Drug Class Review
on
Newer Drugs for Insomnia

Final Report

EVIDENCE TABLES

July 2006

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

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

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

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

TABLE OF CONTENTS

Suggested citation for this report:
Carson S, Yen P, McDonagh MS. Drug Class Review on Newer Sedative Hypnotics. Final Report. 2006

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

Evidence Table 1. Head to head controlled trials: Efficacy

Allain, 2003 **Quality rating: Fair**

Design:

Study design: RCT DB Crossover **Run-in :** 0 days **Setting:** Single Center
Wash out : 0 days **Country:** France

Sample:	Number Screened/	Eligible/	Enrolled	Number Withdrawn/	Lost to follow-up/	Analyzed
	NR/	NR/	53	0/	0/	53

Inclusion 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 medical or psychiatric causes; patients who followed a continuous treatment with the 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.

Population: **Mean age:** 52 years **Ethnicity:** NR
Gender: 49% Female

Intervention:

Drug name	dosage	N=	Duration
Zolpidem	10 mg	53	1 day
Zaleplon	10 mg	53	1 day

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)

Efficacy:

Patient preference

Zolpidem	Zaleplon	
Percentage of patients preferring a drug: (%)		
62	38	P: 0.81

LSEQ

Zolpidem	Zaleplon	
Getting to sleep mean score (lower is better): Score (SD)		
35.9 (20.0)	45.3 (20.7)	P: 0.03
Quality of sleep mean score (lower is better): Score (SD)		
30.6 (18.6)	44.3 (23.2)	P: <0.0001
Ease of waking up mean score (lower is better): Score (SD)		
43.6 (22.8)	43.8 (21.8)	P: 0.27
Behavior following wakefulness mean score (lower is better): Score (SD)		
47.4 (23.2)	51.7 (17.2)	P: 0.31

Evidence Table 1. Head to head controlled trials: Efficacy

Allain, 2003 **Quality rating: Fair**

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

Zolpidem	Zaleplon	
Quality of sleep mean score: Score (SD)		
68.8 (21.8)	50.2 (28.1)	P: <0.0001
Consciousness mean score: Score (SD)		
73.9 (21.3)	73.1 (19.7)	P: 0.18
Dynamism mean score: Score (SD)		
62.6 (26.0)	61.8 (24.9)	P: 0.47
Drowsiness mean score: Score (SD)		
28 (27.4)	27.7 (26.5)	P: 0.53
Anxiety mean score: Score (SD)		
29.3 (30.1)	26.7 (27.7)	P: 0.34
Mood mean score: Score (SD)		
21.6 (25.5)	20.1 (21.6)	P: 0.92
Drowsiness duration (minutes): Number (SD)		
43 (43.8)	38 (21.2)	P: 0.83

Evidence Table 1. Head to head controlled trials: Efficacy

Ancoli-Israel, 1999 **Quality rating: Fair**

Design:

Study design: RCT DB Parallel **Run-in :** 7 days **Setting:** Multicenter
Wash out : 7-21 days **Country:** US

Sample:	Number Screened/	Eligible/	Enrolled	Number Withdrawn/	Lost to follow-up/	Analyzed
	1224/	551/	549	2/	NR/	549

Inclusion 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.

Population: **Mean age:** 72 years **Ethnicity:** 3.3% Black; 1.6% Hispanic; 1.3 Asian; 93.6% White
Gender: 58% Female

Intervention:

Drug name	dosage	N=	Duration	Primary outcome	Outcome:
Placebo	NA mg	107	2 week	☐	Sleep latency
Zaleplon	5 mg	166	2 week	☐	Total sleep time
Zaleplon	10 mg	165	2 week	☐	Number of awakenings
Zolpidem	5 mg	111	2 week	☐	Sleep quality

Efficacy:

Sleep latency

	Zaleplon 5 mg	Zaleplon 10 mg	Zolpidem 5 mg	Placebo
Median subjective sleep latency (minutes) at week 1: Number (p vs placebo)	NS)	<0.001)	<0.05)	
Median subjective sleep latency (minutes) at week 2: Number (p vs placebo)	39 (<0.001)	<0.001)	<0.01)	56

Total sleep time

	Zaleplon 5 mg	Zaleplon 10 mg	Zolpidem 5 mg	Placebo
Median subjective total sleep time at week 1: Number (p vs placebo)	NS)	345 (p<0.05)	360 (<0.001)	318 (NA)
Median subjective total sleep time at week 2: Number (p vs placebo)	NS)	NS)	360 (<0.01)	326 (NA)

Number of awakenings

	Zaleplon 5 mg	Zaleplon 10 mg	Zolpidem 5 mg	Placebo
Number of awakenings at week 1: Number (p vs placebo)	1.8 (NS)	1.8 (NS)	1.7 (<0.01)	2.0 (NA)
Number of awakenings at week 2: Number (p vs placebo)	1.9 (NS)	1.7 (NS)	1.6 (<0.05)	1.9 (NA)

Evidence Table 1. Head to head controlled trials: Efficacy

Ancoli-Israel, 1999 **Quality rating: Fair**

Sleep quality

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

Evidence Table 1. Head to head controlled trials: Efficacy

Elie, 1999 **Quality rating: Fair**

Design:

Study design: RCT DB Parallel **Run-in :** 7-21 days **Setting:** Multicenter
Wash out : 7 days **Country:** Canada and Europe

Sample:	Number Screened/	Eligible/	Enrolled	Number Withdrawn/	Lost to follow-up/	Analyzed
	NR/	NR/	615	41/	NR/	574

Inclusion criteria:

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

Exclusion criteria:

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

Population: **Mean age:** 42.8 years **Ethnicity:** 99% white, <1% black
Gender: 64% Female

Intervention:

Drug name	dosage	N=	Duration
Zaleplon	5 mg	113	4 week
Zaleplon	10 mg	112	4 week
Zaleplon	20 mg	116	4 week
Zolpidem	10 mg	115	4 week
Placebo	NA mg	118	4 week

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

Efficacy:

Sleep duration

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

Evidence Table 1. Head to head controlled trials: Efficacy

Elie, 1999 **Quality rating: Fair**

Number of awakenings

Zaleplon 5 mg	Zaleplon 10 mg	Zaleplon 20 mg	Zolpidem 10 mg	Baseline
Median number of awakenings at baseline: Number (p vs placebo)				
2 (NS)	2 (NS)	2 (NS)	2 (NS)	2
Median number of awakenings at week 1: Number (p vs placebo)				
2 (NS)	2 (NS)	2 (NS)	2 (NS)	2
Median number of awakenings at week 2: Number (p vs placebo)				
2 (NS)	2 (NS)	2 (NS)	2 (NS)	2
Median number of awakenings at week 3: Number (p vs placebo)				
2 (NS)	2 (NS)	1 (NS)	2 (NS)	2
Median number of awakenings at week 4: Number (p vs placebo)				
2 (NS)	2 (NS)	1 (NS)	2 (NS)	2

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

Zaleplon 5 mg	Zaleplon 10 mg	Zaleplon 20 mg	Zolpidem 10 mg	Baseline
Sleep quality mean score at baseline: Score (p vs placebo)				
4.6 (NS)	4.5 (NS)	4.5 (NS)	4.4 (NS)	4.5
Sleep quality mean score at week 1: Score (p vs placebo)				
4.1 (NS)	3.9 (p<0.05)	3.8 (p<0.001)	3.7 (p<0.001)	4.1
Sleep quality mean score at week 2: Score (p vs placebo)				
4.0 (NS)	3.9 (NS)	3.8 (NS)	3.6 (p<0.001)	3.9
Sleep quality mean score at week 3: Score (p vs placebo)				
3.8 (NS)	3.8 (NS)	3.6 (NS)	3.6 (p<0.05)	3.9
Sleep quality mean score at week 4: Score (p vs placebo)				
3.8 (NS)	3.7 (NS)	3.6 (NS)	3.4 (p<0.01)	3.8

Sleep latency

Zaleplon 5 mg	Zaleplon 10 mg	Zaleplon 20 mg	Zolpidem 10 mg	placebo
Time to sleep onset at week 1 (median, minutes): Number (p vs placebo)				
42 (0.005)	36 (<0.001)	33 (<0.001)	45 (0.47)	50
Median time to sleep onset at week 2 (median, minutes): Number (p vs placebo)				
35 (0.002)	32 (0.001)	31 (<0.001)	37 (0.006)	47
Median time to sleep onset at week 3 (median, minutes): Number (p vs placebo)				
31 (0.004)	30 (0.004)	28 (<0.001)	34 (0.043)	41
Median time to sleep onset at week 4 (median, minutes): Number (p vs placebo)				
31 (0.093)	28 (0.010)	27 (0.001)	36 (0.054)	36

Evidence Table 1. Head to head controlled trials: Efficacy

Fry, 2000 **Quality rating: Fair**

Design:

Study design: RCT DB Parallel **Run-in :** 7 days **Setting:** Multicenter
Wash out : 0 days **Country:** US

Sample:	Number Screened/	Eligible/	Enrolled	Number Withdrawn/	Lost to follow-up/	Analyzed
	NR/	830/	595	9/	NR/	586

Inclusion criteria:

Men or non-pregnant women, 18-65 years who met the criteria for primary insomnia or insomnia associated with mild 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 patients with a history or current manifestations of sleep apnea, restless legs syndrome, or a major psychiatric disorder, and patients whose raw score on either the Zung anxiety or depression self-rating scales was 50 or greater.

Population: **Mean age:** 42 years **Ethnicity:** 11% Black; 3% Hispanic; <1% Native American; 1.5% Asian; <1% Other; 84% White
Gender: 59% Female

Intervention:

Drug name	dosage	N=	Duration
Zaleplon	5 mg	118	4 week
Zaleplon	10 mg	119	4 week
Zaleplon	20 mg	116	4 week
Zolpidem	10 mg	115	4 week
Placebo	NA mg	118	4 week

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

Efficacy:

Sleep latency

Zaleplon 5 mg	Zaleplon 10 mg	Zaleplon 20 mg	Zolpidem 10 mg	placebo
Time to sleep onset at week 1 (median, minutes): Number (p vs zolpidem 10 mg)				
45.36 (0.764)	40.71 (0.490)	35.71 (0.003)	45.71	57.5 (0.008)
Time to sleep onset at week 2 (median, minutes): Number (p vs zolpidem 10 mg)				
43.57 (0.959)	36.43 (0.183)	31.67 (<0.001)	46.43	49.29 (0.502)
Time to sleep onset at week 3 (median, minutes): Number (p vs zolpidem 10 mg)				
40.71 (0.323)	35.71 (0.110)	30.00 (<0.001)	44.29	45.00 (0.236)
Time to sleep onset at week 4 (median, minutes): Number (p vs zolpidem 10 mg)				
45.63 (0.124)	35.00 (0.988)	30.00 (0.037)	34.29	47.14 (0.033)

Evidence Table 1. Head to head controlled trials: Efficacy

Fry, 2000 **Quality rating: Fair**

Total sleep time

Zaleplon 5 mg	Zaleplon 10 mg	Zaleplon 20 mg	Zolpidem 10 mg	placebo
Total sleep time at week 1 (median, minutes): Number (p vs placebo)				
360.0 (NS)	360.6 (NS)	368.6 (<0.05)	377.1 (<0.001)	346.8
Total sleep time at week 2 (median, minutes): Number (p vs placebo)				
366.4 (NS)	364.3 (NS)	368.6 (NS)	384.4 (<0.05)	360.0
Total sleep time at week 3 (median, minutes): Number (p vs placebo)				
361.4 (NS)	377.1 (NS)	386.8 (<0.05)	392.1 (<0.01)	366.4
Total sleep time at week 4 (median, minutes): Number (p vs placebo)				
360.0 (NS)	376.3 (NS)	377.5 (NS)	392.9 (<0.05)	364.3

Number of awakenings

Zaleplon 5 mg	Zaleplon 10 mg	Zaleplon 20 mg	Zolpidem 10 mg	placebo
Number of awakenings at week 1 (median): Number (p vs placebo)				
1.93 (NS)	1.69 (NS)	1.75 (NS)	1.59 (<0.01)	1.71
Number of awakenings at week 2 (median): Number (p vs placebo)				
1.67 (NS)	1.69 (NS)	1.50 (<0.001)	1.50 (<0.001)	2.00
Number of awakenings at week 3 (median): Number (p vs placebo)				
1.71 (NS)	1.71 (NS)	1.43 (<0.05)	1.71 (NS)	1.86
Number of awakenings at week 4 (median): Number (p vs placebo)				
1.71 (NS)	1.57 (NS)	1.60 (NS)	1.67 (NS)	1.71

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

Zaleplon 5 mg	Zaleplon 10 mg	Zaleplon 20 mg	Zolpidem 10 mg	placebo
Sleep quality at week 1 (median): Score (p vs placebo)				
3.43 (NS)	3.57 (NS)	3.43 (<0.01)	3.38 (<0.001)	3.73
Sleep quality at week 2 (median): Score (p vs placebo)				
3.43 (NS)	3.57 (NS)	3.43 (NS)	3.29 (<0.05)	3.57
Sleep quality at week 3 (median): Score (p vs placebo)				
3.43 (NS)	3.43 (NS)	3.29 (NS)	3.29 (<0.05)	3.57
Sleep quality at week 4 (median): Score (p vs placebo)				
3.38 (NS)	3.54 (NS)	3.29 (NS)	3.15 (<0.05)	3.43

Evidence Table 1. Head to head controlled trials: Efficacy

Sepracor Study #190-045 **Quality rating: Fair**

Design:

Study design: RCT DB Crossover **Run-in :** 3-7 days **Setting:** Multicenter

Wash out : 3-7 days **Country:** US

Sample:	Number Screened/	Eligible/	Enrolled	Number Withdrawn/	Lost to follow-up/	Analyzed
	NR/	NR/	64	NR/	NR/	64

Inclusion criteria:

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

Exclusion criteria:

NR

Population: **Mean age:** 40.6 years **Ethnicity:** 44 (67.7%) white, 13 (20.0%) black

Gender: 25% Female

Intervention:

Drug name	dosage		N=	Duration
Eszopiclone	1	mg	64	2 day
Eszopiclone	2	mg	64	2 day
Eszopiclone	2.5	mg	64	2 day
Eszopiclone	3	mg	64	2 day
Zolpidem	10	mg	64	2 day
Placebo	NA	mg	64	2 day

Primary outcome	Outcome:
☑	sleep latency
☐	sleep efficiency
☐	total sleep time
☐	wake after sleep onset
☐	wake time during sleep
☐	number of awakenings

Efficacy:

questionnaire

Eszopiclone 1mg	Eszopiclone 2mg	Eszopiclone 2.5mg	Eszopiclone 3mg	Zolpidem
morning sleepiness: Mean (p vs placebo)				
43.8 (0.1842)	44.6 (0.0670)	44.7 (0.0416)	45.4 (0.0307)	43.5 (0.1257)
morning sleepiness: Median (SD)				
42.3 (22)	42 (21.3)	45.3 (19.9)	44.5 (22.8)	43.3 (22)
daytime alertness: Mean (p vs placebo)				
52.5 (0.0968)	55.2 (0.0094)	50.7 (0.2731)	52.2 (0.0567)	55.8 (0.0012)
daytime alertness: Median (SD)				
57 (24.6)	56.5 (24.3)	50 (25.6)	56 (27.5)	27.7 (62.5)
daytime ability to function: Mean (p vs placebo)				
58.7 (0.0134)	59.5 (0.0046)	54.1 (0.4606)	56.6 (0.0424)	56.2 (0.0494)
daytime ability to function: Media (SD)				
58 (21.9)	59 (22.4)	51 (23.8)	60 (26.2)	53 (26.4)
quality of sleep: Median (p vs placebo)				
47 (<0.05)	58 (<0.0001)	55 (<0.05)	62 (<0.0001)	56 (<0.0001)
depth of sleep: Median (p vs placebo)				
46 (<0.05)	56.5 (<0.0001)	53 (<0.0001)	59.9 (<0.0001)	56.5 (<0.0001)

Evidence Table 1. Head to head controlled trials: Efficacy

Sepracor Study #190-045 **Quality rating: Fair**

polysomnography

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

Evidence Table 1. Head to head controlled trials: Efficacy

Staner, 2005 **Quality rating: Poor**

Design:

Study design: RCT DB Crossover **Run-in :** NR **Setting:** Single Center

Wash out : 7 days **Country:** France

Sample:	Number Screened/	Eligible/	Enrolled	Number Withdrawn/	Lost to follow-up/	Analyzed
	NR/	NR/	23	NR/	NR/	23

Inclusion criteria:

To be included in the study, pts needed to fulfil DSM-IV criteria (APA 1994) for primary insomnia (307.42) and have had, during the month preceding the screening visit, at least two of the three following symptoms: (1) sleep-onset latency greater than 30 min for at least four nights each week, (2) duration of wake after sleep onset of 60 min or more for at least four nights per week, and (3) daytime impairment due to the sleep disturbance.

Exclusion criteria:

Population: **Mean age:** 38.8 years **Ethnicity:** NR

Gender: 61% Female

Intervention:

Drug name	dosage	N=	Duration
Zolpidem	10 mg	23	8 day
Zopiclone	7.5 mg	23	8 day
Lormetazepam	1 mg	23	8 day
Placebo	NA mg	23	8 day

Primary outcome	Outcome:
☐	ease to get asleep
☐	sleep quality
☐	awakening from sleep
☐	behavior after waking
☐	driving abilities

Efficacy:

Subjective sleep

Zolpidem	Zopiclone	Lormetazepam	Placebo
ease to get asleep: Score (p vs placebo)			
59.4 (<0.01)	55.4 (<0.05)	55.0 (<0.05)	45.8 (NA)
sleep quality: Score (p vs placebo)			
68.8 (NS)	74.5 (<0.01)	70.0 (<0.05)	61.1 (Na)
awakening from sleep: Score (p vs placebo)			
66.1 (NS)	62.6 (NS)	70.6 (NS)	65.7 (NA)
behavior after waking: Score (p vs placebo)			
63.1 (NS)	62.5 (NS)	69.2 (NS)	63.7 (NA)

Driving abilities

Zolpidem	Zopiclone	Lormetazepam	Placebo
absolute speed deviation: Score (p vs placebo)			
123.3 (NS)	122.8 (NS)	125.1 (NS)	123.7 (MA)
speed limit deviation: Score (p vs placebo)			
-5.7 (NS)	-5.9 (NS)	-3.0 (<0.05)	-4.6 (NA)
Ideal route deviation: Score (p vs placebo)			
-0.17 (NS)	-0.31 (NS)	-0.15 (NS)	-0.18 (NA)
number of collisions: Score (p vs placebo)			
0.15 (NS)	0.66 (<0.01)	0.37 (NS)	0.21 (NA)

Evidence Table 1. Head to head controlled trials: Efficacy

Tsutsui, 2001 **Quality rating: Fair**

Design:

Study design: RCT DB Parallel **Run-in :** 0 days **Setting:** Multicenter
Wash out : 7 days **Country:** Japan

Sample:	Number Screened/	Eligible/	Enrolled	Number Withdrawn/	Lost to follow-up/	Analyzed
	NR/	NR/	479	77/	NR/	428

Inclusion criteria:

Patients with chronic primary insomnia (I.e., experiencing 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 diagnosed 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, breast feeding, participation in other clinical trials within the past 6 months, and inappropriateness for the study according to the investigator's judgment.

Population: **Mean age:** 42.2 years **Ethnicity:** NR
Gender: 58% Female

Intervention:

Drug name	dosage	N=	Duration
Zolpidem	10 mg	209	2 week
Zopiclone	7.5 mg	219	2 week

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

Efficacy:

Global improvement of sleep disorders

	Zolpidem	Zopiclone	
Patients rated by the investigator as "markedly improved": (%)	18.7	16.4	P: NS
Patients rated by the investigator as "moderately improved": (%)	49.3	45.2	P: NS
Patients rated by the investigator as "slightly improved": (%)	26.8	31.1	P: NS
Patients rated by the investigator as "unchanged": (%)	5.3	6.4	P: NS

Patient's impression of treatment efficacy

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

Evidence Table 2. Head to head controlled trials: Rebound

Ancoli-Israel, 1999 **Quality rating: Fair**

Design:

Study design: RCT DB Parallel **Run-in :** 7 days **Setting:** Multicenter

Wash out : 7-21 days **Country:** US

Sample:	Number Screened/	Eligible/	Enrolled	Number Withdrawn/	Lost to follow-up/	Analyzed
	1224/	551/	549	2/	NR/	549

Inclusion 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.

Population: **Mean age:** 72 years **Ethnicity:** 3.3% Black; 1.6% Hispanic; 1.3 Asian; 93.6% White

Gender: 58% Female

Intervention:

Drug name	dosage		N=	Duration
Placebo	NA	mg	107	2 week
Zaleplon	5	mg	166	2 week
Zaleplon	10	mg	165	2 week
Zolpidem	5	mg	111	2 week

Rebound:

rebound

	Zaleplon 5mg	Zaleplon 10mg	Zolpidem 5mg	Placebo
rebound insomnia: sleep latency on discontinuation day 1 (minutes, median): Number (p vs placebo)	30 (NS)	45 (NS)	60 (<0.01)	44 (NA)
rebound insomnia: sleep duration, total sleep time on discontinuation day 1 (minutes, median): Number (p vs placebo)	330 (NS)	315 (<0.05)	300 (<0.001)	317.50 (NA)
rebound insomnia: number of awakenings on discontinuation day 1 (median): Number (p vs placebo)	2 (NS)	2 (NS)	2 (NS)	2 (NA)

Evidence Table 2. Head to head controlled trials: Rebound

Elie, 1999 **Quality rating: Fair**

Design:

Study design: RCT DB Parallel **Run-in :** 7-21 days **Setting:** Multicenter

Wash out : 7 days **Country:** Canada and Europe

Sample:	Number Screened/	Eligible/	Enrolled	Number Withdrawn/	Lost to follow-up/	Analyzed
	NR/	NR/	615	41/	NR/	574

Inclusion criteria:

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

Exclusion criteria:

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

Population: **Mean age:** 42.8 years **Ethnicity:** 99% white <1% black

Gender: 64% Female

Intervention:

Drug name	dosage	N=	Duration
Zaleplon	5 mg	113	4 week
Zaleplon	10 mg	112	4 week
Zaleplon	20 mg	116	4 week
Zolpidem	10 mg	115	4 week
Placebo	NA mg	118	4 week

Rebound:

Rebound insomnia

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

Evidence Table 2. Head to head controlled trials: Rebound

Fry, 2000 **Quality rating: Fair**

Design:

Study design: RCT DB Parallel **Run-in :** 7 days **Setting:** Multicenter

Wash out : 0 days **Country:** US

Sample:	Number Screened/	Eligible/	Enrolled	Number Withdrawn/	Lost to follow-up/	Analyzed
	NR/	830/	595	9/	NR/	586

Inclusion criteria:

Men or non-pregnant women, 18-65 years who met the criteria for primary insomnia or insomnia associated with mild 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 patients with a history or current manifestations of sleep apnea, restless legs syndrome, or a major psychiatric disorder, and patients whose raw score on either the Zung anxiety or depression self-rating scales was 50 or greater.

Population: **Mean age:** 42 years **Ethnicity:** 11% Black; 3% Hispanic; <1% Native American; 1.5% Asian; <1% Other; 84% White

Gender: 59% Female

Intervention:

Drug name	dosage	N=	Duration
Zaleplon	5 mg	118	4 week
Zaleplon	10 mg	119	4 week
Zaleplon	20 mg	116	4 week
Zolpidem	10 mg	115	4 week
Placebo	NA mg	118	4 week

Rebound:

Rebound

	Zaleplon 5mg	Zaleplon 10mg	Zaleplon 20mg	Zolpidem 10mg
rebound : Sleep latency on discontinuation night 1 (minutes, median): Number (p vs placebo)	45 (NS)	40 (NS)	30 (NS)	60 (<0.01)
rebound : Number of awakenings on discontinuation night 1: Number (p vs placebo)	2 (NS)	2 (NS)	2 (NS)	2 (<0.05)
rebound : Sleep duration on discontinuation night 1 (median, minutes): Number (p vs placebo)	360 (NS)	360 (NS)	360 (NS)	330 (<0.001)

Evidence Table 2. Head to head controlled trials: Rebound

Tsutsui, 2001 **Quality rating: Fair**

Design:

Study design: RCT DB Parallel **Run-in :** 0 days **Setting:** Multicenter

Wash out : 7 days **Country:** Japan

Sample:	Number Screened/	Eligible/	Enrolled	Number Withdrawn/	Lost to follow-up/	Analyzed
	NR/	NR/	479	77/	NR/	428

Inclusion criteria:

Patients with chronic primary insomnia (I.e., experiencing 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 diagnosed 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, breast feeding, participation in other clinical trials within the past 6 months, and inappropriateness for the study according to the investigator's judgment.

Population: **Mean age:** 42.2 years **Ethnicity:** NR

Gender: 58% Female

Intervention:

Drug name	dosage	N=	Duration
Zolpidem	10 mg	209	2 week
Zopiclone	7.5 mg	219	2 week

Rebound:

Rebound insomnia: sleep latency

Zolpidem	Zopiclone	
rebound: patients with an aggravation of sleep onset latency by one grade or more at the end of followup: %		
4.5	15.4	P: 0.005

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

Allain, 2003 **Quality rating: Fair**

Design:

Study design: RCT DB Crossover **Run-in :** 0 days **Setting:** Single Center

Wash out : 0 days **Country:** France

Sample:	Number Screened/	Eligible/	Enrolled	Number Withdrawn/	Lost to follow-up/	Analyzed
	NR/	NR/	53	0/	0/	53

Inclusion 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 medical or psychiatric causes; patients who followed a continuous treatment with the 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.

Population: **Mean age:** 52 years **Ethnicity:** NR

Gender: 49% Female

Intervention:

Drug name	dosage	N=	Duration
Zolpidem	10 mg	53	1 day
Zaleplon	10 mg	53	1 day

Adverse Events:

Adverse events reported

	Zolpidem	Zaleplon	
Any adverse event: % (number)	5.7 (3/53)	7.5 (4/53)	P: NR

Total withdrawals: none

Withdrawals due to adverse events: none

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

Ancoli-Israel, 1999 **Quality rating: Fair**

Design:

Study design: RCT DB Parallel **Run-in :** 7 days **Setting:** Multicenter

Wash out : 7-21 days **Country:** US

Sample:	Number Screened/	Eligible/	Enrolled	Number Withdrawn/	Lost to follow-up/	Analyzed
	1224/	551/	549	2/	NR/	549

Inclusion 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.

Population: **Mean age:** 72 years **Ethnicity:** 3.3% Black; 1.6% Hispanic; 1.3 Asian; 93.6% White

Gender: 58% Female

Intervention:

Drug name	dosage	N=	Duration
Placebo	NA mg	107	2 week
Zaleplon	5 mg	166	2 week
Zaleplon	10 mg	165	2 week
Zolpidem	5 mg	111	2 week

Adverse Events:

Adverse events

Placebo	Zaleplon 5 mg	Zaleplon 10 mg	Zolpidem 5 mg	
Frequency of treatment-emergent adverse events: %				
56	56	59	63	P: NS
CNS adverse events: % (p vs placebo)				
14	NR	NR	25 (P<0.05)	
Somnolence: % (p vs placebo)				
2	4	NR	10 (p<0.05)	

Total withdrawals: NR

Withdrawals due to adverse events: NR

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

Elie, 1999 **Quality rating: Fair**

Design:

Study design: RCT DB Parallel **Run-in :** 7-21 days **Setting:** Multicenter

Wash out : 7 days **Country:** Canada and Europe

Sample:	Number Screened/	Eligible/	Enrolled	Number Withdrawn/	Lost to follow-up/	Analyzed
	NR/	NR/	615	41/	NR/	574

Inclusion criteria:

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

Exclusion criteria:

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

Population: **Mean age:** 42.8 years **Ethnicity:** 99% white, <1% black

Gender: 64% Female

Intervention:

Drug name	dosage	N=	Duration
Zaleplon	5 mg	113	4 week
Zaleplon	10 mg	112	4 week
Zaleplon	20 mg	116	4 week
Zolpidem	10 mg	115	4 week
Placebo	NA mg	118	4 week

Adverse Events:

Withdrawal effects

Zolpidem 10 mg	Zaleplon 10 mg
Incidence of 3 or more new withdrawal symptoms after discontinuation of treatment: NR (p vs placebo)	
NR (<0.05)	NR (NS)

Adverse events

Zaleplon 5 mg	Zaleplon 10 mg	Zaleplon 20 mg	Zolpidem 10 mg
Patients with treatment-emergent adverse events: % (N)			
59 (71)	73 (87)	61 (76)	64 (78)

Total withdrawals NR

Withdrawals due to adverse events

Zaleplon 5 mg	Zaleplon 10 mg	Zaleplon 20 mg	Zolpidem 10 mg
Withdrawals due to adverse events: % (N)			
2 (2)	6 (7)	2 (2)	6 (7)

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

Fry, 2000 **Quality rating: Fair**

Design:

Study design: RCT DB Parallel **Run-in :** 7 days **Setting:** Multicenter
Wash out : 0 days **Country:** US

Sample:	Number Screened/	Eligible/	Enrolled	Number Withdrawn/	Lost to follow-up/	Analyzed
	NR/	830/	595	9/	NR/	586

Inclusion criteria:

Men or non-pregnant women, 18-65 years who met the criteria for primary insomnia or insomnia associated with mild 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 patients with a history or current manifestations of sleep apnea, restless legs syndrome, or a major psychiatric disorder, and patients whose raw score on either the Zung anxiety or depression self-rating scales was 50 or greater.

Population: **Mean age:** 42 years **Ethnicity:** 11% Black; 3% Hispanic; <1% Native American; 1.5% Asian; <1% Other; 84% White
Gender: 59% Female

Intervention:

Drug name	dosage		N=	Duration
Zaleplon	5	mg	118	4 week
Zaleplon	10	mg	119	4 week
Zaleplon	20	mg	116	4 week
Zolpidem	10	mg	115	4 week
Placebo	NA	mg	118	4 week

Adverse Events:

Total withdrawals

	Zaleplon 5 mg	Zaleplon 10 mg	Zaleplon 20 mg	Zolpidem 10 mg
Total withdrawals: %	16.9	15.0	14.5	17.2

Withdrawals due to adverse effects

	Zaleplon 5mg	Zaleplon 10mg	Zaleplon 20mg	Zolpidem 10mg
Withdrawals due to adverse effects: %	3	4	9	6

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

Lemoine, 1995 **Quality rating: Fair**

Design:

Study design: RCT DB Parallel **Run-in :** 0 days **Setting:** Multicenter

Wash out : 0 days **Country:** France

Sample:	Number Screened/	Eligible/	Enrolled	Number Withdrawn/	Lost to follow-up/	Analyzed
	NR/	NR/	394	15/	2/	390

Inclusion 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.

Population: **Mean age:** years **Ethnicity:**

Gender: % Female

Intervention:

Drug name	dosage	N=	Duration
	mg	100	

Adverse Events:

Withdrawals: NR

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

Sepracor Study #190-045 **Quality rating: Fair**

Design:

Study design: RCT DB Crossover **Run-in :** 3-7 days **Setting:** Multicenter

Wash out : 3-7 days **Country:** US

Sample:	Number Screened/	Eligible/	Enrolled	Number Withdrawn/	Lost to follow-up/	Analyzed
	NR/	NR/	64	NR/	NR/	64

Inclusion criteria:

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

Exclusion criteria:

NR

Population: **Mean age:** 40.6 years **Ethnicity:** 44 (67.7%) white, 13 (20.0%) black

Gender: 25% Female

Intervention:

Drug name	dosage		N=	Duration
Eszopiclone	1	mg	64	2 day
Eszopiclone	2	mg	64	2 day
Eszopiclone	2.5	mg	64	2 day
Eszopiclone	3	mg	64	2 day
Zolpidem	10	mg	64	2 day
Placebo	NA	mg	64	2 day

Adverse Events:

adverse events

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

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

Staner, 2005 **Quality rating: Poor**

Design:

Study design: RCT DB Crossover **Run-in :** NR **Setting:** Single Center

Wash out : 7 days **Country:** France

Sample:	Number Screened/	Eligible/	Enrolled	Number Withdrawn/	Lost to follow-up/	Analyzed
	NR/	NR/	23	NR/	NR/	23

Inclusion criteria:

To be included in the study, pts needed to fulfil DSM-IV criteria (A 1994) for primary insomnia (307.42) and have had, during the month preceding the screening visit, at least two of the three following symptoms: (1) sleep-onset latency greater than 30 min for at least four nights each week, (2) duration of wake after sleep onset of 60 min or more for at least four nights per week, and (3) daytime impairment due to the sleep disturbance.

Exclusion criteria:

Population: **Mean age:** 38.8 years **Ethnicity:** NR

Gender: 61% Female

Intervention:

Drug name	dosage	N=	Duration
Zolpidem	10 mg	23	8 day
Zopiclone	7.5 mg	23	8 day
Lormetazepam	1 mg	23	8 day
Placebo	NA mg	23	8 day

Adverse Events:

Withdrawals

Zolpidem	Zopiclone	Lormetazepam	Placebo
Total Withdrawals: Number			
0	0	0	0
Withdrawals due to adverse events: Number			
0	0	0	0

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

Tsutsui, 2001 **Quality rating: Fair**

Design:

Study design: RCT DB Parallel **Run-in :** 0 days **Setting:** Multicenter
Wash out : 7 days **Country:** Japan

Sample:	Number Screened/	Eligible/	Enrolled	Number Withdrawn/	Lost to follow-up/	Analyzed
	NR/	NR/	479	77/	NR/	428

Inclusion criteria:

Patients with chronic primary insomnia (I.e., experiencing 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 diagnosed 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, breast feeding, participation in other clinical trials within the past 6 months, and inappropriateness for the study according to the investigator's judgment.

Population: **Mean age:** 42.2 years **Ethnicity:** NR
Gender: 58% Female

Intervention:

Drug name	dosage	N=	Duration
Zolpidem	10 mg	209	2 week
Zopiclone	7.5 mg	219	2 week

Adverse Events:

Total withdrawals

Zolpidem	Zopiclone	
Total withdrawals: %		
13.9	18.1	P: NS

Withdrawals due to adverse events

Zolpidem	Zopiclone	
Withdrawals due to adverse events: %		
6.1	8.1	P: NR

Adverse events

Zolpidem	Zopiclone	
Patients experiencing adverse events "related", "possibly related" or "probably related" to study medication: %		
31	45	P: 0.004

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

Anderson, 1987 **Quality rating: Fair**

Design:

Study design: RCT DB Parallel **Run-in :** 7 days **Setting:** Multicenter
Wash out : 7 days **Country:** UK

Sample:	Number Screened/	Eligible/	Enrolled	Number Withdrawn/	Lost to follow-up/	Analyzed
	NR/	NR/	119	5/	15/	99

Inclusion criteria:

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

Exclusion criteria:

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

Population: **Mean age:** NR years **Ethnicity:** NR
Gender: 0% Female

Intervention:

Drug name	dosage	N=	Duration
Zopiclone	7.5 mg	37	14 day
Nitrazepam	5 mg	NR	14 day
Placebo	NA mg	NR	14 day

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

Efficacy:

100-mm visual analogue scales

	Zopiclone	Nitrazepam	Placebo	
sleep quality at week 3 (in figure), higher score=better: Score (p vs placebo)				
	68 (<0.05)	66 (<0.05)	49 (NA)	
time to fall asleep at week 3 (in figure), higher score=better: Score (p vs placebo)				
	61 (<0.05)	63 (<0.05)	44 (NA)	
all sleep parameters: Score				
	NR	NR		P: NS

sleep questionnaire

	Zopiclone	Nitrazepam	Placebo	
early morning awakenings at week 3 (in figure), higher score=worse: proportion (p vs placebo)				
	0.38 (<0.05)	0.35 (<0.05)	0.78 (NA)	
physicians global assessment: Score				
	NR	NR		P: NS
wide-awake in the morning: Score				
	better	-		P: 0.02

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

Autret, 1987 **Quality rating: Poor**

Design:

Study design: CT DB Crossover **Run-in :** 4 days **Setting:** Single Center
Wash out : 3 days **Country:** France

Sample:	Number Screened/	Eligible/	Enrolled	Number Withdrawn/	Lost to follow-up/	Analyzed
	NR/	NR/	121	NR/	8/	113

Inclusion 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

Population: **Mean age:** 46.3 years **Ethnicity:** NR
Gender: 70% Female

Intervention:

Drug name	dosage	N=	Duration
Zopiclone	7.5 mg	121	7 day
Triazolam	0.5 mg	121	7 day

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

Efficacy:

Spiegel and Norris' visual analogue scale

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

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

Autret, 1987 **Quality rating: Poor**

rated by physicians

Zopiclone	Temazepam	
therapeutic efficacy- preferences of the patients: Number (%)		
62 (54.9)	26 (23)	P: <0.01

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

Begg, 1992 **Quality rating: Poor**

Design:

Study design: RCT SB Parallel **Run-in :** 2 days **Setting:** Single Center

Wash out : 2 days **Country:** NR

Sample:	Number Screened/	Eligible/	Enrolled	Number Withdrawn/	Lost to follow-up/	Analyzed
	NR/	NR/	88	4/	33/	51

Inclusion 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 ingestion within four hours of retiring or more than one glass (10 g) alcohol in the previous 24 hours were not permitted.

Population: **Mean age:** NR years **Ethnicity:** NR

Gender: 0% Female

Intervention:

Drug name	dosage	N=	Duration
Zopiclone	7.5 mg	28	11 day
Midazolam	15 mg	23	11 day

Efficacy:

LSEQ - pre vs. during intervention

Baseline	Midazolam	Zopiclone	
all 10 items (low=beneficial effect): Score (p vs zopiclone)			
High (<0.01)	Low (NS)	Low (NA)	P: p<0.01

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

Baseline	Midazolam	Zopiclone
5 of 10 items: Score (p vs zopiclone)		
Low (<0.01)	NR (NR)	High (NA)
all 10 items: Score (p vs zopiclone)		
Low (NR)	NR (NS)	High (NA)

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

Chaudoir, 1990 **Quality rating: Fair**

Design:

Study design: RCT DB Parallel **Run-in :** no days **Setting:** Multicenter
Wash out : 7 days **Country:** UK

Sample:	Number Screened/	Eligible/	Enrolled	Number Withdrawn/	Lost to follow-up/	Analyzed
	NR/	NR/	38	4/	NR/	38

Inclusion 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 alcohol 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.

Population: **Mean age:** 50.9 years **Ethnicity:** 100% Caucasian
Gender: 71% Female

Intervention:

Drug name	dosage	N=	Duration
Zopiclone	7.5 mg	19	1 week
Triazolam	0.25 mg	19	1 week

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

Efficacy:

LSEQ: Ease of getting to sleep

	Zopiclone	Triazolam	
Mean score at week 1: Score	57.91	65.18	P: NS (NR

LSEQ: Quality of sleep

	Zopiclone	Triazolam	
Mean score at week 1: Score	67.13	72.13	P: NS (NR

LSEQ Ease of awakening

	Zopiclone	Triazolam	
Mean score at week 1: Score	68.79	53.03	P: NS (NR

LSEQ Behavior following wakefulness

	Zopiclone	Triazolam	
Mean score at week 1: Score	58.35	54.49	P: NS (NR

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

Chaudoir, 1990 **Quality rating: Fair**

Global assessment of efficacy

Zopiclone	Triazolam	
Physicians' global assessment of efficacy: Score		
NR, high	NR, high	P: NS
Patients' global assessment of efficacy: Score		
NR, high	NR, high	P: NS

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

Drake (1), 2001 **Quality rating: Fair**

Design:

Study design: RCT DB Crossover **Run-in :** NR **Setting:** Multicenter

Wash out : 5-12 days **Country:** US

Sample:	Number Screened/	Eligible/	Enrolled	Number Withdrawn/	Lost to follow-up/	Analyzed
	NR/	NR/	47	0/	0/	47

Inclusion criteria:

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

Exclusion criteria:

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

Population: **Mean age:** 41.6 years **Ethnicity:** NR

Gender: 51% Female

Intervention:

Drug name	dosage	N=	Duration
Zaleplon	10 mg	47	2 day
Zaleplon	40 mg	47	2 day
Triazolam	0.25 mg	47	2 day
Placebo	NA mg	47	2 day

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

Efficacy:

polysomnography

	Zaleplon 10mg	Zaleplon 40mg	Triazolam 0.25mg
latency to persistent sleep: minutes (p vs triazolam)	22.5 (NS)	18.6 (<0.05)	27.5 (NA)
total sleep time: minutes (p vs triazolam)	386.3 (<0.05)	392.6 (<0.05)	407.8 (NA)

patient reports

	Zaleplon 10mg	Zaleplon 40mg	Triazolam 0.25mg
latency to sleep: minutes (p vs triazolam)	38.8 (NS)	29.3 (NS)	36.4 (NA)
total sleep time: minutes (p vs triazolam)	358.1 (NS)	375.5 (NS)	386.8 (NA)
sleep quality: Score (p vs triazolam)	2.5 (NS)	2.7 (NS)	2.7 (NA)
ease of falling asleep: Score (p vs triazolam)	65.4 (NS)	74.1 (NS)	67.3 (NA)

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

Drake (2), 2000 **Quality rating: Fair**

Design:

Study design: RCT DB Crossover **Run-in :** NR **Setting:** Multicenter

Wash out : 5-12 days **Country:** US

Sample:	Number Screened/	Eligible/	Enrolled	Number Withdrawn/	Lost to follow-up/	Analyzed
	NR/	NR/	36	0/	0/	36

Inclusion criteria:

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

Exclusion criteria:

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

Population: **Mean age:** 38.1 years **Ethnicity:** NR

Gender: 39% Female

Intervention:

Drug name	dosage	N=	Duration
Zaleplon	20 mg	36	2 day
Zaleplon	60 mg	36	2 day
Triazolam	0.25 mg	36	2 day
Placebo	NA mg	36	2 day

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

Efficacy:

polysomnography

	Zaleplon 20mg	Zaleplon 60mg	Triazolam 0.25mg
latency to persistent sleep: minutes (p vs triazolam)	30.5 (NS)	21.7 (<0.05)	27.6 (NA)
total sleep time: minutes (p vs triazolam)	391.3 (<0.05)	404.7 (<0.05)	422.8 (NA)

patient reports

	Zaleplon 20mg	Zaleplon 60mg	Triazolam 0.25mg
latency to sleep: minutes (p vs triazolam)	45.5 (NS)	36.6 (NS)	41.9 (NA)
total sleep time: minutes (p vs triazolam)	356 (<0.05)	376.3 (NS)	393.5 (NA)
sleep quality (higher score=better): Score (p vs triazolam)	2.3 (<0.05)	2.4 (NS)	2.7 (NA)
ease of falling asleep (lower score=better): Score (p vs triazolam)	58.8 (NS)	64.5 (NS)	61 (NA)

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

Elie, 1990b **Quality rating: Fair**

Design:

Study design: RCT DB Parallel **Run-in :** 7 days **Setting:** Single Center

Wash out : 3 days **Country:** Canada

Sample:	Number Screened/	Eligible/	Enrolled	Number Withdrawn/	Lost to follow-up/	Analyzed
	NR/	NR/	36	0/	0/	36

Inclusion criteria:

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

Exclusion criteria:

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

Population: **Mean age:** 37.6 years **Ethnicity:** NR

Gender: 67% Female

Intervention:

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

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

Efficacy:

post-sleep questionnaire

Zopiclone	Flurazepam	Placebo
rapidity of sleep onset at week 4 (higher score=better): Score (p vs placebo)		
11.6 (NS)	11.2 (NS)	10.5 (NA)
duration of sleep at week 4 (higher score=better): Score (p vs placebo)		
7.3 (NS)	7.1 (NS)	6.5 (NA)
nocturnal awakenings at week 4 (higher score=worse): Score (p vs placebo)		
3.5 (<0.01)	3.5 (<0.01)	5.5 (NA)

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

Fleming, 1990 **Quality rating: Fair**

Design:

Study design: RCT DB Parallel **Run-in :** 3 days **Setting:** Multicenter

Wash out : 4 days **Country:** Canada

Sample:	Number Screened/	Eligible/	Enrolled	Number Withdrawn/	Lost to follow-up/	Analyzed
	NR/	NR/	52	4/	0/	48

Inclusion criteria:

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

Exclusion criteria:

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

Population: **Mean age:** 45.5 years **Ethnicity:** NR

Gender: % Female

Intervention:

Drug name	dosage	N=	Duration
Zopiclone	7.5 mg	24	21 day
Triazolam	0.25 mg	24	21 day

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

Efficacy:

Hamilton Anxiety Scale

	Zopiclone	Triazolam	
total score: Score			
	NR	NR	P: NS

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

Fleming, 1995 **Quality rating: Fair**

Design:

Study design: RCT DB Parallel **Run-in :** 1 days **Setting:** Multicenter

Wash out : NR **Country:** Canada

Sample:	Number Screened/	Eligible/	Enrolled	Number Withdrawn/	Lost to follow-up/	Analyzed
	222/	144/	144	7/	1/	141

Inclusion criteria:

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

Exclusion criteria:

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

Population: **Mean age:** NR years **Ethnicity:** NR

Gender: 48% Female

Intervention:

Drug name	dosage	N=	Duration
Zolpidem	10 mg	35	3 day
Zolpidem	20 mg	35	3 day
Flurazepam	30 mg	36	3 day
Placebo	NA mg	35	3 day

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

Efficacy:

polysomnography

	Zolpidem 10mg	Zolpidem 20mg	Flurazepam
sleep latency: minutes (p vs flurazepam)	-14.7 (<0.05)	-28.4 (<0.05)	-11.8 (NA)
sleep efficiency: minutes (p vs placebo)	NR (NS)	NR (NS)	NR (NS)
wake time during sleep: minutes (p vs placebo)	NR (NS)	NR (NS)	NR (NS)

questionnaire

	Zolpidem 10mg	Zolpidem 20mg	Flurazepam	
sleep quality at day 3, (higher score=better): Score (p vs flurazepam)	2.4 (<0.05)	2.5 (<0.05)	1.9 (NA)	P: <0.05

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

Hajak, 1998, 1995, 1994 **Quality rating: Fair**

Design:

Study design: RCT DB Parallel **Run-in :** 7 days **Setting:** Multicenter
Wash out : 3 days **Country:** Germany

Sample:	Number Screened/	Eligible/	Enrolled	Number Withdrawn/	Lost to follow-up/	Analyzed
	NR/	NR/	1507	0/	0/	1507

Inclusion 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

Population: **Mean age:** 51 years **Ethnicity:** 99.3% Caucasian
0.9% Others
Gender: 62% Female

Intervention:

Drug name	dosage	N=	Duration
Zopiclone	7.5 mg	612	28 day
Triazolam	0.2 mg	307	28 day
Placebo	NA mg	298	28 day

Primary outcome	Outcome:
☑	daytime anxiety
☑	total sleep time
☑	number of nocturnal awakenings
☑	a feeling of being refreshed on awakening i
☑	daytime tiredness
☑	daytime anxiety

Efficacy:

Total response

Zopiclone	Triazolam	Placebo	
Improved sleep quality and daytime well-being: % (p vs placebo)			
37.4 (<=0.0017)	32.2 (NS)	26.8 (NA)	
Improved sleep quality and daytime well-being- treatment period: %			
42.3	36.3		P: 0.1133

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

Hayoun, 1989 **Quality rating: Fair**

Design:

Study design: RCT DB Parallel **Run-in :** NR **Setting:** Single Center

Wash out : NR **Country:** France

Sample:	Number Screened/	Eligible/	Enrolled	Number Withdrawn/	Lost to follow-up/	Analyzed
	NR/	NR/	136	9/	0/	127

Inclusion criteria:

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

Exclusion criteria:

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

Population: **Mean age:** 47.9 years **Ethnicity:** NR

Gender: 66% Female

Intervention:

Drug name	dosage	N=	Duration
Zopiclone	7.5 mg	67	7 day
Triazolam	0.25 mg	69	7 day

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

Efficacy:

Norris visual analogue auto-evaluation scale

	Zopiclone	Triazolam	
overall: Score			
	NR	NR	P: NS

global physicians' evaluation scale

	Zopiclone	Triazolam	
Efficacy- good or excellent: %			
	73	69	P: NS

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

Hayoun, 1989 **Quality rating: Fair**

self-evaluation questionnaire

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

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

Liu, 1997 **Quality rating: Poor**

Design:

Study design: RCT DB Crossover **Run-in :** 0 days **Setting:** Single Center
Wash out : 7 days **Country:** Taiwan

Sample:	Number Screened/	Eligible/	Enrolled	Number Withdrawn/	Lost to follow-up/	Analyzed
	NR/	NR/	15	0/	0/	15

Inclusion 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 arouse or drug abuse.

Population: **Mean age:** 40.1 years **Ethnicity:** NR
Gender: 73% Female

Intervention:

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

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

Efficacy:

Clinical Global Impression Scale (CGI)

Zopiclone	Triazolam	
therapeutic efficacy: Score (p vs baseline)		
NR (<0.005)	NR (<0.005)	P: NS

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

Liu, 1997 **Quality rating: Poor**

Spiegel's sleep questionnaire (SSQ)

Zopiclone	Triazolam	
therapeutic efficacy: Score (p vs baseline)		
NR (<0.005)	NR (<0.005)	P: NS
delay in falling asleep at day 14: Score (SD)		
3.94 (0.70)	4.13 (0.64)	P: NS
quality of sleep at day 14: Score (SD)		
4.33 (0.62)	3.47 (0.64)	P: <0.05
length of sleep at day 14: Score (SD)		
3.73 (0.70)	3.53 (0.74)	P: NS
night waking at day 14: Score (SD)		
4.20 (0.68)	3.33 (0.62)	P: <0.05
dream at day 14: Score (SD)		
3.93 (0.70)	3.73 (1.03)	P: NS
morning state at day 14: Score (SD)		
3.93 (0.80)	3.60 (0.91)	P: NS
global evaluation at day 14: Score (SD)		
4.13 (0.92)	3.93 (0.96)	P: NS

Leed's sleep evaluation questionnaire (LSEQ)

Zopiclone	Triazolam	
2 out of 10 items shows more effectiveness in zopiclone: quality of sleep: Score		
NR	NR	P: <0.05

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

Mamelak, 1987 **Quality rating: Fair**

Design:

Study design: RCT DB Parallel **Run-in :** 2 days **Setting:** Single Center

Wash out : 3 days **Country:** Canada

Sample:	Number Screened/	Eligible/	Enrolled	Number Withdrawn/	Lost to follow-up/	Analyzed
	NR/	NR/	30	0/	0/	30

Inclusion criteria:

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

Exclusion criteria:

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

Population: **Mean age:** 50 years **Ethnicity:** NR

Gender: 70% Female

Intervention:

Drug name	dosage	N=	Duration
Zopiclone	7.5 mg	10	12 day
Flurazepam	30 mg	10	12 day
Placebo	NA mg	10	12 day

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

Efficacy:

sleep questionnaire

Zopiclone	Flurazepam	Placebo
total sleep time at day 14, the end of treatment: minutes (p vs baseline)		
417.5 (<0.05)	410.5 (<0.05)	328.0 (<0.05)
sleep latency at day 14, the end of treatment: minutes (p vs baseline)		
28.8 (<0.05)	31.5 (<0.05)	69.8 (NS)
no of awakenings at day 14, the end of treatment: Number (p vs baseline)		
1.15 (<0.05)	1.55 (<0.05)	1.65 (<0.05)
duration of early wakefulness at day 14, the end of treatment: minutes (p vs baseline)		
37.0 (NS)	14.7 (NS)	43.1 (NS)
all sleep items at day 14, the end of treatment: minutes		
as below	as below	P: NS

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

Monti, 1994 **Quality rating: Fair**

Design:

Study design: RCT DB Parallel **Run-in :** 3 days **Setting:** Single Center

Wash out : 3 days **Country:** Uruguay

Sample:	Number Screened/	Eligible/	Enrolled	Number Withdrawn/	Lost to follow-up/	Analyzed
	NR/	NR/	24	1/	0/	24

Inclusion criteria:

All patients were suffering from at least 2 of the following sleep disturbances: time to fall asleep >30 minutes; total sleep time <6 hours,; total nocturnal wake time >20 minutes; number of nocturnal awakenings >3.

Exclusion criteria:

Pregnant women, women of child-bearing age with inadequate contraception, breastfeeding mothers, patients suffering from organic disease or severe psychiatric disorders, and patients in whom insufficient compliance was to be expected. Alcohol abuse or intake of hypnotics or anxiolytics and/or antidepressants in the seven days prior to the baseline period also led to exclusion.

Population: **Mean age:** 47.3 years **Ethnicity:** NR

Gender: 88% Female

Intervention:

Drug name	dosage	N=	Duration
Zolpidem	10 mg	8	27 day
Triazolam	0.5 mg	8	27 day
Placebo	NA mg	8	27 day

Primary outcome	Outcome:
☑	sleep latency
☑	total sleep time
☑	wake time after sleep onset
☑	total waketime
☑	number of awakenings

Efficacy:

polysomnogram

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

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

Nair, 1990 **Quality rating: Fair**

Design:

Study design: RCT DB Parallel **Run-in :** 1 days **Setting:** Single Center
Wash out : NR **Country:** Canada

Sample: Number Screened/ Eligible/ Enrolled Number Withdrawn/ Lost to follow-up/ Analyzed
NR/ NR/ 60

Inclusion criteria:

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

Exclusion criteria:

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

Population: **Mean age:** 46.9 years **Ethnicity:** NR
Gender: 47% Female

Intervention:

Drug name	dosage	N=	Duration
Zopiclone	3.75 mg	10	7 day
Zopiclone	7.5 mg	10	7 day
Zopiclone	11.2 mg	10	7 day
Zopiclone	15 mg	10	7 day
Flurazepam	30 mg	10	7 day
Placebo	NA mg	10	7 day

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

Efficacy:

sleep questionnaire

	Zopiclone	Flurazepam	
sleep induction time: Score			
	NR	NR	P: NS
quality of sleep: Score			
	NR	NR	P: NS
quality of morning awakening: Score			
	NR	NR	P: NS
hangover effects (except zopiclone 3.75mg): Score			
	NR	NR	P: NS
hangover effects (zopiclone 3.75mg only), (higher score=better): Score			
	7	5.5	P: <0.05

CGI

	Zopiclone	Flurazepam	
Severity of illness (except Zopiclone 3.75mg): Score			
	NR	NR	P: NS
Severity of illness (Zopiclone 3.75mg only): Score			
	NR	better	P: NR
global improvement, (Zopiclone at any dose): Score			
	NR	NR	P: NS

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

Ngen, 1990 **Quality rating: Fair**

Design:

Study design: RCT DB Parallel **Run-in :** 7 days **Setting:** Single Center
Wash out : NR **Country:** Malaysia

Sample:	Number Screened/	Eligible/	Enrolled	Number Withdrawn/	Lost to follow-up/	Analyzed
	NR/	NR/	60	16/	0/	44

Inclusion 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 drowsiness, (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

Population: **Mean age:** 38.4 years **Ethnicity:** NR
Gender: 52% Female

Intervention:

Drug name	dosage	N=	Duration
Zopiclone	7.5 mg	20	14 day
Temazepam	20 mg	20	14 day
Placebo	NA mg	20	14 day

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

Efficacy:

sleep diary

	Zopiclone	Temazepam
total duration of sleep at treatment week 1: hours (p vs baseline)	5.97 (<0.01)	5.90 (<0.05)
total duration of sleep at treatment week 2: hours (p vs baseline)	6.03 (<0.01)	5.62 (NS)
sleep latency at treatment week 1: Minutes (p vs baseline)	84 (<0.05)	25.9 (<0.05)
sleep latency at treatment week 2: Minutes (p vs baseline)	64.5 (<0.05)	26.1 (NS)
no. of awakenings at treatment week 1: Number (p vs baseline)	0.77 (NS)	1.2 (<0.05)
no. of awakenings at treatment week 2: Number (p vs baseline)	0.62 (<0.05)	1.28 (NS)

global assessment efficacy

	Zopiclone	Temazepam	
efficacy- good response: Number (p vs placebo)	10 (<0.02)	12 (<0.01)	P: NS

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

Ponciano, 1990 **Quality rating: Fair**

Design:

Study design: RCT DB Parallel **Run-in :** 7 days **Setting:** Single Center

Wash out : 7 days **Country:** Portugal

Sample:	Number Screened/	Eligible/	Enrolled	Number Withdrawn/	Lost to follow-up/	Analyzed
	NR/	NR/	26	2/	0/	24

Inclusion criteria:

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

Exclusion criteria:

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

Population: **Mean age:** 30 years **Ethnicity:** NR

Gender: 46% Female

Intervention:

Drug name	dosage	N=	Duration
Zopiclone	7.5 mg	8	21 day
Flurazepam	30 mg	8	21 day
Placebo	NA mg	10	21 day

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

Efficacy:

clinical interview

	Zopiclone	Flurazepam	Placebo	
sleep onset latency at day 21: minutes (p vs placebo)				
	30 (0.02)	28 (0.04)	60 (NA)	
sleep duration: minutes (p vs placebo)				
	393 (NS)	425 (0.05)	410 (NA)	

visual analogue rating scale

mood changes: Score				
	NR	NR	NR	P: NS

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

Quadens, 1983 **Quality rating: Poor**

Design:

Study design: RCT DB Crossover **Run-in :** 6 days **Setting:** Single Center

Wash out : 35 days **Country:** Belgium

Sample:	Number Screened/	Eligible/	Enrolled	Number Withdrawn/	Lost to follow-up/	Analyzed
	NR/	NR/	12	0/	0/	12

Inclusion criteria:

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

Exclusion criteria:

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

Population: **Mean age:** NR years **Ethnicity:** NR

Gender: 100% Female

Intervention:

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

Primary outcome	Outcome:
☐	no. of awakenings
☐	total sleep time
☐	sleep onset latency
☐	sleep efficient index

Efficacy:

sleep questionnaire

Zopiclone	Flurazepam	Placebo
no. of awakenings: Number (p vs placebo)		
3.2 (<0.05)	1.9 (<0.05)	6 (NA)
total sleep time: seconds (p vs placebo)		
24903 (<0.01)	25129 (<0.05)	23225 (NA)
sleep onset latency: seconds (p vs placebo)		
1117 (<0.05)	1174 (<0.1)	1452 (NA)
sleep efficiency index: Score (p vs placebo)		
91.4 (<0.01)	92.2 (<0.05)	83.6 (NA)
All sleep items comparing two treatment: Number		
as below	as below	P: NS

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

Rosenberg, 1994 **Quality rating: Poor**

Design:

Study design: RCT DB Parallel **Run-in :** NR **Setting:** Multicenter
Wash out : NR **Country:** Denmark

Sample:	Number Screened/	Eligible/	Enrolled	Number Withdrawn/	Lost to follow-up/	Analyzed
	NR/	NR/	178	5/	34/	139

Inclusion criteria:

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

Exclusion criteria:

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

Population: **Mean age:** 54 years **Ethnicity:** NR
Gender: 0% Female

Intervention:

Drug name	dosage	N=	Duration
Zolpidem	10 mg	71	14 day
Triazolam	0.25 mg	68	14 day

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

Efficacy:

reported by patients

	Zolpidem	Triazolam	
total sleep times: hours (range)	6.9 (4.8-9.1)	7.1 (5.0-8.4)	P: NS
No. of awakenings: Number (range)	1 (0-4)	1 (0-5)	P: NS

visual analogue scales

	Zolpidem	Triazolam	
sleep quality, bad-good: Score (Range)	69 (15-96)	69 (18-98)	P: NS
morning feeling, bad-good: Score (Range)	64 (8-94)	56 (9-98)	P: NS
daytime alertness. unalert-alert: Score (Range)	65 (6-92)	63 (26-92)	P: NS
subjective day feeling: Score (Range)	64 (6-93)	60 (9-92)	P: NS

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

Silvestri, 1996 **Quality rating: Fair**

Design:

Study design: RCT DB Parallel **Run-in :** 3 days **Setting:** Multicenter

Wash out : No days **Country:** Italy

Sample:	Number Screened/	Eligible/	Enrolled	Number Withdrawn/	Lost to follow-up/	Analyzed
	NR/	NR/	22	0/	2/	20

Inclusion 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 situational insomnia) or poor sleepers with subjective reporting of at least two out of these four complaints: time to fall asleep >30 minutes, total sleep duration <6 hours, total wake time >20 minutes, and/or number or awakenings >3. These subjective inclusion criteria had to be confirmed by the objective assessment through polysomnography.

Exclusion criteria:

Pregnant or lactating women; women of child-bearing age without 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 (myoclonus, 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 drug during 2 weeks preceding the study start as well as a previous with beta blockers or corticosteroids.

Population: **Mean age:** 33.6 years **Ethnicity:** NR

Gender: 55% Female

Intervention:

Drug name	dosage	N=	Duration
Zolpidem	10 mg	10	2 week
Triazolam	0.25 mg	12	2 week

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

Efficacy:

polysomnography

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

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

Silvestri, 1996 **Quality rating: Fair**

questionnaire

Zolpidem	Triazolam	
time to fall asleep- change from baseline- night 14: minutes (SD)		
-41.8 (32.51)	-19.9 (36.83)	P: NS
total sleep time- change from baseline- night 14: minutes (SD)		
66.9 (44.53)	81.4 (46.9)	P: NS
total wake time- change from baseline- night 14: minutes (SD)		
-12.1 (9.88)	-11.4 (8.53)	P: NS
no. of nocturnal awakenings- change from baseline- night 14: Number (SD)		
-1.4 (0.75)	-1.2 (1.63)	P: NS

visual analogue scale

Zolpidem	Triazolam	
sleep quality- change from baseline- night 14: Score (SD)		
-22.8 (17.90)	-31.8 (20.66)	P: NS
awakening quality- change from baseline- night 14: Score (SD)		
-16.3 (18.14)	-26.9 (23.32)	P: NS

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

Singh, 1990 **Quality rating: Fair**

Design:

Study design: RCT DB Parallel **Run-in :** 4 days **Setting:** Single Center
Wash out : NR **Country:** Canada

Sample:	Number Screened/	Eligible/	Enrolled	Number Withdrawn/	Lost to follow-up/	Analyzed
	NR/	61/	60	3/	0/	57

Inclusion 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, neurological disorders, established sleep apnoea and drug hypersensitivity. Patients with any significant medical condition interfering with sleep, those treatment which could modify drug kinetics were also excluded. Finally, pregnancy, lactation, and child-bearing potential not controlled by a recognized contraceptive programme precluded entry in the study.

Population: **Mean age:** 39.6 years **Ethnicity:** NR
Gender: 53% Female

Intervention:

Drug name	dosage	N=	Duration
Zopiclone	7.5 mg		24 day
Zopiclone	11.2 mg		24 day
Flurazepam	30 mg		24 day

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

Efficacy:

post-sleep questionnaire

	Zopiclone 7.5mg	Zopiclone 11.25mg	Flurazepam 30mg	
duration of sleep onset at week 4: Score (p vs placebo)				
	6.7 (<0.01)	6.9 (<0.01)	7.5 (<0.01)	
sleep soundness at week 4: Score (p vs placebo)				
	6.7 (<0.01)	6.6 (<0.01)	7.5 (<0.01)	
quality of sleep at week 4: Score (p vs placebo)				
	11.2 (<0.01)	11.0 (<0.01)	12.2 (<0.01)	
duration of sleep onset, sleep soundness, quality of sleep at week 4: Score (p vs flurazepam)				
	as above (NS)	as above (NS)	as above (NA)	

CGI

	Zopiclone 7.5mg	Zopiclone 11.25mg	Flurazepam 30mg	
therapeutic index (less score=worse) at week 4: Score				
	3.2	3	2.5	P: <0.05

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

Stip, 1999 **Quality rating: Fair**

Design:

Study design: RCT DB Parallel **Run-in :** 7 days **Setting:** Single Center

Wash out : 7 days **Country:** Canada

Sample:	Number Screened/	Eligible/	Enrolled	Number Withdrawn/	Lost to follow-up/	Analyzed
	NR/	NR/	60	2/	8/	50

Inclusion criteria:

Patients with either primary insomnia or insomnia associated with mild non-psychotic psychiatric disorders (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

Population: **Mean age:** 42.6 years **Ethnicity:** NR

Gender: % Female

Intervention:

Drug name	dosage	N=	Duration
Zopiclone	7.5 mg	19	21 day
Temazepam	30 mg	16	21 day
Placebo	NA mg	15	21 day

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

Efficacy:

Hamilton scale for anxiety

	Zopiclone	Temazepam	Placebo	
anxiety: Score				
	NR	NR	NR	P: NS

Self-rating questionnaire for sleep

	Zopiclone	Temazepam
sleep onset at treatment week 1: Score (p vs placebo)		
	NR (<0.01)	NR (<0.01)
sleep depth at treatment week 1: Score (p vs placebo)		
	NR (<0.01)	NR (<0.01)

auditory and visual span test

	Zopiclone	Nitrazepam	Placebo	
alertness over all 5 weeks: Score				
	multiple data	multiple data	multiple data	P: NS

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

Tamminen, 1987 **Quality rating: Poor**

Design:

Study design: RCT DB Parallel **Run-in :** 7 days **Setting:** Multicenter

Wash out : NR **Country:** Finland

Sample:	Number Screened/	Eligible/	Enrolled	Number Withdrawn/	Lost to follow-up/	Analyzed
	NR/	130/	94	0/	0/	94

Inclusion criteria:

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

Exclusion criteria:

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

Population: **Mean age:** 47 years **Ethnicity:** NR

Gender: 77% Female

Intervention:

Drug name	dosage	N=	Duration
Zopiclone	7.5 mg	52	42 day
Nitrazepam	5 mg	46	42 day

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

Efficacy:

diary

	Zopiclone	Nitrazepam	
sleep onset latency, mean score: Score	32.6	33.1	P: NS
quality of sleep, mean score: Score	34	30.2	

global evaluation

	Zopiclone	Nitrazepam	
efficacy (1=poor; 5=excellent): Score	3.2	3.1	P: NS

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

Tamminen, 1987 **Quality rating: Poor**

sleep questionnaire

Zopiclone	Nitrazepam	
latency of sleep onset >30 min: %		
38	44.4	P: 0.07
duration of sleep <6.5 hours: %		
37.5	37.7	P: NS
>2 night awakenings: %		
18.4	24.4	P: NS
time to fall asleep after a night awakenings >30 min: %		
14.6	22.2	P: NS
awakening at least 2 hours before expected time: %		
20.4	20	P: NS

Norris Mood Rating

Zopiclone	Nitrazepam	
overall: Score		
-	better	P: <0.05

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

van der Kleijn, 1989 **Quality rating: Fair**

Design:

Study design: RCT DB Crossover **Run-in :** 2 days **Setting:** NR

Wash out : 7 days **Country:** Nijmegen

Sample:	Number Screened/	Eligible/	Enrolled	Number Withdrawn/	Lost to follow-up/	Analyzed
	NR/	60/	55	2/	0/	53

Inclusion 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 during the day by unsatisfactory sleep

Exclusion criteria:

1. Patients taking a non-benzodiazepine hypnotic prior to the study 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 benzodiazepine 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

Population: **Mean age:** 53 years **Ethnicity:** NR

Gender: 71% Female

Intervention:

Drug name	dosage	N=	Duration
Zopiclone	7.5 mg	53	5 day
Temazepam	20 mg	53	5 day

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

Efficacy:

Questionnaire in the morning about sleep

Zopiclone	Temazepam	Placebo
Sleep quality - average score: Score (p vs zopiclone)		
3.9 (NA)	3.9 (0.096)	3.4 (<0.001)
Latency of sleep onset - average score: Score (p vs zopiclone)		
3.8 (NA)	3.7 (0.106)	3.1 (<0.01)
Status after awaking - average score: Score (p vs zopiclone)		
3.5 (NA)	3.4 (0.45)	3.2 (<0.01)

Preference

Zopiclone	Temazepam	Placebo	Z and T	
Sleep better: Number				
16	10	6	2	P: NR
Better status during the day: Number				
29	23	0	0	P: NR
8	3	5	2	P: NR

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

Voshaar, 2004 **Quality rating: Fair**

Design:

Study design: RCT DB Parallel **Run-in :** NR **Setting:** Multicenter
Wash out : 4 days **Country:** Netherlands

Sample:	Number Screened/	Eligible/	Enrolled	Number Withdrawn/	Lost to follow-up/	Analyzed
	NR/	NR/	221	9/	5/	159

Inclusion 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

Population: **Mean age:** 46.1 years **Ethnicity:** NR
Gender: 0% Female

Intervention:

Drug name	dosage	N=	Duration
Zolpidem	10 mg	74	28 day
Temazepam	20 mg	85	28 day

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

Efficacy:

Sleep/wake diaries

	Zolpidem	Temazepam	
total sleep time: minutes (SD)	413 (78)	386 (82)	P: NS
sleep onset latency: minutes (SD)	46 (33)	46 (34)	P: NS
wake time after sleep: minutes (SD)	40 (36)	39 (38)	P: NS
time in bed: minutes (SD)	530 (77)	508 (58)	P: NS
SWEL total score: Score (SD)	35.7 (7.7)	35.8 (9.2)	P: NS
STAI-DY-1 sum score: Score (SD)	41.6 (12)	39 (10.7)	P: NS

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

Walsh, 1998a **Quality rating: Fair**

Design:

Study design: RCT DB Parallel **Run-in :** 7 days **Setting:** Multicenter
Wash out : NR **Country:** US

Sample:	Number Screened/	Eligible/	Enrolled	Number Withdrawn/	Lost to follow-up/	Analyzed
	NR/	589/	306	28/	0/	278

Inclusion criteria:

Patients had to have a minimum of a 1-month history of disturbed sleep, characterized by a self-reported sleep latency (SSL) of at least 30 min, and a self-reported sleep duration (SSD) of 4-6 hours at least three nights per week.

Exclusion criteria:

Any significant medical or psychiatric disorder (as determined by clinical interview by a physician), a history suggestive of sleep apnea or periodic limb movement disorder, smoking of more than 10 cigarettes per day, weight varying by more than 25% from desirable weight based on the Metro-politan Life Insurance Table, pregnancy or risk of becoming pregnant, and lactation.

Population: **Mean age:** NR years **Ethnicity:** NR
Gender: 0% Female

Intervention:

Drug name	dosage	N=	Duration
Zolpidem	10 mg	102	14 day
Trazodone	50 mg	100	14 day
Placebo	NA mg	104	14 day

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

Efficacy:

morning questionnaire and 100mm visual analog scales

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

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

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

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

Walsh, 1998b **Quality rating: Good**

Design:

Study design: DB Parallel **Run-in :** 3 days **Setting:**

Wash out : 2 days **Country:** US

Sample:	Number Screened/	Eligible/	Enrolled	Number Withdrawn/	Lost to follow-up/	Analyzed
	673/	456/	132	7/	0/	125

Inclusion 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 Depression scales (scores >40) were excluded, as were those using CNS active medication. Individuals with prior exposure to zaleplon, or sensitivity to benzodiazepines or other psychotropic drugs, were excluded.

Population: **Mean age:** 40.3 years **Ethnicity:** NR

Gender: 58% Female

Intervention:

Drug name	dosage	N=	Duration	Primary outcome	Outcome:
Zaleplon	5 mg	34	14 day	☐	Total sleep time
Zaleplon	10 mg	33	33 day	☐	Sleep duration
Triazolam	0.25 mg	31	14 day	☐	No. of awakenings
Placebo	NA mg	34	14 day	☐	% of total sleep time spent in each sleep st

Efficacy:

Polysomnography

Zaleplon 5mg	Zaleplon 10mg	Triazolam 0.25mg	Placebo	
Total sleep time day 4-5 and day 16-17, minutes: during (after)				
413.6 (18)	402 (396.8)	NR (NR)	400 (411.3)	P: NS
Total sleep time- day 4-5: Minute (p vs triazolam)				
413.6 (<0.001)	402 (0.014)	431 (NA)	400 (<0.001)	
Total sleep time- day 16-17: Minute (p vs triazolam)				
418 (0.63)	396.8 (0.22)	420 (NA)	411.3 (0.35)	
Latency to persistent sleep- day 4-5: Minute (p vs placebo)				
17 (0.019)	19.25 (0.039)	18.5 (NR)	25.38 (NA)	
Latency to persistent sleep- day 16-17: Minute (p vs placebo)				
18 (0.019)	16.75 (0.039)	23.75 (NR)	20.5 (NA)	
No. of awakenings- day 4-5 and day 16-17: Number				
NR	NR	NR	NR	P: NS
% of total sleep time spent in each sleep stage- day 4-5 and day 16-17: Number				
NR	NR	NR	NR	P: NS
Latency to persistent sleep- day 16-17: Minute (p vs placebo)				
416.5 (NS)	400 (NS)	406.75 (NS)	408.5 (NA)	P: NS

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

Walsh, 1998b **Quality rating: Good**

Sleep questionnaire

Zaleplon 5mg	Zaleplon 10mg	Triazolam 0.25mg	Placebo
Subjective sleep latency- day 4-5, score: vs placebo (p vs placebo)			
shorter (0.003)	shorter (0.056)	shorter (0.015)	NR (NA)
Subjective sleep latency- day 6-14, score: vs placebo (p vs placebo)			
shorter (0.67)	shorter (0.03)	shorter (0.168)	NR (NA)
Subjective total sleep time- day 1-2, score: vs placebo (p vs placebo)			
NR (NS)	NR (NS)	NR (<0.001)	NR (NA)
Subjective total sleep time- day 3-19, score: vs placebo (p vs placebo)			
NR (NS)	NR (NS)	NR (NS)	NR (NA)
Subjective no. of awakenings- day 6-14, number: vs placebo (p vs placebo)			
NR (NS)	NR (NS)	NR (0.046)	NR (NA)
Subjective sleep latency after discontinuation night, score: vs placebo (p vs placebo)			
NR (NS)	NR (NS)	longer (0.036)	NR (NA)
Subjective total sleep time after discontinuation night, score: vs placebo (p vs placebo)			
NR (NS)	NR (NS)	shorter (0.022)	NR (NA)

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

Walsh, 2000 **Quality rating: Poor**

Design:

Study design: RCT DB Crossover **Run-in :** NR **Setting:** Single Center

Wash out : NR **Country:** US

Sample:	Number Screened/	Eligible/	Enrolled	Number Withdrawn/	Lost to follow-up/	Analyzed
	73/	39/	30	2/	0/	22

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

Population: **Mean age:** 42 years **Ethnicity:** NR

Gender: % Female

Intervention:

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

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

Efficacy:

Sleep latency testing

Zaleplon	Flurazepam	Placebo
5 hours after drug administration, score: Mean (p vs zaleplon)		
16.6 (NA)	6.8 (<0.001)	14.4 (0.07)
6.5 hours after drug administration, score: Mean (p vs zaleplon)		
14.7 (NA)	5.6 (<0.001)	12.1 (0.111)

sleep questionnaire

Zaleplon	Flurazepam	Placebo	
time to sleep (minute): Median			
27.5	22.5	27.5	P: NR
number of minutes sleep: Median (p vs placebo)			
195 (NR)	206.3 (<0.01)	180 (NA)	P: NR

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

Ware, 1997 **Quality rating: Fair**

Design:

Study design: RCT DB Parallel **Run-in :** 2 days **Setting:** Multicenter
Wash out : 3 days **Country:** US

Sample:	Number Screened/	Eligible/	Enrolled	Number Withdrawn/	Lost to follow-up/	Analyzed
	358/	NR/	110	11/	NR/	99

Inclusion criteria:

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

Exclusion criteria:

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

Population: **Mean age:** NR years **Ethnicity:** 69% white
Gender: 58% Female

Intervention:

Drug name	dosage	N=	Duration
Zolpidem	10 mg	37	28 day
Triazolam	0.5 mg	30	28 day
Placebo	NA mg	35	28 day

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

Efficacy:

polysomnography

Zolpidem	Triazolam	Placebo
latency to persistent sleep- night 27 & 28: minutes (p vs baseline)		
-7 (NS)	0 (NS)	-15 (<0.05)
sleep efficiency- night 27 & 28: % (p vs baseline)		
1 (NS)	3 (<0.05)	5 (<0.05)
no. of awakenings- night 27 & 28: Number (p vs baseline)		
1 (NS)	-2 (<0.05)	-1 (NS)
waking time during sleep: minutes (p vs baseline)		
0 (NS)	-20 (<0.05)	2 (NS)

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

Wheatley, 1985 **Quality rating: Fair**

Design:

Study design: RCT DB Crossover **Run-in :** 3 days **Setting:** NR
Wash out : NR **Country:** NR

Sample:	Number Screened/	Eligible/	Enrolled	Number Withdrawn/	Lost to follow-up/	Analyzed
	NR/	NR/	36	2/	0/	36

Inclusion 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

Population: **Mean age:** 53.2 years **Ethnicity:** NR
Gender: 61% Female

Intervention:

Drug name	dosage	N=	Duration
Zopiclone	7.5 mg	36	7 day
Temazepam	20 mg	36	7 day

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

Efficacy:

Patient Questionnaires

	Zopiclone	Temazepam	Placebo	
Sleep latency: Minutes (p vs baseline)	30.8 (<0.01)	NR (NR)	29.1 (<0.01)	
No. time waking: Number (p vs baseline)	0.75 (<0.01)	0.66 (<0.01)		
Quality of sleep (0-4): Score (p vs baseline)	0.93 (<0.01)	0.87 (<0.01)		
Duration of sleep: Hours (p vs baseline)	6.6 (<0.01)	6.6 (<0.01)		
Dreaming (0-4): Score (p vs baseline)	0.46 (NS)	0.46 (NS)		
State on waking (0-3): Score (p vs baseline)	0.39 (NS)	0.38 (NS)		
At work (0-3): Score (p vs baseline)	0.51 (<0.05)	0.54 (NS)		
With others (0-3): Score (p vs baseline)	0.63 (NS)	0.67 (NS)		
Driving (0-3): Score (p vs baseline)	0.35 (NS)	0.57 (NS)		
All measures: Score	as above	as above		P: NS

Evidence Table 5. Active controlled trials (Adult): Rebound

Elie, 1990b **Quality rating: Fair**

Design:

Study design: RCT DB Parallel **Run-in :** 7 days **Setting:** Single Center

Wash out : 3 days **Country:** Canada

Sample:	Number Screened/	Eligible/	Enrolled	Number Withdrawn/	Lost to follow-up/	Analyzed
	NR/	NR/	36	0/	0/	36

Inclusion criteria:

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

Exclusion criteria:

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

Population: **Mean age:** 37.6 years **Ethnicity:** NR

Gender: 67% Female

Intervention:

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

Rebound:

post-sleep questionnaire

	Zopiclone	Flurazepam	Placebo
rebound: rapidity of sleep onset at day 29 (higher score=better): Score (p vs baseline)	5.8 (NS)	7.3 (NS)	10 (<0.01)
rebound: duration of sleep at day 29 (higher score=better): Score (p vs baseline)	3.6 (NS)	6.2 (NS)	7.3 (<0.05)
rebound: nocturnal awakenings at day 29 (higher score=worse): Score (p vs baseline)	5.0 (NS)	6.3 (NS)	8.0 (NS)

Evidence Table 5. Active controlled trials (Adult): Rebound

Fleming, 1990 **Quality rating: Fair**

Design:

Study design: RCT DB Parallel **Run-in :** 3 days **Setting:** Multicenter
Wash out : 4 days **Country:** Canada

Sample:	Number Screened/	Eligible/	Enrolled	Number Withdrawn/	Lost to follow-up/	Analyzed
	NR/	NR/	52	4/	0/	48

Inclusion criteria:

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

Exclusion criteria:

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

Population: **Mean age:** 45.5 years **Ethnicity:** NR
Gender: % Female

Intervention:

Drug name	dosage	N=	Duration
Zopiclone	7.5 mg	24	21 day
Triazolam	0.25 mg	24	21 day

Rebound:

post-sleep questionnaire

	Zopiclone	Triazolam	
rebound: sleep duration at the last withdrawal day: Score	4.3	5.9	P: <0.05
rebound: sleep induction at the last withdrawal day: Score	4.7	6.1	P: NS
rebound: sleep soundness at the last withdrawal day: Score	7.4	8.6	P: NS

withdrawal effects

	Zopiclone	Triazolam	
rebound insomnia: %	73	71	P: NS
rebound: sleep induction, duration and soundness at the first withdrawal nights: Score (p vs baseline)	NR (NS)	NR, worse (<0.05)	
rebound: sleep soundness: Score	NR	NR, better	P: <0.05
rebound: withdrawal symptoms: Number	3	2	P: NS

Evidence Table 5. Active controlled trials (Adult): Rebound

Hajak, 1998, 1995, 1994 **Quality rating: Fair**

Design:

Study design: RCT DB Parallel **Run-in :** 7 days **Setting:** Multicenter
Wash out : 3 days **Country:** Germany

Sample:	Number Screened/	Eligible/	Enrolled	Number Withdrawn/	Lost to follow-up/	Analyzed
	NR/	NR/	1507	0/	0/	1507

Inclusion 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

Population: **Mean age:** 51 years **Ethnicity:** 99.3% Caucasian, 0.9% Others
Gender: 62% Female

Intervention:

Drug name	dosage	N=	Duration
Zopiclone	7.5 mg	612	28 day
Triazolam	0.2 mg	307	28 day
Placebo	NA mg	298	28 day

Rebound:

Total response

Zopiclone	Triazolam	Placebo	
rebound: Improved sleep quality and daytime well-being: %			
27.0	18.8		P: 0.00126

Rebound rates in treatment responders

Zopiclone	Triazolam	Placebo	
Rebound: overall rebound: % (p vs zopiclone)			
46.07 (NA)	46.63 (NS)	48.56 (<=0.01)	
Rebound: Responder: % (p vs zopiclone)			
9.05 (NA)	7.70 (<=0.01)	4.92 (<=0.01)	P: <=0.01
Rebound: Nonresponder: % (SD)			
36.02 (1.35)	38.93 (1.45)		P: <=0.01

Rebound rates for items of sleep quality

Zopiclone	Triazolam	
Rebound: sleep quality - 1 item: (%) (SD)		
14.33 (1.11)	16.32 (1.33)	P: <0.001
Rebound: sleep quality - 2 items: (%) (SD)		
6.76 (0.83)	8.27 (1.04)	P: <=0.05
Rebound: sleep quality - 3 items: (%) (SD)		
2.36 (0.47)	2.39 (0.85)	P: NS

Evidence Table 5. Active controlled trials (Adult): Rebound

Hajak, 1998, 1995, 1994 **Quality rating: Fair**

Rebound rates for items of daytime well-being

Zopiclone	Triazolam	
Rebound: daytime well-being - 1 item: % (SD)		
18.52 (1.44)	19.04 (2.00)	P: NS
Rebound: daytime well-being - 2 items: % (SD)		
14.09 (1.11)	13.10 (1.91)	P: NS
Rebound: daytime well-being - 3 items: % (SD)		
7.89 (0.82)	7.73 (1.33)	P: NS

Evidence Table 5. Active controlled trials (Adult): Rebound

Liu, 1997 **Quality rating: Poor**

Design:

Study design: RCT DB Crossover **Run-in :** 0 days **Setting:** Single Center
Wash out : 7 days **Country:** Taiwan

Sample:	Number Screened/	Eligible/	Enrolled	Number Withdrawn/	Lost to follow-up/	Analyzed
	NR/	NR/	15	0/	0/	15

Inclusion 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 arouse or drug abuse.

Population: **Mean age:** 40.1 years **Ethnicity:** NR
Gender: 73% Female

Intervention:

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

Rebound:

Spiegel's sleep questionnaire (SSQ)

	Zopiclone	Triazolam	
rebound: 6 out of 7 items shows less rebound effects in Zopiclone: Score			
	multiple data	multiple data	P: <0.05

Leed's sleep evaluation questionnaire (LSEQ)

	Zopiclone	Triazolam	
rebound: 9/10 items show more withdrawal sleep disturbance of triazolam: Score			
	NR	NR	P: <0.05

Evidence Table 5. Active controlled trials (Adult): Rebound

Mamelak, 1987 **Quality rating: Fair**

Design:

Study design: RCT DB Parallel **Run-in :** 2 days **Setting:** Single Center

Wash out : 3 days **Country:** Canada

Sample:	Number Screened/	Eligible/	Enrolled	Number Withdrawn/	Lost to follow-up/	Analyzed
	NR/	NR/	30	0/	0/	30

Inclusion criteria:

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

Exclusion criteria:

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

Population: **Mean age:** 50 years **Ethnicity:** NR

Gender: 70% Female

Intervention:

Drug name	dosage	N=	Duration
Zopiclone	7.5 mg	10	12 day
Flurazepam	30 mg	10	12 day
Placebo	NA mg	10	12 day

Rebound:

sleep questionnaire

	Zopiclone	Flurazepam	Placebo	
rebound: total sleep time at day 15: minutes (p vs baseline)	313.5 (NS)	356.5 (NS)	313.5 (NS)	
rebound: sleep latency at day 15: minutes (p vs baseline)	105.0 (<0.05)	39.7 (<0.05)	75.5 (NS)	
rebound: no. of awakenings at day 15: minutes (p vs baseline)	2.10 (NS)	2.05 (<0.05)	1.70 (<0.05)	
rebound: duration of early wakefulness at day 15: minutes (p vs baseline)	41.5 (NS)	27.8 (NS)	46.9 (NS)	
rebound: sleep latency at day 15: minutes	105.0	39.7		P: <0.05
rebound: no. of awakenings at day 17: Number	3.15	2.05		P: <0.05
other rebounds: number	multiple data	multiple data		P: NS

Evidence Table 5. Active controlled trials (Adult): Rebound

Monti, 1994 **Quality rating: Fair**

Design:

Study design: RCT DB Parallel **Run-in :** 3 days **Setting:** Single Center

Wash out : 3 days **Country:** Uruguay

Sample:	Number Screened/	Eligible/	Enrolled	Number Withdrawn/	Lost to follow-up/	Analyzed
	NR/	NR/	24	1/	0/	24

Inclusion criteria:

All patients were suffering from at least 2 of the following sleep disturbances: time to fall asleep >30 minutes; total sleep time <6 hours,; total nocturnal wake time >20 minutes; number of nocturnal awakenings >3.

Exclusion criteria:

Pregnant women, women of child-bearing age with inadequate contraception, breastfeeding mothers, patients suffering from organic disease or severe psychiatric disorders, and patients in whom insufficient compliance was to be expected. Alcohol abuse or intake of hypnotics or anxiolytics and/or antidepressants in the seven days prior to the baseline period also led to exclusion.

Population: **Mean age:** 47.3 years **Ethnicity:** NR

Gender: 88% Female

Intervention:

Drug name	dosage	N=	Duration
Zolpidem	10 mg	8	27 day
Triazolam	0.5 mg	8	27 day
Placebo	NA mg	8	27 day

Rebound:

polysomnogram

	Zolpidem	Triazolam	Placebo	
rebound: mean wake time (change from baseline): minutes (SD)	-80 (118)	43 (47.4)		P: NR
rebound: mean total sleep time (change from baseline): minutes (SD)	80 (118.5)	-40 (52.2)		P: NR
rebound: mean number of sleep cycles (change from baseline): Number (SD)	1.3 (1.5)	-0.7 (0.7)		P: NR

sleep questionnaire

	Zolpidem	Triazolam	Placebo	
rebound: increased number of awakenings- day 32: Number (%)	3 (37.5)	5 (62.5)	0 (0)	P: NR
rebound: decreased sleep duration- day 32: Number (%)	3 (37.5)	6 (75)	2 (25)	P: NR
rebound: increased time to fall sleep- day 32: Number (%)	3 (37.5)	8 (100)	0 (0)	P: NR

Evidence Table 5. Active controlled trials (Adult): Rebound

Quadens, 1983 **Quality rating: Poor**

Design:

Study design: RCT DB Crossover **Run-in :** 6 days **Setting:** Single Center

Wash out : 35 days **Country:** Belgium

Sample:	Number Screened/	Eligible/	Enrolled	Number Withdrawn/	Lost to follow-up/	Analyzed
	NR/	NR/	12	0/	0/	12

Inclusion criteria:

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

Exclusion criteria:

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

Population: **Mean age:** NR years **Ethnicity:** NR

Gender: 100% Female

Intervention:

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

Rebound:

sleep questionnaire

	Zopiclone	Flurazepam	Placebo
rebound: no. of awakenings: Number (p vs treatment data)	5.5 (<0.05)	6.1 (<0.01)	
rebound: total sleep time: seconds (p vs treatment data)	23490 (<0.05)	23184 (<0.05)	
rebound: sleep onset latency: seconds (p vs treatment data)	1255 (NS)	1042 (NR)	
rebound: sleep efficiency index: Score (p vs treatment data)	86.9 (NS)	84.9 (<0.01)	

Evidence Table 5. Active controlled trials (Adult): Rebound

Silvestri, 1996 **Quality rating: Fair**

Design:

Study design: RCT DB Parallel **Run-in :** 3 days **Setting:** Multicenter

Wash out : No days **Country:** Italy

Sample:	Number Screened/	Eligible/	Enrolled	Number Withdrawn/	Lost to follow-up/	Analyzed
	NR/	NR/	22	0/	2/	20

Inclusion 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 situational insomnia) or poor sleepers with subjective reporting of at least two out of these four complaints: time to fall asleep >30 minutes, total sleep duration <6 hours, total wake time >20 minutes, and/or number or awakenings >3. These subjective inclusion criteria had to be confirmed by the objective assessment through polysomnography.

Exclusion criteria:

Pregnant or lactating women; women of child-bearing age without 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 (myoclonus, 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 drug during 2 weeks preceding the study start as well as a previous with beta blockers or corticosteroids.

Population: **Mean age:** 33.6 years **Ethnicity:** NR

Gender: 55% Female

Intervention:

Drug name	dosage	N=	Duration
Zolpidem	10 mg	10	2 week
Triazolam	0.25 mg	12	2 week

Rebound:

polysomnography

	Zolpidem	Triazolam	
rebound: sleep onset latency- change from baseline- night 15: minutes (SD)	-11.6 (31.98)	7.1 (30.73)	P: NS
rebound: total sleep time- change from baseline- night 15: minutes (SD)	43.8 (62.54)	-34.5 (50.24)	P: <0.01
rebound: sleep efficiency- change from baseline- night 15: % (SD)	9.9 (13.63)	-6.3 (8.55)	P: <0.01
rebound: wake time after sleep onset- change from baseline- night 15: minutes (SD)	9.9-37.5 (49.01)	17.3 (31.89)	P: <0.01
rebound: no. of awakenings- change from baseline- night 15: Number (SD)	-1.9 (7.16)	-1.2 (4.67)	P: NS

Evidence Table 5. Active controlled trials (Adult): Rebound

Silvestri, 1996 **Quality rating: Fair**

questionnaire

Zolpidem	Triazolam	
rebound: time to fall asleep- change from baseline- night 15: minutes (SD)		
-20.8 (28.23)	8.6 (31.65)	P: <0.05
rebound: total sleep time- change from baseline- night 15: minutes (SD)		
51.9 (45.4)	-35.6 (127.92)	P: <0.01
rebound: total wake time- change from baseline- night 15: minutes (SD)		
-2.2 (12.96)	13.2 (38.71)	P: NS
rebound: no. nocturnal awakenings- change from baseline- night 15: Number (SD)		
-0.3 (2.32)	0.4 (0.86)	P: NS

visual analogue scale

Zolpidem	Triazolam	
rebound: sleep quality- change from baseline- night 15: Score (SD)		
-12.9 (20.59)	0.8 (22.88)	P: NS
rebound: awakening quality- change from baseline- night 15: Score (SD)		
-12.9 (21.34)	-1.5 (21.36)	P: NS

Evidence Table 5. Active controlled trials (Adult): Rebound

Stip, 1999 **Quality rating: Fair**

Design:

Study design: RCT DB Parallel **Run-in :** 7 days **Setting:** Single Center

Wash out : 7 days **Country:** Canada

Sample:	Number Screened/	Eligible/	Enrolled	Number Withdrawn/	Lost to follow-up/	Analyzed
	NR/	NR/	60	2/	8/	50

Inclusion criteria:

Patients with either primary insomnia or insomnia associated with mild non-psychotic psychiatric disorders (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

Population: **Mean age:** 42.6 years **Ethnicity:** NR

Gender: % Female

Intervention:

Drug name	dosage	N=	Duration
Zopiclone	7.5 mg	19	21 day
Temazepam	30 mg	16	21 day
Placebo	NA mg	15	21 day

Rebound:

Self-rating questionnaire for sleep

	Zopiclone	Temazepam
sleep onset after discontinuation - rebound: Score (p vs placebo)	NR (NS)	NR, worse (<0.05)
sleep depth after discontinuation- rebound: Score (p vs placebo)	NR, worse (<0.01)	NR, worse (<0.01)

Evidence Table 5. Active controlled trials (Adult): Rebound

Voshaar, 2004 **Quality rating: Fair**

Design:

Study design: RCT DB Parallel **Run-in :** NR **Setting:** Multicenter

Wash out : 4 days **Country:** Netherlands

Sample:	Number Screened/	Eligible/	Enrolled	Number Withdrawn/	Lost to follow-up/	Analyzed
	NR/	NR/	221	9/	5/	159

Inclusion 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

Population: **Mean age:** 46.1 years **Ethnicity:** NR

Gender: 0% Female

Intervention:

Drug name	dosage	N=	Duration
Zolpidem	10 mg	74	28 day
Temazepam	20 mg	85	28 day

Rebound:

rebound

	Zolpidem	Temazepam	
rebound- mean total sleep time: minutes (SD)	370 (84)	352 (89)	P: NS
rebound- prevalence rebound insomnia (TST): %	27	25.9	P: NS
rebound- sleep onset latency: minutes (SD)	60 (51)	73 (53)	P: NS
rebound- prevalence rebound insomnia (SOL): %	53.4	58.3	P: NS

Evidence Table 5. Active controlled trials (Adult): Rebound

Ware, 1997 **Quality rating: Fair**

Design:

Study design: RCT DB Parallel **Run-in :** 2 days **Setting:** Multicenter

Wash out : 3 days **Country:** US

Sample:	Number Screened/	Eligible/	Enrolled	Number Withdrawn/	Lost to follow-up/	Analyzed
	358/	NR/	110	11/	NR/	99

Inclusion criteria:

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

Exclusion criteria:

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

Population: **Mean age:** NR years **Ethnicity:** 69% white

Gender: 58% Female

Intervention:

Drug name	dosage	N=	Duration
Zolpidem	10 mg	37	28 day
Triazolam	0.5 mg	30	28 day
Placebo	NA mg	35	28 day

Rebound:

polysomnography

	Zolpidem	Triazolam	Placebo
rebound: latency to persistent sleep- discontinuation night 1: minutes (p vs baseline)	6 (NS)	47 (<0.05)	-11 (NS)
rebound: latency to persistent sleep- discontinuation night 1: minutes (p vs baseline)	6 (NS)	47 (<0.05)	-11 (NS)
rebound: sleep efficiency- discontinuation night 1: % (p vs baseline)	-3 (NS)	-15 (<0.05)	5 (<0.05)

Evidence Table 5. Active controlled trials (Adult): Rebound

Ware, 1997 **Quality rating: Fair**

rebound questionnaire- discontinuation night 1

Zolpidem	Triazolam	Placebo
rebound: sleep latency: minutes (p vs baseline)		
14 (NS)	72 (<0.05)	-16
rebound: total sleep time: minutes (p vs baseline)		
-4 (NS)	-63 (<0.05)	49 (0.05)
rebound: no. of awakenings: Number (p vs baseline)		
1 (NS)	1 (NS)	-1 (<0.05)
rebound: wake min during sleep: minutes (p vs baseline)		
-4 (NS)	48 (<0.05)	-29 (<0.05)
rebound: quality latency: Score (p vs baseline)		
0.3 (NS)	0.8 (<0.05)	-0.4 (<0.05)
rebound: morning sleepiness: Score (p vs baseline)		
-5 (NS)	-6.7 (NS)	4.5 (NS)
rebound: ability to concentrate: Score (p vs baseline)		
0.2 (<0.05)	0.1 (NS)	-0.1 (NS)
rebound: over all rebounds: %		
15	43	11

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

Anderson, 1987 **Quality rating: Fair**

Design:

Study design: RCT DB Parallel **Run-in :** 7 days **Setting:** Multicenter

Wash out : 7 days **Country:** UK

Sample:	Number Screened/	Eligible/	Enrolled	Number Withdrawn/	Lost to follow-up/	Analyzed
	NR/	NR/	119	5/	15/	99

Inclusion criteria:

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

Exclusion criteria:

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

Population: **Mean age:** NR years **Ethnicity:** NR

Gender: 0% Female

Intervention:

Drug name	dosage		N=	Duration
Zopiclone	7.5	mg	37	14 day
Nitrazepam	5	mg	NR	14 day
Placebo	NA	mg	NR	14 day

Adverse Events:

bitter tastes

Zopiclone	Nitrazepam
no, of patients: Number (%)	
9 (24.3)	NR (NR)

withdrawals

Zopiclone	Nitrazepam	Placebo
total withdrawals: Number		
2	1	2
withdrawals due to AEs: Number		
1	1	1

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

Autret, 1987 **Quality rating: Poor**

Design:

Study design: CT DB Crossover **Run-in :** 4 days **Setting:** Single Center

Wash out : 3 days **Country:** France

Sample:	Number Screened/	Eligible/	Enrolled	Number Withdrawn/	Lost to follow-up/	Analyzed
	NR/	NR/	121	NR/	8/	113

Inclusion 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

Population: **Mean age:** 46.3 years **Ethnicity:** NR

Gender: 70% Female

Intervention:

Drug name	dosage	N=	Duration
Zopiclone	7.5 mg	121	7 day
Triazolam	0.5 mg	121	7 day

Adverse Events:

Guelfi side-effects check list

	Zopiclone	Triazolam	
12 out of 18 items shows favour Zopiclone: Score			
	NR, better	NR	P: <0.05

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

Begg, 1992 **Quality rating: Poor**

Design:

Study design: RCT SB Parallel **Run-in :** 2 days **Setting:** Single Center

Wash out : 2 days **Country:** NR

Sample:	Number Screened/	Eligible/	Enrolled	Number Withdrawn/	Lost to follow-up/	Analyzed
	NR/	NR/	88	4/	33/	51

Inclusion 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 ingestion within four hours of retiring or more than one glass (10 g) alcohol in the previous 24 hours were not permitted.

Population: **Mean age:** NR years **Ethnicity:** NR

Gender: 0% Female

Intervention:

Drug name	dosage	N=	Duration
Zopiclone	7.5 mg	28	11 day
Midazolam	15 mg	23	11 day

Adverse Events:

Averse Events

	Zopiclone	Midazolam	
No. of patients experiencing AEs (overall): Number (%)	15 (31)	16 (40)	P: >0.05
No. of AEs: Number	21	28	P: >0.05
No. of patients experiencing AEs - Daytime tiredness: Number (%)	6 (12.5)	6 (15)	P: NR
No. of patients experiencing AEs - Taste disturbance: Number (%)	6 (12.5)	0 (0)	P: NR
No. of patients experiencing AEs - Dry mouth: Number (%)	2 (4.2)	3 (7.5)	P: NR
No. of patients experiencing AEs - Indigestion/nausea/vomiting: Number (%)	1 (2.1)	5 (12.5)	P: NR
No. of patients experiencing AEs - Clumsiness: Number (%)	0 (0)	4 (10)	P: NR
No. of patients experiencing AEs - Disturbed sleep pattern: Number (%)	2 (4.2)	5 (12.5)	P: NR
No. of patients experiencing AEs - Others: Number	4 (8.3)	5 (12.5)	P: NR

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

Chaudoir, 1990 **Quality rating: Fair**

Design:

Study design: RCT DB Parallel **Run-in :** no days **Setting:** Multicenter
Wash out : 7 days **Country:** UK

Sample:	Number Screened/	Eligible/	Enrolled	Number Withdrawn/	Lost to follow-up/	Analyzed
	NR/	NR/	38	4/	NR/	38

Inclusion 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 alcohol 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.

Population: **Mean age:** 50.9 years **Ethnicity:** 100% Caucasian
Gender: 71% Female

Intervention:

Drug name	dosage	N=	Duration
Zopiclone	7.5 mg	19	1 week
Triazolam	0.25 mg	19	1 week

Adverse Events:

reported by patients

	Zopiclone	Triazolam
no. of patients experiencing severe side effect: Number	1	1

withdrawals

	Zopiclone	Triazolam
total withdrawals: Number	1	3
withdrawals due to AEs: Number	0	1

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

Drake (1), 2001 **Quality rating: Fair**

Design:

Study design: RCT DB Crossover **Run-in :** NR **Setting:** Multicenter

Wash out : 5-12 days **Country:** US

Sample:	Number Screened/	Eligible/	Enrolled	Number Withdrawn/	Lost to follow-up/	Analyzed
	NR/	NR/	47	0/	0/	47

Inclusion criteria:

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

Exclusion criteria:

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

Population: **Mean age:** 41.6 years **Ethnicity:** NR

Gender: 51% Female

Intervention:

Drug name	dosage	N=	Duration
Zaleplon	10 mg	47	2 day
Zaleplon	40 mg	47	2 day
Triazolam	0.25 mg	47	2 day
Placebo	NA mg	47	2 day

Adverse Events:

reported by patients

	Zaleplon 10mg	Zaleplon 40mg	Triazolam
no. of patients experiencing AEs: Number	9	18	8

withdrawals

	Zaleplon 10mg	Zaleplon 40mg	Triazolam 0.25mg
total withdrawals: Number	NR	NR	NR
withdrawals due to AEs: Number	0	0	0

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

Drake (2), 2000 **Quality rating: Fair**

Design:

Study design: RCT DB Crossover **Run-in :** NR **Setting:** Multicenter

Wash out : 5-12 days **Country:** US

Sample:	Number Screened/	Eligible/	Enrolled	Number Withdrawn/	Lost to follow-up/	Analyzed
	NR/	NR/	36	0/	0/	36

Inclusion criteria:

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

Exclusion criteria:

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

Population: **Mean age:** 38.1 years **Ethnicity:** NR

Gender: 39% Female

Intervention:

Drug name	dosage	N=	Duration
Zaleplon	20 mg	36	2 day
Zaleplon	60 mg	36	2 day
Triazolam	0.25 mg	36	2 day
Placebo	NA mg	36	2 day

Adverse Events:

reported by patients

	Zaleplon 20mg	Zaleplon 60mg	Triazolam
no. of patients experiencing AEs: Number	6	17	8

withdrawals

	Zaleplon 20mg	Zaleplon 60mg	Triazolam
total withdrawals: Number	NR	NR	NR
withdrawals due to AEs: Number	0	1	0

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

Elie, 1990b **Quality rating: Fair**

Design:

Study design: RCT DB Parallel **Run-in :** 7 days **Setting:** Single Center

Wash out : 3 days **Country:** Canada

Sample:	Number Screened/	Eligible/	Enrolled	Number Withdrawn/	Lost to follow-up/	Analyzed
	NR/	NR/	36	0/	0/	36

Inclusion criteria:

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

Exclusion criteria:

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

Population: **Mean age:** 37.6 years **Ethnicity:** NR

Gender: 67% Female

Intervention:

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

Adverse Events:

overall AEs

Zopiclone	Flurazepam	Placebo	
somnolence: Number			
11	12	9	P: NS
loss of concentration: Number			
8	8	5	P: NS
excitation: Number			
10	2	7	P: NS
tension: Number			
10	7	9	P: NS
taste disturbance: Number			
10	10	4	P: <0.05
try mouth: Number			
11	7	8	P: NS
thick tongue: Number			
9	7	5	P: NS

withdrawals

Zopiclone	Flurazepam	Placebo
total withdrawals: Number		
0	0	0
withdrawals due to AEs: Number		
0	0	0

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

Fleming, 1990 **Quality rating: Fair**

Design:

Study design: RCT DB Parallel **Run-in :** 3 days **Setting:** Multicenter

Wash out : 4 days **Country:** Canada

Sample:	Number Screened/	Eligible/	Enrolled	Number Withdrawn/	Lost to follow-up/	Analyzed
	NR/	NR/	52	4/	0/	48

Inclusion criteria:

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

Exclusion criteria:

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

Population: **Mean age:** 45.5 years **Ethnicity:** NR

Gender: % Female

Intervention:

Drug name	dosage	N=	Duration
Zopiclone	7.5 mg	24	21 day
Triazolam	0.25 mg	24	21 day

Adverse Events:

overall report

	Zopiclone	Triazolam	
no. of patients experiencing adverse effect: Number (%)			
	18 (75)	20 (83.3)	P: NS
taste perception: Number			
	NR	NR, more	P: <0.05
moderate or severe adverse effects reported: %			
	18	42	P: <0.05

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

Fleming, 1995 **Quality rating: Fair**

Design:

Study design: RCT DB Parallel **Run-in :** 1 days **Setting:** Multicenter

Wash out : NR **Country:** Canada

Sample:	Number Screened/	Eligible/	Enrolled	Number Withdrawn/	Lost to follow-up/	Analyzed
	222/	144/	144	7/	1/	141

Inclusion criteria:

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

Exclusion criteria:

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

Population: **Mean age:** NR years **Ethnicity:** NR

Gender: 48% Female

Intervention:

Drug name	dosage	N=	Duration
Zolpidem	10 mg	35	3 day
Zolpidem	20 mg	35	3 day
Flurazepam	30 mg	36	3 day
Placebo	NA mg	35	3 day

Adverse Events:

reported by patients

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

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

Fleming, 1995 **Quality rating: Fair**

dysarthria: Number (%)				
1 (2.9)	3 (8.6)	0 (0)	0 (0)	
headache: Number (%)				
4 (11.4)	2 (5.7)	4 (11.1)	3 (8.6)	
light-headedness: Number (%)				
0 (0)	0 (0)	2 (5.6)	0 (0)	
vomiting: Number (%)				
0 (0)	3 (8.6)	0 (0)	0 (0)	
myalgia: Number (%)				
0 (0)	2 (5.7)	1 (2.8)	1 (2.9)	
amnesia: Number (%)				
1 (2.9)	3 (8.6)	1 (2.8)	0 (0)	
nervousness: Number (%)				
1 (2.9)	2 (5.7)	1 (2.8)	0 (0)	
pharyngitis: Number (%)				
2 (5.7)	0 (0)	1 (2.8)	0 (0)	
abnormal vision: Number (%)				
0 (0)	2 (5.7)	0 (0)	0 (0)	

withdrawals

Zolpidem 10mg	Zolpidem 20mg	Flurazepam 30mg	Placebo	
total withdrawals: Number				
0	7	1	0	P: NR
withdrawal due to AEs: Number				
0	6	0	0	P: NR

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

Hajak, 1998, 1995, 1994 **Quality rating: Fair**

Design:

Study design: RCT DB Parallel **Run-in :** 7 days **Setting:** Multicenter

Wash out : 3 days **Country:** Germany

Sample:	Number Screened/	Eligible/	Enrolled	Number Withdrawn/	Lost to follow-up/	Analyzed
	NR/	NR/	1507	0/	0/	1507

Inclusion 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

Population: **Mean age:** 51 years **Ethnicity:** 99.3% Caucasian, 0.9% Others

Gender: 62% Female

Intervention:

Drug name	dosage	N=	Duration
Zopiclone	7.5 mg	612	28 day
Triazolam	0.2 mg	307	28 day
Placebo	NA mg	298	28 day

Adverse Events:

withdrawals

Zopiclone	Triazolam	Placebo
total withdrawals: Number		
190	187	193
withdrawals due to AEs: Number		
26	11	25

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

Hayoun, 1989 **Quality rating: Fair**

Design:

Study design: RCT DB Parallel **Run-in :** NR **Setting:** Single Center

Wash out : NR **Country:** France

Sample:	Number Screened/	Eligible/	Enrolled	Number Withdrawn/	Lost to follow-up/	Analyzed
	NR/	NR/	136	9/	0/	127

Inclusion criteria:

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

Exclusion criteria:

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

Population: **Mean age:** 47.9 years **Ethnicity:** NR

Gender: 66% Female

Intervention:

Drug name	dosage	N=	Duration
Zopiclone	7.5 mg	67	7 day
Triazolam	0.25 mg	69	7 day

Adverse Events:

reported by patients

	Zopiclone	Zaleplon	
overall side effects: %			
	NR	NR	P: NS

global evaluation

	Zopiclone	Triazolam	
safety- good or excellent: %			
	86	82	P: NS

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

Liu, 1997 **Quality rating: Poor**

Design:

Study design: RCT DB Crossover **Run-in :** 0 days **Setting:** Single Center

Wash out : 7 days **Country:** Taiwan

Sample:	Number Screened/	Eligible/	Enrolled	Number Withdrawn/	Lost to follow-up/	Analyzed
	NR/	NR/	15	0/	0/	15

Inclusion 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 arouse or drug abuse.

Population: **Mean age:** 40.1 years **Ethnicity:** NR

Gender: 73% Female

Intervention:

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

Adverse Events:

rebound insomnia

	Zopiclone	Triazolam
rebound insomnia- mild degree of poor sleep: Number (%)	6 (40)	1 (6.7)
rebound insomnia- moderate degree of poor sleep: Number (%)	6 (40)	4 (26.7)
rebound insomnia- severe degree of poor sleep: Number (%)	3 (20)	10 (67.6)

overall AEs

	Zopiclone	Triazolam
number of events reported: Number	10	16

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

Mamelak, 1987 **Quality rating: Fair**

Design:

Study design: RCT DB Parallel **Run-in :** 2 days **Setting:** Single Center

Wash out : 3 days **Country:** Canada

Sample:	Number Screened/	Eligible/	Enrolled	Number Withdrawn/	Lost to follow-up/	Analyzed
	NR/	NR/	30	0/	0/	30

Inclusion criteria:

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

Exclusion criteria:

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

Population: **Mean age:** 50 years **Ethnicity:** NR

Gender: 70% Female

Intervention:

Drug name	dosage	N=	Duration
Zopiclone	7.5 mg	10	12 day
Flurazepam	30 mg	10	12 day
Placebo	NA mg	10	12 day

Adverse Events:

withdrawals

	Zopiclone	Flurazepam	Placebo
total withdrawals: Number	0	1	0
withdrawals due to AEs: Number	0	1	0

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

Monti, 1994 **Quality rating: Fair**

Design:

Study design: RCT DB Parallel **Run-in :** 3 days **Setting:** Single Center

Wash out : 3 days **Country:** Uruguay

Sample:	Number Screened/	Eligible/	Enrolled	Number Withdrawn/	Lost to follow-up/	Analyzed
	NR/	NR/	24	1/	0/	24

Inclusion criteria:

All patients were suffering from at least 2 of the following sleep disturbances: time to fall asleep >30 minutes; total sleep time <6 hours,; total nocturnal wake time >20 minutes; number of nocturnal awakenings >3.

Exclusion criteria:

Pregnant women, women of child-bearing age with inadequate contraception, breastfeeding mothers, patients suffering from organic disease or severe psychiatric disorders, and patients in whom insufficient compliance was to be expected. Alcohol abuse or intake of hypnotics or anxiolytics and/or antidepressants in the seven days prior to the baseline period also led to exclusion.

Population: **Mean age:** 47.3 years **Ethnicity:** NR

Gender: 88% Female

Intervention:

Drug name	dosage	N=	Duration
Zolpidem	10 mg	8	27 day
Triazolam	0.5 mg	8	27 day
Placebo	NA mg	8	27 day

Adverse Events:

overall AEs

	Zolpidem	Triazolam	Placebo	
Emergent adverse events: Number				
	13	16	10	P: NR

AEs with significant differences

	Zolpidem	Triazolam	
rebound: pessimist: Number			
	lower	higher	P: 0.096
rebound: tense: Number			
	lower	higher	P: 0.061
rebound: pessimist: Number			
	lower	higher	P: 0.040

withdrawals

	Zolpidem	Triazolam	Placebo
total withdrawals: Number			
	0	1	0
withdrawals due to AEs: Number			
	0	1	0

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

Nair, 1990 **Quality rating: Fair**

Design:

Study design: RCT DB Parallel **Run-in :** 1 days **Setting:** Single Center

Wash out : NR **Country:** Canada

Sample:	Number Screened/	Eligible/	Enrolled	Number Withdrawn/	Lost to follow-up/	Analyzed
	NR/	NR/	60			

Inclusion criteria:

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

Exclusion criteria:

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

Population: **Mean age:** 46.9 years **Ethnicity:** NR

Gender: 47% Female

Intervention:

Drug name	dosage	N=	Duration
Zopiclone	3.75 mg	10	7 day
Zopiclone	7.5 mg	10	7 day
Zopiclone	11.2 mg	10	7 day
Zopiclone	15 mg	10	7 day
Flurazepam	30 mg	10	7 day
Placebo	NA mg	10	7 day

Adverse Events:

overall AEs

	Zopiclone 3.75mg	Zopiclone 7.5mg	Zopiclone 11.25mg	Zopiclone 15mg	Flurazepam
Total number of patients, (Placebo=5): Number	4	4	11	5	10

withdrawals

	Zopiclone 3.75mg	Zopiclone 7.5mg	Zopiclone 11.5mg	Zopiclone 15mg	Flurazepam
total withdrawals, (placebo = 2): Number	0	0	1	1	0
withdrawals due to AEs, (placebo = 1): Number	0	0	1	1	0

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

Ngen, 1990 **Quality rating: Fair**

Design:

Study design: RCT DB Parallel **Run-in :** 7 days **Setting:** Single Center

Wash out : NR **Country:** Malaysia

Sample:	Number Screened/	Eligible/	Enrolled	Number Withdrawn/	Lost to follow-up/	Analyzed
	NR/	NR/	60	16/	0/	44

Inclusion 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 drowsiness, (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

Population: **Mean age:** 38.4 years **Ethnicity:** NR

Gender: 52% Female

Intervention:

Drug name	dosage	N=	Duration
Zopiclone	7.5 mg	20	14 day
Temazepam	20 mg	20	14 day
Placebo	NA mg	20	14 day

Adverse Events:

reported by patients

	Zopiclone	Temazepam	Placebo
excessive sedation: Number	2	0	1

withdrawals

	Zopiclone	Temazepam	Placebo
total withdrawals: Number	7	7	10
withdrawals due to AEs: Number	2	0	1

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

Ponciano, 1990 **Quality rating: Fair**

Design:

Study design: RCT DB Parallel **Run-in :** 7 days **Setting:** Single Center

Wash out : 7 days **Country:** Portugal

Sample:	Number Screened/	Eligible/	Enrolled	Number Withdrawn/	Lost to follow-up/	Analyzed
	NR/	NR/	26	2/	0/	24

Inclusion criteria:

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

Exclusion criteria:

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

Population: **Mean age:** 30 years **Ethnicity:** NR

Gender: 46% Female

Intervention:

Drug name	dosage	N=	Duration
Zopiclone	7.5 mg	8	21 day
Flurazepam	30 mg	8	21 day
Placebo	NA mg	10	21 day

Adverse Events:

withdrawals

Zopiclone	Flurazepam	Placebo
total withdrawals: Number		
0	0	2
withdrawals due to AEs: Number		
0	0	1

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

Quadens, 1983 **Quality rating: Poor**

Design:

Study design: RCT DB Crossover **Run-in :** 6 days **Setting:** Single Center

Wash out : 35 days **Country:** Belgium

Sample:	Number Screened/	Eligible/	Enrolled	Number Withdrawn/	Lost to follow-up/	Analyzed
	NR/	NR/	12	0/	0/	12

Inclusion criteria:

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

Exclusion criteria:

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

Population: **Mean age:** NR years **Ethnicity:** NR

Gender: 100% Female

Intervention:

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

Adverse Events:

Norris questionnaire

	Zopiclone	Flurazepam	
clear headed-mussy: Score (SD)			
	28.1 (9.3)	34.6 (13.4)	P: <0.05
energic-lethargic: Score (SD)			
	29.2 (12.7)	34.9 (10.1)	P: <0.05
tranquil-troubled: Score (SD)			
	19.8 (11.2)	24.7 (9.4)	P: <0.05
relaxed-tense: Score (SD)			
	21.4 (11.7)	25.9 (10.8)	P: <0.05
elated-depressed: Score (SD)			
	48.1 (15.3)	50.5 (14.0)	P: <0.05
sociable-introverted: Score (SD)			
	53.6 (15.3)	52.3 (13.4)	P: <0.05
other 12 items show no difference: Score			
	multiple data	multiple data	P: NS

withdrawals

	Zopiclone	Flurazepam	
total: Number			
	0	0	P: NR
due to AEs: Number			
	0	0	P: NR

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

Rosenberg, 1994 **Quality rating: Poor**

Design:

Study design: RCT DB Parallel **Run-in :** NR **Setting:** Multicenter

Wash out : NR **Country:** Denmark

Sample:	Number Screened/	Eligible/	Enrolled	Number Withdrawn/	Lost to follow-up/	Analyzed
	NR/	NR/	178	5/	34/	139

Inclusion criteria:

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

Exclusion criteria:

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

Population: **Mean age:** 54 years **Ethnicity:** NR

Gender: 0% Female

Intervention:

Drug name	dosage	N=	Duration
Zolpidem	10 mg	71	14 day
Triazolam	0.25 mg	68	14 day

Adverse Events:

Overall AEs

Zolpidem	Triazolam	
CNS-related adverse events: Number (%)		
8 (11.3)	10 (14.7)	P: NS
GI-related adverse events: Number (%)		
2 (2.8)	3 (4.4)	P: NS
other adverse events: Number (%)		
5 (7)	2 (2.9)	P: NS
total: Number (%)		
15 (21.1)	15 (22)	P: NS

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

Silvestri, 1996 **Quality rating: Fair**

Design:

Study design: RCT DB Parallel **Run-in :** 3 days **Setting:** Multicenter

Wash out : No days **Country:** Italy

Sample:	Number Screened/	Eligible/	Enrolled	Number Withdrawn/	Lost to follow-up/	Analyzed
	NR/	NR/	22	0/	2/	20

Inclusion 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 situational insomnia) or poor sleepers with subjective reporting of at least two out of these four complaints: time to fall asleep >30 minutes, total sleep duration <6 hours, total wake time >20 minutes, and/or number or awakenings >3. These subjective inclusion criteria had to be confirmed by the objective assessment through polysomnography.

Exclusion criteria:

Pregnant or lactating women; women of child-bearing age without 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 (myoclonus, 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 drug during 2 weeks preceding the study start as well as a previous with beta blockers or corticosteroids.

Population: **Mean age:** 33.6 years **Ethnicity:** NR

Gender: 55% Female

Intervention:

Drug name	dosage	N=	Duration
Zolpidem	10 mg	10	2 week
Triazolam	0.25 mg	12	2 week

Adverse Events:

withdrawals

	Zolpidem	Triazolam
total withdrawals: Number (%)	0 (0)	2 (16.7)
withdrawals due to AEs: Number	0	0

overall AEs

	Zolpidem	Triazolam	
no. of adverse events reported by patients: Number	1	1	P: NR

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

Singh, 1990 **Quality rating: Fair**

Design:

Study design: RCT DB Parallel **Run-in :** 4 days **Setting:** Single Center
Wash out : NR **Country:** Canada

Sample:	Number Screened/	Eligible/	Enrolled	Number Withdrawn/	Lost to follow-up/	Analyzed
	NR/	61/	60	3/	0/	57

Inclusion 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, neurological disorders, established sleep apnoea and drug hypersensitivity. Patients with any significant medical condition interfering with sleep, those treatment which could modify drug kinetics were also excluded. Finally, pregnancy, lactation, and child-bearing potential not controlled by a recognized contraceptive programme precluded entry in the study.

Population: **Mean age:** 39.6 years **Ethnicity:** NR
Gender: 53% Female

Intervention:

Drug name	dosage	N=	Duration
Zopiclone	7.5 mg		24 day
Zopiclone	11.2 mg		24 day
Flurazepam	30 mg		24 day

Adverse Events:

withdrawals

	Zopiclone 7.5mg	Zopiclone 11.25mg	Flurazepam 30mg
total: Number			
	0	2	1
due to AEs: Number			
	0	1	0

overall AEs

	Zopiclone 7.5mg	Zopiclone 11.25mg	Flurazepam 30mg	
taste perversion: Number				
	7	10	7	P: NR
drowsiness: Number				
	0	1	9	P: <0.05
headache: Number				
	0	5	4	P: NS
taste perversion- moderate and severe: Number				
	0	8	0	

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

Stip, 1999 **Quality rating: Fair**

Design:

Study design: RCT DB Parallel **Run-in :** 7 days **Setting:** Single Center

Wash out : 7 days **Country:** Canada

Sample:	Number Screened/	Eligible/	Enrolled	Number Withdrawn/	Lost to follow-up/	Analyzed
	NR/	NR/	60	2/	8/	50

Inclusion criteria:

Patients with either primary insomnia or insomnia associated with mild non-psychotic psychiatric disorders (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

Population: **Mean age:** 42.6 years **Ethnicity:** NR

Gender: % Female

Intervention:

Drug name	dosage	N=	Duration
Zopiclone	7.5 mg	19	21 day
Temazepam	30 mg	16	21 day
Placebo	NA mg	15	21 day

Adverse Events:

withdrawals

Zopiclone	Temazepam	Placebo
total withdrawals: Number		
0	1	1
withdrawals due to AEs: Number		
0	0	0

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

Tamminen, 1987 **Quality rating: Poor**

Design:

Study design: RCT DB Parallel **Run-in :** 7 days **Setting:** Multicenter
Wash out : NR **Country:** Finland

Sample:	Number Screened/	Eligible/	Enrolled	Number Withdrawn/	Lost to follow-up/	Analyzed
	NR/	130/	94	0/	0/	94

Inclusion criteria:

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

Exclusion criteria:

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

Population: **Mean age:** 47 years **Ethnicity:** NR
Gender: 77% Female

Intervention:

Drug name	dosage	N=	Duration
Zopiclone	7.5 mg	52	42 day
Nitrazepam	5 mg	46	42 day

Adverse Events:

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

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

reported by patients

	Zopiclone	Nitrazepam
number of events reported: Number		
	24	13
number of patients experiencing unwanted effects: Number		
	52	46

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

Tamminen, 1987 **Quality rating: Poor**

global evaluation

Zopiclone	Nitrazepam	
safety score (1=poor; 5=excellent): Score		
3.4	3.5	P: NS

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

van der Kleijn, 1989 **Quality rating: Fair**

Design:

Study design: RCT DB Crossover **Run-in :** 2 days **Setting:** NR

Wash out : 7 days **Country:** Nijmegen

Sample:	Number Screened/	Eligible/	Enrolled	Number Withdrawn/	Lost to follow-up/	Analyzed
	NR/	60/	55	2/	0/	53

Inclusion 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 during the day by unsatisfactory sleep

Exclusion criteria:

1. Patients taking a non-benzodiazepine hypnotic prior to the study 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 benzodiazepine 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

Population: **Mean age:** 53 years **Ethnicity:** NR

Gender: 71% Female

Intervention:

Drug name	dosage	N=	Duration
Zopiclone	7.5 mg	53	5 day
Temazepam	20 mg	53	5 day

Adverse Events:

Reported by patients

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

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

van der Kleijn, 1989 **Quality rating: Fair**

Opinion of the patient about day-time status

Zopiclone	Temazepam	Placebo	
Well/normal: Number (%)			
30 (57)	35 (66)	27 (51)	P: NR
Sleepy/dull/tired: Number (%)			
7 (13)	6 (11)	12 (23)	P: NR
Headache: Number (%)			
3 (6)	3 (6)	1 (2)	P: NR
Irritable/unstable: Number (%)			
4 (8)	4 (8)	6 (11)	P: NR
Trembling/palpitation: Number (%)			
2 (4)	4 (8)	2 (4)	P: NR
Difficulties to concentrate: Number (%)			
2 (4)	0 (0)	0 (0)	P: NR
Depressive: %			
3 (6)	1 (2)	2 (4)	
Unknown: %			
2 (4)	0 (0)	3 (6)	

withdrawals

Zopiclone	Temazepam	
Total withdrawals: Number		
1	1	P: NR
withdrawals due to AEs: Number		
1	1	P: NR

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

Voshaar, 2004 **Quality rating: Fair**

Design:

Study design: RCT DB Parallel **Run-in :** NR **Setting:** Multicenter

Wash out : 4 days **Country:** Netherlands

Sample:	Number Screened/	Eligible/	Enrolled	Number Withdrawn/	Lost to follow-up/	Analyzed
	NR/	NR/	221	9/	5/	159

Inclusion 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

Population: **Mean age:** 46.1 years **Ethnicity:** NR

Gender: 0% Female

Intervention:

Drug name	dosage	N=	Duration
Zolpidem	10 mg	74	28 day
Temazepam	20 mg	85	28 day

Adverse Events:

withdrawals

	Zolpidem	Temazepam
total withdrawals: Number	NR	NR
withdrawals due to AEs: Number	NR	NR

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

Walsh, 1998a **Quality rating: Fair**

Design:

Study design: RCT DB Parallel **Run-in :** 7 days **Setting:** Multicenter
Wash out : NR **Country:** US

Sample:	Number Screened/	Eligible/	Enrolled	Number Withdrawn/	Lost to follow-up/	Analyzed
	NR/	589/	306	28/	0/	278

Inclusion criteria:

Patients had to have a minimum of a 1-month history of disturbed sleep, characterized by a self-reported sleep latency (SSL) of at least 30 min, and a self-reported sleep duration (SSD) of 4-6 hours at least three nights per week.

Exclusion criteria:

Any significant medical or psychiatric disorder (as determined by clinical interview by a physician), a history suggestive of sleep apnea or periodic limb movement disorder, smoking of more than 10 cigarettes per day, weight varying by more than 25% from desirable weight based on the Metro-politan Life Insurance Table, pregnancy or risk of becoming pregnant, and lactation.

Population: **Mean age:** NR years **Ethnicity:** NR
Gender: 0% Female

Intervention:

Drug name	dosage	N=	Duration
Zolpidem	10 mg	102	14 day
Trazodone	50 mg	100	14 day
Placebo	NA mg	104	14 day

Adverse Events:

reported by patients

Zolpidem	Trazodone	Placebo	
total number of events: Number (%)			
78 (76.5)	75 (75)		P: NS
headache (highest incidence): %			
24	30	19	
somnolence (highest incidence): %			
16	23	8	

withdrawals

Zolpidem	Trazodone	Placebo
total withdrawals: Number		
11	10	7
withdrawals due to AEs: Number		
5	5	2

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

Walsh, 1998b **Quality rating: Good**

Design:

Study design: DB Parallel **Run-in :** 3 days **Setting:**

Wash out : 2 days **Country:** US

Sample:	Number Screened/	Eligible/	Enrolled	Number Withdrawn/	Lost to follow-up/	Analyzed
	673/	456/	132	7/	0/	125

Inclusion 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 Depression scales (scores >40) were excluded, as were those using CNS active medication. Individuals with prior exposure to zaleplon, or sensitivity to benzodiazepines or other psychotropic drugs, were excluded.

Population: **Mean age:** 40.3 years **Ethnicity:** NR

Gender: 58% Female

Intervention:

Drug name	dosage	N=	Duration
Zaleplon	5 mg	34	14 day
Zaleplon	10 mg	33	33 day
Triazolam	0.25 mg	31	14 day
Placebo	NA mg	34	14 day

Adverse Events:

Treatment emergent adverse effects

Placebo	Zaleplon 5mg	Zaleplon 10mg	Triazolam	
Overall number of reports: Number (%)				
13 (38)	12 (35)	14 (42)	17 (55)	P: NS
Nausea: Number (p vs triazolam)				
0 (<0.046)	0 (<0.046)	1 (NR)	4 (NA)	
headache- the most common adverse event: Number (%)				
5 (15)	5 (15)	6 (18)	7 (23)	

withdrawals

Zaleplon 5mg	Zaleplon 10mg	Triazolam	Placebo
total withdrawals: Number			
3	1	0	3
withdrawals due to AEs: Number			
1	0	0	0

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

Walsh, 2000 **Quality rating: Poor**

Design:

Study design: RCT DB Crossover **Run-in :** NR **Setting:** Single Center

Wash out : NR **Country:** US

Sample:	Number Screened/	Eligible/	Enrolled	Number Withdrawn/	Lost to follow-up/	Analyzed
	73/	39/	30	2/	0/	22

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

Population: **Mean age:** 42 years **Ethnicity:** NR

Gender: % Female

Intervention:

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

Adverse Events:

NR

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

Ware, 1997 **Quality rating: Fair**

Design:

Study design: RCT DB Parallel **Run-in :** 2 days **Setting:** Multicenter

Wash out : 3 days **Country:** US

Sample:	Number Screened/	Eligible/	Enrolled	Number Withdrawn/	Lost to follow-up/	Analyzed
	358/	NR/	110	11/	NR/	99

Inclusion criteria:

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

Exclusion criteria:

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

Population: **Mean age:** NR years **Ethnicity:** 69% white

Gender: 58% Female

Intervention:

Drug name	dosage	N=	Duration
Zolpidem	10 mg	37	28 day
Triazolam	0.5 mg	30	28 day
Placebo	NA mg	35	28 day

Adverse Events:

withdrawals

Zolpidem	Triazolam	Placebo
withdrawals due to AEs: Number (%)		
3 (8.1)	4 (11.1)	0 (0)
total withdrawals: Number		
NR	NR	NR

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

Wheatley, 1985 **Quality rating: Fair**

Design:

Study design: RCT DB Crossover **Run-in :** 3 days **Setting:** NR
Wash out : NR **Country:** NR

Sample:	Number Screened/	Eligible/	Enrolled	Number Withdrawn/	Lost to follow-up/	Analyzed
	NR/	NR/	36	2/	0/	36

Inclusion 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

Population: **Mean age:** 53.2 years **Ethnicity:** NR
Gender: 61% Female

Intervention:

Drug name	dosage	N=	Duration
Zopiclone	7.5 mg	36	7 day
Temazepam	20 mg	36	7 day

Adverse Events:

Reported by patients

	Zopiclone	Temazepam		
Overall AEs, no. of patients: Number (%)				
	10 (28)	9 (25)	2 (6)	P: NR
Daytime drowsiness: Number				
	3	2		P: NR

withdrawals

	Zopiclone	Temazepam
total withdrawals: Number		
	2	0
withdrawals due to AEs: Number		
	2	0

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

Bergener, 1989 **Quality rating: Fair**

Design:

Study design: RCT DB Parallel **Run-in :** 4 days **Setting:** NR

Wash out : 7 days **Country:** German

Sample:	Number Screened/	Eligible/	Enrolled	Number Withdrawn/	Lost to follow-up/	Analyzed
	NR/	NR/	42	NR/	NR/	42

Inclusion criteria:

Patients who have a minimum 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 predelirium 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

Population: **Mean age:** NR years **Ethnicity:** NR

Gender: 86% Female

Intervention:

Drug name	dosage	N=	Duration
Zopiclone	7.5 mg	20	21 day
Flurazepam	30 mg	22	21 day

Primary outcome	Outcome:
☐	Sleep Disorder Intensity Scale (SDIS)

Efficacy:

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

Zopiclone	Flurazepam	
Day 33: Score (estimate from the figure)		
NR (17)	NR (10)	P: <0.1

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

Elie, 1990a **Quality rating: Fair**

Design:

Study design: RCT DB Parallel **Run-in :** 7 days **Setting:** Multicenter

Wash out : 4 days **Country:** Canada

Sample:	Number Screened/	Eligible/	Enrolled	Number Withdrawn/	Lost to follow-up/	Analyzed
	NR/	NR/	44	0/	0/	44

Inclusion 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.

Population: **Mean age:** 76.0 years **Ethnicity:** NR

Gender: 75% Female

Intervention:

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

Primary outcome	Outcome:
☐	Sleep latency
☐	Sleep soundness
☐	Sleep quality
☐	Status of wakefulness upon arising
☐	Hangover

Efficacy:

Post-sleep questionnaire

	Zopiclone	Triazolam	
sleep latency, mean score: Score (p vs placebo)			
	6.7 (<0.05)	6.8 (<0.05)	
sleep soundness, mean score: Score (p vs placebo)			
	6.8 (<0.01)	6.4 (<0.08)	
quality of sleep, mean score: Score (p vs placebo)			
	10.8 (<0.08)	11.0 (<0.08)	P: NS
morning wake-up, mean score: Score (p vs placebo)			
	10.5 (NS)	10.5 (NS)	P: NS
hangover, mean score: Score (p vs placebo)			
	16.6 (NS)	16.7 (NS)	P: NS

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

Klimm, 1987 **Quality rating: Fair**

Design:

Study design: RCT DB Parallel **Run-in :** 7 days **Setting:** Community practic
Wash out : 7 days **Country:** France

Sample:	Number Screened/	Eligible/	Enrolled	Number Withdrawn/	Lost to follow-up/	Analyzed
	NR/	NR/	74	2/	2/	72

Inclusion criteria:

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

Exclusion criteria:

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

Population: **Mean age:** 73.2 years **Ethnicity:** NR
Gender: 80% Female

Intervention:

Drug name	dosage	N=	Duration
Zopiclone	7.5 mg	36	7 day
Nitrazepam	5 mg	36	7 day

Primary outcome	Outcome:
☐	sleep onset latency
☐	quality of sleep
☐	feeling upon awakening
☐	duration of sleep
☐	awakenings during the night
☐	dreams

Efficacy:

diary: analogue scales

Zopiclone	Nitrazepam	
sleep onset latency- change from placebo baseline: Score (p vs baseline)		
-18.2 (<0.04)	-15.6 (NS)	P: NS
quality of sleep- change from placebo baseline: Score (p vs baseline)		
24 (<0.006)	23.1 (<0.002)	P: NS
feeling on awakening- change from placebo baseline: Score (p vs baseline)		
-5.7 (NS)	6.8 (NS)	P: NS
feeling on awakening- on day 9 and day 11: Score		
better	NR	P: <0.02

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

Klimm, 1987 **Quality rating: Fair**

Spiegel sleep questionnaire

Zopiclone	Nitrazepam	
sleep onset latency: Score (p vs placebo)		
NR (0.003)	NR (0.009)	P: NS
quality of sleep: Score (p vs placebo)		
NR (0.003)	NR (0.007)	P: NS
duration of sleep: Score (p vs placebo)		
NR (0.003)	NR (0.005)	P: NS
awakenings at night: Score (p vs placebo)		
NR (0.004)	NR (0.009)	P: NS
dreams: Score (p vs placebo)		
NR (0.003)	NR (0.01)	P: NS
condition in the morning: Score (p vs placebo)		
NR (0.003)	NR (0.002)	P: NS
general evaluation: Score (p vs placebo)		
NR (0.0004)	NR (0.005)	P: NS
sleep onset latency on day 12: Score		
NR	better	P: <0.001

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

Leppik, 1997 **Quality rating: Fair**

Design:

Study design: RCT DB Parallel **Run-in :** 7 days **Setting:** Multicenter
Wash out : 4 days **Country:** US

Sample:	Number Screened/	Eligible/	Enrolled	Number Withdrawn/	Lost to follow-up/	Analyzed
	NR/	457/	335	40/	0/	335

Inclusion criteria:

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

Exclusion criteria:

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

Population: **Mean age:** 69 years **Ethnicity:** 93% white
Gender: 63% Female

Intervention:

Drug name	dosage	N=	Duration
Zolpidem	5 mg	82	28 day
Triazolam	0.12 mg	85	28 day
Temazepam	15 mg	84	28 day
Placebo	NA mg	84	28 day

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

Efficacy:

morning questionnaire

Zolpidem	Triazolam	Temazepam	Placebo	
sleep latency at week 4: minutes (p vs placebo)				
40.5 (<0.05)	47.7 (NS)	38.0 (<0.05)	57.9 (NA)	
sleep latency at week 1 and week 3: minutes				
shorter	multiple data			P: <0.05
sleep latency at week 1 and week 3: minutes				
multiple data	multiple data			P: NS
sleep duration at week 4: minutes (p vs placebo)				
362.8 (NS)	359.7 (NS)	375.3 (NS)	363 (NA)	
tolerance to treatment: minutes (p vs placebo)				
multiple data (NS)	multiple data (NS)	multiple data (NS)	multiple data (NA)	

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

Leppik, 1997 **Quality rating: Fair**

Global Impression of therapy

	Zolpidem	Temazepam
sleep better: Score (p vs placebo)		
	NR, better (<0.05)	NR, better (<0.05)
sleep latency: Score (p vs placebo)		
	NR, better (<0.05)	NR, better (<0.05)
medication strength: Score (p vs placebo)		
	NR, better (<0.05)	NR, better (<0.05)
overall feeling: Score (p vs placebo)		
	NR, better (<0.05)	NR, better (<0.05)

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

Roger, 1993 **Quality rating: Fair**

Design:

Study design: RCT DB Parallel **Run-in :** 3 days **Setting:** Multicenter

Wash out : 7 days **Country:** France

Sample:	Number Screened/	Eligible/	Enrolled	Number Withdrawn/	Lost to follow-up/	Analyzed
	NR/	NR/	221	16/	0/	205

Inclusion criteria:

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

Exclusion criteria:

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

Population: **Mean age:** 81.1 years **Ethnicity:** NR

Gender: 74% Female

Intervention:

Drug name	dosage	N=	Duration
Zolpidem	5 mg	70	21 day
Zolpidem	10 mg	74	21 day
Triazolam	0.25 mg	77	21 day

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

Efficacy:

questionnaire

	Zaleplon 5mg	Zolpidem 10mg	Triazolam
% of patients falling asleep well at day 24, change from baseline: % (p vs baseline)	55.9 (<0.01)	47.9 (<0.01)	51.9 (<0.01)
% of patients falling asleep well at day 31, change from baseline: % (p vs baseline)	34.6 (<0.01)	19.8 (<0.01)	18.6 (<0.01)
% of patients falling asleep in <30 minutes at day 24, change from baseline: % (p vs baseline)	35 (<0.01)	35 (<0.01)	35 (<0.01)
mean total sleep time at day 24, change from baseline: hours (p vs baseline)	1.6 (NR)	1.9 (NR)	1.9 (NR)
% of patients with >2 awakenings per night at day 24, change from baseline: Number (p vs baseline)	-36.8 (<0.001)	-28.8 (<0.001)	-29.8 (<0.001)
% of patients with a total nocturnal waking time >1 hours: day 3 (day 24)	55.9 (17.6)	47.9 (11.0)	55.8 (15.6)
overall sleep quality at day 24, change from baseline (higher score=better): Score (p vs baseline)	35.5 (<0.001)	34.4 (<0.001)	33.6 (<0.001)
% of patients who reported too early awakening at day 24, change from baseline: % (p vs baseline)	-35 (<0.001)	-38 (<0.001)	-35 (<0.001)

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

Roger, 1993 **Quality rating: Fair**

Clinical Global Impression (CGI)

Zolpidem 5mg	Zolpidem 10mg	Triazolam	
total mean score- safety and efficacy: Score			
2.54	2.43	2.51	P: NS

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

Venter, 1986 **Quality rating: Fair**

Design:

Study design: RCT DB Parallel **Run-in :** 7 days **Setting:** Multicenter

Wash out : 0 days **Country:** South Africa

Sample:	Number Screened/	Eligible/	Enrolled	Number Withdrawn/	Lost to follow-up/	Analyzed
	58/	41/	41	0/	0/	41

Inclusion 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.

Population: **Mean age:** 76.8 years **Ethnicity:** NR

Gender: 76% Female

Intervention:

Drug name	dosage	N=	Duration
Zopiclone	0.33 mg	20	17 day
Triazolam	8.25 mg	21	17 day

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

Efficacy:

Pre- and during-treatment questionnaires

Zopiclone	Triazolam	
Difficulty in falling sleep - day 7 (1=none/very little; 2=some; 3=a lot): Score		
1.21	1.62	P: 0.03
Sleep duration (hr) - day 7: No. hours		
7.4	7.5	P: 0.05
Night awakenings - day 7: Frequency		
1	1.7	P: 0.06
Sleep quality, Early morning awakenings, Mental alertness on rising, Sleep satisfaction- day 7: Score		
NR	NR	P: NS
Daytime sleep - day 7, compare to mean: Minutes		
-8	9	P: 0.07
Daytime sleep - day 17 (no. of patients): Number		
2	5	P: NR
Night awakenings - day 17: Frequency		
NR	1	P: 0.06
Daytime sleep - day 17, compare to mean: Minutes		
-8	4	P: NS

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

Elie, 1990a **Quality rating: Fair**

Design:

Study design: RCT DB Parallel **Run-in :** 7 days **Setting:** Multicenter

Wash out : 4 days **Country:** Canada

Sample:	Number Screened/	Eligible/	Enrolled	Number Withdrawn/	Lost to follow-up/	Analyzed
	NR/	NR/	44	0/	0/	44

Inclusion 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.

Population: **Mean age:** 76.0 years **Ethnicity:** NR

Gender: 75% Female

Intervention:

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

Rebound:

Post-sleep questionnaire

	Zopiclone	Triazolam
rebound: no. of items above show withdrawal effects: Number	0	3

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

Leppik, 1997 **Quality rating: Fair**

Design:

Study design: RCT DB Parallel **Run-in :** 7 days **Setting:** Multicenter

Wash out : 4 days **Country:** US

Sample:	Number Screened/	Eligible/	Enrolled	Number Withdrawn/	Lost to follow-up/	Analyzed
	NR/	457/	335	40/	0/	335

Inclusion criteria:

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

Exclusion criteria:

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

Population: **Mean age:** 69 years **Ethnicity:** 93% white

Gender: 63% Female

Intervention:

Drug name	dosage	N=	Duration
Zolpidem	5 mg	82	28 day
Triazolam	0.12 mg	85	28 day
Temazepam	15 mg	84	28 day
Placebo	NA mg	84	28 day

Rebound:

morning questionnaire

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

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

Roger, 1993 **Quality rating: Fair**

Design:

Study design: RCT DB Parallel **Run-in :** 3 days **Setting:** Multicenter

Wash out : 7 days **Country:** France

Sample:	Number Screened/	Eligible/	Enrolled	Number Withdrawn/	Lost to follow-up/	Analyzed
	NR/	NR/	221	16/	0/	205

Inclusion criteria:

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

Exclusion criteria:

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

Population: **Mean age:** 81.1 years **Ethnicity:** NR

Gender: 74% Female

Intervention:

Drug name	dosage	N=	Duration
Zolpidem	5 mg	70	21 day
Zolpidem	10 mg	74	21 day
Triazolam	0.25 mg	77	21 day

Rebound:

questionnaire

	Zaleplon 5mg	Zolpidem 10mg	Triazolam
rebound: % of patients falling asleep in <30 minutes at day 31, change from baseline: % (p vs baseline)	18 (0.001)	28 (<0.001)	9 (0.06)
rebound: % of patients with a total nocturnal waking time >1 hours: day 3 (day 31)	55.9 (13.6)	47.9 (29.6)	55.8 (26.4)
rebound: feel well rested in the morning, change from baseline (higher score=better): Score (p vs triazolam)	17.2 (0.05)	23.9 (0.05)	10.5 (NA)

Evidence Table 9. Active controlled trials (Elderly): Adverse Events

Bergener, 1989 **Quality rating: Fair**

Design:

Study design: RCT DB Parallel **Run-in :** 4 days **Setting:** NR

Wash out : 7 days **Country:** German

Sample:	Number Screened/	Eligible/	Enrolled	Number Withdrawn/	Lost to follow-up/	Analyzed
	NR/	NR/	42	NR/	NR/	42

Inclusion criteria:

Patients who have a minimum 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 predelirium 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

Population: **Mean age:** NR years **Ethnicity:** NR

Gender: 86% Female

Intervention:

Drug name	dosage	N=	Duration
Zopiclone	7.5 mg	20	21 day
Flurazepam	30 mg	22	21 day

Adverse Events:

Withdrawals

	Zopiclone	Flurazepam	
number of patients: Number (%)			
	8 (40)	8 (36.3)	P: NS
withdrawals due to AEs: Number (%)			
	2 (10)	5 (22.7)	P: NS

Evidence Table 9. Active controlled trials (Elderly): Adverse Events

Elie, 1990a **Quality rating: Fair**

Design:

Study design: RCT DB Parallel **Run-in :** 7 days **Setting:** Multicenter
Wash out : 4 days **Country:** Canada

Sample:	Number Screened/	Eligible/	Enrolled	Number Withdrawn/	Lost to follow-up/	Analyzed
	NR/	NR/	44	0/	0/	44

Inclusion 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.

Population: **Mean age:** 76.0 years **Ethnicity:** NR
Gender: 75% Female

Intervention:

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

Adverse Events:

reported by patients

	Zopiclone	Triazolam
reduction of dreams: Number (p vs placebo)	5 (<0.02)	3 (NS)
bitter taste: Number (p vs placebo)	5 (<0.06)	0 (NS)

withdrawals

	Zopiclone	Trazodone	Placebo
total withdrawals: Number	0	0	0
withdrawals due to AEs: Number	0	0	0

Evidence Table 9. Active controlled trials (Elderly): Adverse Events

Klimm, 1987 **Quality rating: Fair**

Design:

Study design: RCT DB Parallel **Run-in :** 7 days **Setting:** Community practic

Wash out : 7 days **Country:** France

Sample:	Number Screened/	Eligible/	Enrolled	Number Withdrawn/	Lost to follow-up/	Analyzed
	NR/	NR/	74	2/	2/	72

Inclusion criteria:

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

Exclusion criteria:

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

Population: **Mean age:** 73.2 years **Ethnicity:** NR

Gender: 80% Female

Intervention:

Drug name	dosage	N=	Duration
Zopiclone	7.5 mg	36	7 day
Nitrazepam	5 mg	36	7 day

Adverse Events:

reported by patients

	Zopiclone	Nitrazepam
bitter taste: Number	1	0
dizziness: Number	1	0
confusion: Number	0	1
fatigue: Number	0	1
complaints in answer to the standarized question on tolerance: Number (p vs baseline)	less (NS)	more (<0.003)

withdrawals

	Zopiclone	Nitrazepam
total withdrawals: Number	1	1
withdrawals due to AEs: Number	0	1

Evidence Table 9. Active controlled trials (Elderly): Adverse Events

Leppik, 1997 **Quality rating: Fair**

Design:

Study design: RCT DB Parallel **Run-in :** 7 days **Setting:** Multicenter

Wash out : 4 days **Country:** US

Sample:	Number Screened/	Eligible/	Enrolled	Number Withdrawn/	Lost to follow-up/	Analyzed
	NR/	457/	335	40/	0/	335

Inclusion criteria:

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

Exclusion criteria:

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

Population: **Mean age:** 69 years **Ethnicity:** 93% white

Gender: 63% Female

Intervention:

Drug name	dosage	N=	Duration
Zolpidem	5 mg	82	28 day
Triazolam	0.12 mg	85	28 day
Temazepam	15 mg	84	28 day
Placebo	NA mg	84	28 day

Adverse Events:

overall adverse events

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

Evidence Table 9. Active controlled trials (Elderly): Adverse Events

Leppik, 1997 **Quality rating: Fair**

fatigue: Number (%)			
1 (1.2)	2 (2.4)	5 (6.0)	1 (1.2)

withdrawals

Zolpidem	Triazolam	Temazepam	Placebo
total withdrawals: Number			
6	14	10	10
withdrawals due to AEs: Number			
2	5	5	6

Evidence Table 9. Active controlled trials (Elderly): Adverse Events

Roger, 1993 **Quality rating: Fair**

Design:

Study design: RCT DB Parallel **Run-in :** 3 days **Setting:** Multicenter

Wash out : 7 days **Country:** France

Sample:	Number Screened/	Eligible/	Enrolled	Number Withdrawn/	Lost to follow-up/	Analyzed
	NR/	NR/	221	16/	0/	205

Inclusion criteria:

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

Exclusion criteria:

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

Population: **Mean age:** 81.1 years **Ethnicity:** NR

Gender: 74% Female

Intervention:

Drug name	dosage	N=	Duration
Zolpidem	5 mg	70	21 day
Zolpidem	10 mg	74	21 day
Triazolam	0.25 mg	77	21 day

Adverse Events:

overall report

	Zolpidem 5mg	Zolpidem 10mg	Triazolam
no. patients experiencing adverse events: Number (%)	11 (16)	8 (11)	16 (21)
nightmares- the most common adverse effect: Number	2	3	2

withdrawals

	Zolpidem 5mg	Zolpidem 10mg	Triazolam
total withdrawals: Number	7	1	5
withdrawals due to AEs: Number	0	0	2

Evidence Table 9. Active controlled trials (Elderly): Adverse Events

Venter, 1986 **Quality rating: Fair**

Design:

Study design: RCT DB Parallel **Run-in :** 7 days **Setting:** Multicenter
Wash out : 0 days **Country:** South Africa

Sample:	Number Screened/	Eligible/	Enrolled	Number Withdrawn/	Lost to follow-up/	Analyzed
	58/	41/	41	0/	0/	41

Inclusion 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.

Population: **Mean age:** 76.8 years **Ethnicity:** NR
Gender: 76% Female

Intervention:

Drug name	dosage	N=	Duration
Zopiclone	0.33 mg	20	17 day
Triazolam	8.25 mg	21	17 day

Adverse Events:

Reported by the patients

	Zopiclone	Triazolam	
total number of patient: Number (%)			
	7 (35)	8 (38)	P: NR
number of patient reporting AEs on day 7 and day 9: Number			
	more	NR	P: 0.013

Reported by the patients: CNS AEs

	Zopiclone	Triazolam	
depression, tearfulness, drowsiness, dizziness, agitation, nightmares, confusion, and disturbed sleep: Number			
	3	7	P: NR

Reported by the patients: Gastrointestinal AEs

	Zopiclone	Triazolam	
Bad taste: Number			
	6	2	P: NR

Reported by the patients: Other AEs

	Zopiclone	Triazolam	
muscular pain, angina pectoris episodes, and shortness of breath: Number			
	3	1	P: NR

Evidence Table 9. Active controlled trials (Elderly): Adverse Events

Venter, 1986 **Quality rating: Fair**

withdrawals

Zopiclone	Triazolam
total withdrawals: Number	
0	0
withdrawals due to AEs: Number	
0	0

Evidence Table 10. Active controlled trials (Other Subgroups): Efficacy

Agnoli, 1989 **Subgroup:** Anxiety **Quality rating: Poor**

Design:

Study design: RCT DB Crossover **Run-in :** 3 days **Setting:** NR

Wash out : NR **Country:** Rome, Foggia, Italy

Sample:	Number Screened/	Eligible/	Enrolled	Number Withdrawn/	Lost to follow-up/	Analyzed
	NR/	NR/	20	0/	0/	20

Inclusion 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 placebo administration; and pregnancy.

Population: **Mean age:** 38.2 years **Ethnicity:** NR

Gender: 60% Female

Intervention:

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

Primary outcome	Outcome:
☐	anxiety levels
☐	time of sleep induction
☐	hours of sleep
☐	number of nocturnal arousals
☐	quality of sleep
☐	quality of daytime arousal

Efficacy:

Hamilton Rating Scale for Anxiety (HRSA)

	Zopiclone	Nitrazepam	
after the 1st and 2nd weeks of treatment (less score = better): Score			
	lower	-	P: <0.05

Toulouse-Pieron Attention Test

	Zopiclone	Nitrazepam	
reduction of omitted items on the 7th day (more reduction=better): Number			
	more	-	P: <0.01
reduction of omitted items on the 14th day (more reduction=better): Number			
	more	-	P: <0.05
reduction of errors items on the 7th day (more reduction=better): Number			
	more	-	P: <0.01
times of execution (shorter=better): Number			
	shorter	-	P: <0.01

Time-signed semiquantitative scale

	Zopiclone	Nitrazepam	
time of sleep induction (shorter=better): Number			
	shorter	-	P: <0.001
quality of daytime arousal: Number			
	better	-	P: <0.01
number of nocturnal arousals, the quality of sleep, the duration of sleep: Number			
	NR	NR	P: NS

Evidence Table 10. Active controlled trials (Other Subgroups): Efficacy

Ansoms, 1991 **Subgroup:** alcoholism **Quality rating: Fair**

Design:

Study design: RCT DB Parallel **Run-in :** 2 days **Setting:** Multicenter
Wash out : NR **Country:** US

Sample:	Number Screened/	Eligible/	Enrolled	Number Withdrawn/	Lost to follow-up/	Analyzed
	NR/	54/	52	0/	0/	52

Inclusion criteria:

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

Exclusion criteria:

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

Population: **Mean age:** 43.9 years **Ethnicity:** NR
Gender: 33% Female

Intervention:

Drug name	dosage	N=	Duration
Zopiclone	7.5 mg	27	5 day
Lormetazepam	1 mg	25	5 day

Primary outcome	Outcome:
☐	Efficacy (Spiegel Sleep Questionnaire)
☐	Behavior and mood on waking up
☐	Overall evaluation of efficacy and operabilit

Efficacy:

Efficacy (Spiegel Sleep Questionnaire)

	Zopiclone	Lorazepam
Improvement from baseline to end of treatment on time to fall asleep: p-value	NS	0.013
Improvement from baseline to end of treatment on quality of sleep: p-value	NS	0.065
Improvement from baseline to end of treatment on duration of sleep: p-value	NS	NS
Improvement from baseline to end of treatment on nocturnal awakenings: p-value	NS	NS
Improvement from baseline to end of treatment on dreams: p-value	NS	NS
Improvement from baseline to end of treatment on morning disposition: p-value	NS	NS
Improvement from baseline to end of treatment on general evaluation: p-value	NS	NS

Overall evaluation of efficacy and tolerability

	Zopiclone	Lormetazepam	
Physician's overall efficacy assessment after treatment ("excellent or good"): (%)	44	48	P: NS

Evidence Table 10. Active controlled trials (Other Subgroups): Efficacy

Bozin-Juracic, 1998 **Subgroup:** shiftworker **Quality rating: Fair**

Design:

Study design: NR NR Crossover **Run-in :** 0 days **Setting:** Single Center
Wash out : 0 days **Country:** Croatia

Sample:	Number Screened/	Eligible/	Enrolled	Number Withdrawn/	Lost to follow-up/	Analyzed
	NR/	32/	29	0/	0/	29

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

Exclusion criteria:
NR

Population: **Mean age:** NR years **Ethnicity:** NR
Gender: 0% Female

Intervention:

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

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

Efficacy:

sleep questionnaire using visual-analogue scale

	Zopiclone	Nitrazepam	Placebo	
mean total length of main sleep (estimate from the figure): minutes	295	285	270	P: NR
mean sleep efficacy of main sleep (estimate from the figure): %	88	87	82	P: NR
mean sleep efficacy of all day sleep (estimate from the figure): %	88	87	82	P: NR
10 items of main sleep characteristics: Score	NR	NR	NR	P: NS
5 items of all day sleep characteristics: Score	NR	NR	NR	P: NS

Evidence Table 10. Active controlled trials (Other Subgroups): Efficacy

Fontaine, 1990 **Subgroup:** psychiatric **Quality rating: Fair**

Design:

Study design: RCT DB Parallel **Run-in :** 7 days **Setting:** Single Center

Wash out : 21 days **Country:** Canada

Sample:	Number Screened/	Eligible/	Enrolled	Number Withdrawn/	Lost to follow-up/	Analyzed
	NR/	NR/	75	21/	0/	75

Inclusion criteria:

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

Exclusion criteria:

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

Population: **Mean age:** 42.9 years **Ethnicity:** NR

Gender: 53% Female

Intervention:

Drug name	dosage	N=	Duration
Zopiclone	7.5 mg	30	28 day
Triazolam	0.5 mg	30	28 day
Placebo	NA mg	15	28 day

Primary outcome	Outcome:
☐	sleep induction
☐	sleep soundness
☐	duration of sleep
☐	morning awakening
☐	hangover effect

Efficacy:

sleep inventory

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

Evidence Table 10. Active controlled trials (Other Subgroups): Efficacy

Fontaine, 1990 **Subgroup:** psychiatric **Quality rating: Fair**

Hamilton Rating Scale (HAM)

Zopiclone	Triazolam	
somatic anxiety: Score (p vs placebo)		
8.8 (NS)	12.0 (NS)	P: <0.01
psychic anxiety: Score (p vs placebo)		
9.3 (NS)	10.8 (NS)	P: NS
total score: Score (p vs placebo)		
18.2 (NS)	22.4 (NS)	P: <0.01
daytime anxiety: Number (%)		
5 (17)	10 (33)	P: 0.16

Clinical Global Impression (CGI)

Zopiclone	Triazolam	
overall: Score (p vs placebo)		
NR (sig. better)	NR (sig. better)	P: NR

Evidence Table 10. Active controlled trials (Other Subgroups): Efficacy

Li Pi Shan, 2004 **Subgroup:** Stroke (inpatient) **Quality rating: Fair**

Design:

Study design: RCT DB Crossover **Run-in :** 0 days **Setting:** Single Center

Wash out : 0 days **Country:** Canada

Sample:	Number Screened/	Eligible/	Enrolled	Number Withdrawn/	Lost to follow-up/	Analyzed
	44/	27/	18	0/	0/	18

Inclusion 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 read 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.

Population: **Mean age:** 56.6 years **Ethnicity:** NR

Gender: 44% Female

Intervention:

Drug name	dosage	N=	Duration
Zopiclone	3.75 mg	18	eeded for 7 day
Lorazepam	0.5- mg	18	eeded for 7 day

Primary outcome	Outcome:
☐	total time of sleep
☐	quality of sleep
☐	depth of sleep
☐	feeling of rest
☐	daytime drowsiness
☐	lethargy
☐	fatigue

Efficacy:

recorded by nurses

	Zopiclone	Lorazepam	
total time of sleep: hours (SD)	7.23 (0.63)	7.49 (0.77)	P: 0.09
alertness (higher score=better): Score (Range)	4 (3.5-4)	4 (3.5-4)	P: 0.6
feeling of being refreshed (higher score=better): Score (Range)	3.5 (3-4)	4 (3-4)	P: 0.79

sleep questionnaire

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

Evidence Table 10. Active controlled trials (Other Subgroups): Efficacy

Li Pi Shan, 2004 **Subgroup:** Stroke (inpatient) **Quality rating: Fair**

Mini mental state examination score

Zopiclone	Lorazepam	
total score: Score (Range)		
28 (27-30)	27 (25-29)	P: 0.054

Evidence Table 10. Active controlled trials (Other Subgroups): Efficacy

Pagot, 1993 **Subgroup:** psychiatric **Quality rating: Fair**

Design:

Study design: RCT DB Parallel **Run-in :** 4 days **Setting:** Multicenter

Wash out : 30 days **Country:** France

Sample:	Number Screened/	Eligible/	Enrolled	Number Withdrawn/	Lost to follow-up/	Analyzed
	NR/	NR/	95	33/	0/	62

Inclusion 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.

Population: **Mean age:** 48 years **Ethnicity:** NR

Gender: 61% Female

Intervention:

Drug name	dosage	N=	Duration
Zolpidem	20 mg	47	86 day
Triazolam	0.5 mg	48	86 day

Primary outcome	Outcome:
☐	duration of sleep
☐	number of nocturnal awakenings
☐	time awake during the night
☐	subjective status on awakening
☐	therapeutic efficacy
☐	anxiety

Efficacy:

therapeutic efficacy by patients

Zolpidem	Triazolam	
therapeutic effects at day 30- good and excellent: Number (%)		
32 (75)	32 (75)	P: NS
therapeutic effects at day 60- good and excellent: Number (%)		
33 (87)	31 (84)	P: NS
therapeutic effects at day 90- good and excellent: Number (%)		
32 (91)	29 (85)	P: NS
quality of sleep at day 60: %		
74	65	P: NR
quality of sleep at day 90: %		
81	73	P: NR
overall rating: day 0 (day 90)		
38.4 (78.6)	36.3 (76.6)	P: NR
status on awakening and alertness, number of patients: day 4 (day 90)		
28 (44)	40 (42)	P: NR

Evidence Table 10. Active controlled trials (Other Subgroups): Efficacy

Pagot, 1993 **Subgroup:** psychiatric **Quality rating: Fair**

global assessment by the investigator

Zolpidem	Triazolam	
sleep latency at day 90, change from baseline: Score (p vs baseline)		
-1.9 (<0.001)	-1.9 (<0.001)	P: NS
mean sleep time at day 90, change from baseline: hours (p vs baseline)		
2.72 (<0.001)	2.26 (<0.001)	P: NS
number of nocturnal awakenings at day 60, change from baseline: Number (p vs baseline)		
-1.7 (0.02)	-1 (0.02)	P: <0.05
duration of nocturnal awakenings at day 60: minutes (p vs baseline)		
18 (0.02)	14 (0.02)	P: <0.05

Hamilton Rating Scale for anxiety

Zolpidem	Triazolam	
total score: Score		
multiple data	multiple data	P: NS

Evidence Table 10. Active controlled trials (Other Subgroups): Efficacy

Schwartz, 2004 **Subgroup:** psychiatric (inpatie **Quality rating: Poor**

Design:

Study design: RCT Ope Parallel **Run-in :** NR **Setting:** Single Center

Wash out : NR **Country:** US

Sample:	Number Screened/	Eligible/	Enrolled	Number Withdrawn/	Lost to follow-up/	Analyzed
	NR/	NR/	16	0/	0/	16

Inclusion 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.

Population: **Mean age:** NR years **Ethnicity:** NR

Gender: 50% Female

Intervention:

Drug name	dosage	N=	Duration
Zaleplon	10-2 mg	7	AsN
Trazodone	50-1 mg	9	AsN

Primary outcome	Outcome:
☐	sleepiness
☐	sleep duration

Efficacy:

Epworth sleepiness scale (ESS)

	Zaleplon	Trazodone	
median at study entry-matching: Score			
	7	9	P: 0.885
media change from baseline efficacy and tolerability: Score			
	-1	1	P: 0.23

inpatient, nurse-recorded sleep log

	Zaleplon	Trazodone	
sleep- median at study entry-matching: hours			
	3	3	P: 0.894
sleep- median change from baseline efficacy and tolerability: hours			
	0	3	P: 0.181

Evidence Table 10. Active controlled trials (Other Subgroups): Efficacy

Steens, 1993 **Subgroup:** COPD **Quality rating: Fair**

Design:

Study design: RCT DB Crossover **Run-in :** 0 days **Setting:** Multicenter

Wash out : 0 days **Country:** Canada

Sample:	Number Screened/	Eligible/	Enrolled	Number Withdrawn/	Lost to follow-up/	Analyzed
	NR/	NR/	24	0/	0/	24

Inclusion criteria:

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

Exclusion criteria:

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

Population: **Mean age:** 58.2 years **Ethnicity:** NR

Gender: 38% Female

Intervention:

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

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

Efficacy:

overall measures

Zolpidem 5mg	Zolpidem 10mg	Triazolam
total sleep time: minutes (p vs triazolam)		
384.82 (<0.05)	397.12 (NS)	413.79 (NA)
total wake time: minutes (p vs triazolam)		
93.09 (<0.05)	82.37 (NS)	66.10 (NA)
sleep efficacy: % (p vs triazolam)		
79.74 (<0.05)	82.35 (NS)	85.83 (NA)

Evidence Table 10. Active controlled trials (Other Subgroups): Efficacy

Steens, 1993 **Subgroup:** COPD **Quality rating: Fair**

maintenance measures

	Zolpidem 5mg	Zolpidem 10mg	Triazolam
awakenings (no./hours of sleep): Number (p vs triazolam)	4.70 (<0.05)	4.07 (NS)	3.68 (NA)
microarousals (no./hour of sleep): Number (p vs triazolam)	14.08 (NS)	12.57 (NS)	13.23 (NA)
Arousals/total sleep time (no./hour): Number (p vs triazolam)	18.69 (NS)	16.46 (NS)	16.72 (NA)
wake time during sleep: Number (p vs triazolam)	55.57 (NS)	50.69 (NS)	40.47 (NA)

subjective assessment of sleep

	Zolpidem 5mg	Zolpidem 10mg	Triazolam
sleep latency: minutes (p vs triazolam)	38.7 (NS)	30.22 (NS)	25.52 (NA)
ease of falling sleep (lower score=better): Score (p vs triazolam)	46.48 (<0.05)	30.09 (NS)	20.96 (NA)
no. of awakenings: minutes (p vs triazolam)	2.74 (NS)	2.17 (NS)	1.61 (NA)
duration of night waking: minutes (p vs triazolam)	103.04 (NS)	16.78 (NS)	43.83 (NA)
sleep duration: minutes (p vs triazolam)	333.26 (<0.05)	388.22 (NS)	411.17 (NA)
feeling of sleep (1=excellent, 4=poor): minutes (p vs triazolam)	2.61 (<0.05)	2.13 (NS)	1.87 (NA)
sleepy in the morning (higher score=better): minutes (p vs triazolam)	55.04 (NS)	65.44 (NS)	66.52 (NA)
concentration in the morning (1=excellent, 4=poor): minutes (p vs triazolam)	2.30 (NS)	2.26 (NS)	2.13 (NA)

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

Pagot, 1993 **Subgroup:** psychiatric **Quality rating: Fair**

Design:

Study design: RCT DB Parallel **Run-in :** 4 days **Setting:** Multicenter

Wash out : 30 days **Country:** France

Sample:	Number Screened/	Eligible/	Enrolled	Number Withdrawn/	Lost to follow-up/	Analyzed
	NR/	NR/	95	33/	0/	62

Inclusion 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.

Population: **Mean age:** 48 years **Ethnicity:** NR

Gender: 61% Female

Intervention:

Drug name	dosage	N=	Duration
Zolpidem	20 mg	47	86 day
Triazolam	0.5 mg	48	86 day

Rebound:

therapeutic efficacy by patients

Zolpidem	Triazolam	
rebound: therapeutic effects at day 120- good and excellent: Number (%)		
33 (89)	34 (83)	P: NS

Evidence Table 12. Active controlled trials (Other Subgroups): Adverse Events

Agnoli, 1989 **Subgroup:** Anxiety **Quality rating: Poor**

Design:

Study design: RCT DB Crossover **Run-in :** 3 days **Setting:** NR

Wash out : NR **Country:** Rome, Foggia, Italy

Sample:	Number Screened/	Eligible/	Enrolled	Number Withdrawn/	Lost to follow-up/	Analyzed
	NR/	NR/	20	0/	0/	20

Inclusion 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 placebo administration; and pregnancy.

Population: **Mean age:** 38.2 years **Ethnicity:** NR

Gender: 60% Female

Intervention:

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

Adverse Events:

epigastralgia

	Zopiclone	Nitrazepam	
1st week: Number			
	1	1	P: NR

daytime sedation

	Zopiclone	Nitrazepam	
1st week: Number			
	0	6	P: NR
2dn week: Number			
	0	14	P: NR
prolonged into the wash-out period between treatment: Number			
	0	3	P: NR

restlessness

	Zopiclone	Nitrazepam	
1st week: Number			
	0	1	P: NR

Evidence Table 12. Active controlled trials (Other Subgroups): Adverse Events

Ansoms, 1991 **Subgroup:** alcoholism **Quality rating: Fair**

Design:

Study design: RCT DB Parallel **Run-in :** 2 days **Setting:** Multicenter

Wash out : NR **Country:** US

Sample:	Number Screened/	Eligible/	Enrolled	Number Withdrawn/	Lost to follow-up/	Analyzed
	NR/	54/	52	0/	0/	52

Inclusion criteria:

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

Exclusion criteria:

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

Population: **Mean age:** 43.9 years **Ethnicity:** NR

Gender: 33% Female

Intervention:

Drug name	dosage	N=	Duration
Zopiclone	7.5 mg	27	5 day
Lormetazepam	1 mg	25	5 day

Adverse Events:

Overall safety

	Zopiclone	Lormetazepam	
Physician's overall safety assessment ("excellent" or "good"): %			
	93	76	P: NR

withdrawals

	Zopiclone	Lorazepam	
total withdrawals: Number			
	NR	NR	
withdrawals due to AEs: Number			
	NR	NR	

Overall AEs

	Zopiclone	Lormetazepam	
Overall AEs: %			
	26	28	P: NS

Evidence Table 12. Active controlled trials (Other Subgroups): Adverse Events

Bozin-Juracic, 1998 **Subgroup:** shiftworker **Quality rating: Fair**

Design:

Study design: NR NR Crossover **Run-in :** 0 days **Setting:** Single Center
Wash out : 0 days **Country:** Croatia

Sample:	Number Screened/	Eligible/	Enrolled	Number Withdrawn/	Lost to follow-up/	Analyzed
	NR/	32/	29	0/	0/	29

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

Exclusion criteria:
NR

Population: **Mean age:** NR years **Ethnicity:** NR
Gender: 0% Female

Intervention:

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

Adverse Events:

withdrawals

Zopiclone	Nitrazepam	Placebo
total withdrawals: Number		
0	0	0
withdrawals due to AEs: Number		
0	0	0

Evidence Table 12. Active controlled trials (Other Subgroups): Adverse Events

Fontaine, 1990 **Subgroup:** psychiatric **Quality rating: Fair**

Design:

Study design: RCT DB Parallel **Run-in :** 7 days **Setting:** Single Center

Wash out : 21 days **Country:** Canada

Sample:	Number Screened/	Eligible/	Enrolled	Number Withdrawn/	Lost to follow-up/	Analyzed
	NR/	NR/	75	21/	0/	75

Inclusion criteria:

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

Exclusion criteria:

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

Population: **Mean age:** 42.9 years **Ethnicity:** NR

Gender: 53% Female

Intervention:

Drug name	dosage	N=	Duration
Zopiclone	7.5 mg	30	28 day
Triazolam	0.5 mg	30	28 day
Placebo	NA mg	15	28 day

Adverse Events:

Hopkins Symptoms Checklist (SCL-90)

Zopiclone	Triazolam	Placebo	
drowsiness: Number			
3	5	4	P: NS
ataxia: Number			
2	3	1	P: NS
headache: Number			
6	3	3	P: NS
taste perversion: Number			
17	3	1	P: <0.001
nausea: Number			
2	3	4	P: NS
dry mouth: Number			
7	1	1	P: <0.05

withdrawals

Zopiclone	Triazolam	Placebo
total withdrawals: Number		
8	8	5
withdrawals due to AEs: Number		
4	3	0

Evidence Table 12. Active controlled trials (Other Subgroups): Adverse Events

Li Pi Shan, 2004 **Subgroup:** Stroke (inpatient) **Quality rating: Fair**

Design:

Study design: RCT DB Crossover **Run-in :** 0 days **Setting:** Single Center

Wash out : 0 days **Country:** Canada

Sample:	Number Screened/	Eligible/	Enrolled	Number Withdrawn/	Lost to follow-up/	Analyzed
	44/	27/	18	0/	0/	18

Inclusion 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 read 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.

Population: **Mean age:** 56.6 years **Ethnicity:** NR

Gender: 44% Female

Intervention:

Drug name	dosage	N=	Duration
Zopiclone	3.75 mg	18	eeded for 7 day
Lorazepam	0.5- mg	18	eeded for 7 day

Adverse Events:

withdrawals

	Zopiclone	Lorazepam
total withdrawals: Number		
	0	0
withdrawals due to AEs: Number		
	0	0

Evidence Table 12. Active controlled trials (Other Subgroups): Adverse Events

Pagot, 1993 **Subgroup:** psychiatric **Quality rating: Fair**

Design:

Study design: RCT DB Parallel **Run-in :** 4 days **Setting:** Multicenter

Wash out : 30 days **Country:** France

Sample:	Number Screened/	Eligible/	Enrolled	Number Withdrawn/	Lost to follow-up/	Analyzed
	NR/	NR/	95	33/	0/	62

Inclusion 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.

Population: **Mean age:** 48 years **Ethnicity:** NR

Gender: 61% Female

Intervention:

Drug name	dosage	N=	Duration
Zolpidem	20 mg	47	86 day
Triazolam	0.5 mg	48	86 day

Adverse Events:

withdrawals

	Zolpidem 20mg	Triazolam 0.5mg
total withdrawals: Number	15	18
withdrawals due to AEs: Number	1	2

Evidence Table 12. Active controlled trials (Other Subgroups): Adverse Events

Schwartz, 2004 **Subgroup:** psychiatric (inpatie **Quality rating: Poor**

Design:

Study design: RCT Ope Parallel **Run-in :** NR **Setting:** Single Center

Wash out : NR **Country:** US

Sample:	Number Screened/	Eligible/	Enrolled	Number Withdrawn/	Lost to follow-up/	Analyzed
	NR/	NR/	16	0/	0/	16

Inclusion 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.

Population: **Mean age:** NR years **Ethnicity:** NR

Gender: 50% Female

Intervention:

Drug name	dosage	N=	Duration
Zaleplon	10-2 mg	7	AsN
Trazodone	50-1 mg	9	AsN

Adverse Events:

Withdrawals: NR

Evidence Table 12. Active controlled trials (Other Subgroups): Adverse Events

Steens, 1993 **Subgroup:** COPD **Quality rating: Fair**

Design:

Study design: RCT DB Crossover **Run-in :** 0 days **Setting:** Multicenter

Wash out : 0 days **Country:** Canada

Sample:	Number Screened/	Eligible/	Enrolled	Number Withdrawn/	Lost to follow-up/	Analyzed
	NR/	NR/	24	0/	0/	24

Inclusion criteria:

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

Exclusion criteria:

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

Population: **Mean age:** 58.2 years **Ethnicity:** NR

Gender: 38% Female

Intervention:

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

Adverse Events:

withdrawals

	Zolpidem 5mg	Zolpidem 10mg	Triazolam
total withdrawals: Number	0	0	0
withdrawals due to AEs: Number	0	0	0

Lab data- respiratory events

	Zolpidem 5mg	Zolpidem 10mg	Triazolam
reduction of SaO2: Number	0	2	2
apnea-hypopnea: Number	1	2	1

Evidence Table 13. Placebo controlled trials: Efficacy

Allain, 1998 **Quality rating: Fair**

Design:

Study design: RCT DB Parallel **Run-in :** 3 days **Setting:** Multicenter
Wash out : 3 days **Country:** France

Sample:	Number Screened/	Eligible/	Enrolled	Number Withdrawn/	Lost to follow-up/	Analyzed
	NR/	NR/	37	18/	NR/	37

Inclusion 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 susceptible 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 women; liver or respiratory failure, myasthenia, or epilepsy.

Population: **Mean age:** 51.9 years **Ethnicity:** NR
Gender: 0% Female

Intervention:

Drug name	dosage	N=	Duration
Zolpidem	10 mg	18	21 day
Placebo	NA mg	19	21 day

Primary outcome	Outcome:
☐	sleep latency
☐	number of nocturnal awakenings
☐	total sleep time
☐	sleep quality
☐	nightmares
☐	wakefulness
☐	daytime alertness

Efficacy:

clinical global impression

Zolpidem	Placebo	
overall no different except day 21, where zolpidem was more effective, p<0.007: Mean		
NR	NR	P: NS

sleep questionnaire

Zolpidem	Placebo	
daytime alertness: Mean		
NR	NR	P: NS
total sleep time (hr) at day 7: Mean		
6.13	6.40	P: NR
total sleep time (hr) at day 28: Mean		
NR	NR	P: NS
less nightmare: %		
93	less	P: <0.04

Evidence Table 13. Placebo controlled trials: Efficacy

Allain, 1998 **Quality rating: Fair**

sleep diary

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

Evidence Table 13. Placebo controlled trials: Efficacy

Allain, 2001 **Quality rating: Fair**

Design:

Study design: RCT DB Parallel **Run-in :** 3-7 days **Setting:** Multicenter
Wash out : NR **Country:** France

Sample:	Number Screened/	Eligible/	Enrolled	Number Withdrawn/	Lost to follow-up/	Analyzed
	NR/	NR/	245	NR/	NR/	245

Inclusion criteria:

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

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

Exclusion criteria:

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

Population: **Mean age:** 46.1 years **Ethnicity:** NR
Gender: 77% Female

Intervention:

Drug name	dosage	N=	Duration
Zolpidem	10 mg	124	28 day
Placebo	NA mg	121	28 day

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

Efficacy:

sleep diary

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

Evidence Table 13. Placebo controlled trials: Efficacy

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

Evidence Table 13. Placebo controlled trials: Efficacy

Allain, 2001 **Quality rating: Fair**

SF-36 healthy survey

Zolpidem	Placebo	
physical function, change from baseline: Mean (SD)		
2.5 (17.3)	2.7 (4.6)	P: NS
role limitations due to physical problem, change from baseline: Mean (SD)		
7.5 (29)	4.9 (32.5)	P: NS
bodily pain, change from baseline: Mean (SD)		
4.7 (21)	3.7 (22.4)	P: NS
general health perception, change from baseline: Mean (SD)		
3.4 (12.4)	2.5 (12.5)	P: NS
vitality, change from baseline: Mean (SD)		
6.5 (16.6)	5.7 (14)	P: NS
social functioning, change from baseline: Mean (SD)		
6.1 (22.4)	2.8 (21.6)	P: NS
role limitations due to emotional problems, change from baseline: Mean (SD)		
7.9 (39.1)	-0.3 (33.9)	P: NS
general mental health, change from baseline: Mean (SD)		
5.9 (16.8)	5.1 (14.5)	P: NS

Evidence Table 13. Placebo controlled trials: Efficacy

Chaudoir, 1983 **Quality rating: Poor**

Design:

Study design: RCT DB Crossover **Run-in :** NR **Setting:** Single Center
Wash out : NR **Country:** UK

Sample:	Number Screened/	Eligible/	Enrolled	Number Withdrawn/	Lost to follow-up/	Analyzed
	NR/	30/	25	5/	0/	25

Inclusion criteria:

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

Exclusion criteria:

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

Population: **Mean age:** 50 years **Ethnicity:** NR
Gender: 72% Female

Intervention:

Drug name	dosage	N=	Duration
Zopiclone	7.5 mg	25	7 day
Placebo	NA mg	25	7 day

Primary outcome	Outcome:
☐	sleep latency
☐	number of awakenings
☐	sleep quality
☐	feeling after wakening

Efficacy:

daily sleep questionnaire

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

Evidence Table 13. Placebo controlled trials: Efficacy

Chaudoir, 1983 **Quality rating: Poor**

weekly assessment

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

Evidence Table 13. Placebo controlled trials: Efficacy

Dockhorn, 1996 **Quality rating: Fair**

Design:

Study design: RCT DB Parallel **Run-in :** NR **Setting:** Multicenter
Wash out : NR **Country:** US

Sample:	Number Screened/	Eligible/	Enrolled	Number Withdrawn/	Lost to follow-up/	Analyzed
	NR/	NR/	138	9/	2/	136

Inclusion criteria:

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

Exclusion criteria:

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

Population: **Mean age:** 32.7 years **Ethnicity:** NR
Gender: 58% Female

Intervention:

Drug name	dosage	N=	Duration
Zolpidem	10 mg	68	7-10 day
Placebo	NA mg	68	7-10 day

Primary outcome	Outcome:
☑	sleep latency
☑	total sleep time
☐	ease of falling asleep
☐	number of awakenings
☐	wake time after sleep onset
☐	quality of sleep
☐	ability to concentrate in the morning
☐	morning sleepiness

Efficacy:

morning questionnaire

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

Evidence Table 13. Placebo controlled trials: Efficacy

Dockhorn, 1996 **Quality rating: Fair**

morning sleepiness (0=very sleepy; 100=not at all sleepy), day 3-10: Mean (SD)		
53.6 (2.2)	52.1 (2.3)	P: 0.762
clinical global impression scale		
Zolpidem	Placebo	
quality of sleep- excellent or good: %		
78	42	P: <0.001
change in sleep- improved a lot or somewhat: %		
84	48	P: <0.001
change in time to fall asleep: %		
81	42	P: <0.001
change in amount of sleep: %		
79	43	P: <0.001
strength of medication- just right: %		
62	28	P: <0.001
change during posttreatment days- much or somewhat better: %		
75	40	P: 0.002

Evidence Table 13. Placebo controlled trials: Efficacy

Dorsey, 2004 **Quality rating: Fair**

Design:

Study design: RCT DB Parallel **Run-in :** 6-14 days **Setting:** Multicenter

Wash out : NR **Country:** US

Sample:	Number Screened/	Eligible/	Enrolled	Number Withdrawn/	Lost to follow-up/	Analyzed
	242/	141/	141	16/	3/	141

Inclusion criteria:

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

Exclusion criteria:

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

Population: **Mean age:** 50.8 years **Ethnicity:** NR

Gender: 100% Female

Intervention:

Drug name	dosage	N=	Duration
Zolpidem	10 mg	68	28 day
Placebo	NA mg	73	28 day

Primary outcome	Outcome:
☐	sleep latency
☐	number of awakenings
☐	wake time after sleep onset
☐	sleep duration
☐	quality of sleep

Efficacy:

patients global impression rating

	Zolpidem	Placebo	
average summary score (lower score=better sleep): Mean	5.53	6.71	
number of patients with better sleep: %	76.8	43.8	P: <0.001

Evidence Table 13. Placebo controlled trials: Efficacy

Dorsey, 2004 **Quality rating: Fair**

sleep questionnaire

Zolpidem	Placebo	
change in sleep duration (min), 4 weeks average: Mean		
56.5	20.5	P: <0.01
wake after sleep onset (min), 4 weeks average: Mean		
29.75	52.75	P: <0.05
number of awakenings, 4 weeks average: Mean		
1.4	2	P: <0.05
sleep latency (min), 4 weeks average: Mean		
31.25	34.25	P: NS
sleep-related difficulty with daytime functioning: Mean		
2.1	2.2	P: <0.05
quality of life: Mean		
NR	NR	P: NS

Evidence Table 13. Placebo controlled trials: Efficacy

Erman, 2006 **Quality rating: Fair**

Design:

Study design: RCT DB Crossover **Run-in :** NR **Setting:** Multicenter

Wash out : 5-12 days **Country:** US

Sample:	Number Screened/	Eligible/	Enrolled	Number Withdrawn/	Lost to follow-up/	Analyzed
	319/	205/	107	4/	0/	103

Inclusion criteria:

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

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

Exclusion criteria:

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

Population: **Mean age:** 37.7 years **Ethnicity:** 54.7% Caucasian; 22.6 Hispanic; 21.7% Africa- American; 0.9% Asian

Gender: 64% Female

Intervention:

Drug name	dosage		N=	Duration
Ramelteon	4	mg	103	2 day
Ramelteon	8	mg	103	2 day
Ramelteon	16	mg	103	2 day
Ramelteon	32	mg	103	2 day
Placebo	NA	mg	103	2 day

Primary outcome	Outcome:
☑	sleep latency
☐	sleep duration
☐	sleep quality
☐	wake after sleep onset

Efficacy:

polysomnography

Ramelteon 4mg	Ramelteon 8mg	Ramelteon 16mg	Ramelteon 32mg	Placebo
PSG latency to persistent sleep, min: Number (p vs placebo)				
24.0 (<0.001)	24.3 (<0.001)	24.0 (<0.001)	22.9 (<0.001)	37.7 (NA)
PSG total sleep time, min: Number (p vs placebo)				
411.0 (<0.05)	412.9 (<0.01)	411.2 (<0.05)	418.2 (<0.001)	400.2 (NA)
PSG wake after sleep onset (WASO), min: Number (p vs placebo)				
48.8 (NS)	48.3 (NS)	48.3 (NS)	43.0 (NS)	45.5 (NA)

Evidence Table 13. Placebo controlled trials: Efficacy

Erman, 2006 **Quality rating: Fair**

post-sleep questionnaire

Ramelteon 4mg	Ramelteon 8mg	Ramelteon 16mg	Ramelteon 32mg	Placebo
Subjective sleep latency, min: Number (p vs placebo)				
50.9 (NS)	46.7 (NS)	43.9 (<0.05)	46.5 (NS)	57.0 (NA)
Subjective total sleep time, min: Number (p vs placebo)				
364.1 (NS)	370.4 (NS)	370.9 (NS)	372.8 (NS)	360.6 (NA)
Subjective sleep quality: Number (p vs placebo)				
3.6 (NS)	3.7 (NS)	3.7 (NS)	3.7 (NS)	3.8 (NA)
next day, level of alertness: Number (p vs placebo)				
3.5 (NS)	3.6 (NS)	3.5 (NS)	3.6 (NS)	3.6 (NA)
next day, ability to concentrate: Number (p vs placebo)				
3.5 (NS)	3.5 (NS)	3.5 (NS)	3.6 (NS)	3.6 (NA)

Evidence Table 13. Placebo controlled trials: Efficacy

Goldenberg, 1994 **Quality rating: Poor**

Design:

Study design: RCT DB Parallel **Run-in :** NR **Setting:** Multicenter
Wash out : NR **Country:** UK, France

Sample:	Number Screened/	Eligible/	Enrolled	Number Withdrawn/	Lost to follow-up/	Analyzed
	NR/	NR/	524	NR/	NR/	458

Inclusion criteria:

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

Exclusion criteria:

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

Population: **Mean age:** NR years **Ethnicity:** NR
Gender: % Female

Intervention:

Drug name	dosage	N=	Duration
Zopiclone	7.5 mg	231	48 day
Placebo	NA mg	227	44 day

Primary outcome	Outcome:
☐	quality of sleep
☐	quality of waking up
☐	feeling of well being during the day
☐	physician's overall evaluation

Efficacy:

Sleep efficiency at endpoint

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

Evidence Table 13. Placebo controlled trials: Efficacy

Goldenberg, 1994 **Quality rating: Poor**

Quality of life - change from baseline

Zopiclone	Placebo	
PGWBI: Score		
11.8	9.1	P: NS
SEQ: Score		
14.6	2.7	P: <0.0001
Activity: Score		
20	9.9	P: <0.0001
Social: Score		
13.1	5.7	P: <0.01
Profession: Score		
23.3	12.9	P: <0.01
Global: Score		
10.8	5.7	P: NS

Evidence Table 13. Placebo controlled trials: Efficacy

Hedner, 2000 **Quality rating: Fair**

Design:

Study design: RCT DB Parallel **Run-in :** 7 days **Setting:** Multicenter

Wash out : 7 days **Country:** Europe

Sample:	Number Screened/	Eligible/	Enrolled	Number Withdrawn/	Lost to follow-up/	Analyzed
	NR/	NR/	437	22/	NR/	422

Inclusion criteria:

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

Exclusion criteria:

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

Population: **Mean age:** 72.5 years **Ethnicity:** NR

Gender: % Female

Intervention:

Drug name	dosage	N=	Duration
Zaleplon	5 mg	139	14 day
Zaleplon	10 mg	145	14 day
Placebo	NA mg	138	14 day

Primary outcome	Outcome:
☐	sleep latency
☐	sleep duration
☐	number of awakenings
☐	sleep quality

Efficacy:

sleep questionnaire

	Zaleplon 5mg	Zaleplon 10mg	Placebo
subjective sleep latency (min), week 1: Median (p vs placebo)	43 (<0.001)	40 (<0.001)	60 (NA)
subjective sleep latency (min), week 2: Median (p vs placebo)	40 (<0.001)	37 (<0.001)	50 (NA)
subjective total sleep time (min), week 1: Median (p vs placebo)	342 (NS)	342.9 (<0.05)	346.1 (NA)
subjective total sleep time (min), week 2: Median (p vs placebo)	351.7 (NS)	351.4 (NS)	342.9 (NA)
subjective number of awakenings, week 1: Median (p vs placebo)	2 (NS)	2 (<0.05)	2 (NA)
subjective number of awakenings, week 2: Median (p vs placebo)	2 (NS)	1 (NS)	2 (NA)
subjective sleep quality, week 1 (score). 1=excellent; 7=extremely poor: Mean (p vs placebo)	3.8 (<0.01)	3.8 (<0.01)	3.9 (NA)
subjective sleep quality, week 2 (score). 1=excellent; 7=extremely poor: Mean (p vs placebo)	3.7 (<0.05)	3.7 (<0.05)	3.8 (NA)
subjective sleep quality, improvement in sleep quality- week 1: % (p vs placebo)	48 (NS)	55 (<0.0001)	36 (NA)
subjective sleep quality, improvement in sleep quality- week 2: % (p vs placebo)	53 (NS)	63 (<0.0001)	36 (NA)

Evidence Table 13. Placebo controlled trials: Efficacy

Herrmann, 1993 **Quality rating: Poor**

Design:

Study design: RCT DB Parallel **Run-in :** 7 days **Setting:** Single Center

Wash out : 7 days **Country:** France

Sample:	Number Screened/	Eligible/	Enrolled	Number Withdrawn/	Lost to follow-up/	Analyzed
	NR/	25/	21	NR/	NR/	21

Inclusion 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 screening for amphetamines, cannabinoids, morphine derivatives, barbiturates and benzodiazepines. Patients presenting with caffeinism or alcoholism, or shift workers were excluded.

Population: **Mean age:** NR years **Ethnicity:** NR

Gender: 43% Female

Intervention:

Drug name	dosage	N=	Duration
Zolpidem	10 mg	11	14 day
Placebo	NA mg	10	14 day

Primary outcome	Outcome:
☐	sleep efficiency
☐	sleep latency
☐	total sleep time
☐	number of awakenings
☐	wake after sleep onset

Efficacy:

polysomnography

	Zolpidem	Placebo	
sleep efficiency (%), day 21 treatment: Mean (SD)	86.2 (2)	78.3 (5)	P: <0.05
total sleep time (min), day 21 treatment: Mean (SD)	381.3 (10)	360.3 (23)	P: NS
sleep onset latency (min), day 21 treatment: Mean (SD)	28 (7)	41.7 (15)	P: NS
time awake (min), day 21 treatment: Mean (SD)	34.7 (7)	60 (12)	P: NS

sleep questionnaire

	Zolpidem	Placebo	
sleep onset latency (min), day 15-21 treatment: Mean (SD)	40.5 (10)	72.8 (10)	P: <0.05
total sleep time (min), day 15-21 treatment: Mean (SD)	372.7 (12)	327.4 (22)	P: NS
no. of awakenings, day 15-21 treatment: Mean (SD)	1.8 (0.4)	2.3 (0.4)	P: NS
calm/restless, fresh/fatigued, relaxed/anxious, lying down during the day: Mean (SD)	nulti-data (multi-datanulti-data (multi-data		P: NS

Evidence Table 13. Placebo controlled trials: Efficacy

Hindmarch, 1995 **Quality rating: Fair**

Design:

Study design: RCT DB Parallel **Run-in :** NR **Setting:** Multicenter
Wash out : NR **Country:** UK

Sample:	Number Screened/	Eligible/	Enrolled	Number Withdrawn/	Lost to follow-up/	Analyzed
	NR/	NR/	458	NR/	NR/	458

Inclusion 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.

Population: **Mean age:** 42.9 years **Ethnicity:** NR
Gender: 0% Female

Intervention:

Drug name	dosage	N=	Duration
Zopiclone	7.5 mg	231	48 day
Placebo	NA mg	227	42 day

Primary outcome	Outcome:
☐	quality of sleep
☐	quality of waking up
☐	daytime feeling of well being

Efficacy:

questionnaire

Zolpidem	Placebo	
psychological general well-being index (PGWBI), change from baseline, day 14: Mean		
11.8	9.1	P: NS
sleep evaluation questionnaire (SEQ), change from baseline, day 14: Mean		
14.6	2.7	P: <0.0001
activity, change from baseline, day 14: Mean		
20	9.9	P: <0.0001
social, change from baseline, day 14: Mean		
13.4	5.7	P: <0.01
profession, change from baseline, day 14: Mean		
23.3	12.9	P: <0.01
global, change from baseline, day 14: Mean		
10.8	5.7	P: NS
psychological general well-being index (PGWBI), change from baseline, endpoint: Mean		
15.2	12.9	P: NS
sleep evaluation questionnaire (SEQ), change from baseline, endpoint: Mean		
20.9	12.5	P: <0.0001
activity, change from baseline, endpoint: Mean		
21.6	14.2	P: <0.0001
social, change from baseline, endpoint: Mean		
14.9	9.1	P: <0.01

Evidence Table 13. Placebo controlled trials: Efficacy

Hindmarch, 1995		**Quality rating: Fair**
profession, change from baseline, endpoint: Mean		
24.5	18.7	P: NS
global, change from baseline, endpoint: Mean		
13.8	8.9	P: NS
physician's overall evaluation of treatment efficacy as "excellent" or "good" at endpoint: %		
76.7	51.4	

Evidence Table 13. Placebo controlled trials: Efficacy

Krystal (poster) **Quality rating: Fair**

Design:

Study design: RCT DB Parallel **Run-in :** 14 days **Setting:** Multicenter
Wash out : 14 days **Country:** US

Sample:	Number Screened/	Eligible/	Enrolled	Number Withdrawn/	Lost to follow-up/	Analyzed
	NR/	NR/	830	350/	80/	828

Inclusion criteria:
DSM-IV diagnosis of chronic primary insomnia;
Patient-reported average sleep time <= 6.5 hrs/night and/or sleep latency >30 min

Exclusion criteria:
NR

Population: **Mean age:** 45.6 years **Ethnicity:** Caucasian: 71%
Black: 16%
Gender: 61% Female

Intervention:

Drug name	dosage	N=	Duration
Eszopiclone	3 mg	548	180 day
Placebo	NA mg	280	180 day

Primary outcome	Outcome:
☐	sleep latency
☐	sleep maintenance
☐	sleep duration
☐	sleep quality
☐	insomnia severity index
☐	daytime functioning
☐	daytime alertness
☐	well being
☐	discontinuation effects

Efficacy:

Sleep efficacy

	Eszopiclone	Placebo
sleep latency, estimate from figures (data not reported) at month 1, min: median (p vs placebo)	29 (<0.0001)	53
sleep latency, estimate from figures (data not reported) at month 6, min: median (p vs placebo)	25 (<0.0001)	42
wake time after sleep onset, estimate from figures (data not reported) at month 1, min: median (p vs placebo)	18 (<0.0001)	33
wake time after sleep onset, estimate from figures (data not reported) at month 6, min: median (p vs placebo)	15 (<0.0001)	25
total sleep time, estimate from figures (data not reported) at month 1, min: median (p vs placebo)	380 (<0.0001)	330
total sleep time, estimate from figures (data not reported) at month 6, min: median (p vs placebo)	380 (<0.0001)	330
number of awakenings, estimate from figures (data not reported) at month 1: median (p vs placebo)	1.5 (<0.0005)	2.2
number of awakenings, estimate from figures (data not reported) at month 6: median (p vs placebo)	1.4 (<0.0005)	1.8

Evidence Table 13. Placebo controlled trials: Efficacy

Krystal (poster) **Quality rating: Fair**

total severity score with clinical categories at month 1: mean (p vs placebo)

10 (<0.0001)	14

total severity score with clinical categories at month 1: mean (p vs placebo)

8 (<0.0001)	12

Self report at end of treatment, higher=better

Eszopiclone	Placebo
sleep quality: mean (p vs placebo)	
2.5 (<0.0001)	1.7
feeling refreshed/rested: mean (p vs placebo)	
2.3 (<0.0001)	1.8
daytime fatigue: mean (p vs placebo)	
1.4 (<0.0001)	2.0
attention/concentration: mean (p vs placebo)	
1.1 (<0.0001)	1.6
relationship enjoyment: mean (p vs placebo)	
0.7 (<0.0001)	1.0
feeling refreshed/rested: mean (p vs placebo)	
2.3 (<0.0001)	1.8
mood disturbance: mean (p vs placebo)	
0.9 (<0.0001)	1.4
sleep difficulties (nights/wk): mean (p vs placebo)	
3.4 (<0.0001)	5.1
total score =<14: %	
74	46
total score 0-7: %	
44	14
total score 8-14: %	
30	32

Evidence Table 13. Placebo controlled trials: Efficacy

Krystal, 2003 **Quality rating: Fair**

Design:

Study design: RCT DB Parallel **Run-in :** NR **Setting:** Multicenter

Wash out : 5-7 days **Country:** US

Sample:	Number Screened/	Eligible/	Enrolled	Number Withdrawn/	Lost to follow-up/	Analyzed
	1194/	791/	788	320/	60/	788

Inclusion criteria:

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

Exclusion criteria:

NR

Population: **Mean age:** 44 years **Ethnicity:** 80% Caucasian
13.2% African American
Gender: 25% Female

Intervention:

Drug name	dosage		N=	Duration
Eszopiclone	3	mg	593	180 day
Placebo	NA	mg	195	180 day

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

Efficacy:

telephone interview

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

Evidence Table 13. Placebo controlled trials: Efficacy

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

Evidence Table 13. Placebo controlled trials: Efficacy

Lahmeyer, 1997 — Quality rating: Fair

Design:

Study design: RCT DB Parallel **Run-in :** 3 days **Setting:** Multicenter
Wash out : 4 days **Country:** US

Sample:	Number Screened/	Eligible/	Enrolled	Number Withdrawn/	Lost to follow-up/	Analyzed
	178/	33/	145	27/	0/	118

Inclusion criteria:

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

Population: **Mean age:** 44.9 years **Ethnicity:** 92% Caucasian, 6% black
Gender: 56% Female

Intervention:

Drug name	dosage	N=	Duration
Zolpidem	10 mg	45	31 day
Zolpidem	15 mg	46	31 day
Placebo	NA mg	54	31 day

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

Efficacy:

morning questionnaire - 4 weeks average

	Zolpidem 10mg	Zolpidem 15mg	Placebo
sleep latency (min), change from baseline - 4 weeks average: Mean	-30	-33.5	-9
total sleep time (min) - 4 weeks average: Mean	379	381	346
number of awakenings - 4 weeks average: Mean	1.3	1.3	1.9
sleep quality (1=excellent; 4=poor) - 4 weeks average: Mean	2.4	2.4	2.8

Evidence Table 13. Placebo controlled trials: Efficacy

Lahmeyer, 1997 **Quality rating: Fair**

morning questionnaire - at week 4

Zolpidem 10mg	Zolpidem 15mg	Placebo
sleep latency (min), change from baseline - at week 4: Mean (p vs placebo)		
-31 (<0.05)	-31 (NS)	-16 (NA)
total sleep time (min) - at week 4: Mean (p vs placebo)		
390 (NS)	385 (NS)	360 (NA)
number of awakenings - at week 4: Mean (p vs placebo)		
1.4 (NS)	1.2 (NS)	1.7 (NA)
sleep quality (1=excellent; 4=poor) - at week 4: Mean (p vs placebo)		
2.4 (NS)	2.4 (NS)	2.6 (NA)

morning questionnaire - post-treatment

Zolpidem 10mg	Zolpidem 15mg	Placebo
sleep latency (min), change from baseline - post-treatment: Mean (p vs placebo)		
-10 (NS)	-11 (NS)	-25 (NA)
total sleep time (min) - post-treatment: Mean (p vs placebo)		
354 (NS)	332 (NS)	359 (NA)
number of awakenings - post-treatment: Mean (p vs placebo)		
1.7 (NS)	1.9 (NS)	1.9 (NA)
sleep quality (1=excellent; 4=poor) - post-treatment: Mean (p vs placebo)		
2.8 (NS)	2.9 (NS)	2.8 (NA)

clinical global impression

Zolpidem 10mg	Zolpidem 15mg	Placebo
medication helped me - fall asleep faster: % (p vs placebo)		
84 (<0.05)	78 (<0.05)	51 (NA)
medication helped me - sleep longer: % (p vs placebo)		
78 (<0.05)	76 (NS)	51 (NA)
medication helped me - get a better night's sleep: % (p vs placebo)		
84 (,0.05)	84 (<0.05)	49 (NA)
medication strength - too strong: % (p vs placebo)		
0 (NS)	0 (NS)	0 (NA)
medication strength - strong enough: % (p vs placebo)		
71 (<0.05)	72 (<0.05)	44 (NA)
medication strength - too weak: % (p vs placebo)		
29 (NS)	28 (NS)	56 (NA)

Evidence Table 13. Placebo controlled trials: Efficacy

Monchesky, 1986 **Quality rating: Fair**

Design:

Study design: RCT DB Crossover **Run-in :** 7 days **Setting:** Single Center

Wash out : 7 days **Country:** Canada

Sample:	Number Screened/	Eligible/	Enrolled	Number Withdrawn/	Lost to follow-up/	Analyzed
	NR/	NR/	99	0/	2/	91

Inclusion criteria:

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

Exclusion criteria:

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

Population: **Mean age:** NR years **Ethnicity:** NR

Gender: 0% Female

Intervention:

Drug name	dosage	N=	Duration
Zopiclone	7.5 mg	91	7 day
Placebo	NA mg	91	7 day

Primary outcome	Outcome:
☐	sleepiness during the day
☐	sleep latency
☐	sleep duration
☐	number of awakenings

Efficacy:

sleep questionnaire

	Zolpidem	Placebo	
sleepiness during the day, treatment day 7: Mean	2.3	2.65	P: NR
sleep induction time (min), treatment day 7: Mean	51.85	89.9	P: NR
duration of sleep (min), treatment day 7: Mean	384.8	307.4	P: NR
number of awakenings, treatment day 7: Mean	1.8	3.5	P: NR
quality of sleep, treatment day 7: Mean	4.15	3.15	P: NR
soundness of sleep, treatment day 7: Mean	3.8	2.75	P: NR
morning state of rest, treatment day 7: Mean	2.85	1.95	P: NR
sleepiness during the day, treatment day 14 (switch): Mean	2.3	2.9	P: NR
sleep induction time (min), treatment day 14 (switch): Mean	53.8	119.3	P: NR
duration of sleep (min), treatment day 14 (switch): Mean	376.7	299.5	P: NR

Evidence Table 13. Placebo controlled trials: Efficacy

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

Evidence Table 13. Placebo controlled trials: Efficacy

Monti, 1996 **Quality rating: Fair**

Design:

Study design: RCT DB Parallel **Run-in :** 2 days **Setting:** Single Center
Wash out : 3 days **Country:** Uruguay

Sample:	Number Screened/	Eligible/	Enrolled	Number Withdrawn/	Lost to follow-up/	Analyzed
	NR/	NR/	12	NR/	NR/	12

Inclusion criteria:

All patients were suffering from at least 2 of the following sleep disturbances: time to fall asleep >30 minutes; total sleep time <6 hours,; total nocturnal wake time >20 minutes; number of nocturnal awakenings >3.

Exclusion criteria:

Pregnant women, women of child-bearing age with inadequate contraception, breastfeeding mothers, patients suffering from organic disease or severe psychiatric disorders, and patients in whom insufficient compliance was to be expected. Alcohol abuse or intake of hypnotics or anxiolytics and/or antidepressants in the seven days prior to the baseline period also led to exclusion.

Population: **Mean age:** 44.25 years **Ethnicity:** NR
Gender: 83% Female

Intervention:

Drug name	dosage	N=	Duration
Zolpidem	10 mg	6	27 day
Placebo	NA mg	6	27 day

Primary outcome	Outcome:
☐	sleep latency
☐	number of awakenings
☐	total wake time
☐	wake time after sleep onset
☐	total sleep time
☐	sleep efficiency
☐	movement time

Efficacy:

polysomnography

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

Evidence Table 13. Placebo controlled trials: Efficacy

Monti, 1996 **Quality rating: Fair**

questionnaire

Zolpidem	Placebo	
sleep latency (lower score indicates more positive response), night 29-30: Mean (SD)		
2.0 (0.4)	1.8 (0.5)	P: NS
sleep duration (higher score indicates more positive response), night 29-30: Mean (SD)		
2.3 (0.3)	2.5 (0.4)	P: NS
number of awakenings (lower score indicates more positive response), night 29-30: Mean (SD)		
2.6 (0.3)	1.9 (0.3)	P: NS
disturbed sleep (higher score indicates more positive response), night 29-30: Mean (SD)		
73.1 (8.7)	48.5 (8.3)	P: <0.01
daytime alertness (higher score indicates more positive response), night 29-30: Mean (SD)		
69.0 (9.5)	44.2 (8.4)	P: NS

Evidence Table 13. Placebo controlled trials: Efficacy

Monti, 2000 **Quality rating: Poor**

Design:

Study design: RCT DB Parallel **Run-in :** 3 days **Setting:** Single Center

Wash out : 3 days **Country:** Uruguay

Sample:	Number Screened/	Eligible/	Enrolled	Number Withdrawn/	Lost to follow-up/	Analyzed
	NR/	NR/	12	NR/	NR/	12

Inclusion criteria:

Patients aged between 27 and 59 years, with chronic primary insomnia according to the DSM-IV participated in the study.

Exclusion criteria:

Patients with poor health, acute or chronic pain, decompensated hepatic, renal or cardiac disease, known drug allergy or abuse, periodic leg movements during sleep, restless legs or sleep apnea were excluded from the study, and so were pregnant women and breast-feeding mothers.

Patients with poor health; acute or chronic pain; hepatic, renal, respiratory, cardiac, or neuropsychiatric diseases [subjects with a score of HAMD > 18, or a score of HAMA(14 items)>16 were not included]; known drug allergy or abuse; periodic leg movements during sleep; restless legs; or sleep apnea were excluded from the study, as also were pregnancy women, breast-feeding mothers, subjects deemed insufficiently compliant, or those with clinically significant deviations in their laboratory tests. Alcohol abuse, intake of hypnotics or anxiolytics in the seven days prior to baseline period, or a positive benzodiazepine urine screening also led to exclusion.

Population: **Mean age:** 51.9 years **Ethnicity:** NR

Gender: 100% Female

Intervention:

Drug name	dosage	N=	Duration
Zolpidem	10 mg	6	15 day
Placebo	NA mg	6	15 day

Primary outcome	Outcome:
☐	sleep latency
☐	number of awakenings
☐	wake time after sleep onset
☐	total sleep time
☐	sleep efficiency

Efficacy:

polygraphic sleep record

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

Evidence Table 13. Placebo controlled trials: Efficacy

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

Evidence Table 13. Placebo controlled trials: Efficacy

Perlis, 2004 **Quality rating: Fair**

Design:

Study design: RCT DB Parallel **Run-in :** 6-14 days **Setting:** Multicenter
Wash out : NR **Country:** US

Sample:	Number Screened/	Eligible/	Enrolled	Number Withdrawn/	Lost to follow-up/	Analyzed
	322/	277/	199	10/	3/	192

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

Population: **Mean age:** 40.8 years **Ethnicity:** 70% Euro American
Gender: 71% Female

Intervention:

Drug name	dosage	N=	Duration
Zolpidem	10 mg	98	84 day
Placebo	NA mg	101	84 day

Primary outcome	Outcome:
☑	sleep latency
☑	number of awakenings
☑	wake after sleep onset
☑	total sleep time

Efficacy:

sleep diaries

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

Evidence Table 13. Placebo controlled trials: Efficacy

Perlis, 2004		**Quality rating: Fair**
total sleep time (min), with pill: Mean (SD)		
417 (64.4)	359.8 (77.1)	P: <0.05
total sleep time (min), without pill: Mean (SD)		
NR (NR)	NR (NR)	P: NS
total sleep time (min), all condition: Mean (SD)		
394.1 (60.1)	355.6 (69.6)	P: <0.05
global outcome measure		
Zolpidem	Placebo	
IGR scale: Mean (SD)		
6 (0.12)	4.5 (0.14)	P: <0.001

Evidence Table 13. Placebo controlled trials: Efficacy

Roehrs (poster), 2005 **Quality rating: Fair**

Design:

Study design: RCT DB Parallel **Run-in :** no days **Setting:** Multicenter

Wash out : no days **Country:** US, Canada, Argentina, Germany, F

Sample:	Number Screened/	Eligible/	Enrolled	Number Withdrawn/	Lost to follow-up/	Analyzed
	NR/	NR/	205	7/	NR/	NR

Inclusion criteria:

DSM-IV-defined primary insomnia, WASO 1 hour per night for at least 3 nights per week during preceding month, and time in bed of 6.5 to 9 hours per night for 2 weeks prior to enrollment. A 2-night (screening) mean PSG WASO >= 40 minutes (not <30 minutes on either night), and total sleep time 3 to 7 hours each screening night was required.

Exclusion criteria:

Any DSM-IV Axis I psychiatric disorder, sleep disorder, history of substance abuse, use of any substance with CNS effects known to affect sleep, or use of over-the-counter or prescription sleep medication within 1 and 2 weeks prior to screening, respectively.

Population: **Mean age:** 70.2 years **Ethnicity:** 95.1% Caucasian; 4.9% other

Gender: 57% Female

Intervention:

Drug name	dosage	N=	Duration
zolpidem exten	6.25 mg	99	21 day
Placebo	NA mg	106	21 day

Primary outcome	Outcome:
☐	wake after sleep onset
☐	number of awakening
☐	total sleep time
☐	sleep onset latency
☐	sleep quality
☐	patient global impression

Efficacy:

polysomnography

	Zolpidem MR	Placebo	
wake time after sleep onset (WASO), mean change from baseline, Night 1 and 2: Minutes	-32	-6	P: 0.0042
wake time after sleep onset (WASO), mean change from baseline, Night 15 and 16: Minutes	-18	-6	P: <0.001
latency to persistent sleep (LPS), mean change from baseline, Night 1 and 2: Minutes	-17	-6	P: 0.0001
latency to persistent sleep (LPS), mean change from baseline, Night 15 and 16: Minutes	-14	-8	P: 0.0255
sleep efficiency (SE), total sleep time/time in bed x100: %	10.2	3	P: <0.0001
sleep efficiency (SE), total sleep time/time in bed x100: %	5.9	3.5	P: 0.0509

sleep questionnaire

	Zolpidem MR	Placebo	
Patient global impression and sleep quality, data NR: %	better	NR	P: 0.0001
Subjective sleep estimate, data NR: %	better	NR	P: <0.05

Evidence Table 13. Placebo controlled trials: Efficacy

Roth, 2006 **Quality rating: Fair**

Design:

Study design: RCT DB Parallel **Run-in :** 7 days **Setting:** Multicenter
Wash out : 7 days **Country:** US

Sample:	Number Screened/	Eligible/	Enrolled	Number Withdrawn/	Lost to follow-up/	Analyzed
	NR/	NR/	829	128/	NR/	NR

Inclusion criteria:

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

Exclusion criteria:

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

Population: **Mean age:** 72.4 years **Ethnicity:** Not reported
Gender: 0% Female

Intervention:

Drug name	dosage		N=	Duration
Ramelteon	4	mg	281	5 week
Ramelteon	8	mg	274	5 week
Placebo	NA	mg	274	5 week

Primary outcome	Outcome:
☑	Sleep latency
☐	Total sleep time
☐	Number of awakenings
☐	Ease of falling back to sleep
☐	Sleep quality
☐	CGI
☐	Rebound insomnia

Efficacy:

Subjective sleep latency

Ramelteon 4 mg	Ramelteon 8 mg	Placebo
Sleep latency at week 3, minutes (not reported if mean or median): Number (p vs placebo)		
64.9 (0.142)	60.3 (0.003)	69.3
Sleep latency at week 1, minutes (not reported if mean or median): Number (p vs placebo)		
64.9 (0.142)	60.3 (0.003)	69.3

Subjective total sleep time

Ramelteon 4 mg	Ramelteon 8 mg	Placebo
Total sleep time at week 1, minutes (not reported if mean or median): Number (p vs placebo)		
324.6 (0.004)	321.1 (0.055)	313.9
Total sleep time at week 3, minutes (not reported if mean or median): Number (p vs placebo)		
336.0 (0.007)	332.1 (0.071)	324.3
Total sleep time at week 5, minutes (not reported if mean or median): Number (p vs placebo)		
337.5 (0.104)	334.4 (0.347)	330.1

Evidence Table 13. Placebo controlled trials: Efficacy

Scharf, 1994 **Quality rating: Fair**

Design:

Study design: RCT DB Parallel **Run-in :** 11 days **Setting:** Multicenter

Wash out : 2 days **Country:** US

Sample:	Number Screened/	Eligible/	Enrolled	Number Withdrawn/	Lost to follow-up/	Analyzed
	178/	75/	75			

Inclusion criteria:

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

Exclusion criteria:

Population: **Mean age:** 38 years **Ethnicity:** 73.3% white, 26.7% non-white

Gender: 64% Female

Intervention:

Drug name	dosage	N=	Duration
Zolpidem	10 mg	26	35 day
Zolpidem	15 mg	25	35 day
Placebo	NA mg	24	35 day

Primary outcome	Outcome:
☑	sleep latency
☑	sleep efficiency
☐	total sleep time
☐	sleep quality
☐	ease of falling sleep

Efficacy:

polysomnography

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

Evidence Table 13. Placebo controlled trials: Efficacy

Scharf, 1994 **Quality rating: Fair**

morning questionnaire

Zolpidem 10mg	Zolpidem 15mg	Placebo
sleep latency (min), week 6: Mean (p vs placebo)		
38.4 (NS)	31.7 (<0.05)	56.6 (NA)
ease of falling sleep (0=very easy; 100=not easy), week 6: Mean (p vs placebo)		
50.7 (NS)	35.7 (<0.05)	48.4 (NA)
sleep quality (1=excellent; 4=poor), week 6: Mean (p vs placebo)		
2.5 (NS)	2.5 (NS)	2.6 (NA)
total sleep time (min), week 6: Mean (p vs placebo)		
369 (NS)	394 (NS)	356 (NA)
sleep latency (min), posttreatment: Mean (p vs placebo)		
62.3 (NS)	78.2 (NS)	47.5 (NA)
ease of falling sleep (0=very easy; 100=not easy), posttreatment: Mean (p vs placebo)		
63.7 (NS)	64.0 (<0.05)	44.4 (NA)
sleep quality (1=excellent; 4=poor), posttreatment: Mean (p vs placebo)		
2.9 (<0.05)	3.1 (<0.05)	2.6 (NA)
total sleep time (min), posttreatment: Mean (p vs placebo)		
333 (NS)	341 (NS)	333 (NA)
tolerance assessment, change from week 2 to week 6: Mean (p vs placebo)		
multi-data (NS)	multi-data (NS)	multi-data (NA)

Evidence Table 13. Placebo controlled trials: Efficacy

Scharf, 2005 **Quality rating: Fair**

Design:

Study design: RCT DB Parallel **Run-in :** 3-14 days **Setting:** Multicenter
Wash out : NR **Country:** US

Sample:	Number Screened/	Eligible/	Enrolled	Number Withdrawn/	Lost to follow-up/	Analyzed
	353/	NR/	231	21/	NR/	231

Inclusion criteria:

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

Exclusion criteria:

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

Population: **Mean age:** 72.3 years **Ethnicity:** 89.4% Caucasian, 2.2% black
Gender: 58% Female

Intervention:

Drug name	dosage	N=	Duration
Eszopiclone	1 mg	72	14 day
Eszopiclone	2 mg	79	14 day
Placebo	NA mg	80	14 day

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

Efficacy:

morning questionnaire

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

Evidence Table 13. Placebo controlled trials: Efficacy

Scharf, 2005 **Quality rating: Fair**

evening questionnaire

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

Evidence Table 13. Placebo controlled trials: Efficacy

Soubrane (poster), 2005 **Quality rating: Fair**

Design:

Study design: RCT DB Parallel **Run-in :** NR **Setting:** Multicenter
Wash out : NR **Country:** US

Sample:	Number Screened/	Eligible/	Enrolled	Number Withdrawn/	Lost to follow-up/	Analyzed
	NR/	NR/	212	20/	NR/	NR

Inclusion criteria:

DSM-IV-defined primary insomnia, WASO 1 hour per night at least 3 nights per week during the preceding month, and time in bed of 6.5 to 9 hours per night during the 2 weeks prior to enrollment.

Exclusion criteria:

Any DSM-IV Axis I psychiatric disorder, sleep disorder, history of substance abuse, use of any substance with CNS effects known to affect sleep, or use of over-the-counter or prescription sleep medication within 1 and 2 weeks prior to screening, respectively.

Population: **Mean age:** 44.4 years **Ethnicity:** 90% Caucasian, 10% other
Gender: 58% Female

Intervention:

Drug name	dosage	N=	Duration
Zolpidem-CR	12.5 mg	102	3 week
Placebo	NA mg	110	3 week

Primary outcome	Outcome:
☐	wake time after sleep onset
☐	total sleep time
☐	latency to persistent sleep
☐	number of awakenings
☐	sleep quality
☐	patient global impression

Efficacy:

polysomnography

Zolpidem MR	Placebo	
wake time after sleep onset, mean change from baseline, night 1 and 2: Minute		
-33	-10	P: <0.0001
wake time after sleep onset, mean change from baseline, night 15 and 16: Minute		
-30	-13	P: <0.0001
number of awakenings, mean change from baseline, night 1 and 2: Number		
-3.0	-0.9	P: <0.0001
number of awakenings, mean change from baseline, night 15 and 16: Number		
-2.7	-0.8	P: <0.0001
latency to persistent sleep, mean change from baseline, night 1 and 2: Minute		
-23	-13	P: <0.0001
latency to persistent sleep, mean change from baseline, night 15 and 16: Minute		
-21	-13	P: 0.0338
sleep efficiency, total sleep time / time in bed x100, night 1 and 2: %		
13	5.5	P: <0.0001
sleep efficiency, total sleep time / time in bed x100, night 1 and 2: %		
9.4	6.4	P: 0.0172

Evidence Table 13. Placebo controlled trials: Efficacy

Soubrane (poster), 2005 **Quality rating: Fair**

sleep questionnaire

Zolpidem MR	Placebo	
patients global impression and sleep quality, day 2, 15, 22: %		
better	multiple data	P: <0.005
patients global impression and sleep quality, day 2, 15, 22: %		
better	data NR	P: <0.005

Evidence Table 13. Placebo controlled trials: Efficacy

Terzano, 1992 **Quality rating: Poor**

Design:

Study design: RCT DB Parallel **Run-in :** 14 days **Setting:** Single Center
Wash out : NR **Country:** Italy

Sample:	Number Screened/	Eligible/	Enrolled	Number Withdrawn/	Lost to follow-up/	Analyzed
	NR/	NR/	12	NR/	NR/	12

Inclusion 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

Population: **Mean age:** 49.6 years **Ethnicity:** NR
Gender: 67% Female

Intervention:

Drug name	dosage	N=	Duration
Zolpidem	10 mg	0	1 day
Placebo	NA mg	0	1 day

Primary outcome	Outcome:
☐	sleep latency
☐	wake after sleep onset
☐	total sleep time

Efficacy:

polysomnography

Zolpidem	Placebo	
sleep latency (min): Mean (SD)		
8.1 (7.1)	14.5 (14)	P: NR
wake after sleep onset (min): Mean		
16	41	P: NR
total sleep time (min): Mean (SD)		
420 (49.7)	402 (37.9)	P: NR

Evidence Table 13. Placebo controlled trials: Efficacy

Walsh, 2000a **Quality rating: Poor**

Design:

Study design: RCT DB Parallel **Run-in :** 5-12 days **Setting:** Multicenter

Wash out : 5-12 days **Country:** US

Sample:	Number Screened/	Eligible/	Enrolled	Number Withdrawn/	Lost to follow-up/	Analyzed
	311/	54/	48	NR/	NR/	48

Inclusion criteria:

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

Exclusion criteria:

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

Population: **Mean age:** 67.5 years **Ethnicity:** NR

Gender: 35% Female

Intervention:

Drug name	dosage		N=	Duration
Zaleplon	2	mg	12	2 day
Zaleplon	5	mg	12	2 day
Zaleplon	10	mg	12	2 day
Placebo	NA	mg	12	2 day

Primary outcome	Outcome:
☑	sleep latency
☑	sleep duration
☑	number of awakenings

Efficacy:

polysomnography

Zaleplon 2mg	Zaleplon 5mg	Zaleplon 10mg	Placebo
PSG latency to persistent sleep (min): Mean (p vs placebo)			
30.4 (0.015)	26.0 (<0.001)	21.8 (<0.001)	47.7 (NA)
PSG total sleep time (min): Mean (p vs placebo)			
359.3 (0.239)	363.9 (0.003)	362.8 (0.03)	351.2 (NA)
PSG no. of awakenings: Mean (p vs placebo)			
21.6 (0.872)	21.9 (0.623)	22.1 (0.969)	21.6 (NA)

questionnaire

Zaleplon 2mg	Zaleplon 5mg	Zaleplon 10mg	Placebo
subjective sleep latency (min): Mean (p vs placebo)			
55.2 (0.654)	42.0 (0.017)	34.4 (<0.001)	58.3 (NA)
subjective total sleep time (min): Mean (p vs placebo)			
335.8 (0.776)	343.2 (0.140)	351.6 (0.011)	327.9 (NA)
subjective no. of awakenings: Mean (p vs placebo)			
3.4 (0.671)	3.1 (0.906)	2.8 (0.045)	3.3 (NA)

Evidence Table 13. Placebo controlled trials: Efficacy

Walsh, 2000b, 2002 **Quality rating: Fair**

Design:

Study design: RCT DB Parallel **Run-in :** 7 days **Setting:** Multicenter
Wash out : 7 days **Country:** US

Sample:	Number Screened/	Eligible/	Enrolled	Number Withdrawn/	Lost to follow-up/	Analyzed
	365/	163/	163	29/	5/	NR

Inclusion criteria:

1) DSM-IV diagnosis of primary insomnia 2) reported sleep latency (SL) > 45 minutes, or total sleep time (TST) < 6.5 hours, and insomnia-related daytime complaints on at least three of the seven baseline days 3) nightly time-in-bed between 6.5 and 9.0 hours; bedtime and rise time 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 function 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

Population: **Mean age:** 44.1 years **Ethnicity:** 83.4% Caucasian, 16.6% other
Gender: 71% Female

Intervention:

Drug name	dosage	N=	Duration
Zolpidem	10 mg	82	56 day
Placebo	NA mg	81	56 day

Primary outcome	Outcome:
☐	sleep latency
☐	total sleep time
☐	number of awakenings
☐	sleep quality

Efficacy:

morning questionnaire

	Zolpidem	Placebo	
sleep latency (min), all condition, 8 weeks average: Mean	12.39	19.55	P: NS
sleep latency (min), with pill, 8 weeks average: Mean	36.7	50.4	P: <0.05
total sleep time (min), with pill, 8 weeks average: Mean	415.4	364.1	P: <0.05
number of awakenings, with pill, 8 weeks average: Mean	1.1	1.8	P: <0.05
sleep quality (1=excellent; 4=poor), with pill, 8 weeks average: Mean	2.1	2.5	P: <0.05

SF-36

	Zolpidem	Placebo	
quality of life: Mean	multi-data	multi-data	P: NS

Evidence Table 13. Placebo controlled trials: Efficacy

Zammit, 2004 **Quality rating: Fair**

Design:

Study design: RCT DB Parallel **Run-in :** 2 days **Setting:** Single Center
Wash out : 5-7 days **Country:** US

Sample:	Number Screened/	Eligible/	Enrolled	Number Withdrawn/	Lost to follow-up/	Analyzed
	NR/	669/	308	16/	0/	308

Inclusion 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.

Population: **Mean age:** 39.8 years **Ethnicity:** 66.2% Caucasians, 16.6% black
Gender: 61% Female

Intervention:

Drug name	dosage		N=	Duration
Eszopiclone	2	mg	104	44 day
Eszopiclone	3	mg	105	44 day
Placebo	NA	mg	99	44 day

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

Efficacy:

polysomnography

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

Evidence Table 13. Placebo controlled trials: Efficacy

Zammit, 2004 **Quality rating: Fair**

morning questionnaire

Eszopiclone 2mg	Eszopiclone 3mg	Placebo
sleep latency (min): Median (p vs placebo)		
30 (<0.0001)	27.7 (<0.0001)	46 (NA)
total sleep time (min): Median (p vs placebo)		
400 (0.0207)	406 (<0.0001)	366 (NA)
number of awakenings: Median (p vs placebo)		
2.7 (0.2956)	2.4 (0.1720)	3.0 (NA)
WASO (min): Median (p vs placebo)		
37.1 (0.6884)	30.2 (0.0204)	45 (NA)
quality of sleep (0=poor; 100=excellent): Median (p vs placebo)		
54.5 (0.0414)	56.6 (0.0072)	47.7 (NA)
depth of sleep (0=poor; 100=excellent): Median (p vs placebo)		
58.9 (0.0052)	56.7 (0.0457)	51.7 (NA)

evening questionnaire

Eszopiclone 2mg	Eszopiclone 3mg	Placebo
daytime alertness (higher scores indicate improved function): Mean (p vs placebo)		
6.66 (0.873)	7.02 (0.059)	6.67 (NA)
daytime ability to function (higher scores indicate improved function): Mean (p vs placebo)		
6.81 (0.901)	7.15 (0.118)	6.83 (NA)
morning sleepiness (1=very sleepy; 100=not at all sleepy): Mean (p vs placebo)		
51.3 (0.256)	50.8 (0.344)	48.2 (NA)

Evidence Table 14. Placebo controlled trials: Rebound

Hedner, 2000 **Quality rating: Fair**

Design:

Study design: RCT DB Parallel **Run-in :** 7 days **Setting:** Multicenter
Wash out : 7 days **Country:** Europe

Sample:	Number Screened/	Eligible/	Enrolled	Number Withdrawn/	Lost to follow-up/	Analyzed
	NR/	NR/	437	22/	NR/	422

Inclusion criteria:

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

Exclusion criteria:

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

Population: **Mean age:** 72.5 years **Ethnicity:** NR
Gender: % Female

Intervention:

Drug name	dosage	N=	Duration
Zaleplon	5 mg	139	14 day
Zaleplon	10 mg	145	14 day
Placebo	NA mg	138	14 day

Rebound:

sleep questionnaire - rebound insomnia

	Zaleplon 5mg	Zaleplon 10mg	Placebo
rebound: subjective sleep latency (min), withdrawal day 1: Median	45	50	60
rebound: subjective total sleep time (min), withdrawal day 1: Median	330	300	330
rebound: subjective number of awakenings, withdrawal day 1: Median	2	2	2

incidence of rebound insomnia

	Zaleplon 5mg	Zaleplon 10mg	Placebo
rebound insomnia: subjective sleep latency: Number (%)	11 (9)	12 (9)	7 (5)
rebound insomnia: subjective total sleep time: Number (%)	14 (11)	17 (13)	6 (5)
rebound insomnia: number of awakenings: Number (%)	7 (6)	4 (3)	7 (6)

Evidence Table 14. Placebo controlled trials: Rebound

Herrmann, 1993 **Quality rating: Poor**

Design:

Study design: RCT DB Parallel **Run-in :** 7 days **Setting:** Single Center

Wash out : 7 days **Country:** France

Sample:	Number Screened/	Eligible/	Enrolled	Number Withdrawn/	Lost to follow-up/	Analyzed
	NR/	25/	21	NR/	NR/	21

Inclusion 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 screening for amphetamines, cannabinoids, morphine derivatives, barbiturates and benzodiazepines. Patients presenting with caffeinism or alcoholism, or shift workers were excluded.

Population: **Mean age:** NR years **Ethnicity:** NR

Gender: 43% Female

Intervention:

Drug name	dosage	N=	Duration
Zolpidem	10 mg	11	14 day
Placebo	NA mg	10	14 day

Rebound:

polysomnography

	Zolpidem	Placebo	
sleep efficiency (%), day 28 withdrawal, rebound: Mean (SD)	77.4 (4)	68.9 (4)	P: <0.05
total sleep time (min), day 28 withdrawal, rebound: Mean (SD)	341.3 (12)	298.3 (21)	P: <0.05
sleep onset latency (min), day 28 withdrawals, rebound: Mean (SD)	50.7 (11)	36.3 (7)	P: NS
time awake (min), day 28 withdrawal, rebound: Mean (SD)	53.7 (13)	99.3 (17)	P: <0.05

sleep questionnaire

	Zolpidem	Placebo	
sleep onset latency (min), day 22-28 withdrawal, rebound: Mean (SD)	60.8 (14)	70.8 (10)	P: NS
total sleep time (min), day 22-28 withdrawal, rebound: Mean (SD)	341.8 (18)	310.9 (21)	P: NS
no. of awakenings, day 22-28 withdrawal, rebound: Mean (SD)	2.4 (0.5)	2.5 (0)	P: NS

Evidence Table 14. Placebo controlled trials: Rebound

Monti, 1996 **Quality rating: Fair**

Design:

Study design: RCT DB Parallel **Run-in :** 2 days **Setting:** Single Center

Wash out : 3 days **Country:** Uruguay

Sample:	Number Screened/	Eligible/	Enrolled	Number Withdrawn/	Lost to follow-up/	Analyzed
	NR/	NR/	12	NR/	NR/	12

Inclusion criteria:

All patients were suffering from at least 2 of the following sleep disturbances: time to fall asleep >30 minutes; total sleep time <6 hours,; total nocturnal wake time >20 minutes; number of nocturnal awakenings >3.

Exclusion criteria:

Pregnant women, women of child-bearing age with inadequate contraception, breastfeeding mothers, patients suffering from organic disease or severe psychiatric disorders, and patients in whom insufficient compliance was to be expected. Alcohol abuse or intake of hypnotics or anxiolytics and/or antidepressants in the seven days prior to the baseline period also led to exclusion.

Population: **Mean age:** 44.25 years **Ethnicity:** NR

Gender: 83% Female

Intervention:

Drug name	dosage	N=	Duration
Zolpidem	10 mg	6	27 day
Placebo	NA mg	6	27 day

Rebound:

polysomnography

	Zolpidem	Placebo	
stage 2 sleep latency (min), nights 31-33, withdrawal, rebound: Mean (SD)	47.2 (11.1)	32.3 (7.9)	P: NS
total number of awakenings, nights 31-33, withdrawal, rebound: Mean (SD)	28.7 (4.6)	26.1 (3.7)	P: NS
total wake time (min), nights 31-33, withdrawal, rebound: Mean (SD)	97.7 (15.8)	115.9 (18.8)	P: NS
wake time after sleep onset (min), nights 31-33, withdrawal, rebound: Mean (SD)	54.9 (16.1)	92.0 (16.3)	P: NS
total sleep time (min), nights 31-33, withdrawal, rebound: Mean (SD)	378.6 (15.3)	361.2 (17.9)	P: NS
sleep efficiency (%), nights 31-33, withdrawal, rebound: Mean (SD)	79.0 (3.7)	75.3 (3.7)	P: NS
movement time, nights 31-33, withdrawal, rebound: Mean (SD)	3.7 (0.8)	2.9 (0.7)	P: NS

Evidence Table 14. Placebo controlled trials: Rebound

Monti, 1996 **Quality rating: Fair**

questionnaire

Zolpidem	Placebo	
sleep latency (lower score indicates more positive response), night 31-33, withdrawal, rebound: Mean (SD)		
2.4 (0.4)	1.9 (0.3)	P: NS
sleep duration (higher score indicates more positive response), night 31-33, withdrawal, rebound: Mean (SD)		
2.1 (0.2)	2.4 (0.3)	P: NS
number of awakenings (lower score indicates more positive response), night 31-33, withdrawal, rebound: Mean (SD)		
2.3 (0.4)	2.6 (0.3)	P: NS
disturbed sleep (higher score indicates more positive response), night 31-33, withdrawal, rebound: Mean (SD)		
64.9 (8.2)	63.7 (6.8)	P: NS
daytime alertness (higher score indicates more positive response), night 31-33, withdrawal, rebound: Mean (SD)		
73.8 (7.0)	54.1 (7.0)	P: <0.05

Evidence Table 14. Placebo controlled trials: Rebound

Monti, 2000 **Quality rating: Poor**

Design:

Study design: RCT DB Parallel **Run-in :** 3 days **Setting:** Single Center

Wash out : 3 days **Country:** Uruguay

Sample:	Number Screened/	Eligible/	Enrolled	Number Withdrawn/	Lost to follow-up/	Analyzed
	NR/	NR/	12	NR/	NR/	12

Inclusion criteria:

Patients aged between 27 and 59 years, with chronic primary insomnia according to the DSM-IV participated in the study.

Exclusion criteria:

Patients with poor health, acute or chronic pain, decompensated hepatic, renal or cardiac disease, known drug allergy or abuse, periodic leg movements during sleep, restless legs or sleep apnea were excluded from the study, and so were pregnant women and breast-feeding mothers.

Patients with poor health; acute or chronic pain; hepatic, renal, respiratory, cardiac, or neuropsychiatric diseases [subjects with a score of HAMD > 18, or a score of HAMA(14 items)>16 were not included]; known drug allergy or abuse; periodic leg movements during sleep; restless legs; or sleep apnea were excluded from the study, as also were pregnancy women, breast-feeding mothers, subjects deemed insufficiently compliant, or those with clinically significant deviations in their laboratory tests. Alcohol abuse, intake of hypnotics or anxiolytics in the seven days prior to baseline period, or a positive benzodiazepine urine screening also led to exclusion.

Population: **Mean age:** 51.9 years **Ethnicity:** NR

Gender: 100% Female

Intervention:

Drug name	dosage	N=	Duration
Zolpidem	10 mg	6	15 day
Placebo	NA mg	6	15 day

Rebound:

polygraphic sleep record

	Zolpidem	Placebo	
stage 2 sleep latency - night 19-21, withdrawal, rebound: Mean (SD)	55.7 (15.7)	69.7 (12.5)	P: NS
total number of awakenings - night 19-21, withdrawal, rebound: Mean (SD)	25.4 (3.8)	32.2 (5.9)	P: NS
waking time after sleep onset (min) - night 19-21, withdrawal, rebound: Mean (SD)	75.1 (7.9)	137.5 (29.2)	P: NS
total sleep time (min) - night 19-21, withdrawal, rebound: Mean (SD)	334.6 (22)	281.6 (33.2)	P: NS
sleep efficiency (%) - night 19-21, withdrawal, rebound: Mean (SD)	69.7 (4.6)	58.6 (6.9)	P: NS

Evidence Table 14. Placebo controlled trials: Rebound

Monti, 2000 **Quality rating: Poor**

interview

Zolpidem	Placebo	
sleep latency (min) - night 19-21, withdrawal, rebound: Mean (SD)		
94.3 (48.5)	118.4 (34.2)	P: NS
sleep duration (min) - night 19-21, withdrawal, rebound: Mean (SD)		
342.0 (47.5)	207.4 (70.5)	P: NS
disturbed sleep - night 19-21 (1=agree; 100=disagree), withdrawal, rebound: Mean (SD)		
62.7 (11.4)	56.8 (9.3)	P: NS
alert in the morning - night 19-21 (1=agree; 100=disagree), withdrawal, rebound: Mean (SD)		
37.9 (9.5)	61.5 (9.8)	P: NS

Evidence Table 14. Placebo controlled trials: Rebound

Zammit, 2004 **Quality rating: Fair**

Design:

Study design: RCT DB Parallel **Run-in :** 2 days **Setting:** Single Center

Wash out : 5-7 days **Country:** US

Sample:	Number Screened/	Eligible/	Enrolled	Number Withdrawn/	Lost to follow-up/	Analyzed
	NR/	669/	308	16/	0/	308

Inclusion 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.

Population: **Mean age:** 39.8 years **Ethnicity:** 66.2% Caucasians, 16.6% black

Gender: 61% Female

Intervention:

Drug name	dosage		N=	Duration
Eszopiclone	2	mg	104	44 day
Eszopiclone	3	mg	105	44 day
Placebo	NA	mg	99	44 day

Rebound:

polysomnography

	Eszopiclone 2mg	Eszopiclone 3mg
sleep latency (min), rebound insomnia, change vs baseline: Mean (p vs baseline)	NR (NS)	-8.5 (<0.05)
sleep efficiency (%), rebound insomnia, change vs baseline: Mean (p vs baseline)	-2.5 (<0.05)	3.7 (<0.05)
WASO (min), rebound insomnia, change vs baseline: Mean (p vs baseline)	7 (<0.05)	NR (NS)

Evidence Table 15. Placebo controlled trials: Adverse Events

Allain, 1998 **Quality rating: Fair**

Design:

Study design: RCT DB Parallel **Run-in :** 3 days **Setting:** Multicenter

Wash out : 3 days **Country:** France

Sample:	Number Screened/	Eligible/	Enrolled	Number Withdrawn/	Lost to follow-up/	Analyzed
	NR/	NR/	37	18/	NR/	37

Inclusion 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 susceptible 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 women; liver or respiratory failure, myasthenia, or epilepsy.

Population: **Mean age:** 51.9 years **Ethnicity:** NR

Gender: 0% Female

Intervention:

Drug name	dosage	N=	Duration
Zolpidem	10 mg	18	21 day
Placebo	NA mg	19	21 day

Adverse Events:

adverse events

	Zolpidem	Placebo
rebound insomnia: Total (Withdrawal)	0 (0)	15 (14)

withdrawals

	Zolpidem	Placebo
total withdrawals: Number	1	17
withdrawals due to AEs: Number	1	17

Evidence Table 15. Placebo controlled trials: Adverse Events

Allain, 2001 **Quality rating: Fair**

Design:

Study design: RCT DB Parallel **Run-in :** 3-7 days **Setting:** Multicenter
Wash out : NR **Country:** France

Sample:	Number Screened/	Eligible/	Enrolled	Number Withdrawn/	Lost to follow-up/	Analyzed
	NR/	NR/	245	NR/	NR/	245

Inclusion criteria:

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

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

Exclusion criteria:

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

Population: **Mean age:** 46.1 years **Ethnicity:** NR
Gender: 77% Female

Intervention:

Drug name	dosage	N=	Duration
Zolpidem	10 mg	124	28 day
Placebo	NA mg	121	28 day

Adverse Events:

treatment-emergent adverse events

	Zolpidem	Placebo	
overall: Number (%)	23 (19)	18 (15)	P: NS
anxiety: %	4	0	P: NR
headache: %	3.2	0	P: NR
rhinitis: %	0	3.3	P: NR

Withdrawals

	Zolpidem	Placebo
total withdrawals: Number	3	7
withdrawals due to AEs: Number	1	1

Evidence Table 15. Placebo controlled trials: Adverse Events

Chaudoir, 1983 **Quality rating: Poor**

Design:

Study design: RCT DB Crossover **Run-in :** NR **Setting:** Single Center

Wash out : NR **Country:** UK

Sample:	Number Screened/	Eligible/	Enrolled	Number Withdrawn/	Lost to follow-up/	Analyzed
	NR/	30/	25	5/	0/	25

Inclusion criteria:

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

Exclusion criteria:

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

Population: **Mean age:** 50 years **Ethnicity:** NR

Gender: 72% Female

Intervention:

Drug name	dosage	N=	Duration
Zopiclone	7.5 mg	25	7 day
Placebo	NA mg	25	7 day

Adverse Events:

40-item symptom check-list

	Zopiclone	Placebo	
bitter taste (data NR): Number			
	more	less	P: NR
overall adverse event: Number			
	5	2	P: NR
drowsiness/dizziness: Number			
	2	1	P: NR

withdrawals

	Zopiclone	Placebo
total withdrawals: Number		
	2	3
withdrawals due to AEs: Number		
	2	3

Evidence Table 15. Placebo controlled trials: Adverse Events

Dockhorn, 1996 **Quality rating: Fair**

Design:

Study design: RCT DB Parallel **Run-in :** NR **Setting:** Multicenter

Wash out : NR **Country:** US

Sample:	Number Screened/	Eligible/	Enrolled	Number Withdrawn/	Lost to follow-up/	Analyzed
	NR/	NR/	138	9/	2/	136

Inclusion criteria:

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

Exclusion criteria:

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

Population: **Mean age:** 32.7 years **Ethnicity:** NR

Gender: 58% Female

Intervention:

Drug name	dosage		N=	Duration
Zolpidem	10	mg	68	7-10 day
Placebo	NA	mg	68	7-10 day

Adverse Events:

adverse events

	Zolpidem	Placebo
headache: %	31.9	24.6
drowsiness: %	5.8	1.4
diarrhea: %	4.3	0
dizziness: %	4.3	0
myalgia: %	1.4	4.3
nausea: %	1.4	4.3

withdrawals

	Zolpidem	Placebo
total withdrawals: Number	3	6
withdrawals due to AEs: Number	1	2

Evidence Table 15. Placebo controlled trials: Adverse Events

Dorsey, 2004 **Quality rating: Fair**

Design:

Study design: RCT DB Parallel **Run-in :** 6-14 days **Setting:** Multicenter

Wash out : NR **Country:** US

Sample:	Number Screened/	Eligible/	Enrolled	Number Withdrawn/	Lost to follow-up/	Analyzed
	242/	141/	141	16/	3/	141

Inclusion criteria:

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

Exclusion criteria:

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

Population: **Mean age:** 50.8 years **Ethnicity:** NR

Gender: 100% Female

Intervention:

Drug name	dosage	N=	Duration
Zolpidem	10 mg	68	28 day
Placebo	NA mg	73	28 day

Adverse Events:

overall

	Zolpidem	Placebo	
headache: Number (%)			
	36 (52.9)	24 (32.9)	P: 0.08
upper respiratory tract infection: Number (%)			
	11 (16.2)	5 (6.8)	P: 0.11
drowsiness: Number (%)			
	7 (10.3)	1 (4)	P: 0.03
dizziness: Number (%)			
	6 (8.8)	0 (0)	P: 0.01
backache: Number (%)			
	5 (7.4)	0 (0)	P: 0.02
irritability: Number (%)			
	5 (7.4)	2 (2.7)	P: 0.02

withdrawals

	Zolpidem	Placebo
total withdrawals: Number		
	11	5
withdrawals due to AEs: Number		
	5	2

Evidence Table 15. Placebo controlled trials: Adverse Events

Erman, 2006 **Quality rating: Fair**

Design:

Study design: RCT DB Crossover **Run-in :** NR **Setting:** Multicenter

Wash out : 5-12 days **Country:** US

Sample:	Number Screened/	Eligible/	Enrolled	Number Withdrawn/	Lost to follow-up/	Analyzed
	319/	205/	107	4/	0/	103

Inclusion criteria:

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

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

Exclusion criteria:

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

Population: **Mean age:** 37.7 years **Ethnicity:** 54.7% Caucasian; 22.6 Hispanic; 21.7% Africa- American; 0.9% Asian

Gender: 64% Female

Intervention:

Drug name	dosage		N=	Duration
Ramelteon	4	mg	103	2 day
Ramelteon	8	mg	103	2 day
Ramelteon	16	mg	103	2 day
Ramelteon	32	mg	103	2 day
Placebo	NA	mg	103	2 day

Adverse Events:

treatment-emergent adverse events

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

Evidence Table 15. Placebo controlled trials: Adverse Events

Erman, 2006				**Quality rating: Fair**
influenza: %				
1.0	1.0	0.0	0.0	2.9
abdominal pain, upper: %				
1.0	1.0	0.9	0.0	1.0
dysmenorrhea: %				
1.9	1.0	0.0	1.0	0.0
dry mouth: %				
1.9	0.0	0.0	0.0	1.0
fatigue: %				
0.0	1.0	0.9	1.9	0.0
Total withdrawals = 4: Number				
NR	NR	NR	NR	NR
Withdrawals due to adverse events: Number				
0	0	0	0	0

Evidence Table 15. Placebo controlled trials: Adverse Events

Goldenberg, 1994 **Quality rating: Poor**

Design:

Study design: RCT DB Parallel **Run-in :** NR **Setting:** Multicenter

Wash out : NR **Country:** UK, France

Sample:	Number Screened/	Eligible/	Enrolled	Number Withdrawn/	Lost to follow-up/	Analyzed
	NR/	NR/	524	NR/	NR/	458

Inclusion criteria:

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

Exclusion criteria:

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

Population: **Mean age:** NR years **Ethnicity:** NR

Gender: % Female

Intervention:

Drug name	dosage	N=	Duration
Zopiclone	7.5 mg	231	48 day
Placebo	NA mg	227	44 day

Adverse Events:

Adverse events

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

withdrawals: NR

Evidence Table 15. Placebo controlled trials: Adverse Events

Hedner, 2000 **Quality rating: Fair**

Design:

Study design: RCT DB Parallel **Run-in :** 7 days **Setting:** Multicenter

Wash out : 7 days **Country:** Europe

Sample:	Number Screened/	Eligible/	Enrolled	Number Withdrawn/	Lost to follow-up/	Analyzed
	NR/	NR/	437	22/	NR/	422

Inclusion criteria:

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

Exclusion criteria:

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

Population: **Mean age:** 72.5 years **Ethnicity:** NR

Gender: % Female

Intervention:

Drug name	dosage		N=	Duration
Zaleplon	5	mg	139	14 day
Zaleplon	10	mg	145	14 day
Placebo	NA	mg	138	14 day

Adverse Events:

treatment-emergent adverse events

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

Evidence Table 15. Placebo controlled trials: Adverse Events

Herrmann, 1993 **Quality rating: Poor**

Design:

Study design: RCT DB Parallel **Run-in :** 7 days **Setting:** Single Center

Wash out : 7 days **Country:** France

Sample:	Number Screened/	Eligible/	Enrolled	Number Withdrawn/	Lost to follow-up/	Analyzed
	NR/	25/	21	NR/	NR/	21

Inclusion 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 screening for amphetamines, cannabinoids, morphine derivatives, barbiturates and benzodiazepines. Patients presenting with caffeinism or alcoholism, or shift workers were excluded.

Population: **Mean age:** NR years **Ethnicity:** NR

Gender: 43% Female

Intervention:

Drug name	dosage	N=	Duration
Zolpidem	10 mg	11	14 day
Placebo	NA mg	10	14 day

Adverse Events:

adverse events

	Zolpidem	Placebo
headache - during treatment: Number	3	4
headache - withdrawal: Number	2	1

withdrawals: NR

Evidence Table 15. Placebo controlled trials: Adverse Events

Hindmarch, 1995 **Quality rating: Fair**

Design:

Study design: RCT DB Parallel **Run-in :** NR **Setting:** Multicenter
Wash out : NR **Country:** UK

Sample:	Number Screened/	Eligible/	Enrolled	Number Withdrawn/	Lost to follow-up/	Analyzed
	NR/	NR/	458	NR/	NR/	458

Inclusion 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.

Population: **Mean age:** 42.9 years **Ethnicity:** NR
Gender: 0% Female

Intervention:

Drug name	dosage	N=	Duration
Zopiclone	7.5 mg	231	48 day
Placebo	NA mg	227	42 day

Adverse Events:

adverse events

Zaleplon	Placebo	
overall drop out: Number (%)		
30 (11.5)	54 (20.6)	P: NS
bitter taste: Number		
11	0	
dry mouth: Number		
10	5	

withdrawals: NR

Evidence Table 15. Placebo controlled trials: Adverse Events

Krystal (poster) **Quality rating: Fair**

Design:

Study design: RCT DB Parallel **Run-in :** 14 days **Setting:** Multicenter
Wash out : 14 days **Country:** US

Sample:	Number Screened/	Eligible/	Enrolled	Number Withdrawn/	Lost to follow-up/	Analyzed
	NR/	NR/	830	350/	80/	828

Inclusion criteria:
DSM-IV diagnosis of chronic primary insomnia;
Patient-reported average sleep time <= 6.5 hrs/night and/or sleep latency >30 min

Exclusion criteria:
NR

Population: **Mean age:** 45.6 years **Ethnicity:** Caucasian: 71%, Black: 16%
Gender: 61% Female

Intervention:

Drug name	dosage		N=	Duration
Eszopiclone	3	mg	548	180 day
Placebo	NA	mg	280	180 day

Adverse Events:

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

Evidence Table 15. Placebo controlled trials: Adverse Events

Krystal (poster) **Quality rating: Fair**

CNS adverse events during washout

Eszopiclone	Placebo
hypertonia: %	
0.3	0.7
insomnia: %	
0.6	0
confusion: %	
0.3	0
depression: %	
0.3	0
dizziness: %	
0.3	0
hypesthesia: %	
0	0.7
meningitis: %	
0.3	0
vertigo: %	
0.3	0

withdrawals

Eszopiclone	Placebo
total withdrawals: Number (%)	
204 (37.1)	146 (52.1)
withdrawals due to adverse events: Number (%)	
48 (8.8)	22 (7.9)

Evidence Table 15. Placebo controlled trials: Adverse Events

Krystal, 2003 **Quality rating: Fair**

Design:

Study design: RCT DB Parallel **Run-in :** NR **Setting:** Multicenter

Wash out : 5-7 days **Country:** US

Sample:	Number Screened/	Eligible/	Enrolled	Number Withdrawn/	Lost to follow-up/	Analyzed
	1194/	791/	788	320/	60/	788

Inclusion criteria:

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

Exclusion criteria:

NR

Population: **Mean age:** 44 years **Ethnicity:** 80% Caucasian, 13.2% African American

Gender: 25% Female

Intervention:

Drug name	dosage		N=	Duration
Eszopiclone	3	mg	593	180 day
Placebo	NA	mg	195	180 day

Adverse Events:

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

Evidence Table 15. Placebo controlled trials: Adverse Events

Krystal, 2003 **Quality rating: Fair**

nausea: Number (%)		
67 (11.3)	11 (5.6)	P: NR
pain: Number (%)		
67 (11.3)	12. (6.2)	P: NR
pharyngitis: Number (%)		
59 (9.9)	10 (5.1)	P: NR
rash: Number (%)		
31 (5.2)	6 (3.1)	P: NR
rhinitis: Number (%)		
42 (7.1)	9 (4.6)	P: NR
sinusitis: Number (%)		
25 (4.2)	11 (5.6)	P: NR
somnolence: Number (%)		
54 (9.1)	5 (2.6)	P: NR
unpleasant taste: Number (%)		
155 (26.1)	11 (5.6)	P: NR

withdrawals

Eszopiclone	Placebo
total withdrawals: Number	
235	85
withdrawals due to AEs: Number	
76	14

Evidence Table 15. Placebo controlled trials: Adverse Events

Lahmeyer, 1997 **Quality rating: Fair**

Design:

Study design: RCT DB Parallel **Run-in :** 3 days **Setting:** Multicenter
Wash out : 4 days **Country:** US

Sample:	Number Screened/	Eligible/	Enrolled	Number Withdrawn/	Lost to follow-up/	Analyzed
	178/	33/	145	27/	0/	118

Inclusion criteria:

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

Population: **Mean age:** 44.9 years **Ethnicity:** 92% Caucasian, 6% black
Gender: 56% Female

Intervention:

Drug name	dosage	N=	Duration
Zolpidem	10 mg	45	31 day
Zolpidem	15 mg	46	31 day
Placebo	NA mg	54	31 day

Adverse Events:

overall adverse events

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

Evidence Table 15. Placebo controlled trials: Adverse Events

Lahmeyer, 1997 **Quality rating: Fair**

withdrawals

Zolpidem 10mg	Zolpidem 15mg	Placebo
total withdrawals: Number		
8	9	10
withdrawals due to AEs: Number		
4	3	0

Evidence Table 15. Placebo controlled trials: Adverse Events

Monchesky, 1986 **Quality rating: Fair**

Design:

Study design: RCT DB Crossover **Run-in :** 7 days **Setting:** Single Center

Wash out : 7 days **Country:** Canada

Sample:	Number Screened/	Eligible/	Enrolled	Number Withdrawn/	Lost to follow-up/	Analyzed
	NR/	NR/	99	0/	2/	91

Inclusion criteria:

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

Exclusion criteria:

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

Population: **Mean age:** NR years **Ethnicity:** NR

Gender: 0% Female

Intervention:

Drug name	dosage	N=	Duration
Zopiclone	7.5 mg	91	7 day
Placebo	NA mg	91	7 day

Adverse Events:

adverse events

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

withdrawals: NR

Evidence Table 15. Placebo controlled trials: Adverse Events

Monti, 1996 **Quality rating: Fair**

Design:

Study design: RCT DB Parallel **Run-in :** 2 days **Setting:** Single Center

Wash out : 3 days **Country:** Uruguay

Sample:	Number Screened/	Eligible/	Enrolled	Number Withdrawn/	Lost to follow-up/	Analyzed
	NR/	NR/	12	NR/	NR/	12

Inclusion criteria:

All patients were suffering from at least 2 of the following sleep disturbances: time to fall asleep >30 minutes; total sleep time <6 hours,; total nocturnal wake time >20 minutes; number of nocturnal awakenings >3.

Exclusion criteria:

Pregnant women, women of child-bearing age with inadequate contraception, breastfeeding mothers, patients suffering from organic disease or severe psychiatric disorders, and patients in whom insufficient compliance was to be expected. Alcohol abuse or intake of hypnotics or anxiolytics and/or antidepressants in the seven days prior to the baseline period also led to exclusion.

Population: **Mean age:** 44.25 years **Ethnicity:** NR

Gender: 83% Female

Intervention:

Drug name	dosage	N=	Duration
Zolpidem	10 mg	6	27 day
Placebo	NA mg	6	27 day

Adverse Events:

withdrawals: NR

Evidence Table 15. Placebo controlled trials: Adverse Events

Monti, 2000 **Quality rating: Poor**

Design:

Study design: RCT DB Parallel **Run-in :** 3 days **Setting:** Single Center

Wash out : 3 days **Country:** Uruguay

Sample:	Number Screened/	Eligible/	Enrolled	Number Withdrawn/	Lost to follow-up/	Analyzed
	NR/	NR/	12	NR/	NR/	12

Inclusion criteria:

Patients aged between 27 and 59 years, with chronic primary insomnia according to the DSM-IV participated in the study.

Exclusion criteria:

Patients with poor health, acute or chronic pain, decompensated hepatic, renal or cardiac disease, known drug allergy or abuse, periodic leg movements during sleep, restless legs or sleep apnea were excluded from the study, and so were pregnant women and breast-feeding mothers.

Patients with poor health; acute or chronic pain; hepatic, renal, respiratory, cardiac, or neuropsychiatric diseases [subjects with a score of HAMD > 18, or a score of HAMA(14 items)>16 were not included]; known drug allergy or abuse; periodic leg movements during sleep; restless legs; or sleep apnea were excluded from the study, as also were pregnancy women, breast-feeding mothers, subjects deemed insufficiently compliant, or those with clinically significant deviations in their laboratory tests. Alcohol abuse, intake of hypnotics or anxiolytics in the seven days prior to baseline period, or a positive benzodiazepine urine screening also led to exclusion.

Population: **Mean age:** 51.9 years **Ethnicity:** NR

Gender: 100% Female

Intervention:

Drug name	dosage	N=	Duration
Zolpidem	10 mg	6	15 day
Placebo	NA mg	6	15 day

Adverse Events:

withdrawals: NR

Evidence Table 15. Placebo controlled trials: Adverse Events

Perlis, 2004 **Quality rating: Fair**

Design:

Study design: RCT DB Parallel **Run-in :** 6-14 days **Setting:** Multicenter

Wash out : NR **Country:** US

Sample:	Number Screened/	Eligible/	Enrolled	Number Withdrawn/	Lost to follow-up/	Analyzed
	322/	277/	199	10/	3/	192

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

Population: **Mean age:** 40.8 years **Ethnicity:** 70% Euro American

Gender: 71% Female

Intervention:

Drug name	dosage	N=	Duration
Zolpidem	10 mg	98	84 day
Placebo	NA mg	101	84 day

Adverse Events:

withdrawals

	Zolpidem	Placebo
total withdrawals: Number	7	3
withdrawals due to AEs: Number	2	3

Evidence Table 15. Placebo controlled trials: Adverse Events

Roehrs (poster), 2005 **Quality rating: Fair**

Design:

Study design: RCT DB Parallel **Run-in :** no days **Setting:** Multicenter

Wash out : no days **Country:** US, Canada, Argentina, Germany, F

Sample:	Number Screened/	Eligible/	Enrolled	Number Withdrawn/	Lost to follow-up/	Analyzed
	NR/	NR/	205	7/	NR/	NR

Inclusion criteria:

DSM-IV-defined primary insomnia, WASO 1 hour per night for at least 3 nights per week during preceding month, and time in bed of 6.5 to 9 hours per night for 2 weeks prior to enrollment. A 2-night (screening) mean PSG WASO >= 40 minutes (not <30 minutes on either night), and total sleep time 3 to 7 hours each screening night was required.

Exclusion criteria:

Any DSM-IV Axis I psychiatric disorder, sleep disorder, history of substance abuse, use of any substance with CNS effects known to affect sleep, or use of over-the-counter or prescription sleep medication within 1 and 2 weeks prior to screening, respectively.

Population: **Mean age:** 70.2 years **Ethnicity:** 95.1% Caucasian; 4.9% other

Gender: 57% Female

Intervention:

Drug name	dosage	N=	Duration
zolpidem exten	6.25 mg	99	21 day
Placebo	NA mg	106	21 day

Adverse Events:

Treatment emergent adverse events >=5%

	Zolpidem MR	Placebo
any adverse event: Number (%)	38 (38.4)	42 (39.6)
nervous system disorders: Number (%)	25 (25.3)	21 (19.8)
psychiatric disorders: Number (%)	7 (7.1)	7 (6.6)
gastrointestinal disorders: Number (%)	9 (9.1)	13 (12.3)
musculoskeletal and connective tissue disorder: Number (%)	7 (7.1)	7 (6.6)
infections and infestations: Number (%)	9 (9.1)	5 (4.7)
general disorders, administration site conditions: Number (%)	7 (7.1)	8 (7.5)
headache: Number (%)	14 (14.1)	12 (11.3)
dizziness: Number (%)	8 (8.1)	3 (2.8)
somnolence: Number (%)	6 (6.1)	5 (4.7)
nausea: Number (%)	6 (6.1)	6 (5.7)

Evidence Table 15. Placebo controlled trials: Adverse Events

Roehrs (poster), 2005 **Quality rating: Fair**

Withdrawals

Zolpidem MR	Placebo
total withdrawals: Number	
3	1
withdrawal due to AEs: Number	
NR	NR

Evidence Table 15. Placebo controlled trials: Adverse Events

Roth, 2006 **Quality rating: Fair**

Design:

Study design: RCT DB Parallel **Run-in :** 7 days **Setting:** Multicenter

Wash out : 7 days **Country:** US

Sample:	Number Screened/	Eligible/	Enrolled	Number Withdrawn/	Lost to follow-up/	Analyzed
	NR/	NR/	829	128/	NR/	NR

Inclusion criteria:

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

Exclusion criteria:

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

Population: **Mean age:** 72.4 years **Ethnicity:** Not reported

Gender: 0% Female

Intervention:

Drug name	dosage		N=	Duration
Ramelteon	4	mg	281	5 week
Ramelteon	8	mg	274	5 week
Placebo	NA	mg	274	5 week

Adverse Events:

Total withdrawals

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

Withdrawals due to AEs

Withdrawals due to AEs: Number (%)		
8 (2.8)	7 (2.6)	8 (2.9)

Evidence Table 15. Placebo controlled trials: Adverse Events

Roth, 2006 **Quality rating: Fair**

Adverse events

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

Evidence Table 15. Placebo controlled trials: Adverse Events

Scharf, 1994 **Quality rating: Fair**

Design:

Study design: RCT DB Parallel **Run-in :** 11 days **Setting:** Multicenter

Wash out : 2 days **Country:** US

Sample:	Number Screened/	Eligible/	Enrolled	Number Withdrawn/	Lost to follow-up/	Analyzed
	178/	75/	75			

Inclusion criteria:

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

Exclusion criteria:

Population: **Mean age:** 38 years **Ethnicity:** 73.3% white, 26.7% non-white

Gender: 64% Female

Intervention:

Drug name	dosage	N=	Duration
Zolpidem	10 mg	26	35 day
Zolpidem	15 mg	25	35 day
Placebo	NA mg	24	35 day

Adverse Events:

adverse events

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

Evidence Table 15. Placebo controlled trials: Adverse Events

Scharf, 1994 **Quality rating: Fair**

amnesia: Number (%)		
1 (4)	2 (8)	0 (0)
rhinitis: Number (%)		
0 (0)	0 (0)	2 (8)

withdrawals

Zolpidem 10mg	Zolpidem 15mg	Placebo
total withdrawals: Number		
4	3	1
withdrawals due to AEs: Number		
0	2	0

Evidence Table 15. Placebo controlled trials: Adverse Events

Scharf, 2005 **Quality rating: Fair**

Design:

Study design: RCT DB Parallel **Run-in :** 3-14 days **Setting:** Multicenter

Wash out : NR **Country:** US

Sample:	Number Screened/	Eligible/	Enrolled	Number Withdrawn/	Lost to follow-up/	Analyzed
	353/	NR/	231	21/	NR/	231

Inclusion criteria:

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

Exclusion criteria:

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

Population: **Mean age:** 72.3 years **Ethnicity:** 89.4% Caucasian, 2.2% black

Gender: 58% Female

Intervention:

Drug name	dosage		N=	Duration
Eszopiclone	1	mg	72	14 day
Eszopiclone	2	mg	79	14 day
Placebo	NA	mg	80	14 day

Adverse Events:

adverse events

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

Evidence Table 15. Placebo controlled trials: Adverse Events

Soubrane (poster), 2005 **Quality rating: Fair**

Design:

Study design: RCT DB Parallel **Run-in :** NR **Setting:** Multicenter
Wash out : NR **Country:** US

Sample:	Number Screened/	Eligible/	Enrolled	Number Withdrawn/	Lost to follow-up/	Analyzed
	NR/	NR/	212	20/	NR/	NR

Inclusion criteria:

DSM-IV-defined primary insomnia, WASO 1 hour per night at least 3 nights per week during the preceding month, and time in bed of 6.5 to 9 hours per night during the 2 weeks prior to enrollment.

Exclusion criteria:

Any DSM-IV Axis I psychiatric disorder, sleep disorder, history of substance abuse, use of any substance with CNS effects known to affect sleep, or use of over-the-counter or prescription sleep medication within 1 and 2 weeks prior to screening, respectively.

Population: **Mean age:** 44.4 years **Ethnicity:** 90% Caucasian, 10% other
Gender: 58% Female

Intervention:

Drug name	dosage	N=	Duration
Zolpidem-CR	12.5 mg	102	3 week
Placebo	NA mg	110	3 week

Adverse Events:

Treatment emergent adverse events >=5%

	Zolpidem MR	Placebo
any adverse event: Number (%)	58 (56.8)	57 (51.8)
nervous system disorders: Number (%)	41 (40.2)	24 (21.8)
psychiatric disorders: Number (%)	18 (17.6)	11 (10)
gastrointestinal disorders: Number (%)	12 (11.8)	14 (12.7)
musculoskeletal and connective tissue disorders: Number (%)	11 (10.8)	7 (6.4)
eye disorders: Number (%)	8 (7.8)	2 (1.8)
general disorders, administration site conditions: Number (%)	7 (6.9)	7 (6.4)
headache: Number (%)	19 (18.6)	18 (16.4)
somnolence: Number (%)	15 (14.7)	2 (1.8)
dizziness: Number (%)	12 (11.8)	6 (5.5)
nausea: Number (%)	7 (6.9)	4 (3.6)

Evidence Table 15. Placebo controlled trials: Adverse Events

Soubrane (poster), 2005 **Quality rating: Fair**

Withdrawals

Zolpidem MR	Placebo
total withdrawals: Number	
NR	NR
withdrawal due to AEs: Number	
6	2

Evidence Table 15. Placebo controlled trials: Adverse Events

Terzano, 1992 **Quality rating: Poor**

Design:

Study design: RCT DB Parallel **Run-in :** 14 days **Setting:** Single Center

Wash out : NR **Country:** Italy

Sample:	Number Screened/	Eligible/	Enrolled	Number Withdrawn/	Lost to follow-up/	Analyzed
	NR/	NR/	12	NR/	NR/	12

Inclusion 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

Population: **Mean age:** 49.6 years **Ethnicity:** NR

Gender: 67% Female

Intervention:

Drug name	dosage	N=	Duration
Zolpidem	10 mg	0	1 day
Placebo	NA mg	0	1 day

Adverse Events:

withdrawals: NA

Evidence Table 15. Placebo controlled trials: Adverse Events

Walsh, 2000a **Quality rating: Poor**

Design:

Study design: RCT DB Parallel **Run-in :** 5-12 days **Setting:** Multicenter

Wash out : 5-12 days **Country:** US

Sample:	Number Screened/	Eligible/	Enrolled	Number Withdrawn/	Lost to follow-up/	Analyzed
	311/	54/	48	NR/	NR/	48

Inclusion criteria:

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

Exclusion criteria:

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

Population: **Mean age:** 67.5 years **Ethnicity:** NR

Gender: 35% Female

Intervention:

Drug name	dosage		N=	Duration
Zaleplon	2	mg	12	2 day
Zaleplon	5	mg	12	2 day
Zaleplon	10	mg	12	2 day
Placebo	NA	mg	12	2 day

Adverse Events:

withdrawals: NR

Evidence Table 15. Placebo controlled trials: Adverse Events

Walsh, 2000b, 2002 **Quality rating: Fair**

Design:

Study design: RCT DB Parallel **Run-in :** 7 days **Setting:** Multicenter

Wash out : 7 days **Country:** US

Sample:	Number Screened/	Eligible/	Enrolled	Number Withdrawn/	Lost to follow-up/	Analyzed
	365/	163/	163	29/	5/	NR

Inclusion criteria:

1) DSM-IV diagnosis of primary insomnia 2) reported sleep latency (SL) > 45 minutes, or total sleep time (TST) < 6.5 hours, and insomnia-related daytime complaints on at least three of the seven baseline days 3) nightly time-in-bed between 6.5 and 9.0 hours; bedtime and rise time 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 function 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

Population: **Mean age:** 44.1 years **Ethnicity:** 83.4% Caucasian, 16.6% other

Gender: 71% Female

Intervention:

Drug name	dosage	N=	Duration
Zolpidem	10 mg	82	56 day
Placebo	NA mg	81	56 day

Adverse Events:

adverse events

	Zolpidem	Placebo	
overall: Number	1	4	P: NS

withdrawals

	Zolpidem	Placebo
total withdrawals: Number	18	10
withdrawals due to AEs: Number	4	1

Evidence Table 15. Placebo controlled trials: Adverse Events

Zammit, 2004 **Quality rating: Fair**

Design:

Study design: RCT DB Parallel **Run-in :** 2 days **Setting:** Single Center
Wash out : 5-7 days **Country:** US

Sample:	Number Screened/	Eligible/	Enrolled	Number Withdrawn/	Lost to follow-up/	Analyzed
	NR/	669/	308	16/	0/	308

Inclusion 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.

Population: **Mean age:** 39.8 years **Ethnicity:** 66.2% Caucasians, 16.6% black
Gender: 61% Female

Intervention:

Drug name	dosage		N=	Duration
Eszopiclone	2	mg	104	44 day
Eszopiclone	3	mg	105	44 day
Placebo	NA	mg	99	44 day

Adverse Events:

adverse events during treatment

	Eszopiclone 2mg	Eszopiclone 3mg	Placebo
abnormal dreams: Number (%)	2 (2)	3 (2.9)	2 (1.9)
nervousness: Number (%)	2 (2)	5 (4.8)	0 (0)
back pain: Number (%)	2 (2)	1 (1)	4 (3.8)
dizziness: Number (%)	4 (4)	3 (2.9)	5 (4.8)
dry mouth: Number (%)	2 (2)	5 (4.8)	6 (5.7)
headache: Number (%)	8 (8.1)	13 (12.5)	12 (11.4)
somnolence: Number (%)	3 (3)	8 (7.7)	8 (7.6)
unpleasant taste: Number (%)	3 (3)	17 (16.3)	35 (33.3)

adverse events after treatment discontinuation

	Eszopiclone 2mg	Eszopiclone 3mg	Placebo
CNS related: % (p vs placebo)	11.5 (NS)	15.2 (NS)	18.2 (NA)

Evidence Table 15. Placebo controlled trials: Adverse Events

Zammit, 2004 **Quality rating: Fair**

withdrawals

Eszopiclone 2mg	Eszopiclone 3mg	Placebo
total withdrawals: Number		
7	4	5
withdrawals due to AEs: Number		
3	0	0

Evidence Table 16. Quality Assessment of efficacy trials

Internal validity **External validity**

Allain, 1998 **Design:** RCT DB Parallel **Trial type:** Placebo **Quality rating:** Fair

1. Randomization adequate?	NR	8. Reporting of Attrition	No	1. Number Screened/ Eligible/ Enrolled:	NR / NR / 37
2. Allocation adequate?	NR	Crossover	No	3. Run-in/ Wash out (days):	3 / 3
3. Groups similar at baseline?	Yes	Adherence	No	4. Class naive patients only?	NR (all were taking tri
4. Eligibility criteria specified?	Yes	Contamination	No	5. Controlled group standard of care?	NR
9. Loss to follow-up, differential?	NR			2. Exclusion criteria reported?	Yes
5. Outcome assessors masked?	Yes			6. Funding: NR	
6. Care provider masked?	Yes				
7. Patients masked?	Yes				
10. Intention-to-treat analysis?	Unable to determine				
11. Postrandomization exclusions?	NR				

Allain, 2001 **Design:** RCT DB Parallel **Trial type:** Placebo **Quality rating:** Fair

1. Randomization adequate?	NR	8. Reporting of Attrition	Yes	1. Number Screened/ Eligible/ Enrolled:	NR / NR / 245
2. Allocation adequate?	NR	Crossover	No	3. Run-in/ Wash out (days):	3-7 / NR
3. Groups similar at baseline?	Plac	Adherence	Yes	4. Class naive patients only?	NR
4. Eligibility criteria specified?	Yes	Contamination	No	5. Controlled group standard of care?	NR
9. Loss to follow-up, differential?	Yes			2. Exclusion criteria reported?	Yes
5. Outcome assessors masked?	Yes			6. Funding: Sanofi-Synthelabo	
6. Care provider masked?	NR				
7. Patients masked?	Yes				
10. Intention-to-treat analysis?	Yes				
11. Postrandomization exclusions?	No				

Allain, 2003 **Design:** RCT DB Crossover **Trial type:** H2H **Quality rating:** Fair

1. Randomization adequate?	Yes	8. Reporting of Attrition	Yes	1. Number Screened/ Eligible/ Enrolled:	NR / NR / 53
2. Allocation adequate?	NR	Crossover	Yes	3. Run-in/ Wash out (days):	0 / 0
3. Groups similar at baseline?	Yes	Adherence	Yes	4. Class naive patients only?	No
4. Eligibility criteria specified?	Yes	Contamination	No	5. Controlled group standard of care?	Yes
9. Loss to follow-up, differential?	No			2. Exclusion criteria reported?	Yes
5. Outcome assessors masked?	Yes			6. Funding: Sanofi-Synthelabo	
6. Care provider masked?	NR				
7. Patients masked?	Yes				
10. Intention-to-treat analysis?	Yes				
11. Postrandomization exclusions?	No				

Evidence Table 16. Quality Assessment of efficacy trials

Internal validity **External validity**

Ancoli-Israel, 1999

Design: RCT DB Parallel **Trial type:** H2H **Quality rating:** Fair

1. Randomization adequate?	NR	8. Reporting of Attrition	Yes
2. Allocation adequate?	NR	Crossover	No
3. Groups similar at baseline?	Yes	Adherence	No
4. Eligibility criteria specified?	Yes	Contamination	No
9. Loss to follow-up, differential?	No		
5. Outcome assessors masked?	Yes		
6. Care provider masked?	NR		
7. Patients masked?	Yes		
10. Intention-to-treat analysis?	No		
11. Postrandomization exclusions?	Yes		

1. Number Screened/ Eligible/ Enrolled:	1224 /	551 /	549
3. Run-in/ Wash out (days):	7 /	7-21	
4. Class naive patients only?	No		
5. Controlled group standard of care?	Yes		
2. Exclusion criteria reported?	Yes		
6. Funding: Wyeth-Ayerst			

Anderson, 1987

Design: RCT DB Parallel **Trial type:** Active **Quality rating:** Fair

1. Randomization adequate?	NR	8. Reporting of Attrition	Yes
2. Allocation adequate?	NR	Crossover	No
3. Groups similar at baseline?	Yes	Adherence	Yes
4. Eligibility criteria specified?	Yes	Contamination	No
9. Loss to follow-up, differential?	Yes		
5. Outcome assessors masked?	No		
6. Care provider masked?	NR		
7. Patients masked?	Yes		
10. Intention-to-treat analysis?	No		
11. Postrandomization exclusions?	Yes		

1. Number Screened/ Eligible/ Enrolled:	NR /	NR /	119
3. Run-in/ Wash out (days):	7 /	7	
4. Class naive patients only?	No		
5. Controlled group standard of care?	Yes		
2. Exclusion criteria reported?	Yes		
6. Funding: Not reported			

Autret, 1987

Design: CT DB Crossover **Trial type:** Active **Quality rating:** Poor

1. Randomization adequate?	Not r	8. Reporting of Attrition	Yes
2. Allocation adequate?	NR	Crossover	No
3. Groups similar at baseline?	NR	Adherence	Yes
4. Eligibility criteria specified?	Yes	Contamination	No
9. Loss to follow-up, differential?	No		
5. Outcome assessors masked?	Yes, but not described		
6. Care provider masked?	NR		
7. Patients masked?	Yes, but not described		
10. Intention-to-treat analysis?	Unable to determine		
11. Postrandomization exclusions?	Unable to determine		

1. Number Screened/ Eligible/ Enrolled:	NR /	NR /	121
3. Run-in/ Wash out (days):	4 /	3	
4. Class naive patients only?			
5. Controlled group standard of care?			
2. Exclusion criteria reported?	No		
6. Funding:			

Evidence Table 16. Quality Assessment of efficacy trials

Internal validity **External validity**

Begg, 1992

Design: RCT SB Parallel **Trial type:** Active **Quality rating:** Poor

1. Randomization adequate?	Yes	8. Reporting of Attrition	Yes
2. Allocation adequate?	NR	Crossover	No
3. Groups similar at baseline?	No	Adherence	Yes
4. Eligibility criteria specified?	Yes	Contamination	No
9. Loss to follow-up, differential?	Yes		
5. Outcome assessors masked?	Yes		
6. Care provider masked?	NR		
7. Patients masked?	Yes		
10. Intention-to-treat analysis?	No		
11. Postrandomization exclusions?	Yes		

1. Number Screened/ Eligible/ Enrolled:	NR /	NR /	88
3. Run-in/ Wash out (days):	2 /	2	
4. Class naive patients only?	No		
5. Controlled group standard of care?			
2. Exclusion criteria reported?	Yes		
6. Funding: Roche Products (NZ) Ltd.			

Bergener, 1989

Design: RCT DB Parallel **Trial type:** Active **Quality rating:** Fair

1. Randomization adequate?	NR	8. Reporting of Attrition	Yes
2. Allocation adequate?	NR	Crossover	No
3. Groups similar at baseline?	NR	Adherence	No
4. Eligibility criteria specified?	Yes	Contamination	No
9. Loss to follow-up, differential?	Yes		
5. Outcome assessors masked?	Yes, but not described		
6. Care provider masked?	Yes, but not described		
7. Patients masked?	Yes		
10. Intention-to-treat analysis?	Unable to determine		
11. Postrandomization exclusions?	No		

1. Number Screened/ Eligible/ Enrolled:	NR /	NR /	42
3. Run-in/ Wash out (days):	4 /	7	
4. Class naive patients only?	NR		
5. Controlled group standard of care?	Yes		
2. Exclusion criteria reported?	Yes		
6. Funding: Not reported			

Chaudoir, 1983

Design: RCT DB Crossover **Trial type:** Placebo **Quality rating:** Poor

1. Randomization adequate?	NR	8. Reporting of Attrition	Yes
2. Allocation adequate?	NR	Crossover	No
3. Groups similar at baseline?	Yes	Adherence	No
4. Eligibility criteria specified?	Yes	Contamination	No
9. Loss to follow-up, differential?	Yes		
5. Outcome assessors masked?	Yes, but not described		
6. Care provider masked?	NR		
7. Patients masked?	Yes, but not described		
10. Intention-to-treat analysis?	No (25/30 analyzed)		
11. Postrandomization exclusions?	No		

1. Number Screened/ Eligible/ Enrolled:	NR /	30 /	25
3. Run-in/ Wash out (days):	NR /	NR	
4. Class naive patients only?	No		
5. Controlled group standard of care?	NR		
2. Exclusion criteria reported?	Yes		
6. Funding: NR (May & Baker provided medications and placebo)			

Evidence Table 16. Quality Assessment of efficacy trials

Chaudoir, 1990

Design: RCT DB Parallel **Trial type:** Active **Quality rating:** Fair

Internal validity				External validity			
1. Randomization adequate?	NR	8. Reporting of Attrition	Yes	1. Number Screened/ Eligible/ Enrolled:	NR /	NR /	38
2. Allocation adequate?	NR	Crossover	No	3. Run-in/ Wash out (days):	no /	7	
3. Groups similar at baseline?	Yes	Adherence	No	4. Class naive patients only?	No		
4. Eligibility criteria specified?	Yes	Contamination	No	5. Controlled group standard of care?	Yes		
9. Loss to follow-up, differential?	No			2. Exclusion criteria reported?	Yes		
5. Outcome assessors masked?	Yes, but not described			6. Funding: Not reported			
6. Care provider masked?	NR						
7. Patients masked?	Yes						
10. Intention-to-treat analysis?	Not clear						
11. Postrandomization exclusions?	Unable to determine						

Dockhorn, 1996

Design: RCT DB Parallel **Trial type:** Placebo **Quality rating:** Fair

Internal validity				External validity			
1. Randomization adequate?	NR	8. Reporting of Attrition	Yes	1. Number Screened/ Eligible/ Enrolled:	NR /	NR /	138
2. Allocation adequate?	NR	Crossover	No	3. Run-in/ Wash out (days):	NR /	NR	
3. Groups similar at baseline?	Yes	Adherence	No	4. Class naive patients only?	NR		
4. Eligibility criteria specified?	Yes	Contamination	No	5. Controlled group standard of care?	NR		
9. Loss to follow-up, differential?	No			2. Exclusion criteria reported?	Yes		
5. Outcome assessors masked?	Yes			6. Funding: Lorex Pharmaceuticals			
6. Care provider masked?	NR						
7. Patients masked?	Yes						
10. Intention-to-treat analysis?	No (136/139 analyzed)						
11. Postrandomization exclusions?	Yes (1 patient)						

Dorsey, 2004

Design: RCT DB Parallel **Trial type:** Placebo **Quality rating:** Fair

Internal validity				External validity			
1. Randomization adequate?	NR	8. Reporting of Attrition	Yes	1. Number Screened/ Eligible/ Enrolled:	242 /	141 /	141
2. Allocation adequate?	NR	Crossover	No	3. Run-in/ Wash out (days):	6-14 /	NR	
3. Groups similar at baseline?	Yes	Adherence	No	4. Class naive patients only?	NR		
4. Eligibility criteria specified?	Yes	Contamination	No	5. Controlled group standard of care?	NR		
9. Loss to follow-up, differential?	No			2. Exclusion criteria reported?	Yes		
5. Outcome assessors masked?	Yes, but not described			6. Funding: Sanofi-Synthelabo			
6. Care provider masked?	NR						
7. Patients masked?	Yes						
10. Intention-to-treat analysis?	Yes						
11. Postrandomization exclusions?	No						

Evidence Table 16. Quality Assessment of efficacy trials

Internal validity **External validity**

Drake (1), 2001

Design: RCT DB Crossover **Trial type:** Active **Quality rating:** Fair

1. Randomization adequate?	NR	8. Reporting of Attrition	Yes	1. Number Screened/ Eligible/ Enrolled:	NR /	NR /	47
2. Allocation adequate?	NR	Crossover	0	3. Run-in/ Wash out (days):	NR /	5-12	
3. Groups similar at baseline?	NR	Adherence	No	4. Class naive patients only?	No		
4. Eligibility criteria specified?	Yes	Contamination	No	5. Controlled group standard of care?	Yes		
9. Loss to follow-up, differential?	No			2. Exclusion criteria reported?	Yes		
5. Outcome assessors masked?	Yes, but not described			6. Funding: Wyeth-Ayerst Research			
6. Care provider masked?	NR						
7. Patients masked?	Yes						
10. Intention-to-treat analysis?	Unable to determine						
11. Postrandomization exclusions?	No						

Drake (2), 2000

Design: RCT DB Crossover **Trial type:** Active **Quality rating:** Fair

1. Randomization adequate?	NR	8. Reporting of Attrition	Yes	1. Number Screened/ Eligible/ Enrolled:	NR /	NR /	36
2. Allocation adequate?	NR	Crossover	No	3. Run-in/ Wash out (days):	NR /	5-12	
3. Groups similar at baseline?	NR	Adherence	No	4. Class naive patients only?	No		
4. Eligibility criteria specified?	Yes	Contamination	No	5. Controlled group standard of care?	Yes		
9. Loss to follow-up, differential?	No			2. Exclusion criteria reported?	Yes		
5. Outcome assessors masked?	Yes, but not described			6. Funding: Wyeth-Ayerst Research			
6. Care provider masked?	NR						
7. Patients masked?	Yes						
10. Intention-to-treat analysis?	Unable to determine						
11. Postrandomization exclusions?	No						

Elie, 1990a

Design: RCT DB Parallel **Trial type:** Active **Quality rating:** Fair

1. Randomization adequate?	NR	8. Reporting of Attrition	No	1. Number Screened/ Eligible/ Enrolled:	NR /	NR /	44
2. Allocation adequate?	NR	Crossover	No	3. Run-in/ Wash out (days):	7 /	4	
3. Groups similar at baseline?	NR	Adherence	No	4. Class naive patients only?	No		
4. Eligibility criteria specified?	Yes	Contamination	No	5. Controlled group standard of care?	Yes		
9. Loss to follow-up, differential?	NR			2. Exclusion criteria reported?	Yes		
5. Outcome assessors masked?	Yes, but not described			6. Funding: Not reported			
6. Care provider masked?	NR						
7. Patients masked?	Yes						
10. Intention-to-treat analysis?	Yes						
11. Postrandomization exclusions?	Unable to determine						

Evidence Table 16. Quality Assessment of efficacy trials

Internal validity **External validity**

Elie, 1990b

Design: RCT DB Parallel **Trial type:** Active **Quality rating:** Fair

1. Randomization adequate?	NR	8. Reporting of Attrition	No	1. Number Screened/ Eligible/ Enrolled:	NR /	NR /	36
2. Allocation adequate?	NR	Crossover	No	3. Run-in/ Wash out (days):	7 /	3	
3. Groups similar at baseline?	NR	Adherence	No	4. Class naive patients only?	No		
4. Eligibility criteria specified?	Yes	Contamination	No	5. Controlled group standard of care?	Yes		
9. Loss to follow-up, differential?	NR			2. Exclusion criteria reported?	Yes		
5. Outcome assessors masked?	Yes			6. Funding: Not reported			
6. Care provider masked?	NR						
7. Patients masked?	Yes						
10. Intention-to-treat analysis?	Unable to determine						
11. Postrandomization exclusions?	Unable to determine						

Elie, 1999

Design: RCT DB Parallel **Trial type:** H2H **Quality rating:** Fair

1. Randomization adequate?	NR	8. Reporting of Attrition	Yes	1. Number Screened/ Eligible/ Enrolled:	NR /	NR /	615
2. Allocation adequate?	NR	Crossover	No	3. Run-in/ Wash out (days):	7-21 /	7	
3. Groups similar at baseline?	NR	Adherence	Yes	4. Class naive patients only?	No		
4. Eligibility criteria specified?	Yes	Contamination	No	5. Controlled group standard of care?	Yes		
9. Loss to follow-up, differential?	No			2. Exclusion criteria reported?	Yes		
5. Outcome assessors masked?	Yes			6. Funding: Wyeth-Ayerst			
6. Care provider masked?	NR						
7. Patients masked?	Yes						
10. Intention-to-treat analysis?	No						
11. Postrandomization exclusions?	Yes						

Erman, 2006

Design: RCT DB Crossover **Trial type:** Placebo **Quality rating:** Fair

1. Randomization adequate?	Yes	8. Reporting of Attrition	Yes	1. Number Screened/ Eligible/ Enrolled:	319 /	205 /	107
2. Allocation adequate?	NR	Crossover	No	3. Run-in/ Wash out (days):	NR /	5-12	
3. Groups similar at baseline?	Yes	Adherence	No	4. Class naive patients only?	NR		
4. Eligibility criteria specified?	Yes	Contamination	No	5. Controlled group standard of care?	Yes		
9. Loss to follow-up, differential?	No			2. Exclusion criteria reported?	Yes		
5. Outcome assessors masked?	Yes, but not described			6. Funding: Takeda			
6. Care provider masked?	Yes, but not described						
7. Patients masked?	Yes						
10. Intention-to-treat analysis?	No (103/107 analyzed)						
11. Postrandomization exclusions?	Unable to determine						

Evidence Table 16. Quality Assessment of efficacy trials

Internal validity				External validity			
Fleming, 1990	**Design:** RCT DB Parallel		**Trial type:** Active	**Quality rating:** Fair			
1. Randomization adequate?	Yes	8. Reporting of Attrition	Yes	1. Number Screened/ Eligible/ Enrolled:	NR /	NR /	52
2. Allocation adequate?	NR	Crossover	No	3. Run-in/ Wash out (days):	3 /	4	
3. Groups similar at baseline?	NR	Adherence	No	4. Class naive patients only?	No		
4. Eligibility criteria specified?	Yes	Contamination	No	5. Controlled group standard of care?	Yes		
9. Loss to follow-up, differential?	No			2. Exclusion criteria reported?	Yes		
5. Outcome assessors masked?	Yes, but not described			6. Funding: Not reported			
6. Care provider masked?	NR						
7. Patients masked?	Yes						
10. Intention-to-treat analysis?	No (48/52 analyzed)						
11. Postrandomization exclusions?	Yes						
Fleming, 1995	**Design:** RCT DB Parallel		**Trial type:** Active	**Quality rating:** Fair			
1. Randomization adequate?	NR	8. Reporting of Attrition	Yes	1. Number Screened/ Eligible/ Enrolled:	222 /	144 /	144
2. Allocation adequate?	NR	Crossover	Yes	3. Run-in/ Wash out (days):	1 /	NR	
3. Groups similar at baseline?	Yes	Adherence	No	4. Class naive patients only?	No		
4. Eligibility criteria specified?	Yes	Contamination	Yes	5. Controlled group standard of care?	Yes		
9. Loss to follow-up, differential?	Yes			2. Exclusion criteria reported?	Yes		
5. Outcome assessors masked?	Yes, but not described			6. Funding: Not reported			
6. Care provider masked?	NR						
7. Patients masked?	Yes						
10. Intention-to-treat analysis?	No						
11. Postrandomization exclusions?	Yes						
Fry, 2000	**Design:** RCT DB Parallel		**Trial type:** H2H	**Quality rating:** Fair			
1. Randomization adequate?	NR	8. Reporting of Attrition	Yes	1. Number Screened/ Eligible/ Enrolled:	NR /	830 /	595
2. Allocation adequate?	NR	Crossover	No	3. Run-in/ Wash out (days):	7 /	0	
3. Groups similar at baseline?	NR	Adherence	No	4. Class naive patients only?	NR		
4. Eligibility criteria specified?	Yes	Contamination	No	5. Controlled group standard of care?	Yes		
9. Loss to follow-up, differential?	No			2. Exclusion criteria reported?	Yes		
5. Outcome assessors masked?	Yes, but not described			6. Funding: Wyeth-Ayerst			
6. Care provider masked?	NR						
7. Patients masked?	Yes, but not described						
10. Intention-to-treat analysis?	No						
11. Postrandomization exclusions?	Yes						

Evidence Table 16. Quality Assessment of efficacy trials

Internal validity | **External validity**

Goldenberg, 1994

Design: RCT DB Parallel **Trial type:** Placebo **Quality rating:** Poor

1. Randomization adequate?	NR	8. Reporting of Attrition	Yes
2. Allocation adequate?	NR	Crossover	No
3. Groups similar at baseline?	Yes (	Adherence	No
4. Eligibility criteria specified?	Yes	Contamination	No
9. Loss to follow-up, differential?	Yes		
5. Outcome assessors masked?	Yes, but not described		
6. Care provider masked?	NR		
7. Patients masked?	Yes		
10. Intention-to-treat analysis?	No		
11. Postrandomization exclusions?	Unable to determine		

1. Number Screened/ Eligible/ Enrolled:	NR /	NR /	524
3. Run-in/ Wash out (days):	NR /	NR	
4. Class naive patients only?	NR		
5. Controlled group standard of care?	NR		
2. Exclusion criteria reported?	Yes		
6. Funding: NR			

Hajak, 1998, 1995, 1994

Design: RCT DB Parallel **Trial type:** Active **Quality rating:** Fair

1. Randomization adequate?	Yes	8. Reporting of Attrition	Yes
2. Allocation adequate?	NR	Crossover	No
3. Groups similar at baseline?	Yes	Adherence	Yes
4. Eligibility criteria specified?	Yes	Contamination	No
9. Loss to follow-up, differential?	No		
5. Outcome assessors masked?	Yes, but not described		
6. Care provider masked?	NR		
7. Patients masked?	Yes		
10. Intention-to-treat analysis?	Yes		
11. Postrandomization exclusions?	No		

1. Number Screened/ Eligible/ Enrolled:	NR /	NR /	1507
3. Run-in/ Wash out (days):	7 /	3	
4. Class naive patients only?	No		
5. Controlled group standard of care?	Yes		
2. Exclusion criteria reported?	Yes		
6. Funding: Not reported			

Hayoun, 1989

Design: RCT DB Parallel **Trial type:** Active **Quality rating:** Fair

1. Randomization adequate?	NR	8. Reporting of Attrition	Yes
2. Allocation adequate?	NR	Crossover	No
3. Groups similar at baseline?	Yes	Adherence	No
4. Eligibility criteria specified?	Yes	Contamination	Yes
9. Loss to follow-up, differential?	Yes		
5. Outcome assessors masked?	Yes, but not described		
6. Care provider masked?	NR		
7. Patients masked?	Yes		
10. Intention-to-treat analysis?	No		
11. Postrandomization exclusions?	Yes		

1. Number Screened/ Eligible/ Enrolled:	NR /	NR /	136
3. Run-in/ Wash out (days):	NR /	NR	
4. Class naive patients only?	No		
5. Controlled group standard of care?	Yes		
2. Exclusion criteria reported?	Yes		
6. Funding: Not reported (corresponding author from Upjohn)			

Evidence Table 16. Quality Assessment of efficacy trials

Internal validity **External validity**

Hedner, 2000

Design: RCT DB Parallel **Trial type:** Placebo **Quality rating:** Fair

1. Randomization adequate?	NR	8. Reporting of Attrition	No	1. Number Screened/ Eligible/ Enrolled:	NR /	NR /	437
2. Allocation adequate?	NR	Crossover	No	3. Run-in/ Wash out (days):	7 /	7	
3. Groups similar at baseline?	Yes f	Adherence	No	4. Class naive patients only?			
4. Eligibility criteria specified?	Yes	Contamination	No	5. Controlled group standard of care?			
9. Loss to follow-up, differential?	NR			2. Exclusion criteria reported?	Yes		
5. Outcome assessors masked?	Yes			6. Funding:			
6. Care provider masked?	NR						
7. Patients masked?	Yes						
10. Intention-to-treat analysis?	No (422/437 analyzed)						
11. Postrandomization exclusions?	NR						

Herrmann, 1993

Design: RCT DB Parallel **Trial type:** Placebo **Quality rating:** Poor

1. Randomization adequate?	NR	8. Reporting of Attrition	Yes	1. Number Screened/ Eligible/ Enrolled:	NR /	25 /	21
2. Allocation adequate?	NR	Crossover	No	3. Run-in/ Wash out (days):	7 /	7	
3. Groups similar at baseline?	NR	Adherence	No	4. Class naive patients only?	NR		
4. Eligibility criteria specified?	Yes	Contamination	No	5. Controlled group standard of care?	NR		
9. Loss to follow-up, differential?	Yes			2. Exclusion criteria reported?	Yes		
5. Outcome assessors masked?	Yes, but not described			6. Funding: NR			
6. Care provider masked?	NR						
7. Patients masked?	Yes						
10. Intention-to-treat analysis?	No (21/25 analyzed)						
11. Postrandomization exclusions?	Yes (1/25)						

Hindmarch, 1995

Design: RCT DB Parallel **Trial type:** Placebo **Quality rating:** Fair

1. Randomization adequate?	NR	8. Reporting of Attrition	Yes	1. Number Screened/ Eligible/ Enrolled:	NR /	NR /	458
2. Allocation adequate?	NR	Crossover	No	3. Run-in/ Wash out (days):	NR /	NR	
3. Groups similar at baseline?	glob	Adherence	No	4. Class naive patients only?			
4. Eligibility criteria specified?	Yes	Contamination	No	5. Controlled group standard of care?			
9. Loss to follow-up, differential?	Yes			2. Exclusion criteria reported?	Yes		
5. Outcome assessors masked?	Yes, but not described			6. Funding:			
6. Care provider masked?	NR						
7. Patients masked?	Yes, but not described						
10. Intention-to-treat analysis?	No						
11. Postrandomization exclusions?	Unable to determine						

Evidence Table 16. Quality Assessment of efficacy trials

Internal validity **External validity**

Klimm, 1987

Design: RCT DB Parallel **Trial type:** Active **Quality rating:** Fair

1. Randomization adequate?	NR	8. Reporting of Attrition	Yes	1. Number Screened/ Eligible/ Enrolled:	NR /	NR /	74
2. Allocation adequate?	NR	Crossover	No	3. Run-in/ Wash out (days):	7 /	7	
3. Groups similar at baseline?	Yes	Adherence	Yes	4. Class naive patients only?	No		
4. Eligibility criteria specified?	Yes	Contamination	No	5. Controlled group standard of care?	Yes		
9. Loss to follow-up, differential?	No			2. Exclusion criteria reported?	Yes		
5. Outcome assessors masked?	Yes, but not described			6. Funding: Not reported			
6. Care provider masked?	NR						
7. Patients masked?	Yes						
10. Intention-to-treat analysis?	No						
11. Postrandomization exclusions?	No						

Krystal (poster)

Design: RCT DB Parallel **Trial type:** Placebo **Quality rating:** Fair

1. Randomization adequate?	NR	8. Reporting of Attrition	Yes	1. Number Screened/ Eligible/ Enrolled:	NR /	NR /	830
2. Allocation adequate?	NR	Crossover	No	3. Run-in/ Wash out (days):	14 /	14	
3. Groups similar at baseline?	Yes (	Adherence	No	4. Class naive patients only?	NR		
4. Eligibility criteria specified?	Yes	Contamination	No	5. Controlled group standard of care?	NR		
9. Loss to follow-up, differential?	Yes			2. Exclusion criteria reported?			
5. Outcome assessors masked?	"double-blind" but not specified			6. Funding: Sepracor			
6. Care provider masked?	"double-blind" but not specified						
7. Patients masked?	"double-blind" but not specified						
10. Intention-to-treat analysis?	No (2 eszopiclone patients not analyz						
11. Postrandomization exclusions?	No						

Krystal, 2003

Design: RCT DB Parallel **Trial type:** Placebo **Quality rating:** Fair

1. Randomization adequate?	NR	8. Reporting of Attrition	Yes	1. Number Screened/ Eligible/ Enrolled:	1194 /	791 /	788
2. Allocation adequate?	NR	Crossover	No	3. Run-in/ Wash out (days):	NR /	5-7	
3. Groups similar at baseline?	weig	Adherence	No	4. Class naive patients only?	NR		
4. Eligibility criteria specified?	Yes	Contamination	No	5. Controlled group standard of care?	NR		
9. Loss to follow-up, differential?	No			2. Exclusion criteria reported?	No		
5. Outcome assessors masked?	Yes			6. Funding: Sepracor			
6. Care provider masked?	NR						
7. Patients masked?	Yes						
10. Intention-to-treat analysis?	Yes						
11. Postrandomization exclusions?	3 patients discontinued before taking						

Evidence Table 16. Quality Assessment of efficacy trials

Internal validity **External validity**

Lahmeyer, 1997

Design: RCT DB Parallel **Trial type:** Placebo **Quality rating:** Fair

1. Randomization adequate?	NR	8. Reporting of Attrition	Yes
2. Allocation adequate?	NR	Crossover	No
3. Groups similar at baseline?	Yes	Adherence	Yes
4. Eligibility criteria specified?	Yes	Contamination	No
9. Loss to follow-up, differential?	Yes		
5. Outcome assessors masked?	Yes		
6. Care provider masked?	NR		
7. Patients masked?	Yes		
10. Intention-to-treat analysis?	No		
11. Postrandomization exclusions?	No		

1. Number Screened/ Eligible/ Enrolled:	178 /	33 /	145
3. Run-in/ Wash out (days):	3 /	4	
4. Class naive patients only?	NR		
5. Controlled group standard of care?	Yes		
2. Exclusion criteria reported?	Yes		
6. Funding: ?orex Pharmaceuticals			

Lemoine, 1995

Design: RCT DB Parallel **Trial type:** H2H **Quality rating:** Fair

1. Randomization adequate?	NR	8. Reporting of Attrition	Yes
2. Allocation adequate?	NR	Crossover	No
3. Groups similar at baseline?	Yes	Adherence	No
4. Eligibility criteria specified?		Contamination	No
9. Loss to follow-up, differential?	No		
5. Outcome assessors masked?	Yes		
6. Care provider masked?	NR		
7. Patients masked?	Yes		
10. Intention-to-treat analysis?	No		
11. Postrandomization exclusions?	No		

1. Number Screened/ Eligible/ Enrolled:	NR /	NR /	394
3. Run-in/ Wash out (days):	0 /	0	
4. Class naive patients only?	No		
5. Controlled group standard of care?	Yes		
2. Exclusion criteria reported?	Yes		
6. Funding: Not reported			

Leppik, 1997

Design: RCT DB Parallel **Trial type:** Active **Quality rating:** Fair

1. Randomization adequate?	NR	8. Reporting of Attrition	Yes
2. Allocation adequate?	NR	Crossover	No
3. Groups similar at baseline?	Yes	Adherence	No
4. Eligibility criteria specified?	Yes	Contamination	No
9. Loss to follow-up, differential?	No		
5. Outcome assessors masked?	Yes, but not described		
6. Care provider masked?	NR		
7. Patients masked?	Yes		
10. Intention-to-treat analysis?	Yes		
11. Postrandomization exclusions?	No		

1. Number Screened/ Eligible/ Enrolled:	NR /	457 /	335
3. Run-in/ Wash out (days):	7 /	4	
4. Class naive patients only?	No		
5. Controlled group standard of care?	Yes		
2. Exclusion criteria reported?	Yes		
6. Funding: Lornex Pharmaceuticals			

Evidence Table 16. Quality Assessment of efficacy trials

Internal validity **External validity**

Liu, 1997

Design: RCT DB Crossover **Trial type:** Active **Quality rating:** Poor

1. Randomization adequate?	NR	8. Reporting of Attrition	Yes	1. Number Screened/ Eligible/ Enrolled:	NR /	NR /	15
2. Allocation adequate?	NR	Crossover	No	3. Run-in/ Wash out (days):	0 /	7	
3. Groups similar at baseline?	NR	Adherence	Yes	4. Class naive patients only?			
4. Eligibility criteria specified?	Yes	Contamination	No	5. Controlled group standard of care?			
9. Loss to follow-up, differential?	Yes			2. Exclusion criteria reported?	Yes		
5. Outcome assessors masked?	Yes, but not described			6. Funding:			
6. Care provider masked?	NR						
7. Patients masked?	Yes, but not described						
10. Intention-to-treat analysis?	Unable to determine						
11. Postrandomization exclusions?	Unable to determine						

Mamelak, 1987

Design: RCT DB Parallel **Trial type:** Active **Quality rating:** Fair

1. Randomization adequate?	NR	8. Reporting of Attrition	No	1. Number Screened/ Eligible/ Enrolled:	NR /	NR /	30
2. Allocation adequate?	NR	Crossover	No	3. Run-in/ Wash out (days):	2 /	3	
3. Groups similar at baseline?	NR	Adherence	No	4. Class naive patients only?	No		
4. Eligibility criteria specified?	Yes	Contamination	No	5. Controlled group standard of care?	Yes		
9. Loss to follow-up, differential?	No			2. Exclusion criteria reported?	Yes		
5. Outcome assessors masked?	Yes			6. Funding: Not reported			
6. Care provider masked?	NR						
7. Patients masked?	Yes						
10. Intention-to-treat analysis?	Unable to determine						
11. Postrandomization exclusions?	Unable to determine						

Monchesky, 1986

Design: RCT DB Crossover **Trial type:** Placebo **Quality rating:** Fair

1. Randomization adequate?	Yes	8. Reporting of Attrition	Yes	1. Number Screened/ Eligible/ Enrolled:	NR /	NR /	99
2. Allocation adequate?	NR	Crossover	No	3. Run-in/ Wash out (days):	7 /	7	
3. Groups similar at baseline?	Yes (	Adherence	No	4. Class naive patients only?	NR		
4. Eligibility criteria specified?	Yes	Contamination	No	5. Controlled group standard of care?	NR		
9. Loss to follow-up, differential?	Unab			2. Exclusion criteria reported?	Yes		
5. Outcome assessors masked?	Yes, but not described			6. Funding: NR			
6. Care provider masked?	NR						
7. Patients masked?	Yes						
10. Intention-to-treat analysis?	No (91/99 analyzed)						
11. Postrandomization exclusions?	1/99						

Evidence Table 16. Quality Assessment of efficacy trials

Internal validity **External validity**

Monti, 1994 **Design:** RCT DB Parallel **Trial type:** Active **Quality rating:** Fair

1. Randomization adequate?	NR	8. Reporting of Attrition	Yes
2. Allocation adequate?	NR	Crossover	Yes
3. Groups similar at baseline?	Yes	Adherence	Yes
4. Eligibility criteria specified?	Yes	Contamination	Yes
9. Loss to follow-up, differential?	No		
5. Outcome assessors masked?	Yes, but not described		
6. Care provider masked?	NR		
7. Patients masked?	Yes		
10. Intention-to-treat analysis?	Yes		
11. Postrandomization exclusions?	No		

1. Number Screened/ Eligible/ Enrolled:	NR /	NR /	24
3. Run-in/ Wash out (days):	3 /	3	
4. Class naive patients only?	No		
5. Controlled group standard of care?	Yes		
2. Exclusion criteria reported?	Yes		
6. Funding: Not reported			

Monti, 1996 **Design:** RCT DB Parallel **Trial type:** Placebo **Quality rating:** Fair

1. Randomization adequate?	NR	8. Reporting of Attrition	No
2. Allocation adequate?	NR	Crossover	No
3. Groups similar at baseline?	Yes	Adherence	No
4. Eligibility criteria specified?	Yes	Contamination	No
9. Loss to follow-up, differential?	No		
5. Outcome assessors masked?	Yes, but not described		
6. Care provider masked?	NR		
7. Patients masked?	Yes		
10. Intention-to-treat analysis?	Yes		
11. Postrandomization exclusions?	No		

1. Number Screened/ Eligible/ Enrolled:	NR /	NR /	12
3. Run-in/ Wash out (days):	2 /	3	
4. Class naive patients only?	Yes		
5. Controlled group standard of care?	Yes		
2. Exclusion criteria reported?	Yes		
6. Funding: NR			

Monti, 2000 **Design:** RCT DB Parallel **Trial type:** Placebo **Quality rating:** Poor

1. Randomization adequate?	No (s	8. Reporting of Attrition	No
2. Allocation adequate?	No (r	Crossover	No
3. Groups similar at baseline?	Lowe	Adherence	No
4. Eligibility criteria specified?	Yes	Contamination	No
9. Loss to follow-up, differential?	NR		
5. Outcome assessors masked?	Yes		
6. Care provider masked?	NR		
7. Patients masked?	Yes		
10. Intention-to-treat analysis?	Unable to determine		
11. Postrandomization exclusions?	Unable to determine		

1. Number Screened/ Eligible/ Enrolled:	NR /	NR /	12
3. Run-in/ Wash out (days):	3 /	3	
4. Class naive patients only?	No		
5. Controlled group standard of care?	NR		
2. Exclusion criteria reported?	Yes		
6. Funding: NR			

Evidence Table 16. Quality Assessment of efficacy trials

Internal validity **External validity**

Nair, 1990

Design: RCT DB Parallel **Trial type:** Active **Quality rating:** Fair

1. Randomization adequate?	NR	8. Reporting of Attrition	Yes	1. Number Screened/ Eligible/ Enrolled:	NR /	NR /	60
2. Allocation adequate?	NR	Crossover	0	3. Run-in/ Wash out (days):	1 /	NR	
3. Groups similar at baseline?	Yes	Adherence	Yes	4. Class naive patients only?	No		
4. Eligibility criteria specified?	Yes	Contamination	No	5. Controlled group standard of care?	Yes		
9. Loss to follow-up, differential?	No			2. Exclusion criteria reported?	Yes		
5. Outcome assessors masked?	Yes, but not described			6. Funding: Rhone-Poulenc Pharma			
6. Care provider masked?	NR						
7. Patients masked?	Yes						
10. Intention-to-treat analysis?	No						
11. Postrandomization exclusions?	No						

Ngen, 1990

Design: RCT DB Parallel **Trial type:** Active **Quality rating:** Fair

1. Randomization adequate?	Yes	8. Reporting of Attrition		1. Number Screened/ Eligible/ Enrolled:	NR /	NR /	60
2. Allocation adequate?	Yes	Crossover	0	3. Run-in/ Wash out (days):	7 /	NR	
3. Groups similar at baseline?		Adherence		4. Class naive patients only?	No		
4. Eligibility criteria specified?		Contamination		5. Controlled group standard of care?	Yes		
9. Loss to follow-up, differential?	Yes			2. Exclusion criteria reported?	Yes		
5. Outcome assessors masked?	Yes			6. Funding: Rhone-Poulenc Pharma			
6. Care provider masked?	NR						
7. Patients masked?	Yes						
10. Intention-to-treat analysis?	No						
11. Postrandomization exclusions?	No						

Perlis, 2004

Design: RCT DB Parallel **Trial type:** Placebo **Quality rating:** Fair

1. Randomization adequate?	Yes	8. Reporting of Attrition	Yes	1. Number Screened/ Eligible/ Enrolled:	322 /	277 /	199
2. Allocation adequate?	Yes	Crossover	No	3. Run-in/ Wash out (days):	6-14 /	NR	
3. Groups similar at baseline?	More	Adherence	Yes	4. Class naive patients only?			
4. Eligibility criteria specified?	Yes	Contamination	Yes	5. Controlled group standard of care?			
9. Loss to follow-up, differential?	No			2. Exclusion criteria reported?	Yes		
5. Outcome assessors masked?	Yes			6. Funding: Lorex Pharmaceuticals			
6. Care provider masked?	NR						
7. Patients masked?	Yes						
10. Intention-to-treat analysis?	No						
11. Postrandomization exclusions?	No						

Evidence Table 16. Quality Assessment of efficacy trials

Internal validity **External validity**

Ponciano, 1990

Design: RCT DB Parallel **Trial type:** Active **Quality rating:** Fair

1. Randomization adequate?	NR	8. Reporting of Attrition	Yes
2. Allocation adequate?	NR	Crossover	No
3. Groups similar at baseline?	NR	Adherence	No
4. Eligibility criteria specified?	Yes	Contamination	No
9. Loss to follow-up, differential?	No		
5. Outcome assessors masked?	Yes		
6. Care provider masked?	NR		
7. Patients masked?	Yes		
10. Intention-to-treat analysis?	Yes		
11. Postrandomization exclusions?	No		

1. Number Screened/ Eligible/ Enrolled:	NR /	NR /	26
3. Run-in/ Wash out (days):	7 /	7	
4. Class naive patients only?	No		
5. Controlled group standard of care?	Yes		
2. Exclusion criteria reported?	Yes		
6. Funding: Not reported			

Quadens, 1983

Design: RCT DB Crossover **Trial type:** Active **Quality rating:** Poor

1. Randomization adequate?	NR	8. Reporting of Attrition	No
2. Allocation adequate?	NR	Crossover	No
3. Groups similar at baseline?	NR	Adherence	No
4. Eligibility criteria specified?	Yes	Contamination	No
9. Loss to follow-up, differential?	NR		
5. Outcome assessors masked?	Yes, but not described		
6. Care provider masked?	NR		
7. Patients masked?	Yes		
10. Intention-to-treat analysis?	Unable to determine		
11. Postrandomization exclusions?	Unable to determine		

1. Number Screened/ Eligible/ Enrolled:	NR /	NR /	12
3. Run-in/ Wash out (days):	6 /	35	
4. Class naive patients only?	NR		
5. Controlled group standard of care?	Yes		
2. Exclusion criteria reported?	Yes		
6. Funding: Not reported			

Roehrs (poster)

Design: RCT DB Parallel **Trial type:** Placebo **Quality rating:** Fair

1. Randomization adequate?	NR	8. Reporting of Attrition	Yes
2. Allocation adequate?	NR	Crossover	No
3. Groups similar at baseline?	Som	Adherence	No
4. Eligibility criteria specified?	Yes	Contamination	No
9. Loss to follow-up, differential?	No		
5. Outcome assessors masked?	Yes, but not described		
6. Care provider masked?	Yes, but not described		
7. Patients masked?	Yes, but not described		
10. Intention-to-treat analysis?	No		
11. Postrandomization exclusions?	Unable to determine		

1. Number Screened/ Eligible/ Enrolled:	NR /	NR /	205
3. Run-in/ Wash out (days):	no /	no	
4. Class naive patients only?	NR		
5. Controlled group standard of care?	Yes		
2. Exclusion criteria reported?			
6. Funding: Sanofi-Aventis			

Evidence Table 16. Quality Assessment of efficacy trials

Internal validity **External validity**

Roger, 1993

Design: RCT DB Parallel **Trial type:** Active **Quality rating:** Fair

1. Randomization adequate?	NR	8. Reporting of Attrition	Yes	1. Number Screened/ Eligible/ Enrolled:	NR /	NR /	221
2. Allocation adequate?	NR	Crossover	No	3. Run-in/ Wash out (days):	3 /	7	
3. Groups similar at baseline?	Yes	Adherence	No	4. Class naive patients only?	No		
4. Eligibility criteria specified?	Yes	Contamination	No	5. Controlled group standard of care?	Yes		
9. Loss to follow-up, differential?	No			2. Exclusion criteria reported?	Yes		
5. Outcome assessors masked?	Yes, but not described			6. Funding: Not reported			
6. Care provider masked?	Yes, but not described						
7. Patients masked?	Yes						
10. Intention-to-treat analysis?	Unable to determine						
11. Postrandomization exclusions?	No						

Rosenberg, 1994

Design: RCT DB Parallel **Trial type:** Active **Quality rating:** Poor

1. Randomization adequate?	Yes	8. Reporting of Attrition	Yes	1. Number Screened/ Eligible/ Enrolled:	NR /	NR /	178
2. Allocation adequate?	Yes	Crossover	No	3. Run-in/ Wash out (days):	NR /	NR	
3. Groups similar at baseline?	NR	Adherence	No	4. Class naive patients only?	No		
4. Eligibility criteria specified?	Yes	Contamination	No	5. Controlled group standard of care?	Yes		
9. Loss to follow-up, differential?	Yes			2. Exclusion criteria reported?	Yes		
5. Outcome assessors masked?	Yes			6. Funding: Synthelabo Scandinavia A/S			
6. Care provider masked?	Yes						
7. Patients masked?	Yes						
10. Intention-to-treat analysis?	No						
11. Postrandomization exclusions?	Yes						

Roth

Design: RCT DB Parallel **Trial type:** Placebo **Quality rating:** Fair

1. Randomization adequate?	NR	8. Reporting of Attrition	Yes	1. Number Screened/ Eligible/ Enrolled:	NR /	NR /	829
2. Allocation adequate?	NR	Crossover	No	3. Run-in/ Wash out (days):	7 /	7	
3. Groups similar at baseline?	Yes (	Adherence	No	4. Class naive patients only?	NR		
4. Eligibility criteria specified?	Yes	Contamination	No	5. Controlled group standard of care?	Yes		
9. Loss to follow-up, differential?	NR			2. Exclusion criteria reported?			
5. Outcome assessors masked?	Yes, but not described			6. Funding: Takeda Pharmaceuticals			
6. Care provider masked?	Yes, but not described						
7. Patients masked?	Yes, but not described						
10. Intention-to-treat analysis?	Unable to determine						
11. Postrandomization exclusions?	No						

Evidence Table 16. Quality Assessment of efficacy trials

Internal validity				External validity			
Scharf, 1994	**Design:** RCT DB Parallel	**Trial type:** Placebo	**Quality rating:** Fair				
1. Randomization adequate?	NR	8. Reporting of Attrition	Yes	1. Number Screened/ Eligible/ Enrolled:	178 /	75 /	75
2. Allocation adequate?	NR	Crossover	No	3. Run-in/ Wash out (days):	11 /	2	
3. Groups similar at baseline?	Yes	Adherence	No	4. Class naive patients only?	NR		
4. Eligibility criteria specified?	Yes	Contamination	Yes	5. Controlled group standard of care?	NR		
9. Loss to follow-up, differential?	No			2. Exclusion criteria reported?			
5. Outcome assessors masked?	Yes			6. Funding: NR			
6. Care provider masked?	NR						
7. Patients masked?	Yes						
10. Intention-to-treat analysis?	Unable to determine						
11. Postrandomization exclusions?	No						
Scharf, 2005	**Design:** RCT DB Parallel	**Trial type:** Placebo	**Quality rating:** Fair				
1. Randomization adequate?	NR	8. Reporting of Attrition	Yes	1. Number Screened/ Eligible/ Enrolled:	353 /	NR /	231
2. Allocation adequate?	NR	Crossover	No	3. Run-in/ Wash out (days):	3-14 /	NR	
3. Groups similar at baseline?	Yes	Adherence	No	4. Class naive patients only?	No		
4. Eligibility criteria specified?	Yes	Contamination	No	5. Controlled group standard of care?	NR		
9. Loss to follow-up, differential?	No			2. Exclusion criteria reported?	Yes		
5. Outcome assessors masked?	Yes			6. Funding:			
6. Care provider masked?	NR						
7. Patients masked?	Yes						
10. Intention-to-treat analysis?	Yes						
11. Postrandomization exclusions?	Unable to determine						
Sepracor Study #190-045	**Design:** RCT DB Crossover	**Trial type:** H2H	**Quality rating:** Fair				
1. Randomization adequate?	NR	8. Reporting of Attrition	No	1. Number Screened/ Eligible/ Enrolled:	NR /	NR /	64
2. Allocation adequate?	NR	Crossover	No	3. Run-in/ Wash out (days):	3-7 /	3-7	
3. Groups similar at baseline?	NR	Adherence	No	4. Class naive patients only?	NR		
4. Eligibility criteria specified?	Yes	Contamination	No	5. Controlled group standard of care?	NR		
9. Loss to follow-up, differential?	NR			2. Exclusion criteria reported?	No		
5. Outcome assessors masked?	Yes (but concern re. unpleasant taste)			6. Funding: Sepracor			
6. Care provider masked?	NR						
7. Patients masked?	Yes (but concern re. unpleasant taste)						
10. Intention-to-treat analysis?	Pts who rec'd at least one dose of me						
11. Postrandomization exclusions?	Unable to determine						

Evidence Table 16. Quality Assessment of efficacy trials

Internal validity **External validity**

Silvestri, 1996

Design: RCT DB Parallel **Trial type:** Active **Quality rating:** Fair

1. Randomization adequate?	NR	8. Reporting of Attrition	Yes	1. Number Screened/ Eligible/ Enrolled:	NR /	NR /	22
2. Allocation adequate?	NR	Crossover	No	3. Run-in/ Wash out (days):	3 /	No	
3. Groups similar at baseline?	Yes	Adherence	No	4. Class naive patients only?	No		
4. Eligibility criteria specified?	Yes	Contamination	No	5. Controlled group standard of care?	Yes		
9. Loss to follow-up, differential?	Yes			2. Exclusion criteria reported?	Yes		
5. Outcome assessors masked?	Yes, but not described			6. Funding: Not reported			
6. Care provider masked?	NR						
7. Patients masked?	Yes, but not described						
10. Intention-to-treat analysis?	No						
11. Postrandomization exclusions?	Yes						

Singh, 1990

Design: RCT DB Parallel **Trial type:** Active **Quality rating:** Fair

1. Randomization adequate?	NR	8. Reporting of Attrition	Yes	1. Number Screened/ Eligible/ Enrolled:	NR /	61 /	60
2. Allocation adequate?	NR	Crossover	No	3. Run-in/ Wash out (days):	4 /	NR	
3. Groups similar at baseline?	NR	Adherence	No	4. Class naive patients only?	NR		
4. Eligibility criteria specified?	No	Contamination	No	5. Controlled group standard of care?	Yes		
9. Loss to follow-up, differential?	No			2. Exclusion criteria reported?	Yes		
5. Outcome assessors masked?	Yes, but not described			6. Funding: Rhone-Poulenc Pharma Inc.			
6. Care provider masked?	NR						
7. Patients masked?	Yes						
10. Intention-to-treat analysis?	Yes						
11. Postrandomization exclusions?	Yes (1 patient)						

Soubrane (poster)

Design: RCT DB Parallel **Trial type:** Placebo **Quality rating:** Fair

1. Randomization adequate?	NR	8. Reporting of Attrition	Yes	1. Number Screened/ Eligible/ Enrolled:	NR /	NR /	212
2. Allocation adequate?	NR	Crossover	No	3. Run-in/ Wash out (days):	/		
3. Groups similar at baseline?	Yes	Adherence	No	4. Class naive patients only?	NR		
4. Eligibility criteria specified?	Yes	Contamination	No	5. Controlled group standard of care?	Yes		
9. Loss to follow-up, differential?	No			2. Exclusion criteria reported?			
5. Outcome assessors masked?	Yes, but not described			6. Funding: Sanofi-Aventis			
6. Care provider masked?	Yes, but not described						
7. Patients masked?	Yes, but not described						
10. Intention-to-treat analysis?	No						
11. Postrandomization exclusions?	Unable to determine						

Evidence Table 16. Quality Assessment of efficacy trials

Internal validity **External validity**

Staner, 2005

Design: RCT DB Crossover **Trial type:** H2H **Quality rating:** Poor

1. Randomization adequate?	Meth	8. Reporting of Attrition	No	1. Number Screened/ Eligible/ Enrolled:	NR /	NR /	23
2. Allocation adequate?	NR	Crossover	No	3. Run-in/ Wash out (days):	NR /	7	
3. Groups similar at baseline?	NR	Adherence	No	4. Class naive patients only?	No		
4. Eligibility criteria specified?	Yes	Contamination	No	5. Controlled group standard of care?	Yes		
9. Loss to follow-up, differential?	NR			2. Exclusion criteria reported?			
5. Outcome assessors masked?	Yes, but not described			6. Funding: Sanofi-Aventis			
6. Care provider masked?	Yes, but not described						
7. Patients masked?	Yes						
10. Intention-to-treat analysis?	Unable to determine						
11. Postrandomization exclusions?	Unable to determine						

Stip, 1999

Design: RCT DB Parallel **Trial type:** Active **Quality rating:** Fair

1. Randomization adequate?	NR	8. Reporting of Attrition	Yes	1. Number Screened/ Eligible/ Enrolled:	NR /	NR /	60
2. Allocation adequate?	NR	Crossover	No	3. Run-in/ Wash out (days):	7 /	7	
3. Groups similar at baseline?	NR	Adherence	No	4. Class naive patients only?	NR		
4. Eligibility criteria specified?	Yes	Contamination	No	5. Controlled group standard of care?	Yes		
9. Loss to follow-up, differential?	Yes			2. Exclusion criteria reported?	No		
5. Outcome assessors masked?	Yes, but not described			6. Funding: Not reported			
6. Care provider masked?	NR						
7. Patients masked?	Yes						
10. Intention-to-treat analysis?	No						
11. Postrandomization exclusions?	Yes						

Tamminen, 1987

Design: RCT DB Parallel **Trial type:** Active **Quality rating:** Poor

1. Randomization adequate?	NR	8. Reporting of Attrition	Yes	1. Number Screened/ Eligible/ Enrolled:	NR /	130 /	94
2. Allocation adequate?	NR	Crossover	No	3. Run-in/ Wash out (days):	7 /	NR	
3. Groups similar at baseline?	NR	Adherence	No	4. Class naive patients only?	No		
4. Eligibility criteria specified?	Yes	Contamination	No	5. Controlled group standard of care?	Yes		
9. Loss to follow-up, differential?	Yes			2. Exclusion criteria reported?	Yes		
5. Outcome assessors masked?	Yes, but not described			6. Funding: Not reported			
6. Care provider masked?	NR						
7. Patients masked?	Yes						
10. Intention-to-treat analysis?	No						
11. Postrandomization exclusions?	Yes						

Evidence Table 16. Quality Assessment of efficacy trials

Internal validity **External validity**

Terzano, 1992

Design: RCT DB Parallel **Trial type:** Placebo **Quality rating:** Poor

1. Randomization adequate?	NR	8. Reporting of Attrition	No
2. Allocation adequate?	NR	Crossover	No
3. Groups similar at baseline?	NR	Adherence	No
4. Eligibility criteria specified?	Yes	Contamination	No
9. Loss to follow-up, differential?	NR		
5. Outcome assessors masked?	Yes, but not described		
6. Care provider masked?	NR		
7. Patients masked?	Yes, but not described		
10. Intention-to-treat analysis?	NR		
11. Postrandomization exclusions?	NR		

1. Number Screened/ Eligible/ Enrolled:	NR /	NR /	12
3. Run-in/ Wash out (days):	14 /	NR	
4. Class naive patients only?	NR		
5. Controlled group standard of care?	NR		
2. Exclusion criteria reported?	Yes		

6. Funding: Partially supported by Italian Ministry of University and Scientific Research

Tsutsui, 2001

Design: RCT DB Parallel **Trial type:** H2H **Quality rating:** Fair

1. Randomization adequate?	NR	8. Reporting of Attrition	Yes
2. Allocation adequate?	NR	Crossover	No
3. Groups similar at baseline?	NR	Adherence	Yes
4. Eligibility criteria specified?	Yes	Contamination	No
9. Loss to follow-up, differential?	Yes		
5. Outcome assessors masked?	Yes		
6. Care provider masked?	NR		
7. Patients masked?	Yes		
10. Intention-to-treat analysis?	No		
11. Postrandomization exclusions?	Yes		

1. Number Screened/ Eligible/ Enrolled:	NR /	NR /	479
3. Run-in/ Wash out (days):	0 /	7	
4. Class naive patients only?	No		
5. Controlled group standard of care?	Yes		
2. Exclusion criteria reported?	Yes		

6. Funding: Not reported

van der Kleijn, 1989

Design: RCT DB Crossover **Trial type:** Active **Quality rating:** Fair

1. Randomization adequate?	NR	8. Reporting of Attrition	Yes
2. Allocation adequate?	NR	Crossover	No
3. Groups similar at baseline?	NR	Adherence	No
4. Eligibility criteria specified?	Yes	Contamination	No
9. Loss to follow-up, differential?	No		
5. Outcome assessors masked?	Yes, but not described		
6. Care provider masked?	NR		
7. Patients masked?	Yes		
10. Intention-to-treat analysis?	No		
11. Postrandomization exclusions?	Unable to determine		

1. Number Screened/ Eligible/ Enrolled:	NR /	60 /	55
3. Run-in/ Wash out (days):	2 /	7	
4. Class naive patients only?	No		
5. Controlled group standard of care?	Yes		
2. Exclusion criteria reported?	Yes		

6. Funding: Rhone-Poulenc Pharma

Evidence Table 16. Quality Assessment of efficacy trials

Internal validity **External validity**

Venter, 1986

Design: RCT DB Parallel **Trial type:** Active **Quality rating:** Fair

1. Randomization adequate?	NR	8. Reporting of Attrition	No	1. Number Screened/ Eligible/ Enrolled:	58 / 41 / 41
2. Allocation adequate?	NR	Crossover	No	3. Run-in/ Wash out (days):	7 / 0
3. Groups similar at baseline?	Yes	Adherence	No	4. Class naive patients only?	No
4. Eligibility criteria specified?	Yes	Contamination	No	5. Controlled group standard of care?	Yes
9. Loss to follow-up, differential?	No			2. Exclusion criteria reported?	Yes
5. Outcome assessors masked?	Yes, but not described			6. Funding: Not reported	
6. Care provider masked?	Yes, but not described				
7. Patients masked?	Yes, but not described				
10. Intention-to-treat analysis?	Yes				
11. Postrandomization exclusions?	No				

Voshaar, 2004

Design: RCT DB Parallel **Trial type:** Active **Quality rating:** Fair

1. Randomization adequate?	NR	8. Reporting of Attrition	Yes	1. Number Screened/ Eligible/ Enrolled:	NR / NR / 221
2. Allocation adequate?	NR	Crossover	0	3. Run-in/ Wash out (days):	NR / 4
3. Groups similar at baseline?	Yes	Adherence	No	4. Class naive patients only?	No
4. Eligibility criteria specified?	Yes	Contamination	No	5. Controlled group standard of care?	Yes
9. Loss to follow-up, differential?	Yes			2. Exclusion criteria reported?	Yes
5. Outcome assessors masked?	Yes, but not described			6. Funding: Sanfi-Synthelabo	
6. Care provider masked?	NR				
7. Patients masked?	Yes				
10. Intention-to-treat analysis?	No				
11. Postrandomization exclusions?	Yes				

Walsh, 1998a

Design: RCT DB Parallel **Trial type:** Active **Quality rating:** Fair

1. Randomization adequate?	NR	8. Reporting of Attrition	Yes	1. Number Screened/ Eligible/ Enrolled:	NR / 589 / 306
2. Allocation adequate?	NR	Crossover	No	3. Run-in/ Wash out (days):	7 / NR
3. Groups similar at baseline?	Yes	Adherence	No	4. Class naive patients only?	No
4. Eligibility criteria specified?	Yes	Contamination	No	5. Controlled group standard of care?	Yes
9. Loss to follow-up, differential?	No			2. Exclusion criteria reported?	Yes
5. Outcome assessors masked?	Yes, but not described			6. Funding: Lorex Pharmaceuticals	
6. Care provider masked?	NR				
7. Patients masked?	Yes				
10. Intention-to-treat analysis?	No				
11. Postrandomization exclusions?	Yes				

Evidence Table 16. Quality Assessment of efficacy trials

Internal validity **External validity**

Walsh, 1998b

Design: **Trial type:** Active **Quality rating:** Good

1. Randomization adequate?	Yes	8. Reporting of Attrition	Yes
2. Allocation adequate?	NR	Crossover	No
3. Groups similar at baseline?	Yes	Adherence	No
4. Eligibility criteria specified?	Yes	Contamination	No
9. Loss to follow-up, differential?	No		
5. Outcome assessors masked?	Yes, but not described		
6. Care provider masked?	NR		
7. Patients masked?	Yes		
10. Intention-to-treat analysis?	Yes		
11. Postrandomization exclusions?	No		

1. Number Screened/ Eligible/ Enrolled:	673 /	456 /	132
3. Run-in/ Wash out (days):	3 /	2	
4. Class naive patients only?	No		
5. Controlled group standard of care?	Yes		
2. Exclusion criteria reported?	Yes		
6. Funding: Wyeth Ayerst			

Walsh, 2000

Design: RCT DB Crossover **Trial type:** Active **Quality rating:** Poor

1. Randomization adequate?	NR	8. Reporting of Attrition	Yes
2. Allocation adequate?	NR	Crossover	0
3. Groups similar at baseline?	NR	Adherence	Yes
4. Eligibility criteria specified?	Yes	Contamination	No
9. Loss to follow-up, differential?	Yes		
5. Outcome assessors masked?	Yes, but not described		
6. Care provider masked?	NR		
7. Patients masked?	Yes, but not described		
10. Intention-to-treat analysis?	No		
11. Postrandomization exclusions?	Yes		

1. Number Screened/ Eligible/ Enrolled:	73 /	39 /	30
3. Run-in/ Wash out (days):	NR /	NR	
4. Class naive patients only?	Yes		
5. Controlled group standard of care?	Yes		
2. Exclusion criteria reported?	Yes		
6. Funding: Wyeth-Ayerst Research			

Walsh, 2000a

Design: RCT DB Parallel **Trial type:** Placebo **Quality rating:** Poor

1. Randomization adequate?	Not c	8. Reporting of Attrition	Yes
2. Allocation adequate?	Not c	Crossover	No
3. Groups similar at baseline?	NR	Adherence	No
4. Eligibility criteria specified?	Yes	Contamination	No
9. Loss to follow-up, differential?	No-		
5. Outcome assessors masked?	Yes, but not described		
6. Care provider masked?	NR		
7. Patients masked?	Yes, but not described		
10. Intention-to-treat analysis?	No (48/54 analyzed)		
11. Postrandomization exclusions?	Yes		

1. Number Screened/ Eligible/ Enrolled:	311 /	54 /	48
3. Run-in/ Wash out (days):	5-12 /	5-12	
4. Class naive patients only?			
5. Controlled group standard of care?			
2. Exclusion criteria reported?	Yes		
6. Funding:			

Evidence Table 16. Quality Assessment of efficacy trials

Internal validity **External validity**

Walsh, 2000b, 2002

Design: RCT DB Parallel **Trial type:** Placebo **Quality rating:** Fair

1. Randomization adequate?	Yes	8. Reporting of Attrition	Yes
2. Allocation adequate?	NR	Crossover	No
3. Groups similar at baseline?	Yes	Adherence	Yes
4. Eligibility criteria specified?	Yes	Contamination	Yes
9. Loss to follow-up, differential?	Yes		
5. Outcome assessors masked?	Yes, but not described		
6. Care provider masked?	NR		
7. Patients masked?	Yes		
10. Intention-to-treat analysis?	No		
11. Postrandomization exclusions?	Yes		

1. Number Screened/ Eligible/ Enrolled:	365 /	163 /	163
3. Run-in/ Wash out (days):	7 /	7	
4. Class naive patients only?	NR		
5. Controlled group standard of care?	Yes		
2. Exclusion criteria reported?	No		
6. Funding: Lorex Pharmaceuticals			

Ware, 1997

Design: RCT DB Parallel **Trial type:** Active **Quality rating:** Fair

1. Randomization adequate?	NR	8. Reporting of Attrition	Yes
2. Allocation adequate?	NR	Crossover	No
3. Groups similar at baseline?	Yes	Adherence	No
4. Eligibility criteria specified?	Yes	Contamination	No
9. Loss to follow-up, differential?	No		
5. Outcome assessors masked?	Yes, but not described		
6. Care provider masked?	NR		
7. Patients masked?	Yes, but not described		
10. Intention-to-treat analysis?	No		
11. Postrandomization exclusions?	No		

1. Number Screened/ Eligible/ Enrolled:	358 /	NR /	110
3. Run-in/ Wash out (days):	2 /	3	
4. Class naive patients only?	Yes		
5. Controlled group standard of care?	Yes		
2. Exclusion criteria reported?	Yes		
6. Funding: Lorex Pharmaceuticals			

Wheatley, 1985

Design: RCT DB Crossover **Trial type:** Active **Quality rating:** Fair

1. Randomization adequate?	NR	8. Reporting of Attrition	Yes
2. Allocation adequate?	NR	Crossover	No
3. Groups similar at baseline?	No	Adherence	No
4. Eligibility criteria specified?	No	Contamination	No
9. Loss to follow-up, differential?	No		
5. Outcome assessors masked?	Yes, but not described		
6. Care provider masked?	NR		
7. Patients masked?	Yes		
10. Intention-to-treat analysis?	Unable to determine		
11. Postrandomization exclusions?	Unable to determine		

1. Number Screened/ Eligible/ Enrolled:	NR /	NR /	36
3. Run-in/ Wash out (days):	3 /	NR	
4. Class naive patients only?	No		
5. Controlled group standard of care?	Yes		
2. Exclusion criteria reported?	No		
6. Funding: Not reported			

Evidence Table 16. Quality Assessment of efficacy trials

Internal validity				External validity			
Zammit, 2004	**Design:** RCT DB Parallel	**Trial type:** Placebo	**Quality rating:** Fair				
1. Randomization adequate?	NR	8. Reporting of Attrition	Yes	1. Number Screened/ Eligible/ Enrolled:	NR /	669 /	308
2. Allocation adequate?	NR	Crossover	No	3. Run-in/ Wash out (days):	2 /	5-7	
3. Groups similar at baseline?	Differ	Adherence	No	4. Class naive patients only?	NR		
4. Eligibility criteria specified?	Yes	Contamination	No	5. Controlled group standard of care?	NR		
9. Loss to follow-up, differential?	No			2. Exclusion criteria reported?	Yes		
5. Outcome assessors masked?	Yes			6. Funding: Sepracor			
6. Care provider masked?	NR						
7. Patients masked?	Yes						
10. Intention-to-treat analysis?	No (303/308 at night 1; 293/308 at 1						
11. Postrandomization exclusions?	No						

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	Neuropsychiatric adverse events, no. of AEs (%)/ no. of drop-outs 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 Agitation/ excitation: 56(0.27%)/ 41 Irritability: 17(0.07%)/ 8 Aggressiveness: 4(0.02%)/ 2 Tremor: 12(0.06%)/ 9 Hallucinations: 7(0.03%)/ 7 Confusion: 7(0.03%)/ 5 Difficulty concentrating: 6(0.03%)/ 1 Memory complaints: 15(0.07%)/ 2 Reduced libido: 4(0.02%)/ 2 Various neuropsychiatric disorders: 15(0.07%)/ 12	Gastrointestinal adverse events, no. of AEs (%)/ no. of drop-outs 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 Somatic adverse events, no. of AEs (%)/ no. of drop-outs Asthenia: 38(0.19%)/ 6 Malaise: 14(0.07%)/ 8 Dyspnea: 8(0.02%)/ 5 Palpitation: 4(0.02%)/ 4 Rash: 8(0.04%)/ 8 Pruritus: 3(0.16%)/ 3 Other: 15(0.07%)/ 7	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 followed by 7 to 28 treatment-free days without adverse effects, and return to the clinic after the treatment free interval with a minimum of five daily sleep questionnaires to confirm the need for continued sleep therapy.
Bain, 2003 US	4,752 (687 zolpidem, 4,065 temazepam)	Zolpidem or temazepam	Not reported	Patients prescribed zolpidem or temazepam in one hospice practice setting.

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; open label continuation phase of RCT	Monthly safety assessments which included routine physical exams, laboratory determinations, vital signs including blood pressure, and electrocardiograms.	7 days	Treatment emergent adverse events were defined as any adverse event that first appeared or that intensified after the initiation of open-label treatment. Discontinuation effects.
Bain, 2003 US	Hospice patients	Retrospective database analysis 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 switch to zolpidem] vs. [use zolpidem and then switch to temazepam], (%) adverse drug reaction or others- 10.6% vs. 7.5% Discontinuation due to adverse events after filtering out "change in dose" as a reason for discontinuation. Among discontinuation except "change in dose": adverse drug reaction- 4.3% vs.10.1%	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), anxiety depressive disorder (n=3), anxiety (n=2), bipolar disorder (n=2), and schizophrenia (n=2). 16 did not specify and 2 did not know indication.	Prospective cohort study	Mailed patient questionnaire	Not reported	Daytime sleepiness, anxiousness, bad taste, weakness, drowsiness/fatigue, dry mouth, poor memory, poor concentration, Rage/aggression/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), anxiety depressive disorder (n=3), anxiety (n=2), bipolar disorder (n=2), and schizophrenia (n=2). 16 did not specify and 2 did not know indication.	Prospective cohort study	Followup by telephone interview after the expected date of delivery, using a structured questionnaire.	1993-1997	Pregnancy outcome.

Evidence Table 17: Observational Studies

Author Year Country	Results	Funding
Diav-Citrin, 1999 Canada	Pregnancy outcome, zopiclone vs. control: Pregnancy 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 initiating 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 insomnia in the department of psychiatry at one hospital.
Peeters, 1997 Belgium	1,219	Zolpidem	1 month	Men or women age 50 years or older, suffering from insomnia.

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), paraphrenia (n=1), dementia (n=1), nonorganic insomnia (n=3).	Retrospective chart review.	Medical record review.	Not clear-appears to be 1999-2000	Ataxia, hyperexcitability, daytime anxiety, agitation and confusion, amnesia, affective disturbance, somnambulism, or morning drowsiness.
Peeters, 1997 Belgium	461 males, 751 females, not recorded.	Multicenter, open label postmarketing surveillance study; before-after.	sleep parameters assessed on entry and at the follow-up visit by the investigator.	January 1st to May 31st, 1994	Reported by the patient at the followup visit.

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 confusion, amnesia, affective disturbance, somnambulism or morning drowsiness.	Not reported
Peeters, 1997 Belgium	Adverse events reported: All patients (n=1219)/ Patients <65 (n=720)/ Patients >=65 (n=495) Autonomic nervous system: 5/ 4/ 1 Central/ peripheral nervous system: 27/ 14/ 13 Gastro-intestinal system: 4/ 2/ 2 Heart rate and rhythm: 3/ 0/ 3 Musculoskeletal system: 1/ 0/ 1 Neoplasms: 2/ 1/ 1 Psychiatric system: 48/ 25/ 23 Special senses: 2/ 2/ 0 Vision: 1/ 0/ 1 Unknown: 5/ 5/ 0 Patients with at least one adverse events: 87/ 46/ 41	

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 death: 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 death: 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 death: 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 defined daily doses: 0.3(0-1.8)	Not reported

Evidence Table 17: Observational Studies

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

Evidence Table 17: Observational Studies

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

Evidence Table 17: Observational Studies

Author Year Country	Results	Funding
Schneeweiss, 2005 US	Zolpidem (n=62) vs benzodiazepine (n=567) vs none (n=6434) Patients characteristics: ADL score >=1 point: 54.8% vs 41.3% vs 27.3% Cognitive impairment: 16.1% vs 15.2% vs 10.2% Rosow-Breslau, impairments: 75.8% vs 69.5% vs 55.9% Z vs B; Z vs None; B vs none: Quantitative assessment of confounding bias in risk estimates ADL score (>1 points): 10.00; 21.48; 9.96 Cognitive impairment (yes vs no): 1.19; 7.00; 5.78 Rosow-Breslau (>=1 impairments): 3.43; 10.58; 6.54	NR
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 claims for a nonprescription service between January 1, 1994 and December 31, 1994 and have filled at least one prescription for any medication through the Medicaid or PAAD programs of New Jersey in each of four consecutive 6-month periods beginning January 1, 1993.

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 Institute on Aging.

Evidence Table 18. Case Reports

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

Evidence Table 18. Case Reports

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

Evidence Table 18. Case Reports

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

Evidence Table 18. Case Reports

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

Evidence Table 18. Case Reports

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

Evidence Table 18. Case Reports

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

Evidence Table 18. Case Reports

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

Evidence Table 18. Case Reports

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

Evidence Table 18. Case Reports

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

Alderman, C. P., Gebauer, M. G., Gilbert, A. L., & Condon, J. T. (2001). Possible interaction of zopiclone and nefazodone. *Annals of Pharmacotherapy, 35*(11), 1378-1380.

Aragona, M. (2000). Abuse, dependence, and epileptic seizures after zolpidem withdrawal: Review and case report. *Clinical Neuropharmacology, 23*(5), 281-283.

Aranko, K., Henriksson, M., Hublin, C., & Seppalainen, A. M. (1991). Misuse of zopiclone and convulsions during withdrawal. *Pharmacopsychiatry, 24*(4), 138-140.

Bhatia, S. C., Arora, M., & Bhatia, S. K. (2001). Perceptual disturbances with zaleplon. *Psychiatric Services, 52*(1), 109-110.

Bramness, J. G., Arnestad, M., Karinen, R., & Hilberg, T. (2001). Fatal overdose of zopiclone in an elderly woman with bronchogenic carcinoma. *Journal of Forensic Sciences, 46*(5), 1247-1249.

Brodeur, M. R., & Stirling, A. L. (2001). Delirium associated with zolpidem. *Annals of Pharmacotherapy, 35*(12), 1562-1564.

Canaday, B. R. (1996). Amnesia possibly associated with zolpidem administration. *Pharmacotherapy, 16*(4), 687-689.

Clark, A. (1999). Worsening hepatic encephalopathy secondary to zolpidem. *Journal of Pharmacy Technology, 15*(4), 139-141.

Elko, C. J., Burgess, J. L., & Robertson, W. O. (1998). Zolpidem-associated hallucinations and serotonin reuptake inhibition: a possible interaction. *Journal of Toxicology - Clinical Toxicology, 36*(3), 195-203.

Evidence Table 18. Case Reports

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

Evidence Table 18. Case Reports

Quaglio, G., Lugoboni, F., Fornasiero, A., Lechi, A., Gerra, G., & Mezzelani, P. (2005). Dependence on zolpidem: Two case reports of detoxification with flumazenil infusion. *International Clinical Psychopharmacology, 20*(5), 285-287.

Sattar, S. P., Ramaswamy, S., Bhatia, S. C., & Petty, F. (2003). Somnambulism due to probable interaction of valproic acid and zolpidem. *Annals of Pharmacotherapy, 37*(10), 1429-1433.

Stebbing, J., Waters, L., Davies, L., Mandalia, S., Nelson, M., Gazzard, B., et al. (2005). Incidence of cancer in individuals receiving chronic zopiclone or eszopiclone requires prospective study. *Journal of Clinical Oncology, 23*(31), 8134-8136.

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

Sullivan, G., McBride, A. J., & Clee, W. B. (1995). Zopiclone abuse in South Wales: Three case reports. *Human Psychopharmacology, 10*(4), 351-352.

Thakore, J., & Dinan, T. G. (1992). Physical dependence following zopiclone usage: A case report. *Human Psychopharmacology, 7*(2), 143-145.

Van Puijenbroek, E. P., Egberts, A. C. G., & Krom, H. J. (1996). Visual hallucinations and amnesia associated with the use of zolpidem *International Journal of Clinical Pharmacology and Therapeutics, 34*, 318%N 317.

Vartzopoulos, D., Bozikas, V., Phocas, C., Karavatos, A., & Kaprinis, G. (2000). Dependence on zolpidem in high dose. *International Clinical Psychopharmacology, 15*(3), 181-182.