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REVIEW ARTICLE

Comparative efficacy of newer hypnotic drugs for the short-term management of insomnia: a systematic review and meta-analysis

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Objectives To compare the clinical effectiveness of zaleplon, zolpidem or zopiclone (Z-drugs) with either benzodiazepines licensed and approved for use in the UK for the short-term management of insomnia (diazepam, loprazolam, lorazepam, lormetazepam, nitrazepam, temazepam) or with each other.
Methods MEDLINE, EMBASE, PsycINFO, Science Citation Index/Web of Science were searched from 1966 to March 2003 and The Cochrane Library, reference lists of included studies and a number of psychopharmacology journals. Randomized controlled trials comparing either benzodiazepines with the Z-drugs or any two of the Z-drugs in patients with insomnia were included. Outcome measures included: sleep onset latency, total sleep duration, number of awakenings, quality of sleep, adverse events, tolerance, rebound insomnia and daytime alertness.
Results and conclusions Twenty four eligible studies were identified with a total study population of 3909 (17 studies comparing a Z-drug with a benzodiazepine and 7 comparing a Z-drug). Insufficient or inappropriately reported data meant that meta-analysis was possible only for a small number of outcomes. There are few clear, consistent differences between the drugs. Some evidence suggests that zaleplon gives shorter sleep latency but shorter duration of sleep than zolpidem, reflecting the pharmacological profiles of the drugs. Copyright © 2004 John Wiley & Sons, Ltd.

KEY WORDS — insomnia; sleep disorders; systematic review; health technology assessment

INTRODUCTION

Insomnia is a common complaint of dissatisfaction with the quantity or quality of sleep (Holbrook *et al*., 2000). Estimates of the impact of insomnia vary within and between countries. In a cross-country study of the general population, Chevalier and colleagues reported the prevalence of insomnia between 4% and 9% in Germany, Sweden, Ireland and Belgium, whereas in the UK, 22% of the population were affected (Chevalier *et al.*, 1999).

Insomnia can be classified by the duration, severity, co-morbidity or by the quantity and/or quality of sleep (Holbrook *et al*., 2000). Given the variety of classifications and lack of consistency in diagnostic criteria, diagnosis and research in insomnia are difficult. There is evidence of clinical effectiveness of non-pharmacological treatments, but pharmacological treatments are widely used. Of these, benzodiazepines, introduced in the 1960s, are often prescribed. However, adverse

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effects of benzodiazepines include decreased psychomotor performance (e.g. next day drowsiness), tolerance, dependency and withdrawal symptoms.

Non-benzodiazepine hypnotics (Z-drugs) were introduced for the short-term management of insomnia in the late 1980s and early 1990s, allegedly in the hope of overcoming some of these adverse effects. These newer hypnotic drugs have made it necessary to examine the available research evidence comparing the clinical effectiveness of older and newer agents used for the short-term management of insomnia. We therefore conducted a review as part of an on-going programme of research designed to inform the development of national guidance through the National Institute for Clinical Excellence (NICE) in the UK. The Institute's policy is to issue guidance only on drugs that hold a marketing authorization in the UK. This therefore limited the scope of this review and benzodiazepines such as flunitrazepam and flurazepam, which hold a UK marketing authorization but are not approved for use in the NHS, and triazolam, for which marketing authorization was withdrawn in the UK are not included in the review.

METHODS

This systematic review was conducted and reported according to QUOROM guidelines (Moher *et al.*, 1999).

Searching

The review was restricted to randomized controlled trials (RCTs) comparing the clinical effectiveness of the Z-drugs with either benzodiazepines licensed and approved for the treatment of insomnia (diazepam, loprazolam, lorazepam, lormetazepam, nitrazepam, temazepam) or with each other. To identify relevant studies, MEDLINE, EMBASE, Science Citation Index (Web of Science and ISI Proceedings) were searched from 1966 to March 2003 and the Cochrane Library (Issue 1:2003). Also searched were the reference lists of identified studies and ten psychopharmacology journals (October 2002 to July 2003) were hand-searched. Internet resources, including web pages supported by manufacturers of the drugs, were checked regularly during the review process. Manufacturers' and others' submissions to NICE were also examined for further studies and data. No language restriction was applied.

Selection, validity assessment and data extraction

Identified citations were assessed for inclusion in two stages. Two reviewers independently scanned all titles and abstracts. Full text copies of the selected papers were obtained and assessed independently by at least two reviewers for inclusion and study quality, using nationally accepted guidelines (NHS Centre for Reviews and Dissemination, 2001). Individual study data relating to study designs and findings were independently extracted and checked by two reviewers using a pre-tested data extraction form.

Quality assessment

The study design was assessed, including randomization, allocation concealment, double blinding and whether or not an intention-to-treat analysis was performed.

Statistical analysis

Meta-analyses were carried utilizing data from studies that compared the same drugs. Crossover studies with less than two nights of washout period were excluded from meta-analyses. Data were pooled using a fixed effect model with odds ratio and 95% confidence intervals. Outcomes of interest included sleep onset latency, total sleep duration, number of awakenings, quality of sleep, adverse events and rebound insomnia.

RESULTS

Included studies

Out of 72 references identified, 24 fulfilled the inclusion criteria. These included 17 studies (Leppik *et al.*, 1997; Ansoms *et al.*, 1991; Agnoli *et al.*, 1989; Anderson, 1987; Kazamatsuri *et al.*, 1993; Klimm *et al.*, 1987; Kudo *et al.*, 1993; Kerkhof *et al.*, 1996; Jovanovic and Dreyfus, 1983; Ohtomo, 1985a, Ohtomo, 1985b, Pull *et al.*, 1983; Tamminen and Hansen, 1987; Ngen and Hassan, 1990; Stip *et al.*, 1999; Van der Kleijn, 1989; Wheatley, 1985) comparing a Z-drug with a benzodiazepine and seven (reported in six publications) (Allain *et al.*, 2003; Elie *et al.*, 1999; Fry *et al.*, 2000; Ancoli-Israel *et al.*, 1999; Zammit, 2000; Tsutsui, 2001) comparing a Z-drug with another Z-drug. Of these 19 were parallel group designs and five were crossover studies (Agnoli *et al.*, 1989; Pull *et al.*, 1983; Van der Kleijn, 1989; Wheatley, 1985; Allain *et al.*, 2003). Twenty-one studies were assessed from reports published in peer-reviewed journals. The remainder were published as

abstracts of conference proceedings (Kerkhof *et al.*, 1996; Zammit, 2000). Of these, two studies are reported in one abstract (Zammit, 2000). No studies compared diazepam, loprazolam or lorazepam with any Z-drug or zaleplon with zopiclone.

Quality assessment

Overall, the methodological quality of studies was poor. The studies varied in the level of detail for reporting outcomes. Only one study (Ngen and Hassan, 1990) reported the method of randomization or whether the allocation sequence was concealed. All studies were described as double blind but made no mention of methods of blinding or reported the assessment of the blinding procedures. Fourteen studies reported the number and reason for withdrawals and only four studies appeared to have carried out an intention-to-treat analysis (Klimm *et al.*, 1987; Jovanovic and Dreyfus, 1983; Wheatley, 1985; Allain *et al.*, 2003).

Study and patient characteristics

Characteristics of the included studies and patient populations are provided in Table 1. The 24 included studies involved 3909 participants, and ranged in size from 10 to 615 patients. Thirteen studies had fewer than 100 patients in total and only three studies had over 500 patients (Elie *et al.*, 1999; Fry *et al.*, 2000; Ancoli-Israel *et al.*, 1999). Most patients were female. Three studies (Leppik *et al.*, 1997, Ohtomo, 1985a, Ohtomo, 1985b) included only patients over 60 years of age and two studies (Klimm *et al.*, 1987; Ancoli-Israel *et al.*, 1999) included only those aged over 65 years. Six studies (Agnoli *et al.*, 1989; Stip *et al.*, 1999; Elie *et al.*, 1999; Fry *et al.*, 2000; Pull *et al.*, 1983; Kazamatsuri *et al.*, 1993) included patients with a psychiatric disorder and one study (Ansoms *et al.*, 1991) only included alcoholic patients who had undergone a withdrawal period.

The majority of studies incorporated key characteristics of the DSM IV criteria for the diagnosis of insomnia. One study (Pull *et al.*, 1983) did not state the diagnostic criteria used and three (Wheatley, 1985; Allain *et al.*, 2003; Tsutsui, 2001) reported only that participants experienced sleep difficulties. Eight studies (Leppik *et al.*, 1997; Ngen and Hassan, 1990; Van der Kleijn, 1989; Wheatley, 1985; Elie *et al.*, 1999; Fry *et al.*, 2000; Ancoli-Israel *et al.*, 1999; Tsutsui, 2001) acknowledged funding or other support from a pharmaceutical company for the trial.

Studies lasted from one night to 6 weeks. Clinical follow-up after the end of the trial was reported in ten studies (see Table 1).

Outcomes

Sleep efficacy outcomes included patients' estimates of sleep onset latency, total sleep duration, number of awakenings and quality of sleep. In all but three studies these were recorded using post-sleep questionnaires and sleep diaries. Recorded adverse events included central nervous system (CNS) related events (e.g. dizziness, daytime drowsiness, nervousness, light-headedness, headache and fatigue) as well as some not related to the CNS (e.g. gastrointestinal symptoms).

The data from ten studies with a post-treatment follow-up period offer some information regarding rebound insomnia, or temporary worsening from baseline. All data, except in one study (Jovanovic and Dreyfus, 1983), were self-reported.

Results have been grouped by treatment comparisons, with results from the studies examining Z-drugs versus benzodiazepines first, followed by comparisons of two Z-drugs. The results related to key outcomes are summarized in Table 2.

A summary of the results related to the key outcomes provided from comparisons in the studies is presented in Table 3.

Zolpidem versus nitrazepam

Sleep outcomes. Two studies (Kudo *et al.*, 1993; Kazamatsuri *et al.*, 1993) compared zolpidem with nitrazepam. There were no significant differences between the two drugs in sleep onset latency or duration. Kudo *et al.* (1993) reported that 66.7% of patients taking zolpidem experienced an improvement in sleep quality compared with just 37.5% on nitrazepam. Kazamatsuri *et al.* (1993) reported significantly fewer awakenings with zolpidem ($p = 0.031$).

Adverse events. Meta-analysis of adverse event rates from both studies indicates (Figure 1a) that there was no significant difference between treatments (OR 0.70, 95% CI 0.37 to 1.30).

Daytime alertness and global impression of treatment. No significant differences were reported between treatments regarding mental and physical status on awakening and during the day and global impression of treatment in either study.

Table 1. Study design and participants

Study name	Interventions Drug and dose, *n*	Sex, female (%)	Study design	Setting	Commercial support	Outcomes	Inclusion criteria	Duration	Follow-up
Kazamatsuri, 1993	Zolpidem 10 mg ($n=73$) Nitrazepam 5 mg ($n=74$)	36 36	RCT DB parallel	Majority in-patients	Not stated	SL, SD, NAW, QoS, feeling on waking up and during day, safety, anxiety	Age 16–70, insomniacs with schizophrenia and manic-depressive psychosis sleep disturbance >3 days/week	1 week	None
Kudo, 1993	Zolpidem 10 mg ($n=64$) Nitrazepam 5 mg ($n=67$)	63 61	RCT DB parallel	Mostly out-patients	Not stated	SL, SD, NAW, QoS, feeling on waking up and during day, safety, anxiety	Age 16–70, chronic primary insomnia sleep difficulties >3 days/week	1 week	None
Kerkhof, 1996	Zolpidem 10 mg ($n=17$ in analysis) Temazepam 20 mg ($n=13$ in analysis)	70	RCT DB parallel	Not stated	Not stated	Polysomnographic parameters, motor activity, subjective estimates of sleep times and sleep quality	Not stated	10 nights	11 days
Leppik, 1997	Zolpidem 5 mg ($n=82$) Temazepam 15 mg ($n=82$)	63	RCT DB parallel	Not stated	Acknowledged Lornex Pharmaceuticals, Skokie, IL, USA	Primary: Self-reported sleep latency, (SLL), self-reported sleep duration (SSD) Secondary: Ease of falling asleep, NAW, wake time after sleep onset, QoS, morning sleepiness, ability to concentrate	Age 60–85, chronic insomnia >3 mo, SSL of 30 min, SSD of 4–6/night, impairment of daytime function, deprivation, stable mental and physical health	4 weeks	4 days
Ansoms, 1991	Zopiclone 7.5 mg ($n=27$ in analysis) Lormetazepam 1 mg ($n=25$ in analysis) *Overall*: $n=54$	37 28	RCT DB parallel	Unclear	Rhone-Poulenc Rorer, Inc. Brussels, Belgium (co-author)	Hypnotic efficacy, behaviour and mood at awakening, overall evaluation of tolerability and efficacy	Age 21–55, need daily hypnotic for alcohol withdrawal, sleep latency >30 min, several nocturnal awakenings, waking up too early, trouble during the day because of lack of sleep at night	5 nights	None
Agnoli, 1989	Zopiclone 7.5 mg Nitrazepam 5 mg *Overall*: $n=20$	60	RCT DB cross-over (1 week washout)	Not stated	None reported	SD, NAW, QoS, quality of daytime arousal, time of sleep induction	Age 20–50, generalized anxiety disorder (Hamilton Rating <20), absence of factors related to onset or persistence of insomnia	2 weeks	None

Anderson, 1987	Zopiclone 7.5 mg Nitrazepam 5 mg *Overall*: $n=119$		RCT DB parallel	General practice	May & Baker, Ltd, Essex, UK (author)	SL, SD, NAW, QoS, feeling on awakening, adverse events	Age 20–69, unable to fall asleep within 45 min, or >2 nocturnal awakenings with difficulty returning to sleep no known cause, or sleeping <6 h per night	2 weeks	1 week
Jovanovic, 1983	Zopiclone 7.5 mg ($n=5$) Nitrazepam 5 mg ($n=5$)	40 60	RCT DB parallel	Sleep lab	Rhone-Poulenc Sante, Courbevoie, France (co-author)	SD, NAW	Age 21–49, 3 of the following symptoms over 2 mo: sleep onset >45 min, sleep duration <6 h, 3 nocturnal awakenings, waking up in the morning at least 2 h before expected, poor morning conditioning	14 nights	10 nights (first week on placebo)
Klimm, 1987	Zopiclone 7.5 mg Nitrazepam 5 mg *Overall*: $n=74$	80	RCT DB parallel	Community residence	Rhone-Poulenc-Sante, Courbevoie, France (2 co-authors)	SL, SD, NAW, QoS, feeling on awakening, condition in the morning, general evaluation	Age >65, any two of the following criteria: hypnotics 5x per week for 3 months, sleep latency >1 h, sleep duration <6 h, waking >3 times per night; IQ and memory test within normal range for age	1 week	None
Ohtomo, 1985a	Zopiclone 7.5 mg ($n=54$) Nitrazepam 5 mg ($n=74$)	57.8	RCT DB parallel	In and out-patients	Not stated	SL, NAW, QoS, side-effects	Age >60, difficulty with sleeping 3 days/week	1 week	None
Ohtomo, 1985b	Zopiclone 5 mg ($n=66$) Nitrazepam 5 mg ($n=71$)	56.2	RCT DB parallel	In and out-patients	Not stated	SL, NAW, QoS, side-effects	Age >60, 35–81 kg, difficulty with sleeping 1 day/week	1 week	None
Pull, 1983	Zopiclone 7.5 mg Zopiclone 15 mg Nitrazepam 5mg Nitrazepam 15 mg *Overall*: $n=40$		RCT DB cross-over(no washout period)	Hospital	Rhone-Poulenc Sante, Courbevoie, France (co-author)	SL, SD, NAW, QoS, vigilance after awakening, feeling after awakening, memory, side effects	Age 18–65, hospitalized for depression, schizophrenia, alcoholism, stabilized, but suffering from insomnia	1 night	None

Continues

Table 1. Continued

Study name	Interventions Drug and dose, *n*	Sex, female (%)	Study design	Setting	Commercial support	Outcomes	Inclusion criteria	Duration	Follow-up
Tamminen, 1987	Zopiclone 7.5 mg ($n=49$) Nitrazepam 5 mg ($n=45$) *Overall*: $n=130$ (94 included in analysis)	77	RCT DB parallel	Out-patients	Rhone-Poulenc Pharma Norden, Birkerod, Denmark (co-author)	SL, QoS, sleep questionnaire, investigator's global evaluation, general morning condition, working ability, somatic complaints	Age 18–70, insomnia 3 months, 2 of the following: SL >30 min, SD <6.5 h, NAW >2 per night, time to fall asleep after at least one nocturnal awakening >30 min, awakening >2 h before scheduled time	6 weeks	None
Ngen, 1990	Zopiclone 7.5 mg ($n=20$) Temazepam 20 mg ($n=20$)	60 60	RCT DB parallel	Home-based (unclear)	Acknowledged Rhone Poulenc	SL, SD, NAW, psychomotor performance and physician global assessment	Age 18–70, one of the following for 2 weeks: >45 min sleep latency, NAW >2/night without known cause and difficulty returning to sleep, SD<6 h	2 weeks	None
Stip, 1999	Zopiclone 7.5 mg Temazepam 30 mg *Overall*: $n=60$		RCT DB parallel	Not stated	None stated	Primary: Cognitive functioning Secondary: Anxiety, SL, SD, NAW, QoS, residual effects, memory, attention and concentration	Adult patients, primary insomnia or insomnia associated with mild non-psychotic psychiatric disorders (DSM III-R) daytime fatigability, diminished power of concentration and 2 of the following: SL >30 min, SD <5 h, NAW >2 per night, early wake up in the morning	3 weeks	1 week
Van der Kleijn, 1989	Zopiclone 7.5 mg Temazepam 20 mg *Overall*: $n=60$	70	DB cross-over (2 night washout)	Out-patients	Acknowledged Rhone-Poulenc Pharma	SL, QoS, status after awakening, mood and behaviour during the day, somatic symptoms and side effects	Age 18–70, one of the following: SL >30 min, waking too early, several nocturnal awakenings with difficulty in returning to sleep, bothered during day by unsatisfactory sleep	5 nights following 2 nights washout	(1 week placebo)

Wheatley, 1985	Zopiclone 7.5 mg ($n=17$) Temazepam 20 mg ($n=19$) *Overall*: $n=36$	61	RCT DB cross-over(no wash out)	Not stated	Acknowledged May & Baker	SL, SD, NAW, QoS, state on waking, at work, with others, driving, and side effects	Age 18, difficulty sleeping for 1 week	1 week	None
Allain, 2003	Zaleplon 10 mg Zolpidem 10 mg *Overall*: $n=53$	49	RCT DB cross-over (no wash out)	General practice		Drug preference, SL, SD, QoS, ease of waking up, behaviour following wakefulness, quality of the day	Age: 40–65, untreated insomnia characterized by difficulties falling asleep, with previous history of recurrent episodes of insomnia	2 nights	None
Ancoli-Israel, 1999	Zaleplon 5 mg ($n=166$) Zaleplon 10 mg ($n=165$) Zolpidem 5 mg ($n=111$)	58 58 57	RCT DB parallel	Out-patients	Wyeth-Ayerst Research, Radnor, Pa, USA (2 co-authors)	SL, SD, NAW, QoS, rebound insomnia	Age 65, SL >30 min, awakenings on average per night >3, SD 6.5 h	2 weeks	1 week
Elie, 1999	Zaleplon 5 mg ($n=122$) Zaleplon 10 mg ($n=121$) Zaleplon 20 mg ($n=124$) Zolpidem 10 mg ($n=122$)	58 64 70 67	RCT DB parallel	Out-patients	Wyeth-Ayerst Research, Radnor, Pa, USA (2 co-authors)	SL, QoS, sleep maintenance, rebound insomnia, withdrawal effects	Age 18–65, primary insomnia or insomnia associated with mild non-psychotic disorders (DSM-III-R), SL 30 min, daytime impairment due to sleep disturbance, and either mean SD 6.5 h or prolonged or frequent nocturnal awakenings	4 weeks	3 days
Fry, 2000	Zaleplon 5 mg ($n=118$) Zaleplon 10 mg ($n=120$) Zaleplon 20 mg ($n=121$) Zolpidem 10 mg ($n=117$)	69 54 61 54	RCT DB parallel	Out-patients	Wyeth-Ayerst Research, Radnor, Pa, USA (co-author)	Primary: Self-reported sleep latency, (SLL) Secondary: SD, QoS, NAW, rebound, withdrawal effects, adverse effects	Age 16–85, primary insomnia or insomnia associated with mild non-psychotic psychiatric disorders, SL 30 min, daytime impairment due to sleep disturbance, average SD/night 6.5, or prolonged or frequent nocturnal awakenings	4 weeks	3 days
Zammit 1, 2000	Zaleplon 10 mg Zolpidem 10 mg *Overall*: $n=42$		RCT DB cross-over	Sleep lab	None reported	SL, SD, next-day residual sedation	Age 18–65, objectively verified sleep maintenance insomnia	2 nights	None
Zammit 2, 2000	Zaleplon 10 mg Zolpidem 10 mg *Overall*: $=37$		RCT DB cross-over	Sleep lab	None reported	SL, SD, next-day residual sedation	Age 18–65 objectively verified sleep maintenance insomnia	2 nights	None

Continues

Table 1. Continued

Study name	Interventions Drug and dose, *n*	Sex, female (%)	Study design	Setting	Commercial support	Outcomes	Inclusion criteria	Duration	Follow-up
Tsutsui, 2001	Zolpidem 10 mg ($n = 231$) Zopiclone 7.5 mg ($n = 218$)	65	RCT DB parallel	Home-based vs. lab-based?	Drugs supplied by Fujisawa Pharmaceutical Co. Ltd (Japan); Rhone-Poulenc Rorer, Inc. (Japan)	Primary: Global improvement of sleep disorders (rated by investigators) Secondary: Patient's impression of treatment efficacy, investigator's assessment of the usefulness of the treatment, adverse events; dependence; QoS; physical condition parameters	Age: not stated, chronic primary insomnia (i.e. experiencing non-restorative sleep or difficulty initiating or maintaining sleep >1 mo), sleep difficulties >3 times/week	2 weeks	1 week

Zolpidem versus temazepam

Sleep outcomes. Leppik *et al.* (1997) reported no significant differences between zolpidem and temazepam regarding sleep latency, whereas Kerkhof *et al.* (1996) reported significant improvements with regards to sleep latency ($p = 0.05$) and subjective estimates of sleep quality ($p = 0.03$) for zolpidem compared with temazepam (sleep latency after 10 days' treatment: zolpidem 38.8 min, temazepam: 61.6 min).

Adverse events. Leppik *et al.* (1997) reported a statistically non-significant difference in proportions of subjects experiencing treatment emergent adverse events (63%, on zolpidem, 67% on temazepam).

Daytime alertness. Leppik *et al.* (1997) reported that sporadic statistically significant differences were observed between treatments at different time points in terms of morning sleepiness and the ability to concentrate. There was not a consistent pattern and no data were provided.

Zopiclone versus lormetazepam

Sleep outcomes. One study (Ansoms *et al.*, 1991) compared zopiclone and lormetazepam and the only significant difference between treatments was in sleep onset latency where lormetazepam resulted in shorter latency than zopiclone ($p = 0.029$).

Adverse events and global impression of treatment. No statistically significant differences were found between treatment groups.

Zopiclone versus nitrazepam

Sleep outcomes. Six out of eight studies that compared zopiclone with nitrazepam reported data on sleep latency and number of awakenings and seven reported on sleep duration and quality. Overall, there was no convincing evidence of any differences for sleep outcomes measured between two treatments.

Regarding sleep latency, three studies (Jovanovic and Dreyfus, 1983; Pull *et al.*, 1983; Tamminen and Hansen, 1987) reported statistically non-significant results between treatments and one study (Anderson, 1987) did not make direct comparisons between treatments. Klimm *et al.* (1987) found that nitrazepam resulted in a greater reduction in sleep latency on day 5 of treatment (of 7) than zopiclone, whereas

Table 2. Outcomes

Study name	Interventions	Sleep onset latency (min), Mean	Total sleep duration (min), Mean	Number of awakenings, Mean	Quality of sleep, Mean	Adverse events (number/total, %)	Withdrawal
Zolpidem versus nitrazepam							
Kazamatsuri, 1993	Zolpidem 10 mg	4.1 (<15 min) 24.7 (15–30 min) 41.1 (30–60 min) 30.1 (>60 min)	360 (108)	17.8 (none) 35.6 (1) 43.8 (2–4) 2.8 (5+)		7/82 (8.5)	
	Nitrazepam 5 mg	10.8 (<15 min) 24.3 (15–30 min) 33.8 (30–60 min) 31.1 (>60 min)	366 (120)	13.5 (none) 25.7 (1) 45.9 (2–4) 14.9 (+)		12/79 (15.2)	
		%, (amount of time needed to fall asleep)	Mean (SD)	%, (number of awakenings)			
Kudo, 1993	Zolpidem 10 mg	68.4			66.7	13/79 (16.5)	
	Nitrazepam 5 mg	56.4			37.5	15/80 (18.8)	
		Total improvement (%)			Total improvement (%)		
Zolpidem versus temazepam							
Kerkhof, 1996	Zolpidem 10 mg	Base. 52.2 Final 38.8 ($n=17$)			Base. 7.76 Final 9.22 ($n=17$)		
	Temazepam 20 mg	Base. 57.7 Final 61.6 ($n=13$) Final result is post 11-day follow-up period			Base. 6.46 Final 6.66 ($n=13$) Scale unknown but increase indicates improvement. Final result is post 11-day follow-up period		
Leppik, 1997	Zolpidem 5 mg	Base. 78.1(47.1) ($n=82$) Final 40.5 (27.2) ($n=77$) Change −39.7 (41.2)	Base. 294.5 (62.5) ($n=82$) Final 362.8 (64.9) ($n=77$) Change 70.0 (64.9)			52/82 (63.4)	
	Temazepam 15 mg	Base. 74.1 (44.9) ($n=84$) Final 38.0 (26.2) ($n=76$) Change −39.4 (41.0) Mean (SD) Skewed variable, not included in MA	Base. 312.4 (49.5) ($n=84$) Final 375.3 (58.4) ($n=76$) Change 61.8 (55.8) Mean (SD) Skewed variable, not included in MA			56/84 (66.7) Treatment-emergent adverse events	
Zopiclone versus lormetazepam							
Ansoms, 1991	Zopiclone 5 mg	Base. 2 ($n=26$) Final 3 ($n=25$)	Base. 3 ($n=26$) Final 3 ($n=25$)	Base. 3 ($n=26$) Final 3 ($n=25$)	Base. 3 ($n=26$) Final 3 ($n=25$)	7/27 (26) (*6/25 (24))	
	Lormetazepam 1 mg	Base. 2 ($n=25$) Final 4 ($n=25$) Medians calculated from raw data, scale: 1 = long, 5 = short	Base. 3 ($n=25$) Final 3 ($n=25$) Medians calculated from raw data, scale: 1 = short, 5 = long	Base. 3 ($n=25$) Final 4 ($n=25$) Calculated from raw data, scale: 1 = frequent, 5 = never	Base. 3 ($n=25$) Final 4 ($n=25$) Calculated from raw data, scale: 1 = bad, 5 = good	7/25 (28) (*5/25 (20)) Any side-effects (*Side effects related to drug)	

Continues

Table 2. Continued

Study name	Interventions	Sleep onset latency (min), Mean	Total sleep duration (min), Mean	Number of awakenings, Mean	Quality of sleep, Mean	Adverse events (number/total, %)	Withdrawal
Zopiclone versus nitrazepam							
Agnoli, 1989	Zopiclone 7.5 mg	Base. 36 (1.5) ($n=20$) Final 8 (5.7) ($n=20$)					
	Nitrazepam 5 mg	Base. 33 (1.9) ($n=20$) Final 12 (9.6) ($n=20$) Mean (SD), data estimated from graph					
Anderson, 1987	Zopiclone 7.5 mg	Base. 42.5 Final 60			Base. 41.3 Final 67.3		
	Nitrazepam 5 mg	Base. 35.5 Final 64 Data estimated from graph; scale: 0 = long, 100 = short			Base. 43.5 Final 65 Data estimated from graph; scale 0 = bad, 100 = good		
Jovanovic, 1983	Zopiclone 7.5 mg	Base. 97.8 ($n=5$) Final 17.5 ($n=5$)	Base. 351.8 ($n=5$) Final 465.7 ($n=5$)	Base. 1.5 ($n=5$) Final 0.1 ($n=5$)			
	Nitrazepam 5 mg	Base. 83.4 ($n=5$) Final 24.1 ($n=5$)	Base. 376.6 ($n=5$) Final 441.9 ($n=5$)	Base. 1.1 ($n=5$) Final 0.05 ($n=5$)			
Klimm, 1987	Zopiclone 7.5 mg	Change from Base. 18.2 (48.3) ($n=36$)			Change from Base. 24 (45.6) ($n=36$)		
	Nitrazepam 5 mg	Change from Base. 15.6 (49.5) ($n=36$) Mean (SD) of differences between first day of active treatment and last day of placebo run-in period, scale: 0 = fast, 100 = slow			Change from Base. 23.1 (37.8) ($n=36$) Mean (SD) of differences between first day of active treatment and last day of placebo run-in period, scale: 0 = bad, 100 = good		
Ohtomo, 1985a	Zopiclone 7.5 mg		10.9 (very effective) 31.3 (effective) 29.7 (little effective) 26.6 (no change) 1.6 (worse)	9.4 (very effective) 25 (effective) 23.4 (little effective) 42.2 (no change) 0 (worse)	25 (very effective) 31.3 (effective) 18.8 (little effective) 23.4 (no change) 1.6 (worse)	5/64 (7.8)	
	Nitrazepam 5 mg		1.6 (very effective) 26.6 (effective) 25.0 (little effective) 43.8 (no change) 3.1 (worse) % (scale: very effective to worse)	7.8 (very effective) 26.6 (effective) 28.1 (little effective) 37.5 (no change) 0 (worse) % (Scale: very effective to worse)	3.1 (very effective) 34.4 (effective) 32.8 (little effective) 29.7 (no change) 0 (worse) % (scale: very effective to worse)	7/64 (10.9)	
Ohtomo 1985b	Zopiclone 5 mg		6.9 (excellent) 25.9 (good) 25.9 (O.K.) 37.9 (not good) 3.4 (worse)	3.3 (excellent) 11.7 (good) 31.7 (O.K.) 50 (not good) 3.3 (worse)	1.6 (excellent) 32.8 (good) 29.5 (O.K.) 31.1 (not good) 4.9 (worse)	10/66 (15.2)	

	Nitrazepam 5 mg		3.0 (excellent) 19.7 (good) 28.8 (O.K.) 42.4 (not good) 6.1 (worse) % (scale: excellent to worse)	3.3 (excellent) 16.9 (good) 26.2 (O.K.) 50.8 (not good) 3.3 (worse) % (*scale: excellent to worse*)	10.3 (excellent) 32.4 (good) 35.3 (O.K.) 22.1 (not good) 0 (worse) % (*scale: excellent to worse*)	4/71 (5.6)
Pull, 1983	Zopiclone 7.5 mg	3.5	2.8	2.93	3.0	
	Zopiclone 15 mg	2.8	3.6	2.3	2.4	
	Nitrazepam 5 mg	4.2	2.6	2.95	3.5	
	Nitrazepam 10 mg	3.2	3.7	2.35	2.5	
		Data estimated from graph; scale: smaller score = shorter onset latency	Data estimated from graph; scale: larger score = longer sleep duration	Data estimated from graph; scale: smaller score = fewer awakenings	Data estimated from graph; scale: lower score = better quality of sleep	
Tamminen, 1987	Zopiclone 7.5 mg	Base. 58 (31.2) ($n = 49$)	Base. 75	Base. 63.3	Base. 55.8 (33.7) ($n = 49$)	
		Final 31.5 (27.2)	Final 37.5	Final 18.4	Final 33.8 (24.4)	
	Nitrazepam 5 mg	Base. 52.5 (33.7) ($n = 45$)	Base. 73.3	Base. 75.6	Base. 49.9 (30.7) ($n = 45$)	
		Final 32.7 (29.4)	Final 37.7	Final 24.4	Final 34.0 (27.8)	
		Mean (SD), scale: 0 fast, 100 slow	% with duration of sleep < 6.5 h	% with >2 nocturnal awakenings	Mean (SD), scale: 0 good, 100 bad	
Zopiclone versus temazepam						
Ngen, 1990	Zopiclone 7.5 mg	Base. 122.8 ($n = 13$)	Base. 262.8 ($n = 13$)	Base. 0.95 ($n = 13$)		
		Final 64.5 ($n = 13$)	Final 361.8 ($n = 13$)	Final 0.62 ($n = 13$)		
	Temazepam 20 mg	Base. 50.4 ($n = 13$)	Base. 295.2 ($n = 13$)	Base. 2 ($n = 13$)		
		Final 26.1 ($n = 13$)	Final 337.2 ($n = 13$)	Final 1.28 ($n = 13$)		
		Note: very poorly balanced groups at Base				
Stip, 1999	Zopiclone 7.5 mg			Base. 4.8 (1.96) ($n = 19$)		
				Final 6.8 (2.05)		
	Temazepam 30 mg			Base. 5.1 (2.4) ($n = 16$)		
				Final 5.8 (1.96)		
				Mean (SD), scale (likely) larger score = fewer awakenings		
Van der Kleijn, 1989	Zopiclone 7.5 mg	Base. 2.8 (1.82) ($n = 53$)*			Base. 3.0 (1.31) ($n = 53$)	26
		Final 3.8 (1.46)			Final 3.9 (1.46)	
	Temazepam 20 mg	Base. 2.8 (1.82) ($n = 53$)*			Base. 3.0 (1.31) ($n = 53$)	17
		Final 3.7 (1.46)			Final 3.8 (1.53)	
		Mean (SD), data estimated from graph; scale: 1 = long, 5 = short			Mean (SD), data estimated from graph; scale: 1 = bad, 5 = good	
Wheatley, 1985	Zopiclone 7.5 mg	Base. 82.9 ($n = 36$)	Base. 300 ($n = 36$)	Base. 1.9 ($n = 36$)	Base. 2.1 ($n = 36$)	9/35 (26)
		Final 30.8 ($n = 35$)	Final 396 ($n = 35$)	Final 0.75 ($n = 35$)	Final 0.93 ($n = 35$)	
	Temazepam 20 mg	Base. 82.9 ($n = 36$)	Base. 300 ($n = 36$)	Base. 1.9 ($n = 36$)	Base. 2.1 ($n = 36$)	5/32 (16)
		Final 29.1 ($n = 32$)	Final 396 ($n = 32$)	Final 0.66 ($n = 32$)	Final 0.87 ($n = 32$)	
		Assume $n = 36$ at Base., $n = 35$ on zopiclone and $n = 32$ on temazepam (by calculation from no. (%) given under 'Side-effects')	Assume $n = 36$ at Base., $n = 35$ on zopiclone and $n = 32$ on temazepam (by calculation from no. (%) given under 'Side-effects')	Assume $n = 36$ at Base., $n = 35$ on zopiclone and $n = 32$ on temazepam (by calculation from no. (%) given under 'Side-effects')	Assume $n = 36$ at Base., $n = 35$ on zopiclone and $n = 32$ on temazepam (by calculation from no. (%) given under 'Side-effects'); scale 0 good, 4 bad	Side-effects

Continues

Table 2. Continued

Study name	Interventions	Sleep onset latency (min), Mean	Total sleep duration (min), Mean	Number of awakenings, Mean	Quality of sleep, Mean	Adverse events (number/total, %)	Withdrawal
Zaleplon versus zolpidem							
Allain, 2003	Zaleplon 10 mg	45.3 (20.7)	480		44.3 (23.2)		
	Zolpidem 10 mg	35.9 (20.0)	498		30.6 (18.6)		
		Mean (SD)			Mean (SD)		
Ancoli-Israel, 1999	Zaleplon 5 mg	Base. 75.75 ($n=148$)	Base. 290.71 ($n=150$)		82/162 (51)	56	
		Final 38	Final 325				
	Zaleplon 10 mg	Base. 62.5 ($n=150$)	Base. 316.14 ($n=151$)		86/163(53)	59	
		Final 31	Final 348				
	Zolpidem 5 mg	Base. 58.75 ($n=101$)	Base. 308.57 ($n=105$)		72/109 (66)	63	
		Final 42	Final 360				
		Medians, estimated from graph	Medians, estimated from graph		Number/total (%) with improvement at week 4 in sleep quality from Base./total	%, treatment-emergent adverse events	
Elie, 1999	Zaleplon 5 mg	Base. 66 ($n=113$)	Base. 313 ($n=113$)	Base. 2 ($n=112$)	66/101 (65.3)	71/121 (59)	(8)
		Final 31	Final 372 ($n=102$)	Final 2 ($n=87$)			
	Zaleplon 10 mg	Base. 57 ($n=112$)	Base. 331 ($n=112$)	Base. 2 ($n=111$)	59/100 (59.0)	87/120 (73)	(9)
		Final 28.8	Final 384 ($n=99$)	Final 2 ($n=82$)			
	Zaleplon 20 mg	Base. 55 ($n=116$)	Base. 328 ($n=116$)	Base. 2 ($n=114$)	64/102 (62.7)	76/124 (61)	(10)
		Final 27.5	Final 385 ($n=103$)	Final 1 ($n=86$)			
	Zolpidem 10 mg	Base. 64 ($n=115$)	Base. 330 ($n=115$)	Base. 2 ($n=114$)	66/99 (66.7)	78/122 (64)	(16)
		Final 36.5	Final 400 ($n=100$)	Final 2 ($n=84$)			
		Medians; data extracted from graph	Medians	Medians	Number with improvement at week 4 in sleep quality from Base./total (%)	Treatment-emergent adverse events	(%) with 3 + withdrawal symptoms first night after discontinuation of treatment; data estimated from graph
Fry, 2000	Zaleplon 5 mg	Base. 69.3 ($n=118$)	Base. 334.3 ($n=118$)	Base. 2 ($n=115$)	49/101 (48.5)	90/118 (76)	1/91 (1.1)
		Final 45.6 ($n=101$)	Final 360.0 ($n=101$)	Final 1.71 ($n=90$)			
	Zaleplon 10 mg	Base. 62.5 ($n=119$)	Base. 334.3 ($n=119$)	Base. 1.86 ($n=117$)	52/102 (51.0)	89/120 (74)	1/83 (1.2)
		Final 35.0 ($n=102$)	Final 376.3 ($n=102$)	Final 1.57 ($n=91$)			
	Zaleplon 20 mg	Base. 61.1 ($n=116$)	Base. 343.0 ($n=116$)	Base. 2 ($n=114$)	57/101 (56.4)	93/117 (79)	2/91 (2.2)
		Final 30.0 ($n=101$)	Final 377.5 ($n=101$)	Final 1.6 ($n=90$)			
	Zolpidem 10 mg	Base. 60.7 ($n=115$)	Base. 334.3 ($n=115$)	Base. 2.14 ($n=112$)	61/98 (62.2)	96/116 (83)	6/85 (7.1)
		Final 34.3 ($n=98$)	Final 392.9 ($n=98$)	Final 1.67 ($n=89$)			
		Medians	Medians	Medians	Number with improvement at week 4 in sleep quality from Base./total (%); data extracted from graph	Treatment-emergent adverse events	(%) with 3 + withdrawal symptoms first night after discontinuation of treatment
Zammit 1 & 2, 2000	Zaleplon 10 mg						
	Zolpidem 10 mg						
Zolpidem versus zopiclone							
Tsutsui, 2001	Zolpidem 10 mg	179/209 (85.8)				66/211 (31.3)	
	Zopiclone 7.5 mg	170/219 (77.5)				102/225 (45.3)	
		Number/total (%) with improvement of 1 + scale from Base. (scale 1–5); numbers estimated from percentage				Drug related adverse events	

Table 3. Summary of results

Comparison $n =$ of studies	Shorter sleep latency	Longer sleep duration	Fewer number of awakenings	Better quality of sleep	Fewer adverse events	Less rebound insomnia	Daytime alertness
Zolpidem vs nitrazepam $n=2$	NS ($n=2$)	NS ($n=1$)	Zol > N ($n=1$)	NDC ($n=1$)	NS ($n=2$)	No data	NS ($n=2$)
Zolpidem vs temazepam $n=2$	Zol > T ($n=1$) NS ($n=1$)	NDC ($n=1$)	No data	Zol > T($n=1$)	NS ($n=1$)	NDC ($n=1$)	NS ($n=1$)
Zopiclone vs lormetazepam $n=1$	L > Zop	NS	NS	NS	NS	No data	No data
Zopiclone vs nitrazepam $n=8$	NS ($n=3$) Zop > N ($n=1$) N > Zop ($n=1$)[a] NDC ($n=1$)	NS ($n=6$) Zop > N ($n=1$)	NS ($n=6$)	NS ($n=5$) NDC ($n=1$) Zop > N ($n=1$)	NS ($n=2$)	NDC ($n=2$)	Zop > N ($n=4$)[c] NS ($n=3$)
Zopiclone vs temazepam $n=4$	NS ($n=2$) NDC ($n=2$)	NS ($n=1$) NDC ($n=1$)	NS ($n=1$) NDC ($n=2$)	NS ($n=2$)	NS ($n=1$) NDC ($n=1$)	T > Zop ($n=1$)[b] NS ($n=1$)	NS ($n=3$) NDC ($n=1$)
Zaleplon vs zolpidem $n=6$	Zal > Zol ($n=1$) Zol > Zal ($n=1$) NDC ($n=3$)	Zol > Zal ($n=1$) NS ($n=1$) NDC ($n=4$)	NDC ($n=2$)	Zol > Zal ($n=2$)[d] NS ($n=2$)[d]	NS ($n=3$)	Zal > Zol ($n=2$)	NDC ($n=2$)
Zolpidem vs zopiclone $n=1$	Zol > Zop	No data	No data	No data	Zol > Zop	Zol>Zop[b]	NDC

Zol, zolpidem; N, nitrazepam; T, temazepam; L, lormetazepam; Zop, zopiclone; Zal, zaleplon. NS, no statistical significance, > shows statistically significant difference, NDC, No direct comparisons. Number of studies is shown in brackets.

[a]Nitrazepam resulted in a greater reduction in sleep onset latency on day 5 (out of 7) of treatment than zopiclone ($p < 0.001$).

[b]Rebound insomnia of sleep latency only.

[c]One study reports significant differences on 2 out of 7 active treatment days only.

[d]Meta-analysis of three of these studies is significant in favour of zolpidem.

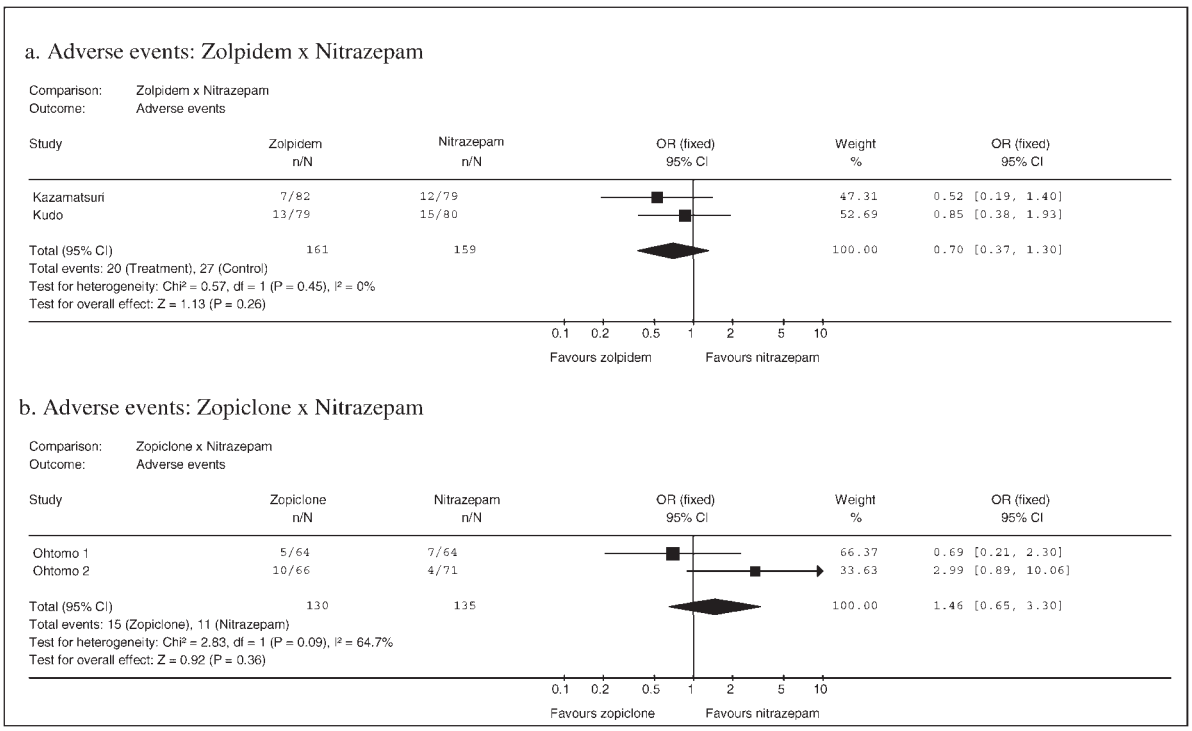

Figure 1. Z versus benzodiazepines

Agnoli *et al.* (1989) reported that sleep latency was significantly shorter after zopiclone was administered than after nitrazepam ($p < 0.001$).

Of the seven studies that reported sleep quality, only one (Ohtomo, 1985a) reported a significant difference in favour of zopiclone ($p < 0.05$); the others reported non-significant differences. There were no statistically significant differences between treatments in number of nocturnal awakenings.

Adverse events. Only two studies (Ohtomo, 1985a, Ohtomo, 1985b) provided data on adverse events, and meta-analysis (Figure 1a) of this outcome indicates no significant difference between treatments (OR 1.46, 95% CI 0.65 to 3.30).

Daytime alertness/feeling upon awakening and global impression of treatment. Four studies (Ohtomo, 1985a; Agnoli *et al.*, 1989; Klimm *et al.*, 1987; Anderson, 1987) suggest a statistically significant difference in favour of zopiclone, but three studies (Ohtomo, 1985b; Tamminen and Hansen, 1987; Pull *et al.*, 1983) reported no significant differences. Ohtomo (1985a) reported a significantly higher global improvement rate ($p = 0.05$) with zopiclone compared with nitrazepam while four studies (Ohtomo, 1985b; Anderson, 1987; Pull *et al.*, 1983; Tamminen and Hansen, 1987) reported no significant between-treatment differences.

Zopiclone versus temazepam

Sleep outcomes. Of the four studies that compared zopiclone and temazapam, only two (Van der Kleijn, 1989; Wheatley, 1985) made direct comparisons between treatments regarding sleep onset latency, number of awakenings and sleep quality and duration. No statistically significant differences were found.

Adverse events. Van der Kleijn (1989) did not make a formal comparison of adverse events and Wheatley (1985) reported a no significant difference between treatments.

Rebound insomnia, alertness and global impression of treatment. Van der Kleijn (1989) states that after zopiclone, rebound insomnia of sleep onset latency was significantly worse than after temazepam. Ngen and Hassan (1990), Stip *et al.* (1999), van der Kleijn

(1989) and Wheatley (1985) reported no significant differences in alertness or global impression of treatment.

Zaleplon versus zolpidem

Sleep outcomes. Only two of the six studies that reported on sleep onset latency made direct treatment comparisons but with conflicting results: Ancoli-Israel *et al.* (1999) reported a significantly shorter sleep latency with zaleplon ($p < 0.001$), whereas Allain *et al.* (2003) presented results in favour of zolpidem ($p = 0.03$). Six studies reported on sleep duration but only two made direct comparisons: Ancoli-Israel *et al.* (1999) reported that sleep duration was significantly less in the zaleplon group (290.7 min for zaleplon and 308.6 min for zolpidem, $p = 0.05$) but Allain *et al.* (2003) found no difference (8.3 h on zolpidem, 8 h on zaleplon).

Two studies (Elie *et al.*, 1999; Fry *et al.*, 2000) reported on number of awakenings but made no direct comparisons.

We pooled the results for the meta-analysis (Figure 2a) from three studies (Ancoli-Israel *et al.*, 1999; Elie *et al.*, 1999; Fry *et al.*, 2000) comparing improvements in sleep quality at the end of the treatment to baseline: patients on zaleplon were less likely to experience an improvement in sleep quality than those on zolpidem (OR 0.66, 95% CI 0.51 to 0.87). Allain *et al.* (2003) also reported statistically significant improvements in quality of sleep ($p < 0.0001$) in favour of zolpidem.

Adverse events. Of the three studies reporting the frequency of treatment-emergent adverse events, only two (Elie *et al.*, 1999; Fry *et al.*, 2000) reported sufficient data for inclusion in the meta-analysis (Figure 2b), and this showed no statistically significant difference (OR 0.86, 95% CI 0.62 to 1.20).

Withdrawal symptoms. Two studies (Elie *et al.*, 1999; Fry *et al.*, 2000) report the incidence of withdrawal symptoms on the first 3 nights after discontinuation of treatment (when placebos were administered). Data could be formally assessed only from the first night of the placebo run-out phase of Fry (Fry *et al.*, 2000). Patients taking zaleplon were less likely to suffer withdrawal symptoms than those on zolpidem (1.5% and 7.1% respectively, $p = 0.01$).

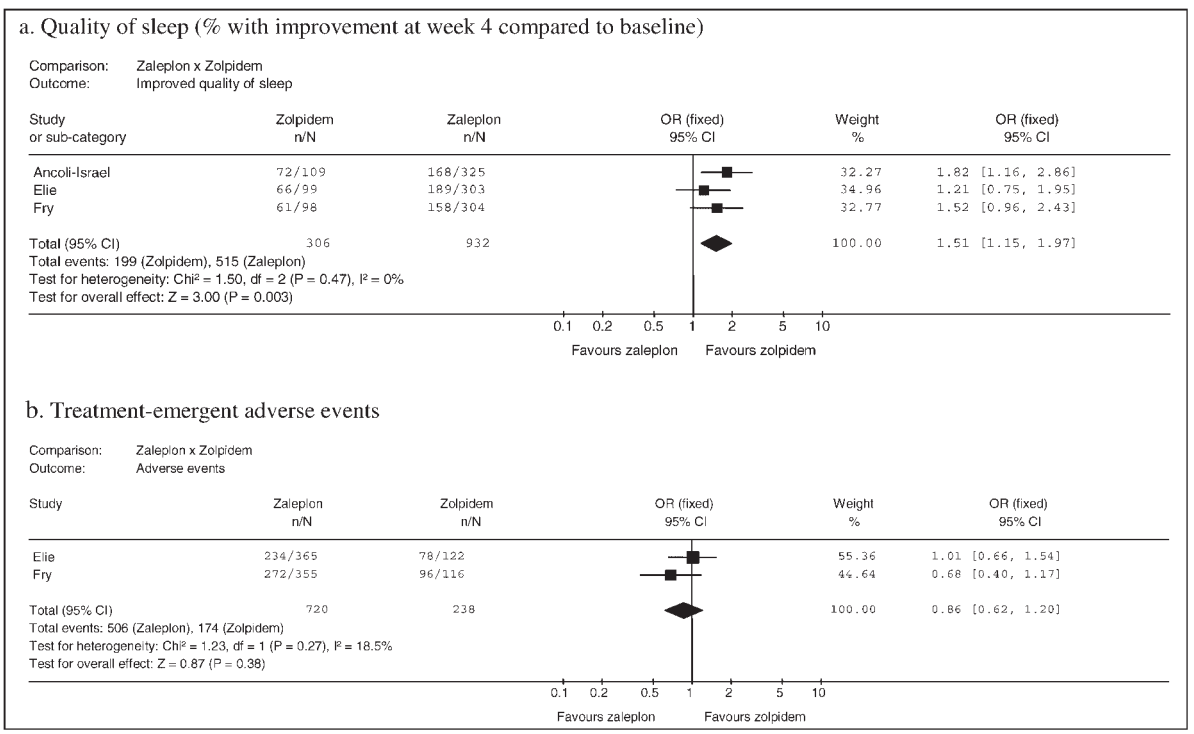

Figure 2. Zaleplon versus Zolpidem

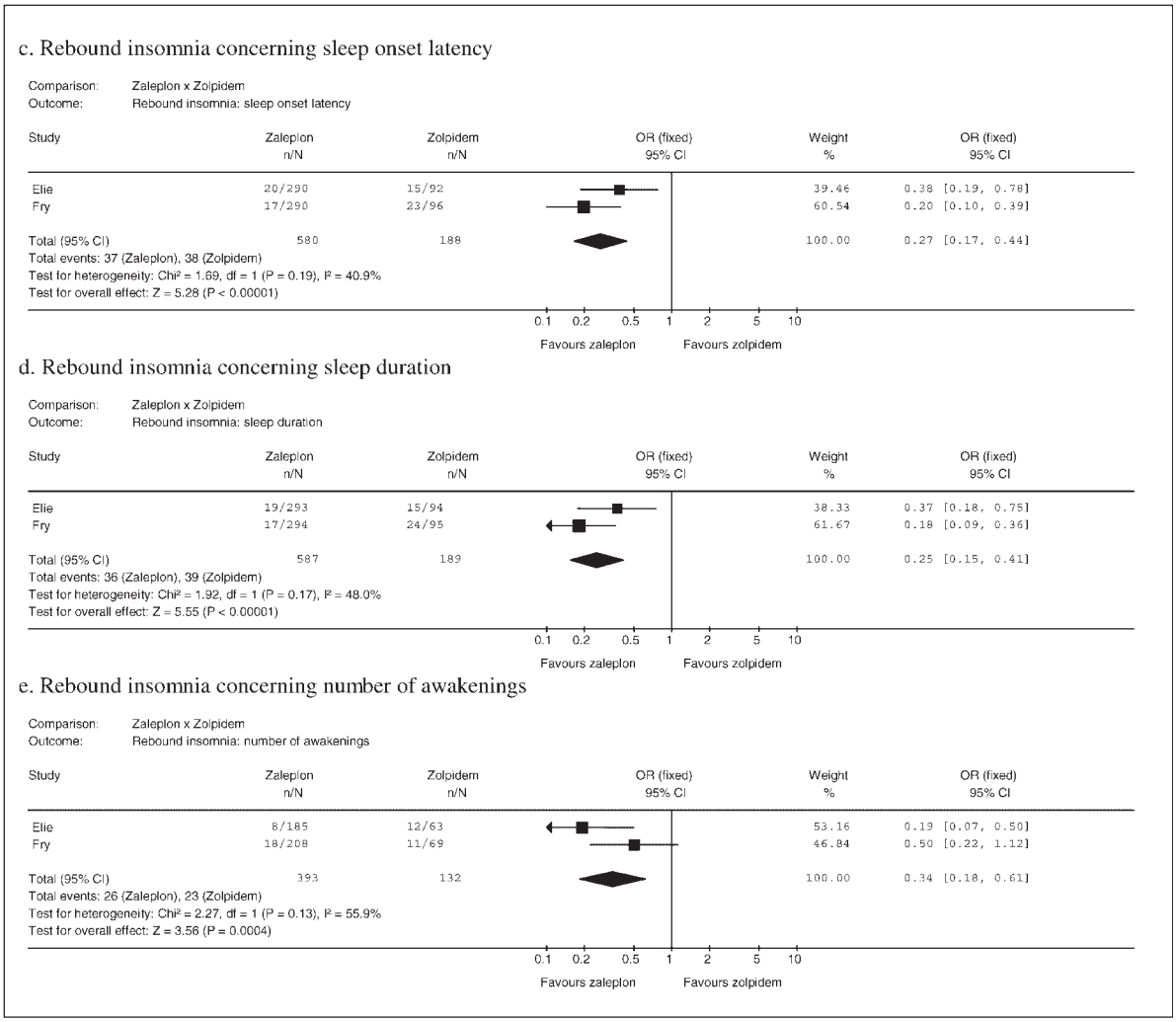

Figure 2. Continued

Tolerance and rebound insomnia. Fry *et al.* (2000) reported no evidence of tolerance in sleep latency, duration, quality, or number of awakenings, comparing data from week 1 and 4. Results from Elie *et al.* (1999) supported this.

Elie *et al.* (1999) and Fry *et al.* (2000) reported the proportion of patients experiencing rebound insomnia after the first placebo night post-treatment. Patients on zaleplon were less likely to experience rebound insomnia measured by sleep latency (OR 0.27 95% CI to 0.17 to 0.44), sleep duration (OR 0.25 95% CI 0.15 to 0.41) and number of awakenings (OR 0.34 95% CI 0.18 to 0.61) compared with those on zolpidem (Figures 2c to 2e, respectively).

Daytime alertness and global impression of treatment. Two studies by Zammit (2000) assessed measures of sedation and psychomotor performance but no direct treatment comparisons were made. In the crossover study by Allain *et al.* (2003) 62.3% of patients favoured zolpidem compared with 37.7% who favoured zaleplon ($p = 0.08$).

Zolpidem versus zopiclone

Sleep outcomes. Only one study by Tsutsui (2001) compared zolpidem with zopiclone. Sleep latency improved from baseline at the end of treatment and

the proportion of patients showing an improvement in sleep latency was significantly higher with zolpidem than with zopiclone (85.8% versus 77.5% respectively, $p = 0.041$).

Adverse events. Fewer patients in the zolpidem group experienced adverse events 'related', 'possibly related' or 'probably related' to treatment than with those in the zopiclone group (31.3 and 45.3% respectively, $p = 0.004$).

Rebound insomnia. The percentage of patients experiencing deterioration from baseline in sleep onset latency differed significantly between treatments (4.5% in the zolpidem group and 15.4% in the zopiclone group, $p = 0.005$). None of the other changes in sleep parameters differed significantly between the treatments.

Daytime alertness, global impression of treatment. No direct comparisons assessing daytime physical condition were made. The study reported a non-significant difference with regard to global impression of treatment (69.7% of patients in the zolpidem group and 61.6% in the zopiclone group were rated as at least moderately improved by the investigator).

DISCUSSION

Limitations of the data hamper the ability to draw conclusions from this systematic review. There seem to be minor differences between the drugs, but it is difficult to quantify these or evaluate their clinical importance. Zolpidem may give rise to less rebound insomnia and shorter sleep latency than zopiclone, but there is no convincing difference when compared with the benzodiazepines. Zaleplon gives shorter sleep latency than zolpidem, but a shorter duration and quality of sleep, and less rebound. Some of these differences seem to be related to the pharmacological profiles of the drugs. For instance, zaleplon is more rapidly absorbed and cleared in contrast to the other drugs, which may result in shorter sleep onset latency but shorter duration of sleep than zolpidem. Zaleplon might therefore be a more appropriate drug than zolpidem for patients with problems falling asleep, but not for those who tend to wake during the night or suffer from early awakening. In absolute terms, however, the benefit in sleep latency seems small and the value of zaleplon over zolpidem is open to question. Some drugs, on the other hand, show less daytime drowsiness than others, usually again a function of the pharmacokinetics of the drugs, with drugs with a long half-life such as nitrazepam the worst offenders in this regard. However, our review has not found any consistent differences between the drugs, in part because of lack of sufficient evidence and the poor quality of reporting. In summary, the short-acting drugs seem to have minor differences that may lead prescribers to favour one over another in certain patients.

The results from this review must be interpreted with considerable caution. Many of the studies are of poor methodological quality and it has been difficult to extract and compare data from the studies to address the review question. Furthermore, sample size calculations were not reported in any studies (except in Allain *et al.* (2003)) and therefore it is difficult to assess whether studies were underpowered to detect clinically important differences between treatments. There was also evidence of multiple statistical testing without adjustment in some studies, which may have led to the reporting of spurious findings. Some cross-over studies (Pull *et al.*, 1983; Van der Kleijn, 1989; Wheatley, 1985; Allain *et al.*, 2003) did not have adequate washout periods between treatments. Only few studies reported their results in sufficient detail to allow us to undertake a meta-analysis.

Clinical pharmacological trials, which included volunteer subjects (e.g. those not experiencing insomnia), did not meet the review inclusion criteria. However, examination of these studies could provide useful comparative data to discriminate between different compounds.

A final reason for caution is that most included studies were conducted with pharmaceutical company involvement, a factor known to cause bias in reported studies (Rochon *et al*., 1994; Bhandari *et al*., 2004).

Therefore, due to limitations of available research, no firm conclusions can be drawn and there are clear research needs in this area. We would recommend that further consideration should be given to a sufficiently large non-commercially supported double blind randomized placebo-controlled trial of at least 4 weeks' duration to allow direct comparisons of some of the key drugs and reliable conclusions to be made.

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TW and RD managed the project, YD coordinated the review and developed search strategies and managed information resources. YD, JS, AB, RD, TW had input into conducting all aspects of the systematic review. SD acted as statistical advisor and had input into aspects of the review. YD drafted the paper; all authors read and commented on draft copies of the paper.

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