Evidence Table 1. Head to head controlled trials: Efficacy

Author: **Allain** **Trial type:** **H2H** **Quality rating:** **Fair**

Year: **2003** **Country:** **France** **Funding:** **Sanofi-Synthelabo**

Design:

Study design RCT
DB
Crossover

Setting Single Center

Age: 52
Range: NR
SD: 7

Gender: 26 (49 %) Female

Ethnicity: NR

Number Screened: NR
Eligible: NR
Enrolled: 53

Number Withdrawn: 0
Lost to fu: 0
Analyzed: 53

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.

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.

Comments:

Intervention:

Run-in : No
Wash out : No
Allow other medication : NR

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

Evidence Table 1. Head to head controlled trials: Efficacy

Author: **Allain** **Trial type:** **H2H** **Quality rating:** **Fair**

Year: **2003** **Country:** **France** **Funding:** **Sanofi-Synthelabo**

Outcome Measurement:

Patient preference questionnaire
LSEQ
Visual analogue scale for day quality
#
#

Efficacy Outcome List:

Primary outcome	Outcome:
☑	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 preference

Percentage of patients preferring a drug

Zolpidem	Zaleplon			P value
62 ( )	38 ( )	( )	( )	0.81

(%) ( )

Evidence Table 1. Head to head controlled trials: Efficacy

Author: **Allain** **Trial type:** **H2H** **Quality rating:** **Fair**

Year: **2003** **Country:** **France** **Funding:** **Sanofi-Synthelabo**

LSEQ

Getting to sleep mean score (lower is better)

Zolpidem		Zaleplon				P value
35.9	(20.0)	45.3	(20.7)	( )	( )	0.03

Score (SD)

Quality of sleep mean score (lower is better)

Zolpidem		Zaleplon				P value
30.6	(18.6)	44.3	(23.2)	( )	( )	<0.0001

Score (SD)

Ease of waking up mean score (lower is better)

Zolpidem		Zaleplon				P value
43.6	(22.8)	43.8	(21.8)	( )	( )	0.27

Score (SD)

Behavior following wakefulness mean score (lower is better)

Zolpidem		Zaleplon				P value
47.4	(23.2)	51.7	(17.2)	( )	( )	0.31

Score (SD)

Evidence Table 1. Head to head controlled trials: Efficacy

Author: **Allain** **Trial type:** **H2H** **Quality rating:** **Fair**

Year: **2003** **Country:** **France** **Funding:** **Sanofi-Synthelabo**

VAS for day quality (0-100, higher is better)

Quality of sleep mean score

Zolpidem		Zaleplon				P value
68.8	(21.8)	50.2	(28.1)	( )	( )	<0.0001
Score	(SD		)			

Consciousness mean score

Zolpidem		Zaleplon				P value
73.9	(21.3)	73.1	(19.7)	( )	( )	0.18
Score	(SD		)			

Dynamism mean score

Zolpidem		Zaleplon				P value
62.6	(26.0)	61.8	(24.9)	( )	( )	0.47
Score	(SD		)			

Drowsiness mean score

Zolpidem		Zaleplon				P value
28	(27.4)	27.7	(26.5)	( )	( )	0.53
Score	(SD		)			

Anxiety mean score

Zolpidem		Zaleplon				P value
29.3	(30.1)	26.7	(27.7)	( )	( )	0.34
Score	(SD		)			

Mood mean score

Zolpidem		Zaleplon				P value
21.6	(25.5)	20.1	(21.6)	( )	( )	0.92
Score	(SD		)			

Drowsiness duration (minutes)

Zolpidem		Zaleplon				P value
43	(43.8)	38	(21.2)	( )	( )	0.83
Number	(SD		)			

Evidence Table 1. Head to head controlled trials: Efficacy

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

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

Design:

Study design RCT
DB
Parallel

Setting Multicenter

Age: 72
Range:
SD: 5

Gender: 318 (58 %) Female

Ethnicity:

Number Screened: 1224
Eligible: 551
Enrolled: 549

Number Withdrawn: 2
Lost to fu:
Analyzed: 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:

Run-in : 7
Wash out : 7-21
Allow other medication : No

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

Evidence Table 1. Head to head controlled trials: Efficacy

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

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

Outcome Measurement:

Patient questionnaire

Efficacy Outcome List:

Primary outcome	Outcome:
☐	Sleep latency
☐	Total sleep time
☐	Number of awakenings
☐	Sleep quality

Results

Sleep latency

Median subjective sleep latency (minutes) at week 1

Zaleplon 5 mg	Zaleplon 10 mg	Zolpidem 5 mg		P value
(NS)	(<0.001)	(<0.05)	( )	

Number (p vs placebo)

Median subjective sleep latency (minutes) at week 2

Zaleplon 5 mg	Zaleplon 10 mg	Zolpidem 5 mg		P value
39 (<0.001)	(<0.001)	(<0.01)	( )	

Number (p vs placebo)

Total sleep time

Median subjective total sleep time at week 1

Zaleplon 5 mg	Zaleplon 10 mg	Zolpidem 5 mg	Placebo	P value
(NS)	345 (p<0.05)	360 (<0.00)	318 ( )	

Number (p vs placebo)

Median subjective total sleep time at week 2

Zaleplon 5 mg	Zaleplon 10 mg	Zolpidem 5 mg	Placebo	P value
(NS)	(NS)	360 (<0.01)	326 ( )	

Number (p vs placebo)

Evidence Table 1. Head to head controlled trials: Efficacy

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

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

Number of awakenings

Number of awakenings at week 1

Zaleplon 5 mg	Zaleplon 10 mg	Zolpidem 5 mg	Placebo	P value
1.8 (NS)	1.8 (NS)	1.7 (<0.01)	2.0 (NA)	

Number (p vs placebo)

Number of awakenings at week 2

Zaleplon 5 mg	Zaleplon 10 mg	Zolpidem 5 mg	Placebo	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)

Zaleplon 5 mg	Zaleplon 10 mg	Zolpidem 5 mg	Placebo	P value
3.83 (NS)	3.67 (<0.05)	3.50 (<0.00)	4.00 (NA)	

Score (p vs placebo)

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

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)	

Score (p vs placebo)

Evidence Table 1. Head to head controlled trials: Efficacy

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

Age: 42.8
Range: NR
SD: 12.4

Gender: 394 (64 %) Female

Ethnicity: 99% white
<1% black
<1% Asian

Number Screened: NR
Eligible: NR
Enrolled: 615

Number Withdrawn: 41
Lost to fu: NR
Analyzed: 574

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.

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	dosage	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	/

Evidence Table 1. Head to head controlled trials: Efficacy

Author: **Elie** **Trial type:** **H2H** **Quality rating:** **Fair**

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

Outcome Measurement:

Sleep maintenance and sleep quality questionnaire

Efficacy Outcome List:

Primary outcome	Outcome:
☑	Sleep latency
☐	Sleep duration
☐	Number of awakenings
☐	Sleep quality

Results

Sleep duration

Median sleep duration at baseline (minutes)

Zaleplon 5 mg	Zaleplon 10 mg	Zaleplon 20 mg	Zolpidem 10 mg	P value
313 (NS)	331 (NS)	328 (NS)	330 (NS)	

Number (p vs placebo)

Median sleep duration at week 1 (minutes)

Zaleplon 5 mg	Zaleplon 10 mg	Zaleplon 20 mg	Zolpidem 10 mg	P value
351 (NS)	370 (NS)	370 (p<0.0)	379 (p<0.00)	

Number (p vs placebo)

Median sleep duration at week 2 (minutes)

Zaleplon 5 mg	Zaleplon 10 mg	Zaleplon 20 mg	Zolpidem 10 mg	P value
359 (NS)	368 (NS)	369 (p<0.0)	387 (p<0.00)	

Number (p vs placebo)

Median sleep duration at week 3 (minutes)

Zaleplon 5 mg	Zaleplon 10 mg	Zaleplon 20 mg	Zolpidem 10 mg	P value
384 (NS)	371 (NS)	374 (NS)	385 (<0.001)	

Number (p vs placebo)

Median sleep duration at week 4 (minutes)

Zaleplon 5 mg	Zaleplon 10 mg	Zaleplon 20 mg	Zolpidem 10 mg	P value
372 (NS)	384 (NS)	385 (<0.05)	400 (<0.001)	

Number (p vs placebo)

Evidence Table 1. Head to head controlled trials: Efficacy

Author: **Elie** **Trial type:** **H2H** **Quality rating:** **Fair**

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

Number of awakenings

Median number of awakenings at baseline

Zaleplon 5 mg	Zaleplon 10 mg	Zaleplon 20 mg	Zolpidem 10 mg	P value
2 (NS)	2 (NS)	2 (NS)	2 (NS)	

Number (p vs placebo)

Median number of awakenings at week 1

Zaleplon 5 mg	Zaleplon 10 mg	Zaleplon 20 mg	Zolpidem 10 mg	P value
2 (NS)	2 (NS)	2 (NS)	2 (NS)	

Number (p vs placebo)

Median number of awakenings at week 2

Zaleplon 5 mg	Zaleplon 10 mg	Zaleplon 20 mg	Zolpidem 10 mg	P value
2 (NS)	2 (NS)	2 (NS)	2 (NS)	

Number (p vs placebo)

Median number of awakenings at week 3

Zaleplon 5 mg	Zaleplon 10 mg	Zaleplon 20 mg	Zolpidem 10 mg	P value
2 (NS)	2 (NS)	1 (NS)	2 (NS)	

Number (p vs placebo)

Median number of awakenings at week 4

Zaleplon 5 mg	Zaleplon 10 mg	Zaleplon 20 mg	Zolpidem 10 mg	P value
2 (NS)	2 (NS)	1 (NS)	2 (NS)	

Number (p vs placebo)

Evidence Table 1. Head to head controlled trials: Efficacy

Author: **Elie** **Trial type:** **H2H** **Quality rating:** **Fair**

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

Sleep quality (1=excellent, 7=extremely poor)

Sleep quality mean score at baseline

Zaleplon 5 mg	Zaleplon 10 mg	Zaleplon 20 mg	Zolpidem 10 mg	P value
4.6 (NS)	4.5 (NS)	4.5 (NS)	4.4 (NS)	

Score (p vs placebo)

Sleep quality mean score at week 1

Zaleplon 5 mg	Zaleplon 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 placebo)

Sleep quality mean score at week 2

Zaleplon 5 mg	Zaleplon 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 placebo)

Sleep quality mean score at week 3

Zaleplon 5 mg	Zaleplon 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 placebo)

Sleep quality mean score at week 4

Zaleplon 5 mg	Zaleplon 10 mg	Zaleplon 20 mg	Zolpidem 10 mg	P value
3.8 (NS)	3.7 (NS)	3.6 (NS)	3.4 (p<0.01)	

Score (p vs placebo)

Evidence Table 1. Head to head controlled trials: Efficacy

Author: **Elie** **Trial type:** **H2H** **Quality rating:** **Fair**

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

Sleep latency

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

Zaleplon 5 mg	Zaleplon 10 mg	Zaleplon 20 mg	Zolpidem 10 mg	P value
42 (0.005)	36 (<0.001)	33 (<0.00)	45 (0.47)	

Number (p vs placebo)

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

Zaleplon 5 mg	Zaleplon 10 mg	Zaleplon 20 mg	Zolpidem 10 mg	P value
35 (0.002)	32 (0.001)	31 (<0.00)	37 (0.006)	

Number (p vs placebo)

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

Zaleplon 5 mg	Zaleplon 10 mg	Zaleplon 20 mg	Zolpidem 10 mg	P value
31 (0.004)	30 (0.004)	28 (<0.00)	34 (0.043)	

Number (p vs placebo)

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

Zaleplon 5 mg	Zaleplon 10 mg	Zaleplon 20 mg	Zolpidem 10 mg	P value
31 (0.093)	28 (0.010)	27 (0.001)	36 (0.054)	

Number (p vs placebo)

Evidence Table 1. Head to head controlled trials: Efficacy

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: 351 (59 %) Female

Ethnicity: 11% Black
3% Hispanic
<1% Native American
1.5% Asian
<1% Other
84% White

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.

Number Screened: NR
Eligible: 830
Enrolled: 595

Number Withdrawn: 9
Lost to fu: NR
Analyzed: 586

Intervention:

Run-in : 7
Wash out : no
Allow other medication : NR

Drug name	dosage	N=	Duration	Withdrawals due to AEs/ Total withdrawal
Zaleplon	5 mg	118	4 week	3 / 20
Zaleplon	10 mg	119	4 week	5 / 18

Evidence Table 1. Head to head controlled trials: Efficacy

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	

Evidence Table 1. Head to head controlled trials: Efficacy

Author: **Fry** **Trial type:** **H2H** **Quality rating:** **Fair**

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

Outcome Measurement:

Patient questionnaire

Efficacy Outcome List:

Primary outcome	Outcome:
☑	Sleep latency
☐	Total sleep time
☐	Number of awakenings
☐	Sleep quality

Results

Sleep latency

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

Zaleplon 5 mg	Zaleplon 10 mg	Zaleplon 20 mg	Zolpidem 10 mg	P value
45.36 (0.764)	40.71 (0.490)	35.71 (0.003)	45.71 ( )	

Number (p vs zolpidem 10 mg)

Time to sleep onset at week 2 (median, minutes)

Zaleplon 5 mg	Zaleplon 10 mg	Zaleplon 20 mg	Zolpidem 10 mg	P value
43.57 (0.959)	36.43 (0.183)	31.67 (<0.00)	46.43 ( )	

Number (p vs zolpidem 10 mg)

Time to sleep onset at week 3 (median, minutes)

Zaleplon 5 mg	Zaleplon 10 mg	Zaleplon 20 mg	Zolpidem 10 mg	P value
40.71 (0.323)	35.71 (0.110)	30.00 (<0.00)	44.29 ( )	

Number (p vs zolpidem 10 mg)

Time to sleep onset at week 4 (median, minutes)

Zaleplon 5 mg	Zaleplon 10 mg	Zaleplon 20 mg	Zolpidem 10 mg	P value
45.63 (0.124)	35.00 (0.988)	30.00 (0.037)	34.29 ( )	

Number (p vs zolpidem 10 mg)

Evidence Table 1. Head to head controlled trials: Efficacy

Author: **Fry** **Trial type:** **H2H** **Quality rating:** **Fair**

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

Total sleep time

Total sleep time at week 1 (median, minutes)

Zaleplon 5 mg	Zaleplon 10 mg	Zaleplon 20 mg	Zolpidem 10 mg	P value
360.0 (NS)	360.6 (NS)	368.6 (<0.05)	377.1 (<0.001)	

Number (p vs placebo)

Total sleep time at week 2 (median, minutes)

Zaleplon 5 mg	Zaleplon 10 mg	Zaleplon 20 mg	Zolpidem 10 mg	P value
366.4 (NS)	364.3 (NS)	368.6 (NS)	384.4 (<0.05)	

Number (p vs placebo)

Total sleep time at week 3 (median, minutes)

Zaleplon 5 mg	Zaleplon 10 mg	Zaleplon 20 mg	Zolpidem 10 mg	P value
361.4 (NS)	377.1 (NS)	386.8 (<0.05)	392.1 (<0.01)	

Number (p vs placebo)

Total sleep time at week 4 (median, minutes)

Zaleplon 5 mg	Zaleplon 10 mg	Zaleplon 20 mg	Zolpidem 10 mg	P value
360.0 (NS)	376.3 (NS)	377.5 (NS)	392.9 (<0.05)	

Number (p vs placebo)

Number of awakenings

Number of awakenings at week 1 (median)

Zaleplon 5 mg	Zaleplon 10 mg	Zaleplon 20 mg	Zolpidem 10 mg	P value
1.93 (NS)	1.69 (NS)	1.75 (NS)	1.59 (<0.01)	

Number (p vs placebo)

Number of awakenings at week 2 (median)

Zaleplon 5 mg	Zaleplon 10 mg	Zaleplon 20 mg	Zolpidem 10 g	P value
1.67 (NS)	1.69 (NS)	1.50 (<0.00)	1.50 (<0.001)	

Number (p vs placebo)

Number of awakenings at week 3 (median)

Zaleplon 5 mg	Zaleplon 10 mg	Zaleplon 20 mg	Zolpidem 10 mg	P value
1.71 (NS)	1.71 (NS)	1.43 (<0.05)	1.71 (NS)	

Number (p vs placebo)

Number of awakenings at week 4 (median)

Zaleplon 5 mg	Zaleplon 10 mg	Zaleplon 20 mg	Zolpidem 10 mg	P value
1.71 (NS)	1.57 (NS)	1.60 (NS)	1.67 (NS)	

Number (p vs placebo)

Evidence Table 1. Head to head controlled trials: Efficacy

Author: **Fry** **Trial type:** **H2H** **Quality rating:** **Fair**

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

Sleep quality (1=excellent, 7=extremely poor)

Sleep quality at week 1 (median)

Zaleplon 5 mg	Zaleplon 10 mg	Zaleplon 20 mg	Zolpidem 10 mg	P value
3.43 (NS)	3.57 (NS)	3.43 (<0.01)	3.38 (<0.001)	
Score (p vs placebo)				

Sleep quality at week 2 (median)

Zaleplon 5 mg	Zaleplon 10 mg	Zaleplon 20 mg	Zolpidem 10 mg	P value
3.43 (NS)	3.57 (NS)	3.43 (NS)	3.29 (<0.05)	
Score (p vs placebo)				

Sleep quality at week 3 (median)

Zaleplon 5 mg	Zaleplon 10 mg	Zaleplon 20 mg	Zolpidem 10 mg	P value
3.43 (NS)	3.43 (NS)	3.29 (NS)	3.29 (<0.05)	
Score (p vs placebo)				

Sleep quality at week 4 (median)

Zaleplon 5 mg	Zaleplon 10 mg	Zaleplon 20 mg	Zolpidem 10 mg	P value
3.38 (NS)	3.54 (NS)	3.29 (NS)	3.15 (<0.05)	
Score (p vs placebo)				

Evidence Table 1. Head to head controlled trials: Efficacy

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
SD: 12.7

Gender: 277 (58 %) Female

Ethnicity: NR

Number Screened: NR
Eligible: NR
Enrolled: 479

Number Withdrawn: 77
Lost to fu: NR
Analyzed: 428

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
Allow other medication : No

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

Evidence Table 1. Head to head controlled trials: Efficacy

Author: **Tsutsui** **Trial type:** **H2H** **Quality rating:** **Fair**

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

Outcome Measurement:

Patient diary

Efficacy Outcome List:

Primary outcome	Outcome:
☑	Global improvement of sleep disorders
☐	Patient's impression of treatment efficacy

Results

Global improvement of sleep disorders

Patients rated by the investigator as "markedly improved"

Zolpidem	Zopiclone			P value
18.7 ( )	16.4 ( )	( )	( )	NS

(%) ( )

Patients rated by the investigator as "moderately improved"

Zolpidem	Zopiclone			P value
49.3 ( )	45.2 ( )	( )	( )	NS

(%) ( )

Patients rated by the investigator as "slightly improved"

Zolpidem	Zopiclone			P value
26.8 ( )	31.1 ( )	( )	( )	NS

(%) ( )

Patients rated by the investigator as "unchanged"

Zolpidem	Zopiclone			P value
5.3 ( )	6.4 ( )	( )	( )	NS

(%) ( )

Evidence Table 1. Head to head controlled trials: Efficacy

Author: **Tsutsui** **Trial type:** **H2H** **Quality rating:** **Fair**

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

Patient's impression of treatment efficacy

# Patients rating the treatment as "markedly effective"	Zolpidem	Zopiclone			P value
	18.2 ( )	16.0 ( )	( )	( )	NS
	(%) ( )				
# Patients rating the treatment as "moderately effective"	Zolpidem	Zopiclone			P value
	46.4 ( )	45.2 ( )	( )	( )	NS
	(%) ( )				
# Patients rating the treatment as "slightly effective"	Zolpidem	Zopiclone			P value
	29.7 ( )	33.3 ( )	( )	( )	NS
	(%) ( )				
# Patients rating the treatment as "ineffective"	Zolpidem	Zopiclone			P value
	5.7 ( )	5.5 ( )	( )	( )	NS
	(%) ( )				

Evidence Table 2. Head to head controlled trials: Rebound Insomnia

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

Number Screened: 1224
Eligible: 551
Enrolled: 549

Number Withdrawn: 2
Lost to fu:
Analyzed: 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:

Drug name	dosage		N=	Duration	Withdrawals due to AEs/ 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	Zolpidem 5mg	Placebo	P value
30 (NS)	45 (NS)	60 (<0.01)	44 (NA)	
Number (p vs placebo)				

Evidence Table 2. Head to head controlled trials: Rebound Insomnia

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

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

Zaleplon 5mg	Zaleplon 10mg	Zolpidem 5mg	Placebo	P value
330 (NS)	315 (<0.05)	300 (<0.00)	317.50 (NA)	

Number (p vs placebo)

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)

Evidence Table 2. Head to head controlled trials: Rebound Insomnia

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

Age: 42.8
Range: NR
SD: 12.4

Gender: 39 (64 %) Female

Ethnicity: 99% white
<1% black
<1% Asian

Number Screened: NR
Eligible: NR
Enrolled: 615

Number Withdrawn: 41
Lost to fu: NR
Analyzed: 574

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.

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:

Drug name	dosage	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	/

Rebound:

Rebound insomnia

# Rebound: Sleep latency on night +1 (median, minutes)	Zaleplon 5mg	Zaleplon 10mg	Zaleplon 20mg	Zolpidem 10mg	P value
	51.7 (NS)	57.6 (NS)	50.4 (NS)	91.6 (<0.00)	

Evidence Table 2. Head to head controlled trials: Rebound Insomnia

Author:	**Elie**	**Trial type:**	**H2H**	**Quality rating:**	**Fair**
Year:	**1999**	**Country:**	**Multinational (Canada and Europe)**	**Funding:**	**Wyeth-Ayerst**

Number (p vs placebo)

#		Zaleplon 5mg	Zaleplon 10mg	Zaleplon 20mg	Zolpidem 10mg	P value
	Rebound: Sleep duration on night +1 (median, minutes)	344.3 (NS)	349.6 (NS)	339.2 (NS)	324.7 (<0.05)	

Number (p vs placebo)

#		Zaleplon 5mg	Zaleplon 10mg	Zaleplon 20mg	Zolpidem 10mg	P value
	Rebound: Number of awakenings on night +1 (median)	2.3 (NS)	2.0 (NS)	1.8 (NS)	2.6 (<0.01)	

Number (p vs placebo)

Evidence Table 2. Head to head controlled trials: Rebound Insomnia

Author: Fry | **Trial type:** H2H | **Quality rating:** Fair

Year: 2000 | **Country:** US | **Funding:** Wyeth-Ayerst

Design:

Study design RCT
DB
Parallel

Setting Multicenter

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

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.

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.

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:

Drug name	dosage	N=	Duration	Withdrawals due to AEs/ 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

Evidence Table 2. Head to head controlled trials: Rebound Insomnia

Author:	**Fry**	**Trial type:**	**H2H**	**Quality rating:**	**Fair**
Year:	**2000**	**Country:**	**US**	**Funding:**	**Wyeth-Ayerst**

Rebound:

Rebound

	Zaleplon 5mg	Zaleplon 10mg	Zaleplon 20mg	Zolpidem 10mg	P value
# rebound : Sleep latency on discontinuation night 1 (minutes, median)	45 (NS)	40 (NS)	30 (NS)	60 (<0.01)	
	Number (p vs placebo)				
# rebound : Number of awakenings on discontinuation night 1	Zaleplon 5mg	Zaleplon 10mg	Zaleplon 20mg	Zolpidem 10mg	P value
	2 (NS)	2 (NS)	2 (NS)	2 (<0.05)	
	Number (p vs placebo)				
# rebound : Sleep duration on discontinuation night 1 (median, minutes)	Zaleplon 5mg	Zaleplon 10mg	Zaleplon 20mg	Zolpidem 10mg	P value
	360 (NS)	360 (NS)	360 (NS)	330 (<0.00)	
	Number (p vs placebo)				

Evidence Table 2. Head to head controlled trials: Rebound Insomnia

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
SD: 12.7

Gender: 27 (58 %) Female

Ethnicity: NR

Number Screened: NR
Eligible: NR
Enrolled: 479

Number Withdrawn: 77
Lost to fu: NR
Analyzed: 428

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:

Drug name	dosage	N=	Duration	Withdrawals due to AEs/ 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	Zopiclone			P value
	4.5 ( )	15.4 ( )	( )	( )	0.005
	% ( )				

Evidence Table 2. Head to head controlled trials: Rebound Insomnia

Author:	**Tsutsui**	**Trial type:**	**H2H**	**Quality rating:**	**Fair**
Year:	**2001**	**Country:**	**Japan**	**Funding:**	**Not reported**

Evidence Table 3. Head to head controlled trials: Adverse Events

Author: **Allain** **Trial type:** **H2H** **Quality rating:** **Fair**

Year: **2003** **Country:** **France** **Funding:** **Sanofi-Synthelabo**

Design:

Study design RCT
DB
Crossover

Setting Single Center

Age: 52
Range: NR
SD: 7

Gender: 26 (49 %) Female

Ethnicity: NR

Number Screened: NR
Eligible: NR
Enrolled: 53

Number Withdrawn: 0
Lost to fu: 0
Analyzed: 53

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.

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.

Comments:

Intervention:

Run-in : No
Wash out : No
Allow other medication : NR

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

Adverse Events:

Adverse events reported

Any adverse event

Zolpidem	Zaleplon			P value:
5.7 (3/53)	7.5 (4/53)	( )	( )	NR

% (number)

Evidence Table 3. Head to head controlled trials: Adverse Events

Author:	**Allain**	**Trial type:**	**H2H**	**Quality rating:**	**Fair**
Year:	**2003**	**Country:**	**France**	**Funding:**	**Sanofi-Synthelabo**

Total withdrawals: none

Withdrawals due to adverse events: none

Evidence Table 3. Head to head controlled trials: Adverse Events

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

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:

Number Screened: 1224
Eligible: 551
Enrolled: 549

Number Withdrawn: 2
Lost to fu:
Analyzed: 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:

Run-in : 7
Wash out : 7-21
Allow other medication : No

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

Adverse Events:

Adverse events

Frequency of treatment-emergent adverse events

Placebo	Zaleplon 5 mg	Zaleplon 10 mg	Zolpidem 5 mg	P value:
56 ( )	56 ( )	59 ( )	63 ( )	NS
% ( )				

Evidence Table 3. Head to head controlled trials: Adverse Events

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

Year: **1999** **Country:** **US** **Funding:** **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	Zaleplon 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

Evidence Table 3. Head to head controlled trials: Adverse Events

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

Age: 42.8
Range: NR
SD: 12.4

Gender: 39 (64 %) Female

Ethnicity: 99% white
<1% black
<1% Asian

Number Screened: NR
Eligible: NR
Enrolled: 615

Number Withdrawn: 41
Lost to fu: NR
Analyzed: 574

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.

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	dosage	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	/

Evidence Table 3. Head to head controlled trials: Adverse Events

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

Zaleplon 5 mg	Zaleplon 10 mg	Zaleplon 20 mg	Zolpidem 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)

Evidence Table 3. Head to head controlled trials: Adverse Events

Author: Erman **Trial type:** H2H **Quality rating:** Poor

Year: NR **Country:** US **Funding:**

Design:

Study design

Setting

Age:
Range:
SD:

Gender: 0 (0 %) Female

Ethnicity:

Number Screened:
Eligible:
Enrolled:

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:

Evidence Table 3. Head to head controlled trials: 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

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

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 impairment due to sleep disturbance, and either an average total sleep duration per night of 6.5 hours or less or prolonged (30 minutes or more) or frequent nocturnal awakenings (three or more per night) with difficulty returning to sleep.

Exclusion criteria:

Patients excluded if they experienced transient insomnia, situational insomnia, or insomnia associated with sleep-wake schedules (e.g., shift-work) or the use of alcohol or drugs. Also excluded were 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.

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 : 7
Wash out : no
Allow other medication : NR

Drug name	dosage	N=	Duration	Withdrawals due to AEs/ Total withdrawal
Zaleplon	5 mg	118	4 week	3 / 20
Zaleplon	10 mg	119	4 week	5 / 18

Evidence Table 3. Head to head controlled trials: Adverse Events

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

Zaleplon 5 mg	Zaleplon 10 mg	Zaleplon 20 mg	Zolpidem 10 mg	P value:
16.9 ( )	15.0 ( )	14.5 ( )	17.2 ( )	NR
% ( )				

Withdrawals due to adverse effects

Withdrawals due to adverse effects

Zaleplon	Zaleplon	Zaleplon	Zolpidem	P value:
3 ( )	4 ( )	9 ( )	6 ( )	NR
% ( )				

Evidence Table 3. Head to head controlled trials: Adverse Events

Author: **Lemoine** **Trial type:** **H2H** **Quality rating:** **Fair**

Year: **1995** **Country:** **France** **Funding:** **Not reported**

Design:

Study design RCT
DB
Parallel

Setting Multicenter

Age:
Range:
SD:

Gender: (%) Female

Ethnicity:

Number Screened: NR
Eligible: NR
Enrolled: 394

Number Withdrawn: 15
Lost to fu: 2
Analyzed: 390

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 :

Drug name	dosage	N=	Duration	Withdrawals due to AEs/ Total withdrawal
	mg	100		/

Adverse Events:

Evidence Table 3. Head to head controlled trials: Adverse Events

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
SD: 12.7

Gender: 27 (58 %) Female

Ethnicity: NR

Number Screened: NR
Eligible: NR
Enrolled: 479

Number Withdrawn: 77
Lost to fu: NR
Analyzed: 428

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
Allow other medication : No

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

Adverse Events:

Total withdrawals

#	Zolpidem	Zopiclone			P value:

Evidence Table 3. Head to head controlled trials: Adverse Events

Author: **Tsutsui** **Trial type:** **H2H** **Quality rating:** **Fair**

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

Total withdrawals

Zolpidem	Zopiclone			P value:
13.9 ( )	18.1 ( )	( )	( )	NS

% ( )

Withdrawals due to adverse evects

\# Withdrawals due to adverse evects

Zolpidem	Zopiclone			P value:
6.1 ( )	8.1 ( )	( )	( )	NR

% ( )

Adverse events

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

Zolpidem	Zopiclone			P value:
31 ( )	45 ( )	( )	( )	0.004

% ( )

Evidence Table 4. Active controlled trials (Adults): Efficacy

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

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

Design:

Study design RCT
DB
Parallel

Setting Multicenter

Age: NR
Range: 20-69
SD:

Gender: NR (0 %) Female

Ethnicity: NR

Number Screened: NR
Eligible: NR
Enrolled: 119

Number Withdrawn: 5
Lost to fu: 15
Analyzed: 99

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

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.

Comments:

Intervention:

Run-in : 7
Wash out : 7
Allow other medication : No

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

Evidence Table 4. Active controlled trials (Adults): Efficacy

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

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

Outcome Measurement:

Diary
100-mm visual analogue scales
sleep questionnaire

Efficacy Outcome List:

Primary outcome	Outcome:
☐	The time they took medicine
☐	Sleep duration
☐	No. of times woke-up
☐	Wake up earlier then wished
☐	Sleep latency
☐	How much they dreamed
☐	Slept well - sleep quality
☐	Feeling wide awake
☐	

Results

100-mm visual analogue scales

sleep quality at week 3 (in figure), higher score=better

Zopiclone	Nitrazepam	Placebo		P value
68 (<0.05)	66 (<0.05)	49 (NA)	( )	

Score (p vs placebo)

time to fall asleep at week 3 (in figure), higher score=better

Zopiclone	Nitrazepam	Placebo		P value
61 (<0.05)	63 (<0.05)	44 (NA)	( )	

Score (p vs placebo)

all sleep parameters

Zopiclone	Nitrazepam			P value
NR ( )	NR ( )	( )	( )	NS

Score ( )

Evidence Table 4. Active controlled trials (Adults): Efficacy

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

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

sleep questionnaire

\# early morning awakenings at week 3 (in figure), higher score=worse

Zopiclone		Nitrazepam		Placebo				P value
0.38	(<0.05)	0.35	(<0.05)	0.78	(NA)		( )	

proportion (p vs placebo)

\# physicians global assessment

Zopiclone		Nitrazepam						P value
NR	( )	NR	( )		( )		( )	NS

Score ( )

\# wide-awake in the morning

Zopiclone		Nitrazepam						P value
better	( )	-	( )		( )		( )	0.02

Score ( )

Evidence Table 4. Active controlled trials (Adults): Efficacy

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 Screened: NR
Eligible: NR
Enrolled: 121

Number Withdrawn: NR
Lost to fu: 8
Analyzed: 113

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	Withdrawals due to AEs/ Total withdrawal
Zopiclone	7.5 mg	121	7 day	0 / 8
Triazolam	0.5 mg	121	7 day	0 / 8

Evidence Table 4. Active controlled trials (Adults): Efficacy

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

Year: **1987** **Country:** **France** **Funding:**

Outcome Measurement:

Spiegel and Norris' visual analogue scale
rated by physicians

Efficacy Outcome List:

Primary outcome	Outcome:
☑	Sleep latency
☑	Sleep quality
☑	Sleep duration
☑	Night waking
☑	Dreams
☑	Morning state
☑	Global evaluation
☐	severity of insomnia
☐	therapeutic efficacy
☐	intensity of side-effects

Results

Spiegel and Norris' visual analogue scale

Delay in falling asleep (higher score=better)- change from baseline

Zopiclone		Triazolam				P value
1.86	(1.35)	1.43	(1.12)	( )	( )	<0.01

Score (SD)

quality of sleep (higher score=better)- change from baseline

Zopiclone		Triazolam				P value
1.98	(1.25)	1.47	(1.06)	( )	( )	<0.01

Score (SD)

length of sleep (higher score=better)- change from baseline

Zopiclone		Triazolam				P value
1.47	(1.26)	1.26	(0.97)	( )	( )	NS

Score (SD)

night waking (higher score=better)- change from baseline

Zopiclone		Triazolam				P value
1.64	(1.38)	1.34	(1.11)	( )	( )	<0.05

Score (SD)

Evidence Table 4. Active controlled trials (Adults): Efficacy

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

Year: **1987** **Country:** **France** **Funding:**

dream (higher score=better)- change from baseline

Zopiclone		Triazolam				P value
0.40	(1.44)	0.32	(1.10)	( )	( )	NS

Score (SD)

morning state (higher score=better)- change from baseline

Zopiclone		Triazolam				P value
1.66	(1.46)	1.13	(1.04)	( )	( )	<0.001

Score (SD)

global evaluation (higher score=better)- change from baseline

Zopiclone		Triazolam				P value
1.96	(1.40)	1.43	(1.04)	( )	( )	<0.001

Score (SD)

rated by physicians

therapeutic efficacy- preferences of the patients

Zopiclone		Temazepam				P value
62	(54.9)	26	(23)	( )	( )	<0.01

Number (%)

Evidence Table 4. Active controlled trials (Adults): Efficacy

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

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

Design:

Study design RCT
SB
Parallel

Setting Single Center

Age: NR
Range: >18
SD:

Gender: NR (0 %) Female

Ethnicity: NR

Number Screened: NR
Eligible: NR
Enrolled: 88

Number Withdrawn: 4
Lost to fu: 33
Analyzed: 51

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

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

Evidence Table 4. Active controlled trials (Adults): Efficacy

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

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

Outcome Measurement:

Leeds sleep evaluation questionnaire (LSEQ)

Efficacy Outcome List:

Results

LSEQ - pre vs. during intervention

all 10 items (low=beneficial effect)

Zopiclone				P value
Low ( )	( )	( )	( )	p<0.01

Score ( )

6 of the 10 items - getting to sleep and quality of sleep

Midazolam				P value
Low ( )	( )	( )	( )	p<0.01

Score ( )

all 10 items

Zopiclone	Midazolam			P value
NR ( )	NR ( )	( )	( )	NS

Score ( )

LSEQ - pre vs. two nights after medication was discontinued (rebound)

5 of 10 items

Zopiclone				P value
High ( )	( )	( )	( )	<0.01

Score ( )

all 10 items

Midazolam				P value
NR ( )	( )	( )	( )	NS

Score ( )

all 10 items

Zopiclone	Midazolam			P value
NR ( )	NR ( )	( )	( )	NS

Score ( )

Evidence Table 4. Active controlled trials (Adults): Efficacy

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

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

Design:

Study design RCT
DB
Parallel

Setting Multicenter

Age: 50.9
Range: 30-65
SD:

Gender: 27 (71 %) Female

Ethnicity: 100% caucasian

Number Screened: NR
Eligible: NR
Enrolled: 38

Number Withdrawn: 4
Lost to fu: NR
Analyzed: 38

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.

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.

Comments:

Intervention:

Run-in : no
Wash out : 7
Allow other medication : No medication known to cause drowsiness

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

Evidence Table 4. Active controlled trials (Adults): Efficacy

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

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

Outcome Measurement:

LSEQ
Patient diary

Efficacy Outcome List:

Primary outcome	Outcome:
☐	LSEQ: Ease of getting to sleep
☐	LSEQ: Quality of sleep
☐	LSEQ: Ease of awakening
☐	LSEQ: Behavior following wakefulness
☐	Global assessment of efficacy

Results

LSEQ: Ease of getting to sleep

Mean score at week 1

Zopiclone	Triazolam			P value
57.91 ( )	65.18 ( )	( )	( )	NS (NR)

Score ( )

LSEQ: Quality of sleep

Mean score at week 1

Zopiclone	Triazolam			P value
67.13 ( )	72.13 ( )	( )	( )	NS (NR)

Score ( )

LSEQ Ease of awakening

Mean score at week 1

Zopiclone	Triazolam			P value
68.79 ( )	53.03 ( )	( )	( )	NS (NR)

Score ( )

LSEQ Behavior following wakefulness

Mean score at week 1

Zopiclone	Triazolam			P value
58.35 ( )	54.49 ( )	( )	( )	NS (NR)

Score ( )

Evidence Table 4. Active controlled trials (Adults): Efficacy

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

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

Global assessment of efficacy

Physicians' global assessment of efficacy

Zopiclone	Triazolam			P value
NR, high ( )	NR, high ( )	( )	( )	NS

Score ( )

Patients' global assessment of efficacy

Zopiclone	Triazolam			P value
NR, high ( )	NR, high ( )	( )	( )	NS

Score ( )

Evidence Table 4. Active controlled trials (Adults): Efficacy

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

Age: 41.6
Range: 21-60
SD: 9.5

Gender: 24 (51 %) Female

Ethnicity: NR

Number Screened: NR
Eligible: NR
Enrolled: 47

Number Withdrawn: 0
Lost to fu: 0
Analyzed: 47

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.

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.

Comments:

Intervention:

Run-in : NR
Wash out : 5-12
Allow other medication : No

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

Evidence Table 4. Active controlled trials (Adults): Efficacy

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

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

Outcome Measurement:

polysomnography
patient reports

Efficacy Outcome List:

Primary outcome	Outcome:
☐	latency to persistent sleep
☐	total sleep time
☐	sleep quality
☐	ease of falling asleep

Results

polysomnography

latency to persistent sleep

Zaleplon 10mg	Zaleplon 40mg	Triazolam 0.25mg		P value
22.5 (NS)	18.6 (<0.05)	27.5 (NA)	( )	

minutes (p vs triazolam)

total sleep time

Zaleplon 10mg	Zaleplon 40mg	Triazolam 0.25mg		P value
386.3 (<0.05)	392.6 (<0.05)	407.8 (NA)	( )	

minutes (p vs triazolam)

Evidence Table 4. Active controlled trials (Adults): Efficacy

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

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

patient reports

latency to sleep

Zaleplon 10mg	Zaleplon 40mg	Triazolam 0.25mg		P value
38.8 (NS)	29.3 (NS)	36.4 (NA)	( )	

minutes (p vs triazolam)

total sleep time

Zaleplon 10mg	Zaleplon 40mg	Triazolam 0.25mg		P value
358.1 (NS)	375.5 (NS)	386.8 (NA)	( )	

minutes (p vs triazolam)

sleep quality

Zaleplon 10mg	Zaleplon 40mg	Triazolam 0.25mg		P value
2.5 (NS)	2.7 (NS)	2.7 (NA)	( )	

Score (p vs triazolam)

ease of falling asleep

Zaleplon 10mg	Zaleplon 40mg	Triazolam 0.25mg		P value
65.4 (NS)	74.1 (NS)	67.3 (NA)	( )	

Score (p vs triazolam)

Evidence Table 4. Active controlled trials (Adults): Efficacy

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

Age: 38.1
Range: 21-60
SD: 11.1

Gender: 14 (39 %) Female

Ethnicity: NR

Number Screened: NR
Eligible: NR
Enrolled: 36

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

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.

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.

Comments:

Intervention:

Run-in : NR
Wash out : 5-12
Allow other medication : No

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

Evidence Table 4. Active controlled trials (Adults): Efficacy

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

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

Outcome Measurement:

polysomnography
patient reports

Efficacy Outcome List:

Primary outcome	Outcome:
☐	latency to persistent sleep
☐	total sleep time
☐	sleep quality
☐	ease of falling asleep

Results

polysomnography

latency to persistent sleep

Zaleplon 20mg	Zaleplon 60mg	Triazolam 0.25mg		P value
30.5 (NS)	21.7 (<0.05)	27.6 (NA)	( )	

minutes (p vs triasolam)

total sleep time

Zaleplon 20mg	Zaleplon 60mg	Triazolam 0.25mg		P value
391.3 (<0.05)	404.7 (<0.05)	422.8 (NA)	( )	

minutes (p vs triasolam)

Evidence Table 4. Active controlled trials (Adults): Efficacy

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

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

patient reports

# latency to sleep	Zaleplon 20mg	Zaleplon 60mg	Triazolam 0.25mg		P value
	45.5 (NS)	36.6 (NS)	41.9 (NA)	( )	
	minutes (p vs triazolam)				

# total sleep time	Zaleplon 20mg	Zaleplon 60mg	Triazolam 0.25mg		P value
	356 (<0.05)	376.3 (NS)	393.5 (NA)	( )	
	minutes (p vs triazolam)				

# sleep quality (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 triazolam)				

# ease of falling asleep (lower score=better)	Zaleplon 20mg	Zaleplon 60mg	Triazolam 0.25mg		P value
	58.8 (NS)	64.5 (NS)	61 (NA)	( )	
	Score (p vs triazolam)				

Evidence Table 4. Active controlled trials (Adults): Efficacy

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

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

Number Screened: NR
Eligible: NR
Enrolled: 36

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

Run-in : 7
Wash out : 3
Allow other medication : NR

Drug name	dosage	N=	Duration	Withdrawals due to AEs/ 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

Evidence Table 4. Active controlled trials (Adults): Efficacy

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

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

Outcome Measurement:

post-sleep questionnaire

Efficacy Outcome List:

Primary outcome	Outcome:
☐	rapidity of sleep onset
☐	duration of sleep
☐	nocturnal awakenings

Results

post-sleep quesionnaire

rapidity of sleep onset at week 4 (higher score=better)

Zopiclone		Flurazepam		Placebo				P value
11.6	(NS)	11.2	(NS)	10.5	(NA)		( )	

Score (p vs placebo)

duration of sleep at week 4 (higher score=better)

Zopiclone		Flurazepam		Placebo				P value
7.3	(NS)	7.1	(NS)	6.5	(NA)		( )	

Score (p ve placebo)

nocturnal awakenings at week 4 (higher score=worse)

Zopiclone		Flurazepam		Placebo				P value
3.5	(<0.01)	3.5	(<0.01)	5.5	(NA)		( )	

Score (p vs placebo)

Evidence Table 4. Active controlled trials (Adults): Efficacy

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

Year: **1995** **Country:** **Canada** **Funding:** **Not reported**

Design:

Study design RCT
DB
Parallel

Setting Multicenter

Age: NR
Range: 33-37
SD:

Gender: 69 (48 %) Female

Ethnicity: NR

Number Screened: 222
Eligible: 144
Enrolled: 144

Number Withdrawn: 7
Lost to fu: 1
Analyzed: 141

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.

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.

Comments:

Intervention:

Run-in : 1
Wash out : NR
Allow other medication : NR

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

Evidence Table 4. Active controlled trials (Adults): Efficacy

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

Year: **1995** **Country:** **Canada** **Funding:** **Not reported**

Outcome Measurement:

questionnaire
polysomnography

Efficacy Outcome List:

Primary outcome	Outcome:
☐	sleep latency
☐	wake time
☐	sleep quality
☐	sleep efficiency

Results

polysomnography

sleep latency

Zolpidem 10mg	Zolpidem 20mg	Flurazepam		P value
-14.7 (<0.05)	-28.4 (<0.05)	-11.8 (NA)	( )	

minutes (p vs flurazepam)

sleep efficiency

Zolpidem 10mg	Zolpidem 20mg	Flurazepam		P value
NR (NS)	NR (NS)	NR (NS)	( )	

minutes (p vs placebo)

wake time during sleep

Zolpidem 10mg	Zolpidem 20mg	Flurazepam		P value
NR (NS)	NR (NS)	NR (NS)	( )	

minutes (p vs placebo)

questionnaire

sleep quality at day 3, (higher score=better)

Zolpidem 10mg	Zolpidem 20mg	Flurazepam		P value
2.4 (<0.05)	2.5 (<0.05)	1.9 (NA)	( )	<0.05

Score (p vs flurazepam)

Evidence Table 4. Active controlled trials (Adults): Efficacy

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
Range:
SD:

Gender: NR (%) Female

Ethnicity: NR

Number Screened: NR
Eligible: NR
Enrolled: 52

Number Withdrawn: 4
Lost to fu: 0
Analyzed: 48

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 characterisics 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	Withdrawals due to AEs/ Total withdrawal
Zopiclone	7.5 mg	24	21 day	2 / 2
Triazolam	0.25 mg	24	21 day	10 / 10

Evidence Table 4. Active controlled trials (Adults): Efficacy

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

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

Outcome Measurement:

post-sleep questionnaire
Hamilton Anxiety Scale

Efficacy Outcome List:

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 Anxiety Scale

# total score	Zopiclone	Triazolam			P value
	NR ( )	NR ( )	( )	( )	NS
	Score ( )				

Evidence Table 4. Active controlled trials (Adults): Efficacy

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

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

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:

Run-in : 7
Wash out : 3
Allow other medication : NR

Drug name	dosage	N=	Duration	Withdrawals due to AEs/ 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

Evidence Table 4. Active controlled trials (Adults): Efficacy

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

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

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

Zopiclone	Triazolam	Placebo		P value
37.4 (<=0.00)	32.2 (NS)	26.8 (NA)	( )	

% (p vs placebo)

Improved sleep quality and daytime well-being- treatment period

Zopiclone	Triazolam			P value
42.3 ( )	36.3 ( )	( )	( )	0.1133

% ( )

Evidence Table 4. Active controlled trials (Adults): Efficacy

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

Age: 47.9
Range: 18-65
SD:

Gender: 90 (66 %) Female

Ethnicity: NR

Number Screened: NR
Eligible: NR
Enrolled: 136

Number Withdrawn: 9
Lost to fu: 0
Analyzed: 127

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).

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

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

Evidence Table 4. Active controlled trials (Adults): Efficacy

Author:	**Hayoun**	**Trial type:**	**Active**	**Quality rating:**	**Fair**
Year:	**1989**	**Country:**	**France**	**Funding:**	**Not reported (corresponding**

Outcome Measurement:

- # Norris visual analogue auto-evaluation scale
- # global physician's evaluation scale
- # self-evaluation questionnaire

Efficacy Outcome List:

Primary outcome	Outcome:
☐	sleep latency
☐	sleep duration
☐	no. of awakenings
☐	sleep soundness
☐	awakening without concentration difficultie

Results

Norris visual analogue auto-evaluation scale

# overall	Zopiclone	Triazolam			P value
	NR ( )	NR ( )	( )	( )	NS
	Score ( )				

global physicians' evaluation scale

# Efficacy- good or excellent	Zopiclone	Triazolam			P value
	73 ( )	69 ( )	( )	( )	NS
	% ( )				

Evidence Table 4. Active controlled trials (Adults): Efficacy

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

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

self-evaluation questionnaire

# falling asleep in less than 30 minutes	Zopiclone	Triazolam			P value
	63 ( )	84 ( )	( )	( )	NS
	% ( )				
# sleep more than 7 hours	Zopiclone	Triazolam			P value
	50 ( )	69 ( )	( )	( )	NS
	% ( )				
# awakening at night once or not at all	Zopiclone	Triazolam			P value
	64 ( )	89 ( )	( )	( )	NS
	% ( )				
# sleep heavily while still reporting a good awakening state	Zopiclone	Triazolam			P value
	55 ( )	70 ( )	( )	( )	NS
	% ( )				
# feel more rest	Zopiclone	Triazolam			P value
	80 ( )	92 ( )	( )	( )	NS
	% ( )				
# awakening with no concentration difficulties (with a significant investigator-by-treatment group interaction, p<0.01)	Zopiclone	Triazolam			P value
	56 ( )	82 ( )	( )	( )	0.04
	% ( )				
# medication aided sleep	Zopiclone	Triazolam			P value
	multiple d ( )	multiple d ( )	( )	( )	NS
	% ( )				

Evidence Table 4. Active controlled trials (Adults): Efficacy

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 Screened: NR
Eligible: NR
Enrolled: 15

Number Withdrawn: 0
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	Withdrawals due to AEs/ 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

Evidence Table 4. Active controlled trials (Adults): Efficacy

Author:	**Liu**	**Trial type:**	**Active**	**Quality rating:**	**Poor**
Year:	**1997**	**Country:**	**Taiwan**	**Funding:**	

Outcome Measurement:

- # Spiegel's sleep questionnaire (SSQ)
- # Clinical Global Impression Scale (CGI)
- # Hamilton Anxiety Rating Scale
- # Leed's sleep evaluation questionnaire (LSEQ)

Efficacy Outcome List:

Primary outcome	Outcome:
☐	therapeutic efficacy
☐	delay in falling asleep
☐	quality of sleep
☐	length of sleep
☐	night waking
☐	dream
☐	morning state
☐	global evaluation

Results

Clinical Global Impression Scale (CGI)

therapeutic efficacy

Zopiclone		Triazolam				P value
NR	(<0.005)	NR	(<0.005)	( )	( )	NS

Score (p vs baseline)

Evidence Table 4. Active controlled trials (Adults): Efficacy

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

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
4.33 (0.62)	3.47 (0.64)	( )	( )	<0.05

Score (SD)

length of aleep at day 14

Zopiclone	Triazolam			P value
3.73 (0.70)	3.53 (0.74)	( )	( )	NS

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

Score (SD)

morning state at day 14

Zopiclone	Triazolam			P value
3.93 (0.80)	3.60 (0.91)	( )	( )	NS

Score (SD)

global evaluation at day 14

Zopiclone	Triazolam			P value
4.13 (0.92)	3.93 (0.96)	( )	( )	NS

Score (SD)

Evidence Table 4. Active controlled trials (Adults): Efficacy

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 ( )

Evidence Table 4. Active controlled trials (Adults): Efficacy

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

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

Design:

Study design RCT
DB
Parallel

Setting Single Center

Age: 50
Range: 32-60
SD:

Gender: 21 (70 %) Female

Ethnicity: NR

Number Screened: NR
Eligible: NR
Enrolled: 30

Number Withdrawn: 0
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:

Run-in : 2
Wash out : 3
Allow other medication : NR

Drug name	dosage	N=	Duration	Withdrawals due to AEs/ 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

Evidence Table 4. Active controlled trials (Adults): Efficacy

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

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

Outcome Measurement:

sleep questionnaire

Efficacy Outcome List:

Primary outcome	Outcome:
☐	total sleep time
☐	sleep latency
☐	no. of awakenings
☐	duration of early wakefulness

Results

sleep questionnaire

total sleep time at day 14, the end of treatment

Zopiclone	Flurazepam	Placebo		P value
417.5 (<0.05)	410.5 (<0.05)	328.0 (<0.05)	( )	

minutes (p vs baseline)

sleep latency at day 14, the end of treatment

Zopiclone	Flurazepam	Placebo		P value
28.8 (<0.05)	31.5 (<0.05)	69.8 (NS)	( )	

minutes (p vs baseline)

no of awakenings at day 14, the end of treatment

Zopiclone	Flurazepam	Placebo		P value
1.15 (<0.05)	1.55 (<0.05)	1.65 (<0.05)	( )	

Number (p vs baseline)

duration of early wakefulness at day 14, the end of treatment

Zopiclone	Flurazepam	Placebo		P value
37.0 (NS)	14.7 (NS)	43.1 (NS)	( )	

minutes (p vs baseline)

all sleep itmes at day 14, the end of treatment

Zopiclone	Flurazepam			P value
as above ( )	as above ( )	( )	( )	NS

minutes ( )

Evidence Table 4. Active controlled trials (Adults): Efficacy

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

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 Screened: NR
Eligible: NR
Enrolled: 24

Number Withdrawn: 1
Lost to fu: 0
Analyzed: 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:

Run-in : 3
Wash out : 3
Allow other medication : NR

Drug name	dosage	N=	Duration	Withdrawals due to AEs/ 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

Evidence Table 4. Active controlled trials (Adults): Efficacy

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

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

Outcome Measurement:

polysomnogram
sleep questionnaire

Efficacy Outcome List:

Primary outcome	Outcome:
☑	sleep latency
☑	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	Triazolam			P value
-117 (114.6)	-39 (44.5)	( )	( )	NR

minutes (SD)

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

Zolpidem	Triazolam			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	Triazolam			P value
1.8 (2.1)	0.3 (1.3)	( )	( )	NR

Number (SD)

Evidence Table 4. Active controlled trials (Adults): Efficacy

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

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

number of sleep cycles (change from baseline) - night 15-16

Zolpidem		Triazolam				P value
1.7	(2.0)	0	(1)	( )	( )	NR

Number (SD)

number of sleep cycles (change from baseline) - night 29-30

Zolpidem		Triazolam				P value
1.2	(1.3)	0.3	(1.5)	( )	( )	NR

Number (SD)

Evidence Table 4. Active controlled trials (Adults): Efficacy

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

Age: 46.9
Range:
SD: 1.4

Gender: 28 (47 %) Female

Ethnicity: NR

Number Screened: NR
Eligible: NR
Enrolled: 60

Number Withdrawn:
Lost to fu:
Analyzed:

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.

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.

Comments:

Intervention:

Run-in : 1
Wash out : NR
Allow other medication : NR

Drug name	dosage	N=	Duration	Withdrawals due to AEs/ 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

Evidence Table 4. Active controlled trials (Adults): Efficacy

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

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

Outcome Measurement:

sleep quesionnaire
clinical global impression (CGI)

Efficacy Outcome List:

Primary outcome	Outcome:
☐	sleep induction time
☐	quality of sleep
☐	quality of morning awakening
☐	hangover effects

Results

sleep quesionnaire

sleep induction time

Zopiclone(any dose)	Flurazepam			P value
NR ( )	NR ( )	( )	( )	NS

Score ( )

quality of sleep

Zopiclone(any dose)	Flurazepam			P value
NR ( )	NR ( )	( )	( )	NS

Score ( )

quality of morning awakening

Zopiclone(any dose)	Flurazepam			P value
NR ( )	NR ( )	( )	( )	NS

Score ( )

hangover effects (except zopiclone 3.75mg)

Zopiclone	Flurazepam			P value
NR ( )	NR ( )	( )	( )	NS

Score ( )

hangover effects (zopiclone 3.75mg only), (higher score=better)

Zopiclone	Flurazepam			P value
7 ( )	5.5 ( )	( )	( )	<0.05

Score ( )

Evidence Table 4. Active controlled trials (Adults): Efficacy

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

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

CGI

\# Severity of illness (except Zopiclone 3.75mg)

Zopiclone		Flurazepam				P value
NR	( )	NR	( )	( )	( )	NS

Score ( )

\# Severity of illness (Zopiclone 3.75mg only)

Zopiclone		Flurazepam				P value
NR	( )	better	( )	( )	( )	NR

Score ( )

\# global improvement

Zopiclone(any dose)		Flurazepam				P value
NR	( )	NR	( )	( )	( )	NS

Score ( )

Evidence Table 4. Active controlled trials (Adults): Efficacy

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

Age: 38.4
Range:
SD:

Gender: 31 (52 %) Female

Ethnicity: NR

Number Screened: NR
Eligible: NR
Enrolled: 60

Number Withdrawn: 16
Lost to fu: 0
Analyzed: 44

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

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

Comments:

Intervention:

Run-in : 7
Wash out : NR
Allow other medication : NR

Drug name	dosage	N=	Duration	Withdrawals due to AEs/ 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

Evidence Table 4. Active controlled trials (Adults): Efficacy

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

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

Outcome Measurement:

sleep diary
global assessmnet efficacy

Efficacy Outcome List:

Primary outcome	Outcome:
☐	sleep latency
☐	no. of times of awakening
☐	total duration sleep

Results

sleep diary

total duration of sleep at treatment week 1

Zopiclone		Temazepam				P value
5.97	(<0.01)	5.90	(<0.05)	( )	( )	

hours (p vs baseline)

total duration of sleep at treatment week 2

Zopiclone		Temazepam				P value
6.03	(<0.01)	5.62	(NS)	( )	( )	

hours (p vs baseline)

sleep latency at treatment week 1

Zopiclone		Temazepam				P value
84	(<0.05)	25.9	(<0.05)	( )	( )	

Minutes (p vs baseline)

sleep latency at treatment week 2

Zopiclone		Temazepam				P value
64.5	(<0.05)	26.1	(NS)	( )	( )	

Minutes (p vs baseline)

no. of awakenings at treatment week 1

Zopiclone		Temazepam				P value
0.77	(NS)	1.2	(<0.05)	( )	( )	

Number (p vs baseline)

no. of awakenings at treatment week 2

Zopiclone		Temazepam				P value
0.62	(<0.05)	1.28	(NS)	( )	( )	

Number (p vs baseline)

Evidence Table 4. Active controlled trials (Adults): Efficacy

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)					

Evidence Table 4. Active controlled trials (Adults): Efficacy

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 Screened: NR
Eligible: NR
Enrolled: 26

Number Withdrawn: 2
Lost to fu: 0
Analyzed: 24

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 : 7
Wash out : 7
Allow other medication : NR

Drug name	dosage	N=	Duration	Withdrawals due to AEs/ 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

Evidence Table 4. Active controlled trials (Adults): Efficacy

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

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

Outcome Measurement:

- # Leeds sleep evaluation questionnaire (LSEQ)
- # visual analogue rating scale
- # clinical interview

Efficacy Outcome List:

Primary outcome	Outcome:
☐	the ease of getting to sleep
☐	quality of sleep
☐	ease of awakening
☐	integrity of daytime behavior
☐	mood changes
☐	sleep onset
☐	sleep duration time

Results

clinical interview

sleep onset latency at day 21

Zopiclone		Flurazepam		Placebo				P value
30	(0.02)	28	(0.04)	60	(NA)		( )	

minutes (p vs placebo)

sleep duration

Zopiclone		Flurazepam		Placebo				P value
393	(NS)	425	(0.05)	410	(NA)		( )	

minutes (p vs placebo)

visual analogue rating scale

mood changes

Zopiclone		Flurazepam		Placebo				P value
NR	( )	NR	( )	NR	( )		( )	NS

Score ( )

Evidence Table 4. Active controlled trials (Adults): Efficacy

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

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

Design:

Study design RCT
DB
Crossover

Setting Single Center

Age: NR
Range: 50-59
SD:

Gender: 12 (100 %) Female

Ethnicity: NR

Number Screened: NR
Eligible: NR
Enrolled: 12

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:

(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:

Run-in : 6
Wash out : 35
Allow other medication : No

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

Evidence Table 4. Active controlled trials (Adults): Efficacy

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

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

Outcome Measurement:

sleep questionnaire

Efficacy Outcome List:

Primary outcome	Outcome:
☐	no. of awakeninngs
☐	total sleep time
☐	sleep onset latency
☐	sleep efficienct index

Results

sleep questionnaire

no. of awakenings

Zopiclone	Flurazepam	Placebo		P value
3.2 (<0.05)	1.9 (<0.05)	6 (NA)	( )	

Number (p vs placebo)

total sleep time

Zopiclone	Flurazepam	Placebo		P value
24903 (<0.01)	25129 (<0.05)	23225 (NA)	( )	

seconds (p vs placebo)

sleep onset latency

Zopiclone	Flurazepam	Placebo		P value
1117 (<0.05)	1174 (<0.1)	1452 (NA)	( )	

seconds (p vs placebo)

sleep efficiency index

Zopiclone	Flurazepam	Placebo		P value
91.4 (<0.01)	92.2 (<0.05)	83.6 (NA)	( )	

Score (p vs placebo)

All sleep items comparing two treatment

Zopiclone	Flurazepam			P value
as above ( )	as above ( )	( )	( )	NS

Number ( )

Evidence Table 4. Active controlled trials (Adults): Efficacy

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

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

Design:

Study design RCT
DB
Parallel

Setting Multicenter

Age: 54
Range: 25-79
SD:

Gender: NR (0 %) Female

Ethnicity: NR

Number Screened: NR
Eligible: NR
Enrolled: 178

Number Withdrawn: 5
Lost to fu: 34
Analyzed: 139

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 characterstics 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	Withdrawals due to AEs/ Total withdrawal
Zolpidem	10 mg	71	14 day	/
Triazolam	0.25 mg	68	14 day	/

Evidence Table 4. Active controlled trials (Adults): Efficacy

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

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

Outcome Measurement:

\# reported by patients

\# visual analogue scales

Efficacy Outcome List:

Primary outcome	Outcome:
☐	duration of sleep
☐	no. of nocturnal awakenings
☐	sleep quality
☐	day quality

Results

reported by patients

\# total sleep times

Zolpidem		Triazolam				P value
6.9	(4.8-9.1)	7.1	(5.0-8.4)	( )	( )	NS

hours (range)

\# No. of awakenings

Zolpidem		Triazolam				P value
1	(0-4)	1	(0-5)	( )	( )	NS

Number (range)

Evidence Table 4. Active controlled trials (Adults): Efficacy

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

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

visual analogue scales

sleep quality, bad-good

Zolpidem	Triazolam			P value
69 (15-96)	69 (18-98)	( )	( )	NS

Score (Range)

morning feeling, bad-good

Zolpidem	Triazolam			P value
64 (8-94)	56 (9-98)	( )	( )	NS

Score (Range)

daytime alertness. unalert-alert

Zolpidem	Triazolam			P value
65 (6-92)	63 (26-92)	( )	( )	NS

Score (Range)

subjective day feeling

Zolpidem	Triazolam			P value
64 (6-93)	60 (9-92)	( )	( )	NS

Score (Range)

Evidence Table 4. Active controlled trials (Adults): Efficacy

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 Screened: NR
Eligible: NR
Enrolled: 22

Number Withdrawn: 0
Lost to fu: 2
Analyzed: 20

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 objecive assessment through polysomnography.

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.

Comments:

Intervention:

Run-in : 3
Wash out : No
Allow other medication : No

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

Evidence Table 4. Active controlled trials (Adults): Efficacy

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

Year: **1996** **Country:** **Italy** **Funding:** **Not reported**

Outcome Measurement:

- # polysomnography
- # visual analogue scale
- # quesionnaire

Efficacy Outcome List:

Primary outcome	Outcome:
☐	total sleep time
☐	sleep onset latency
☐	sleep efficiency
☐	no. of awakenings
☐	wake time after sleep onset
☐	REM sleep
☐	quiet-disturbed sleep
☐	alert-drowsy awakening

Results

polysomnography

# sleep onset latency- change from baseline- night 14	Zolpidem		Triazolam					P value
	-23	(21.38)	-14.8	(30.92)		( )	( )	NS
	minutes	(SD		)				
# total sleep time- change from baseline- night 14	Zolpidem		Triazolam					P value
	61.1	(43.97)	54.4	(49.70)		( )	( )	NS
	minutes	(SD		)				
# sleep efficiency- change from baseline- night 14	Zolpidem		Triazolam					P value
	14.3	(10.39)	10.7	(7.35)		( )	( )	NS
	%	(SD		)				
# wake time after sleep onset- change from baseline- night 14	Zolpidem		Triazolam					P value
	-44.9	(44.82)	-37	(25.62)		( )	( )	NS
	minutes	(SD		)				

Evidence Table 4. Active controlled trials (Adults): Efficacy

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

Year: **1996** **Country:** **Italy** **Funding:** **Not reported**

no. of awakenings- change from baseline- night 14

Zolpidem		Triazolam				P value
-2.2	(3.51)	-3.5	(2.45)	( )	( )	NS

Number (SD)

quesionnaire

time to fall asleep- change from baseline- night 14

Zolpidem		Triazolam				P value
-41.8	(32.51)	-19.9	(36.83)	( )	( )	NS

minutes (SD)

total sleep time- change from baseline- night 14

Zolpidem		Triazolam				P value
66.9	(44.53)	81.4	(46.9)	( )	( )	NS

minutes (SD)

total wake time- change from baseline- night 14

Zolpidem		Triazolam				P value
-12.1	(9.88)	-11.4	(8.53)	( )	( )	NS

minutes (SD)

no. of nocturnal awakenings- change from baseline- night 14

Zolpidem		Triazolam				P value
-1.4	(0.75)	-1.2	(1.63)	( )	( )	NS

Number (SD)

visual analogue scale

sleep quality- change from baseline- night 14

Zolpidem		Triazolam				P value
-22.8	(17.90)	-31.8	(20.66)	( )	( )	NS

Score (SD)

awakening quality- change from baseline- night 14

Zolpidem		Triazolam				P value
-16.3	(18.14)	-26.9	(23.32)	( )	( )	NS

Score (SD)

Evidence Table 4. Active controlled trials (Adults): Efficacy

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

Age: 39.6
Range: 19-64
SD: 1.5

Gender: 32 (53 %) Female

Ethnicity: NR

Number Screened: NR
Eligible: 61
Enrolled: 60

Number Withdrawn: 3
Lost to fu: 0
Analyzed: 57

Eligibility criteria:
NR

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	Withdrawals due to AEs/ 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

Evidence Table 4. Active controlled trials (Adults): Efficacy

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

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

Outcome Measurement:

post-sleep quesionnaire
clinical global impression (CGI)

Efficacy Outcome List:

Primary outcome	Outcome:
☐	duration of sleep onset
☐	sleep soundness
☐	quality of sleep

Results

post-sleep quesionnaire

duration of sleep onset at week 4

Zopiclone 7.5mg	Zopiclone 11.25mg	Flurazepam 30mg		P value
6.7 (<0.01)	6.9 (<0.01)	7.5 (<0.01)	( )	

Score (p vs placebo)

sleep soundness at week 4

Zopiclone 7.5mg	Zopiclone 11.25mg	Flurazepam 30mg		P value
6.7 (<0.01)	6.6 (<0.01)	7.5 (<0.01)	( )	

Score (p vs placebo)

quality of sleep at week 4

Zopiclone 7.5mg	Zopiclone 11.25mg	Flurazepam 30mg		P value
11.2 (<0.01)	11.0 (<0.01)	12.2 (<0.01)	( )	

Score (p vs placebo)

duration of sleep onset, sleep soundness, quality of sleep at week 4

Zopiclone 7.5mg	Zopiclone 11.25mg	Flurazepam 30mg		P value
as above (NS)	as above (NS)	as above (NA)	( )	

Score (p vs flueazepam)

CGI

therapeutic index (less score=worse) at week 4

Zopiclone 7.5mg	Zopiclone 11.25mg	Flurazepam 30mg		P value
3.2 ( )	3 ( )	2.5 ( )	( )	<0.05

Score ( )

Evidence Table 4. Active controlled trials (Adults): Efficacy

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 Screened: NR
Eligible: NR
Enrolled: 60

Number Withdrawn: 2
Lost to fu: 8
Analyzed: 50

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 : NR

Drug name	dosage	N=	Duration	Withdrawals due to AEs/ 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

Evidence Table 4. Active controlled trials (Adults): Efficacy

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

Year: **1999** **Country:** **Canada** **Funding:** **Not reported**

Outcome Measurement:

Hamilton scale for anxiety
Self-rating questionnaire for sleep
auditory and visual span test

Efficacy Outcome List:

Primary outcome	Outcome:
☐	anxiety
☐	quality of sleep
☐	sleep onset
☐	sleep depth
☐	wakefullness and attention

Results

Hamilton scale for anxiety

anxiety

Zopiclone	Temazepam	Placebo		P value
NR ( )	NR ( )	NR ( )	( )	NS

Score ( )

Self-rating questionnaire for sleep

sleep onset at treatment week 1

Zopiclone	Temazepam			P value
NR (<0.01)	NR (<0.01)	( )	( )	

Score (p vs placebo)

sleep depth at treatment week 1

Zopiclone	Temazepam			P value
NR (<0.01)	NR (<0.01)	( )	( )	

Score (p vs placebo)

auditory and visual span test

alertness over all 5 weeks

Zopiclone	Nitrazepam	Placebo		P value
multiple d ( )	multiple d ( )	multiple ( )	( )	NS

Score ( )

Evidence Table 4. Active controlled trials (Adults): Efficacy

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

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

Design:

Study design RCT
DB
Parallel

Setting Multicenter

Age: 47
Range: 26-71
SD:

Gender: 72 (77 %) Female

Ethnicity: NR

Number Screened: NR
Eligible: 130
Enrolled: 94

Number Withdrawn: 0
Lost to fu: 0
Analyzed: 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
Wash out : NR
Allow other medication : NR

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

Evidence Table 4. Active controlled trials (Adults): Efficacy

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

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

Outcome Measurement:

- # diary
- # sleep questionnaire
- # global evaluation
- # Norris Mood Rating

Efficacy Outcome List:

Primary outcome	Outcome:
☐	sleep onset latency
☐	sleep quality
☐	night awakenings
☐	duration of sleep

Results

diary

sleep onset latency, mean score

Zopiclone	Nitrazepam			P value
32.6 ( )	33.1 ( )	( )	( )	NS

Score ( )

quality of sleep, mean score

Zopiclone	Nitrazepam			P value
34 ( )	30.2 ( )	( )	( )	

Score ( )

global evaluation

efficacy (1=poor; 5=excellent)

Zopiclone	Nitrazepam			P value
3.2 ( )	3.1 ( )	( )	( )	NS

Score ( )

Evidence Table 4. Active controlled trials (Adults): Efficacy

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

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

sleep questionnaire

latency of sleep onset >30 min

Zopiclone	Nitrazepam			P value
38 ( )	44.4 ( )	( )	( )	0.07

% ( )

duration of sleep <6.5 hours

Zopiclone	Nitrazepam			P value
37.5 ( )	37.7 ( )	( )	( )	NS

% ( )

>2 night awakenings

Zopiclone	Nitrazepam			P value
18.4 ( )	24.4 ( )	( )	( )	NS

% ( )

time to fall askeep after a nught awakenings >30 min

Zopiclone	Nitrazepam			P value
14.6 ( )	22.2 ( )	( )	( )	NS

% ( )

awakening at least 2 hours before expected time

Zopiclone	Nitrazepam			P value
20.4 ( )	20 ( )	( )	( )	NS

% ( )

Norris Mood Rating

overall

Zopiclone	Nitrazepam			P value
- ( )	better ( )	( )	( )	<0.05

Score ( )

Evidence Table 4. Active controlled trials (Adults): Efficacy

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

Age: 53
Range: 28-69
SD:

Gender: 39 (71 %) Female

Ethnicity: NR

Number Screened: NR
Eligible: 60
Enrolled: 55

Number Withdrawn: 2
Lost to fu: 0
Analyzed: 53

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

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

Comments:

Intervention:

Run-in : 2
Wash out : 7
Allow other medication : No

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

Evidence Table 4. Active controlled trials (Adults): Efficacy

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

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

Outcome Measurement:

Questionnaire

Efficacy Outcome List:

Primary outcome	Outcome:
☑	Sleep quality
☑	Latency of sleep onset
☑	Status after awaking

Results

Questionnaire in the morning about sleep

# Sleep quality - average score	Zopiclone	Temazepam			P value
	3.9 (0.2)	3.9 (0.21)	( )	( )	0.096
	Score (SD)				
# Sleep quality - average score	Zopiclone	Placebo			P value
	3.9 (0.2)	3.4 (0.21)	( )	( )	<0.001
	Score (SD)				
# Latency of sleep onset - average score	Zopiclone	Temazepam			P value
	3.8 (0.2)	3.7 (0.2)	( )	( )	0.106
	Score (SD)				
# Latency of sleep onset - average score	Zopiclone	Placebo			P value
	3.8 (0.2)	3.1 (0.22)	( )	( )	<0.01
	Score (SD)				
# Status after awaking - average score	Zopiclone	Temazepam			P value
	3.5 (0.19)	3.4 (0.18)	( )	( )	0.45
	Score (SD)				
# Status after awaking - average score	Zopiclone	Placebo			P value
	3.5 (0.19)	3.2 (0.19)	( )	( )	<0.01
	Score (SD)				

Evidence Table 4. Active controlled trials (Adults): Efficacy

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

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

Preference

Sleep better

Zopiclone	Temazepam	Placebo	Z and T	P value
16 ( )	10 ( )	6 ( )	2 ( )	NR

Number ( )

Better status during the day

Zopiclone	Temazepam	Placebo	Z and T	P value
29 ( )	23 ( )	0 ( )	0 ( )	NR

Number ( )

Preferred drug to continue

Zopiclone	Temazepam	Placebo	Z and T	P value
8 ( )	3 ( )	5 ( )	2 ( )	NR

( )

Evidence Table 4. Active controlled trials (Adults): Efficacy

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:

Gender: NR (0 %) Female

Ethnicity: NR

Number Screened: NR
Eligible: NR
Enrolled: 221

Number Withdrawn: 9
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 : NR

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

Evidence Table 4. Active controlled trials (Adults): Efficacy

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

Year: **2004** **Country:** **Netherlands** **Funding:** **Sanfi-Synthelabo**

Outcome Measurement:

- # sleep/wake diary
- # SWEL self-report questionnaires
- # State-Trait-Anxiety-Inventory version DY-1

Efficacy Outcome List:

Primary outcome	Outcome:
☑	Total sleep time (TST)
☑	Sleep onset latency (SOL)
☐	Wake time after sleep onset (WASO)
☐	Time in bed (TIB)

Results

Sleep/wake diaries

total sleep time

Zolpidem		Temazepam				P value
413	(78)	386	(82)	( )	( )	NS
minutes	(SD		)			

sleep onset latency

Zolpidem		Temazepam				P value
46	(33)	46	(34)	( )	( )	NS
minutes	(SD		)			

wake time after sleep

Zolpidem		Temazepam				P value
40	(36)	39	(38)	( )	( )	NS
minutes	(SD		)			

time in bed

Zolpidem		Temazepam				P value
530	(77)	508	(58)	( )	( )	NS
minutes	(SD		)			

SWEL total score

Zolpidem		Temazepam				P value
35.7	(7.7)	35.8	(9.2)	( )	( )	NS
Score	(SD		)			

Evidence Table 4. Active controlled trials (Adults): Efficacy

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

Year: **2004** **Country:** **Netherlands** **Funding:** **Sanfi-Synthelabo**

STAI-DY-1 sum score

Zolpidem	Temazepam			P value
41.6 (12)	39 (10.7)	( )	( )	NS

Score (SD)

Evidence Table 4. Active controlled trials (Adults): Efficacy

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

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

Design:

Study design RCT
DB
Parallel

Setting Multicenter

Age: NR
Range: 21-65
SD:

Gender: NR (0 %) Female

Ethnicity: NR

Number Screened: NR
Eligible: 589
Enrolled: 306

Number Withdrawn: 28
Lost to fu: 0
Analyzed: 278

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	Withdrawals due to AEs/ 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

Evidence Table 4. Active controlled trials (Adults): Efficacy

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

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

Outcome Measurement:

- # morning questionnaire
- # patients global impressions
- # Sheehan Disability Scale
- # 100mm visual analog scales

Efficacy Outcome List:

Primary outcome	Outcome:
☑	sleep latency
☑	sleep duration
☐	ease of falling asleep
☐	number of awakenings
☐	wake time after sleep onset
☐	quality of sleep
☐	morning sleepiness
☐	ability to concentrate in the morning
☐	disruption caused by insomnia
☐	social life or family life

Results

morning questionnaire and 100mm visual analog scales

sleep latency at week 1

Zolpidem		Trazodone				P value
48.2	(2.7)	57.7	(4.0)	( )	( )	<0.037

minutes (SD)

sleep latency at week 2

Zolpidem		Trazodone				P value
48.1	(3.1)	54.5	(4.1)	( )	( )	NS

minutes (SD)

sleep duration at week 1

Zolpidem		Trazodone				P value
378.8	(5.3)	366.4	(6.4)	( )	( )	NR

minutes (SD)

sleep duration at week 2

Zolpidem		Trazodone				P value
NR	(NR)	NR	(NR)	( )	( )	NS

minutes (SD)

Evidence Table 4. Active controlled trials (Adults): Efficacy

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

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

# ease of falling asleep at week 2	Zolpidem	Trazodone			P value
	44.3 (1.8)	44.0 (2.3)	( )	( )	NS
	Score (SD)				
# number of awakenings at week 2	Zolpidem	Trazodone			P value
	1.5 (0.2)	1.4 (0.1)	( )	( )	NS
	minutes (SD)				
# subjective waking time after sleep onset at week 2	Zolpidem	Trazodone			P value
	39.5 (3.6)	42.1 (4.3)	( )	( )	NS
	minutes (SD)				
# sleep quality at week 2	Zolpidem	Trazodone			P value
	2.45 (0.05)	2.43 (0.07)	( )	( )	NS
	minutes (SD)				
<u>patients global impressions</u>					
# sleep status (excellent and good) at week 2	Zolpidem	Trazodone			P value
	49 (53.8)	47 (52.2)	( )	( )	NS
	Number (%)				
# sleep improvement (a lot and somewhat) at week 2	Zolpidem	Trazodone			P value
	60 (66)	62 (68.8)	( )	( )	NS
	Number (%)				
# time to fall asleep (shortened a lot and shortened somewhat) at week 2	Zolpidem	Trazodone			P value
	56 (61.5)	50 (55.5)	( )	( )	NS
	Number (%)				
# sleep time (increased a lot and increased somewhat) at week 2	Zolpidem	Trazodone			P value
	56 (61.5)	61 (67.8)	( )	( )	NS
	Number (%)				

Evidence Table 4. Active controlled trials (Adults): Efficacy

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

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

Sheehan Disability Scale

overall

Zolpidem	Trazodone			P value
NR ( )	NR ( )	( )	( )	NS

Score ( )

Evidence Table 4. Active controlled trials (Adults): Efficacy

Author: Walsh_ **Trial type:** Active **Quality rating:** Good

Year: 1998b **Country:** US **Funding:** Wyeth Ayerst

Design:

Study design

DB

Parallel

Setting

Age: 40.3
Range: 18-60
SD:

Gender: 77 (58 %) Female

Ethnicity: NR

Number Screened: 673
Eligible: 456
Enrolled: 132

Number Withdrawn: 7
Lost to fu: 0
Analyzed: 125

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).

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.

Comments:

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

Intervention:

Run-in : 3
Wash out : 2
Allow other medication : NR

Drug name	dosage	N=	Duration	Withdrawals due to AEs/ 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

Evidence Table 4. Active controlled trials (Adults): Efficacy

Author: **Walsh_** **Trial type:** **Active** **Quality rating:** **Good**

Year: **1998b** **Country:** **US** **Funding:** **Wyeth Ayerst**

Outcome Measurement:

Polysomnography
Sleep questionnaire

Efficacy Outcome List:

Primary outcome	Outcome:
☐	Total sleep time
☐	Sleep duration
☐	No. of awakenings
☐	% of total sleep time spent in each sleep st

Results

Polysomnography

Total sleep time day 4-5 and day 16-17, minutes

Zaleplon 5mg	Zaleplon 10mg	Placebo		P value
413.6 (18)	402 (396.8)	400 (411.3)	( )	NS

during (after)

Total sleep time- day 4-5

Zaleplon 5mg	Zaleplon 10mg	Triazolam 0.25mg	Placebo	P value
413.6 (<0.001)	402 (0.014)	431 (NA)	400 (<0.001)	

Minute (p vs triazolam)

Total sleep time- day 16-17

Zaleplon 5mg	Zaleplon 10mg	Triazolam 0.25mg	Placebo	P value
418 (0.63)	396.8 (0.22)	420 (NA)	411.3 (0.35)	

Minute (p vs triazolam)

Latency to persistent sleep- day 4-5

Zaleplon 5mg	Zaleplon 10mg	Triazolam 0.25mg	Placebo	P value
17 (0.019)	19.25 (0.039)	18.5 (NR)	25.38 (NA)	

Minute (p vs placebo)

Latency to persistent sleep- day 16-17

Zaleplon 5mg	Zaleplon 10mg	Triazolam 0.25mg	Placebo	P value
18 (0.019)	16.75 (0.039)	23.75 (NR)	20.5 (NA)	

Minute (p vs placebo)

Evidence Table 4. Active controlled trials (Adults): Efficacy

Author: **Walsh_** **Trial type:** **Active** **Quality rating:** **Good**

Year: **1998b** **Country:** **US** **Funding:** **Wyeth Ayerst**

No. of awakenings- day 4-5 and day 16-17

Zaleplon 5mg	Zaleplon 10mg	Triazolam 0.25mg	Placebo	P value
NR ( )	NR ( )	NR ( )	NR ( )	NS

Number ( )

% of total sleep time spent in each sleep stage- day 4-5 and day 16-17

Zaleplon 5mg	Zaleplon 10mg	Triazolam 0.25mg	Placebo	P value
NR ( )	NR ( )	NR ( )	NR ( )	NS

Number ( )

Latency to persistent sleep- day 16-17

Zaleplon 5mg	Zaleplon 10mg	Triazolam 0.25mg	Placebo	P value
416.5 (NS)	400 (NS)	406.75 (NS)	408.5 (NA)	NS

Minute (p vs placebo)

Evidence Table 4. Active controlled trials (Adults): Efficacy

Author: **Walsh_** **Trial type:** **Active** **Quality rating:** **Good**

Year: **1998b** **Country:** **US** **Funding:** **Wyeth Ayerst**

Sleep questionnaire

Subjective sleep latency- day 4-5, score

Zaleplon 5mg	Zaleplon 10mg	Triazolam 0.25mg	Placebo	P value
shorter (0.003)	shorter (0.056)	shorter (0.015)	NR (NA)	

vs placebo (p vs placebo)

Subjective sleep latency- day 6-14, score

Zaleplon 5mg	Zaleplon 10mg	Triazolam 0.25mg	Placebo	P value
shorter (0.67)	shorter (0.03)	shorter (0.168)	NR (NA)	

vs placebo (p vs placebo)

Subjective total sleep time- day 1-2, score

Zaleplon 5mg	Zaleplon 10mg	Triazolam 0.25mg	Placebo	P value
NR (NS)	NR (NS)	NR (<0.00)	NR (NA)	

vs placebo (p vs placebo)

Subjective total sleep time- day 3-19, score

Zaleplon 5mg	Zaleplon 10mg	Triazolam 0.25mg	Placebo	P value
NR (NS)	NR (NS)	NR (NS)	NR (NA)	

vs placebo (p vs placebo)

Subjective no. of awakenings- day 6-14, number

Zaleplon 5mg	Zaleplon 10mg	Triazolam 0.25mg	Placebo	P value
NR (NS)	NR (NS)	NR (0.046)	NR (NA)	

vs placebo (p vs placebo)

Subjective sleep latency after discontinuation night, score

Zaleplon 5mg	Zaleplon 10mg	Triazolam 0.25mg	Placebo	P value
NR (NS)	NR (NS)	longer (0.036)	NR (NA)	

vs placebo (p vs placebo)

Subjective total sleep time after discontinuation night, score

Zaleplon 5mg	Zaleplon 10mg	Triazolam 0.25mg	Placebo	P value
NR (NS)	NR (NS)	shorter (0.022)	NR (NA)	

vs placebo (p vs placebo)

Evidence Table 4. Active controlled trials (Adults): Efficacy

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

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

Design:

Study design RCT
DB
Crossover

Setting Single Center

Age: 42
Range: 22-49
SD:

Gender: NR (%) Female

Ethnicity: NR

Number Screened: 73
Eligible: 39
Enrolled: 30

Number Withdrawn: 2
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-in : NR
Wash out : NR
Allow other medication : No

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

Evidence Table 4. Active controlled trials (Adults): Efficacy

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

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

Outcome Measurement:

sleep latency testing
sleep questionnaire

Efficacy Outcome List:

Primary outcome	Outcome:
☑	Sleep latency
☑	Number of minutes sleep

Results

Sleep latency testing

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

Evidence Table 4. Active controlled trials (Adults): Efficacy

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

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

sleep questionnaire

time to sleep (minute)

Zaleplon	Flurazepam			P value
27.5 ( )	22.5 ( )	( )	( )	NR

Median ( )

number of minutes sleep

Zaleplon				P value
195 ( )	( )	( )	( )	NR

Median ( )

number of minutes sleep

Flurazepam				P value
206.3 ( )	( )	( )	( )	<0.01

Median ( )

number of minutes sleep

Flurazepam				P value
206.3 ( )	( )	( )	( )	<0.05

Median ( )

Evidence Table 4. Active controlled trials (Adults): Efficacy

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

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

Design:

Study design RCT
DB
Parallel

Setting Multicenter

Age: NR
Range: 21-55
SD:

Gender: 64 (58 %) Female

Ethnicity: 69% white

Number Screened: 358
Eligible: NR
Enrolled: 110

Number Withdrawn: 11
Lost to fu: NR
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:

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	Withdrawals due to AEs/ 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

Evidence Table 4. Active controlled trials (Adults): Efficacy

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

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

Outcome Measurement:

- # polysomnography
- # evening questionnaire
- # drug effects questionnaire

Efficacy Outcome List:

Primary outcome	Outcome:
☑	Sleep Latency
☑	Sleep Efficiency
☐	no. of awakenings
☐	waking time during sleep
☐	wake time after sleep
☐	% of time spent in REM and deep sleep
☐	quality of sleep
☐	morning sleepiness
☐	ability to concentrate

Results

polysomnography

latency to persistent sleep- nigtht 27 & 28

Zolpidem		Triazolam		Placebo				P value
-7	(NS)	0	(NS)	-15	(<0.05)		( )	

minutes (p vs baseline)

sleep efficiency- nigtht 27 & 28

Zolpidem		Triazolam		Placebo				P value
1	(NS)	3	(<0.05)	5	(<0.05)		( )	

% (p vs baseline)

no. of awakenings- night 27 & 28

Zolpidem		Triazolam		Placebo				P value
1	(NS)	-2	(<0.05)	-1	(NS)		( )	

Number (p vs baseline)

waking time during sleep

Zolpidem		Triazolam		Placebo				P value
0	(NS)	-20	(<0.05)	2	(NS)		( )	

minutes (p vs baseline)

Evidence Table 4. Active controlled trials (Adults): Efficacy

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 Screened: NR
Eligible: NR
Enrolled: 36

Number Withdrawn: 2
Lost to fu: 0
Analyzed: 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

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

Evidence Table 4. Active controlled trials (Adults): Efficacy

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

Year: **1985** **Country:** **NR** **Funding:** **Not reported**

Outcome Measurement:

Patient Questionnaires

Efficacy Outcome List:

Primary outcome	Outcome:
☑	Sleep latency
☑	No. time waking
☑	Quality of sleep
☑	Duration of sleep
☑	Dreaming
☑	State on waking

Results

Patient Questionnaires

Sleep latency

Zopiclone	Placebo			P value
30.8 (<0.01)	29.1 (<0.01)	( )	( )	

Minutes (p vs baseline)

No. time waking

Zopiclone	Temazepam			P value
0.75 (<0.01)	0.66 (<0.01)	( )	( )	

Number (p vs baseline)

Quality of sleep (0-4)

Zopiclone	Temazepam			P value
0.93 (<0.01)	0.87 (<0.01)	( )	( )	

Score (p vs baseline)

Duration of sleep

Zopiclone	Temazepam			P value
6.6 (<0.01)	6.6 (<0.01)	( )	( )	

Hours (p vs baseline)

Dreaming (0-4)

Zopiclone	Temazepam			P value
0.46 (NS)	0.46 (NS)	( )	( )	

Score (p vs baseline)

Evidence Table 4. Active controlled trials (Adults): Efficacy

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

( )

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

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

Number Screened: NR
Eligible: NR
Enrolled: 36

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

Drug name	dosage	N=	Duration	Withdrawals due to AEs/ 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 (NS)	7.3 (<0.05)	( )	

Score (p vs baseline)

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

Author:	**Elie**	**Trial type:**	**Active**	**Quality rating:**	**Fair**
Year:	**1990b**	**Country:**	**Canada**	**Funding:**	**Not reported**

		Zopiclone	Flurazepam	Placebo		P value
#	rebound: nocturnal awakenings at day 29 (higher score=worse)	5.0 (NS)	6.3 (NS)	8.0 (NS)	( )	
		Score (p vs baseline)				

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

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
Range:
SD:
Gender: NR (%) Female
Ethnicity: NR

Number Screened: NR
Eligible: NR
Enrolled: 52
Number Withdrawn: 4
Lost to fu: 0
Analyzed: 48

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

Intervention:

Drug name	dosage	N=	Duration	Withdrawals due to AEs/ 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

Zopiclone	Triazolam			P value
4.3 ( )	5.9 ( )	( )	( )	<0.05

Score ( )

\# rebound: sleep induction at the last withdrawal day

Zopiclone	Triazolam			P value
4.7 ( )	6.1 ( )	( )	( )	NS

Score ( )

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

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

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

# rebound: sleep soundness at the last withdrawal day	Zopiclone	Triazolam			P value
	7.4 ( )	8.6 ( )	( )	( )	NS
	Score ( )				

withdrawal effects

# rebound insomnia	Zopiclone	Triazolam			P value
	73 ( )	71 ( )	( )	( )	NS
	% ( )				

# rebound: sleep induction, duration and soundness at the first withdrawal nights	Zopiclone	Triazolam			P value
	NR (NS)	NR, wor (<0.05)	( )	( )	
	Score (p vs baseline)				

# rebound: sleep soundness	Zopiclone	Triazolam			P value
	NR ( )	NR, bett ( )	( )	( )	<0.05
	Score ( )				

# rebound: withdrawal symptoms	Zopiclone	Triazolam			P value
	3 ( )	2 ( )	( )	( )	NS
	Number ( )				

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

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

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

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:

Drug name	dosage	N=	Duration	Withdrawals due to AEs/ 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

#						P value
rebound: Improved sleep quality and daytime well-being	Zopiclone	Triazolam	( )	( )		0.00126
	27.0 ( ) % ( )	18.8 ( )				

Rebound rates in treatment respnders

#					P value
overall rebound	Zopiclone	Triazolam	( )	( )	NS
	46.07 (1.42) % (SD)	46.63 (1.93)			

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

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

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

# Rebound: overall rebound	Zopiclone	Placebo			P value
	46.07 (1.42)	48.56 (3.28)	( )	( )	<=0.01
	% (SD)				
# Rebound: Responder	Zopiclone	Triazolam			P value
	9.05 (1.16)	7.70 (0.88)	( )	( )	<=0.01
	% (SD)				
# Rebound: Responder	Zopiclone	Placebo			P value
	9.05 (1.16)	4.92 (1.20)	( )	( )	<=0.01
	% (SD)				
# Rebound: Nonresponder	Zopiclone	Triazolam			P value
	36.02 (1.35)	38.93 (1.45)	( )	( )	<=0.01
	% (SD)				
Rebound rates for items of sleep quality					
# Rebound: sleep quality - 1 item	Zopiclone	Triazolam			P value
	14.33 (1.11)	16.32 (1.33)	( )	( )	<0.001
	(%) (SD)				
# Rebound: sleep quality - 2 items	Zopiclone	Triazolam			P value
	6.76 (0.83)	8.27 (1.04)	( )	( )	<=0.05
	(%) (SD)				
# Rebound: sleep quality - 3 items	Zopiclone	Triazolam			P value
	2.36 (0.47)	2.39 (0.85)	( )	( )	NS
	(%) (SD)				
Rebound rates for items of daytime well-being					
# Rebound: daytime well-being - 1 item	Zopiclone	Triazolam			P value
	18.52 (1.44)	19.04 (2.00)	( )	( )	NS
	% (SD)				

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

Author:	**Hajak**	**Trial type:**	**Active**	**Quality rating:**	**Fair**
Year:	**1998, 1995, 1994**	**Country:**	**Germany**	**Funding:**	**Not reported**

Rebound: daytime well-being - 2 items

Zopiclone	Triazolam			P value
14.09 (1.11)	13.10 (1.91)	( )	( )	NS

% (SD)

Rebound: daytime well-being - 3 items

Zopiclone	Triazolam			P value
7.89 (0.82)	7.73 (1.33)	( )	( )	NS

% (SD)

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

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 Screened: NR
Eligible: NR
Enrolled: 15

Number Withdrawn: 0
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:

Drug name	dosage	N=	Duration	Withdrawals due to AEs/ 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

Rebound:

Spiegel's sleep questionnaire (SSQ)

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

Leed's sleep evaluation questionnaire (LSEQ)

#						
#	rebound: 9/10 items show more withdrawal sleep distrubance of triazolam	Zopiclone NR ( )	Triazolam NR ( )	( )	( )	P value <0.05
		Score ( )				

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

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

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

Design:

Study design RCT
DB
Parallel

Setting Single Center

Age: 50
Range: 32-60
SD:

Gender: 21 (70 %) Female

Ethnicity: NR

Number Screened: NR
Eligible: NR
Enrolled: 30

Number Withdrawn: 0
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:

Drug name	dosage	N=	Duration	Withdrawals due to AEs/ 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	Flurazepam	Placebo		P value
105.0 (<0.05)	39.7 (<0.05)	75.5 (NS)	( )	

minutes (p vs baseline)

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

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

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

rebound: no. of awakenings at day 15

Zopiclone	Flurazepam	Placebo		P value
2.10 (NS)	2.05 (<0.05)	1.70 (<0.05)	( )	

minutes (p vs baseline)

rebound: duration of early wakefulness at day 15

Zopiclone	Flurazepam	Placebo		P value
41.5 (NS)	27.8 (NS)	46.9 (NS)	( )	

minutes (p vs baseline)

rebound: sleep latency at day 15

Zopiclone	Flurazepam			P value
105.0 ( )	39.7 ( )	( )	( )	<0.05

minutes ( )

rebound: no. of awakenings at day 17

Zopiclone	Flurazepam			P value
3.15 ( )	2.05 ( )	( )	( )	<0.05

Number ( )

other rebounds

Zopiclone	Flurazepam			P value
multiple d ( )	multiple ( )	( )	( )	NS

number ( )

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

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

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 Screened: NR
Eligible: NR
Enrolled: 24

Number Withdrawn: 1
Lost to fu: 0
Analyzed: 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:

Drug name	dosage	N=	Duration	Withdrawals due to AEs/ 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

Rebound:

polysomnogram

\# rebound: mean wake time (change from baseline)

Zolpidem	Triazolam			P value
-80 (118)	43 (47.4)	( )	( )	NR

minutes (SD)

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

Zolpidem	Triazolam			P value
80 (118.5)	-40 (52.2)	( )	( )	NR

minutes (SD)

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

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

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

rebound: mean number of sleep cycles (change from baseline)

Zolpidem	Triazolam			P value
1.3 (1.5)	-0.7 (0.7)	( )	( )	NR

Number (SD)

sleep questionnaire

rebound: increased number of awakenings- day 32

Zolpidem	Triazolam	Placebo		P value
3 (37.5)	5 (62.5)	0 (0)	( )	NR

Number (%)

rebound: decreased sleep duration- day 32

Zolpidem	Triazolam	Placebo		P value
3 (37.5)	6 (75)	2 (25)	( )	NR

Number (%)

rebound: increased time to fall sleep- day 32

Zolpidem	Triazolam	Placebo		P value
3 (37.5)	8 (100)	0 (0)	( )	NR

Number (%)

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

Author: Quadens | **Trial type:** Active | **Quality rating:** Poor

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

Design:

Study design RCT
DB
Crossover

Setting Single Center

Age: NR
Range: 50-59
SD:

Gender: 12 (100 %) Female

Ethnicity: NR

Number Screened: NR
Eligible: NR
Enrolled: 12

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:

(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:

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

Rebound:

sleep questionnaire

\# rebound: no. of awakenings

Zopiclone	Flurazepam			P value
5.5 (<0.05)	6.1 (<0.01)	( )	( )	

Number (p vs treatment data)

\# rebound: total sleep time

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

seconds (p vs treatment data)

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

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

\# rebound: sleep onset latency

Zopiclone	Flurazepam			P value
1255 (NS)	1042 (NR)	( )	( )	

seconds (p vs treatment data)

\# rebound: sleep efficiency index

Zopiclone	Flurazepam			P value
86.9 (NS)	84.9 (<0.01)	( )	( )	

Score (p vs treatment data)

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

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 Screened: NR
Eligible: NR
Enrolled: 22

Number Withdrawn: 0
Lost to fu: 2
Analyzed: 20

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 objecive assessment through polysomnography.

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.

Comments:

Intervention:

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

Rebound:

polysomnography

\# rebound: sleep onset latency- change from baseline- night 15

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

minutes (SD)

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

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

minutes (SD)

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

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

Year: **1996** **Country:** **Italy** **Funding:** **Not reported**

# rebound: sleep efficiency- change from baseline- night 15	Zolpidem	Triazolam			P value
	9.9 (13.63)	-6.3 (8.55)	( )	( )	<0.01
	% (SD)				
# rebound: wake time after sleep onset- change from baseline- night 15	Zolpidem	Triazolam			P value
	9.9-37.5 (49.01)	17.3 (31.89)	( )	( )	<0.01
	minutes (SD)				
# rebound: no. of awakenings- change from baseline- night 15	Zolpidem	Triazolam			P value
	-1.9 (7.16)	-1.2 (4.67)	( )	( )	NS
	Number (SD)				

<u>quesionnaire</u>

# rebound: time to fall asleep- change from baseline- night 15	Zolpidem	Triazolam			P value
	-20.8 (28.23)	8.6 (31.65)	( )	( )	<0.05
	minutes (SD)				
# rebound: total sleep time- change from baseline- night 15	Zolpidem	Triazolam			P value
	51.9 (45.4)	-35.6 (127.9)	( )	( )	<0.01
	minutes (SD)				
# rebound: total wake time- change from baseline- night 15	Zolpidem	Triazolam			P value
	-2.2 (12.96)	13.2 (38.71)	( )	( )	NS
	minutes (SD)				
# rebound: no. nocturnal awakenings- change from baseline- night 15	Zolpidem	Triazolam			P value
	-0.3 (2.32)	0.4 (0.86)	( )	( )	NS
	Number (SD)				

<u>visual analogue scale</u>

# rebound: sleep quality- change from baseline- night 15	Zolpidem	Triazolam			P value
	-12.9 (20.59)	0.8 (22.88)	( )	( )	NS
	Score (SD)				

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

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

#						
	rebound: awakening quality- change from baseline- night 15	Zolpidem	Triazolam			P value
		-12.9 (21.34)	-1.5 (21.36)	( )	( )	NS
		Score (SD)				

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

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 Screened: NR
Eligible: NR
Enrolled: 60

Number Withdrawn: 2
Lost to fu: 8
Analyzed: 50

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:

Drug name	dosage	N=	Duration	Withdrawals due to AEs/ 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

Rebound:

Self-rating questionnaire for sleep

\# sleep onset after discontinuation - rebound

Zopiclone	Temazepam			P value
NR (NS)	NR, wor (<0.05)	( )	( )	

Score (p vs placebo)

\# sleep depth after discontinuation- rebound

Zopiclone	Temazepam			P value
NR, wors (<0.01)	NR, wor (<0.01)	( )	( )	

Score (p vs placebo)

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

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:

Gender: NR (0 %) Female

Ethnicity: NR

Number Screened: NR
Eligible: NR
Enrolled: 221

Number Withdrawn: 9
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:

Drug name	dosage	N=	Duration	Withdrawals due to AEs/ 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	Temazepam			P value
370 (84)	352 (89)	( )	( )	NS

minutes (SD)

\# rebound- prevalence rebound insomnia (TST)

Zolpidem	Temazepam			P value
27 ( )	25.9 ( )	( )	( )	NS

% ( )

\# rebound- sleep onset latency

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

minutes (SD)

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

Author:	**Voshaar**	**Trial type:**	**Active**	**Quality rating:**	**Fair**
Year:	**2004**	**Country:**	**Netherlands**	**Funding:**	**Sanfi-Synthelabo**

#	rebound- prevalence rebound insomnia (SOL)	Zolpidem	Temazepam			P value
		53.4 ( )	58.3 ( )	( )	( )	NS
		% ( )				

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

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

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

Design:

Study design RCT
DB
Parallel

Setting Multicenter

Age: NR
Range: 21-55
SD:

Gender: 64 (58 %) Female

Ethnicity: 69% white

Number Screened: 358
Eligible: NR
Enrolled: 110

Number Withdrawn: 11
Lost to fu: NR
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:

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:

Drug name	dosage	N=	Duration	Withdrawals due to AEs/ 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

#		Zolpidem	Triazolam	Placebo		P value
	rebound: latency to persistent sleep-discontinuation nigtht 1	6 (NS)	47 (<0.05)	-11 (NS)	( )	
		minutes (p vs baseline)				
#		Zolpidem	Triazolam	Placebo		P value
	rebound: latency to persistent sleep-discontinuation nigtht 1	6 (NS)	47 (<0.05)	-11 (NS)	( )	
		minutes (p vs baseline)				

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: sleep efficiency-discontinuation nigtht 1

Zolpidem	Triazolam	Placebo		P value
-3 (NS)	-15 (<0.05)	5 (<0.05)	( )	

% (p vs baseline)

rebound questionnaire- discontinuation night 1

rebound: sleep latency

Zolpidem	Triazolam	Placebo		P value
14 (NS)	72 (<0.05)	-16 ( )	( )	

minutes (p vs baseline)

rebound: total sleep time

Zolpidem	Triazolam	Placebo		P value
-4 (NS)	-63 (<0.05)	49 (0.05)	( )	

minutes (p vs baseline)

rebound: no. of awakenings

Zolpidem	Triazolam	Placebo		P value
1 (NS)	1 (NS)	-1 (<0.05)	( )	

Number (p vs baseline)

rebound: wake min during sleep

Zolpidem	Triazolam	Placebo		P value
-4 (NS)	48 (<0.05)	-29 (<0.05)	( )	

minutes (p vs baseline)

rebound: quality lantency

Zolpidem	Triazolam	Placebo		P value
0.3 (NS)	0.8 (<0.05)	-0.4 (<0.05)	( )	

Score (p vs baseline)

rebound: morning sleepiness

Zolpidem	Triazolam	Placebo		P value
-5 (NS)	-6.7 (NS)	4.5 (NS)	( )	

Score (p vs baseline)

rebound: ability to concentrate

Zolpidem	Triazolam	Placebo		P value
0.2 (<0.05)	0.1 (NS)	-0.1 (NS)	( )	

Score (p vs baseline)

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	Triazolam	Placebo		P value
15 ( )	43 ( )	11 ( )	( )	
% ( )				

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

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

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

Design:

Study design RCT
DB
Parallel

Setting Multicenter

Age: NR
Range: 20-69
SD:

Gender: NR (0 %) Female

Ethnicity: NR

Number Screened: NR
Eligible: NR
Enrolled: 119

Number Withdrawn: 5
Lost to fu: 15
Analyzed: 99

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

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.

Comments:

Intervention:

Run-in : 7
Wash out : 7
Allow other medication : No

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

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

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

Zopiclone	Nitrazepam	Placebo		P value:
2 ( )	1 ( )	2 ( )	( )	

Number ( )

\# withdrawals due to AEs

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

Number ( )

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

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 Screened: NR
Eligible: NR
Enrolled: 121

Number Withdrawn: NR
Lost to fu: 8
Analyzed: 113

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	Withdrawals due to AEs/ Total withdrawal
Zopiclone	7.5 mg	121	7 day	0 / 8
Triazolam	0.5 mg	121	7 day	0 / 8

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

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			P value:
NR, bett ( )	NR ( )	( )	( )	<0.05

Score ( )

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

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

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

Design:

Study design RCT
SB
Parallel

Setting Single Center

Age: NR
Range: >18
SD:

Gender: NR (0 %) Female

Ethnicity: NR

Number Screened: NR
Eligible: NR
Enrolled: 88

Number Withdrawn: 4
Lost to fu: 33
Analyzed: 51

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

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

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

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

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

Adverse Events:

Averse Events

#						
#	No. of patients experiencing AEs (overall)	Zopiclone	Midazolam			P value:
		15 (31)	16 (40)	( )	( )	>0.05
		Number (%)				
#	No. of AEs	Zopiclone	Midazolam			P value:
		21 ( )	28 ( )	( )	( )	>0.05
		Number ( )				
#	No. of patients ecperiencing AEs - Daytime tiredness	Zopiclone	Midazolam			P value:
		6 (12.5)	6 (15)	( )	( )	NR
		Number (%)				
#	No. of patients ecperiencing AEs - Taste disturbance	Zopiclone	Midazolam			P value:
		6 (12.5)	0 (0)	( )	( )	NR
		Number (%)				
#	No. of patients ecperiencing AEs - Dry mouth	Zopiclone	Midazolam			P value:
		2 (4.2)	3 (7.5)	( )	( )	NR
		Number (%)				
#	No. of patients ecperiencing AEs - Indigestion/nousea/vomiting	Zopiclone	Midazolam			P value:
		1 (2.1)	5 (12.5)	( )	( )	NR
		Number (%)				
#	No. of patients ecperiencing AEs - Clumsiness	Zopiclone	Midazolam			P value:
		0 (0)	4 (10)	( )	( )	NR
		Number (%)				

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

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

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

No. of patients ecperiencing AEs - Disturbed sleep pattern

Zopiclone	Midazolam			P value:
2 (4.2)	5 (12.5)	( )	( )	NR

Number (%)

No. of patients ecperiencing AEs - Others

Zopiclone	Midazolam			P value:
4 (8.3)	5 (12.5)	( )	( )	NR

Number ( )

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

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

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

Design:

Study design RCT
DB
Parallel

Setting Multicenter

Age: 50.9
Range: 30-65
SD:

Gender: 27 (71 %) Female

Ethnicity: 100% caucasian

Number Screened: NR
Eligible: NR
Enrolled: 38

Number Withdrawn: 4
Lost to fu: NR
Analyzed: 38

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.

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.

Comments:

Intervention:

Run-in : no

Wash out : 7

Allow other medication : No medication known to cause drowsiness

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

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

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

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

Adverse Events:

reported by patients

\# no. of patients ecpereincing severe side effect

Zopiclone	Triazolam			P value:
1 ( )	1 ( )	( )	( )	

Number ( )

withdrawals

\# total withdrawals

Zopiclone	Triazolam			P value:
1 ( )	3 ( )	( )	( )	

Number ( )

\# withdrawals due to Aes

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

Number ( )

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

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

Age: 41.6
Range: 21-60
SD: 9.5

Gender: 24 (51 %) Female

Ethnicity: NR

Number Screened: NR
Eligible: NR
Enrolled: 47

Number Withdrawn: 0
Lost to fu: 0
Analyzed: 47

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.

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.

Comments:

Intervention:

Run-in : NR
Wash out : 5-12
Allow other medication : No

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

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

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

Zaleplon 10mg	Zaleplon 40mg	Triazolam		P value:
9 ( )	18 ( )	8 ( )	( )	

Number ( )

withdrawals

total withdrawals

Zaleplon 10mg	Zaleplon 40mg	Triazolam 0.25mg		P value:
NR ( )	NR ( )	NR ( )	( )	

( )

withdrawals due to AEs

Zaleplon 10mg	Zaleplon 40mg	Triazolam 0.25mg		P value:
0 ( )	0 ( )	0 ( )	( )	

( )

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

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

Age: 38.1
Range: 21-60
SD: 11.1

Gender: 14 (39 %) Female

Ethnicity: NR

Number Screened: NR
Eligible: NR
Enrolled: 36

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

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.

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.

Comments:

Intervention:

Run-in : NR
Wash out : 5-12
Allow other medication : No

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

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

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

Zaleplon 20mg	Zaleplon 60mg	Triazolam		P value:
6 ( )	17 ( )	8 ( )	( )	

Number ( )

withdrawals

total withdrawals

Zaleplon 20mg	Zaleplon 60mg	Triazolam		P value:
NR ( )	NR ( )	NR ( )	( )	

Number ( )

withdrawals due to AEs

Zaleplon 20mg	Zaleplon 60mg	Triazolam		P value:
0 ( )	1 ( )	0 ( )	( )	

Number ( )

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

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

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

Number Screened: NR
Eligible: NR
Enrolled: 36

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

Run-in : 7
Wash out : 3
Allow other medication : NR

Drug name	dosage	N=	Duration	Withdrawals due to AEs/ 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

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

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

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

Adverse Events:

overall AEs

\# somnolence

Zopiclone	Flurazepam	Placebo		P value:
11 ( )	12 ( )	9 ( )	( )	NS

Number ( )

\# loss of concentration

Zopiclone	Flurazepam	Placebo		P value:
8 ( )	8 ( )	5 ( )	( )	NS

Number ( )

\# excitation

Zopiclone	Flurazepam	Placebo		P value:
10 ( )	2 ( )	7 ( )	( )	NS

Number ( )

\# tension

Zopiclone	Flurazepam	Placebo		P value:
10 ( )	7 ( )	9 ( )	( )	NS

Number ( )

\# taste disturbance

Zopiclone	Flurazepam	Placebo		P value:
10 ( )	10 ( )	4 ( )	( )	<0.05

Number ( )

\# try mouth

Zopiclone	Flurazepam	Placebo		P value:
11 ( )	7 ( )	8 ( )	( )	NS

Number ( )

\# thick tongue

Zopiclone	Flurazepam	Placebo		P value:
9 ( )	7 ( )	5 ( )	( )	NS

Number ( )

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

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

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

withdrawals

\# total withdrawals

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

Number ( )

\# withdrawals due to Aes

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

Number ( )

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

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

Year: **1995** **Country:** **Canada** **Funding:** **Not reported**

Design:

Study design RCT
DB
Parallel

Setting Multicenter

Age: NR
Range: 33-37
SD:

Gender: 69 (48 %) Female

Ethnicity: NR

Number Screened: 222
Eligible: 144
Enrolled: 144

Number Withdrawn: 7
Lost to fu: 1
Analyzed: 141

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.

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.

Comments:

Intervention:

Run-in : 1
Wash out : NR
Allow other medication : NR

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

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

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

Year: **1995** **Country:** **Canada** **Funding:** **Not reported**

Adverse Events:

reported by patients

any event

Zolpidem 10mg	Zolpidem 20mg	Flurazepam 30mg	Placebo	P value:
14 (40)	23 (6537)	15 (41.7)	15 (42.9)	<0.05

Number (%)

dry mouth

Zolpidem 10mg	Zolpidem 20mg	Flurazepam 30mg	Placebo	P value:
0 (0)	1 (2.9)	2 (5.6)	0 (0)	

Number (%)

back pain

Zolpidem 10mg	Zolpidem 20mg	Flurazepam 30mg	Placebo	P value:
0 (0)	2 (5.7)	0 (0)	0 (0)	

Number (%)

fatigue

Zolpidem 10mg	Zolpidem 20mg	Flurazepam 30mg	Placebo	P value:
3 (8.6)	2 (5.7)	0 (0)	1 (2.9)	

Number (%)

ataxia

Zolpidem 10mg	Zolpidem 20mg	Flurazepam 30mg	Placebo	P value:
1 (2.9)	3 (8.6)	0 (0)	1 (2.9)	

Number (%)

confusion

Zolpidem 10mg	Zolpidem 20mg	Flurazepam 30mg	Placebo	P value:
0 (0)	2 (5.7)	0 (0)	0 (0)	

Number (%)

difficulty concentrating

Zolpidem 10mg	Zolpidem 20mg	Flurazepam 30mg	Placebo	P value:
0 (0)	0 (0)	1 (2.8)	2 (5.7)	

Number (%)

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

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

Year: **1995** **Country:** **Canada** **Funding:** **Not reported**

dizziness

Zolpidem 10mg	Zolpidem 20mg	Flurazepam 30mg	Placebo	P value:
0 (0)	3 (8.6)	1 (2.8)	0 (0)	

Number (%)

drugged feeling

Zolpidem 10mg	Zolpidem 20mg	Flurazepam 30mg	Placebo	P value:
0 (0)	2 (5.7)	1 (2.8)	0 (0)	

Number (%)

dysarthria

Zolpidem 10mg	Zolpidem 20mg	Flurazepam 30mg	Placebo	P value:
1 (2.9)	3 (8.6)	0 (0)	0 (0)	

Number (%)

headache

Zolpidem 10mg	Zolpidem 20mg	Flurazepam 30mg	Placebo	P value:
4 (11.4)	2 (5.7)	4 (11.1)	3 (8.6)	

Number (%)

light-headedness

Zolpidem 10mg	Zolpidem 20mg	Flurazepam 30mg	Placebo	P value:
0 (0)	0 (0)	2 (5.6)	0 (0)	

Number (%)

vomiting

Zolpidem 10mg	Zolpidem 20mg	Flurazepam 30mg	Placebo	P value:
0 (0)	3 (8.6)	0 (0)	0 (0)	

Number (%)

myalgia

Zolpidem 10mg	Zolpidem 20mg	Flurazepam 30mg	Placebo	P value:
0 (0)	2 (5.7)	1 (2.8)	1 (2.9)	

Number (%)

amnesia

Zolpidem 10mg	Zolpidem 20mg	Flurazepam 30mg	Placebo	P value:
1 (2.9)	3 (8.6)	1 (2.8)	0 (0)	

Number (%)

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

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

Year: **1995** **Country:** **Canada** **Funding:** **Not reported**

nervousness

Zolpidem 10mg	Zolpidem 20mg	Flurazepam 30mg	Placebo	P value:
1 (2.9)	2 (5.7)	1 (2.8)	0 (0)	

Number (%)

pharyngitis

Zolpidem 10mg	Zolpidem 20mg	Flurazepam 30mg	Placebo	P value:
2 (5.7)	0 (0)	1 (2.8)	0 (0)	

Number (%)

abnormal vision

Zolpidem 10mg	Zolpidem 20mg	Flurazepam 30mg	Placebo	P value:
0 (0)	2 (5.7)	0 (0)	0 (0)	

Number (%)

withdrawals

total withdrawals

Zolpidem 10mg	Zolpidem 20mg	Flurazepam 30mg	Placebo	P value:
0 ( )	7 ( )	1 ( )	0 ( )	NR

( )

withdrawal due to AEs

Zolpidem 10mg	Zolpidem 20mg	Flurazepam 30mg	Placebo	P value:
0 ( )	6 ( )	0 ( )	0 ( )	NR

( )

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

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
Range:
SD:

Gender: NR (%) Female

Ethnicity: NR

Number Screened: NR
Eligible: NR
Enrolled: 52

Number Withdrawn: 4
Lost to fu: 0
Analyzed: 48

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 characterisics 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	Withdrawals due to AEs/ Total withdrawal
Zopiclone	7.5 mg	24	21 day	2 / 2
Triazolam	0.25 mg	24	21 day	10 / 10

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

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

Zopiclone	Triazolam			P value:
18 (75)	20 (83.3)	( )	( )	NS

Number (%)

\# taste percersion

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

Number ( )

\# moderate or severe adverse effects reported

Zopiclone	Triazolam			P value:
18 ( )	42 ( )	( )	( )	<0.05

% ( )

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

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

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

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:

Run-in : 7
Wash out : 3
Allow other medication : NR

Drug name	dosage	N=	Duration	Withdrawals due to AEs/ 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

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

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

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

Adverse Events:

withdrawals

\# total withdrawals

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

Number ( )

\# withdrawals due to Aes

Zopiclone	Triazolam	Placebo		P value:
26 ( )	11 ( )	25 ( )	( )	

Number ( )

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

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

Age: 47.9
Range: 18-65
SD:

Gender: 90 (66 %) Female

Ethnicity: NR

Number Screened: NR
Eligible: NR
Enrolled: 136

Number Withdrawn: 9
Lost to fu: 0
Analyzed: 127

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).

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

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

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

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

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

Adverse Events:

reported by patients

overall sife effects

Zopiclone	Zaleplon			P value:
NR ( )	NR ( )	( )	( )	NS

% ( )

global evaluation

safety- good or excellent

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

% ( )

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

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 Screened: NR
Eligible: NR
Enrolled: 15

Number Withdrawn: 0
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	Withdrawals due to AEs/ 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

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

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

Year: **1997** **Country:** **Taiwan** **Funding:**

Adverse Events:

rebound insomnia

rebound insomnia- mild degree of poor sleep

Zopiclone	Triazolam			P value:
6 (40)	1 (6.7)	( )	( )	

Number (%)

rebound insomnia- moderate degree of poor sleep

Zopiclone	Triazolam			P value:
6 (40)	4 (26.7)	( )	( )	

Number (%)

rebound insomnia- severe degree of poor sleep

Zopiclone	Triazolam			P value:
3 (20)	10 (67.6)	( )	( )	

Number (%)

overall AEs

number of events reported

Zopiclone	Triazolam			P value:
10 ( )	16 ( )	( )	( )	

Number ( )

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

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

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

Design:

Study design RCT
DB
Parallel

Setting Single Center

Age: 50
Range: 32-60
SD:

Gender: 21 (70 %) Female

Ethnicity: NR

Number Screened: NR
Eligible: NR
Enrolled: 30

Number Withdrawn: 0
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:

Run-in : 2
Wash out : 3
Allow other medication : NR

Drug name	dosage	N=	Duration	Withdrawals due to AEs/ 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

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

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

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

Adverse Events:

withdrawals

\# total withdrawals

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

Number ( )

\# withdrawals due to AEs

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

Number ( )

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

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

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 Screened: NR
Eligible: NR
Enrolled: 24

Number Withdrawn: 1
Lost to fu: 0
Analyzed: 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:

Run-in : 3
Wash out : 3
Allow other medication : NR

Drug name	dosage	N=	Duration	Withdrawals due to AEs/ 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

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

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

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

Adverse Events:

overall AEs

\# Emergent adverse events

Zolpidem	Triazolam	Placebo		P value:
13 ( )	16 ( )	10 ( )	( )	NR

Number ( )

AEs with significant differences

\# rebound: pessimist

Zolpidem	Triazolam			P value:
lower ( )	higher ( )	( )	( )	0.096

Number ( )

\# rebound: tense

Zolpidem	Triazolam			P value:
lower ( )	higher ( )	( )	( )	0.061

Number ( )

\# rebound: pessimist

Zolpidem	Triazolam			P value:
lower ( )	higher ( )	( )	( )	0.040

Number ( )

withdrawals

\# total withdrawals

Zolpidem	Triazolam	Placebo		P value:
0 ( )	1 ( )	0 ( )	( )	

Number ( )

\# withdrawals due to AEs

Zolpidem	Triazolam	Placebo		P value:
0 ( )	1 ( )	0 ( )	( )	

Number ( )

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

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

Age: 46.9
Range:
SD: 1.4

Gender: 28 (47 %) Female

Ethnicity: NR

Number Screened: NR
Eligible: NR
Enrolled: 60

Number Withdrawn:
Lost to fu:
Analyzed:

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.

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.

Comments:

Intervention:

Run-in : 1
Wash out : NR
Allow other medication : NR

Drug name	dosage	N=	Duration	Withdrawals due to AEs/ 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

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

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

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

Adverse Events:

overall AEs

\# Total number of patients

Zopiclone 3.75	Zopiclone 7.5mg	Zopiclone 11.25mg	Zopiclone 15mg	P value:
4 ( )	4 ( )	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:
0 ( )	0 ( )	1 ( )	1 ( )	

Number ( )

\# total withdrawals

Flurazepam	Placebo			P value:
0 ( )	2 ( )	( )	( )	

Number ( )

\# withdrawals due to AEs

Zopiclone 3.75mg	Zopiclone 7.5mg	Zopiclone 11.5mg	Zopiclone 15mg	P value:
0 ( )	0 ( )	1 ( )	1 ( )	

Number ( )

\# withdrawals due to AEs

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

Number ( )

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

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

Age: 38.4
Range:
SD:

Gender: 31 (52 %) Female

Ethnicity: NR

Number Screened: NR
Eligible: NR
Enrolled: 60

Number Withdrawn: 16
Lost to fu: 0
Analyzed: 44

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

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

Comments:

Intervention:

Run-in : 7
Wash out : NR
Allow other medication : NR

Drug name	dosage	N=	Duration	Withdrawals due to AEs/ 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

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

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

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

Adverse Events:

reported by patients

\# excessive sedation

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

Number ( )

withdrawals

\# total withdrawals

Zopiclone	Temazepam	Placebo		P value:
7 ( )	7 ( )	10 ( )	( )	

Number ( )

\# withdrawals due to AEs

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

Number ( )

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

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 Screened: NR
Eligible: NR
Enrolled: 26

Number Withdrawn: 2
Lost to fu: 0
Analyzed: 24

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 : 7
Wash out : 7
Allow other medication : NR

Drug name	dosage	N=	Duration	Withdrawals due to AEs/ 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

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

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

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

Adverse Events:

withdrawals

\# total withdrawals

Zopiclone	Flurazepam	Placebo		P value:
0 ( )	0 ( )	2 ( )	( )	

Number ( )

\# withdrawals due to AEs

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

Number ( )

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

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

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

Design:

Study design RCT
DB
Crossover

Setting Single Center

Age: NR
Range: 50-59
SD:

Gender: 12 (100 %) Female

Ethnicity: NR

Number Screened: NR
Eligible: NR
Enrolled: 12

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:

(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:

Run-in : 6
Wash out : 35
Allow other medication : No

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

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

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

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

Adverse Events:

Norris quesionnaire

clear headed-muzzy

Zopiclone	Flurazepam			P value:
28.1 (9.3)	34.6 (13.4)	( )	( )	<0.05

Score (SD)

energic-lethargic

Zopiclone	Flurazepam			P value:
29.2 (12.7)	34.9 (10.1)	( )	( )	<0.05

Score (SD)

tranquil-troubled

Zopiclone	Flurazepam			P value:
19.8 (11.2)	24.7 (9.4)	( )	( )	<0.05

Score (SD)

relaxed-tense

Zopiclone	Flurazepam			P value:
21.4 (11.7)	25.9 (10.8)	( )	( )	<0.05

Score (SD)

elated-depressed

Zopiclone	Flurazepam			P value:
48.1 (15.3)	50.5 (14.0)	( )	( )	<0.05

Score (SD)

sociable-introverted

Zopiclone	Flurazepam			P value:
53.6 (15.3)	52.3 (13.4)	( )	( )	<0.05

Score (SD)

other 12 items show no difference

Zopiclone	Flurazepam			P value:
multiple ( )	multiple ( )	( )	( )	NS

Score ( )

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

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

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

withdrawals

\# total

Zopiclone	Flurazepam			P value:
0 ( )	0 ( )	( )	( )	NR

Number ( )

\# due to AEs

Zopiclone	Flurazepam			P value:
0 ( )	0 ( )	( )	( )	NR

Number ( )

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

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

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

Design:

Study design RCT
DB
Parallel

Setting Multicenter

Age: 54
Range: 25-79
SD:

Gender: NR (0 %) Female

Ethnicity: NR

Number Screened: NR
Eligible: NR
Enrolled: 178

Number Withdrawn: 5
Lost to fu: 34
Analyzed: 139

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 characterstics 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	Withdrawals due to AEs/ Total withdrawal
Zolpidem	10 mg	71	14 day	/
Triazolam	0.25 mg	68	14 day	/

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

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

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

Adverse Events:

Overall AEs

CNS-related adverse events

	Zolpidem	Triazolam		P value:
( )	8 (11.3)	10 (14.7)	( )	NS

Number (%)

GI-related adverse events

	Zolpidem	Triazolam		P value:
( )	2 (2.8)	3 (4.4)	( )	NS

Number (%)

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

Number (%)

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

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 Screened: NR
Eligible: NR
Enrolled: 22

Number Withdrawn: 0
Lost to fu: 2
Analyzed: 20

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 objecive assessment through polysomnography.

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.

Comments:

Intervention:

Run-in : 3
Wash out : No
Allow other medication : No

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

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

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

Year: **1996** **Country:** **Italy** **Funding:** **Not reported**

Adverse Events:

withdrawals

\# total withdrawals

Zolpidem	Triazolam			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	Triazolam			P value:
1 ( )	1 ( )	( )	( )	NR

Number ( )

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

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

Age: 39.6
Range: 19-64
SD: 1.5

Gender: 32 (53 %) Female

Ethnicity: NR

Number Screened: NR
Eligible: 61
Enrolled: 60

Number Withdrawn: 3
Lost to fu: 0
Analyzed: 57

Eligibility criteria:
NR

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	Withdrawals due to AEs/ 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

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

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

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 ( )	1 ( )	( )	

Number ( )

due to AEs

Zopiclone 7.5mg	Zopiclone 11.25mg	Flurazepam 30mg		P value:
0 ( )	1 ( )	0 ( )	( )	

Number ( )

overall AEs

taste perversion

Zopiclone 7.5mg	Zopiclone 11.25mg	Flurazepam 30mg		P value:
7 ( )	10 ( )	7 ( )	( )	NR

Number ( )

drowsiness

Zopiclone 7.5mg	Zopiclone 11.25mg	Flurazepam 30mg		P value:
0 ( )	1 ( )	9 ( )	( )	<0.05

Number ( )

headache

Zopiclone 7.5mg	Zopiclone 11.25mg	Flurazepam 30mg		P value:
0 ( )	5 ( )	4 ( )	( )	NS

Number ( )

taste perversion- moderate and severe

Zopiclone 7.5mg	Zopiclone 11.25mg	Flurazepam 30mg		P value:
0 ( )	8 ( )	0 ( )	( )	

Number ( )

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

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 Screened: NR
Eligible: NR
Enrolled: 60

Number Withdrawn: 2
Lost to fu: 8
Analyzed: 50

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 : NR

Drug name	dosage	N=	Duration	Withdrawals due to AEs/ 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

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

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

Year: **1999** **Country:** **Canada** **Funding:** **Not reported**

Adverse Events:

withdrawals

\# total withdrawals

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

Number ( )

\# withdrawals due to AEs

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

Number ( )

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

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

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

Design:

Study design RCT
DB
Parallel

Setting Multicenter

Age: 47
Range: 26-71
SD:

Gender: 72 (77 %) Female

Ethnicity: NR

Number Screened: NR
Eligible: 130
Enrolled: 94

Number Withdrawn: 0
Lost to fu: 0
Analyzed: 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
Wash out : NR
Allow other medication : NR

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

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

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

Year: **1987** **Country:** **Finland** **Funding:** **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 (p vs baseline)

sweating

Zopiclone	Nitrazepam			P value:
5.7 (<0.00)	-7.1 (<0.05)	( )	( )	NS

Score (p vs baseline)

nausea

Zopiclone	Nitrazepam			P value:
4.3 (NS)	-3.2 (NS)	( )	( )	<0.05

Score (p vs baseline)

loss of appetite

Zopiclone	Nitrazepam			P value:
0 (NS)	-6.5 (<0.05)	( )	( )	NS

Score (p vs baseline)

restlessness

Zopiclone	Nitrazepam			P value:
2.2 (NS)	-5.9 (<0.05)	( )	( )	NS

Score (p vs baseline)

physical tiredness

Zopiclone	Nitrazepam			P value:
-3.5 (<0.00)	-10.3 (<0.00)	( )	( )	NS

Score (p vs baseline)

dizziness

Zopiclone	Nitrazepam			P value:
3.5 (NS)	-7.8 (<0.00)	( )	( )	<0.05

Score (p vs baseline)

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

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

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

indigestion

Zopiclone		Nitrazepam				P value:
8.8	(<0.05)	-10	(<0.01)	( )	( )	<0.05

Score (p vs baseline)

reported by patients

number of events reported

Zopiclone		Nitrazepam				P value:
24	( )	13	( )	( )	( )	

Number ( )

number of patients experiencing unwanted effects

Zopiclone		Nitrazepam				P value:
52	( )	46	( )	( )	( )	

Number ( )

global evaluation

safety score (1=poor; 5=excellent)

Zopiclone		Nitrazepam				P value:
3.4	( )	3.5	( )	( )	( )	NS

Score ( )

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

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

Age: 53
Range: 28-69
SD:

Gender: 39 (71 %) Female

Ethnicity: NR

Number Screened: NR
Eligible: 60
Enrolled: 55

Number Withdrawn: 2
Lost to fu: 0
Analyzed: 53

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

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

Comments:

Intervention:

Run-in : 2
Wash out : 7
Allow other medication : No

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

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

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	Temazepam	Placebo		P value:
8 ( )	12 ( )	14 ( )	( )	NR

% ( )

Very severe perspiration

Zopiclone	Temazepam	Placebo		P value:
8 ( )	18 ( )	10 ( )	( )	NR

% ( )

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

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

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

Oponion of the patient about day-time status

\# Well/normal

Zopiclone	Temazepam	Placebo		P value:
30 (57)	35 (66)	27 (51)	( )	NR

Number (%)

\# Sleepy/dull/tired

Zopiclone	Temazepam	Placebo		P value:
7 (13)	6 (11)	12 (23)	( )	NR

Number (%)

\# Headache

Zopiclone	Temazepam	Placebo		P value:
3 (6)	3 (6)	1 (2)	( )	NR

Number (%)

\# Irritable/unstable

Zopiclone	Temazepam	Placebo		P value:
4 (8)	4 (8)	6 (11)	( )	NR

Number (%)

\# Trembling/palpitation

Zopiclone	Temazepam	Placebo		P value:
2 (4)	4 (8)	2 (4)	( )	NR

Number (%)

\# Difficulties to concentrate

Zopiclone	Temazepam	Placebo		P value:
2 (4)	0 (0)	0 (0)	( )	NR

Number (%)

\# Depressive

Zopiclone	Temazepam	Placebo		P value:
3 (6)	1 (2)	2 (4)	( )	

% ( )

\# Unknown

Zopiclone	Temazepam	Placebo		P value:
2 (4)	0 (0)	3 (6)	( )	

% ( )

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

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

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

withdrawals

Total withdrawals

Zopiclone	Temazepam			P value:
1 ( )	1 ( )	( )	( )	NR

Number ( )

withdrawals due to Aes

Zopiclone	Temazepam			P value:
1 ( )	1 ( )	( )	( )	NR

Number ( )

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

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:

Gender: NR (0 %) Female

Ethnicity: NR

Number Screened: NR
Eligible: NR
Enrolled: 221

Number Withdrawn: 9
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 : NR

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

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

Author:	**Voshaar**	**Trial type:**	**Active**	**Quality rating:**	**Fair**
Year:	**2004**	**Country:**	**Netherlands**	**Funding:**	**Sanfi-Synthelabo**

Adverse Events:

withdrawals

# total withdrawals- not reported					P value:
	( )	( )	( )	( )	
	( )				
# withdrawals due to AEs- not reported					P value:
	( )	( )	( )	( )	
	( )				

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

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

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

Design:

Study design RCT
DB
Parallel

Setting Multicenter

Age: NR
Range: 21-65
SD:

Gender: NR (0 %) Female

Ethnicity: NR

Number Screened: NR
Eligible: 589
Enrolled: 306

Number Withdrawn: 28
Lost to fu: 0
Analyzed: 278

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	Withdrawals due to AEs/ 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

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

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			P value:
78 (76.5)	75 (75)	( )	( )	NS

Number (%)

\# headache (highest incidence)

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

% ( )

\# somnolence (highest incidence)

Zolpidem	Trazodone	Placebo		P value:
16 ( )	23 ( )	8 ( )	( )	

% ( )

withdrawals

\# total withdrawals

Zolpidem	Trazodone	Placebo		P value:
11 ( )	10 ( )	7 ( )	( )	

( )

\# withdrawals due to AEs

Zolpidem	Trazodone	Placebo		P value:
5 ( )	5 ( )	2 ( )	( )	

( )

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

Author: Walsh_ **Trial type:** Active **Quality rating:** Good

Year: 1998b **Country:** US **Funding:** Wyeth Ayerst

Design:

Study design

DB

Parallel

Setting

Age: 40.3
Range: 18-60
SD:

Gender: 77 (58 %) Female

Ethnicity: NR

Number Screened: 673
Eligible: 456
Enrolled: 132

Number Withdrawn: 7
Lost to fu: 0
Analyzed: 125

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).

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.

Comments:

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

Intervention:

Run-in : 3
Wash out : 2
Allow other medication : NR

Drug name	dosage	N=	Duration	Withdrawals due to AEs/ 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

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

Author: **Walsh_** **Trial type:** **Active** **Quality rating:** **Good**

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:
13 (38)	12 (35)	14 (42)	17 (55)	NS

Number (%)

Nausea

Placebo	Zaleplon 5mg	Zaleplon 10mg	Triazolam	P value:
0 (<0.04)	0 (<0.04)	1 (NR)	4 (NA)	

Number (p vs triazolam)

headache- the most common adverse event

Placebo	Zaleplon 5mg	Zaleplon 10mg	Triazolam	P value:
5 (15)	5 (15)	6 (18)	7 (23)	

Number (%)

withdrawals

total withdrawals

Zaleplon 5mg	Zaleplon 10mg	Triazolam	Placebo	P value:
3 ( )	1 ( )	0 ( )	3 ( )	

Number ( )

withdrawals due to AEs

Zaleplon 5mg	Zaleplon 10mg	Triazolam	Placebo	P value:
1 ( )	0 ( )	0 ( )	0 ( )	

Number ( )

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

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

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

Design:

Study design RCT
DB
Crossover

Setting Single Center

Age: 42
Range: 22-49
SD:

Gender: NR (%) Female

Ethnicity: NR

Number Screened: 73
Eligible: 39
Enrolled: 30

Number Withdrawn: 2
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-in : NR
Wash out : NR
Allow other medication : No

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

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

Author:	**Walsh__**	**Trial type:**	**Active**	**Quality rating:**	**Poor**
Year:	**2000**	**Country:**	**US**	**Funding:**	**Wyeth-Ayerst Research**

Adverse Events:

Evidence Table 6. Active controlled trials (Adults): 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

Age: NR
Range: 21-55
SD:

Gender: 64 (58 %) Female

Ethnicity: 69% white

Number Screened: 358
Eligible: NR
Enrolled: 110

Number Withdrawn: 11
Lost to fu: NR
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:

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	Withdrawals due to AEs/ 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

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

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

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

Adverse Events:

withdrawals

withdrawals due to Aes

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

Number (%)

total withdrawals

Zolpidem	Triazolam	Placebo		P value:
NR ( )	NR ( )	NR ( )	( )	

Number ( )

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

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 Screened: NR
Eligible: NR
Enrolled: 36

Number Withdrawn: 2
Lost to fu: 0
Analyzed: 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

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

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

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

Year: **1985** **Country:** **NR** **Funding:** **Not reported**

Adverse Events:

Reported by patients

\# Overall AEs, no. of patients

Zopiclone	Temazepam			P value:
10 (28)	9 (25)	( )	( )	NR

Number (%)

\# Daytime drowsiness

Zopiclone	Temazepam			P value:
3 ( )	2 ( )	( )	( )	NR

Number ( )

withdrawals

\# total withdrawals

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

Number ( )

\# withdrawals due to Aes

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

Number ( )

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

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

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

Design:

Study design RCT
DB
Parallel

Setting NR

Age: NR
Range: 64-80
SD:

Gender: 36 (86 %) Female

Ethnicity: NR

Number Screened: NR
Eligible: NR
Enrolled: 42

Number Withdrawn: NR
Lost to fu: NR
Analyzed: 42

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.

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

Comments:

Intervention:

Run-in : 4
Wash out : 7
Allow other medication : NR

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

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

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

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

Outcome Measurement:

Sleep Disorder Intensity Scale (SDIS)
Visual Analogue Self-rating scales afternoon - VIS-A
Visual Analogue Self-rating scales morning - VIS-M

Efficacy Outcome List:

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

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

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

Design:

Study design RCT
DB
Parallel

Setting Multicenter

Age: 76.0
Range: 60-90
SD: 1.3

Gender: 33 (75 %) Female

Ethnicity: NR

Number Screened: NR
Eligible: NR
Enrolled: 44

Number Withdrawn: 0
Lost to fu: 0
Analyzed: 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

Drug name	dosage	N=	Duration	Withdrawals due to AEs/ 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

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

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

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

Outcome Measurement:

Post-sleep questionnaire, administered by a research nurse

Efficacy Outcome List:

Primary outcome	Outcome:
☐	Sleep latency
☐	Sleep soundness
☐	Sleep quality
☐	Status of wakefulness upon arising
☐	Hangover

Results

Post-sleep questionnaire

sleep latency, mean score

Zopiclone		Triazolam				P value
6.7	(<0.05)	6.8	(<0.05)	( )	( )	

Score (p vs placebo)

sleep soundness, mean score

Zopiclone		Triazolam				P value
6.8	(<0.01)	6.4	(<0.08)	( )	( )	

Score (p vs placebo)

quality of sleep, mean score

Zopiclone		Triazolam				P value
10.8	(<0.08)	11.0	(<0.08)	( )	( )	NS

Score (p vs placebo)

morning wake-up, mean score

Zopiclone		Triazolam				P value
10.5	(NS)	10.5	(NS)	( )	( )	NS

Score (p vs placebo)

hangover, mean score

Zopiclone		Triazolam				P value
16.6	(NS)	16.7	(NS)	( )	( )	NS

Score (p vs placebo)

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

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 Screened: NR
Eligible: NR
Enrolled: 74

Number Withdrawn: 2
Lost to fu: 2
Analyzed: 72

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

Drug name	dosage	N=	Duration	Withdrawals due to AEs/ Total withdrawal
Zopiclone	7.5 mg	36	7 day	0 / 1
Nitrazepam	5 mg	36	7 day	1 / 1

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

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

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

Outcome Measurement:

diary: analogue scales
Spiegel sleep questionnaire

Efficacy Outcome List:

Primary outcome	Outcome:
☐	sleep onset latency
☐	quality of sleep
☐	feeling upon awakening
☐	duration of sleep
☐	awakenings during the night
☐	dreams

Results

diary: analogue scales

sleep onset latency- change from placebo baseline

Zopiclone	Nitrazepam			P value
-18.2 (<0.04)	-15.6 (NS)	( )	( )	NS

Score (p vs baseline)

quality of sleep- change from placebo baseline

Zopiclone	Nitrazepam			P value
24 (<0.006)	23.1 (<0.002)	( )	( )	NS

Score (p vs baseline)

feeling on awakening- change from placebo baseline

Zopiclone	Nitrazepam			P value
-5.7 (NS)	6.8 (NS)	( )	( )	NS

Score (p vs baseline)

feeling on awakening- on day 9 and day 11

Zopiclone	Nitrazepam			P value
better ( )	NR ( )	( )	( )	<0.02

Score ( )

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

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

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

Spiegel sleep questionnaire

sleep onset latency

Zopiclone		Nitrazepam				P value
NR	(0.003)	NR	(0.009)	( )	( )	NS

Score (p vs placebo)

quality of sleep

Zopiclone		Nitrazepam				P value
NR	(0.003)	NR	(0.007)	( )	( )	NS

Score (p vs placebo)

duration of sleep

Zopiclone		Nitrazepam				P value
NR	(0.003)	NR	(0.005)	( )	( )	NS

Score (p vs placebo)

awakenings at night

Zopiclone		Nitrazepam				P value
NR	(0.004)	NR	(0.009)	( )	( )	NS

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

Score (p vs placebo)

sleep onset latency on day 12

Zopiclone		Nitrazepam				P value
NR	( )	better	( )	( )	( )	<0.001

Score ( )

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

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

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 Screened: NR
Eligible: 457
Enrolled: 335

Number Withdrawn: 40
Lost to fu: 0
Analyzed: 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:

Run-in : 7
Wash out : 4
Allow other medication : NR

Drug name	dosage	N=	Duration	Withdrawals due to AEs/ 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

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

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

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

Outcome Measurement:

morning questionnaire
Global Impression of therapy

Efficacy Outcome List:

Primary outcome	Outcome:
☑	sleep latency
☑	sleep duration
☐	ease of falling asleep
☐	no. of awakenings
☐	wake time after sleep onset
☐	quality of sleep
☐	morning sleepiness
☐	ability to concentrate

Results

morning questionnaire

sleep latency at week 4

Zolpidem	Triazolam	Temazepam	Placebo	P value
40.5 (<0.05)	47.7 (NS)	38.0 (<0.05)	57.9 (NA)	

minutes (p vs placebo)

sleep latency at week 1 and week 3

Zolpidem	Triazolam			P value
shorter ( )	multiple d ( )	( )	( )	<0.05

minutes ( )

sleep latency at week 1 and week 3

Zolpidem	Temazepam			P value
multiple d ( )	multiple d ( )	( )	( )	NS

minutes ( )

sleep duration at week 4

Zolpidem	Triazolam	Temazepam	Placebo	P value
362.8 (NS)	359.7 (NS)	375.3 (NS)	363 (NA)	

minutes (p vs placebo)

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

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

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

tolerance to treatment

Zolpidem	Triazolam	Temazepam	Placebo	P value
multiple d (NS)	multiple d (NS)	multiple (NS)	multiple (NA)	

minutes (p vs placebo)

Global Impression of therapy

sleep better

Zolpidem	Temazepam			P value
NR, better (<0.05)	NR, bette (<0.05)	( )	( )	

Score (p vs placebo)

sleep latency

Zolpidem	Temazepam			P value
NR, better (<0.05)	NR, bette (<0.05)	( )	( )	

Score (p vs placebo)

medication strength

Zolpidem	Temazepam			P value
NR, better (<0.05)	NR, bette (<0.05)	( )	( )	

Score (p vs placebo)

overall feeling

Zolpidem	Temazepam			P value
NR, better (<0.05)	NR, bette (<0.05)	( )	( )	

Score (p vs placebo)

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

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

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 Screened: NR
Eligible: NR
Enrolled: 221

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

Drug name	dosage	N=	Duration	Withdrawals due to AEs/ 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

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

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

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

Outcome Measurement:

questionnaire
Clinical Global Impression (CGI)

Efficacy Outcome List:

Primary outcome	Outcome:
☐	sleep onset
☐	total sleep time
☐	number of nocturnal awakenings
☐	total duration of nocturnal awakenings
☐	time of awakening
☐	feeling of too early awakening
☐	quality of sleep
☐	quality of awakening

Results

questionnaire

% of patients falling asleep well at day 24, change from baseline

Zolpidem 5mg	Zolpidem 10mg	Triazolam		P value
55.9 (<0.01)	47.9 (<0.01)	51.9 (<0.01)	( )	

% (p vs baseline)

% of patients falling asleep well at day 31, change from baseline

Zolpidem 5mg	Zolpidem 10mg	Triazolam		P value
34.6 (<0.01)	19.8 (<0.01)	18.6 (<0.01)	( )	

% (p vs baseline)

% of patients falling asleep in <30 minutes at day 24, change from baseline

Zolpidem 5mg	Zolpidem 10mg	Triazolam		P value
35 (<0.01)	35 (<0.01)	35 (<0.01)	( )	

% (p vs baseline)

mean total sleep time at day 24, change from baseline

Zolpidem 5mg	Zolpidem 10mg	Triazolam		P value
1.6 (NR)	1.9 (NR)	1.9 (NR)	( )	

hours (p vs baseline)

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

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

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

% of patients with >2 awakenings per night at day 24, change from baseline

Zolpidem 5mg	Zolpidem 10mg	Triazolam		P value
-36.8 (<0.001)	-28.8 (<0.001)	-29.8 (<0.00)	( )	

Number (p vs baseline)

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

Zolpidem 5mg	Zolpidem 10mg	Triazolam		P value
55.9 (17.6)	47.9 (11.0)	55.8 (15.6)	( )	

day 3 (day 24)

overall sleep quality at day 24, change from baseline (higher score=better)

Zolpidem 5mg	Zolpidem 10mg	Triazolam		P value
35.5 (<0.001)	34.4 (<0.001)	33.6 (<0.00)	( )	

Score (p vs baseline)

% of patients who reported too early awakening at day 24, chagne from baseline

Zolpidem 5mg	Zolpidem 10mg	Triazolam		P value
-35 (<0.001)	-38 (<0.001)	-35 (<0.00)	( )	

% (p vs baseline)

Clinical Global Impression (CGI)

total mean score- safety and efficacy

Zolpidem 5mg	Zolpidem 10mg	Triazolam		P value
2.54 ( )	2.43 ( )	2.51 ( )	( )	NS

Score ( )

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

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

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

Design:

Study design RCT
DB
Parallel

Setting Multicenter

Age: 76.8
Range: 60-96
SD:

Gender: 31 (76 %) Female

Ethnicity: NR

Number Screened: 58
Eligible: 41
Enrolled: 41

Number Withdrawn: 0
Lost to fu: 0
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 : 7
Wash out : 0
Allow other medication : NR

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

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

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

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

Outcome Measurement:

Pre- and during-treatment questionnaires

Efficacy Outcome List:

Primary outcome	Outcome:
☐	Difficulty in falling asleep, 3 points, 1: diff
☐	Sleep duration (hr)
☐	Sleep quality
☐	Night awakenings (no. of times)
☐	Early morning awakenings (no. of times)
☐	Daytime sleep
☐	Sleep satisfaction
☐	Daytime sleep

Results

Pre- and during-treatment questionnaires

Difficulty in falling sleep - day 7 (1=none/very little; 2=some; 3=a lot)

Zopiclone		Triazolam				P value
1.21	( )	1.62	( )	( )	( )	0.03

Score ( )

Sleep duration (hr) - day 7

Zopiclone		Triazolam				P value
7.4	( )	7.5	( )	( )	( )	0.05

No. hours ( )

Night awakenings - day 7

Zopiclone		Triazolam				P value
1	( )	1.7	( )	( )	( )	0.06

Frequency ( )

Sleep quality, Early morning awakenings, Mental alertness on rising, Sleep satisfaction- day 7

Zopiclone		Triazolam				P value
NR	( )	NR	( )	( )	( )	NS

( )

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

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

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

Daytime sleep - day 7, compare to mean

Zopiclone		Triazolam				P value
-8	( )	9	( )	( )	( )	0.07

Minutes ( )

Daytime sleep - day 17 (no. of patients)

Zopiclone		Triazolam				P value
2	( )	5	( )	( )	( )	NR

Number ( )

Night awakenings - day 17

Zopiclone		Triazolam				P value
NR	( )	1	( )	( )	( )	0.06

Frequency ( )

Daytime sleep - day 17, compare to mean

Zopiclone		Triazolam				P value
-8	( )	4	( )	( )	( )	NS

Minutes ( )

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

Author:	**Elie_**	**Trial type:**	**Active**	**Quality rating:**	**Fair**
Year:	**1990a**	**Country:**	**Canada**	**Funding:**	**Not reported**

Design:

Study design RCT
DB
Parallel

Setting Multicenter

Age: 76.0
Range: 60-90
SD: 1.3

Gender: 33 (75 %) Female

Ethnicity: NR

Number Screened: NR
Eligible: NR
Enrolled: 44

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

Drug name	dosage	N=	Duration	Withdrawals due to AEs/ 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 ( )

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

Author: Leppik | **Trial type:** Active | **Quality rating:** Fair

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 Screened: NR
Eligible: 457
Enrolled: 335

Number Withdrawn: 40
Lost to fu: 0
Analyzed: 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:

Drug name	dosage	N=	Duration	Withdrawals due to AEs/ 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

Triazolam				P value
worse (<0.05)	( )	( )	( )	
Score (p vs baseline)				

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

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)				

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

Author:	**Roger**	**Trial type:**	**Active**	**Quality rating:**	**Fair**
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 Screened: NR
Eligible: NR
Enrolled: 221

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:

Drug name	dosage	N=	Duration	Withdrawals due to AEs/ 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

Zolpidem 5mg	Zolpidem 10mg	Triazolam		P value
18 (0.001)	28 (<0.00)	9 (0.06)	( )	

% (p vs baseline)

\# 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 3 (day 31)

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

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)	Zaleplon 5mg		Zolpidem 10mg		Triazolam			P value
		17.2	(0.05)	23.9	(0.05)	10.5	(NA)	( )	
		Score	(p vs triazolam)						

Evidence Table 9. Active controlled trials (Elderly): Adverse Events

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

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

Design:

Study design RCT
DB
Parallel

Setting NR

Age: NR
Range: 64-80
SD:

Gender: 36 (86 %) Female

Ethnicity: NR

Number Screened: NR
Eligible: NR
Enrolled: 42

Number Withdrawn: NR
Lost to fu: NR
Analyzed: 42

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.

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

Comments:

Intervention:

Run-in : 4
Wash out : 7
Allow other medication : NR

Drug name	dosage	N=	Duration	Withdrawals due to AEs/ 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 (%)

Evidence Table 9. Active controlled trials (Elderly): Adverse Events

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

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

withdrawals due to AEs

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

Number (%)

Evidence Table 9. Active controlled trials (Elderly): Adverse Events

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

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

Design:

Study design RCT
DB
Parallel

Setting Multicenter

Age: 76.0
Range: 60-90
SD: 1.3

Gender: 33 (75 %) Female

Ethnicity: NR

Number Screened: NR
Eligible: NR
Enrolled: 44

Number Withdrawn: 0
Lost to fu: 0
Analyzed: 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

Drug name	dosage	N=	Duration	Withdrawals due to AEs/ 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

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

Number (p vs placebo)

Evidence Table 9. Active controlled trials (Elderly): Adverse Events

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

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

bitter taste

Zopiclone	Triazolam			P value:
5 (<0.06)	0 (NS)	( )	( )	

Number (p vs placebo)

withdrawals

total withdrawals

Zopiclone	Trazodone	Placebo		P value:
0 ( )	0 ( )	0 ( )	( )	

Number ( )

withdrawals due to AEs

Zopiclone	Trazodone	Placebo		P value:
0 ( )	0 ( )	0 ( )	( )	

Number ( )

Evidence Table 9. Active controlled trials (Elderly): Adverse Events

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 Screened: NR
Eligible: NR
Enrolled: 74

Number Withdrawn: 2
Lost to fu: 2
Analyzed: 72

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

Drug name	dosage	N=	Duration	Withdrawals due to AEs/ 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 ( )

Evidence Table 9. Active controlled trials (Elderly): Adverse Events

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

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

dizziness

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

Number ( )

confusion

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

Number ( )

fatigue

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

Number ( )

complaints in answer to the standarized question on tolerance

Zopiclone	Nitrazepam			P value:
less (NS)	more (<0.00)	( )	( )	

Number (p vs baseline)

<u>withdrawals</u>

total withdrawals

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

Number ( )

withdrawals due to AEs

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

Number ( )

Evidence Table 9. Active controlled trials (Elderly): Adverse Events

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

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 Screened: NR
Eligible: 457
Enrolled: 335

Number Withdrawn: 40
Lost to fu: 0
Analyzed: 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:

Run-in : 7
Wash out : 4
Allow other medication : NR

Drug name	dosage	N=	Duration	Withdrawals due to AEs/ 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

Zolpidem	Triazolam	Temazepam	Placebo	P value:
52 (63)	54 (64)	56 (67)	47 (56)	

Evidence Table 9. Active controlled trials (Elderly): Adverse Events

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

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

Number (%)

# headache	Zolpidem	Triazolam	Temazepam	Placebo	P value:
	15 (18.3)	22 (25.9)	18 (21.4)	16 (19)	

Number (%)

# drowsiness	Zolpidem	Triazolam	Temazepam	Placebo	P value:
	4 (4.9)	7 (8.2)	8 (9.5)	3 (3.6)	

Number (%)

# myalgia	Zolpidem	Triazolam	Temazepam	Placebo	P value:
	8 (9.8)	7 (8.2)	8 (9.5)	9 (10.7)	

Number (%)

# nausea	Zolpidem	Triazolam	Temazepam	Placebo	P value:
	6 (7.3)	6 (7.1)	4 (4.8)	6 (7.1)	

Number (%)

# upper resp infection	Zolpidem	Triazolam	Temazepam	Placebo	P value:
	6 (7.3)	2 (2.4)	7 (8.3)	7 (8.3)	

Number (%)

# dyspepsia	Zolpidem	Triazolam	Temazepam	Placebo	P value:
	5 (6.1)	3 (3.5)	5 (6.0)	7 (8.3)	

Number (%)

# nervousness	Zolpidem	Triazolam	Temazepam	Placebo	P value:
	2 (2.4)	7 (8.2)	3 (3.6)	4 (4.8)	

Number (%)

Evidence Table 9. Active controlled trials (Elderly): Adverse Events

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

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

arthralgia

Zolpidem	Triazolam	Temazepam	Placebo	P value:
4 (4.9)	5 (5.9)	0 (0)	3 (3.6)	

Number (%)

fatigue

Zolpidem	Triazolam	Temazepam	Placebo	P value:
1 (1.2)	2 (2.4)	5 (6.0)	1 (1.2)	

Number (%)

withdrawals

total withdrawals

Zolpidem	Triazolam	Temazepam	Placebo	P value:
6 ( )	14 ( )	10 ( )	10 ( )	

Number ( )

withdrawals due to AEs

Zolpidem	Triazolam	Temazepam	Placebo	P value:
2 ( )	5 ( )	5 ( )	6 ( )	

Number ( )

Evidence Table 9. Active controlled trials (Elderly): Adverse Events

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

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 Screened: NR
Eligible: NR
Enrolled: 221

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

Drug name	dosage	N=	Duration	Withdrawals due to AEs/ 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

Zolpidem 5mg	Zolpidenm 10mg	Triazolam		P value:
11 (16)	8 (11)	16 (21)	( )	

Number (%)

Evidence Table 9. Active controlled trials (Elderly): Adverse Events

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

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

nightmares- the most common adverse effect

Zolpidem 5mg	Zolpidenm 10mg	Triazolam		P value:
2 ( )	3 ( )	2 ( )	( )	

Number ( )

<u>withdrawals</u>

total withdrawals

Zolpidem 5mg	Zolpidem 10mg	Triazolam		P value:
7 ( )	1 ( )	5 ( )	( )	

Number ( )

withdrawals dur to Aes

Zolpidem 5mg	Zolpidem 10mg	Triazolam		P value:
0 ( )	0 ( )	2 ( )	( )	

Number ( )

Evidence Table 9. Active controlled trials (Elderly): Adverse Events

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

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

Design:

Study design RCT
DB
Parallel

Setting Multicenter

Age: 76.8
Range: 60-96
SD:

Gender: 31 (76 %) Female

Ethnicity: NR

Number Screened: 58
Eligible: 41
Enrolled: 41

Number Withdrawn: 0
Lost to fu: 0
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 : 7
Wash out : 0
Allow other medication : NR

Drug name	dosage	N=	Duration	Withdrawals due to AEs/ 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 (%)

Evidence Table 9. Active controlled trials (Elderly): Adverse Events

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

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

number of patient reporting AEs on day 7 and day 9

Zopiclone	Triazolam			P value:
more ( )	NR ( )	( )	( )	0.013

Number ( )

Reported by the patients: CNS AEs

depression, tearfulness, drowsiness, dizziness, agitation, nightmares, confusion, and disturbed sleep

Zopiclone	Triazolam			P value:
3 ( )	7 ( )	( )	( )	NR

Number ( )

Reported by the patients: Gastrointestinal AEs

Bad taste

Zopiclone	Triazolam			P value:
6 ( )	2 ( )	( )	( )	NR

Number ( )

Reported by the patients: Other AEs

muscular pain, angina pectoris episodes, and shortness of breath

Zopiclone	Triazolam			P value:
3 ( )	1 ( )	( )	( )	NR

Number ( )

withdrawals

total withdrawals

Zopiclone	Triazolam			P value:
0 ( )	0 ( )	( )	( )	

Number ( )

withdrawals due to AEs

Zopiclone	Triazolam			P value:
0 ( )	0 ( )	( )	( )	

Number ( )

Evidence Table 10. Active controlled trials (Other Subgroups): Efficacy

Author: Agnoli **Trial type:** Active **Subgroup:** Anxiety **Quality rating:** Poor

Year: 1989 **Country:** Rome, Foggia, Italy **Funding:** Not reported

Design:

Study design RCT
DB
Crossover

Setting NR

Age: 38.2
Range:
SD: 2.1

Gender: 12 (60 %) Female

Ethnicity: NR

Number Screened: NR
Eligible: NR
Enrolled: 20

Number Withdrawn: 0
Lost to fu: 0
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.

Exclusion criteria:

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

Comments:

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

Intervention:

Run-in : 3
Wash out : NR
Allow other medication : NR

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

Evidence Table 10. Active controlled trials (Other Subgroups): Efficacy

Author: **Agnoli** **Trial type:** **Active** **Subgroup:** **Anxiety** **Quality rating:** **Poor**

Year: **1989** **Country:** **Rome, Foggia, Italy** **Funding:** **Not reported**

Outcome Measurement:

Hamilton Rating Scale for Anxiety (HRSA)
Toulouse-Pieron Attention Test (TPAT)
Time-signed semiquantitative scale

Efficacy Outcome List:

Primary outcome	Outcome:
☐	anxiety levels
☐	time of sleep induction
☐	hours of sleep
☐	number of nocturnal arousals
☐	quality of sleep
☐	quality of daytime arousal

Results

Hamilton Rating Scale for Anxiety (HRSA)

after the 1st and 2nd weeks of treatment (less score = better)

Nitrazepam				P value
- ( )	( )	( )	( )	<0.05
Score ( )				

Evidence Table 10. Active controlled trials (Other Subgroups): Efficacy

Author: **Agnoli** **Trial type:** **Active** **Subgroup:** **Anxiety** **Quality rating:** **Poor**

Year: **1989** **Country:** **Rome, Foggia, Italy** **Funding:** **Not reported**

Toulouse-Pieron Attention Test

# reduction of omitted items on the 7th day (more reduction=better)	Nitrazepam				P value
	- ( )	( )	( )	( )	<0.01
	Number ( )				
# reduction of omitted items on the 14th day (more reduction=better)	Nitrazepam				P value
	- ( )	( )	( )	( )	<0.05
	Number ( )				
# reduction of errors items on the 7th day (more reduction=better)	Nitrazepam				P value
	- ( )	( )	( )	( )	<0.01
	Number ( )				
# times of excution (shorter=better)	Nitrazepam				P value
	- ( )	( )	( )	( )	<0.01
	Number ( )				

Time-signed semiquantitative scale

# time of sleep induction (shorter=better)	Nitrazepam				P value
	- ( )	( )	( )	( )	<0.001
	Number ( )				
# quality of daytime arousal	Nitrazepam				P value
	- ( )	( )	( )	( )	<0.01
	Number ( )				
# number of nocturnal arousals, the quality of sleep, the duration of sleep	Nitrazepam				P value
	NR ( )	( )	( )	( )	NS
	Number ( )				

Evidence Table 10. Active controlled trials (Other Subgroups): Efficacy

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

Age: 43.9
Range: 20-55
SD:

Gender: 17 (33 %) Female

Ethnicity: NR

Number Screened: NR
Eligible: 54
Enrolled: 52

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

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.

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

Comments:

Intervention:

Run-in : 2
Wash out : NR
Allow other medication : No

Drug name	dosage	N=	Duration	Withdrawals due to AEs/ Total withdrawal
Zopiclone	7.5 mg	27	5 day	0 / 0
Lormetazepam	1 mg	25	5 day	0 / 0

Evidence Table 10. Active controlled trials (Other Subgroups): Efficacy

Author: **Ansoms** **Trial type:** **Active** **Subgroup:** **alcoholism** **Quality rating:** **Fair**

Year: **1991** **Country:** **US** **Funding:** **Not reported**

Outcome Measurement:

Spiegel Sleep Questionnaire
Visual Analogue Scale
Investigator-completed scale (1=excellent, 2=good, 3=fair, 4=poor)

Efficacy Outcome List:

Primary outcome	Outcome:
☐	Efficacy (Spiegel Sleep Questionnaire)
☐	Behavior and mood on waking up
☐	Overall evaluation of efficacy and tolerabilit

Results

Efficacy (Spiegel Sleep Questionnaire)

Improvement from baseline to end of treatment on time to fall asleep

Zopiclone	Lormetazepam			P value
NS ( )	0.013 ( )	( )	( )	

p-value ( )

Improvement from baseline to end of treatment on quality of sleep

Zopiclone	Lormetazepam			P value
NS ( )	0.065 ( )	( )	( )	

p-value ( )

Improvement from baseline to end of treatment on duration of sleep

Zopiclone	Lormetazepam			P value
NS ( )	NS ( )	( )	( )	

p-value ( )

Improvement from baseline to end of treatment on nocturnal awakenings

Zopiclone	Lormetazepam			P value
NS ( )	NS ( )	( )	( )	

p-value ( )

Improvement from baseline to end of treatment on dreams

Zopiclone	Lormetazepam			P value
NS ( )	NS ( )	( )	( )	

p-value ( )

Improvement from baseline to end of treatment on morning disposition

Zopiclone	Lormetazepam			P value
NS ( )	NS ( )	( )	( )	

p-value ( )

Evidence Table 10. Active controlled trials (Other Subgroups): Efficacy

Author: **Ansoms** **Trial type:** **Active** **Subgroup:** **alcoholism** **Quality rating:** **Fair**

Year: **1991** **Country:** **US** **Funding:** **Not reported**

# Improvement from baseline to end of treatment on general evaluation	Zopiclone	Lormetazepam			P value
	NS ( )	NS ( )	( )	( )	
	p-value ( )				

Overall evaluation of efficacy and tolerability

# Physician's overall efficacy assessment after treatment ("excellent or good")	Zopiclone	Lormetazepam			P value
	44 ( )	48 ( )	( )	( )	NS
	(%) ( )				

Behavior and mood on waking up

# No differences between treatments on any of 18 items based on Norris mood rating scale	0				P value
	( )	( )	( )	( )	
	( )				

Evidence Table 10. Active controlled trials (Other Subgroups): Efficacy

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 Screened: NR
Eligible: 32
Enrolled: 29

Number Withdrawn: 0
Lost to fu: 0
Analyzed: 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
Allow other medication : NR

Drug name	dosage	N=	Duration	Withdrawals due to AEs/ 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

Evidence Table 10. Active controlled trials (Other Subgroups): Efficacy

Author:	**Bozin-Juracic**	**Trial type:**	**Active**	**Subgroup:**	**shiftworker**	**Quality rating:**	**Fair**
Year:	**1995**	**Country:**	**Croatia**			**Funding:**	**May and Becker and Rhone-**

Outcome Measurement:

\# sleep questionnaire using visual-analogue scale

Efficacy Outcome List:

Primary outcome	Outcome:
☐	time in bed
☐	length of sleep episode
☐	total sleep time
☐	sleep efficacy
☐	sleep latency
☐	sleep quality
☐	no. of awakenings
☐	spontaneous final awakenings

Results

sleep questionnaire using visual-analogue scale

# mean total length of main sleep (estimate from the figure)	Zopiclone	Nitrazepam	Placebo		P value
	295 ( )	285 ( )	270 ( )	( )	NR
	minutes ( )				
# mean sleep efficacy of main sleep (estimate from the figure)	Zopiclone	Nitrazepam	Placebo		P value
	88 ( )	87 ( )	82 ( )	( )	NR
	% ( )				
# mean sleep efficacy of all day sleep (estimate from the figure)	Zopiclone	Nitrazepam	Placebo		P value
	88 ( )	87 ( )	82 ( )	( )	NR
	% ( )				
# 10 items of main sleep characteristics	Zopiclone	Nitrazepam	Placebo		P value
	NR ( )	NR ( )	NR ( )	( )	NS
	Score ( )				

Evidence Table 10. Active controlled trials (Other Subgroups): Efficacy

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

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

5 items of all day sleep characteristics

Zopiclone	Nitrazepam	Placebo		P value
NR ( )	NR ( )	NR ( )	( )	NS

Score ( )

Evidence Table 10. Active controlled trials (Other Subgroups): Efficacy

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

Age: 42.9
Range: 26-58
SD: 1.1

Gender: 40 (53 %) Female

Ethnicity: NR

Number Screened: NR
Eligible: NR
Enrolled: 75

Number Withdrawn: 21
Lost to fu: 0
Analyzed: 75

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.

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).

Comments:

Subgroup: generalized anxiety disorder

Intervention:

Run-in : 7
Wash out : 21
Allow other medication : no psychotopic medications

Drug name	dosage	N=	Duration	Withdrawals due to AEs/ 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

Evidence Table 10. Active controlled trials (Other Subgroups): Efficacy

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

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

Outcome Measurement:

sleep inventory
Hamilton Rating Scale (HAM)
Clinical Global Impression (CGI)

Efficacy Outcome List:

Primary outcome	Outcome:
☐	sleep induction
☐	sleep soundness
☐	duration of sleep
☐	morning awakening
☐	hangover effect

Results

sleep inventory

sleep induction time

Zopiclone		Triazolam				P value
3.5	(<0.01)	3.5	(<0.05)	( )	( )	NS

Score (p vs placebo)

sleep induction cluster

Zopiclone		Triazolam				P value
14.7	(<0.05)	14.1	(NS)	( )	( )	NS

Score (p vs placebo)

duration of sleep

Zopiclone		Triazolam				P value
2.9	(NS)	2.9	(NS)	( )	( )	NS

Score (p vs placebo)

sleep soundness

Zopiclone		Triazolam				P value
11.0	(<0.05)	10.5	(NS)	( )	( )	NS

Score (p vs placebo)

global sleep index

Zopiclone		Triazolam				P value
35.7	(NS)	34.6	(NS)	( )	( )	NS

Score (p vs placebo)

Evidence Table 10. Active controlled trials (Other Subgroups): Efficacy

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

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

# morning awakening	Zopiclone	Triazolam			P value
	7.3 (NS)	6.7 (NS)	( )	( )	NS
	Score (p vs placebo)				
# hangover	Zopiclone	Triazolam			P value
	6.8 (NS)	6.3 (NS)	( )	( )	NS
	Score (p vs placebo)				
Hamilton Rating Scale (HAM)					
# somatic anxiety	Zopiclone	Triazolam			P value
	8.8 (NS)	12.0 (NS)	( )	( )	<0.01
	Score (p vs placebo)				
# psychic anxiety	Zopiclone	Triazolam			P value
	9.3 (NS)	10.8 (NS)	( )	( )	NS
	Score (p vs placebo)				
# total score	Zopiclone	Triazolam			P value
	18.2 (NS)	22.4 (NS)	( )	( )	<0.01
	Score (p vs placebo)				
# daytime anxiety	Zopiclone	Triazolam			P value
	5 (17)	10 (33)	( )	( )	0.16
	Number (%)				
Clinical Global Impression (CGI)					
# overall	Zopiclone	Triazolam			P value
	NR (sig. bet)	NR (sig. bet)	( )	( )	NR
	Score (p vs placebo)				

Evidence Table 10. Active controlled trials (Other Subgroups): Efficacy

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 Center

Age: 56.6
Range: 20-78
SD:

Gender: 8 (44 %) Female

Ethnicity: NR

Number Screened: 44
Eligible: 27
Enrolled: 18

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

Drug name	dosage	N=	Duration	Withdrawals due to AEs/ 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

Evidence Table 10. Active controlled trials (Other Subgroups): Efficacy

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

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

Outcome Measurement:

- # recorded by nurses
- # sleep questionnaire
- # Mini mentalstate examination score

Efficacy Outcome List:

Primary outcome	Outcome:
☐	total time of sleep
☐	quality of sleep
☐	depth of sleep
☐	feeling of rest
☐	daytime drowsiness
☐	lethargy
☐	fatigue

Results

recorded by nurses

total time of sleep

Zopiclone	Lorazepam			P value
7.23 (0.63)	7.49 (0.77)	( )	( )	0.09

hours (SD)

alertness (higer score=better)

Zopiclone	Lorazepam			P value
4 (3.5-4)	4 (3.5-4)	( )	( )	0.6

Score (Range)

feeling of being refreshed (higer score=better)

Zopiclone	Lorazepam			P value
3.5 (3-4)	4 (3-4)	( )	( )	0.79

Score (Range)

Evidence Table 10. Active controlled trials (Other Subgroups): Efficacy

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

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

sleep questionnaire

quality of sleep (higher score=better)

Zopiclone	Lorazepam			P value
8 (5-9)	8.5 (7.5-10)	( )	( )	0.17

Score (Range)

depth of sleep (higher score=better)

Zopiclone	Lorazepam			P value
8 (6-10)	8 (7-10)	( )	( )	0.21

Score (Range)

feeling of being refreshed (higher score=better)

Zopiclone	Lorazepam			P value
8 (6.5-10)	8 (6.5-9.5)	( )	( )	0.52

Score (Range)

alertness (higher score=better)

Zopiclone	Lorazepam			P value
9 (6.5-10)	9 (8-10)	( )	( )	0.6

Score (Range)

tiredness (higher score=better)

Zopiclone	Lorazepam			P value
8 (5.5-8.5)	7.5 (5-10)	( )	( )	0.29

Score (Range)

Mini mentalstate examination score

total score

Zopiclone	Lorazepam			P value
28 (27-30)	27 (25-29)	( )	( )	0.054

Score (Range)

Evidence Table 10. Active controlled trials (Other Subgroups): Efficacy

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

Age: 48
Range:
SD:

Gender: 58 (61 %) Female

Ethnicity: NR

Number Screened: NR
Eligible: NR
Enrolled: 95

Number Withdrawn: 33
Lost to fu: 0
Analyzed: 62

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:

Run-in : 4
Wash out : 30
Allow other medication : no other hypnotic drugs

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

Evidence Table 10. Active controlled trials (Other Subgroups): Efficacy

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

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

Outcome Measurement:

- # global assessment by the investigator
- # therapeutic efficacy by patients
- # Hamilton Rating Scale for anxiety

Efficacy Outcome List:

Primary outcome	Outcome:
☐	duration of sleep
☐	number of nocturnal awakenings
☐	time awake during the night
☐	subjective status on awakening
☐	therapeutic efficacy
☐	anxiety

Results

therapeutic efficacy by patients

therapeutic effects at day 30- good and excellent

Zolpidem		Triazolam				P value
32	(75)	32	(75)	( )	( )	NS

Number (%)

therapeutic effects at day 60- good and excellent

Zolpidem		Triazolam				P value
33	(87)	31	(84)	( )	( )	NS

Number (%)

therapeutic effects at day 90- good and excellent

Zolpidem		Triazolam				P value
32	(91)	29	(85)	( )	( )	NS

Number (%)

quality of sleep at day 60

Zolpidem		Triazolam				P value
74	( )	65	( )	( )	( )	NR

% ( )

quality of sleep at day 90

Zolpidem		Triazolam				P value
81	( )	73	( )	( )	( )	NR

% ( )

Evidence Table 10. Active controlled trials (Other Subgroups): Efficacy

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

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

overall rating

Zolpidem		Triazolam				P value
38.4	(78.6)	36.3	(76.6)	( )	( )	NR

day 0 (day 90)

status on awakening and alertness, number of patients

Zolpidem		Triazolam				P value
28	(44)	40	(42)	( )	( )	NR

day 4 (day 90)

global assessment by the investigator

sleep latency at day 90, change from baseline

Zolpidem		Triazolam				P value
-1.9	(<0.001)	-1.9	(<0.001)	( )	( )	NS

Score (p vs baseline)

mean sleep time at day 90, change from baseline

Zolpidem		Triazolam				P value
2.72	(<0.001)	2.26	(<0.001)	( )	( )	NS

hours (p vs baseline)

number of nocturnal awakenings at day 60, change from baseline

Zolpidem		Triazolam				P value
-1.7	(0.02)	-1	(0.02)	( )	( )	<0.05

Number (p vs baseline)

duration of nocturnal awakenings at day 60

Zolpidem		Triazolam				P value
18	(0.02)	14	(0.02)	( )	( )	<0.05

minutes (p vs baseline)

Hamilton Rating Scale for anxiety

total score

Zolpidem		Triazolam				P value
multiple d	( )	multiple d	( )	( )	( )	NS

Score ( )

Evidence Table 10. Active controlled trials (Other Subgroups): Efficacy

Author: Schwartz | **Trial type:** Active | **Subgroup:** psychiatric (inpati | **Quality rating:** Poor

Year: 2004 | **Country:** US | **Funding:** Not reported

Design:

Study design RCT
Open
Parallel

Setting Single Center

Age: NR
Range: 18-65
SD:

Gender: 8 (50 %) Female

Ethnicity: NR

Number Screened: NR
Eligible: NR
Enrolled: 16

Number Withdrawn: 0
Lost to fu: 0
Analyzed: 16

Eligibility criteria:
inpatient psychiatric care

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.

Comments:
Psychiatric inpatients

Intervention:

Run-in : NR
Wash out : NR
Allow other medication : NR

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

Evidence Table 10. Active controlled trials (Other Subgroups): Efficacy

Author: Schwartz **Trial type:** Active **Subgroup:** psychiatric (inpati **Quality rating:** Poor

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

Outcome Measurement:

- # Epworth sleepiness scale (ESS)
- # analogue sleep quality scale
- # inpatient, nurse-recorded sleep log

Efficacy Outcome List:

Primary outcome	Outcome:
☐	sleepiness
☐	sleep duration

Results

Epworth sleepiness scale (ESS)

median at study entry-matching

Zaleplon		Trazodone				P value
7	( )	9	( )	( )	( )	0.885

Score ( )

media change from baseline efficacy and tolerability

Zaleplon		Trazodone				P value
-1	( )	1	( )	( )	( )	0.23

Score ( )

inpatient, nurse-recorded sleep log

sleep- median at study entry-matching

Zaleplon		Trazodone				P value
3	( )	3	( )	( )	( )	0.894

hours ( )

sleep- median change from baseline efficacy and tolerability

Zaleplon		Trazodone				P value
0	( )	3	( )	( )	( )	0.181

hours ( )

Evidence Table 10. Active controlled trials (Other Subgroups): Efficacy

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

Age: 58.2
Range:
SD: 5.5

Gender: 9 (38 %) Female

Ethnicity: NR

Number Screened: NR
Eligible: NR
Enrolled: 24

Number Withdrawn: 0
Lost to fu: 0
Analyzed: 24

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.

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

Drug name	dosage	N=	Duration	Withdrawals due to AEs/ 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

Evidence Table 10. Active controlled trials (Other Subgroups): Efficacy

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

Year: **1993** **Country:** **Canada** **Funding:** **Lorex Pharmaceuticals**

Outcome Measurement:

evening questionnaire
polysomnography
morning questionnaire

Efficacy Outcome List:

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

Results

overall measures

total sleep time

Zolpidem 5mg	Zolpidem 10mg	Triazolam		P value
384.82 (<0.05)	397.12 (NS)	413.79 (NA)	( )	

minutes (p vs triazolam)

total wake time

Zolpidem 5mg	Zolpidem 10mg	Triazolam		P value
93.09 (<0.05)	82.37 (NS)	66.10 (NA)	( )	

minutes (p vs triazolam)

sleep efficacy

Zolpidem 5mg	Zolpidem 10mg	Triazolam		P value
79.74 (<0.05)	82.35 (NS)	85.83 (NA)	( )	

% (p vs triazolam)

Evidence Table 10. Active controlled trials (Other Subgroups): Efficacy

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

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)	( )	

Number (p vs triazolam)

microarousals (no./hour of sleep)

Zolpidem 5mg	Zolpidem 10mg	Triazolam		P value
14.08 (NS)	12.57 (NS)	13.23 (NA)	( )	

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)	50.69 (NS)	40.47 (NA)	( )	

Number (p vs triazolam)

Evidence Table 10. Active controlled trials (Other Subgroups): Efficacy

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

Year: 1993 **Country:** Canada **Funding:** Lorex Pharmaceuticals

subjective assessment of sleep

sleep latency

Zolpidem 5mg	Zolpidem 10mg	Triazolam		P value
38.7 (NS)	30.22 (NS)	25.52 (NA)	( )	

minutes (p vs triazolam)

ease of falling sleep (lower score=better)

Zolpidem 5mg	Zolpidem 10mg	Triazolam		P value
46.48 (<0.05)	30.09 (NS)	20.96 (NA)	( )	

Score (p vs triazolam)

no. of awakenings

Zolpidem 5mg	Zolpidem 10mg	Triazolam		P value
2.74 (NS)	2.17 (NS)	1.61 (NA)	( )	

minutes (p vs triazolam)

duration of night waking

Zolpidem 5mg	Zolpidem 10mg	Triazolam		P value
103.04 (NS)	16.78 (NS)	43.83 (NA)	( )	

minutes (p vs triazolam)

sleep duration

Zolpidem 5mg	Zolpidem 10mg	Triazolam		P value
333.26 (<0.05)	388.22 (NS)	411.17 (NA)	( )	

minutes (p vs triazolam)

feeling of sleep (1=excellent, 4=poor)

Zolpidem 5mg	Zolpidem 10mg	Triazolam		P value
2.61 (<0.05)	2.13 (NS)	1.87 (NA)	( )	

minutes (p vs triazolam)

sleepy in the morning (higher score=better)

Zolpidem 5mg	Zolpidem 10mg	Triazolam		P value
55.04 (NS)	65.44 (NS)	66.52 (NA)	( )	

minutes (p vs triazolam)

concentration in the morning (1=excellent, 4=poor)

Zolpidem 5mg	Zolpidem 10mg	Triazolam		P value
2.30 (NS)	2.26 (NS)	2.13 (NA)	( )	

minutes (p vs triazolam)

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

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

Age: 48
Range:
SD:

Gender: 58 (61 %) Female

Ethnicity: NR

Number Screened: NR
Eligible: NR
Enrolled: 95

Number Withdrawn: 33
Lost to fu: 0
Analyzed: 62

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:

Drug name	dosage	N=	Duration	Withdrawals due to AEs/ 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	Triazolam			P value
33 (89)	34 (83)	( )	( )	NS
Number (%)				

Evidence Table 12. Active controlled trials (Other Subgroups): Adverse Events

Author: Agnoli **Trial type:** Active **Subgroup:** Anxiety **Quality rating:** Poor

Year: 1989 **Country:** Rome, Foggia, Italy **Funding:** Not reported

Design:

Study design RCT
DB
Crossover

Setting NR

Age: 38.2
Range:
SD: 2.1

Gender: 12 (60 %) Female

Ethnicity: NR

Number Screened: NR
Eligible: NR
Enrolled: 20

Number Withdrawn: 0
Lost to fu: 0
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.

Exclusion criteria:

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

Comments:

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

Intervention:

Run-in : 3
Wash out : NR
Allow other medication : NR

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

Adverse Events:

<u>epigestralgia</u>

1st week

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

Number ( )

Evidence Table 12. Active controlled trials (Other Subgroups): Adverse Events

Author: **Agnoli** **Trial type:** **Active** **Subgroup:** **Anxiety** **Quality rating:** **Poor**

Year: **1989** **Country:** **Rome, Foggia, Italy** **Funding:** **Not reported**

daytime sedation

\# 1st week

Zopiclone	Nitrazepam			P value:
0 ( )	6 ( )	( )	( )	NR

Number ( )

\# 2dn week

Zopiclone	Nitrazepam			P value:
0 ( )	14 ( )	( )	( )	NR

Number ( )

\# prolonged into the wash-out period between treatment

Zopiclone	Nitrazepam			P value:
0 ( )	3 ( )	( )	( )	NR

Number ( )

restlessness

\# 1st week

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

Number ( )

Evidence Table 12. Active controlled trials (Other Subgroups): Adverse Events

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

Age: 43.9
Range: 20-55
SD:

Gender: 17 (33 %) Female

Ethnicity: NR

Number Screened: NR
Eligible: 54
Enrolled: 52

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

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.

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

Comments:

Intervention:

Run-in : 2
Wash out : NR
Allow other medication : No

Drug name	dosage	N=	Duration	Withdrawals due to AEs/ 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")		Zopiclone	Lormetazepam	P value:
	( )	93 ( )	76 ( )	( ) NR

% ( )

Evidence Table 12. Active controlled trials (Other Subgroups): Adverse Events

Author: **Ansoms** **Trial type:** **Active** **Subgroup:** **alcoholism** **Quality rating:** **Fair**

Year: **1991** **Country:** **US** **Funding:** **Not reported**

withdrawals

total withdrawals not reported

				P value:
( )	( )	( )	( )	

( )

withdrawals due to AEs not reported

				P value:
( )	( )	( )	( )	

( )

Overall AEs

Overall AEs

	Zopiclone	Lormetazepam		P value:
( )	26 ( )	28 ( )	( )	NS

% ( )

Evidence Table 12. Active controlled trials (Other Subgroups): Adverse Events

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 Screened: NR
Eligible: 32
Enrolled: 29

Number Withdrawn: 0
Lost to fu: 0
Analyzed: 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
Allow other medication : NR

Drug name	dosage	N=	Duration	Withdrawals due to AEs/ 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

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

Number ( )

withdrawals due to AEs

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

Number ( )

Evidence Table 12. Active controlled trials (Other Subgroups): Adverse Events

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

Age: 42.9
Range: 26-58
SD: 1.1

Gender: 40 (53 %) Female

Ethnicity: NR

Number Screened: NR
Eligible: NR
Enrolled: 75

Number Withdrawn: 21
Lost to fu: 0
Analyzed: 75

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.

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).

Comments:

Subgroup: generalized anxiety disorder

Intervention:

Run-in : 7
Wash out : 21
Allow other medication : no psychotopic medications

Drug name	dosage	N=	Duration	Withdrawals due to AEs/ 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)

Evidence Table 12. Active controlled trials (Other Subgroups): Adverse Events

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

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

drowsiness

Zopiclone	Triazolam	Placebo		P value:
3 ( )	5 ( )	4 ( )	( )	NS

Number ( )

ataxia

Zopiclone	Triazolam	Placebo		P value:
2 ( )	3 ( )	1 ( )	( )	NS

Number ( )

headache

Zopiclone	Triazolam	Placebo		P value:
6 ( )	3 ( )	3 ( )	( )	NS

Number ( )

taste perversion

Zopiclone	Triazolam	Placebo		P value:
17 ( )	3 ( )	1 ( )	( )	<0.001

Number ( )

nausea

Zopiclone	Triazolam	Placebo		P value:
2 ( )	3 ( )	4 ( )	( )	NS

Number ( )

dry mouth

Zopiclone	Triazolam	Placebo		P value:
7 ( )	1 ( )	1 ( )	( )	<0.05

Number ( )

Evidence Table 12. Active controlled trials (Other Subgroups): Adverse Events

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

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

withdrawals

\# total withdrawals

Zopiclone	Triazolam	Placebo		P value:
8 ( )	8 ( )	5 ( )	( )	

Number ( )

\# withdrawals due to AEs

Zopiclone	Triazolam	Placebo		P value:
4 ( )	3 ( )	0 ( )	( )	

Number ( )

Evidence Table 12. Active controlled trials (Other Subgroups): Adverse Events

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 Center

Age: 56.6
Range: 20-78
SD:

Gender: 8 (44 %) Female

Ethnicity: NR

Number Screened: 44
Eligible: 27
Enrolled: 18

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

Drug name	dosage	N=	Duration	Withdrawals due to AEs/ 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

Zopiclone	Lorazepam			P value:
0 ( )	0 ( )	( )	( )	

Number ( )

Evidence Table 12. Active controlled trials (Other Subgroups): Adverse Events

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	Lorazepam			P value:
0 ( )	0 ( )	( )	( )	

Number ( )

Evidence Table 12. Active controlled trials (Other Subgroups): Adverse Events

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

Age: 48
Range:
SD:

Gender: 58 (61 %) Female

Ethnicity: NR

Number Screened: NR
Eligible: NR
Enrolled: 95

Number Withdrawn: 33
Lost to fu: 0
Analyzed: 62

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:

Run-in : 4
Wash out : 30
Allow other medication : no other hypnotic drugs

Drug name	dosage	N=	Duration	Withdrawals due to AEs/ 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 ( )

Evidence Table 12. Active controlled trials (Other Subgroups): Adverse Events

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

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

withdrawals due to AEs

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

Number ( )

Evidence Table 12. Active controlled trials (Other Subgroups): Adverse Events

Author: **Schwartz** **Trial type:** **Active** **Subgroup:** **psychiatric (inpati** **Quality rating:** **Poor**

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

Design:

Study design RCT
Open
Parallel

Setting Single Center

Age: NR
Range: 18-65
SD:

Gender: 8 (50 %) Female

Ethnicity: NR

Number Screened: NR
Eligible: NR
Enrolled: 16

Number Withdrawn: 0
Lost to fu: 0
Analyzed: 16

Eligibility criteria:
inpatient psychiatric care

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.

Comments:
Psychiatric inpatients

Intervention:

Run-in : NR
Wash out : NR
Allow other medication : NR

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

Adverse Events:

Evidence Table 12. Active controlled trials (Other Subgroups): Adverse Events

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

Year: **1993** **Country:** **Canada** **Funding:** **Lorex Pharmaceuticals**

total withdrawals

Zolpidem 5mg	Zolpidem 10mg	Triazolam		P value:
0 ( )	0 ( )	0 ( )	( )	

Number ( )

withdrawals due to AEs

Zolpidem 5mg	Zolpidem 10mg	Triazolam		P value:
0 ( )	0 ( )	0 ( )	( )	

Number ( )

<u>Lab data- respiratory events</u>

reduction of SaO2

Zolpidem 5mg	Zolpidem 10mg	Triazolam		P value:
0 ( )	2 ( )	2 ( )	( )	

Number ( )

apnea-hypopnea

Zolpidem 5mg	Zolpidem 10mg	Triazolam		P value:
1 ( )	2 ( )	1 ( )	( )	

Number ( )

Evidence Table 12. Active controlled trials (Other Subgroups): Adverse Events

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

Age: 58.2
Range:
SD: 5.5

Gender: 9 (38 %) Female

Ethnicity: NR

Number Screened: NR
Eligible: NR
Enrolled: 24

Number Withdrawn: 0
Lost to fu: 0
Analyzed: 24

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.

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

Drug name	dosage	N=	Duration	Withdrawals due to AEs/ 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 Screened: NR
Eligible: NR
Enrolled: 37

Number Withdrawn: 18
Lost to fu: NR
Analyzed: 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

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

Evidence Table 13. Placebo controlled trials: Efficacy

Author:	**Allain**	**Trial type:**	**Placebo**	**Quality rating:**	**Fair**
Year:	**1998**	**Country:**	**France**	**Funding:**	**NR**

Outcome Measurement:

- # clinical global impression
- # sleep quesionnaire
- # sleep diary

Efficacy Outcome List:

Primary outcome	Outcome:
☐	sleep latency
☐	number of nocturnal awakenings
☐	total sleep time
☐	sleep quality
☐	nightmares
☐	wakefulness
☐	daytime alertness
☐	anxity
☐	mood
☐	energy

Results

clinical global impression

overall no different except day 21, where zolpidem was more effective, p<0.007

Zolpidem	Placebo			P value
NR ( )	NR ( )	( )	( )	NS

Mean ( )

Evidence Table 13. Placebo controlled trials: Efficacy

Author: **Allain** **Trial type:** **Placebo** **Quality rating:** **Fair**

Year: **1998** **Country:** **France** **Funding:** **NR**

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	( )				
# less nightmare	Zolpidem		Placebo			P value
	93	( )	less	( )	( ) ( )	<0.04
	%	( )				

sleep diary

# number of awakenings	Zolpidem		Placebo			P value
	better	( )	NR	( )	( ) ( )	<0.0001
		( )				
# anxiety	Zolpidem		Placebo			P value
	better	( )	NR	( )	( ) ( )	<0.0003
		( )				
# amount of sleep	Zolpidem		Placebo			P value
	better	( )	NR	( )	( ) ( )	<0.0001
		( )				
# energy	Zolpidem		Placebo			P value
	better	( )	NR	( )	( ) ( )	<0.01
		( )				

Evidence Table 13. Placebo controlled trials: Efficacy

Author: **Allain_** **Trial type:** **Placebo** **Quality rating:** **Fair**

Year: **2001** **Country:** **France** **Funding:** **Sanofi-Synthelabo**

Design:

Study design RCT
DB
Parallel

Setting Multicenter

Age: 46.1
Range: 25-64
SD: 10.5

Gender: 188 (77 %) Female

Ethnicity: NR

Number Screened: NR
Eligible: NR
Enrolled: 245

Number Withdrawn: NR
Lost to fu: NR
Analyzed: 245

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.

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.

Comments:

Zolpidem was administrated as needed, not every night.

Intervention:

Run-in : 3-7
Wash out : NR
Allow other medication : NR

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

Evidence Table 13. Placebo controlled trials: Efficacy

Author: **Allain_** **Trial type:** **Placebo** **Quality rating:** **Fair**

Year: **2001** **Country:** **France** **Funding:** **Sanofi-Synthelabo**

Outcome Measurement:

sleep diary
clinical global impression
SF-36 healthy survey

Efficacy Outcome List:

Primary outcome	Outcome:
☑	sleep duration
☐	quality of sleep
☐	drowsiness during the day
☐	anxious during the day
☐	sadness during the day
☐	duration of daytime sleep
☐	sleep-onset latency
☐	number of nocturnal awakenings
☐	wake time after sleep onset

Results

sleep diary

total sleep time (min), change from baseline, all condition

Zolpidem		Placebo				P value
74.6	(77.7)	63.2	(69.9)	( )	( )	NS
Mean	(SD)					

total sleep time (min), change from baseline, with pill

Zolpidem		Placebo				P value
82.7	(80.1)	62.8	(77.2)	( )	( )	<0.05
Mean	(SD)					

sleep quality (1=worse; 100=better), change from baseline

Zolpidem		Placebo				P value
14.1	(17.4)	20.6	(22.3)	( )	( )	0.01
Mean	(SD)					

daytime drowsiness (1=worse; 100=better), change from baseline

Zolpidem		Placebo				P value
-1.8	(12.6)	-5.3	(14.9)	( )	( )	0.048
Mean	(SD)					

Evidence Table 13. Placebo controlled trials: Efficacy

Author: **Allain_** **Trial type:** **Placebo** **Quality rating:** **Fair**

Year: **2001** **Country:** **France** **Funding:** **Sanofi-Synthelabo**

# anxiety during the day (1=worse; 100=better), change from baseline	Zolpidem	Placebo			P value	
	-1.5 (16.2)	-2.9 (19.7)	( )	( )	0.55	
	Mean (SD)					
# sadness during the day (1=worse; 100=better), change from baseline	Zolpidem	Placebo			P value	
	-0.6 (15.4)	-2.8 (17.7)	( )	( )	0.30	
	Mean (SD)					
# vitality in the morning (1=worse; 100=better), change from baseline	Zolpidem	Placebo			P value	
	9.1 (16.2)	9.6 (21.3)	( )	( )	0.83	
	Mean (SD)					
# lucidity in the morning (1=worse; 100=better), change from baseline	Zolpidem	Placebo			P value	
	2.9 (16.2)	2.3 (18.4)	( )	( )	0.77	
	Mean (SD)					
# sleep onset latency (min), change from baseline	Zolpidem	Placebo			P value	
	-23 (38.7)	-18.8 (35.4)	( )	( )	<0.05	
	Mean (SD)					
# wake time after sleep onset (min), change from baseline	Zolpidem	Placebo			P value	
	-32.8 (37.7)	-31.4 (37.1)	( )	( )	NR	
	Mean (SD)					
# number of nocturnal awakenings, change from baseline	Zolpidem	Placebo			P value	
	-1.2 (NR)	-1.2 (NR)	( )	( )	<0.05	
	Mean (SD)					
# daytime sleep duration (min), change from baseline	Zolpidem	Placebo			P value	
	-2.6 (19.6)	-0.9 (15.1)	( )	( )	NR	
	Mean (SD)					

Evidence Table 13. Placebo controlled trials: Efficacy

Author: **Allain_** **Trial type:** **Placebo** **Quality rating:** **Fair**

Year: **2001** **Country:** **France** **Funding:** **Sanofi-Synthelabo**

clinical 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 improved

Zolpidem		Placebo				P value
67	(54)	29	(24)	( )	( )	<0.0001

Number (%)

efficacy index- when efficacy outseighs safety)

Zolpidem		Placebo				P value
108	(87)	84	(71)	( )	( )	0.0004

Number (%)

Evidence Table 13. Placebo controlled trials: Efficacy

Author: **Allain_** **Trial type:** **Placebo** **Quality rating:** **Fair**

Year: **2001** **Country:** **France** **Funding:** **Sanofi-Synthelabo**

SF-36 healthy survey

physical function, change from baseline

Zolpidem		Placebo				P value
2.5	(17.3)	2.7	(4.6)	( )	( )	NS

Mean (SD)

role limitations due to physical problem, change from baseline

Zolpidem		Placebo				P value
7.5	(29)	4.9	(32.5)	( )	( )	NS

Mean (SD)

bodily pain, change from baseline

Zolpidem		Placebo				P value
4.7	(21)	3.7	(22.4)	( )	( )	NS

Mean (SD)

general health perception, change from baseline

Zolpidem		Placebo				P value
3.4	(12.4)	2.5	(12.5)	( )	( )	NS

Mean (SD)

vitality, change from baseline

Zolpidem		Placebo				P value
6.5	(16.6)	5.7	(14)	( )	( )	NS

Mean (SD)

social functioning, change from baseline

Zolpidem		Placebo				P value
6.1	(22.4)	2.8	(21.6)	( )	( )	NS

Mean (SD)

role limitations due to emotional problems, change from baseline

Zolpidem		Placebo				P value
7.9	(39.1)	-0.3	(33.9)	( )	( )	NS

Mean (SD)

general mental health, change from baseline

Zolpidem		Placebo				P value
5.9	(16.8)	5.1	(14.5)	( )	( )	NS

Mean (SD)

Evidence Table 13. Placebo controlled trials: Efficacy

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

Age: 50
Range: 35-65
SD: NR

Gender: 18 (72 %) Female

Ethnicity: NR

Number Screened: NR
Eligible: 30
Enrolled: 25

Number Withdrawn: 5
Lost to fu: 0
Analyzed: 25

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.

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

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

Evidence Table 13. Placebo controlled trials: Efficacy

Author: **Chaudoir** **Trial type:** **Placebo** **Quality rating:** **Poor**

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

Outcome Measurement:

sleep questionnaire
interview by investigator

Efficacy Outcome List:

Primary outcome	Outcome:
☐	sleep latency
☐	number of awakenings
☐	sleep quality
☐	feeling after wakening

Results

daily sleep questionnaire

feelings after wakening (VAS - mm), 0=very badly; 100=very well

Zopiclone		Placebo				P value
59	(4.4)	59	(4.2)	( )	( )	NS
Mean	(SD)					

sleep onset latency (min)

Zopiclone		Placebo				P value
31.1	(4.0)	49.1	(4.5)	( )	( )	<0.001
Mean	(SD)					

number of night awakenings

Zopiclone		Placebo				P value
1.5	(0.2)	2.1	(0.3)	( )	( )	<0.05
Mean	(SD)					

sleep quality (VAS - mm), 0=very badly; 100=very well

Zopiclone		Placebo				P value
67	(4.0)	51	(3.5)	( )	( )	<0.05
Mean	(SD)					

Evidence Table 13. Placebo controlled trials: Efficacy

Author: **Chaudoir** **Trial type:** **Placebo** **Quality rating:** **Poor**

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

weekly assessment

# sleep onset latency (min)	Zopiclone	Placebo			P value
	28.6 (3.9)	45.2 (5.5)	( )	( )	<0.05
	Mean (SD)				
# number of night awakenings	Zopiclone	Placebo			P value
	1.6 (0.3)	2.1 (0.3)	( )	( )	NS
	Mean (SD)				
# sleep quality (VAS mm), 0=very badly; 100=very well	Zopiclone	Placebo			P value
	63 (4.8)	48 (5.0)	( )	( )	<0.01
	Mean (SD)				
# feelings after awakening (VAS mm), 0=very badly; 100=very well	Zopiclone	Placebo			P value
	67 (4.9)	67 (4.7)	( )	( )	NS
	Mean (SD)				
# percentage of patients with early awakenings (%)	Zopiclone	Placebo			P value
	44 ( )	56 ( )	( )	( )	NS
	Mean ( )				
# mood rating scales (mm) - factor I alertness	Zopiclone	Placebo			P value
	59 (3.6)	59 (4.2)	( )	( )	NS
	Mean (SD)				
# mood rating scales (mm) - factor II contentedness	Zopiclone	Placebo			P value
	61 (4.5)	63 (3.9)	( )	( )	NS
	Mean (SD)				
# mood rating scales (mm) - factor III calmness	Zopiclone	Placebo			P value
	57 (3.7)	59 (4.7)	( )	( )	NS
	Mean (SD)				

Evidence Table 13. Placebo controlled trials: Efficacy

Author: **Dockhorn** **Trial type:** **Placebo** **Quality rating:** **Fair**

Year: **1996** **Country:** **US** **Funding:** **Lorex Pharmaceuticals**

Design:

Study design RCT
DB
Parallel

Setting Multicenter

Age: 32.7
Range: 20-55
SD: NR

Gender: 80 (58 %) Female

Ethnicity: NR

Number Screened: NR
Eligible: NR
Enrolled: 138

Number Withdrawn: 9
Lost to fu: 2
Analyzed: 136

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)

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

Comments:

Intervention:

Run-in : NR
Wash out : NR
Allow other medication : NR

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

Evidence Table 13. Placebo controlled trials: Efficacy

Author: **Dockhorn** **Trial type:** **Placebo** **Quality rating:** **Fair**

Year: **1996** **Country:** **US** **Funding:** **Lorex Pharmaceuticals**

Outcome Measurement:

morning questionnaire
clinical global impression scale

Efficacy Outcome List:

Primary outcome	Outcome:
☑	sleep latency
☑	total sleep time
☐	ease of falling asleep
☐	number og awakenings
☐	wake time after sleep onset
☐	quality of sleep
☐	ability to concentrate in the morning
☐	morning sleepiness

Results

morning questionnaire

# sleep latency (min), day 3-10	Zolpidem		Placebo						P value
	43.2	(6.9)	64.0	(7.7)		( )		( )	0.001
	Mean	(SD)							
# total sleep time (min), day 3-10	Zolpidem		Placebo						P value
	422.2	(11)	389	(10.1)		( )		( )	0.054
	Mean	(SD)							
# ease of falling asleep (0=very easy; 100= not all easy), day 3-10	Zolpidem		Placebo						P value
	34.8	(2.2)	45.2	(2.3)		( )		( )	0.004
	Mean	(SD)							
# number of awakenings, day 3-10	Zolpidem		Placebo						P value
	0.8	(0.1)	1.2	(0.1)		( )		( )	0.014
	Mean	(SD)							

Evidence Table 13. Placebo controlled trials: Efficacy

Author: **Dockhorn** **Trial type:** **Placebo** **Quality rating:** **Fair**

Year: **1996** **Country:** **US** **Funding:** **Lorex Pharmaceuticals**

wake time after sleep onset (min), day 3-10

Zolpidem		Placebo				P value
18.1	(3.4)	34.6	(4.8)	( )	( )	0.008

Mean (SD)

quality of sleep (1=excellent; 4=poor), day 3-10

Zolpidem		Placebo				P value
2.2	(0.1)	2.5	(0.01)	( )	( )	0.007

Mean (SD)

ability to concentrate (1=excellent; 4=poor), day 3-10

Zolpidem		Placebo				P value
2.3	(0.1)	2.4	(0.1)	( )	( )	0.358

Mean (SD)

morning sleepiness (0=very sleepy; 100=not at all sleepy), day 3-10

Zolpidem		Placebo				P value
53.6	(2.2)	52.1	(2.3)	( )	( )	0.762

Mean (SD)

Evidence Table 13. Placebo controlled trials: Efficacy

Author: **Dockhorn** **Trial type:** **Placebo** **Quality rating:** **Fair**

Year: **1996** **Country:** **US** **Funding:** **Lorex Pharmaceuticals**

clinical global impression scale

quality of sleep- excellent or good

Zolpidem		Placebo				P value
78	( )	42	( )	( )	( )	<0.001
%	( )					

change in sleep- improved a lot or somewhat

Zolpidem		Placebo				P value
84	( )	48	( )	( )	( )	<0.001
%	( )					

change in time to fall asleep

Zolpidem		Placebo				P value
81	( )	42	( )	( )	( )	<0.001
%	( )					

change in amount of sleep

Zolpidem		Placebo				P value
79	( )	43	( )	( )	( )	<0.001
%	( )					

strength of medication- just right

Zolpidem		Placebo				P value
62	( )	28	( )	( )	( )	<0.001
%	( )					

change during posttreatment days- much or somewhat better

Zolpidem		Placebo				P value
75	( )	40	( )	( )	( )	0.002
%	( )					

Evidence Table 13. Placebo controlled trials: Efficacy

Author: **Dorsey** **Trial type:** **Placebo** **Quality rating:** **Fair**

Year: **2004** **Country:** **US** **Funding:** **Sanofi-Synthelabo**

Design:

Study design RCT
DB
Parallel

Setting Multicenter

Age: 50.8
Range: 39-60
SD: 4.5

Gender: 141 (100 %) Female

Ethnicity: NR

Number Screened: 242
Eligible: 141
Enrolled: 141

Number Withdrawn: 16
Lost to fu: 3
Analyzed: 141

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.

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.

Comments:

Intervention:

Run-in : 6-14
Wash out : NR
Allow other medication : NR

Drug name	dosage	N=	Duration	Withdrawals due to AEs/ Total withdrawal
Zolpidem	10 mg	68	28 day	5 / 11
Placebo	NA mg	73	28 day	2 / 5

Evidence Table 13. Placebo controlled trials: Efficacy

Author: **Dorsey** **Trial type:** **Placebo** **Quality rating:** **Fair**

Year: **2004** **Country:** **US** **Funding:** **Sanofi-Synthelabo**

Outcome Measurement:

patients global impression rating
sleep questionnaire

Efficacy Outcome List:

Primary outcome	Outcome:
☐	sleep latency
☐	number of awakenings
☐	wake time after sleep onset
☐	sleep duration
☐	quality of sleep

Results

patients global impression rating

average summary score (lower score=better sleep)

Zolpidem		Placebo				P value
5.53	( )	6.71	( )	( )	( )	

Mean ( )

number of patients with better sleep

Zolpidem		Placebo				P value
76.8	( )	43.8	( )	( )	( )	<0.001

% ( )

Evidence Table 13. Placebo controlled trials: Efficacy

Author: **Dorsey** **Trial type:** **Placebo** **Quality rating:** **Fair**

Year: **2004** **Country:** **US** **Funding:** **Sanofi-Synthelabo**

sleep questionnaire

# change in sleep duration (min), 4 weeks average	Zolpidem	Placebo			P value
	56.5 ( )	20.5 ( )	( )	( )	<0.01
	Mean ( )				
# wake after sleep onset (min), 4 weeks average	Zolpidem	Placebo			P value
	29.75 ( )	52.75 ( )	( )	( )	<0.05
	Mean ( )				
# number of awakenings, 4 weeks average	Zolpidem	Placebo			P value
	1.4 ( )	2 ( )	( )	( )	<0.05
	Mean ( )				
# sleep latency (min), 4 weeks average	Zolpidem	Placebo			P value
	31.25 ( )	34.25 ( )	( )	( )	NS
	Mean ( )				
# sleep-related difficulty with daytime functioning	Zolpidem	Placebo			P value
	2.1 ( )	2.2 ( )	( )	( )	<0.05
	Mean ( )				
# quality of life	Zolpidem	Placebo			P value
	NR ( )	NR ( )	( )	( )	NS
	Mean ( )				

Evidence Table 13. Placebo controlled trials: Efficacy

Author: **Goldenberg** **Trial type:** **Placebo** **Quality rating:** **Poor**

Year: **1994** **Country:** **UK, France** **Funding:** **NR**

Design:

Study design RCT
DB
Parallel

Setting Multicenter

Age: NR
Range: 25-60
SD: NR

Gender: NR (%) Female

Ethnicity: NR

Number Screened: NR
Eligible: NR
Enrolled: 524

Number Withdrawn: NR
Lost to fu: NR
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:

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 : NR

Drug name	dosage	N=	Duration	Withdrawals due to AEs/ Total withdrawal
Zopiclone	7.5 mg	231	48 day	N / NR
Placebo	NA mg	227	44 day	N / NR

Evidence Table 13. Placebo controlled trials: Efficacy

Author: **Goldenberg** **Trial type:** **Placebo** **Quality rating:** **Poor**

Year: **1994** **Country:** **UK, France** **Funding:** **NR**

Outcome Measurement:

- # psyhological general well being index (PGWBI)
- # sleep eveluation questionnaire (SEQ)
- # leeds sleep evaluation questionnaire (LSEQ)

Efficacy Outcome List:

Primary outcome	Outcome:
☐	quality of sleep
☐	quality of waking up
☐	feeling of well being during the day
☐	physician's overall evaluation

Results

Sleep efficiancy at endpoint

quality of sleep

Zopiclone		Placebo				P value
1.9	(1.1)	1.3	(1.2)	( )	( )	<0.0001

Mean (SD)

quality of waking up

Zopiclone		Placebo				P value
1.5	(1.2)	1.0	(1.1)	( )	( )	<0.0001

Mean (SD)

feeling of well being during the day

Zopiclone		Placebo				P value
1.3	(1.1)	0.8	(1.1)	( )	( )	<0.0001

Mean (SD)

physician's overall evaluation: average, good or excellent

Zopiclone		Placebo				P value
187	(92.5)	125	(66.9)	( )	( )	<0.0001

Number (%)

Evidence Table 13. Placebo controlled trials: Efficacy

Author: **Goldenberg** **Trial type:** **Placebo** **Quality rating:** **Poor**

Year: **1994** **Country:** **UK, France** **Funding:** **NR**

Quality of life - change from baseline

PGWBI

Zopiclone	Placebo			P value
11.8 ( )	9.1 ( )	( )	( )	NS

Score ( )

SEQ

Zolpidem	Placebo			P value
14.6 ( )	2.7 ( )	( )	( )	<0.0001

Score ( )

Activity

Zopiclone	Placebo			P value
20 ( )	9.9 ( )	( )	( )	<0.0001

Score ( )

Social

Zolpidem	Placebo			P value
13.1 ( )	5.7 ( )	( )	( )	<0.01

Score ( )

Profession

Zopiclone	Placebo			P value
23.3 ( )	12.9 ( )	( )	( )	<0.01

Score ( )

Global

Zopiclone	Placebo			P value
10.8 ( )	5.7 ( )	( )	( )	NS

Score ( )

Evidence Table 13. Placebo controlled trials: Efficacy

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 Screened: NR
Eligible: NR
Enrolled: 437

Number Withdrawn: 22
Lost to fu: NR
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 : NR

Drug name	dosage	N=	Duration	Withdrawals due to AEs/ 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

Evidence Table 13. Placebo controlled trials: Efficacy

Author: **Hedner** **Trial type:** **Placebo** **Quality rating:** **Fair**

Year: **2000** **Country:** **Europe** **Funding:**

Outcome Measurement:

sleep questionnaire

Efficacy Outcome List:

Primary outcome	Outcome:
☐	sleep latency
☐	sleep dutation
☐	number of awakenings
☐	sleep quality

Results

sleep questionnaire

subjective sleep latency (min), week 1

Zaleplon 5mg	Zaleplon 10mg	Placebo		P value
43 (<0.001)	40 (<0.001)	60 (NA)	( )	

Median (p vs placebo)

subjective sleep latency (min), week 2

Zaleplon 5mg	Zaleplon 10mg	Placebo		P value
40 (<0.001)	37 (<0.001)	50 (NA)	( )	

Median (p vs placebo)

subjective total sleep time (min), week 1

Zaleplon 5mg	Zaleplon 10mg	Placebo		P value
342 (NS)	342.9 (<0.05)	346.1 (NA)	( )	

Median (p vs placebo)

subjective total sleep time (min), week 2

Zaleplon 5mg	Zaleplon 10mg	Placebo		P value
351.7 (NS)	351.4 (NS)	342.9 (NA)	( )	

Median (p vs placebo)

subjective number of awakenings, week 1

Zaleplon 5mg	Zaleplon 10mg	Placebo		P value
2 (NS)	2 (<0.05)	2 (NA)	( )	

Median (p vs placebo)

Evidence Table 13. Placebo controlled trials: Efficacy

Author: **Hedner** **Trial type:** **Placebo** **Quality rating:** **Fair**

Year: **2000** **Country:** **Europe** **Funding:**

subjective number of awakenings, week 2

Zaleplon 5mg	Zaleplon 10mg	Placebo		P value
2 (NS)	1 (NS)	2 (NA)	( )	

Median (p vs placebo)

subjective sleep quality, week 1 (score). 1=excellent; 7=extremely poor

Zaleplon 5mg	Zaleplon 10mg	Placebo		P value
3.8 (<0.01)	3.8 (<0.01)	3.9 (NA)	( )	

Mean (p vs placebo)

subjective sleep quality, week 2 (score). 1=excellent; 7=extremely poor

Zaleplon 5mg	Zaleplon 10mg	Placebo		P value
3.7 (<0.05)	3.7 (<0.05)	3.8 (NA)	( )	

Mean (p vs placebo)

subjective sleep quality, improvement in sleep quality- week 1

Zaleplon 5mg	Zaleplon 10mg	Placebo		P value
48 (NS)	55 (<0.000)	36 (NA)	( )	

% (p vs placebo)

subjective sleep quality, improvement in sleep quality- week 2

Zaleplon 5mg	Zaleplon 10mg	Placebo		P value
53 (NS)	63 (<0.000)	36 (NA)	( )	

% (p vs placebo)

Evidence Table 13. Placebo controlled trials: Efficacy

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 Screened: NR
Eligible: 25
Enrolled: 21

Number Withdrawn: NR
Lost to fu: NR
Analyzed: 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:

Run-in : 7
Wash out : 7
Allow other medication : NR

Drug name	dosage	N=	Duration	Withdrawals due to AEs/ Total withdrawal
Zolpidem	10 mg	11	14 day	N / NR
Placebo	NA mg	10	14 day	N / NR

Evidence Table 13. Placebo controlled trials: Efficacy

Author: **Herrmann** **Trial type:** **Placebo** **Quality rating:** **Poor**

Year: **1993** **Country:** **France** **Funding:** **NR**

Outcome Measurement:

polysomnography
sleep questionnaire

Efficacy Outcome List:

Primary outcome	Outcome:
☐	sleep efficiency
☐	sleep latency
☐	total sleep time
☐	number of awakenings
☐	wake after sleep onset

Results

polysomnography

sleep efficiency (%), day 21 treatment

Zolpidem		Placebo				P value
86.2	(2)	78.3	(5)	( )	( )	<0.05

Mean (SD)

total sleep time (min), day 21 treatment

Zolpidem		Placebo				P value
381.3	(10)	360.3	(23)	( )	( )	NS

Mean (SD)

sleep onset latency (min), day 21 treatment

Zolpidem		Placebo				P value
28	(7)	41.7	(15)	( )	( )	NS

Mean (SD)

time awake (min), day 21 treatment

Zolpidem		Placebo				P value
34.7	(7)	60	(12)	( )	( )	NS

Mean (SD)

Evidence Table 13. Placebo controlled trials: Efficacy

Author: **Herrmann** **Trial type:** **Placebo** **Quality rating:** **Poor**

Year: **1993** **Country:** **France** **Funding:** **NR**

sleep questionnaire

# sleep onset latency (min), day 15-21 treatment	Zolpidem	Placebo			P value
	40.5 (10)	72.8 (10)	( )	( )	<0.05
	Mean (SD)				
# total sleep time (min), day 15-21 treatment	Zolpidem	Placebo			P value
	372.7 (12)	327.4 (22)	( )	( )	NS
	Mean (SD)				
# no. of awakenings, day 15-21 treatment	Zolpidem	Placebo			P value
	1.8 (0.4)	2.3 (0.4)	( )	( )	NS
	Mean (SD)				
# calm/restless, fresh/fatigued, relaxed/anxious, lying down during the day	Zolpidem	Placebo			P value
	multi-data (multi-d)	multi-data (multi-d)	( )	( )	NS
	Mean (SD)				

Evidence Table 13. Placebo controlled trials: Efficacy

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

Ethnicity: NR

Number Screened: NR
Eligible: NR
Enrolled: 458

Number Withdrawn: NR
Lost to fu: NR
Analyzed: 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.

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.

Comments:

Intervention:

Run-in : NR
Wash out : NR
Allow other medication : NR

Drug name	dosage	N=	Duration	Withdrawals due to AEs/ Total withdrawal
Zopiclone	7.5 mg	231	48 day	N / NR
Placebo	NA mg	227	42 day	N / NR

Evidence Table 13. Placebo controlled trials: Efficacy

Author:	**Hindmarch**	**Trial type:**	**Placebo**	**Quality rating:**	**Fair**
Year:	**1995**	**Country:**	**UK**	**Funding:**	

Outcome Measurement:

questionnaire

Efficacy Outcome List:

Primary outcome	Outcome:
☐	quality of sleep
☐	quality of waking up
☐	daytime feeling of well being

Results

questionnaire

# psychological general well-bing index (PGWBI), change from baseline, day 14	Zolpidem	Placebo			P value	
	11.8 ( )	9.1 ( )	( )	( )	NS	
	Mean ( )					
# sleep evaluation questionnaire (SEQ), change from baseline, day 14	Zolpidem	Placebo			P value	
	14.6 ( )	2.7 ( )	( )	( )	<0.0001	
	Mean ( )					
# activity, change from baseline, day 14	Zolpidem	Placebo			P value	
	20 ( )	9.9 ( )	( )	( )	<0.0001	
	Mean ( )					
# social, change from baseline, day 14	Zolpidem	Placebo			P value	
	13.4 ( )	5.7 ( )	( )	( )	<0.01	
	Mean ( )					
# profession, change from baseline, day 14	Zolpidem	Placebo			P value	
	23.3 ( )	12.9 ( )	( )	( )	<0.01	
	Mean ( )					
# global, change from baseline, day 14	Zolpidem	Placebo			P value	
	10.8 ( )	5.7 ( )	( )	( )	NS	
	Mean ( )					

Evidence Table 13. Placebo controlled trials: Efficacy

Author: **Hindmarch** **Trial type:** **Placebo** **Quality rating:** **Fair**

Year: **1995** **Country:** **UK** **Funding:**

# psychological general well-bing index (PGWBI), change from baseline, endpoint	Zolpidem	Placebo			P value
	15.2 ( )	12.9 ( )	( )	( )	NS
	Mean ( )				
# sleep evaluation questionnaire (SEQ), change from baseline, endpoint	Zolpidem	Placebo			P value
	20.9 ( )	12.5 ( )	( )	( )	<0.0001
	Mean ( )				
# activity, change from baseline, endpoint	Zolpidem	Placebo			P value
	21.6 ( )	14.2 ( )	( )	( )	<0.0001
	Mean ( )				
# social, change from baseline, endpoint	Zolpidem	Placebo			P value
	14.9 ( )	9.1 ( )	( )	( )	<0.01
	Mean ( )				
# profession, change from baseline, endpoint	Zolpidem	Placebo			P value
	24.5 ( )	18.7 ( )	( )	( )	NS
	Mean ( )				
# global, change from baseline, endpoint	Zolpidem	Placebo			P value
	13.8 ( )	8.9 ( )	( )	( )	NS
	Mean ( )				
# physician's oveall evaluation of treatment efficacy as "excellent" or "good" at endpoint	Zolpidem	Placebo			P value
	76.7 ( )	51.4 ( )	( )	( )	
	% ( )				

Evidence Table 13. Placebo controlled trials: Efficacy

Author: **Krystal** **Trial type:** **Placebo** **Quality rating:** **Fair**

Year: **2003** **Country:** **US** **Funding:** **Sepracor**

Design:

Study design RCT
DB
Parallel

Setting Multicenter

Age: 44
Range: 21-69
SD: 11.3

Gender: 195 (25 %) Female

Ethnicity: 80% caucasian
13.2% african american
7.9% other

Number Screened: 1194
Eligible: 791
Enrolled: 788

Number Withdrawn: 320
Lost to fu: 60
Analyzed: 788

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.

Exclusion criteria:

NR

Comments:

Intervention:

Run-in : NR
Wash out : 5-7
Allow other medication : NR

Drug name	dosage	N=	Duration	Withdrawals due to AEs/ Total withdrawal
Eszopiclone	3 mg	593	180 day	76 / 235
Placebo	NA mg	195	180 day	14 / 85

Evidence Table 13. Placebo controlled trials: Efficacy

Author: **Krystal** **Trial type:** **Placebo** **Quality rating:** **Fair**

Year: **2003** **Country:** **US** **Funding:** **Sepracor**

Outcome Measurement:

telephone interview

Efficacy Outcome List:

Primary outcome	Outcome:
☐	sleep latency
☐	wake time after sleep onset
☐	total sleep time
☐	number of awakenings
☐	number of nights during the week
☐	sleep quality
☐	daytime ability to function
☐	daytime alertness
☐	sense of physical well-being

Results

telephone interview

sleep latency, month 6

Eszopiclone		Placebo				P value
47.0	(50.6)	63.1	(57.9)	( )	( )	<0.001

Mean (SD)

wake after sleep onset, month 6

Eszopiclone		Placebo				P value
44.2	(74.2)	48.2	(59.4)	( )	( )	0.0032

Mean (SD)

number of awakenings, month 6

Eszopiclone		Placebo				P value
1.9	(1.5)	2.6	(2.7)	( )	( )	<0.0001

Mean (SD)

number of night awakenings per week, month 6

Eszopiclone		Placebo				P value
3.9	(2.5)	4.7	(2.4)	( )	( )	0.0001

Mean (SD)

Evidence Table 13. Placebo controlled trials: Efficacy

Author: **Krystal** **Trial type:** **Placebo** **Quality rating:** **Fair**

Year: **2003** **Country:** **US** **Funding:** **Sepracor**

total sleep time, month 6

Eszopiclone	Placebo			P value
378.3 (72.3)	339.3 (77.1)	( )	( )	<0.001

Mean (SD)

sleep quality, month 6

Eszopiclone	Placebo			P value
6.4 (1.8)	5.5 (1.8)	( )	( )	<0.0001

Mean (SD)

daytime ability to function, month 6

Eszopiclone	Placebo			P value
6.8 (1.7)	6.2 (1.8)	( )	( )	<0.0001

Mean (SD)

daytime alertness, month 6

Eszopiclone	Placebo			P value
6.5 (1.7)	5.9 (1.7)	( )	( )	<.0001

Mean (SD)

sense of physical well-being, month 6

Eszopiclone	Placebo			P value
6.7 (1.7)	6.1 (1.8)	( )	( )	0.0002

Mean (SD)

Evidence Table 13. Placebo controlled trials: Efficacy

Author: **Lahmeyer** **Trial type:** **Placebo** **Quality rating:** **Fair**

Year: **1997** **Country:** **US** **Funding:** **?orex Pharmaceuticals**

Design:

Study design RCT
DB
Parallel

Setting Multicenter

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

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.

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 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.

Comments:

Intervention:

Run-in : 3
Wash out : 4
Allow other medication : NR

Drug name	dosage	N=	Duration	Withdrawals due to AEs/ 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

Evidence Table 13. Placebo controlled trials: Efficacy

Author: **Lahmeyer** **Trial type:** **Placebo** **Quality rating:** **Fair**

Year: **1997** **Country:** **US** **Funding:** **?orex Pharmaceuticals**

Outcome Measurement:

morning questionnaire
clinical global impression

Efficacy Outcome List:

Primary outcome	Outcome:
☑	sleep duration
☑	sleep latency
☐	ease of falling asleep
☐	number of awakenings
☐	wake after sleep onset
☐	quality of sleep
☐	morning sleepiness
☐	ability to concentrate

Results

morning questionnaire - 4 weeks average

# sleep latency (min), change from baseline - 4 weeks average	Zolpidem 10mg	Zolpidem 15mg	Placebo		P value
	-30 ( )	-33.5 ( )	-9 ( )	( )	
	Mean ( )				
# total sleep time (min) - 4 weeks average	Zolpidem 10mg	Zolpidem 15mg	Placebo		P value
	379 ( )	381 ( )	346 ( )	( )	
	Mean ( )				
# number of awakenings - 4 weeks average	Zolpidem 10mg	Zolpidem 15mg	Placebo		P value
	1.3 ( )	1.3 ( )	1.9 ( )	( )	
	Mean ( )				
# sleep quality (1=excellent; 4=poor) - 4 weeks average	Zolpidem 10mg	Zolpidem 15mg	Placebo		P value
	2.4 ( )	2.4 ( )	2.8 ( )	( )	
	Mean ( )				

Evidence Table 13. Placebo controlled trials: Efficacy

Author: **Lahmeyer** **Trial type:** **Placebo** **Quality rating:** **Fair**

Year: **1997** **Country:** **US** **Funding:** **?orex Pharmaceuticals**

morning questionnaire - at week 4

sleep latency (min), change from baseline - at week 4

Zolpidem 10mg	Zolpidem 15mg	Placebo		P value
-31 (<0.05)	-31 (NS)	-16 (NA)	( )	

Mean (p vs placebo)

total sleep time (min) - at week 4

Zolpidem 10mg	Zolpidem 15mg	Placebo		P value
390 (NS)	385 (NS)	360 (NA)	( )	

Mean (p vs placebo)

number of awakenings - at week 4

Zolpidem 10mg	Zolpidem 15mg	Placebo		P value
1.4 (NS)	1.2 (NS)	1.7 (NA)	( )	

Mean (p vs placebo)

sleep quality (1=excellent; 4=poor) - at week 4

Zolpidem 10mg	Zolpidem 15mg	Placebo		P value
2.4 (NS)	2.4 (NS)	2.6 (NA)	( )	

Mean (p vs placebo)

morning questionnaire - post-treatment

sleep latency (min), change from baseline - post-treatment

Zolpidem 10mg	Zolpidem 15mg	Placebo		P value
-10 (NS)	-11 (NS)	-25 (NA)	( )	

Mean (p vs placebo)

total sleep time (min) - post-treatment

Zolpidem 10mg	Zolpidem 15mg	Placebo		P value
354 (NS)	332 (NS)	359 (NA)	( )	

Mean (p vs placebo)

number of awakenings - post-treatment

Zolpidem 10mg	Zolpidem 15mg	Placebo		P value
1.7 (NS)	1.9 (NS)	1.9 (NA)	( )	

Mean (p vs placebo)

sleep quality (1=excellent; 4=poor) - post-treatment

Zolpidem 10mg	Zolpidem 15mg	Placebo		P value
2.8 (NS)	2.9 (NS)	2.8 (NA)	( )	

Mean (p vs placebo)

Evidence Table 13. Placebo controlled trials: Efficacy

Author: **Lahmeyer** **Trial type:** **Placebo** **Quality rating:** **Fair**

Year: **1997** **Country:** **US** **Funding:** **?orex Pharmaceuticals**

clinical global impression

medication helped me - fall asleep faster

Zolpidem 10mg	Zolpidem 15mg	Placebo		P value
84 (<0.05)	78 (<0.05)	51 (NA)	( )	
% (p vs placebo)				

medication helped me - sleep longer

Zolpidem 10mg	Zolpidem 15mg	Placebo		P value
78 (<0.05)	76 (NS)	51 (NA)	( )	
% (p vs placebo)				

medication helped me - get a better night's sleep

Zolpidem 10mg	Zolpidem 15mg	Placebo		P value
84 (,0.05)	84 (<0.05)	49 (NA)	( )	
% (p vs placebo)				

medication strength - too strong

Zolpidem 10mg	Zolpidem 15mg	Placebo		P value
0 (NS)	0 (NS)	0 (NA)	( )	
% (p vs placebo)				

medication strength - strong enough

Zolpidem 10mg	Zolpidem 15mg	Placebo		P value
71 (<0.05)	72 (<0.05)	44 (NA)	( )	
% (p vs placebo)				

medication strength - too weak

Zolpidem 10mg	Zolpidem 15mg	Placebo		P value
29 (NS)	28 (NS)	56 (NA)	( )	
% (p vs placebo)				

Evidence Table 13. Placebo controlled trials: Efficacy

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 Screened: NR
Eligible: NR
Enrolled: 99

Number Withdrawn: 0
Lost to fu: 2
Analyzed: 91

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

Drug name	dosage	N=	Duration	Withdrawals due to AEs/ Total withdrawal
Zopiclone	7.5 mg	91	7 day	N / NR
Placebo	NA mg	91	7 day	N / NR

Evidence Table 13. Placebo controlled trials: Efficacy

Author:	**Monchesky**	**Trial type:**	**Placebo**	**Quality rating:**	**Fair**
Year:	**1986**	**Country:**	**Canada**	**Funding:**	**NR**

Outcome Measurement:

sleep questionnaire

Efficacy Outcome List:

Primary outcome	Outcome:
☐	sleepiness during the day
☐	sleep latency
☐	sleep duration
☐	number of awakenings

Results

sleep questionnaire

# duration of sleep (min), treatment day 7	Zolpidem	Placebo			P value
	384.8 ( )	307.4 ( )	( )	( )	NR
	Mean ( )				
# number of awakenings, treatment day 7	Zolpidem	Placebo			P value
	1.8 ( )	3.5 ( )	( )	( )	NR
	Mean ( )				
# quality of sleep, treatment day 7	Zolpidem	Placebo			P value
	4.15 ( )	3.15 ( )	( )	( )	NR
	Mean ( )				
# soundness of sleep, treatment day 7	Zolpidem	Placebo			P value
	3.8 ( )	2.75 ( )	( )	( )	NR
	Mean ( )				
# morning state of rest, treatment day 7	Zolpidem	Placebo			P value
	2.85 ( )	1.95 ( )	( )	( )	NR
	Mean ( )				

Evidence Table 13. Placebo controlled trials: Efficacy

Author: **Monchesky** **Trial type:** **Placebo** **Quality rating:** **Fair**

Year: **1986** **Country:** **Canada** **Funding:** **NR**

# sleepiness during the day, treatment day 14 (switch)	Zolpidem	Placebo			P value
	2.3 ( )	2.9 ( )	( )	( )	NR
	Mean ( )				
# sleep induction time (min), treatment day 14 (switch)	Zolpidem	Placebo			P value
	53.8 ( )	119.3 ( )	( )	( )	NR
	Mean ( )				
# duration of sleep (min), treatment day 14 (switch)	Zolpidem	Placebo			P value
	376.7 ( )	299.5 ( )	( )	( )	NR
	Mean ( )				
# number of awakenings, treatment day 14 (switch)	Zolpidem	Placebo			P value
	2.0 ( )	2.45 ( )	( )	( )	NR
	Mean ( )				
# quality of sleep, treatment day 14 (switch)	Zolpidem	Placebo			P value
	4.35 ( )	2.95 ( )	( )	( )	NR
	Mean ( )				
# soundness of sleep, treatment day 14 (switch)	Zolpidem	Placebo			P value
	4.0 ( )	2.4 ( )	( )	( )	NR
	Mean ( )				
# morning state of rest, treatment day 14 (switch)	Zolpidem	Placebo			P value
	2.9 ( )	2.15 ( )	( )	( )	NR
	Mean ( )				
# sleepiness during the day, treatment day 7	Zolpidem	Placebo			P value
	2.3 ( )	2.65 ( )	( )	( )	NR
	Mean ( )				

Evidence Table 13. Placebo controlled trials: Efficacy

Author: **Monchesky** **Trial type:** **Placebo** **Quality rating:** **Fair**

Year: **1986** **Country:** **Canada** **Funding:** **NR**

sleep induction time (min), treatment day 7

Zolpidem		Placebo				P value
51.85	( )	89.9	( )	( )	( )	NR

Mean ( )

Evidence Table 13. Placebo controlled trials: Efficacy

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 Screened: NR
Eligible: NR
Enrolled: 12

Number Withdrawn: NR
Lost to fu: NR
Analyzed: 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:

Run-in : 2
Wash out : 3
Allow other medication : No

Drug name	dosage	N=	Duration	Withdrawals due to AEs/ Total withdrawal
Zolpidem	10 mg	6	27 day	N / NR
Placebo	NA mg	6	27 day	N / NR

Evidence Table 13. Placebo controlled trials: Efficacy

Author: **Monti** **Trial type:** **Placebo** **Quality rating:** **Fair**

Year: **1996** **Country:** **Uruguay** **Funding:** **NR**

Outcome Measurement:

polysomnography
questionnaire

Efficacy Outcome List:

Primary outcome	Outcome:
☐	sleep latency
☐	number of awakenings
☐	total wake time
☐	wake time after sleep onset
☐	total sleep time
☐	sleep efficiency
☐	movement time

Results

polysomnography

stage 2 sleep latency (min), nights 29-30

Zolpidem		Placebo				P value
23.6	(7.1)	35.1	(5.6)	( )	( )	NS

Mean (SD)

total number of awakenings, nights 29-30

Zolpidem		Placebo				P value
24.8	(4.3)	25.5	(5.7)	( )	( )	NS

Mean (SD)

total wake time (min), nights 29-30

Zolpidem		Placebo				P value
53.8	(6.9)	104.8	(21.8)	( )	( )	<0.05

Mean (SD)

wake time after sleep onset (min), nights 29-30

Zolpidem		Placebo				P value
26.3	(7.0)	85.3	(24.2)	( )	( )	NS

Mean (SD)

total sleep time (min), nights 29-30

Zolpidem		Placebo				P value
419.3	(7.1)	370.9	(21.2)	( )	( )	<0.05

Mean (SD)

Evidence Table 13. Placebo controlled trials: Efficacy

Author: **Monti** **Trial type:** **Placebo** **Quality rating:** **Fair**

Year: **1996** **Country:** **Uruguay** **Funding:** **NR**

# sleep efficiency (%), nights 29-30	Zolpidem	Placebo			P value
	87.3 (1.5)	77.3 (4.4)	( )	( )	NS
	Mean (SD)				
# movement time, nights 29-30	Zolpidem	Placebo			P value
	6.9 (2.6)	4.3 (1.2)	( )	( )	NS
	Mean (SD)				
<u>questionnaire</u>					
# sleep latency (lower score indicates more positive response), night 29-30	Zolpidem	Placebo			P value
	2.0 (0.4)	1.8 (0.5)	( )	( )	NS
	Mean (SD)				
# sleep duration (higher score indicates more positive response), night 29-30	Zolpidem	Placebo			P value
	2.3 (0.3)	2.5 (0.4)	( )	( )	NS
	Mean (SD)				
# number of awakenings (lower score indicates more positive response), night 29-30	Zolpidem	Placebo			P value
	2.6 (0.3)	1.9 (0.3)	( )	( )	NS
	Mean (SD)				
# disturbed sleep (higher score indicates more positive response), night 29-30	Zolpidem	Placebo			P value
	73.1 (8.7)	48.5 (8.3)	( )	( )	<0.01
	Mean (SD)				
# daytime alertness (higher score indicates more positive response), night 29-30	Zolpidem	Placebo			P value
	69.0 (9.5)	44.2 (8.4)	( )	( )	NS
	Mean (SD)				

Evidence Table 13. Placebo controlled trials: Efficacy

Author: **Monti_** **Trial type:** **Placebo** **Quality rating:** **Poor**

Year: **2000** **Country:** **Uruguay** **Funding:** **NR**

Design:

Study design RCT
DB
Parallel

Setting Single Center

Age: 51.9
Range: NR
SD: 3.6

Gender: 12 (100 %) Female

Ethnicity: NR

Number Screened: NR
Eligible: NR
Enrolled: 12

Number Withdrawn: NR
Lost to fu: NR
Analyzed: 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 cliniclally 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

Drug name	dosage	N=	Duration	Withdrawals due to AEs/ Total withdrawal
Zolpidem	10 mg	6	15 day	N / NR
Placebo	NA mg	6	15 day	N / NR

Evidence Table 13. Placebo controlled trials: Efficacy

Author: **Monti_** **Trial type:** **Placebo** **Quality rating:** **Poor**

Year: **2000** **Country:** **Uruguay** **Funding:** **NR**

Outcome Measurement:

Interview
polygraphic sleep record

Efficacy Outcome List:

Primary outcome	Outcome:
☐	sleep latency
☐	number of awakenings
☐	wake time after sleep onset
☐	total sleep time
☐	sleep efficiency

Results

polygraphic sleep record

total sleep time (min) - night 17-18

Zolpidem		Placebo				P value
361.2	(25.8)	264.4	(33.3)	( )	( )	<0.02

Mean (SD)

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)

stage 2 sleep latency - night 17-18

Zolpidem		Placebo				P value
29.2	(6.8)	48.3	(6.9)	( )	( )	NS

Mean (SD)

Evidence Table 13. Placebo controlled trials: Efficacy

Author: **Monti_** **Trial type:** **Placebo** **Quality rating:** **Poor**

Year: **2000** **Country:** **Uruguay** **Funding:** **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 17-18

Zolpidem	Placebo			P value
26.9 (2.2)	26.5 (4.9)	( )	( )	NS

Mean (SD)

waking time after sleep onset (min) - night 4-5

Zolpidem	Placebo			P value
75.1 (7.9)	137.5 (29.2)	( )	( )	<0.03

Mean (SD)

waking time after sleep onset (min) - night 17-18

Zolpidem	Placebo			P value
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)

Evidence Table 13. Placebo controlled trials: Efficacy

Author: **Monti_** **Trial type:** **Placebo** **Quality rating:** **Poor**

Year: **2000** **Country:** **Uruguay** **Funding:** **NR**

interview

# sleep latency (min) - night 4-5	Zolpidem	Placebo			P value
	34.6 (8.2)	228.0 (80.8)	( )	( )	<0.01
	Mean (SD)				

# sleep latency (min) - night 17-18	Zolpidem	Placebo			P value
	49.5 (8.2)	154.0 (52.1)	( )	( )	<0.01
	Mean (SD)				

# sleep duration (min) - night 4-5	Zolpidem	Placebo			P value
	384.0 (29.1)	180.0 (61.3)	( )	( )	NS
	Mean (SD)				

# sleep duration (min) - night 17-18	Zolpidem	Placebo			P value
	342.0 (40.5)	225.0 (55.3)	( )	( )	NS
	Mean (SD)				

# disturbed sleep - night 4-5 (1=agree; 100=disagree)	Zolpidem	Placebo			P value
	78.4 (6.2)	46.4 (12.9)	( )	( )	NS
	Mean (SD)				

# disturbed sleep - night 17-18 (1=agree; 100=disagree)	Zolpidem	Placebo			P value
	74.6 (8.4)	40.1 (14.8)	( )	( )	NS
	Mean (SD)				

# alert in the morning - night 4-5 (1=agree; 100=disagree)	Zolpidem	Placebo			P value
	20.8 (6.3)	57.5 (16.1)	( )	( )	NS
	Mean (SD)				

# alert in the morning - night 17-18 (1=agree; 100=disagree)	Zolpidem	Placebo			P value
	30.3 (10.6)	65.9 (12.1)	( )	( )	NS
	Mean (SD)				

Evidence Table 13. Placebo controlled trials: Efficacy

Author: **Perlis** **Trial type:** **Placebo** **Quality rating:** **Fair**

Year: **2004** **Country:** **US** **Funding:** **Lorex Pharmaceuticals**

Design:

Study design RCT
DB
Parallel

Setting Multicenter

Age: 40.8
Range: 18-64
SD: 12.7

Gender: 141 (71 %) Female

Ethnicity: 70% euro-american

Number Screened: 322
Eligible: 277
Enrolled: 199

Number Withdrawn: 10
Lost to fu: 3
Analyzed: 192

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.

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

Drug name	dosage	N=	Duration	Withdrawals due to AEs/ Total withdrawal
Zolpidem	10 mg	98	84 day	7 / 7
Placebo	NA mg	101	84 day	3 / 3

Evidence Table 13. Placebo controlled trials: Efficacy

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)

sleep latency (min), all condition significant at week 10 only

Zolpidem		Placebo				P value
NR	(NR)	NR	(NR)	( )	( )	NS

Mean (SD)

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)

number of awakenings, all condition, significant at week 2 and 12 only

Zolpidem		Placebo				P value
1.38	(1.00)	1.69	(1.28)	( )	( )	NS

Mean (SD)

Evidence Table 13. Placebo controlled trials: Efficacy

Author: **Perlis** **Trial type:** **Placebo** **Quality rating:** **Fair**

Year: **2004** **Country:** **US** **Funding:** **Lorex Pharmaceuticals**

wake after sleep onset (min), with pill

Zolpidem		Placebo				P value
32.6	(43.5)	55.4	(56.1)	( )	( )	<0.05

Mean (SD)

wake after sleep onset (min), without pill

Zolpidem		Placebo				P value
NR	(NR)	NR	(NR)	( )	( )	NS

Mean (SD)

wake after sleep onset (min), all condition, significant at week 2 only

Zolpidem		Placebo				P value
NR	(NR)	NR	(NR)	( )	( )	NS

Mean (SD)

total sleep time (min), with pill

Zolpidem		Placebo				P value
417	(64.4)	359.8	(77.1)	( )	( )	<0.05

Mean (SD)

total sleep time (min), without pill

Zolpidem		Placebo				P value
NR	(NR)	NR	(NR)	( )	( )	NS

Mean (SD)

total sleep time (min), all condition

Zolpidem		Placebo				P value
394.1	(60.1)	355.6	(69.6)	( )	( )	<0.05

Mean (SD)

sleep latency (min), with pill

Zolpidem		Placebo				P value
38.4	(33.1)	55.1	(52.3)	( )	( )	<0.05

Mean (SD)

<u>global outcome measure</u>

IGR scale

Zolpidem		Placebo				P value
6	(0.12)	4.5	(0.14)	( )	( )	<0.001

Mean (SD)

Evidence Table 13. Placebo controlled trials: Efficacy

Author: **Scharf** **Trial type:** **Placebo** **Quality rating:** **Fair**

Year: **2005** **Country:** **US** **Funding:**

Design:

Study design RCT
DB
Parallel

Setting Multicenter

Age: 72.3
Range: 64-85
SD: 4.9

Gender: 133 (58 %) Female

Ethnicity: 89.4% caucasian
2.2% black
1.3% hispanic

Number Screened: 353
Eligible: NR
Enrolled: 231

Number Withdrawn: 21
Lost to fu: NR
Analyzed: 231

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

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.

Comments:

Intervention:

Run-in : 3-14
Wash out : NR
Allow other medication : NR

Drug name	dosage	N=	Duration	Withdrawals due to AEs/ 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

Evidence Table 13. Placebo controlled trials: Efficacy

Author:	**Scharf**	**Trial type:**	**Placebo**	**Quality rating:**	**Fair**
Year:	**2005**	**Country:**	**US**	**Funding:**	

Outcome Measurement:

morning questionnaire
evening questionnaire

Efficacy Outcome List:

Primary outcome	Outcome:
☑	sleep latency
☑	total sleep time
☐	wake time after sleep onset
☐	number of awakenings
☐	sleep quality
☐	sleep depth
☐	daytime alertness
☐	ability to function
☐	sense of physical well-being
☐	number of naps taken
☐	length of naps

Results

morning questionnaire

number of awakenings - average

Eszopiclone 1mg	Eszopiclone 2mg	Placebo		P value
2 (NS)	1.7 (NS)	1.9 (NA)	( )	

Mean (p vs placebo)

sleep quality (0=poor; 10=excellent) - average

Eszopiclone 1mg	Eszopiclone 2mg	Placebo		P value
6.6 (NS)	7.2 (0.0006)	6.3 (NA)	( )	

Mean (p vs placebo)

sleep depth (0=very light; 10=very deep) - average

Eszopiclone 1mg	Eszopiclone 2mg	Placebo		P value
6.5 (NS)	7.1 (0.0015)	6.2 (NA)	( )	

Mean (p vs placebo)

Evidence Table 13. Placebo controlled trials: Efficacy

Author: **Scharf** **Trial type:** **Placebo** **Quality rating:** **Fair**

Year: **2005** **Country:** **US** **Funding:**

sleep latency (min) - average

Eszopiclone 1mg		Eszopiclone 2mg		Placebo				P value
53.6	(<0.05)	50	(0.0034)	85.5	(NA)		( )	

Mean (p vs placebo)

total sleep time (min) - average

Eszopiclone 1mg		Eszopiclone 2mg		Placebo				P value
349.8	(NS)	372.3	(0.0003)	328.2	(NA)		( )	

Mean (p vs placebo)

wake after sleep onset (min) - average

Eszopiclone 1mg		Eszopiclone 2mg		Placebo				P value
72.6	(NS)	58.5	(0.423)	74.1	(NA)		( )	

Mean (p vs placebo)

Evidence Table 13. Placebo controlled trials: Efficacy

Author: **Scharf** **Trial type:** **Placebo** **Quality rating:** **Fair**

Year: **2005** **Country:** **US** **Funding:**

evening questionnaire

daytime alertness (0=drowsy; 10=alert), average

Eszopiclone 1mg	Eszopiclone 2mg	Placebo		P value
7.1 (NS)	7.3 (0.0223)	6.8 (NA)	( )	

Mean (p vs placebo)

physical well-being (0=poor; 10=excellent), average

Eszopiclone 1mg	Eszopiclone 2mg	Placebo		P value
7.5 (NS)	7.7 (0.0474)	7.2 (NA)	( )	

Mean (p vs placebo)

morning sleepiness (0=very sleepy; 10=not at all sleepy), average

Eszopiclone 1mg	Eszopiclone 2mg	Placebo		P value
6.9 (NS)	7.2 (0.054)	6.6 (NA)	( )	

Mean (p vs placebo)

daily ability to function (0=poor; 10=excellent), average

Eszopiclone 1mg	Eszopiclone 2mg	Placebo		P value
7.4 (NS)	7.6 (0.0579)	7.2 (NA)	( )	

Mean (p vs placebo)

number of naps taken, total

Eszopiclone 1mg	Eszopiclone 2mg	Placebo		P value
5.0 (NS)	4.3 (0.0276)	5.9 (NA)	( )	

Mean (p vs placebo)

duration per nap (min), average

Eszopiclone 1mg	Eszopiclone 2mg	Placebo		P value
47.7 (<0.05)	52.7 (0.0113)	59.2 (NA)	( )	

Mean (p vs placebo)

Evidence Table 13. Placebo controlled trials: Efficacy

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
26.7% non-white

Number Screened: 178
Eligible: 75
Enrolled: 75

Number Withdrawn:
Lost to fu:
Analyzed:

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.

Exclusion criteria:

Comments:

Intervention:

Run-in : 11
Wash out : 2
Allow other medication : NR

Drug name	dosage	N=	Duration	Withdrawals due to AEs/ 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

Evidence Table 13. Placebo controlled trials: Efficacy

Author: **Scharf_** **Trial type:** **Placebo** **Quality rating:** **Fair**

Year: **1994** **Country:** **US** **Funding:** **NR**

Outcome Measurement:

polysomnography
morning questionnaire

Efficacy Outcome List:

Primary outcome	Outcome:
☑	sleep latency
☑	sleep efficiency
☐	total sleep time
☐	sleep quality
☐	ease of falling sleep

Results

polysomnography

sleep latency (min), week 6

Zolpidem 10mg	Zolpidem 15mg	Placebo		P value
25.8 (0.063)	28.1 (p<0.05)	48 (NA)	( )	

Mean (p vs placebo)

sleep efficiency (%), week 6

Zolpidem 10mg	Zolpidem 15mg	Placebo		P value
87.9 (0.063)	87.3 (p<0.05)	80.7 (NA)	( )	

Mean (p vs placebo)

sleep latency (min), week 6

Zolpidem 10mg	Zolpidem 15mg	Placebo		P value
47.1 (NS)	47.7 (NS)	48.0 (NA)	( )	

Mean (p vs placebo)

sleep efficiency (%), week 6

Zolpidem 10mg	Zolpidem 15mg	Placebo		P value
83.1 (NS)	79.9 (NS)	81.9 (NA)	( )	

Mean (p vs placebo)

Evidence Table 13. Placebo controlled trials: Efficacy

Author: **Scharf_** **Trial type:** **Placebo** **Quality rating:** **Fair**

Year: **1994** **Country:** **US** **Funding:** **NR**

morning questionnaire

# sleep latency (min), week 6	Zolpidem 10mg	Zolpidem 15mg	Placebo		P value
	38.4 (NS)	31.7 (<0.05)	56.6 (NA)	( )	
	Mean (p vs placebo)				
# ease of falling sleep (0=very easy; 100=not easy), week 6	Zolpidem 10mg	Zolpidem 15mg	Placebo		P value
	50.7 (NS)	35.7 (<0.05)	48.4 (NA)	( )	
	Mean (p vs placebo)				
# sleep quality (1=excellent; 4=poor), week 6	Zolpidem 10mg	Zolpidem 15mg	Placebo		P value
	2.5 (NS)	2.5 (NS)	2.6 (NA)	( )	
	Mean (p vs placebo)				
# total sleep time (min), week 6	Zolpidem 10mg	Zolpidem 15mg	Placebo		P value
	369 (NS)	394 (NS)	356 (NA)	( )	
	Mean (p vs placebo)				
# sleep latency (min), posttreatment	Zolpidem 10mg	Zolpidem 15mg	Placebo		P value
	62.3 (NS)	78.2 (NS)	47.5 (NA)	( )	
	Mean (p vs placebo)				
# ease of falling sleep (0=very easy; 100=not easy), posttreatment	Zolpidem 10mg	Zolpidem 15mg	Placebo		P value
	63.7 (NS)	64.0 (<0.05)	44.4 (NA)	( )	
	Mean (p vs placebo)				
# sleep quality (1=excellent; 4=poor), posttreatment	Zolpidem 10mg	Zolpidem 15mg	Placebo		P value
	2.9 (<0.05)	3.1 (<0.05)	2.6 (NA)	( )	
	Mean (p vs placebo)				
# total sleep time (min), posttreatment	Zolpidem 10mg	Zolpidem 15mg	Placebo		P value
	333 (NS)	341 (NS)	333 (NA)	( )	
	Mean (p vs placebo)				

Evidence Table 13. Placebo controlled trials: Efficacy

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)

Evidence Table 13. Placebo controlled trials: Efficacy

Author: **Terzano** **Trial type:** **Placebo** **Quality rating:** **Poor**

Year: **1992** **Country:** **Italy** **Funding:** **Partially supported by Italian**

Design:

Study design RCT
DB
Parallel

Setting Single Center

Age: 49.6
Range: 40-60
SD: 5.1

Gender: 8 (67 %) Female

Ethnicity: NR

Number Screened: NR
Eligible: NR
Enrolled: 12

Number Withdrawn: NR
Lost to fu: NR
Analyzed: 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.

Exclusion criteria:

patients had nocturnal myoclonus or sleep apnea syndrome

Comments:

Intervention:

Run-in : 14
Wash out : NR
Allow other medication : NR

Drug name	dosage	N=	Duration	Withdrawals due to AEs/ Total withdrawal
Zolpidem	10 mg	0	1 day	N / NA
Placebo	NA mg	0	1 day	N / NA

Evidence Table 13. Placebo controlled trials: Efficacy

Author: **Terzano** **Trial type:** **Placebo** **Quality rating:** **Poor**

Year: **1992** **Country:** **Italy** **Funding:** **Partially supported by Italian**

Outcome Measurement:

polysomnography

Efficacy Outcome List:

Primary outcome	Outcome:
☐	sleep latency
☐	wake after sleep onset
☐	total sleep time

Results

polysomnography

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	(		)			

total sleep time (min)

Zolpidem		Placebo				P value
420	(49.7)	402	(37.9)	( )	( )	NR
Mean	(SD		)			

Evidence Table 13. Placebo controlled trials: Efficacy

Author: **Walsh** **Trial type:** **Placebo** **Quality rating:** **Poor**

Year: **2000a** **Country:** **US** **Funding:**

Design:

Study design RCT
DB
Parallel

Setting Multicenter

Age: 67.5
Range: 60-79
SD: NR

Gender: 17 (35 %) Female

Ethnicity: NR

Number Screened: 311
Eligible: 54
Enrolled: 48

Number Withdrawn: NR
Lost to fu: NR
Analyzed: 48

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.

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.

Comments:

Intervention:

Run-in : 5-12
Wash out : 5-12
Allow other medication : NR

Drug name	dosage	N=	Duration	Withdrawals due to AEs/ 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

Evidence Table 13. Placebo controlled trials: Efficacy

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)

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)

PSG total sleep time (min)

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)

PSG no. of awakenings

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)

Evidence Table 13. Placebo controlled trials: Efficacy

Author: **Walsh** **Trial type:** **Placebo** **Quality rating:** **Poor**

Year: **2000a** **Country:** **US** **Funding:**

questionnaire

subjective 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 placebo)

subjective total sleep time (min)

Zaleplon 2mg		Zaleplon 5mg		Zaleplon 10mg		Placebo		P value
335.8	(0.776)	343.2	(0.140)	351.6	(0.011)	327.9	(NA)	

Mean (p vs placebo)

subjective no. of awakenings

Zaleplon 2mg		Zaleplon 5mg		Zaleplon 10mg		Placebo		P value
3.4	(0.671)	3.1	(0.906)	2.8	(0.045)	3.3	(NA)	

Mean (p vs placebo)

Evidence Table 13. Placebo controlled trials: Efficacy

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 Screened: 365
Eligible: 163
Enrolled: 163

Number Withdrawn: 29
Lost to fu: 5
Analyzed: NR

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

Drug name	dosage	N=	Duration	Withdrawals due to AEs/ Total withdrawal
Zolpidem	10 mg	82	56 day	4 / 18
Placebo	NA mg	81	56 day	1 / 10

Evidence Table 13. Placebo controlled trials: Efficacy

Author: **Walsh_** **Trial type:** **Placebo** **Quality rating:** **Fair**

Year: **2000b, 2002** **Country:** **US** **Funding:** **Lorex Pharmaceuticals**

Outcome Measurement:

morning quesionnaire
SF-36

Efficacy Outcome List:

Primary outcome	Outcome:
☐	sleep latency
☐	total sleep time
☐	number of awakenings
☐	sleep quality

Results

morning questionniare

sleep latency (min), all condition, 8 weeks average

Zolpidem	Placebo			P value
12.39 ( )	19.55 ( )	( )	( )	NS

Mean ( )

sleep latency (min), with pill, 8 weeks average

Zolpidem	Placebo			P value
36.7 ( )	50.4 ( )	( )	( )	<0.05

Mean ( )

total sleep time (min), with pill, 8 weeks average

Zolpidem	Placebo			P value
415.4 ( )	364.1 ( )	( )	( )	<0.05

Mean ( )

number of awakenings, with pill, 8 weeks average

Zolpidem	Placebo			P value
1.1 ( )	1.8 ( )	( )	( )	<0.05

Mean ( )

sleep quality (1=excellent; 4=poor), with pill, 8 weeks average

Zolpidem	Placebo			P value
2.1 ( )	2.5 ( )	( )	( )	<0.05

Mean ( )

Evidence Table 13. Placebo controlled trials: Efficacy

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 ( )

Evidence Table 13. Placebo controlled trials: Efficacy

Author: **Zammit** **Trial type:** **Placebo** **Quality rating:** **Fair**

Year: **2004** **Country:** **US** **Funding:** **Sepracor**

Design:

Study design RCT
DB
Parallel

Setting Single Center

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

Number Screened: NR
Eligible: 669
Enrolled: 308

Number Withdrawn: 16
Lost to fu: 0
Analyzed: 308

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:

Run-in : 2
Wash out : 5-7
Allow other medication : NR

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

Evidence Table 13. Placebo controlled trials: Efficacy

Author: **Zammit** **Trial type:** **Placebo** **Quality rating:** **Fair**

Year: **2004** **Country:** **US** **Funding:** **Sepracor**

Outcome Measurement:

- # polysomnography
- # morning questionnaire
- # evening questionnaire

Efficacy Outcome List:

Primary outcome	Outcome:
☐	sleep latency
☐	sleep duration
☐	number of awakenings
☐	wake time after sleep onset
☐	quality of sleep
☐	depth of sleep
☐	daytime alertness
☐	daytime ability to function
☐	morning sleepiness

Results

polysomnography

sleep latency (minute) - night 1, 15, 29 average

Eszopiclone 2mg	Eszopiclone 3mg	Placebo		P value
15 (<0.001)	13.1 (<0.001)	29 (NA)	( )	

Median (p vs placebo)

sleep efficiency (%) - night 1, 15, 29 average

Eszopiclone 2mg	Eszopiclone 3mg	Placebo		P value
88.1 (<0.01)	90.1 (<0.001)	85.7 (NA)	( )	

Median (p vs placebo)

wake time after sleep onset, WASO (min) - night 1, 15, 29 average

Eszopiclone 2mg	Eszopiclone 3mg	Placebo		P value
37.1 (NS)	33.8 (<0.01)	44.1 (NA)	( )	

Median (p vs placebo)

number of awakenings, NAW - night 1, 15, 29 average

Eszopiclone 2mg	Eszopiclone 3mg	Placebo		P value
6.5 (NS)	5.7 (NS)	6.0 (NA)	( )	

Median (p vs placebo)

Evidence Table 13. Placebo controlled trials: Efficacy

Author: **Zammit** **Trial type:** **Placebo** **Quality rating:** **Fair**

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)				

# quality of sleep (0=poor; 100=excellent)	Eszopiclone 2mg	Eszopiclone 3mg	Placebo		P value
	54.5 (0.0414)	56.6 (0.0072)	47.7 (NA)	( )	
	Median (p vs placebo)				

# depth of sleep (0=poor; 100=excellent)	Eszopiclone 2mg	Eszopiclone 3mg	Placebo		P value
	58.9 (0.0052)	56.7 (0.0457)	51.7 (NA)	( )	
	Median (p vs placebo)				

Evidence Table 13. Placebo controlled trials: Efficacy

Author: **Zammit** **Trial type:** **Placebo** **Quality rating:** **Fair**

Year: **2004** **Country:** **US** **Funding:** **Sepracor**

evening questionnaire

daytime alertness (higher scores indicate improved function)

Eszopiclone 2mg	Eszopiclone 3mg	Placebo		P value
6.66 (0.873)	7.02 (0.059)	6.67 (NA)	( )	

Mean (p vs placebo)

daytime ability to function (higher scores indicate improved function)

Eszopiclone 2mg	Eszopiclone 3mg	Placebo		P value
6.81 (0.901)	7.15 (0.118)	6.83 (NA)	( )	

Mean (p vs placebo)

morning sleepiness (1=very sleepy; 100=not at all sleepy)

Eszopiclone 2mg	Eszopiclone 3mg	Placebo		P value
51.3 (0.256)	50.8 (0.344)	48.2 (NA)	( )	

Mean (p vs placebo)

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

Number Screened: NR
Eligible: NR
Enrolled: 437

Number Withdrawn: 22
Lost to fu: NR
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:

Drug name	dosage	N=	Duration	Withdrawals due to AEs/ 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

Rebound:

sleep questionnaire - rebound insomnia

\# rebound: subjective sleep latency (min), withdrawal day 1

Zaleplon 5mg	Zaleplon 10mg	Placebo		P value
45 ( )	50 ( )	60 ( )	( )	

Median ( )

\# rebound: subjective total sleep time (min), withdrawal day 1

Zaleplon 5mg	Zaleplon 10mg	Placebo		P value
330 ( )	300 ( )	330 ( )	( )	

Median ( )

Evidence Table 14. Placebo controlled trials: Rebound Insomnia

Author: **Hedner** **Trial type:** **Placebo** **Quality rating:** **Fair**

Year: **2000** **Country:** **Europe** **Funding:**

rebound: subjective number of awakenings, withdrawal day 1

Zaleplon 5mg	Zaleplon 10mg	Placebo		P value
2 ( )	2 ( )	2 ( )	( )	

Median ( )

<u>incidence of rebound insomnia</u>

rebound insomnia: subjective sleep latency

Zaleplon 5mg	Zaleplon 10mg	Placebo		P value
11 (9)	12 (9)	7 (5)	( )	

Number (%)

rebound insomnia: subjective total sleep time

Zaleplon 5mg	Zaleplon 10mg	Placebo		P value
14 (11)	17 (13)	6 (5)	( )	

Number (%)

rebound insomnia: number of awakenings

Zaleplon 5mg	Zaleplon 10mg	Placebo		P value
7 (6)	4 (3)	7 (6)	( )	

Number (%)

Evidence Table 14. Placebo controlled trials: Rebound Insomnia

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 Screened: NR
Eligible: 25
Enrolled: 21

Number Withdrawn: NR
Lost to fu: NR
Analyzed: 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:

Drug name	dosage	N=	Duration	Withdrawals due to AEs/ Total withdrawal
Zolpidem	10 mg	11	14 day	N / NR
Placebo	NA mg	10	14 day	N / NR

Rebound:

polysomnography

sleep efficiency (%), day 28 wistrawal, rebound

Zolpidem	Placebo			P value
77.4 (4)	68.9 (4)	( )	( )	<0.05
Mean (SD)				

total sleep time (min), day 28 wistrawal, rebound

Zolpidem	Placebo			P value
341.3 (12)	298.3 (21)	( )	( )	<0.05
Mean (SD)				

sleep onset latency (min), day 28 wistrawal, rebound

Zolpidem	Placebo			P value
50.7 (11)	36.3 (7)	( )	( )	NS
Mean (SD)				

Evidence Table 14. Placebo controlled trials: Rebound Insomnia

Author: **Herrmann** **Trial type:** **Placebo** **Quality rating:** **Poor**

Year: **1993** **Country:** **France** **Funding:** **NR**

time awake (min), day 28 wistrawal, rebound

Zolpidem	Placebo			P value
53.7 (13)	99.3 (17)	( )	( )	<0.05
Mean (SD)				

sleep questionnaire

sleep onset latency (min), day 22-28 withdrawal, rebound

Zolpidem	Placebo			P value
60.8 (14)	70.8 (10)	( )	( )	NS
Mean (SD)				

total sleep time (min), day 22-28 withdrawal, rebound

Zolpidem	Placebo			P value
341.8 (18)	310.9 (21)	( )	( )	NS
Mean (SD)				

no. of awakenings, day 22-28 withdrawal, rebound

Zolpidem	Placebo			P value
2.4 (0.5)	2.5 (0)	( )	( )	NS
Mean (SD)				

Evidence Table 14. Placebo controlled trials: Rebound Insomnia

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 Screened: NR
Eligible: NR
Enrolled: 12

Number Withdrawn: NR
Lost to fu: NR
Analyzed: 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:

Drug name	dosage	N=	Duration	Withdrawals due to AEs/ Total withdrawal
Zolpidem	10 mg	6	27 day	N / NR
Placebo	NA mg	6	27 day	N / NR

Rebound:

polysomnography

\# stage 2 sleep latency (min), nights 31-33, withdrawal, rebound

Zolpidem	Placebo			P value
47.2 (11.1)	32.3 (7.9)	( )	( )	NS
Mean (SD)				

\# total number of awakenings, nights 31-33, withdrawal, rebound

Zolpidem	Placebo			P value
28.7 (4.6)	26.1 (3.7)	( )	( )	NS
Mean (SD)				

\# total wake time (min), nights 31-33, withdrawal, rebound

Zolpidem	Placebo			P value
97.7 (15.8)	115.9 (18.8)	( )	( )	NS
Mean (SD)				

Evidence Table 14. Placebo controlled trials: Rebound Insomnia

Author: **Monti** **Trial type:** **Placebo** **Quality rating:** **Fair**

Year: **1996** **Country:** **Uruguay** **Funding:** **NR**

# wake time after sleep onset (min), nights 31-33, withdrawal, rebound	Zolpidem	Placebo			P value
	54.9 (16.1)	92.0 (16.3)	( )	( )	NS
	Mean (SD)				
# total sleep time (min), nights 31-33, withdrawal, rebound	Zolpidem	Placebo			P value
	378.6 (15.3)	361.2 (17.9)	( )	( )	NS
	Mean (SD)				
# sleep efficiency (%), nights 31-33, withdrawal, rebound	Zolpidem	Placebo			P value
	79.0 (3.7)	75.3 (3.7)	( )	( )	NS
	Mean (SD)				
# movement time, nights 31-33, withdrawal, rebound	Zolpidem	Placebo			P value
	3.7 (0.8)	2.9 (0.7)	( )	( )	NS
	Mean (SD)				
<u>questionnaire</u>					
# sleep latency (lower score indicates more positive response), night 31-33, withdrawal, rebound	Zolpidem	Placebo			P value
	2.4 (0.4)	1.9 (0.3)	( )	( )	NS
	Mean (SD)				
# sleep duration (higher score indicates more positive response), night 31-33, withdrawal, rebound	Zolpidem	Placebo			P value
	2.1 (0.2)	2.4 (0.3)	( )	( )	NS
	Mean (SD)				
# number of awakenings (lower score indicates more positive response), night 31-33, withdrawal, rebound	Zolpidem	Placebo			P value
	2.3 (0.4)	2.6 (0.3)	( )	( )	NS
	Mean (SD)				
# disturbed sleep (higher score indicates more positive response), night 31-33, withdrawal, rebound	Zolpidem	Placebo			P value
	64.9 (8.2)	63.7 (6.8)	( )	( )	NS
	Mean (SD)				

Evidence Table 14. Placebo controlled trials: Rebound Insomnia

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

Zolpidem	Placebo			P value
73.8 (7.0)	54.1 (7.0)	( )	( )	<0.05
Mean (SD)				

Evidence Table 14. Placebo controlled trials: Rebound Insomnia

Author: **Monti_** **Trial type:** **Placebo** **Quality rating:** **Poor**

Year: **2000** **Country:** **Uruguay** **Funding:** **NR**

Design:

Study design RCT
DB
Parallel

Setting Single Center

Age: 51.9
Range: NR
SD: 3.6

Gender: 12 (100 %) Female

Ethnicity: NR

Number Screened: NR
Eligible: NR
Enrolled: 12

Number Withdrawn: NR
Lost to fu: NR
Analyzed: 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 cliniclally 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:

Drug name	dosage	N=	Duration	Withdrawals due to AEs/ 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)				

Evidence Table 14. Placebo controlled trials: Rebound Insomnia

Author: **Monti_** **Trial type:** **Placebo** **Quality rating:** **Poor**

Year: **2000** **Country:** **Uruguay** **Funding:** **NR**

# sleep efficiency (%) - night 19-21, withdrawal, rebound	Zolpidem	Placebo			P value
	69.7 (4.6)	58.6 (6.9)	( )	( )	NS
	Mean (SD)				
# stage 2 sleep latency - night 19-21, withdrawal, rebound	Zolpidem	Placebo			P value
	55.7 (15.7)	69.7 (12.5)	( )	( )	NS
	Mean (SD)				
# total number of awakenings - night 19-21, withdrawal, rebound	Zolpidem	Placebo			P value
	25.4 (3.8)	32.2 (5.9)	( )	( )	NS
	Mean (SD)				
# waking time after sleep onset (min) - night 19-21, withdrawal, rebound	Zolpidem	Placebo			P value
	75.1 (7.9)	137.5 (29.2)	( )	( )	NS
	Mean (SD)				
<u>interview</u>					
# sleep latency (min) - night 19-21, withdrawal, rebound	Zolpidem	Placebo			P value
	94.3 (48.5)	118.4 (34.2)	( )	( )	NS
	Mean (SD)				
# sleep duration (min) - night 19-21, withdrawal, rebound	Zolpidem	Placebo			P value
	342.0 (47.5)	207.4 (70.5)	( )	( )	NS
	Mean (SD)				
# disturbed sleep - night 19-21 (1=agree; 100=disagree), withdrawal, rebound	Zolpidem	Placebo			P value
	62.7 (11.4)	56.8 (9.3)	( )	( )	NS
	Mean (SD)				
# alert in the morning - night 19-21 (1=agree; 100=disagree), withdrawal, rebound	Zolpidem	Placebo			P value
	37.9 (9.5)	61.5 (9.8)	( )	( )	NS
	Mean (SD)				

Evidence Table 14. Placebo controlled trials: Rebound Insomnia

Author: **Zammit** **Trial type:** **Placebo** **Quality rating:** **Fair**

Year: **2004** **Country:** **US** **Funding:** **Sepracor**

Design:

Study design RCT
DB
Parallel

Setting Single Center

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

Number Screened: NR
Eligible: 669
Enrolled: 308

Number Withdrawn: 16
Lost to fu: 0
Analyzed: 308

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:

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

Rebound:

polysomnography

\# sleep latency (min), rebound insomnia, change vs baseline

Eszopiclone 2mg	Eszopiclone 3mg			P value
NR (NS)	-8.5 (<0.05)	( )	( )	

Mean (p vs baseline)

\# sleep efficiency (%), rebound insomnia, change vs baseline

Eszopiclone 2mg	Eszopiclone 3mg			P value
-2.5 (<0.05)	3.7 (<0.05)	( )	( )	

Mean (p vs baseline)

Evidence Table 14. Placebo controlled trials: Rebound Insomnia

Author:	**Zammit**	**Trial type:**	**Placebo**	**Quality rating:**	**Fair**
Year:	**2004**	**Country:**	**US**	**Funding:**	**Sepracor**

#						
	WASO (min), rebound insomnia, change vs baseline	Eszopiclone 2mg	Eszopiclone 3mg			P value
		7 (<0.05)	NR (NS)	( )	( )	
		Mean (p vs baseline)				

Evidence Table 15. Placebo controlled trials: Adverse Events

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 Screened: NR
Eligible: NR
Enrolled: 37

Number Withdrawn: 18
Lost to fu: NR
Analyzed: 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

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

Evidence Table 15. Placebo controlled trials: Adverse Events

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)

Evidence Table 15. Placebo controlled trials: Adverse Events

Author: **Allain_** **Trial type:** **Placebo** **Quality rating:** **Fair**

Year: **2001** **Country:** **France** **Funding:** **Sanofi-Synthelabo**

Design:

Study design RCT
DB
Parallel

Setting Multicenter

Age: 46.1
Range: 25-64
SD: 10.5

Gender: 188 (77 %) Female

Ethnicity: NR

Number Screened: NR
Eligible: NR
Enrolled: 245

Number Withdrawn: NR
Lost to fu: NR
Analyzed: 245

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.

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.

Comments:

Zolpidem was administrated as needed, not every night.

Intervention:

Run-in : 3-7
Wash out : NR
Allow other medication : NR

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

Evidence Table 15. Placebo controlled trials: Adverse Events

Author: **Allain_** **Trial type:** **Placebo** **Quality rating:** **Fair**

Year: **2001** **Country:** **France** **Funding:** **Sanofi-Synthelabo**

Adverse Events:

treatment-emergent adverse events

overall

Zolpidem	Placebo			P value:
23 (19)	18 (15)	( )	( )	NS

Number (%)

anxiety

Zolpidem	Placebo			P value:
4 ( )	0 ( )	( )	( )	NR

% ( )

headache

Zolpidem	Placebo			P value:
3.2 ( )	0 ( )	( )	( )	NR

% ( )

rhinitis

Zolpidem	Placebo			P value:
0 ( )	3.3 ( )	( )	( )	NR

% ( )

Evidence Table 15. Placebo controlled trials: Adverse Events

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

Age: 50
Range: 35-65
SD: NR

Gender: 18 (72 %) Female

Ethnicity: NR

Number Screened: NR
Eligible: 30
Enrolled: 25

Number Withdrawn: 5
Lost to fu: 0
Analyzed: 25

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.

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

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

Evidence Table 15. Placebo controlled trials: Adverse Events

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

Zopiclone	Placebo			P value:
5 ( )	2 ( )	( )	( )	NR

Number ( )

\# drowsiness/dizziness

Zopiclone	Placebo			P value:
2 ( )	1 ( )	( )	( )	NR

Number ( )

Evidence Table 15. Placebo controlled trials: Adverse Events

Author: **Dockhorn** **Trial type:** **Placebo** **Quality rating:** **Fair**

Year: **1996** **Country:** **US** **Funding:** **Lorex Pharmaceuticals**

Design:

Study design RCT
DB
Parallel

Setting Multicenter

Age: 32.7
Range: 20-55
SD: NR

Gender: 80 (58 %) Female

Ethnicity: NR

Number Screened: NR
Eligible: NR
Enrolled: 138

Number Withdrawn: 9
Lost to fu: 2
Analyzed: 136

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)

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

Comments:

Intervention:

Run-in : NR
Wash out : NR
Allow other medication : NR

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

Evidence Table 15. Placebo controlled trials: Adverse Events

Author: **Dockhorn** **Trial type:** **Placebo** **Quality rating:** **Fair**

Year: **1996** **Country:** **US** **Funding:** **Lorex Pharmaceuticals**

Adverse Events:

adverse events

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 ( )	( )	( )	

% ( )

Evidence Table 15. Placebo controlled trials: Adverse Events

Author: **Dorsey** **Trial type:** **Placebo** **Quality rating:** **Fair**

Year: **2004** **Country:** **US** **Funding:** **Sanofi-Synthelabo**

Design:

Study design RCT
DB
Parallel

Setting Multicenter

Age: 50.8
Range: 39-60
SD: 4.5

Gender: 141 (100 %) Female

Ethnicity: NR

Number Screened: 242
Eligible: 141
Enrolled: 141

Number Withdrawn: 16
Lost to fu: 3
Analyzed: 141

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.

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.

Comments:

Intervention:

Run-in : 6-14
Wash out : NR
Allow other medication : NR

Drug name	dosage	N=	Duration	Withdrawals due to AEs/ Total withdrawal
Zolpidem	10 mg	68	28 day	5 / 11
Placebo	NA mg	73	28 day	2 / 5

Evidence Table 15. Placebo controlled trials: Adverse Events

Author: **Dorsey** **Trial type:** **Placebo** **Quality rating:** **Fair**

Year: **2004** **Country:** **US** **Funding:** **Sanofi-Synthelabo**

Adverse Events:

overall

headache

Zolpidem	Placebo			P value:
36 (52.9)	24 (32.9)	( )	( )	0.08

Number (%)

upper respiratory tract infection

Zolpidem	Placebo			P value:
11 (16.2)	5 (6.8)	( )	( )	0.11

Number (%)

drowsiness

Zolpidem	Placebo			P value:
7 (10.3)	1 (4)	( )	( )	0.03

Number (%)

dizziness

Zolpidem	Placebo			P value:
6 (8.8)	0 (0)	( )	( )	0.01

Number (%)

backache

Zolpidem	Placebo			P value:
5 (7.4)	0 (0)	( )	( )	0.02

Number (%)

irritability

Zolpidem	Placebo			P value:
5 (7.4)	2 (2.7)	( )	( )	0.02

Number (%)

Evidence Table 15. Placebo controlled trials: Adverse Events

Author: **Goldenberg** **Trial type:** **Placebo** **Quality rating:** **Poor**

Year: **1994** **Country:** **UK, France** **Funding:** **NR**

Design:

Study design RCT
DB
Parallel

Setting Multicenter

Age: NR
Range: 25-60
SD: NR

Gender: NR (%) Female

Ethnicity: NR

Number Screened: NR
Eligible: NR
Enrolled: 524

Number Withdrawn: NR
Lost to fu: NR
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:

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 : NR

Drug name	dosage	N=	Duration	Withdrawals due to AEs/ Total withdrawal
Zopiclone	7.5 mg	231	48 day	N / NR
Placebo	NA mg	227	44 day	N / NR

Evidence Table 15. Placebo controlled trials: Adverse Events

Author: **Goldenberg** **Trial type:** **Placebo** **Quality rating:** **Poor**

Year: **1994** **Country:** **UK, France** **Funding:** **NR**

Adverse Events:

Adverse events

overall reported

Zopiclone	Placebo			P value:
54 (20.6)	30 (11.5)	( )	( )	

Number (%)

dry mouth

Zopiclone	Placebo			P value:
10 ( )	5 ( )	( )	( )	

Number ( )

bitter taste

Zopiclone	Placebo			P value:
11 ( )	0 ( )	( )	( )	

Number ( )

Evidence Table 15. Placebo controlled trials: Adverse Events

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 Screened: NR
Eligible: NR
Enrolled: 437

Number Withdrawn: 22
Lost to fu: NR
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 : NR

Drug name	dosage	N=	Duration	Withdrawals due to AEs/ 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

Evidence Table 15. Placebo controlled trials: Adverse Events

Author: **Hedner** **Trial type:** **Placebo** **Quality rating:** **Fair**

Year: **2000** **Country:** **Europe** **Funding:**

Adverse Events:

treatment-emergent adverse events

overall

Zaleplon 5mg	Zaleplon 10mg	Placebo		P value:
68 (48)	59 (40)	74 (51)	( )	NS

Number (%)

withdrawals

Zaleplon 5mg	Zaleplon 10mg	Placebo		P value:
10 (7)	5 (3)	7 (5)	( )	NS

Number (%)

Evidence Table 15. Placebo controlled trials: Adverse Events

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 Screened: NR
Eligible: 25
Enrolled: 21

Number Withdrawn: NR
Lost to fu: NR
Analyzed: 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:

Run-in : 7
Wash out : 7
Allow other medication : NR

Drug name	dosage	N=	Duration	Withdrawals due to AEs/ Total withdrawal
Zolpidem	10 mg	11	14 day	N / NR
Placebo	NA mg	10	14 day	N / NR

Evidence Table 15. Placebo controlled trials: Adverse Events

Author: **Herrmann** **Trial type:** **Placebo** **Quality rating:** **Poor**

Year: **1993** **Country:** **France** **Funding:** **NR**

Adverse Events:

adverse events

\# headache - during treatment

Zolpidem	Placebo			P value:
3 ( )	4 ( )	( )	( )	

Number ( )

\# headache - withdrawal

Zolpidem	Placebo			P value:
2 ( )	1 ( )	( )	( )	

Number ( )

Evidence Table 15. Placebo controlled trials: Adverse Events

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

Ethnicity: NR

Number Screened: NR
Eligible: NR
Enrolled: 458

Number Withdrawn: NR
Lost to fu: NR
Analyzed: 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.

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.

Comments:

Intervention:

Run-in : NR
Wash out : NR
Allow other medication : NR

Drug name	dosage	N=	Duration	Withdrawals due to AEs/ Total withdrawal
Zopiclone	7.5 mg	231	48 day	N / NR
Placebo	NA mg	227	42 day	N / NR

Evidence Table 15. Placebo controlled trials: Adverse Events

Author: **Hindmarch** **Trial type:** **Placebo** **Quality rating:** **Fair**

Year: **1995** **Country:** **UK** **Funding:**

Adverse Events:

adverse events

\# overall drop out

Zolpidem	Placebo			P value:
30 (11.5)	54 (20.6)	( )	( )	NS

Number (%)

\# bitter taste

Zolpidem	Placebo			P value:
11 ( )	0 ( )	( )	( )	

Number ( )

\# dry mouth

Zaleplon	Placebo			P value:
10 ( )	5 ( )	( )	( )	

Number ( )

Evidence Table 15. Placebo controlled trials: Adverse Events

Author: **Krystal** **Trial type:** **Placebo** **Quality rating:** **Fair**

Year: **2003** **Country:** **US** **Funding:** **Sepracor**

Design:

Study design RCT
DB
Parallel

Setting Multicenter

Age: 44
Range: 21-69
SD: 11.3

Gender: 195 (25 %) Female

Ethnicity: 80% caucasian
13.2% african american
7.9% other

Number Screened: 1194
Eligible: 791
Enrolled: 788

Number Withdrawn: 320
Lost to fu: 60
Analyzed: 788

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.

Exclusion criteria:

NR

Comments:

Intervention:

Run-in : NR
Wash out : 5-7
Allow other medication : NR

Drug name	dosage	N=	Duration	Withdrawals due to AEs/ Total withdrawal
Eszopiclone	3 mg	593	180 day	76 / 235
Placebo	NA mg	195	180 day	14 / 85

Evidence Table 15. Placebo controlled trials: Adverse Events

Author: **Krystal** **Trial type:** **Placebo** **Quality rating:** **Fair**

Year: **2003** **Country:** **US** **Funding:** **Sepracor**

Adverse Events:

adverse events

overall

Eszopiclone	Placebo			P value:
81.1 ( )	70.8 ( )	( )	( )	NR

% ( )

abdominal pain

Eszopiclone	Placebo			P value:
48 (8.1)	11 (5.6)	( )	( )	NR

Number (%)

Accidental injury

Eszopiclone	Placebo			P value:
43 (7.3)	11 (5.6)	( )	( )	NR

Number (%)

asthenia

Eszopiclone	Placebo			P value:
26 (4.4)	11 (5.6)	( )	( )	NR

Number (%)

back pain

Eszopiclone	Placebo			P value:
45 (7.6)	6 (3.1)	( )	( )	NR

Number (%)

diarrhea

Eszopiclone	Placebo			P value:
45 (7.6)	14 (7.2)	( )	( )	NR

Number (%)

dizziness

Eszopiclone	Placebo			P value:
58 (9.8)	6 (3.1)	( )	( )	NR

Number (%)

Evidence Table 15. Placebo controlled trials: Adverse Events

Author: **Krystal** **Trial type:** **Placebo** **Quality rating:** **Fair**

Year: **2003** **Country:** **US** **Funding:** **Sepracor**

dry mouth

Eszopiclone	Placebo			P value:
39 (6.6)	3 (1.5)	( )	( )	NR

Number (%)

dyspepsia

Eszopiclone	Placebo			P value:
41 (6.9)	13 (6.7)	( )	( )	NR

Number (%)

headache

Eszopiclone	Placebo			P value:
116 (19.6)	37 (19)	( )	( )	NR

Number (%)

infection

Eszopiclone	Placebo			P value:
94 (15.9)	13 (6.7)	( )	( )	NR

Number (%)

nausea

Eszopiclone	Placebo			P value:
67 (11.3)	11 (5.6)	( )	( )	NR

Number (%)

pain

Eszopiclone	Placebo			P value:
67 (11.3)	12. (6.2)	( )	( )	NR

Number (%)

pharyngitis

Eszopiclone	Placebo			P value:
59 (9.9)	10 (5.1)	( )	( )	NR

Number (%)

rash

Eszopiclone	Placebo			P value:
31 (5.2)	6 (3.1)	( )	( )	NR

Number (%)

Evidence Table 15. Placebo controlled trials: Adverse Events

Author: **Krystal** **Trial type:** **Placebo** **Quality rating:** **Fair**

Year: **2003** **Country:** **US** **Funding:** **Sepracor**

rhinitis

Eszopiclone	Placebo			P value:
42 (7.1)	9 (4.6)	( )	( )	NR

Number (%)

sinusitis

Eszopiclone	Placebo			P value:
25 (4.2)	11 (5.6)	( )	( )	NR

Number (%)

somnolence

Eszopiclone	Placebo			P value:
54 (9.1)	5 (2.6)	( )	( )	NR

Number (%)

unpleasant taste

Eszopiclone	Placebo			P value:
155 (26.1)	11 (5.6)	( )	( )	NR

Number (%)

Evidence Table 15. Placebo controlled trials: Adverse Events

Author: **Lahmeyer** **Trial type:** **Placebo** **Quality rating:** **Fair**

Year: **1997** **Country:** **US** **Funding:** **?orex Pharmaceuticals**

Design:

Study design RCT
DB
Parallel

Setting Multicenter

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

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.

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 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.

Comments:

Intervention:

Run-in : 3
Wash out : 4
Allow other medication : NR

Drug name	dosage	N=	Duration	Withdrawals due to AEs/ 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

Evidence Table 15. Placebo controlled trials: Adverse Events

Author: **Lahmeyer** **Trial type:** **Placebo** **Quality rating:** **Fair**

Year: **1997** **Country:** **US** **Funding:** **?orex Pharmaceuticals**

Adverse Events:

overall adverse events

\# drowsiness

Zolpidem 10mg	Zolpidem 15mg	Placebo		P value:
11 ( )	12 ( )	6 ( )	( )	

% ( )

\# dizziness

Zolpidem 10mg	Zolpidem 15mg	Placebo		P value:
5 ( )	7 ( )	4 ( )	( )	

% ( )

\# pharyngitis

Zolpidem 10mg	Zolpidem 15mg	Placebo		P value:
2 ( )	9 ( )	2 ( )	( )	

% ( )

\# rhinitis

Zolpidem 10mg	Zolpidem 15mg	Placebo		P value:
0 ( )	7 ( )	2 ( )	( )	

% ( )

\# lethargy

Zolpidem 10mg	Zolpidem 15mg	Placebo		P value:
7 ( )	2 ( )	0 ( )	( )	

% ( )

\# overall

Zolpidem 10mg	Zolpidem 15mg	Placebo		P value:
25 (57)	30 (70)	56 (43)	( )	

Number (%)

\# CNS related

Zolpidem 10mg	Zolpidem 15mg	Placebo		P value:
19 (28.3)	15 (43.2)	15 (34.8)	( )	

Number (%)

Evidence Table 15. Placebo controlled trials: Adverse Events

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 Screened: NR
Eligible: NR
Enrolled: 99

Number Withdrawn: 0
Lost to fu: 2
Analyzed: 91

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

Drug name	dosage	N=	Duration	Withdrawals due to AEs/ Total withdrawal
Zopiclone	7.5 mg	91	7 day	N / NR
Placebo	NA mg	91	7 day	N / NR

Evidence Table 15. Placebo controlled trials: Adverse Events

Author: **Monchesky** **Trial type:** **Placebo** **Quality rating:** **Fair**

Year: **1986** **Country:** **Canada** **Funding:** **NR**

Adverse Events:

adverse events

headache

Zopiclone	Placebo			P value:
11 ( )	11 ( )	( )	( )	

Number ( )

dizziness

Zopiclone	Placebo			P value:
4 ( )	6 ( )	( )	( )	

Number ( )

nausea

Zopiclone	Placebo			P value:
7 ( )	4 ( )	( )	( )	

Number ( )

bad/bitter taste

Zopiclone	Placebo			P value:
4 ( )	3 ( )	( )	( )	

Number ( )

back pain

Zopiclone	Placebo			P value:
1 ( )	3 ( )	( )	( )	

Number ( )

stomach pain

Zopiclone	Placebo			P value:
3 ( )	2 ( )	( )	( )	

Number ( )

Evidence Table 15. Placebo controlled trials: Adverse Events

Author: **Scharf** **Trial type:** **Placebo** **Quality rating:** **Fair**

Year: **2005** **Country:** **US** **Funding:**

Design:

Study design RCT
DB
Parallel

Setting Multicenter

Age: 72.3
Range: 64-85
SD: 4.9

Gender: 133 (58 %) Female

Ethnicity: 89.4% caucasian
2.2% black
1.3% hispanic

Number Screened: 353
Eligible: NR
Enrolled: 231

Number Withdrawn: 21
Lost to fu: NR
Analyzed: 231

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

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.

Comments:

Intervention:

Run-in : 3-14
Wash out : NR
Allow other medication : NR

Drug name	dosage	N=	Duration	Withdrawals due to AEs/ 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

Evidence Table 15. Placebo controlled trials: Adverse Events

Author: **Scharf** **Trial type:** **Placebo** **Quality rating:** **Fair**

Year: **2005** **Country:** **US** **Funding:**

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

Eszopiclone 1mg	Eszopiclone 2mg	Placebo		P value:
15.3 ( )	15.2 ( )	15.0 ( )	( )	

% ( )

\# unpleasant taste

Eszopiclone 1mg	Eszopiclone 2mg	Placebo		P value:
8.3 ( )	11.4 ( )	1.3 ( )	( )	

% ( )

\# somnolence

Eszopiclone 1mg	Eszopiclone 2mg	Placebo		P value:
6.9 ( )	3.8 ( )	8.8 ( )	( )	

% ( )

\# dyspepsia

Eszopiclone 1mg	Eszopiclone 2mg	Placebo		P value:
5.6 ( )	1.3 ( )	2.5 ( )	( )	

% ( )

Evidence Table 15. Placebo controlled trials: Adverse Events

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
26.7% non-white

Number Screened: 178
Eligible: 75
Enrolled: 75

Number Withdrawn:
Lost to fu:
Analyzed:

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.

Exclusion criteria:

Comments:

Intervention:

Run-in : 11
Wash out : 2
Allow other medication : NR

Drug name	dosage	N=	Duration	Withdrawals due to AEs/ 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

Evidence Table 15. Placebo controlled trials: Adverse Events

Author: **Scharf_** **Trial type:** **Placebo** **Quality rating:** **Fair**

Year: **1994** **Country:** **US** **Funding:** **NR**

Adverse Events:

adverse events

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 (%)

dizziness

Zolpidem 10mg	Zolpidem 15mg	Placebo		P value:
3 (12)	4 (16)	0 (0)	( )	

Number (%)

lethargy

Zolpidem 10mg	Zolpidem 15mg	Placebo		P value:
2 (8)	1 (4)	1 (4)	( )	

Number (%)

drugged

Zolpidem 10mg	Zolpidem 15mg	Placebo		P value:
2 (8)	1 (4)	0 (0)	( )	

Number (%)

confusion

Zolpidem 10mg	Zolpidem 15mg	Placebo		P value:
0 (0)	2 (8)	0 (0)	( )	

Number (%)

Evidence Table 15. Placebo controlled trials: Adverse Events

Author: **Scharf_** **Trial type:** **Placebo** **Quality rating:** **Fair**

Year: **1994** **Country:** **US** **Funding:** **NR**

nausea

Zolpidem 10mg	Zolpidem 15mg	Placebo		P value:
1 (4)	3 (12)	1 (4)	( )	

Number (%)

dyspepsia

Zolpidem 10mg	Zolpidem 15mg	Placebo		P value:
2 (8)	2 (8)	0 (0)	( )	

Number (%)

arthralgia

Zolpidem 10mg	Zolpidem 15mg	Placebo		P value:
1 (4)	0 (0)	2 (8)	( )	

Number (%)

amnesia

Zolpidem 10mg	Zolpidem 15mg	Placebo		P value:
1 (4)	2 (8)	0 (0)	( )	

Number (%)

rhinitis

Zolpidem 10mg	Zolpidem 15mg	Placebo		P value:
0 (0)	0 (0)	2 (8)	( )	

Number (%)

Evidence Table 15. Placebo controlled trials: Adverse Events

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 Screened: 365
Eligible: 163
Enrolled: 163

Number Withdrawn: 29
Lost to fu: 5
Analyzed: NR

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

Drug name	dosage	N=	Duration	Withdrawals due to AEs/ Total withdrawal
Zolpidem	10 mg	82	56 day	4 / 18
Placebo	NA mg	81	56 day	1 / 10

Evidence Table 15. Placebo controlled trials: Adverse Events

Author: **Walsh_** **Trial type:** **Placebo** **Quality rating:** **Fair**

Year: **2000b, 2002** **Country:** **US** **Funding:** **Lorex Pharmaceuticals**

Adverse Events:

adverse events

overall

Zolpidem	Placebo			P value:
1 ( )	4 ( )	( )	( )	NS

Number ( )

Evidence Table 15. Placebo controlled trials: Adverse Events

Author: **Zammit** **Trial type:** **Placebo** **Quality rating:** **Fair**

Year: **2004** **Country:** **US** **Funding:** **Sepracor**

Design:

Study design RCT
DB
Parallel

Setting Single Center

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

Number Screened: NR
Eligible: 669
Enrolled: 308

Number Withdrawn: 16
Lost to fu: 0
Analyzed: 308

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:

Run-in : 2
Wash out : 5-7
Allow other medication : NR

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

Evidence Table 15. Placebo controlled trials: Adverse Events

Author: **Zammit** **Trial type:** **Placebo** **Quality rating:** **Fair**

Year: **2004** **Country:** **US** **Funding:** **Sepracor**

Adverse Events:

adverse 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 (%)

\# somnolence

Eszopiclone 2mg	Eszopiclone 3mg	Placebo		P value:
3 (3)	8 (7.7)	8 (7.6)	( )	

Number (%)

Evidence Table 15. Placebo controlled trials: Adverse Events

Author: **Zammit** **Trial type:** **Placebo** **Quality rating:** **Fair**

Year: **2004** **Country:** **US** **Funding:** **Sepracor**

unpleasant taste

Eszopiclone 2mg	Eszopiclone 3mg	Placebo		P value:
3 (3)	17 (16.3)	35 (33.3)	( )	

Number (%)

adverse events after treatment discontinuation

CNS related

Eszopiclone 2mg	Eszopiclone 3mg	Placebo		P value:
11.5 (NS)	15.2 (NS)	18.2 (NA)	( )	

% (p vs placebo)

Evidence Table 16. Quality Assessment

Author:	**Agnoli**	**Trial type:**	**Active**	**Quality rating:**	**Poor**
Year:	**1989**	**Country:**	**Rome, Foggia, Italy**	**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	No
If Yes, please report:	
10. Intention-to-treat analysis:	Unable to determine
11. Postramdomization exclusions:	Unable to determine
12. Quality rating:	Poor

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
7. Relevance: patients with gener

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

Evidence Table 16. Quality Assessment

Author:	**Allain**	**Trial type:**	**Placebo**	**Quality rating:**	**Fair**
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:	
10. Intention-to-treat analysis:	Unable to determine
11. Postramdomization exclusions:	NR
12. Quality rating:	Fair

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
7. Relevance: Patients discontinui

Comment:

Evidence Table 16. Quality Assessment

Author: **Allain** **Trial type:** **Placebo** **Quality rating:** **Fair**

Year: **1998** **Country:** **France** **Funding:** **NR**

Internal valididy

1. Randomization adequate?	Yes
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	Yes
Adherence	Yes
Contamination	No
9. Loss to follow-up differential/ high	No
If Yes, please report:	
10. Intention-to-treat analysis:	Yes
11. Postramdomization exclusions:	No
12. Quality rating:	Fair

External valididy

1. Number Screened: NR
   Eligible: NR
   Enrolled: 53
2. 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.
3. Run-in: No
   Wash out: No
4. Class naive patients only No
5. Controlled group standard of care: Yes
6. Funding: Sanofi-Synthelabo
7. Relevance: No (single dose)

Comment:

Evidence Table 16. Quality Assessment

Author: **Allain_** **Trial type:** **Placebo** **Quality rating:** **Fair**

Year: **2001** **Country:** **France** **Funding:** **Sanofi-Synthelabo**

Internal valididy

1. Randomization adequate?	NR
2. 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:	Yes
11. 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.

Evidence Table 16. Quality Assessment

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:	
10. Intention-to-treat analysis:	No
11. Postramdomization exclusions:	Yes
12. Quality rating:	Fair

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
7. Relevance: Yes

Comment: Elderly

Evidence Table 16. Quality Assessment

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
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.
10. Intention-to-treat analysis: No
11. Postramdomization exclusions: Yes
12. Quality rating: Fair

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
7. Relevance: Yes

Comment:

Evidence Table 16. Quality Assessment

Author:	**Ansoms**	**Trial type:**	**Active**	**Quality rating:**	**Fair**
Year:	**1991**	**Country:**	**US**	**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:	
54 enrolled, 27 zopiclone and 25 lormetazepam evaluable, but numbers randomized not reported.	
10. Intention-to-treat analysis:	No
11. 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

Comment:

Evidence Table 16. Quality Assessment

Author:	**Autret**	**Trial type:**	**Active**	**Quality rating:**	**Poor**
Year:	**1987**	**Country:**	**France**	**Funding:**	

Internal valididy

1. Randomization adequate?	Not randomized
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, but not describe
8. Reporting of Attrition	Yes
Crossover	No
Adherence	Yes
Contamination	No
9. Loss to follow-up differential/ high	No
If Yes, please report:	
10. Intention-to-treat analysis:	Unable to determine
11. Postramdomization exclusions:	Unable to determine
12. Quality rating:	Poor

External valididy

1. Number Screened:	NR
Eligible:	NR
Enrolled:	121
2. Exclusion criteria:	
NR	
3. Run-in:	4
Wash out:	3
4. Class naive patients only	
5. Controlled group standard of care:	
6. Funding:	
7. Relevance:	

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

Evidence Table 16. Quality Assessment

Author:	**Begg**	**Trial type:**	**Active**	**Quality rating:**	**Poor**
Year:	**1992**	**Country:**	**NR**	**Funding:**	**Roche Products (NZ) Ltd.**

Internal valididy

1. Randomization adequate? Yes
2. Allocation adequate? NR
3. Groups similar at baseline: No
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:
   - 42% withdrew, but not differential.
10. Intention-to-treat analysis: No
11. Postramdomization exclusions: Yes
12. Quality rating: Poor

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 No
5. Controlled group standard of care:
6. Funding: Roche Products (NZ) Ltd.
7. Relevance:

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

Evidence Table 16. Quality Assessment

Author:	**Bergener**	**Trial type:**	**Active**	**Quality rating:**	**Fair**
Year:	**1989**	**Country:**	**German**	**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, but not describe
6. Care provider masked	Yes, but not describe
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 of 42 patients (38%) dropped out, but not differential (8 in each group) and information provided on reasons for dropout.	
10. Intention-to-treat analysis:	Unable to determine
11. Postramdomization exclusions:	No
12. Quality rating:	Fair

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
7. Relevance:	elderly inpatients

Comment:

Evidence Table 16. Quality Assessment

Author:	**Bozin-Juracic**	**Trial type:**	**Active**	**Quality rating:**	**Fair**
Year:	**1995**	**Country:**	**Croatia**	**Funding:**	**May and Becker and Rhone-**

Internal valididy

1. Randomization adequate?	NR
2. Allocation adequate?	NR
3. Groups similar at baseline:	Yes
4. Eligibility criteria specified	No
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	No
If Yes, please report:	
10. Intention-to-treat analysis:	Unable to determine
11. Postramdomization exclusions:	Yes
12. Quality rating:	Fair

External valididy

1. Number Screened:	NR
Eligible:	32
Enrolled:	29
2. Exclusion criteria:	
NR	
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
7. Relevance:	Shiftworkers

Comment: Not clear if randomized.

Evidence Table 16. Quality Assessment

Author:	**Chaudoir**	**Trial type:**	**Placebo**	**Quality rating:**	**Poor**
Year:	**1983**	**Country:**	**UK**	**Funding:**	**NR (May & Baker provided m**

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:	
High (16.7%, 2 zopiclone, 3 placebo)	
10. Intention-to-treat analysis:	No (25/30 analyzed)
11. Postramdomization exclusions:	No
12. Quality rating:	Poor

External valididy

1. Number Screened: NR
   - Eligible: 30
   - Enrolled: 25
2. 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.

3. Run-in: NR
   Wash out: NR
4. Class naive patients only No
5. Controlled group standard of care: NR
6. Funding: NR (May & Baker provided medications and placebo)
7. Relevance: Yes

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

Evidence Table 16. Quality Assessment

Author:	**Chaudoir**	**Trial type:**	**Placebo**	**Quality rating:**	**Poor**
Year:	**1983**	**Country:**	**UK**	**Funding:**	**NR (May & Baker provided m**

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:	
10. Intention-to-treat analysis:	Not clear
11. Postramdomization exclusions:	Unable to determine
12. Quality rating:	Fair

External valididy

1. Number Screened: NR
   Eligible: NR
   Enrolled: 38
2. 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.
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:

Evidence Table 16. Quality Assessment

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:	
10. Intention-to-treat analysis:	No (136/139 analyzed
11. Postramdomization exclusions:	Yes (1 patient)
12. Quality rating:	Fair

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
7. Relevance: Acute insomnia

Comment:

Evidence Table 16. Quality Assessment

Author: **Dorsey** **Trial type:** **Placebo** **Quality rating:** **Fair**

Year: **2004** **Country:** **US** **Funding:** **Sanofi-Synthelabo**

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:	
10. Intention-to-treat analysis:	Yes
11. Postramdomization exclusions:	No
12. Quality rating:	Fair

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
7. Relevance: Women

Comment:

Evidence Table 16. Quality Assessment

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

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

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	0
Adherence	No
Contamination	No
9. Loss to follow-up differential/ high	No
If Yes, please report:	
10. Intention-to-treat analysis:	Unable to determine
11. Postramdomization exclusions:	No
12. Quality rating:	Fair

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: 5-12
4. Class naive patients only No
5. Controlled group standard of care: Yes
6. Funding: Wyeth-Ayerst Research
7. Relevance: Yes

Comment:

Evidence Table 16. Quality Assessment

Author:	**Drake (2)**	**Trial type:**	**Active**	**Quality rating:**	**Fair**
Year:	**2000**	**Country:**	**US**	**Funding:**	**Wyeth-Ayerst Research**

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	No
If Yes, please report:	
10. Intention-to-treat analysis:	Unable to determine
11. Postramdomization exclusions:	No
12. Quality rating:	Fair

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:	Yes
6. Funding:	Wyeth-Ayerst Research
7. Relevance:	Yes

Comment:

Evidence Table 16. Quality Assessment

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:	
10. Intention-to-treat analysis:	Unable to determine
11. Postramdomization exclusions:	Unable to determine
12. Quality rating:	Fair

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
7. Relevance: Yes

Comment:

Evidence Table 16. Quality Assessment

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, but not describe
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:	
10. Intention-to-treat analysis:	Yes
11. Postramdomization exclusions:	Unable to determine
12. Quality rating:	Fair

External valididy

1. Number Screened: NR
   Eligible: NR
   Enrolled: 44
2. 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.
3. Run-in: 7
   Wash out: 4
4. Class naive patients only No
5. Controlled group standard of care: Yes
6. Funding: Not reported
7. Relevance: elderly residents of

Comment: Elderly patients living in nursing homes.

Evidence Table 16. Quality Assessment

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	Yes
Crossover	No
Adherence	Yes
Contamination	No
9. Loss to follow-up differential/ high	No
If Yes, please report:	
10. Intention-to-treat analysis:	No
11. Postramdomization exclusions:	Yes
12. Quality rating:	Fair

External valididy

1. Number Screened: NR
   Eligible: NR
   Enrolled: 615
2. 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.
3. Run-in: Yes
   Wash out: Yes
4. Class naive patients only No
5. Controlled group standard of care: Yes
6. Funding: Wyeth-Ayerst
7. Relevance: 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.

Evidence Table 16. Quality Assessment

Author:	**Erman (FDA #190-0**	**Trial type:**	**H2H**	**Quality rating:**	**Fair**
Year:	**NR**	**Country:**	**US**	**Funding:**	**Sepracor**

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 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:	
10. Intention-to-treat analysis:	Pts who rec'd at least
11. Postramdomization exclusions:	Unable to determine
12. Quality rating:	Fair

External valididy

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
7. Relevance: Yes

Comment:

Evidence Table 16. Quality Assessment

Author:	**Fleming**	**Trial type:**	**Active**	**Quality rating:**	**Fair**
Year:	**1990**	**Country:**	**Canada**	**Funding:**	**Not reported**

Internal valididy

1. Randomization adequate?	Yes
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	No
If Yes, please report:	
10. Intention-to-treat analysis:	No (48/52 analyzed)
11. Postramdomization exclusions:	Yes
12. Quality rating:	Fair

External valididy

1. Number Screened: NR
   Eligible: NR
   Enrolled: 52
2. 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.
3. Run-in: 3
   Wash out: 4
4. Class naive patients only No
5. Controlled group standard of care: Yes
6. Funding: Not reported
7. Relevance: Yes

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

Evidence Table 16. Quality Assessment

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

Year: **1990** **Country:** **Canada** **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
8. Reporting of Attrition	Yes
Crossover	Yes
Adherence	No
Contamination	Yes
9. Loss to follow-up differential/ high	Yes
If Yes, please report:	
7 (10%) zolpidem vs 1 (3%) flurazepam discontinued	
10. Intention-to-treat analysis:	No
11. Postramdomization exclusions:	Yes
12. Quality rating:	Fair

External valididy

1. Number Screened: 222
   Eligible: 144
   Enrolled: 144
2. 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.
3. Run-in: 1
   Wash out: NR
4. Class naive patients only No
5. Controlled group standard of care: Yes
6. Funding: Not reported
7. Relevance: Yes

Comment:

Evidence Table 16. Quality Assessment

Author:	**Fontaine**	**Trial type:**	**Active**	**Quality rating:**	**Fair**
Year:	**1990**	**Country:**	**Canada**	**Funding:**	**Rhone-Poulenc Pharma**

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:	
10. Intention-to-treat analysis:	Yes
11. Postramdomization exclusions:	No
12. Quality rating:	Fair

External valididy

1. Number Screened: NR
   Eligible: NR
   Enrolled: 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 No
5. Controlled group standard of care: Yes
6. Funding: Rhone-Poulenc Pharma
7. Relevance: Yes

Comment: Subgroup: generalized anxiety disorder

Evidence Table 16. Quality Assessment

Author:	**Fry**	**Trial type:**	**H2H**	**Quality rating:**	**Fair**
Year:	**2000**	**Country:**	**US**	**Funding:**	**Wyeth-Ayerst**

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, 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:	
10. Intention-to-treat analysis:	No
11. Postramdomization exclusions:	Yes
12. Quality rating:	Fair

External valididy

1. Number Screened: NR
   - Eligible: 830
   - Enrolled: 595
2. 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.

3. Run-in: 7
   Wash out: no
4. Class naive patients only NR
5. Controlled group standard of care: Yes
6. Funding: Wyeth-Ayerst
7. Relevance: Yes

Comment: 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.

Evidence Table 16. Quality Assessment

Author:	**Goldenberg**	**Trial type:**	**Placebo**	**Quality rating:**	**Poor**
Year:	**1994**	**Country:**	**UK, France**	**Funding:**	**NR**

Internal valididy

1. Randomization adequate?	NR
2. 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	
10. Intention-to-treat analysis:	No
11. Postramdomization exclusions:	Unable to determine
12. Quality rating:	Poor

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
7. Relevance: Yes

Comment: Only analyzed population characteristics were reported: Mean age=42.9 years; 36.4% male; Ethnicity NR.

Evidence Table 16. Quality Assessment

Author:	**Hajak**	**Trial type:**	**Active**	**Quality rating:**	**Fair**
Year:	**1998, 1995, 1994**	**Country:**	**Germany**	**Funding:**	**Not reported**

Internal valididy

1. Randomization adequate?	Yes
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	Yes
Contamination	No
9. Loss to follow-up differential/ high	No
If Yes, please report:	
10. Intention-to-treat analysis:	Yes
11. Postramdomization exclusions:	No
12. Quality rating:	Fair

External valididy

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 No
5. Controlled group standard of care: Yes
6. Funding: Not reported
7. Relevance: Yes

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

Evidence Table 16. Quality Assessment

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

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

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 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.
10. Intention-to-treat analysis: No
11. Postramdomization exclusions: Yes
12. Quality rating: Fair

External valididy

1. Number Screened: NR
   - Eligible: NR
   - Enrolled: 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: Yes
6. Funding: Not reported (corresponding author from Upjohn)
7. Relevance: Yes

Comment: 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.

Evidence Table 16. Quality Assessment

Author:	**Hedner**	**Trial type:**	**Placebo**	**Quality rating:**	**Fair**
Year:	**2000**	**Country:**	**Europe**	**Funding:**	

Internal valididy

1. Randomization adequate?	NR
2. Allocation adequate?	NR
3. Groups similar at baseline:	Yes for analyzed pop
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:	
10. Intention-to-treat analysis:	No (422/437 analyzed
11. Postramdomization exclusions:	NR
12. Quality rating:	Fair

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:	7
Wash out:	7
4. Class naive patients only	
5. Controlled group standard of care:	
6. Funding:	
7. Relevance:	Older adults

Comment: Only analyzed population characteristics were reported: Mean age=72.5 years; 32.3% male; 99% white, 1% black.

Evidence Table 16. Quality Assessment

Author:	**Herrmann**	**Trial type:**	**Placebo**	**Quality rating:**	**Poor**
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	
10. Intention-to-treat analysis:	No (21/25 analyzed)
11. Postramdomization exclusions:	Yes (1/25)
12. Quality rating:	Poor

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: 7
   Wash out: 7
4. Class naive patients only NR
5. Controlled group standard of care: NR
6. Funding: NR
7. Relevance: Yes

Comment:

Evidence Table 16. Quality Assessment

Author:	**Hindmarch**	**Trial type:**	**Placebo**	**Quality rating:**	**Fair**
Year:	**1995**	**Country:**	**UK**	**Funding:**	

Internal valididy

1. Randomization adequate?	NR
2. 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	
10. Intention-to-treat analysis:	No
11. Postramdomization exclusions:	Unable to determine
12. Quality rating:	Fair

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:	NR
4. Class naive patients only	
5. Controlled group standard of care:	
6. Funding:	
7. Relevance:	

Comment:

Evidence Table 16. Quality Assessment

Author:	**Klimm**	**Trial type:**	**Active**	**Quality rating:**	**Fair**
Year:	**1987**	**Country:**	**France**	**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
8. Reporting of Attrition	Yes
Crossover	No
Adherence	Yes
Contamination	No
9. Loss to follow-up differential/ high	No
If Yes, please report:	
10. Intention-to-treat analysis:	No
11. Postramdomization exclusions:	No
12. Quality rating:	Fair

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
7. 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.

Evidence Table 16. Quality Assessment

Author:	**Krystal**	**Trial type:**	**Placebo**	**Quality rating:**	**Fair**
Year:	**2003**	**Country:**	**US**	**Funding:**	**Sepracor**

Internal valididy

1. Randomization adequate?	NR
2. Allocation adequate?	NR
3. Groups similar at baseline:	weight and BMI > in e
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:	
10. Intention-to-treat analysis:	Yes
11. Postramdomization exclusions:	3 patients discontinue
12. Quality rating:	Fair

External valididy

1. Number Screened:	1194
Eligible:	791
Enrolled:	788
2. Exclusion criteria:	
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
7. Relevance:	Yes

Comment:

Evidence Table 16. Quality Assessment

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: No
11. 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 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.
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

Comment:

Evidence Table 16. Quality Assessment

Author: **Lemoine** **Trial type:** **H2H** **Quality rating:** **Fair**

Year: **1995** **Country:** **France** **Funding:** **Not reported**

Internal valididy

1. Randomization adequate?	NR
2. Allocation adequate?	NR
3. Groups similar at baseline:	Yes
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:	
10. Intention-to-treat analysis:	No
11. Postramdomization exclusions:	No
12. Quality rating:	Fair

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
6. Funding: Not reported
7. Relevance: Yes

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

Evidence Table 16. Quality Assessment

Author:	**Leppik**	**Trial type:**	**Active**	**Quality rating:**	**Fair**
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:	
10. Intention-to-treat analysis:	Yes
11. Postramdomization exclusions:	No
12. Quality rating:	Fair

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
4. Class naive patients only No
5. Controlled group standard of care: Yes
6. Funding: Lornex Pharmaceuticals
7. Relevance: Elderly

Comment:

Evidence Table 16. Quality Assessment

Author:	**Li Pi Shan**	**Trial type:**	**Active**	**Quality rating:**	**Fair**
Year:	**2004**	**Country:**	**Canada**	**Funding:**	**Not reported**

Internal valididy

1. Randomization adequate?	Yes
2. Allocation adequate?	NR
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
8. Reporting of Attrition	Yes
Crossover	No
Adherence	No
Contamination	No
9. Loss to follow-up differential/ high	No
If Yes, please report:	
10. Intention-to-treat analysis:	No
11. Postramdomization exclusions:	No
12. Quality rating:	Fair

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
7. Relevance: Inpatients with stro

Comment: Although there was no formal washout period between weeks 1 and 2, the questionnaire wsas 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.

Evidence Table 16. Quality Assessment

Author:	**Liu**	**Trial type:**	**Active**	**Quality rating:**	**Poor**
Year:	**1997**	**Country:**	**Taiwan**	**Funding:**	

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, but not describe
8. Reporting of Attrition	Yes
Crossover	No
Adherence	Yes
Contamination	No
9. Loss to follow-up differential/ high	Yes
If Yes, please report:	
8 patients did not finish the trial due to lack of compliance.	
10. Intention-to-treat analysis:	Unable to determine
11. Postramdomization exclusions:	Unable to determine
12. Quality rating:	Poor

External valididy

1. Number Screened:	NR
Eligible:	NR
Enrolled:	15
2. Exclusion criteria:	
Patients with psychoses or mood disorders, history of severe physical illness, alcohol abouse or drug abuse.	
3. Run-in:	0
Wash out:	7
4. Class naive patients only	
5. Controlled group standard of care:	
6. Funding:	
7. Relevance:	

Comment: 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).

Evidence Table 16. Quality Assessment

Author:	**Mamelak**	**Trial type:**	**Active**	**Quality rating:**	**Fair**
Year:	**1987**	**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	No
If Yes, please report:	
10. Intention-to-treat analysis:	Unable to determine
11. Postramdomization exclusions:	Unable to determine
12. Quality rating:	Fair

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
7. Relevance: assessments perfo

Comment: Ethanol-drug interaction study.

Evidence Table 16. Quality Assessment

Author:	**Monchesky**	**Trial type:**	**Placebo**	**Quality rating:**	**Fair**
Year:	**1986**	**Country:**	**Canada**	**Funding:**	**NR**

Internal valididy

1. Randomization adequate?	Yes
2. Allocation adequate?	NR
3. Groups similar at baseline:	Yes (for 91/99 analyz
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	Unable to determine
If Yes, please report:	
10. Intention-to-treat analysis:	No (91/99 analyzed)
11. Postramdomization exclusions:	1/99
12. Quality rating:	Fair

External valididy

1. Number Screened: NR
   - Eligible: NR
   - Enrolled: 99
2. 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

3. Run-in: 7
   Wash out: 7
4. Class naive patients only NR
5. Controlled group standard of care: NR
6. Funding: NR
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.

Evidence Table 16. Quality Assessment

Author:	**Monti**	**Trial type:**	**Active**	**Quality rating:**	**Fair**
Year:	**1994**	**Country:**	**Uruguay**	**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
8. Reporting of Attrition	Yes
Crossover	Yes
Adherence	Yes
Contamination	Yes
9. Loss to follow-up differential/ high	No
If Yes, please report:	
10. Intention-to-treat analysis:	Yes
11. Postramdomization exclusions:	No
12. Quality rating:	Fair

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
7. Relevance: Yes

Comment:

Evidence Table 16. Quality Assessment

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

Year: **1994** **Country:** **Uruguay** **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
8. Reporting of Attrition	No
Crossover	No
Adherence	No
Contamination	No
9. Loss to follow-up differential/ high	No
If Yes, please report:	
10. Intention-to-treat analysis:	Yes
11. Postramdomization exclusions:	No
12. Quality rating:	Fair

External valididy

1. Number Screened: NR
   Eligible: NR
   Enrolled: 12
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: 2
   Wash out: 3
4. Class naive patients only Yes
5. Controlled group standard of care: Yes
6. Funding: NR
7. Relevance: Yes

Comment:

Evidence Table 16. Quality Assessment

Author: **Monti_** **Trial type:** **Placebo** **Quality rating:** **Poor**

Year: **2000** **Country:** **Uruguay** **Funding:** **NR**

Internal valididy

1. Randomization adequate?	No (sequential order)
2. Allocation adequate?	No (randomized in se
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:	
10. Intention-to-treat analysis:	Unable to determine
11. Postramdomization exclusions:	Unable to determine
12. Quality rating:	Poor

External valididy

1. Number Screened: NR
   Eligible: NR
   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 cliniclally 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: 3
   Wash out: 3
4. Class naive patients only No
5. Controlled group standard of care: NR
6. Funding: NR
7. Relevance: Women

Comment:

Evidence Table 16. Quality Assessment

Author:	**Nair**	**Trial type:**	**Active**	**Quality rating:**	**Fair**
Year:	**1990**	**Country:**	**Canada**	**Funding:**	**Rhone-Poulenc Pharma**

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	0
Adherence	Yes
Contamination	No
9. Loss to follow-up differential/ high	No
If Yes, please report:	
10. Intention-to-treat analysis:	No
11. Postramdomization exclusions:	No
12. Quality rating:	Fair

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
7. Relevance:

Comment:

Evidence Table 16. Quality Assessment

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

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

Internal valididy

1. Randomization adequate? Yes
2. Allocation adequate? Yes
3. 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
   - 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)
10. Intention-to-treat analysis: No
11. Postramdomization exclusions: No
12. Quality rating: Fair

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
7. Relevance: Yes

Comment:

Evidence Table 16. Quality Assessment

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

Year: **1993** **Country:** **France** **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
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	
10. Intention-to-treat analysis:	No
11. Postramdomization exclusions:	No
12. Quality rating:	Fair

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 No
5. Controlled group standard of care: Yes
6. Funding: Not reported
7. Relevance: patients with anxiet

Comment:

Evidence Table 16. Quality Assessment

Author:	**Perlis**	**Trial type:**	**Placebo**	**Quality rating:**	**Fair**
Year:	**2004**	**Country:**	**US**	**Funding:**	**Lorex Pharmaceuticals**

Internal valididy

1. Randomization adequate?	Yes
2. Allocation adequate?	Yes
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 differential/ high	No
If Yes, please report:	
10. Intention-to-treat analysis:	No
11. Postramdomization exclusions:	No
12. Quality rating:	Fair

External valididy

1. Number Screened: 322
   Eligible: 277
   Enrolled: 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
7. Relevance:

Comment: 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.

Evidence Table 16. Quality Assessment

Author:	**Ponciano**	**Trial type:**	**Active**	**Quality rating:**	**Fair**
Year:	**1990**	**Country:**	**Portugal**	**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	Yes
Crossover	No
Adherence	No
Contamination	No
9. Loss to follow-up differential/ high	No
If Yes, please report:	
10. Intention-to-treat analysis:	Yes
11. Postramdomization exclusions:	No
12. Quality rating:	Fair

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
7. Relevance: Yes

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

Evidence Table 16. Quality Assessment

Author:	**Quadens**	**Trial type:**	**Active**	**Quality rating:**	**Poor**
Year:	**1983**	**Country:**	**Belgium**	**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, but not describe
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:	
10. Intention-to-treat analysis:	Unable to determine
11. Postramdomization exclusions:	Unable to determine
12. Quality rating:	Poor

External valididy

1. Number Screened: NR
   Eligible: NR
   Enrolled: 12
2. 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.
3. Run-in: 6
   Wash out: 35
4. Class naive patients only NR
5. Controlled group standard of care: Yes
6. Funding: Not reported
7. Relevance: postmenopausal w

Comment: Poor quality- insufficient information to assess quality.

Evidence Table 16. Quality Assessment

Author:	**Roger**	**Trial type:**	**Active**	**Quality rating:**	**Fair**
Year:	**1993**	**Country:**	**France**	**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	Yes, but not describe
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:	
10. Intention-to-treat analysis:	Unable to determine
11. Postramdomization exclusions:	No
12. Quality rating:	Fair

External valididy

1. Number Screened: NR
   Eligible: NR
   Enrolled: 221
2. 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.
3. Run-in: 3
   Wash out: 7
4. Class naive patients only No
5. Controlled group standard of care: Yes
6. Funding: Not reported
7. Relevance: Elderly inpatients

Comment: Inpatients at geriatric wards.

Evidence Table 16. Quality Assessment

Author:	**Rosenberg**	**Trial type:**	**Active**	**Quality rating:**	**Poor**
Year:	**1994**	**Country:**	**Denmark**	**Funding:**	**Synthelabo Scandinavia A/S**

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
8. Reporting of Attrition	Yes
Crossover	No
Adherence	No
Contamination	No
9. Loss to follow-up 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
7. Relevance: Yes

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

Evidence Table 16. Quality Assessment

Author:	**Scharf**	**Trial type:**	**Placebo**	**Quality rating:**	**Fair**
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
Contamination	No
9. Loss to follow-up differential/ high	No
If Yes, please report:	
10. Intention-to-treat analysis:	Yes
11. Postramdomization exclusions:	Unable to determine
12. Quality rating:	Fair

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. Run-in: 3-14
   Wash out: NR
4. Class naive patients only No
5. Controlled group standard of care: NR
6. Funding:
7. Relevance: Older adults

Comment:

Evidence Table 16. Quality Assessment

Author:	**Scharf_**	**Trial type:**	**Placebo**	**Quality rating:**	**Fair**
Year:	**1994**	**Country:**	**US**	**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	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:	
10. Intention-to-treat analysis:	Unable to determine
11. Postramdomization exclusions:	No
12. Quality rating:	Fair

External valididy

1. Number Screened:	178
Eligible:	75
Enrolled:	75
2. Exclusion criteria:	
3. Run-in:	11
Wash out:	2
4. Class naive patients only	NR
5. Controlled group standard of care:	NR
6. Funding:	NR
7. Relevance:	Yes

Comment:

Evidence Table 16. Quality Assessment

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

Internal valididy

1. Randomization adequate?	NR
2. 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:	
10. Intention-to-treat analysis:	Yes
11. Postramdomization exclusions:	No
12. Quality rating:	Poor

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
7. Relevance: psychiatric inpatien

Comment: Psychiatric inpatients

Evidence Table 16. Quality Assessment

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

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	
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.
3. Run-in: 3
   Wash out: No
4. Class naive patients only No
5. Controlled group standard of care: Yes
6. Funding: Not reported
7. Relevance: Yes

Comment:

Evidence Table 16. Quality Assessment

Author:	**Singh**	**Trial type:**	**Active**	**Quality rating:**	**Fair**
Year:	**1990**	**Country:**	**Canada**	**Funding:**	**Rhone-Poulenc Pharma Inc.**

Internal valididy

1. Randomization adequate?	NR
2. Allocation adequate?	NR
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:	
10. Intention-to-treat analysis:	Yes
11. Postramdomization exclusions:	Yes (1 patient)
12. Quality rating:	Fair

External valididy

1. Number Screened: NR
   - Eligible: 61
   - Enrolled: 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, 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.

3. Run-in: 4
   Wash out: NR
4. Class naive patients only NR
5. Controlled group standard of care: Yes
6. Funding: Rhone-Poulenc Pharma Inc.
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 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. (?!)

Evidence Table 16. Quality Assessment

Author:	**Steens**	**Trial type:**	**Active**	**Quality rating:**	**Fair**
Year:	**1993**	**Country:**	**Canada**	**Funding:**	**Lorex Pharmaceuticals**

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	No
Crossover	No
Adherence	No
Contamination	No
9. Loss to follow-up differential/ high	No
If Yes, please report:	
10. Intention-to-treat analysis:	Yes
11. Postramdomization exclusions:	No
12. Quality rating:	Fair

External valididy

1. Number Screened: NR
   Eligible: NR
   Enrolled: 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 No
5. Controlled group standard of care: Yes
6. Funding: Lorex Pharmaceuticals
7. Relevance: Patients with COP

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

Evidence Table 16. Quality Assessment

Author:	**Stip**	**Trial type:**	**Active**	**Quality rating:**	**Fair**
Year:	**1999**	**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, 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:	
17% excluded from analysis	
10. Intention-to-treat analysis:	No
11. Postramdomization exclusions:	Yes
12. Quality rating:	Fair

External valididy

1. Number Screened:	NR
Eligible:	NR
Enrolled:	60
2. Exclusion criteria:	
NR	
3. Run-in:	7
Wash out:	7
4. Class naive patients only	NR
5. Controlled group standard of care:	Yes
6. Funding:	Not reported
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

Evidence Table 16. Quality Assessment

Author:	**Tamminen**	**Trial type:**	**Active**	**Quality rating:**	**Poor**
Year:	**1987**	**Country:**	**Finland**	**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, 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:	
28% not includedi n the analysis (10 zopiclone, 16 nitrazepam excluded)	
10. Intention-to-treat analysis:	No
11. Postramdomization exclusions:	Yes
12. Quality rating:	Poor

External valididy

1. Number Screened:	NR
Eligible:	130
Enrolled:	94
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.	
3. Run-in:	7
Wash out:	NR
4. Class naive patients only	No
5. Controlled group standard of care:	Yes
6. Funding:	Not reported
7. Relevance:	Yes

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

Evidence Table 16. Quality Assessment

Author: **Terzano** **Trial type:** **Placebo** **Quality rating:** **Poor**

Year: **1992** **Country:** **Italy** **Funding:** **Partially supported by Italian**

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, 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:	
10. Intention-to-treat analysis:	NR
11. Postramdomization exclusions:	NR
12. Quality rating:	Poor

External valididy

1. Number Screened:	NR
Eligible:	NR
Enrolled:	12
2. Exclusion criteria:	
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:	NR
6. Funding:	Partially supported by Italian Ministry of University and Scientific Research
7. Relevance:	Yes

Comment:

Evidence Table 16. Quality Assessment

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
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:	
13.9% zolpidem vs 18.1% zopiclone withdrew (p=NS)	
10. Intention-to-treat analysis:	No
11. 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).

Evidence Table 16. Quality Assessment

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

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

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	No
If Yes, please report:	
10. Intention-to-treat analysis:	No
11. Postramdomization exclusions:	Unable to determine
12. Quality rating:	Fair

External valididy

1. Number Screened: NR
   Eligible: 60
   Enrolled: 55
2. 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
3. Run-in: 2
   Wash out: 7
4. Class naive patients only No
5. Controlled group standard of care: Yes
6. Funding: Rhone-Poulenc Pharma
7. Relevance: Yes

Comment:

Evidence Table 16. Quality Assessment

Author:	**Venter**	**Trial type:**	**Active**	**Quality rating:**	**Fair**
Year:	**1986**	**Country:**	**South Africa**	**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	Yes, but not describe
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	No
If Yes, please report:	
10. Intention-to-treat analysis:	Yes
11. Postramdomization exclusions:	No
12. Quality rating:	Fair

External valididy

1. Number Screened: 58
   Eligible: 41
   Enrolled: 41
2. 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.
3. Run-in: 7
   Wash out: 0
4. Class naive patients only No
5. Controlled group standard of care: Yes
6. Funding: Not reported
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.

Evidence Table 16. Quality Assessment

Author:	**Voshaar**	**Trial type:**	**Active**	**Quality rating:**	**Fair**
Year:	**2004**	**Country:**	**Netherlands**	**Funding:**	**Sanfi-Synthelabo**

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 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)
10. Intention-to-treat analysis: No
11. Postramdomization exclusions: Yes
12. Quality rating: Fair

External valididy

1. Number Screened: NR
   - Eligible: NR
   - Enrolled: 221
2. 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
3. Run-in: NR
   - Wash out: 4
4. Class naive patients only No
5. Controlled group standard of care: Yes
6. Funding: Sanfi-Synthelabo
7. Relevance: Yes

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

Evidence Table 16. Quality Assessment

Author:	**Walsh**	**Trial type:**	**Placebo**	**Quality rating:**	**Poor**
Year:	**2000a**	**Country:**	**US**	**Funding:**	

Internal valididy

1. Randomization adequate?	Not clear (allocation s
2. Allocation adequate?	Not clear (allocation s
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, but not describe
8. Reporting of Attrition	Yes
Crossover	No
Adherence	No
Contamination	No
9. Loss to follow-up differential/ high	No- unclear if different
If Yes, please report:	
10. Intention-to-treat analysis:	No (48/54 analyzed)
11. Postramdomization exclusions:	Yes
12. Quality rating:	Poor

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: 5-12
   Wash out: 5-12
4. Class naive patients only
5. Controlled group standard of care:
6. Funding:
7. Relevance: Older adults

Comment:

Evidence Table 16. Quality Assessment

Author: **Walsh** **Trial type:** **Placebo** **Quality rating:** **Poor**

Year: **2000a** **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, 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:	
10. Intention-to-treat analysis:	No
11. Postramdomization exclusions:	Yes
12. Quality rating:	Fair

External valididy

1. Number Screened: NR
   Eligible: 589
   Enrolled: 306
2. 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.
3. Run-in: 7
   Wash out: NR
4. Class naive patients only No
5. Controlled group standard of care: Yes
6. Funding: Lorex Pharmaceuticals
7. Relevance: Yes

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

Evidence Table 16. Quality Assessment

Author: **Walsh** **Trial type:** **Placebo** **Quality rating:** **Poor**

Year: **2000a** **Country:** **US** **Funding:**

Internal valididy

1. Randomization adequate?	Yes
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:	
10. Intention-to-treat analysis:	Yes
11. Postramdomization exclusions:	No
12. Quality rating:	Good

External valididy

1. Number Screened: 673
   Eligible: 456
   Enrolled: 132
2. 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.
3. Run-in: 3
   Wash out: 2
4. Class naive patients only No
5. Controlled group standard of care: Yes
6. Funding: Wyeth Ayerst
7. Relevance: Yes

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

Evidence Table 16. Quality Assessment

Author: **Walsh** **Trial type:** **Placebo** **Quality rating:** **Poor**

Year: **2000a** **Country:** **US** **Funding:**

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, 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.	
10. Intention-to-treat analysis:	No
11. Postramdomization exclusions:	Yes
12. Quality rating:	Poor

External valididy

1. Number Screened:	73
Eligible:	39
Enrolled:	30
2. 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.	
3. Run-in:	NR
Wash out:	NR
4. Class naive patients only	Yes
5. Controlled group standard of care:	Yes
6. Funding:	Wyeth-Ayerst Research
7. Relevance:	No- very stringent e

Comment: 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.

Evidence Table 16. Quality Assessment

Author: **Walsh_** **Trial type:** **Placebo** **Quality rating:** **Fair**

Year: **2000b, 2002** **Country:** **US** **Funding:** **Lorex Pharmaceuticals**

Internal valididy

1. Randomization adequate?	Yes
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	Yes
Contamination	Yes
9. Loss to follow-up differential/ high	Yes
If Yes, please report:	
18% withdrew:12.3% placebo, 30% zolpidem	
10. Intention-to-treat analysis:	No
11. Postramdomization exclusions:	Yes
12. Quality rating:	Fair

External valididy

1. Number Screened:	365
Eligible:	163
Enrolled:	163
2. Exclusion criteria:	
NR	
3. Run-in:	7
Wash out:	7
4. Class naive patients only	NR
5. Controlled group standard of care:	Yes
6. Funding: Lorex Pharmaceuticals	
7. Relevance:	Yes

Comment: Patients were instructed to "take the medication when you thini you need it, at bed time, between three and five nights per week".

Evidence Table 16. Quality Assessment

Author:	**Ware**	**Trial type:**	**Active**	**Quality rating:**	**Fair**
Year:	**1997**	**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, 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:	
10. Intention-to-treat analysis:	No
11. Postramdomization exclusions:	No
12. Quality rating:	Fair

External valididy

1. Number Screened: 358
   - Eligible: NR
   - Enrolled: 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 Yes
5. Controlled group standard of care: Yes
6. Funding: Lorex Pharmaceuticals
7. Relevance: Yes

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

Evidence Table 16. Quality Assessment

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

Internal valididy

1. Randomization adequate?	NR
2. Allocation adequate?	NR
3. Groups similar at baseline:	No
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:	
10. Intention-to-treat analysis:	Unable to determine
11. Postramdomization exclusions:	Unable to determine
12. Quality rating:	Fair

External valididy

1. Number Screened:	NR
Eligible:	NR
Enrolled:	36
2. Exclusion criteria:	
NR	
3. Run-in:	3
Wash out:	NR
4. Class naive patients only	No
5. Controlled group standard of care:	Yes
6. Funding:	Not reported
7. Relevance:	Yes

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

Evidence Table 16. Quality Assessment

Author:	**Zammit**	**Trial type:**	**Placebo**	**Quality rating:**	**Fair**
Year:	**2004**	**Country:**	**US**	**Funding:**	**Sepracor**

Internal valididy

1. Randomization adequate?	NR
2. Allocation adequate?	NR
3. Groups similar at baseline:	Differences in gener a
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:	
10. Intention-to-treat analysis:	No (303/308 at night
11. Postramdomization exclusions:	No
12. Quality rating:	Fair

External valididy

1. Number Screened:	NR
Eligible:	669
Enrolled:	308
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
7. Relevance:	Yes

Comment:

Evidence Table 17: Observational Studies

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.

Evidence Table 17: Observational Studies

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

Evidence Table 17: Observational Studies

Author Year Country	Results		Funding
Allain, 1991 France; Delahaye, France	<u>Neuropsychiatric adverse events, no. of AEs (%)/ no. of drop-outs</u> Difficulty arising in the morning: 267(1.3%)/ 85 Sleepiness: 107(0.52%)/ 44 Hypersomnia: 6(0.03%)/ 2 Increased frequency of dreams: 38(0.19%)/ 6 Nightmares: 101(0.49%)/ 59 Headache: 61(0.30%)/ 27 Light headedness/heavy headedness: 11(0.05%)/ 3 Ebrious feeling: 53(0.26%)/ 32 Dizziness: 57(0.28%)/ 24 Fall: 8(0.04%)/ 5 Anxiety: 10(0.05%)/ 5 Angitation/ excitation: 56(0.27%)/ 41 Irritability: 17(0.07%)/ 8 Aggressiveness: 4(0.02%)/ 2 Tremor: 12(0.06%)/ 9 Hallucinations: 7(0.03%)/ 7 Confusion: 7(0.03%)/ 5 Difficulty concentrating: 6(0.03%)/ 1 Memory complaints: 15(0.07%)/ 2 Reduced libido: 4(0.02%)/ 2 Various neuropsychiatric disorders: 15(0.07%)/ 12	<u>Gastrointestinal adverse events, no. of AEs (%)/ no. of drop-outs</u> Bitter taste: 746(3.64%)/ 181 Dysgeusia: 20(0.10%)/ 6 Dry mouth: 325(1.58%)/ 53 Gastric pain: 61(0.30%)/ 33 Nausea: 101(0.49%)/ 49 Vomiting: 101(0.05%)/ 8 Diarrhea: 3(0.01%)/ 2 Constipation: 6(0.03%)/ 1 Various GI disorders: 46(0.22%)/ 23 <u>Somatic adverse events, no. of AEs (%)/ no. of drop-outs</u> Asthenia: 38(0.19%)/ 6 Malaise: 14(0.07%)/ 8 Dyspnea: 8(0.02%)/ 5 Palpitation: 4(0.02%)/ 4 Rash: 8(0.04%)/ 8 Pruritus: 3(0.16%)/ 3 Other: 15(0.07%)/ 7	Not reported

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

Evidence Table 17: Observational Studies

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% 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%	Not reported

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/irritability, illness intrusiveness, depressive symptoms

Evidence Table 17: Observational Studies

Author Year Country	Results	Funding
Buckley, 2004 UK	Fatal toxicity index: total no. of deaths 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)	None
Devins, 1995 Canada	Adverse events: [zopiclone] vs. [lorazepam] vs. [triazolan] vs. [nitrazepam or flurazepam] vs. [temazepam], no.(%) Daytime sleepiness: 5.6(4.71) vs. 6.1(3.91) vs. 6.6(4.28) vs. 6.4(4.3) vs. 5.5(4.7), p<0.001 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)	Rhone-Poulenc Rorer and Health Canada.

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.

Evidence Table 17: Observational Studies

Author Year Country	Results	Funding
Diav-Citrin, 1999 Canada	Pregnancy outcome, zopiclone vs. control: 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±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.

Evidence Table 17: Observational Studies

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. drop-outs(%) Gastrointestinal: 33(1.7)/ 25(1.3) Headache, head pressure: 21(1.1)/ 8(0.4) Pruritus, eczema, rash, rash, urticaria, skin papules: 10(0.5)/ 5(0.3) Fall, gait abnormal, coordination impaired, muscle weakness: 9(0.5)/ 4(0.2) Dyspnoea, tachypnoea, respiration regulation impaired: 7(0.4)/ 6(0.3) Palpitation, tachycardia, precordialgia: 6(0.3)/ 4(0.2) Malaise, weakness: 5(0.3)/ 5(0.3) Eating activity, bulimia: 4(0.2)/ 2(0.1) Dry mouth: 3(0.2)/ 0(0.0) Bone/head contusion, skin wound: 3(0.2)/ 1(0.1) Hypotension: 2(0.1)/ 1(0.1) Polyuria: 2(0.1)/ 2(0.1) Loss of appetite: 1(0.1)/ 0(0.0) Myocardial infarction: 1(0.1)/ 0(0.0) Nasal congestion: 1(0.1)/ 1(0.1) Retching: 1(0.1)/ 1(0.1) 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.

Evidence Table 17: Observational Studies

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.

Evidence Table 17: Observational Studies

Author Year Country	Results	Funding
Hajak, 1998 Germany	Tolerance: moderate-1.4%, poor- 0.6% Adverse events: no. patients /% of 268 AEs/ % of 16944 treated patients/ no. drop-outs Total: 268/ 100/ 1.5/ 118 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	Synthelabo Arzeimittel GmbH, Germany

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.

Evidence Table 17: Observational Studies

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

Evidence Table 17: Observational Studies

Author Year Country	Results	Funding
Jaffe, 2003 UK	Drug use pattern: zolpidem vs. zopiclone (n=297) % 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	Sepracor
Maarek, 1992 France	7(7.3%) of all patients withdrew because of adverse events: 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.

Evidence Table 17: Observational Studies

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 Belgium	Adverse events reported: All patients (n=1219)/ Patients <65 (n=720)/ 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.

Evidence Table 17: Observational Studies

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

Evidence Table 17: Observational Studies

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/100,000 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/100,000 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 death: 0 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/100,000 prescriptions: 0(0-35) Deaths/1,000,000 defined daily doses: 0(0-22.2) No. of primary agent death: 0 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/100,000 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.

Evidence Table 17: Observational Studies

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.

Evidence Table 17: Observational Studies

Author Year Country	Results	Funding
Scharf, 1994	Adverse events: zolpidem 10mg (n=33) vs. zolpidem 15mg (n=229), no.(%) 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 January 1, 1993

Evidence Table 17: Observational Studies

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

Evidence Table 17: Observational Studies

Author Year Country	Results	Funding
Schlich, 1991 France	Tolerance: no evidence 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 US	Hip Fracture: Adjusted OR (95% CI)- adjusted for age and gender zolpidem: 1.95 (1.09-3.51) benzodiazepine: 1.46 (1.21-1.76) antipsychotic medication: 1.61 (1.29-2.01) antidepression: 1.46 (1.22-1.75) other psychoactive medication: 1.23 (0.90-1.68) thiazide diuretic: 0.85 (0.71-1.02)	National Institute on drug Abuse and the National Institue on Aging.

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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