Hilberg, 2001)	1	dependence	smoker respiratory problems anxiety	difficulty in breathing death caused by 337.5mg overdose	not reported
Zopiclone	(Ancoli-Israel et al., 2005)	4	dependence	no common characteristics	dependence	severe anxiety with tachycardia, tremor, sweating, rebound insomnia, flushes, palpitations, and derealisation.
Zopiclone	(Sullivan, McBride, & Clee, 1995)	3	others	history of drug abuse alcohol abuse	no evidence of dependence	not reported
Zaleplon	(Stillwell, 2003)	1	CNS side effect	drug abuse concurrent use of other drugs	CNS depression including slow movements and reactions, poor coordination, lack of balance, and poor attention	not reported

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