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About home unit

The Liverpool Reviews and Implementation Group (LRIG) was established within the Department of Pharmacology and Therapeutics in April 2001. It is a multi-disciplinary research group whose purpose, in the first instance is to conduct systematic reviews commissioned by the Health Technology Assessment Programme.

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Responsibility of report

The views expressed in this publication are those of the authors and not necessarily those of the review panel, peer reviewers, the HTA Programme, National Institute for Clinical Excellence or the Department of Health.

Summary

Objectives

To assess the clinical and cost-effectiveness of zaleplon, zolpidem and zopiclone (Z-drugs) compared to the benzodiazepines licensed and approved for use in the UK for the short-term management of insomnia.

Specifically the review includes comparisons of:

- zaleplon, zolpidem or zopiclone with benzodiazepines (diazepam, loprazolam, lorazepam, lormetazepam, nitrazepam, temazepam)
- any two of the three non-benzodiazepine drugs (zaleplon, zolpidem or zopiclone)

Background

Insomnia is a common complaint of dissatisfaction with the quantity or quality of sleep. The estimates of population prevalence vary between ten per cent to nearly 38%. Although there is evidence of effectiveness of non-pharmacological treatments, benzodiazepines are often prescribed. Non-benzodiazepine hypnotics (Z-drugs) were introduced for short-term treatment of insomnia in the late 1980s and 1990s. They were introduced as an alternative which might overcome some of these adverse effects associated with benzodiazepines including tolerance, dependency, withdrawal symptoms and decreased psychomotor performance. In 2002, the UK Prescription Pricing Authority recorded over 6 million prescriptions for benzodiazepines and 4 million for the Z-drugs.

The development and introduction of these newer hypnotic drugs have made it necessary to examine the available research evidence to establish the clinical and cost effectiveness of older and newer agents used for short-term management of insomnia to inform national guidance.

Methods

The review was conducted following accepted guidelines for conducting systematic reviews including the identification of clinical and economic studies, application of inclusion criteria, quality assessment of included studies and data extraction and analysis.

Inclusion criteria

Randomised controlled trials that compared either benzodiazepines to the Z-drugs or any two of the non-benzodiazepine drugs in patients with insomnia were included in the review. Data on the following outcome measures were considered: sleep onset latency, total sleep duration, number of awakenings, and quality of sleep, adverse effects and rebound insomnia.

The review team also carried out an extended search to identify other study designs that evaluated issues related to adverse events (e.g. dependency and withdrawal symptoms).

Full economic evaluations that compared two or more options and consider both costs and consequences including cost-effectiveness, cost-utility analysis or cost-benefit analysis undertaken in the context of high quality randomised controlled trials were considered for inclusion in the review.

Clinical Findings

Twenty-four studies, involving a total study population of 3909 patients, met the inclusion criteria. These included seventeen studies comparing a Z-drug with a benzodiazepine and seven comparing a Z drug with another Z drug.

The diversity of possible comparisons and the range of outcome measures in the review may be confusing. This is compounded by the fact that outcomes were rarely standardised and even when reported, differed in interpretation. In addition, variation in assessment and variety in the level of information provided make study comparisons difficult. As a result meta-analysis has been possible on only a small number of outcomes. However, some broad conclusions might be reached based on the limited data provided.

1. *Concerning zolpidem*:

    a) Zolpidem with nitrazepam (n=2)

    - One study reports statistically significantly fewer awakenings with zolpidem

    b) Zolpidem with temazepam (n=2)

    - One study reports significantly favourable results for sleep latency and sleep quality in the zolpidem group

    c) Zolpidem with zopiclone (n=1)

    - Results from the only study in this comparator group suggest a statistically significant difference in favour of zolpidem for sleep latency, rebound insomnia of sleep latency and adverse events

2. *Concerning zopiclone*:

    a) Zopiclone with lormetazepam (n=1)

    - Only one study in this group reports that lormetazepam results in shorter sleep onset latency than zopiclone

    b) Zopiclone with nitrazepam (n=8)

    - There is no convincing evidence of any differences in the outcomes measured between zopiclone and nitrazepam (two studies suggest sleep latency is significantly shorter with zopiclone and one study reports significant improvements in sleep quality for zopiclone).
    - Results from four studies suggest a statistically significant difference in favour of zopiclone in daytime alertness.

c) Zopiclone with temazepam (n=4)

- There is no convincing evidence of any differences in the outcomes measured between zopiclone and temazepam (only one study reports that rebound insomnia of sleep latency is significantly worse following zopiclone than after temazepam).

3. *Concerning zaleplon*:

Zaleplon with zolpidem (n=6)

- Some evidence suggests that zaleplon results in shorter sleep latency than zolpidem but zolpidem results in longer sleep duration than zaleplon
- Evidence suggests that zolpidem is statistically significantly more likely to improve sleep quality than zaleplon
- Evidence suggests that withdrawal is less likely and rebound insomnia significantly less likely on zaleplon compared to zolpidem

Economic evaluation

The existing published economic literature in this area is very limited. No relevant economic evaluations were identified for inclusion in the review. The industry submissions did not include detailed evidence of cost-effectiveness. Given the lack of robust clinical evidence, no economic model describing the costs and benefits of the newer hypnotic drugs for insomnia was developed. While we accept that the burden of disease imposed by insomnia is significant for both individuals and the NHS, the available evidence does not give a basis on which we can provide any firm guidance with regard to the comparative cost-effectiveness of different drugs in this area.

The systematic review provided in this document suggests that an agnostic approach to cost-effectiveness is required at this stage. In the short-term, no systematic evidence is available concerning significant outcome variations between either the different classes of drugs or between individual drugs within each class. Within this short-term horizon, the one element that does vary significantly is the acquisition cost of the individual drugs.

Implications for the NHS

Analysis of the additional costs to the NHS, depending on the rate of change from benzodiazepine prescriptions to Z-drug prescriptions, at current levels of hypnotic prescribing, range from £2 million to £17 million per year.

Recommendations for further research

There are clear research needs in this area: in particular, none of the existing trials adequately compare these medications. We would urge therefore that further consideration should be given to a non-commercially supported formal trial to allow head to head comparison of some of the key drugs in a double blind RCT lasting at least two weeks, and of sufficient size to draw reasonable conclusions. We would also recommend that any such trial should include a placebo arm. It should also collect good quality data around sleep outcomes and in

particular quality of life and daytime drowsiness. We do not believe that any formal study of risk of dependency is feasible at present.

Finally the major research issue is perhaps not around the management of short-term insomnia, but around the management of long term insomnia: considering the frequency of this symptom and its recurring course, the short-term trial of medication and lack of long term follow-up undermine attempts to develop evidence-based guidelines for the use of hypnotics in this condition, or indeed for its whole management.

ABBREVIATIONS:

CBA	cost benefit analysis
CEA	cost effectiveness analysis
CMA	cost minimisation analysis
CUA	cost utility analysis
CNS	central nervous system
CFF	critical flicker fusion
CRT	choice reaction time
DSM	diagnostic and statistical manual
DSST	digit symbol substitution test
HRQOL	health related quality of life
NAW	number of awakenings
OR	odds ratio
PSG	polysomnography
QALY	quality adjusted life year
RCT	randomised controlled trial
RR	relative risk
REM	rapid eye movement
SLT	sleep latency test
SSD	self-reported sleep duration
STAR-PU	specific therapeutic area – prescribing unit
SSL	self-reported sleep latency
STM	short term memory
VAS	visual analogue scale
WHO	world health organization
Z-drugs	zaleplon, zolpidem, and zopiclone

DEFINITIONS OF TERMS:

Abuse potential	Tendency of a drug to induce improper use
Drug dependence	A state, psychic and sometimes also physical, resulting from the interaction between a living organism and a drug, characterised by behavioural and other responses that always include a compulsion to take the drug on a continuous or a periodic basis in order to experience its psychic effects, and sometimes to avoid the discomfort of its absence. (WHO definition)
Nocturnal awakening	Waking up during the night
Non-benzodiazepine hypnotic	A hypnotic that is a benzodiazepine receptor agonist
Objective assessment	Evaluation of treatment based on the quantitative measurement of defined outcomes
Primary insomnia	Insomnia that is not caused by a known physical or mental condition and persists for at least one month.
Rebound insomnia	Worsening of sleep compared to pre-treatment levels on abrupt discontinuation of a hypnotic agent
Sleep onset latency	The amount of time required to fall asleep
Short-term insomnia	Insomnia lasting up to 3-4 weeks
Subjective assessment	Evaluation of treatment based on the perceived effect reported by patient and/or investigator
Tolerance	Reduction in response to the drug after repeated administration
Total sleep duration	Actual time spent asleep
Transient insomnia	Insomnia that lasts less than a week and does not reoccur
Withdrawal syndrome	A complex of clinical manifestations (insomnia, compulsive episodes, irritability, anxiety) that occur when the drug administration in a physically dependent person is abruptly discontinued.

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1 Review aims

To assess the clinical and cost-effectiveness of zaleplon, zolpidem and zopiclone compared to benzodiazepines licensed and approved for use in the UK for the short-term management of insomnia.

Specifically the review includes comparisons of:

- zaleplon, zolpidem or zopiclone with benzodiazepines (diazepam, loprazolam, lorazepam, lormetazepam, nitrazepam, temazepam)

- any two of the three non-benzodiazepine drugs (zaleplon, zolpidem or zopiclone).

2 Background

2.1 Normal sleep

If questioned, most individuals would agree that the perfect sleep is one in which you fall asleep quickly and easily (sleep latency), stay asleep (total sleep time and number of awakenings) and awake refreshed and alert (daytime alertness). Individuals may experience differences in these parameters on a day to day basis and between individuals, differences may also be large.(1) These within and between individual variations limit the development of definitions for the precise parameters of good quality sleep and assessment of existing research indicate there is limited data available regarding the stability of these measures over time.(2)

However, objective and subjective methods have been developed to assess the quality of various aspects of the sleep experience. Objective measures of sleep include the use of polysomnography (PSG). This includes the monitoring of multiple electrophysiological parameters including parameters such as electroencephalographic (EEG), electromyographic activity and eye movements.(3) Data from these assessments provide a picture of sleep architecture which includes the cyclic nature of sleep, various stages of sleep and assessment of rapid eye movement (REM) and non-REM sleep. These data also allow for the evaluation of quantitative sleep measures such as sleep onset latency, total sleep time and number of awakenings.

However, 'while such objective assessments can measure the quantity of sleep, they can only provide information on the theoretical quality of sleep'.(4) Numerous subjective tools have been developed to assess the quality of sleep (i.e. sleep diaries, sleep quality index).(5) Debate continues regarding the correlation of the objective and subjective measures related to both the qualitative and quantitative measures related to sleep.(6)

2.2 Insomnia

2.2.1 Classification and diagnosis of insomnia

In general terms, insomnia is defined as dissatisfaction with the quantity or quality of sleep.(7) This may include the ability to fall asleep, to remain asleep or a lack of feeling refreshed upon waking. Insomnia is also very variable and marked night-to-night variations complicate the process of diagnosis. Specific diagnosis of insomnia is complex. Insomnia can be classified by: duration, severity, co-morbidity or by quantity and/or quality of sleep. The definitions vary substantially across the classification systems. The various components of the accepted classification criteria are presented in *Table 2A*. Previous definitions also included duration of insomnia. However, iIt has been argued that the concept of diagnosis by duration is in fact done only retrospectively (especially in the case of transient insomnia) and is therefore clinically unhelpful. (Kevin Morgan, University of Loughborough, Leicestershire: personal communication, July 2003)

*Table 2A Classifications/ clinical features of insomnia**

Severity (ICSD) (8)	**Comorbidity (DSM-IV) (9)**	**Quantity and/or quality of sleep (ICD-10) (10)**
Mild: occurring almost every night with a minimum or no evidence of impairment of quality of life	Primary insomnia	Difficulty falling asleep or maintaining sleep, or of poor quality of sleep
Moderate: occurring every night, mild to moderate impairment with associated symptoms	Insomnia related to another mental disorder (nonorganic) (e.g. major depressive disorder, generalised anxiety disorder)	Occurrence of sleep disturbance >3 times/ week for <1 month
Severe: occurring every night, severe impairment with significant associated symptoms (irritability, fatigue, anxiety etc.)	Insomnia related to a general medical condition (organic)	Preoccupation with the sleeplessness, excessive concern over its consequences
	Substance-induced insomnia	Unsatisfactory quantity and/or quality of sleep either causing marked distress or interfering with ordinary activities

*Adapted from Holbrook 2000(7)

There is also a need to differentiate whether the insomnia is the primary syndrome or a symptom of some other disease process.(11) It is well known that many patients complaining of insomnia suffer significant co-morbidities, such as depression, other mental health problems, or organic disorders. The World Health Organisation 1996 survey report(12) indicates that internationally 27% of patients reported some form of sleep problem. Of these, 52% also had a well-defined mental health disorder and 54% reported a physical disorder.

Given these variations in classification and symptom presentation, there is a lack of consistency in the use of diagnostic criteria. Recommendations for the assessment of patients presenting with insomnia vary but the majority require a comprehensive history that includes: definition of the sleep disorder including a description of actual sleep patterns, consideration of possible concurrent medical conditions, substance use (caffeine, nicotine or alcohol), psychiatric disorders and any other physical or psychological factors that may be affecting the person's ability to sleep.(7, 11, 13, 14)

Researchers have attempted to address the issues related to the diagnosis of insomnia. A 2003 consensus document from Spain provides an extensive list of issues to be addressed when considering diagnosis.(15) A similar Canadian document actually goes on to say that the diagnosis of primary insomnia needs to be made by exclusion: by ruling out other conditions that may be causing the sleep disturbance, a decision can be made that the primary problem is the insomnia.(16) Presenting the issues from a public health perspective, Dement and Pelayo(13) provide detailed recommendations for the evaluation of insomnia including differential diagnosis, while a European consensus document related to diagnosis and management outlines the importance of the problem and the apparent lack of attention being paid to the diagnosis and treatment.(17)

2.2.2 Epidemiology

Epidemiological reports related to insomnia utilise differing definitions, classification systems and diagnostic criteria and therefore are often not directly comparable.(18) As a result, the estimates of population prevalence of insomnia have, unsurprisingly, variy from 10% to as high as 38%.(7, 19, 20)

In a survey of five European countries, Chevalier and colleguesl(21) counducted face-to-face interviews in the general population using DSM-IV criteria. They report a prevalence of insomnia of 4% to 9% in Germany, Sweden, Ireland and Belgium, whereas 22% of the population in the UK were affected. This figure for the UK is slightly lower than the individual UK data reported in the WHO report(12) where any sleep problem was reported by 32% of those patients surveyed.

Leger et al(22) surveyed more than 12000 people in France using 'strict' DSM-IV criteria and identified 9% of the population with 'severe insomnia'. They found a higher prevalence in women. In Norway, Pallesen et al(23) conducted a telephone survey using DSM-IV criteria and report a prevalence of 12% with seasonal variations and increased sleep disorders reported in the winter months.

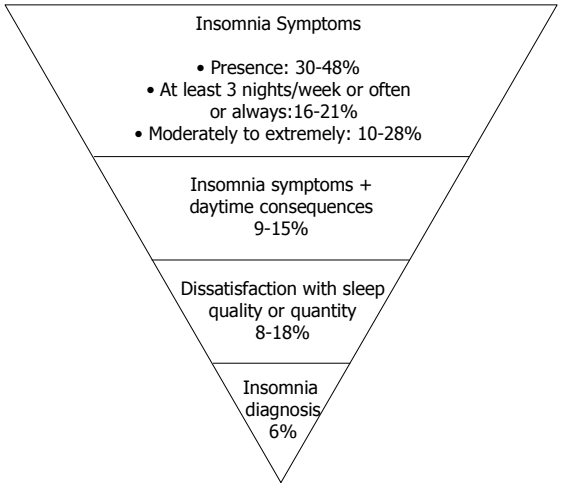
From a more pragmatic perspective, Simon and VonKorff(24) analysed the WHO data on patients under 65 within their health maintenance organisation in the USA. Prevalence rates were 10% and assessment of patient data indicated the patients with insomnia had greater functional impairment, lower productivity and an excess of health care utilisation.

A recent systematic review of epidemiological literature provides an excellent summary of the problems of measurement and reporting of this data.(18) This report details insomnia data from four perspectives:

- insomnia symptoms
- insomnia symptoms accompanied with daytime consequences
- dissatisfaction with sleep quality or quantity
- insomnia diagnosis

The review is based on analysis of available epidemiological data and provides estimates within each of these categories. The summary of this analysis is presented in *Figure 2A*.

*Figure 2A: Average prevalence of insomnia symptoms and diagnoses**



* Figure adapted from Ohayon 2002(18)

The prevalence of insomnia has historically been reported to be higher in women and to increase with age.(18) Multi-variant analysis of the French population data(25) identified that low family income, being female, being >65 years of age and being separated, divorced or widowed were significantly associated with sleep difficulty. Recent research cited by Holbrook et al(7) suggests that insomnia may be less correlated to age and more closely related to other physiological conditions and treatment of these conditions. Regression analysis carried out by Pallenson et al(23) in the Nowegian survey revealed that somatic and psychiatric health were in fact the strongest predictors of insomnia. Given that physiological complaints increase with age it could be expected that prevalence of insomnia would also increase. Overall prevalence of insomnia among older people living in the community varies from 12% to 39.8%.(26)

Pallesen et al(23) also reported that 6.9% of the population reported using hypnotics. This rate of use of hypnotics is similar to the results of a French survey(25) that identified 10% of the population who were taking sleep medication and that for most, consumption had been long term. Of those taking medication 82% had been using hypnotics for more than six months and 31% had been using them for more than five years.

2.2.3 Burden of illness

It is difficult to estimate the impact of insomnia. Some argue that insomnia is under-treated.(13, 27) Reasons for this may be attributed to the response of the individual to the symptoms or the response of the health care providers to individuals presenting for treatment.

In the first instance, there may be an individual under-estimation of the problem and subsequent lack of presentation for treatment. Only 1 in 20 individuals are believed to present to health care professionals with insomnia-related symptoms.(28) This may reflect an individual preference to self-treat using alternative treatments which are not included in the true costs of insomnia e.g. anti-histamines or alcohol.(27) There may also be an association of insomnia as a stigma and therefore a reticence to present for treatment even when the severity of symptoms significantly impacts on quality of life.(29)

In the area of health care provision, there may be a lack of comprehensive assessment and treatment of symptoms. A failure to include questions regarding sleep and sleep quality in routine health visits limits the case detection rates and therefore the prevalence and effect of insomnia can never be adequately assessed.(29) Hypotheses that explain the lack of comprehensive assessment of insomnia have been put forward but not researched. They include issues related to health professionals' knowledge and training regarding the diagnosis and treatment of insomnia, a lack of belief in an ability to provide effective care, and time constraints.(30)

Assesment tools have been developed to assess the impact of insomnia (and treatment) on quality of life (QoL).(31) Some of the tools are general health measures (i.e. SF-36) while others have been specifically designed to assess insomnia and may or may not have been validated.(32) In some studies a combination of tools have been utilised.(31) Leger and collegues,(33) in their evaluation of the SF 36 in relation to insomnia, point out that surprisingly few studies have investigated QoL related to insomnia and go on to say that they were able to identify only four studies that included QoL as an outcome. Leger and collegues(33) indicate that quality of life is decreased in those individuals suffering from insomnia and that degradation of QoL was correlated with the severity of the insomnia. However, they go on to point out that the original cause of the insomnia may have a significant effect on their findings. This is discussed specifically in relation to general health status of the individuals suffering from insomnia. For instance, if the initial problem leading to insomnia is a chronic disease, it is not possible to differentiate the effects of the disease from the effects of the insomnia on the QoL.

The difficulties experienced in differentiating between effects of recurrent, persistent or multiple health problems and insomnia in relation to QoL are also experienced when attempting to assess the effects of insomnia on measures such as disability and health care utilisation. Epidemiological surveys consistently report higher levels of physical illness and disability and health care utilisation in respondents reporting insomnia.(21, 24, 25, 33) As stated by Leger et al (33) 'we could conclude only that insomnia was related to a worse health status and not whether it was a cause or consequence of this worse health status.'

In a similar context it is difficult to measure the impact of insomnia on daily alertness and productivity. As an example one company submission(34) included extensive discussion regarding sleepiness and the incidence of road traffic accidents (RTA). Although there may well be data to support a causal link between RTAs and sleepiness, that data does not directly link to insomnia.

2.3 Treatment options

Treatment may vary depending on the presenting symptoms and other co-existing health problems. In cases of primary insomnia, the treatment will aim to reduce insomnia symptoms alone, whereas in cases where insomnia symptoms are linked to other general health complaints (i.e. physical or mental), the treatment will aim to address the more complex combination of symptoms.

Ideally, effective treatment for insomnia should normalise sleep patterns but importantly, not impair next day function. However, the use of prescribed medication will be influenced to a great extent by the patient's perception of efficacy and the absence of what could be considered adverse effects such as impact on mood and daytime function.

2.3.1 Non-pharmacological treatment

Non-pharmacological treatments include interventions such as sleep hygiene measures and a variety of behavioural activities such as cognitive therapies, relaxation, sleep restriction etc. In the UK, guidelines for these were published in 1992.(35)

A number of systematic reviews have compared the effectiveness of non-pharmacological interventions to pharmacotherapy and report similar results. In one systematic review by Morin and collegues published in 1994,(36) the authors identified 59 studies that examined the effectiveness of non-pharmacological interventions to improve sleep-onset, maintenance or mixed insomnia. They concluded that non-pharmacological interventions are effective in producing reliable and durable changes in sleep patterns in patients with chronic insomnia. A more recent systematic review by Petit and collegues(5) that examines diagnosis and treatment of insomnia in the elderly recommends the initial use of non-pharmacological interventions. Consensus statements such as the one published in Canada(16) recommend the use of non-pharmacological interventions as first line treatment for insomnia. In general, the systematic reviews indicate that behavioural interventions appear to be as effective as pharmacotherapy in the short term (37-39) and in some cases are reported as superior in the long term.(40) The limited use of these interventions has been highlighted in the systematic review carried out by Perlis and collegues(39) who discuss causes as a lack of trained providers, cost, lack of third party reimbursement and lack of understanding of the treatment methods.

2.3.2 Pharmacological treatment

Pharmacological agents are generally accepted as effective in reducing sleep latency, increasing total sleep time and reducing periods of awakening, although the extent of the benefit is questioned by some.(41) Benzodiazepines have been the treatment of

choice for insomnia since the mid 1960s.(16) They act at specific benzodiazepine receptors to enhance the binding of the inhibitory neurotransmitter GABA. There are a variety of benzodiazepines licensed in the UK as hypnotics, while others are licensed as sedatives or anxiolytics. There is little real difference in the effects of these drugs: the decision whether a drug is an anxiolytic or a hypnotic is partly based on its pharmacokinetics, but is largely a commercial decision. A recent systematic review by Holbrook et al in Canada(41) of their use concluded that 'the use of benzodiazepines in the treatment of insomnia is associated with an increase in sleep duration, but this is countered by a number of adverse effects.' The adverse effects tolerance, dependence, rebound insomnia and impairment of daytime functioning.(16)

Zaleplon, zolpidem, and zopiclone are non-benzodiazepine hypnotics introduced in the late 1980s and 1990s and are only licensed for short-term (2-4 weeks) use for the treatment of insomnia in the UK. Although not chemically benzodiazepines, they interact with the benzodiazepine receptors, or with some particular types of benzodiazepine receptors. It was hoped that these drugs might avoid some of the adverse effects of benzodiazepines, such as tolerance, dependency and withdrawal symptoms.

Zaleplon, the most recently approved drug, is a pyrazolopyrimidine compound and binds selectively to the omega-1 site of the receptor. Two published reviews with slightly different inclusion criteria examined the effectiveness of zaleplon versus placebo.(42, 43) The reviews included studies that evaluated both patients with insomnia and healthy volunteers and came to slightly differing conclusions.

Eight studies summarised by Maidment(42) report a six to 16 minute decrease in sleep latency with zaleplon. Results related to symptoms of rebound insomnia were mixed, but consistently indicated less hangover effect from use of the drug compared to placebo. Patat et al(43) identified 16 studies comparing zaleplon to placebo of which nine assessed the administration of twice the normal dose of the drug. The primary focus of the review was the effect on psychomotor performance. Data on sleep latency and duration were discussed but not presented. The authors concluded that the recommended dose of 10 mg did not impair psychomotor and memory performance but that administration of double the dose was found to impair participant performance. A third review by Dooley and Plosker(44) also included the comparison of zaleplon to placebo and,consistent with the other reviews, identified a decrease in sleep latency. Insufficient data was available at the time of that review to compare the effectiveness of zaleplon to the other two Z-drugs.

Zolpidem is an imidazopyridine, which binds selectively to only one (omega-1) receptor subtype of benzodiazepine. A review examining the safety of zolpidem(45) included reports on post marketing surveillance, rebound insomnia and safety of use in the elderly. The authors conclude that there was a low incidence of adverse events, no statistically significant rebound insomnia and a minimal risk of abuse when the drug is prescribed as recommended and used in short-term treatment. Unden and Schechter(46) included 30 trials in a systematic review assessing the next day effects of zolpidem and concluded that there were limited next day effects but that use of the drug was recommended when the individual could get a full nights sleep prior to resuming next day activities. The review by Holm and Goa(47) drew the same

conclusions. A review by Rush(48) compared behavioural effects of zolpidem to benzodiazepines and concluded that there was not enough research to draw firm conclusions.

Zopiclone belongs to the cyclopyrrolone group, and like benzodiazepines, is less selective in its binding. A general review of the this agent indicates that compared to placebo, it is effective in decreasing sleep latency, increasing sleep duration and decreasing number of awakenings.(49) This same report in addition to a summary by Terzano and collegues,(50) indicates that the drug may cause some next day impairment, especially in higher doses.

The following table includes the hypnotic agents currently listed in the British National Formulary, March, 2003(51) for the short-term management of insomnia and included in this review.

Table 2B: Pharmacological agents included in this review

Pharmaceutical agent	Product name (Supplier)*	Dose	T Max** (hours)	Elimination half-life (h)
Diazepam	Tablets* Tensium® *Rimapam*® Oral solution: Dialar®	5-15mg	0.5-1.5	24-48
Loprazolam	Tablets*	1mg, increased to 1.5 or 2mg; elderly (or debilitated) 0.5 - 1mg	2-4	4-11
Lorazepam	Tablets*	1-2mg	2	10-20
Lormetazepam	Tablets*	0.5–1.5mg; elderly (or debilitated) 500micrograms	1-1.5	11
Nitrazepam	Tablets* *Remnos*® *Mogadon*® Oral suspension: *Somnite*®	5–10mg; elderly (or debilitated) 2.5–5mg	1.5-2	24-30
Temazepam	Tablets* Oral solution*	10–20mg, up to 30–40mg; elderly (or debilitated) 10mg, up to 20mg	0.3-0.7	8-15
Zaleplon	Capsules: *Sonata*® (Wyeth)	10mg; elderly 5mg	1	1
Zolpidem	Tablets*: *Stilnoct*® (Sanofi-Synthelabo)	10mg; elderly (or debilitated) 5mg	<3	2.5
Zopiclone	Tablets*: *Zimovane*® (Rhone-Poulenc Rorer)	7.5mg; elderly initially 3.75mg increased if necessary	2	3.5-6.5

*Indicates availability as non-proprietary ** Time to peak plasma concentration

Although pharmokinetic parameters are important, as we shall see, the elimination half-life is a poor guide to duration of action, particularly as some of these drugs have active metobolites.

Several other benzodiazepines used for the treatment of insomnia are not included in this review. These are flunitrazepam and flurazepam, which hold a UK marketing authorisation but are not approved for use in the NHS, and triazolam for which marketing authorisation has been withdrawn in the UK.

There are other drugs licensed as hypnotics, such as chloral hydrate and its derivatives or clomethiazole but these are considered less suitable because of the dangers of overdose and of dependency, and are little used: these are not considered further in this report.

Other drug therapies include over the counter (OTC) drugs available through pharmacies without prescription. These have a limited efficacy and safety database in this indication. The extent of their use is not clear but a recent report raises concerns that perhaps as many as half of the users of such drugs are using them in an inappropriate manner.(52) Again, these drugs are not considered further in this report.

2.4 Outcome measures

2.4.1 Sleep measures

As noted earlier, the assessment of sleep can be subjective or objective. Subjective measures may include the use of patient diaries that report perceived quality and quantity of sleep, as well as reports of feelings of well-being the next day. Objective measures include evaluation of the quantitative aspects of sleep and may include: sleep latency (how long it takes to get to sleep), total sleep time (how long you stay asleep) and number of awakenings after falling asleep. Other less common measures assess the amount of time it takes the individual to return to sleep if they wake and whether they wake earlier than desired and are unable to return to sleep.

2.4.2 Psychomotor, mood and memory outcomes

Measures of mood and sleep quality are normally undertaken via self-reported measures. The efficacy and correlation of self-reported measures for post sleep questionnaires has been reported(53) and validated mood questionnaires are available. Self-reported measures often use visual analogue or Likert scales to obtain scores.

Table 2C outlines the primary measures and scoring tools used to assess psychomotor functioning, memory, mood and sleep quality.

Table 2C: Measures and Scoring Mechanisms of Measures

Measure	Test	Scoring Mechanism
Spiegal Sleep Questionnaire	Quality of sleep Morning condition	Likert scale, score range1 – 5 i.e. Morning disposition 1 very bad, 2 bad, 3 as usual, 4 good, 5 excellent
Norris Mood Rating Scale	Mood	18 item VAS i.e. alert/drowsy, calm excited, attentive/dreamy, elated/depressed
Hamilton Rating Scale for Anxiety	Anxiety	Likert scale
Tolouse-Peron Attention Test	Graphic symbols	Interval
Sleep Questionnaire/diary (unspecified)	Sleep quality Daytime arousal Sleep quality Morning alertness	VAS or Likert scale VAS or Likert scale VAS or Likert scale VAS or Likert scale
Patient Rating of Efficacy (unspecified)	Sleep quality	VAS or Likert scale
Patient Questionnaire	Sleep quality	VAS or Likert scale
Memory Test (unspecified)	Graphic symbols	Interval
Alertness (unspecified)	Cancellation test	Interval
Psychomotor Tests (unspecified)	Symbol copying Digit symbol substitution Tapping rate Auditory reaction time	Interval Interval Interval Interval
Syndrom-Kurztest	9 sub scales test short-term memory and concentration	Interval
Leeds Psychomotor Tester	Choice reaction time Critical flicker fusion	Interval Interval
Cancellation Test (unspecified)	Letter cancellation	Interval
Short-Term Memory (unspecified)	Number recall Cued recall Implicit recall Alertness	Interval Interval Interval Interval
Long-Term Memory (unspecified)	Sustained attention Divided attention	Interval Interval
Mood Question (study designed)	Seven questions (all unspecified)	Likert (probable but not specified)
Life Events (unspecified)	Unspecified	Unspecified

2.5 Adverse events

2.5.1 Dependency, withdrawal and tolerance

Perhaps the adverse effects of these drugs which give rise to greatest concern are their potential to lead to the related phenomena of dependence, withdrawal and tolerance. Drug dependence is not only a function of the drug, but also of the user – not all users of hypnotics become dependent, as described by Tyrer,(54) and careful patient selection can reduce the risk of dependency.

The World Health Organisation (quoted in Lader(55) p.54) defines drug dependence as "A state, psychic and sometimes also physical, resulting from the interaction between a living organism and a drug, characterised by behavioural and other responses that always include a compulsion to take the drug on a continuous or a periodic basis in order to experience its psychic effects, and sometimes to avoid the discomfort of its absence." This concept of dependence has caused confusion when researchers begin to refer to either physical or psychological dependence.(56)

In a systematic review, Linsen and colleagues (57) identified a large degree of disagreement between definitions of dependence used in studies of benzodiazepines. The most consistently used criteria for physical dependence included specific

withdrawal syndromes or symptoms after discontinuation of the drug. Many consider the most important adverse effect of hypnotic use to be physical dependence(58) which the WHO defines as "the development of an altered physiological state which requires continued administration of a drug to prevent the appearance of a characteristic illness, the abstinence syndrome." (World Health Organisation, quoted in Lader (55) p.54).

Researchers define the withdrawal syndrome in different ways. In Lader's view(59), withdrawal syndrome is generally accepted to include a minimum of three new symptoms emerging after withdrawal of the drug (i.e. symptoms not present before treatment). He lists the typical withdrawal symptoms as perceptual hypersensitivity with photophobia, hyperacusis and hyperalgesia, and systemic symptoms such as anorexia, malaise and bodyweight loss. Further psychological symptoms, such as insomnia or anxiety, may be difficult to identify and distinguish from symptoms present prior to treatment. This same phenomena is called 'discontinuation syndrome' by Nutt and may be linked to physical symptoms that were not originally associated with a need for the drug (Nutt D, University of Bristol, Bristol: personal communication, July 2003). In the case of benzodiazepines this may include sensations such as metallic taste or hypersensitivity to light or sound.(60)

Nutt explains these phenomena as follows: 'Physical dependence manifests itself through the expression of a withdrawal syndrome that is thought to occur as a consequence of adaptive changes developing to attenuate or compensate for the actions of a drug. These lead to a change in physiological activity when the drug is stopped. Such withdrawal syndromes come in two distinct forms that I suggest should be called rebound and discontinuation syndromes'. Nutt goes on to define rebound as the worsening of the condition for which the drug was originally prescribed. This may include increased sleep latency, decreased total sleep time or an increase in the number of nocturnal awakenings. He also points out that these rebound symptoms may be so severe that in fact patients experience worse symptoms than those for which they were originally treated – a process he describes as 'overshoot' (Nutt D, University of Bristol, Bristol: personal communication, July 2003). It has been suggested that the study of rebound phenomena is complicated by the fact that blinding of subjects and assessors in a trial is difficult to maintain in a withdrawal phase.(1)

There are several methodological problems in studying withdrawal. These include a lack of double-blind comparisons, the selection of subjects already having difficulty discontinuing their drugs (rather than the general population), poor compliance in discontinuation studies, the required length of observation, particularly for longer acting drugs, and the inconsistency in defining and measuring withdrawal, as well as the overlap between withdrawal symptoms and symptoms for which the drug was taken.(58, 61, 62)

Tolerance is generally defined as a decrease in a drug's effect over continued administration, which results in the need to increase the dose of the drug.(59) A progressive decrease in pharmacological effects of a drug with repeated administration is an indication of the development of tolerance.(Lader(63) p.136).

2.5.2 Benzodiazepines

Dependence can occur after discontinuation of therapeutic doses of benzodiazepines.(64, 65) It has been suggested that the proportion of chronic users who are physically dependent on their treatment may be as high as 10-30%, even on therapeutic doses.(66) Noyes and colleagues(61) note that controlled studies of long-term use of benzodiazepines (over 1 year) report an incidence of withdrawal syndromes (equated with dependence) in nearly half of the patients.

It has been suggested that shorter-acting benzodiazepines may be more likely than long-acting ones to induce dependence.(62). But Woods and colleagues(65) were not able to conclude from their literature review that there was a difference between different benzodiazepines with regard to their potential to induce physical dependence.

Gudex(58) suggests that slowly eliminated drugs show milder rebound insomnia than rapidly eliminated benzodiazepines. Lader(59) concurs with this view, whereas Woods and colleagues(65) conclude more optimistically that long-acting benzodiazepines do not appear to produce rebound insomnia. However, the systematic review of sleep laboratory studies by Soldatos et al(67) examines the issue from a slightly differenct perspective and concludes that one rapidly eliminated benzodiazepine (triazolam) has more pronounced tolerance and rebound symptoms than zolpidem.

Long-term use, high doses, high-potency, alcoholism and other drug dependency, personality disorders and use without medical supervision have been suggested to be major risk factors for developing dependence when using benzodiazepines.(68) Woods and colleagues(65) report that there is no clear relationship between either dose or duration and the development of dependence on benzodiazepines. Others, however, disagree(61) and would point to the clear dose-effect relationship for the occurrence of rebound insomnia following benzodiazepine withdrawal. However, Lader(63) concludes that there appears to be no relationship between rebound insomnia and duration of treatment with benzodiazepines. Petursson and Lader(64) suggest that some degree of tissue tolerance or adaptation might occur in most patients using benzodiazepines, but this does not equate to dependency since most patients maintain constant doses.

2.5.3 Zaleplon

There are reports from placebo controlled studies of withdrawal symptoms including rebound insomnia following zaleplon discontinuation, but the incidence is suggested to be low.(44, 69) Reviews of trials and follow-up studies involving zaleplon concluded that no significant rebound events had been identified following zaleplon discontinuation,(42, 44) although some trials have identified rebound insomnia (see review by Maidment.(42)) A review by Dooley and Plosker(44) notes that there is no evidence of tolerance in the available small number of trials and longer-term non-comparative follow-up studies.

The WHO Expert Committee on Drug Dependence (56) reviewed zaleplon at its September 2002 meeting in Geneva. The Committee notes that zaleplon produces a benzodiazepine-type withdrawal syndrome and considers its abuse potential to be

similar to that of zolpidem and triazolam. Nevertheless, the Committee stopped short of recommending a critical review, because of insufficient evidence as yet of an associated significant public health and social problem.

2.5.4 Zolpidem

The WHO Expert Committee on Drug Dependence in 2000 recommended zolpidem be placed in Schedule IV of the 1971 Convention. The Committee observed "rates of actual abuse and dependence on zolpidem appear to be similar to those of other hypnotic benzodiazepines currently listed in Schedule IV. In terms of the numbers of cases for abuse, dependence and withdrawal syndrome reported to the WHO Adverse Drug Reaction database, less than 10 benzodiazepines are ranked higher than zolpidem" (WHO,(70) p.15).

Lader(59) notes that there is little evidence for rebound after zolpidem 10mg, but suggests caution in using higher doses. A relatively recent meta-analysis of sleep laboratory trials and before-after studies assessed tolerance and rebound insomnia following the use of rapidly eliminated hypnotics, and concluded that there was evidence of only marginal tolerance and mild rebound insomnia following cessation of zolpidem, compared to clear tolerance and intense rebound insomnia after triazolam discontinuation.(67)

2.5.5 Zopiclone

The incidence of withdrawal symptoms after zopiclone discontinuation is suggested to be considerably lower than that of benzodiazepine comparators.(71) Hajak(71) holds that nearly all reports of zopiclone dependency concerned patients with a history of other drug abuse. Lader(63) concludes that the risk of dependence after normal doses is negligible. However, caution with the use of zopiclone as well as zolpidem is recommended, given an as yet "unclear dependence potential".(50, 72)

Bianchi and Musch(73) reviewed 25 sleep laboratory studies and clinical trials observing zopiclone discontinuation, 20 of which were performed on insomniacs. No rebound effect on sleep variables and few withdrawal effects were observed after zopiclone. For the purpose of their review, any signs or symptoms during withdrawal were counted as withdrawal effects, whereas rebound was defined as a statistically significant worsening of sleep variables during withdrawal compared to baseline. Anxiety and vertigo were the main withdrawal symptoms reported after zopiclone use.

Several authors have concluded that zopiclone shows a potential to cause rebound,(1) but much less likelihood to do so than benzodiazepine comparators.(59, 63) It has been suggested however, that pill discontinuation per se may cause rebound insomnia, as demonstrated in a placebo group.(71) Similarly, Lader(63) suggests that most studies show no evidence for tolerance developing during treatment with zopiclone.

The WHO Expert Committee on Drug Dependence(56) reviewed zopiclone again at its September 2002 meeting in Geneva and recommended the substance for "critical review". The Committee notes zopiclone's capacity to produce withdrawal syndrome and abuse potential, as evidenced by the adverse drug reaction reports to the international drug monitoring programme.

2.6 Current service provision

The Committee on Safety of Medicines has, since 1988, had clear guidance on containing the use of these drugs to no more than four weeks,(51) and these are echoed by the Royal College of Psychiatrists.(74) The British National Formulary(51) now stipulates that hypnotics should not be prescribed for more than three weeks and preferably for intermittent use. They should thus be reserved for short courses for acutely distressed patients. Despite this advice, long term use of these drugs is common: in a recently published study conducted in The Netherlands and Sweden, a third of patients prescribed benzodiazepines had continued use over eight years follow-up.(75) More recent survey data from the UK indicates that chronic (4 years+) hypnotic use was common among older patients.(76)

In the second quarter of 2002, the UK Prescription Pricing Authority(77) recorded over 1.5 million items of benzodiazepines (i.e. temazepam, nitrazepam, loprazolam, and lormetazepam, with over 1 million items for temazepam alone) having been prescribed at a net ingredient cost (NIC) of over £2.39 million. In the case of benzodiazepines it is not possible to differentiate whether the drugs were prescribed for hypnotics or anxiolytic purposes. The three Z-drugs accounted for £3.86 million (NIC) for over 940,000 items, with zopiclone accounting for over 80% of the prescribed items.

Data from the DIN-LINK network(4) and the General Practice Research Database(78) suggest that at any given time approximately 0.5 to 1.4 million people are using hypnotics in the UK. The extent of this use is discussed in chapter 7. However there is general concern about the misuse of these drugs in medical practice (as well as concern about their diversion to illicit use).

Reflecting this, Prodigy(79) (Department of Health/NICE funded computer decision support system for general practitioners) outlines guidelines on the use of hypnotics which are in effect a consensus statement and these state:

- Use non-drug treatments where possible, including simple advice and counselling

- If the insomnia is severe, disabling or subjecting the individual to extreme distress, consider prescribing a hypnotic as an adjunct to non-drug treatment:

    - Use the lowest effective dose for a maximum of 1 week.
    - Consider using intermittently (e.g. once every other day, every third day)

The National Service Framework on Mental Health(80) contains a number of recommendations around monitoring benzodiazepine use in local audit (and though not explicitly stated, usually taken to include the newer hypnotics). Although there are no explicit recommendations on standards for this audit, it is implicit that high usage of these drugs would be considered bad prescribing.

Against this background, this report considers the clinical and economic evidence around the comparative benefits of newer medicines compared to the older drugs. We have not considered how appropriate it is that these drugs should ever be used, as this is outside our remit, but this is clearly an important issue.

3 Methods

3.1 Methods for reviewing clinical effectiveness

3.1.1 Search strategy

The search included a number of strategies. The electronic databases were searched for the period from 1966 to March 2003 (See *Table 3A*). The search had no language restrictions. Search terms for electronic databases included a combination of index terms (e.g. sleep initiation and maintenance disorders or insomnia) and free text words (e.g. insomnia or sleeplessness) combined with specific drug terms (e.g. zaleplon or Sonata, zolpidem or Stilnoct, zopiclone or Zimovane). Details of the search strategies used and the number of references retrieved for each search are provided in *Table A1*, Appendix 1.

Reference lists of retrieved articles and pharmaceutical company submissions were searched to identify further studies. Recent issues (October 2002 to June 2003) of relevant journals that might not yet have been indexed in electronic databases were handsearched; the journals searched included: European Psychiatry, Human Psychopharmacology: Clinical and Experimental, International Clinical Psychopharmacology, Psycho-pharmacology, Sleep, Sleep Medicine, Sleep Medicine Reviews, The British Journal of Psychiatry, The Journal of Clinical Psychiatry. Internet resources (including industry supported websites) were examined for information on clinical trials.

An advisory panel was established to guide the review process. The role of the advisory panel was to comment on the review protocol, to answer specific questions as the review progressed and to comment on an early draft of the review including identifying missed or ongoing studies.

All references were exported to *EndNote* reference database, *Version 6*, ISI Research Soft, Cal., USA.

3.1.2 Inclusion and exclusion criteria

The identified citations were assessed for inclusion through two stages and disagreements were resolved by discussion at each stage. Two reviewers (YD, JS) independently scanned all the titles and abstracts and identified the potentially relevant articles to be retrieved. Full text copies of the selected papers were obtained and each assessed independently by at least two reviewers for inclusion (YD, JS, RD).

Details of inclusion and exclusion criteria are presented in *Table 3A*.

3.1.3 Data extraction

Data extraction was carried out by four reviewers (YD, RD, JS, SD). Individual study data relating to study design and findings were extracted and checked by two reviewers using a pre-tested data extraction form. Data from baseline and first night after discontinuation of treatment were extracted where more than one data point was available.

3.1.4 Quality assessment

At least two reviewers (YD, RD, JS, SD) independently evaluated the included studies for methodological quality. This involved methodological assessment for clinical effectiveness based on the Centre for Reviews and Dissemination, York, Report 4(81) (see Appendix 2). Any discrepancies were resolved through consensus.

3.2 Extended review on dependence and withdrawal symptoms

Drug trials are usually too short to be able to assess the development of drug dependence. Therefore the research group conducted an extended search to identify studies of other designs which might help address the question of the relative potential of the comparison drugs to induce drug dependence and withdrawal.

3.2.1 Search strategy, inclusion and exclusion criteria

Search terms for this expanded search included a combination of index terms (e.g. withdrawal syndrome, drug tolerance, drug withdrawal) and free text words (e.g. withdrawal, dependency, tolerance, rebound) combined with specific drug names including zaleplon or Sonata, zolpidem or Stilnoct, zopiclone or Zimovane. Search strategies did not include filters that would limit results to specific publication types or study designs. Only English-language reports were identified because of time restrictions. Details of the search strategies used and the number of references retrieved for each search are provided in *Table A2* in Appendix 1. Electronic databases searched and inclusion and exclusion criteria are detailed in *Table 3A*.

3.2.2 Data extraction

Data extraction was carried out by two reviewers (YD, JS). Individual study data relating to study design and findings were extracted independently by one reviewer into a pre-designed data extraction form and checked by a second reviewer.

3.3 Methods for reviewing cost effectiveness

3.3.1 Search strategy

A comprehensive review of the literature was undertaken to identify all published articles that could provide evidence with regard to the cost-effectiveness of newer hypnotic drugs for the management of insomnia.

The search included a number of strategies. Search terms for electronic databases included a combination of index terms (e.g. sleep initiation and maintenance disorders or insomnia) and free text words (e.g. insomnia or sleeplessness) combined with specific drug terms (e.g. zaleplon or Sonata, zolpidem or Stilnoct, zopiclone or Zimovane). Clinical terms were combined with economic terms (e.g. cost or economic).

Reference lists of retrieved articles and pharmaceutical company submissions were also searched to identify further studies. Internet resources (including industry supported websites) were examined for information on clinical trials.

Electronic databases searched are presented in *Table 3A*. Search strategies and results of the searches undertaken are provided in *Table A3*, Appendix 1.

3.3.2 Inclusion and exclusion criteria

The aim of the economic review was to identify economic evaluations informed by clinical data from randomised controlled trials. After scanning the abstracts, all papers that appeared to be of potential value to the study were obtained. Using explicit, predetermined criteria (see *Table 3A*), two reviewers (AB, AH) independently identified studies for inclusion in the cost-effectiveness review process. Disagreements were resolved through discussion. The inclusion and exclusion criteria used in the review are presented below.

All the references were exported to *Endnote* reference database Version 6.0, ISI Research Soft, Cal., USA.

Table 3A: Databases searched and inclusion and exclusion criteria for clinical and cost-effectiveness

	Clinical effectiveness	Extended review-dependency and withdrawal symptoms	Cost-effectiveness
Electronic databases	MEDLINE (1966-2003) EMBASE (1980-2003) PsycINFO (1966-2003) SCI//Web of Science (1981-2003) SCI/ISI Proceedings (1990-2003) The Cochrane Library 2003 (1)	MEDLINE EMBASE PsycINFO	MEDLINE (1987-2003) EMBASE (1987-2003) PsycINFO (1974-2003) SCI//Web of Science (1987-2003) SCI/ISI Proceedings (1990-2003) The Cochrane Library 2003 (1)
Study design	RCT	RCT Case-control studies Case series Case reports Cohort studies Surveys	RCT
Patient population	Individuals with insomnia	Individuals with insomnia	Individuals with insomnia
Interventions	Zaleplon, Zolpidem, Zopiclone: • compared to benzodiazepines • compared with each other	Zaleplon, Zolpidem, Zopiclone: • compared to benzodiazepines* • individually or compared to each other	Zaleplon, Zolpidem, Zopiclone: • compared to benzodiazepines* • compared with each other
Outcomes	• Sleep latency • Sleep duration • Number of awakenings • Sleep quality • Daytime alertness • Tolerance • Rebound • Abuse potential • Adverse effects including dependency and withdrawal	• Dependency • Withdrawal symptoms	• Cost per increase in sleep duration • Cost per decrease in sleep latency • Cost per adverse effect avoided • Cost per quality adjusted life year gained
Exclusion criteria	RCTs that: • provide data on a sub-group of the enrolled patients • provide only unplanned, interim findings • are continuing to recruit patients • include volunteer subjects that do not report symptoms of insomnia in their study population • compares benzodiazepines not currently licensed for use in the management of insomnia in the UK	RCTs that: • provide only unplanned, interim findings • provide data on a sub-group of the enrolled patients • are continuing to recruit patients • include individuals without symptoms of insomnia	Papers were excluded if: • main source of clinical efficacy data was from a non-RCT or not explicitly stated • there was no attempt to synthesise costs and benefits • they were letters, editorials, commentaries or methodological papers

* The BNF(51) refers the following benzodiazepines for the short-term management of insomnia: diazepam, loprazolam, lorazepam, lormetazepam, nitrazepam and temazepam.

3.3.3 Meta-analysis of results

The outcomes that were considered in the identified studies were:

- sleep onset latency
- total sleep duration
- number of awakenings
- quality of sleep
- adverse effects
- rebound insomnia (sleep onset latency, total sleep duration, number of awakenings, quality of sleep)

The studies identified were grouped and presented according to the following comparisons:

I. Z x BZD comparisons:

- Zolpidem versus Nitrazepam
- Zolpidem versus Temazepam
- Zopiclone versus Lormetazepam
- Zopiclone versus Nitrazepam
- Zopiclone versus Temazepam.

II. Z x Z comparisons:

- Zaleplon versus Zolpidem
- Zolpidem versus Zopiclone

Meta-analyses were carried out when possible between studies that compared the same drugs. If extracted data were unsuitable for combination using meta-analysis, data were shown in a forest plot. Scales used to assess outcomes differed between studies, and therefore, to avoid problems in interpretation when scale direction differed also, mean values were negated when a decreased score indicated improvement. This was carried out to create a uniform direction of improvement on the forest plots, so that an increase in mean score indicated improvement. Crossover trials with less than two nights washout were excluded from the analysis. Data were pooled using a fixed effect model (as there was no evidence of statistical heterogeneity) with odds ratio and 95% confidence intervals.

4 Results

4.1 Clinical effectiveness

4.1.1 Selection of included studies

A total of 72 references were identified to which the inclusion criteria were applied. Of these, 24 studies met the inclusion criteria (*Table 4A)*. These included 17 studies comparing a Z-drug with a benzodiazepine(82-98) and seven (reported in six reports) comparing a Z-drug with another Z-drug.(99-104) Reports of studies which did not fulfil the inclusion criteria are available in *Appendix 4*. The reason for exclusion is given for each of these excluded references.

Twenty studies were assessed from reports published in peer-reviewed journals. The remainder were published abstracts of conference proceedings.(89, 99, 103) Of these, two studies are reported in one abstract.(103)

Four studies(86, 88, 91, 92) were published in Japanese language journals. A Japanese native speaker assisted the review team with data extraction and interpretation, but we were not able to extract data related to specific measures used to assess psychomotor, memory and mood outcomes.

The review team identified two reports (presented as conference posters) from one of the Industry Submissions to NICE.(4) One(105) was a pooled analysis of three RCTs evaluating global assessment of the efficacy of zaleplon 5, 10, and 20 mg and zolpidem 10 mg, compared with a placebo in the treatment of outpatients (1840 patients) with insomnia. The other(106) was also a pooled analysis including two RCTs and assessing the efficacy and safety of zaleplon 5 and 10 mg with zolpidem 5 mg and placebo in a large population of elderly outpatients (986 patients) with insomnia. Individual study data have been requested from the involved company but no data has yet been received. One additional RCT was identified within a previously published review(44). It compared zaleplon 10 and 20 mg zolpidem 10 mg and a placebo in patients with primary insomnia (130 patients). A request to the author revealed that the study was part of a pan-European multicentre study initiated by the pharmaceutical company Wyeth Ayerst. The author did not have access to the data. Identification of this study occurred in the final stages of the preparation of this report. It has not yet been possible to ascertain if the data from these studies are already included in this review. This is being investigated.

Table 4A: Summary of included clinical studies:

Zolpidem/ Nitrazepam	Zolpidem/ Temazepam	Zopiclone/ Lormetazepam	Zopiclone/ Nitrazepam	Zopiclone/ Temazepam	Zaleplon/ Zolpidem	Zolpidem/ Zopiclone
KAZAMATSURI 1993(86) KUDO 1993(88)	KERKHOF 1996(89) LEPPIK 1997(82)	ANSOMS 1991(83)	AGNOLI 1989(84) ANDERSON 1987(85) JOVANOVIC 1983(90) KLIMM 1987(87) OHTOMO 1 1985(91) OHTOMO 2(92) PULL 1983(93) TAMMINEN 1987(94)	NGEN 1990(95) STIP 1999(96) Van der KLEIJN 1989(97) WHEATLEY 1985(98)	ALLAIN 2001(99) ANCOLI-ISRAEL 1999(102) ELIE 1999(100) FRY 2000(101) ZAMMIT 1 2000(103) ZAMMIT 2 2000(103)	TSUTSUI 2001(104)

4.1.2 Study characteristics

The 24 included studies involved a total study population of 3909 patients, ranging in size from 10 patients(90) to 615 patients.(100) Thirteen studies had fewer than 100 patients in total; only three studies(100-102) had over 500 patients.

Fifteen of the included studies were multicentred. Of these, six were conducted in Europe (83-85, 89, 94, 99), five in Japan (86, 88, 91, 92, 104), three in the USA(82, 101, 102), and one in Canada and Europe.(100) The remainder were single centred. Five were carried out in Europe(87, 90, 93, 97, 98), two (published in one report) in the USA(103) and one each in Malaysia(95) and Canada.(96)

The majority of studies incorporated key characteristics of the DSM IV criteria for the diagnosis of insomnia. One study did not state insomnia criteria,(93) and three listed only that participants experienced sleep difficulties.(98, 99, 104)

Seven studies(82, 95, 97, 98, 100-102) acknowledged funding from a pharmaceutical company for the trial, while one(104) stated they received the drugs used in the trial from a pharmaceutical company. In ten of the included studies, at least one of the co-authors was an employee of a pharmaceutical company.(83, 85, 87, 90, 93, 94, 99-102)

Study duration varied and ranged from from one night(93)to six weeks(94). In ten studies(82, 85, 89, 90, 96, 97, 100-102, 104) clinical follow-up after the end of the study was available, ranging from three(100, 101) to 11 days.(89)

Details of study characteristics are provided in *Table A4* within Appendix 3.

4.1.3 Participant characteristics

Patients were primarily female. The lowest proportion of females was seen in the study by Ansoms and colleagues(83) (zopiclone group 37%, lormetazepam group 28%) and the highest was in the study by Klimm and colleagues (80%).(87) The mean age of patients (reported in 15 studies) varied across the trials ranging between 30.1(90) and 73.2 years.(87)

Three studies(82, 91, 92) included only patients over 60 years of age and two studies (87, 102) included those aged over 65 years. Six studies included patients diagnosed with a psychiatric disorder. Of these, four(84, 96, 100, 101) included patients with mild non-psychotic psychiatric disorders, one(93) only included patients hospitalised for depression, schizophrenia or alcoholism, and one study(86) only included those with schizophrenia and manic-depressive psychosis. One study(83) only included alcoholic patients who had undergone a withdrawal period.

Participant characteristics are presented in *Table A5* in Appendix 3.

4.1.4 Quality assessment

The methodological quality of the included studies is presented in *Table 4B* using the criteria based on the CRD Report No.4 (see *Appendix 2*).(81) The CRD checklist includes key aspects of RCT design and quality.

Overall, the methodological quality of the included studies was poor. The studies varied in the level of detail for reporting outcomes. Of the 24 included studies, 21 reported that they used randomisation to allocate participants to a study group, but only one study reported the method of randomisation or whether the allocation sequence was concealed.(95)

The baseline comparability for each treatment group was adequately or partially presented in 16 studies and adequately or partially achieved in ten studies. All studies presented the participant eligibility criteria but co-interventions were not reported in any of the included studies.

All included studies were described as double blind but made no mention of methods of blinding or reported assessment of the blinding procedure. Fifteen studies reported the number of and reason for withdrawals. Only four studies(87, 90, 98, 99) appeared to include an intention-to-treat-analysis.

Table 4B: Quality Assessment of included studies

	Randomisation:			Baseline comparability				Blinding:				Withdrawals		
Checklist items	Truly Random	Allocation concealment	Number stated	Presented	Achieved	Eligibility criteria specified	Co-interventions identified	Assessors	Administration	Participants	Procedure assessed	>80% in final analysis	Reasons stated	Intention to treat
ALLAIN* 2001(99)	NS	NS	✔	NS	NS	✔ ✘	NS	NS	✔	✔	NS	✔	NA	✔
AGNOLI 1989(84)	NS	NS	✔	NA	NA	✔	✘	NS	✔	✔	NS	✔	✘	✘
ANCOLI-ISRAEL 1999(102)	NS	NS	✔	✔	✔ ✘	✔	✘	NS	✔	✔	NS	✔	✔	✘
ANDERSON 1987(85)	NS	NS	✔	✔ ✘	✔ ✘	✔	✘	NS	✔	✔	NS	✔	✔	✘
ANSOMS 1991(83)	NS	NS	✔	✔ ✘	✔ ✘	✔	✘	NS	✔	✔	NS	✔	✔	✘
ELIE 1999(100)	NS	NS	✔	✔	✔ ✘	✔	✘	NS	✔	✔	NS	✔	✔	✘
FRY 2000(101)	NS	NS	✔	✔	✔ ✘	✔	✘	NS	✔	✔	NS	✔	✔	✘
JOVANOVIC 1983(90)	NS	NS	✔	✔ ✘	✔ ✘	✔	✘	NS	✔	✔	NS	✔	NA	✔
KAZAMATSURI 1993(86)	NS	NS	✔	✔	✔	✔	✘	NS	✔	✔	NS	✔	✔	✘
KERKHOF* 1996(89)	NS	NS	✔	NS	NS	✔ ✘	NS	NS	✔	✔	NS	✔	✔	✘
KLIMM 1987(87)	NS	NS	✔	✘	✘	✔	✘	NS	✔	✔	NS	✔	✔	✔
KUDO 1993(88)	NS	NS	✔	✔	✔	✔	✘	NS	✔	✔	NS	✔	✔	✘
LEPPIK 1997(82)	NS	NS	✔	✔ ✘	✔ ✘	✔	✘	NS	✔	✔	NS	✔	✔ ✘	✘
NGEN 1990(95)	✔	✔	✔	✔ ✘	✔ ✘	✔	✘	NS	✔	✔	NS	✘	✔ ✘	✘
OHTOMO 1 1985(91)	NS	NS	✔	✔	✔	✔	✘	NS	✔	✔	NS	✔	✔	✘
OHTOMO 2 1985(92)	NS	NS	✔	✔	✔	✔	✘	NS	✔	✔	NS	✔	✔	✘
PULL 1983(93)	NS	NS	✔	NA	NA	✔	✘	NS	✔	✔	NS	✔	✔	✘
STIP 1999(96)	NS	NS	✔	✔	✔	✔	✘	NS	✔	✔	NS	✔	✔	✘
TAMMINEN 1987(94)	NS	NS	✔	✔	✔	✔	✘	NS	✔	✔	NS	✘	✔	✘
TSUTSUI 2001(104)	NS	NS	✔	✔	✔ ✘	✔	✘	NS	✔	✔	NS	✔	✔	✘
Van der KLEIJN 1989(97)	NS	NS	✔	NA	NA	✔	✘	NS	✔	✔	NS	✔	✘	✘
WHEATLEY 1985(98)	NS	NS	✔	NA	NA	✘	✘	NS	✔	✔	NS	✔	NA	✔
ZAMMIT 1&2* 2000(103)	NS	NS	✔	✘	✘	✔ ✘	NS	NS	✔	✔	NS	✔	✘	✘

✔ yes (item adequately addressed), ✘ no (item not adequately addressed), ✔/✘ partially (item partially addressed), NA not applicable or NS not stated. * Quality assessment based on conference abstract only

4.1.5 Clinical results and analysis

Results have been grouped by treatment with results from the studies examining Z-drugs versus benzodiazepines first, followed by head-to-head comparisons of Z-drugs.

In assessment of sleep outcomes, ten studies included placebo groups and compared active treatment to placebo alone, assessing significance of change from baseline within each group. Direct comparisons between active treatments were not always presented. We report all significant findings when direct between-treatment comparisons in the studies were made. However, the findings should be interpreted with caution: there is evidence of multiple significance testing of data in most studies, which increases the chance of spurious findings. In cases where direct between-treatment comparisons were not made by authors and insufficient data were available for us to formally assess between-treatment differences, the results are described in a qualitative manner to allow the detection of any trends. Data from the run-in baseline period and final week of treatment were extracted to determine the efficacy of the treatments. None of the studies reported sample size calculations, which may be an indication of insufficient power.

Sleep efficacy outcomes reported include patients' estimates of sleep onset latency, total sleep duration, number of awakenings and quality of sleep, recorded from post-sleep questionnaires and from sleep diaries in all but three studies. The study by Jovanovic 1989(90) and two studies reported by Zammit 2000(103) used polysomnographic tracings in a sleep laboratory to establish sleep outcomes. In all studies, a variety of rating scales were used for reporting quality of sleep.

Reporting of adverse events was not consistent across the studies. Some studies reported on all adverse effects whereas others reported treatment-emergent adverse events, which were defined as new events that began after the first dose of active treatment or events that worsened during therapy. These generally include central nervous system (CNS) related events (e.g. dizziness, daytime drowsiness, nervousness, light-headedness, headache and fatigue) and those not related to the CNS (e.g. gastrointestinal symptoms).

Key outcomes extracted from the included studies are presented in *Table A6* in Appendix 3. The summary of results related to the key outcomes is provided in Table *4C*.

Ten trials had a period of post-treatment follow-up. These data offer some information regarding rebound insomnia, or temporary worsening from baseline (*Table A7*, in Appendix 3). All data are self-reported except in the Jovanovic 1983 study.(90)

Forest plots of the meta-analysis are included in *Figures 4A* to *4C*. Summary details describing the psychomotor, memory, mood and patient satisfaction outcomes and the specific measures utilised in the included studies are provided in *Table A8* in Appendix 3.

Zolpidem versus Nitrazepam

Two studies by Kazamatsuri 1993(86) and Kudo 1993,(88) compared zolpidem (10 mg) with nitrazepam (5 mg).

Sleep onset latency

Both studies reported data on sleep latency. No significant differences were found between treatments by Kazamatsuri 1993.(86) Kudo 1993(88) reports a non-significant improvement, with 68.4% of patients on zolpidem experiencing an improvement in sleep onset latency during the trial compared to 56.4% on nitrazepam.

Total sleep duration

Kazamatsuri 1993(86)reports on sleep duration, indicating no significant differences between the two drugs.

Number of awakenings

Kazamatsuri 1993(86) reports significantly fewer awakenings with zolpidem (p=0.031).

Quality of sleep

Kudo 1993(88) reports results in favour of zolpidem over nitrazepam regarding improvement in the quality of sleep, but authors did not make a direct statistical comparison of this difference using a significance test. Overall 66.7% of patients taking zolpidem reported an improvement in sleep quality compared to just 37.5% on nitrazepam.

Adverse events

Both studies(86, 88) in this group reported data concerning side effects (e.g. dizziness, sleepiness, insomnia, fatigue, headache). Meta-analysis of binary data in this group was possible, and the difference between treatments was not statistically significant with an odds ratio (95% CI) for side effects on zolpidem compared to nitrazepam of 0.70 (0.37 to 1.30).

Daytime alertness

Neither study reported a statistically significant difference between active treatment groups regarding mental and physical status on awakening and during the day.

Global impression of treatment

Kudo 1993(88) reported a global improvement rate of 65.6% in the zolpidem group and 52.2% in the nitrazepam group and Kazamatsuri 1993(86) reported a rate of 58.9% in the zolpidem group and 58.1% in the nitrazepam group. Neither of these differences was statistically significant (χ^2 test).

Zolpidem versus Temazepam

Two studies compared these agents. In Leppik 1997(82) (compared zolpidem 5 mg with temazepam 15 mg) sleep onset latency data were reported as being skewed and therefore sleep duration data were likely to be skewed also (i.e. distribution of measurements is asymmetrical and therefore not appropriate for meta-analysis). Kerkhof 1996(89) compared zolpidem 10 mg with temazepam 20 mg.

Sleep onset latency

Leppik 1997(82) reported no significant differences between zolpidem and temazepam with regard to sleep latency whereas Kerkhof 1996(89) reported significantly favourable results for sleep latency in the zolpidem group (after ten days' treatment and 11 days' follow-up: zolpidem 38.8 min, temazepam: 61.6 min, p= 0.05).

Total sleep duration

Leppik 1997(82) presented data on sleep duration but direct comparisons between treatments were not reported. Zolpidem resulted in a slightly larger increase of sleep duration from baseline than temazepam, but the statistical significance of this difference could not be assessed from the extracted data, as the variable was skewed.

Quality of sleep

Kerkhof 1996(89) reported significant improvements with regard to subjective estimates of sleep quality for the zolpidem group compared to the temazepam group (p= 0.03). However, the measurement scale was not defined.

Adverse events

Leppik 1997(82) reported very similar proportions of subjects experiencing treatment-emergent adverse events (63% on zolpidem, 67% on temazepam). The resultant OR of 0.87 (95% CI 0.46 to 1.64) indicates that this difference was not statistically significant.

Tolerance

Leppik 1997(82) reported data for sleep onset latency and duration on a weekly basis. Both zolpidem and temazepam showed improvements in those outcomes from week 1 to week 4, except for sleep duration, which decreased insignificantly from week 1 to week 4 in the temazepam group.

Rebound insomnia

Leppik 1997(82) reported that, for sleep latency and duration, no rebound effects were found in each of the active treatment groups and the only observed significant differences from baseline were improvements. Sleep quality deteriorated on the first night after withdrawal compared to baseline in both treatment groups.

Daytime alertness

Leppik 1997(82) used a morning questionnaire to assess morning sleepiness and ability to concentrate. The study reports that statistically significant differences were "sporadically noted" for these, as well as other secondary outcomes (ease of falling asleep, number of awakenings, wake time after sleep onset, sleep quality). However, no consistent pattern was noted.

Global impression of treatment

In Leppik 1997(82) a global impression of therapy was elicited but no direct comparisons for active treatment groups were undertaken.

Zopiclone versus Lormetazepam

Only one study by Ansoms 1991 compared zopiclone (7.5 mg) and lormetazepam (1 mg).(83)

Sleep outcomes

Data were extracted on sleep onset latency, total sleep duration, number of awakenings, quality of sleep and adverse events. Medians were calculated from raw data given in the paper. All outcomes were measured on a five-point ordinal scale. Lormetazepam resulted in shorter sleep onset latency than zopiclone, and this was the only statistically significant difference between treatments ($p = 0.013$).

Adverse events

The percentage of patients who reported adverse effects was similar in both groups (26% in the zopiclone group compared to 28% in the lormetazepam group).

Global impression of treatment

The study utilised a four-point categorical scale (excellent, good, fair and poor), rated by the investigator, to assess medication efficacy and tolerability (overall safety) after active treatment, but no significant difference was found between treatment groups.

Zopiclone versus Nitrazepam

Eight studies compared zopiclone with nitrazepam. Agnoli 1989(84), Anderson 1987(85), Jovanovic 1983(90), Klimm 1987(87), Ohtomo 1 1985(91) and Tamminen 1987(94) compared zopiclone 7.5 mg with nitrazepam 5 mg; Ohtomo 2(92) 1985 compared zopiclone 5 mg with nitrazepam 5 mg and Pull 1983(93) compared two doses of zopiclone (7.5 and 15 mg) with nitrazepam (5 and 10 mg). Of these, studies by Agnoli 1989(84) and Pull 1983(93) were crossover trials. However, there was no washout period in Pull 1983 so the results were not included in the meta-analysis. Agnoli 1989(84) presented data from each treatment pooled over both sequence groups, so within subject paired comparisons were not possible.

Sleep onset latency

Data on sleep onset latency were extracted from six trials, but only Agnoli 1989(84), Tamminen 1987(94) and Klimm 1987(87) reported both means and standard deviations. Data from Tamminen 1987(94) were skewed and therefore excluded from the forest plots. Klimm 1987(87) presented data from a scale of 0 (fast) to 100 (slow) in terms of means and standard deviations of changes from baseline, while Agnoli 1989(84) presented means and standard deviations at baseline and the end of treatment separately. Sleep onset latency data from Agnoli 1989(84) were extracted from a graph and indicated actual latency time in minutes. Means from both studies were negated for the forest plots, as a decreased mean denoted improvement in sleep onset latency. Meta-analysis of this data was not possible, as the units of measurement differed between studies, and it was decided that change scores and final values should not be combined in a meta-analysis of standardised mean differences.

Klimm 1987(87) reported mean differences between the first day of the active treatment and the last day of the placebo run-in period for sleep latency and the Spiegel Sleep Questionnaire was used to assess sleep onset latency. The authors found only one significant difference between the two groups: nitrazepam resulted in a

greater reduction in sleep onset latency on the fifth day (out of seven) of treatment than zopiclone ($p<0.001$).

In the crossover study Agnoli 1989(84) reported sleep latency was significantly shorter after zopiclone was administered ($p<0.001$) than after nitrazepam.

Data regarding sleep onset latency were extracted from a graph given in Anderson 1987.(85) However, direct comparisons between treatment groups were not made in the paper, and no formal statistical testing could be carried out using the extracted data. However, nitrazepam was observed to lead to a slightly greater reduction in sleep onset latency from baseline compared to zopiclone.

In the sleep laboratory study, Jovanovic 1983(90) reported a borderline statistically significant difference ($p<0.08$) between the groups during the early period of active treatment with patients taking zopiclone having shorter sleep latency than those taking nitrazepam. However, they also acknowledge that, as 50 statistical tests were carried out in this study and that the number of statistically significant differences they obtained between the groups was in the range of that expected purely by chance, great emphasis should not be placed on this result.

Pull 1983(93) compared two doses of zopiclone (7.5 and 15 mg) with nitrazepam (5 and 10 mg) in a cross-over trial with no washout between treatments. There appears to be a dose-response relationship in both drugs, as increased doses of zopiclone and nitrazepam resulted in more favourable results for sleep onset latency, but no significant differences were observed in sleep onset latency between nitrazepam (10 mg) and zopiclone (15 mg) or between nitrazepam (5 mg) or zopiclone (7.5 mg). However, results from this trial should again be interpreted with caution, given the lack of washout period between treatments and a small sample size (acknowledged by the authors).

Tamminen 1987(94) reported a trend in favour of zopiclone in terms of sleep latency (>30 min, zopiclone 38%, nitrazepam 44.4%, after active treatment, $p=0.07$).

Total sleep duration

Klimm 1987(87) used the Spiegel Sleep Questionnaire to assess duration of sleep and reported no significant difference between treatment groups. In the studies by Agnoli 1989(84) and Tamminen 1987,(94) no significant differences in duration of sleep between treatments were found.

In Jovanovic 1983(90) a trend in favour of zopiclone was observed in a change from the baseline but the authors did not report the difference between treatment groups as being significant.

In Pull 1983,(93) increased doses of zopiclone and nitrazepam resulted in increased sleep duration. However, the differences in sleep duration between nitrazepam (10 mg) and zopiclone (15 mg) or between nitrazepam (5mg) or zopiclone (7.5mg) were not statistically significant.

Two Japanese studies(91, 92) reported on sleep duration but only Ohtomo1 1985(91) observed a statistically significant difference ($p<0.05$) between treatments in favour of zopiclone.

Number of awakenings

Six of the included studies in this comparison group reported on the number of awakenings. Klimm 1987(87) used the Spiegel Sleep Questionnaire to assess the number of awakenings but found no significant difference between treatment groups. In the crossover studies by Agnoli 1989(84) and Tamminen 1987,(94) the difference in the number of nocturnal awakenings between treatments was not statistically significant.

In Pull 1983,(93) increased doses of zopiclone and nitrazepam resulted in more favourable results for the number of awakenings, but neither of the differences in the number of awakenings between nitrazepam (10 mg) and zopiclone (15 mg) or between nitrazepam (5 mg) and zopiclone (7.5 mg) were statistically significant.

Two Japanese studies (91, 92) report on the number of awakenings. Both trials reported no significant differences between treatment groups regarding the number of awakenings.

Quality of sleep

Seven studies reported on sleep quality. Klimm 1987,(87) Agnoli 1989,(84) and Tamminen 1987(94) report no difference in quality of sleep measures.

Only Tamminen 1987(94) and Klimm 1987(87) reported both means and standard deviations. Tamminen 1987(94) indicated final scores from a scale from 0 (good) to 100 (bad) but the data were skewed and therefore not shown on the forest plot. Klimm 1987(87) presented changes from baseline from a scale from 0 (bad) to 100 (good).

Data regarding quality of sleep were extracted from a graph given in the study by Anderson 1987(85) but no direct comparisons were made between the active treatment arms. Although no formal statistical testing could be carried out using the extracted data, it was observed that the use of zopiclone resulted in a slightly greater improvement in quality of sleep from baseline compared to nitrazepam.

In Pull 1983,(93) increased doses of zopiclone and nitrazepam resulted in more favourable results for quality of sleep, but neither of the differences in sleep quality between nitrazepam (10 mg) and zopiclone (15 mg) or between nitrazepam (5mg) and zopiclone (7.5mg) were reported as being statistically significant.

Two Japanese studies(91, 92)in this group report on quality of sleep. Of these, Ohtomo 1 1985(91) reported a significant difference between treatment groups in favour of zopiclone ($p<0.05$), while no significant difference between treatment groups was detected in the Ohtomo 2 1985(92)

Adverse events

Only two studies (Ohtomo 1 1985(91) and Ohtomo 2 1985(92)) comparing zopiclone with nitrazepam provided data regarding adverse event rates. The difference between

treatments was not statistically significant. (OR (95%CI) for side-effects on zopiclone compared to nitrazepam 1.46 (0.65,3.30)).

Tolerance

The 6-week trial by Tamminen 1987(94) presented week 2 and week 6 data on sleep onset latency and quality of sleep for zopiclone and nitrazepam. There was a 24% deterioration between weeks 2 and 6 of sleep quality, but a slight improvement in sleep onset latency, in the nitrazepam group. In the zopiclone group, both outcomes showed improvements from week 2 to week 6.

Data on tolerance could not be statistically assessed, as standard deviations were not provided for the changes between initial and final treatment periods.

Rebound insomnia

Two included studies, which compared zopiclone with nitrazepam, included post-treatment follow-up, which allowed assessment of rebound insomnia. The study by Anderson 1987(85) reported no significant change in sleep measures between baseline and follow-up placebo week in either the zopiclone or nitrazepam group. Data extracted on sleep latency and quality show an improvement in both groups in the follow-up week compared to baseline. Jovanovic 1983(90) reported average data for the first 3 nights post-treatment. No deteriorations from baseline were observed in either zopiclone or nitrazepam in the main sleep efficacy outcomes. Nights nine and ten after withdrawal show a statistically significant deterioration in the number of awakenings for nitrazepam patients relative to baseline, but no other deteriorations are observed in either treatment group on nights 9 and 10 relative to baseline.

Formal between-treatment assessment of these data could not be carried out as authors presented means only.

Alertness

Alertness/feeling upon awakening

Two Japanese studies (Ohtomo 1 1985(91) and Ohtomo 2 1985(92)) measured mental and physical alertness on awakening. The first study (91) found a significant difference ($p<0.05$) in favour of zopiclone for both mental and physical alertness, but no significant difference was found in the second study.(92)

The study by Agnoli(84) reported a significantly better quality of daytime arousal after zopiclone ($p<0.01$).

Tamminen and Hansen(94) reported no significant difference between the groups in feeling upon awakening.

Daytime alertness

Two Japanese studies (Ohtomo 1 1985(91) and Ohtomo 2 1985(92)) measured next-day mental and physical condition. The first study (91) reported a significant difference ($p<0.05$) in favour of zopiclone for next day mental condition and a trend in favour of zopiclone ($p<0.1$) for next-day physical condition. The second study(92) found no significant difference in these outcomes between groups.

Agnoli 1989(84) assessed daytime alertness levels evaluated by the Toulouse-Pieron Attention Test and found significant differences in favour of zopiclone at the end of treatment (omitted items, $p<0.05$; execution time, $p<0.01$).

In Anderson 1987,(85) a subjective assessment of residual effects was carried out each day by patients shortly after rising. Patients on zopiclone judged themselves to be significantly more wide-awake in the morning than did those on nitrazepam.

In Klimm 1987,(87) the comparison between the two active treatment groups showed only two significant differences: patients on zopiclone felt more alert in the morning than those receiving nitrazepam on two out of seven active treatment days (day 9, $p<0.02$ and day 11, $p<0.01$). The Syndrom Kurztest was used to assess short-term memory and concentration and the authors report no significant differences in these outcomes between active treatment groups.

In Pull 1983(93) a cancellation test was used to assess vigilance and awakening, but no statistically significant difference was found between groups. A memory test showed a trend ($p<0.1$) in favour of zopiclone.

Tamminen 1987(94) used psychomotor tests (symbol copying, digit symbol substitution, tapping rate and auditory reaction time) to assess residual effects but no significant differences were found between groups. However, a trend in favour of zopiclone ($p=0.1$) was found on assessment of tapping rate scores. Baseline scores for the reaction time test were very imbalanced between groups; on average patients in the zopiclone group scored much higher. This meant that despite the dramatic decrease in reaction time in the zopiclone group, final scores were similar between groups.

Global impression of treatment

Ohtomo 1 1985(91) reported a significantly higher global improvement rate ($p<0.05$) with zopiclone compared to nitrazepam while Ohtomo 2 1985 (92) reported no significant difference in global improvement between treatments.

Anderson 1987,(85) Pull 1983(93)and Tamminen 1987(94) reported no difference in global assessment of efficacy between treatments.

Zopiclone versus Temazepam

Four trials(95-98) compared zopiclone and temazepam. Van der Kleijn 1989(97) and Wheatley 1985(98) were crossover trials. Data provided by Wheatley were not included in the meta-analysis, as there was no washout period reported. The trial by Stip 1999(96) compared temazepam 30 mg with zopiclone 7.5 mg, while the remaining three trials compared zopiclone 7.5 mg with temazepam 20 mg.

Sleep onset latency

Ngen 1990,(95) Van der Kleijn 1989,(97), Stip 1999(96) and Wheatley 1985(98) all reported data on sleep onset latency.

Ngen 1990(95) did not compare zopiclone and temazepam directly. Comparisons were made with baseline only. Although the sleep latency results from the last week

of the trial favour temazepam (mean sleep latency in minutes): 64.5 for zopiclone and 26.1 for temazepam), it should be noted that there was a great imbalance between mean sleep latency in the two groups at baseline (122.8 for zopiclone and 50.4 for temazepam) and that the two treatments resulted in very similar relative reduction of sleep latency (47% reduction in zopiclone group compared to 48% in temazepam group).

Both van der Kleijn 1989(97) and Wheatley 1989(98) report no significant treatment differences related to latency of sleep onset. However Van der Kleijn 1989(97) reports a trend favouring zopiclone (p= 0.106). Results from Wheatley 1985(98) should be interpreted with caution, however, as there was no washout period in this crossover study. Stip 1999 (96) collected data on sleep onset latency but only comparisons with the placebo were made.

Total sleep duration

In Ngen 1990,(95) comparisons were made against baseline only. However zopiclone resulted in a greater improvement from baseline in duration of sleep (average increase of 99 minutes) compared to temazepam (average increase of 42 minutes) ($p<0.01$)**.**

Wheatley 1985(98) reports a statistically non-significant between-drug difference of sleep duration (396 minutes for both zopiclone and temazepam), but there was no washout period in this crossover study so results should be interpreted with caution.

Number of awakenings

Number of awakenings was reported by Ngen 1990,(95) Stip 1999,(96) and Wheatley 1985.(98)

The study by Ngen 1990(95) did not compare zopiclone and temazepam directly; comparisons were made against baseline only and mean values were given. Zopiclone resulted in a smaller improvement in number of awakenings (average 0.33 fewer awakenings) compared to temazepam (average decrease of 0.72 awakenings).

Wheatley 1985(98) reported that the between-drug difference of the number of awakenings was not statistically significant, but there was no washout period in this crossover study so results should be interpreted with caution.

In Stip 1999(96) no direct comparisons between treatments were made by the authors but extracted data indicated a trend in favour of zopiclone.

Quality of sleep

Van der Kleijn 1989(97) and Wheatley 1985(98) presented data on quality of sleep. Van der Kleijn 1989(97) reported a trend favouring zopiclone (average mean scores over 5 days: zopiclone: 3.9, temazepam: 3.8; p=0.1) whereas Wheatley 1985 reported no significant difference between drugs.

Adverse events

Only van der Kleijn and colleagues(97)and Wheatley(98) present data regarding adverse side-effects. Van der Kleijn 1989(97) does not make a formal comparison of adverse event rates but presents rates in favour of temazepam (26% of patients on

zopiclone report side-effects (headache, perspiration, trembling/shaking, lightheadedness and nervousness) compared to 17% on temazepam). Wheatley 1985(98) reports a statistically non-significant between-drug difference in terms of adverse events (e.g. daytime drowsiness, migraine).

Rebound insomnia

Two included studies(96, 97), included follow-up data which could be compared to baseline. From the cross-over study by Van der Kleijn 1989(97), data on the last placebo run-in and first placebo follow-up/washout night could be compared. Extracted data suggest that there is worsening in both sleep quality and sleep onset latency following treatment with zopiclone compared to baseline. The temazepam group experienced less deterioration from baseline in sleep quality and none in sleep onset latency. The authors state that, following zopiclone, sleep onset latency was significantly worse than after temazepam.

Data given by Stip 1999(96) indicates that the mean score relating to quantity of nocturnal awakenings had deteriorated in the temazepam group in the follow-up week compared to baseline, but the deterioration was not reported as statistically significant. Scores on nocturnal awakenings for patients on zopiclone had not deteriorated.

Alertness

No significant differences between active comparator groups were found in this comparator group for daytime alertness.

Ngen 1990(95) assessed psychomotor function using the Leeds Psychomotor Tester (choice reaction time and cricital flicker fusion) and a letter cancellation test but no direct comparisons were made.

Stip 1999(96) assessed memory, alertness, attention and concentration and found no statistically significant differences between groups.

In Van der Kleijn 1989(97) no statistically significant difference was found between groups on awakening.

Wheatley 1985(98) assessed state on awakening and condition at work, with others and driving. No statistically significant differences were found for any of these outcomes between groups.

Global impression of treatment

Global assessment of efficacy was compared between groups but no statistically significant difference was found.

Zaleplon versus Zolpidem

Six studies compared zaleplon with zolpidem.(99-103) Of these, two(100, 101) compared three doses of zaleplon (5, 10 and 20 mg) with zolpidem (10 mg), one(102) compared two doses of zaleplon (5 and 10 mg) with zolpidem (5 mg) and three(99, 103) compared zaleplon (10 mg) with zolpidem (10 mg).

Sleep onset latency

Comparisons made in the studies by Zammit 2000(103) and Allain 2001(99) were with placebo only, and no sleep latency data were available to compare the effects of active treatments (available only as abstract). Elie 1999(100) and Fry 2000(101) did not make direct comparisons between active treatments, but a significant dose-response trend with increasing doses of zaleplon was reported in both studies: the higher the dose, the shorter the sleep onset latency. Ancoli-Israel 1999(102) reported that sleep latency was significantly shorter with zaleplon (10 mg) compared to zolpidem (5 mg) during both weeks of treatment ($p<0.001$). In real terms this is derived from a reported median sleep latency with zaleplon (10 mg) of 31 minutes and with zolpidem (5 mg) of 42 minutes. A similar trend is observed in Elie's study, where zolpidem (10 mg) resulted in a longer sleep onset latency throughout the four weeks of treatment.

Total sleep duration

Six studies(99-103) in this group evaluated total sleep duration. Comparisons made in the studies by Zammit 2000(103) were with placebo only, and no sleep duration data were available to compare the effects of active treatments.

No direct comparisons were made between active treatment arms in Elie 1999(100) and Fry 2000.(101) However, Ancoli-Israel 1999(102) reports that the median sleep time was significantly less in the zaleplon (5mg) group compared to the zolpidem (5mg) group during both weeks of treatment (290.7 minutes and 308.57 minutes, respectively; $p<0.05$). In Elie 1999(100) and Fry 2000(101), a similar trend is observed, as the change in median values from baseline is greater in the zolpidem group than in the zaleplon groups.

In Allain 2001,(99) the authors state that there were no significant differences observed between the treatment arms related to total sleep duration (8.3 hours for zolpidem and 8 hours for zaleplon).

Number of awakenings

Two studies in this group(100, 101) reported data on the median number of awakenings, but direct comparisons were not made.

Quality of sleep

Four studies evaluated sleep quality.(99-102) Of these, Elie 1999{Elie, 1999 #125}, Fry 2000{Fry, 2000 #146} and Ancoli-Israel 1999{Ancoli-Israel, 1999 #291} reported results in terms of median sleep quality as well as the percentage of patients with improved sleep quality relative to baseline for each week of treatment. There was no consistent trend observed between zaleplon groups and therefore the results from the zaleplon groups were pooled from three studies for the meta-analysis. Patients on zaleplon were significantly less likely to experience an improvement in sleep quality than those on zolpidem. The odds ratio when zaleplon is compared to zolpidem for improvement at the end of treatment compared to baseline is 0.66 (95% CI 0.51 to 0.87).

Allain 2001(99) states that there was a statistically significant improvement in quality of sleep favouring zolpidem as measured on both visual analogue scale (VAS) and the

sleep questionnaire (LSEQ) ($p<0.0001$ on both VAS and LSEQ). However, data are not provided to evaluate this result.

Adverse events

Three studies (100-102) reported the frequency of treatment-emergent adverse events, but only Elie 1999(100) and Fry 2000 (101) report sufficient data for inclusion in meta-analysis. No dose response trend was evident among the zaleplon treatment groups and data from these groups were again pooled for the meta-analysis. Treatment with zaleplon was less likely to result in treatment-emergent adverse effects but this difference was not statistically significant. Subjects seemed to be more likely to suffer treatment-emergent adverse events on zolpidem but this was not statistically significant. The odds ratio for adverse events when zaleplon is compared to zolpidem is 0.86, (95% CI 0.62 to 1.20).

Withdrawal symptoms

None of the included studies reported any assessment of dependence. Elie 1999(100) and Fry 2000(101) formally assessed the occurrence of withdrawal symptoms following the discontinuation of therapy with zaleplon (5, 10, or 20 mg), zolpidem (10 mg) or placebo. Both studies used the Benzodiazepine Withdrawal Symptom Questionnaire (a listing of 20 commonly reported symptoms) by Tyrer and colleagues.(107) Both studies report the incidence of withdrawal symptoms on night 1, 2, and 3 after the discontinuation of treatment (when placebos were administered). Elie 1999(100) reported the incidence of three or more new withdrawal symptoms, and Fry 2000 (101) reported the incidence of three or more new or more severe withdrawal symptoms.

Direct comparisons of the incidence of withdrawal symptoms were not made between the active treatments in either study. Instead the incidence in each active treatment group was compared with that in the placebo group. Data on withdrawal could be formally assessed only from the first night of the placebo run-out phase of Fry 2000(101). Patients taking zaleplon were statistically significantly less likely to suffer withdrawal symptoms than those on zolpidem (OR 0.2 (95% CI 0.05 to 0.72), $p=0.01$). There does appear to be a general trend favouring zaleplon from all three nights of the run-out phase from both studies, as patients taking zolpidem tended to be at least 50% more likely to suffer withdrawal as those on zaleplon. The percentage of patients reporting withdrawal symptoms in each group was far higher in Elie 1999(100) than in Fry 2000,(101), but the relative differences between zaleplon and zolpidem were greater in the Fry 2000(101) study.

Tolerance

Two included studies(100, 101) involved a minimum of four weeks active treatment and could thus be used to extract data on tolerance. Data on sleep efficacy outcomes from the first available and final weeks of treatment were extracted. All relevant data were self-report data.

Fry 2000(101) observed no evidence of tolerance in any of the active treatment groups on sleep onset latency, duration, quality, or number of awakenings, comparing week 1 and week 4 data (minor deterioration in two of the 16 data points, compared to 13 improvements and one identical result). The data in Elie 1999(100) presented a

very similar picture, with only improvements (or identical results) reported between the first and final readings on all four outcomes.

Rebound insomnia

Two studies(100, 101) reported the percentage of patients in each group experiencing rebound insomnia after the first placebo run-out night in terms of sleep latency, duration, and number of awakenings. In all groups, some patients experienced rebound. Subjects on zaleplon were statistically significantly less likely to experience rebound insomnia of sleep onset latency, sleep duration and number of awakenings compared with those on zolpidem (OR 0.27 (95% CI 0.17 to 0.44), 0.25 (0.15 to 0.41), 0.34 (0.18 to 0.61) respectively).

Daytime alertness

Two studies by Zammit 2000(103) were the only ones in this comparator group to assess subjective measures of sedation and psychomotor performance. However, there were no direct comparisons made between active treatments.

Global impression of treatment

In the crossover study by Allain 2001(99), it was reported that 62.3% of patients favoured zolpidem compared with 37.7% who favoured zaleplon (p=0.08) when asked to choose between drugs.

Zolpidem versus Zopiclone

Only one study by Tsustsui 2001(104) provided data comparing zolpidem (10 mg) with zopiclone (7.5 mg).

Sleep onset latency

Tsutsui 2001(104) reported data regarding sleep onset latency as percentages with improvement from baseline (scale 1-5). Improvement of one grade or more in sleep onset latency at the end of treatment was significantly higher with zolpidem than with zopiclone (85.8% versus 77.5% respectively, OR 1.72 (95%CI 1.04,2.84)).

Adverse events

Tsutsui 2001(104) reported a statistically significantly lower proportion of patients in the zolpidem group experiencing adverse events ‘related’, ‘possibly related’ or ‘probably related’ to treatment with those in the zopiclone group (OR (95% CI) 0.55(0.37,0.81), p=0.004).

Rebound insomnia

The incidence of rebound in terms of deterioration at the end of a maximum 1-week follow-up relative to baseline was reported. The proportion of patients who experienced deterioration from baseline in sleep onset latency was statistically significantly different between treatment groups (4.5% and 15.4% after treatment with zolpidem or zopiclone respectively; OR 0.28 (95% CI 0.13, 0.60), p=0.005) but none of the other changes in sleep parameters differed significantly between the treatment groups. Overall, sleep onset latency, duration and the number of awakenings remained significantly better in both treatment groups at the end of follow-up relative to baseline.

Dependence

An assessment of dependence took place in the study by Tsutsui(104)at the end of the treatment and follow-up, but no specific data were reported.

Daytime alertness

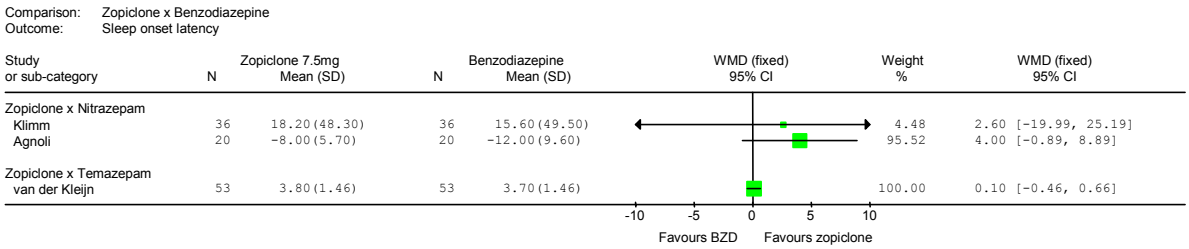
The study assessed daytime physical condition, but no direct comparison was made.

Global Impression of Treatment

The study reports that 69.7% of patients in the zolpidem group were rated by the investigator as “at least moderately improved” using the modified Clinical Global Impression Scale compared to 61.6% in the zopiclone group. However, this difference was not statistically significant.

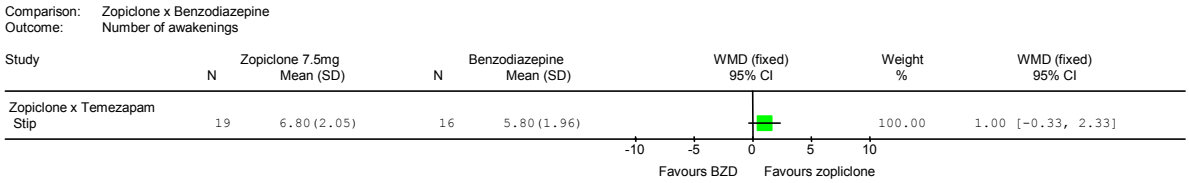
Figure 4A: Z versus Benzodiazepines

i. Sleep onset latency*



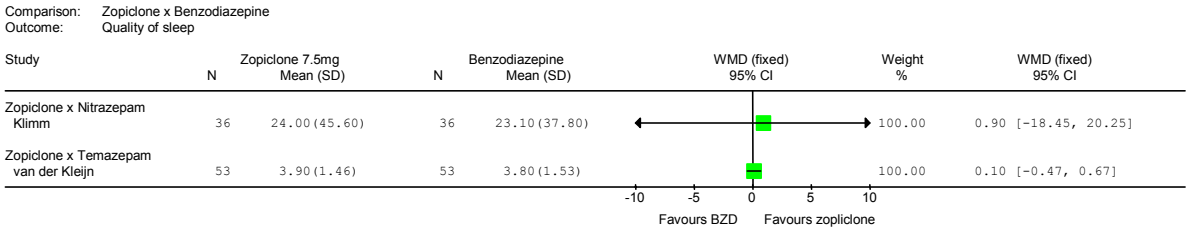
* Agnoli: minutes multiplied by –1; Klimm: change from baseline; scale 0 fast, 100 slow; multiplied by –1, van der Kleijn: scale 1 slow, 5 fast

ii. Number of awakenings*



* Stip: scale unknown, but increase indicates improvement

iii. Quality of sleep*



* Klimm: change from baseline, scale 0 bad, 100 good; van der Klejn: scale 1 bad, 5 good

Figure 4A: (continued) Z versus Benzodiazepines

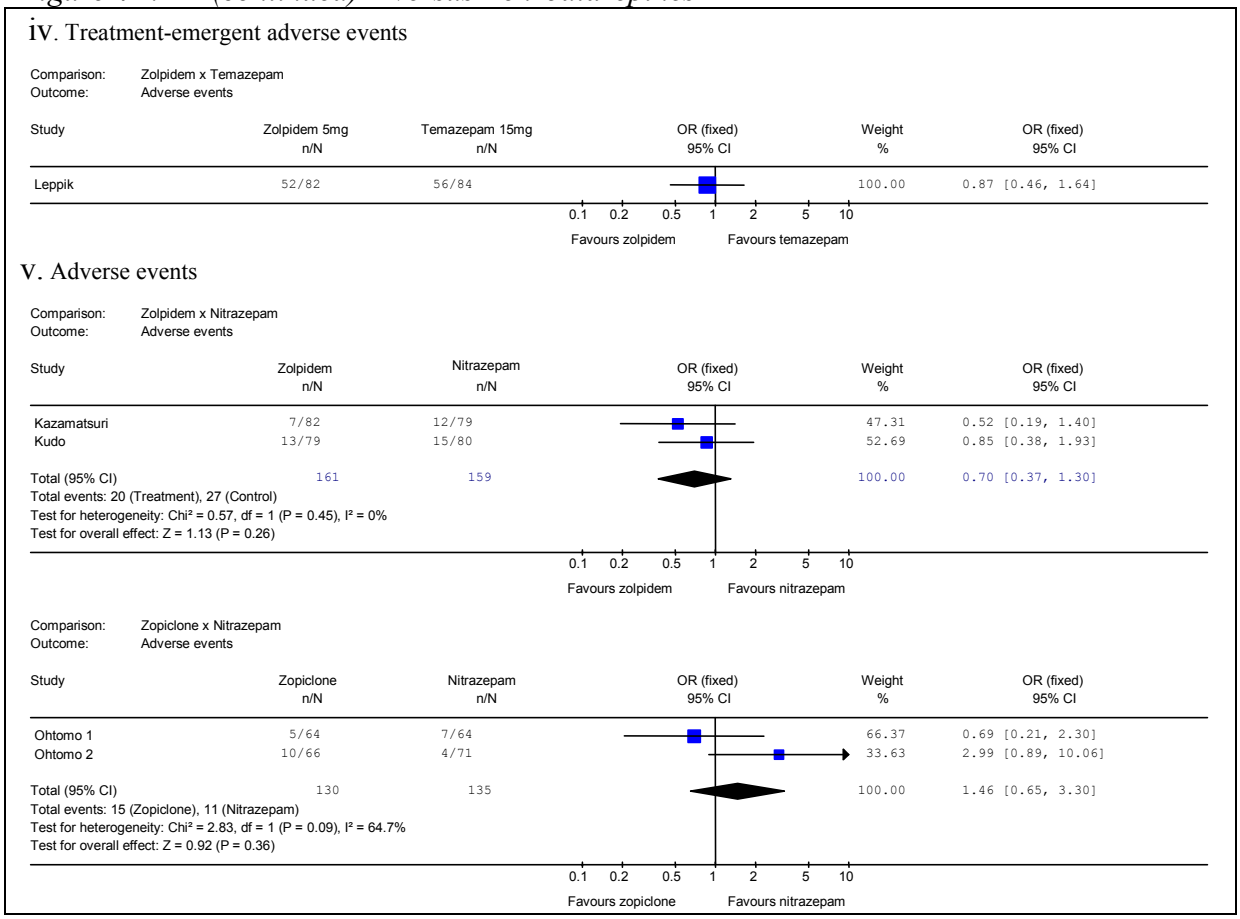
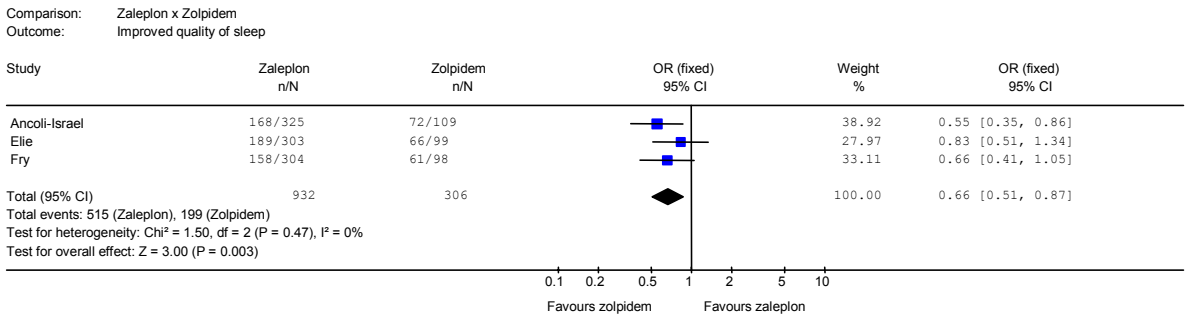


Figure 4B: Zaleplon versus Zolpidem

i. Quality of sleep (%, with improvement at week 4 compared to baseline)



ii. Treatment-emergent adverse events

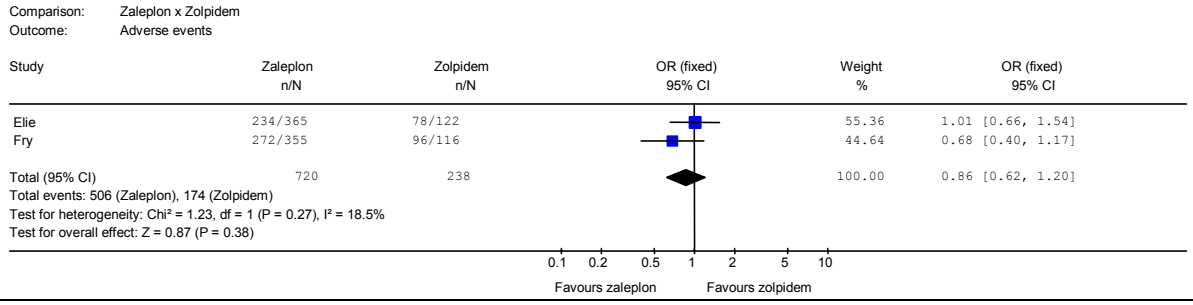
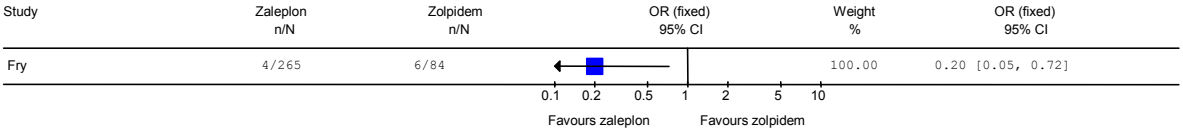


Figure 4B: (Continued) Zaleplon versus Zolpidem

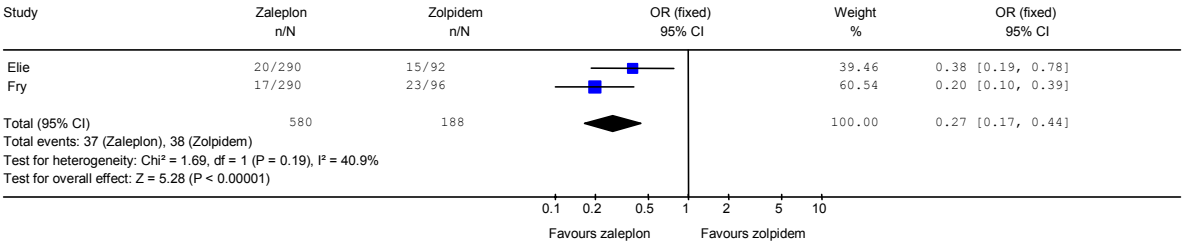
iii. Withdrawal symptoms

Comparison: Zaleplon x Zolpidem
Outcome: Withdrawal



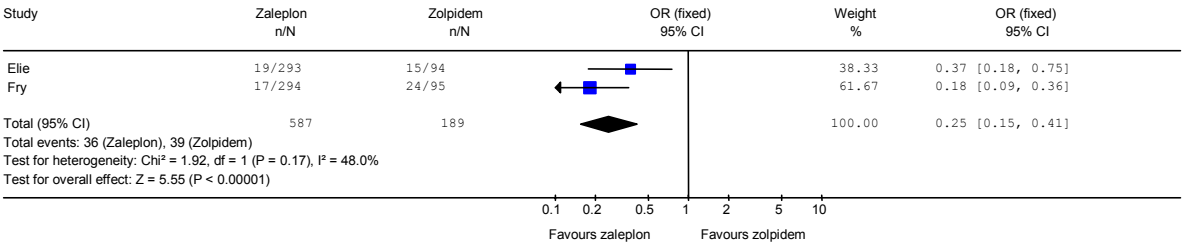
iv. Rebound insomnia concerning sleep onset latency

Comparison: Zaleplon x Zolpidem
Outcome: Rebound insomnia: sleep onset latency



v. Rebound insomnia concerning sleep duration

Comparison: Zaleplon x Zolpidem
Outcome: Rebound insomnia: sleep duration



vi. Rebound insomnia concerning number of awakenings

Comparison: Zaleplon x Zolpidem
Outcome: Rebound insomnia: number of awakenings

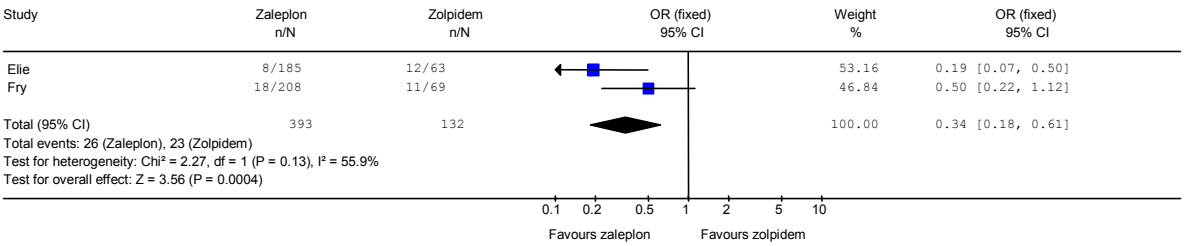
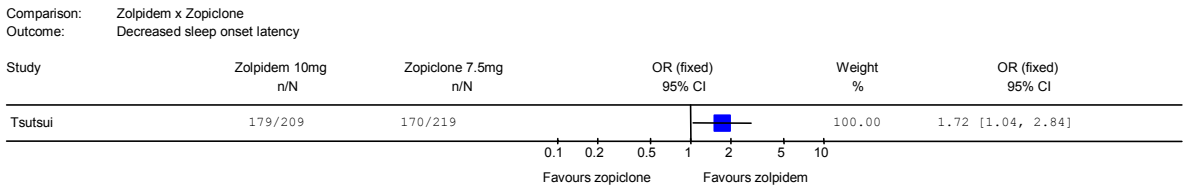


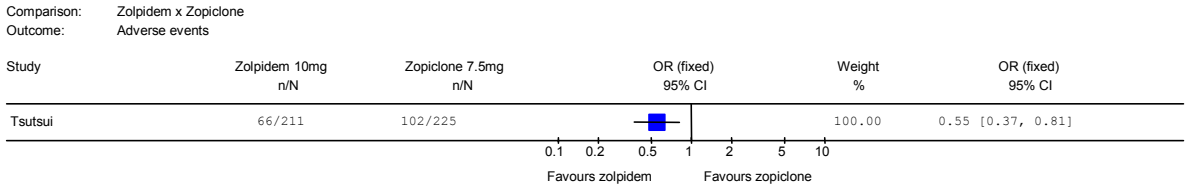
Figure 4C: Zolpidem versus Zopiclone

i. Sleep onset latency*

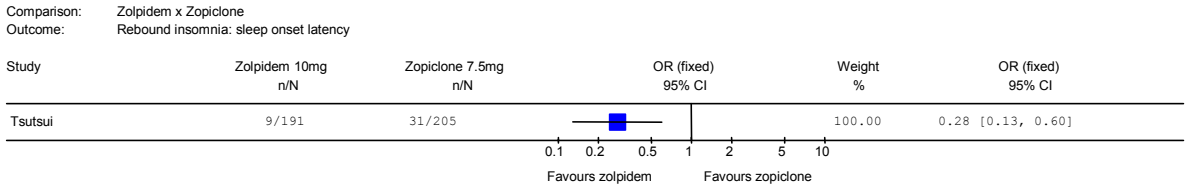


* %, showing an improvement in sleep latency of 1+ grade (scale 1-5) at week 2 compared to baseline

ii. Drug related adverse events



iii. Rebound insomnia concerning sleep onset latency*



* %, with a worsening of sleep onset latency by 1+ grade at the end of follow up (2 weeks treatment, max 1 week follow up) relative to baseline

4.2 Measures of psychomotor performance and memory

A summary of the results of the assessment of the quality of sleep has been reported in *Section 4.1.5*. In this section we present the other measures used to assess sleep quality and sequelae as reported in the included trials. A summary of the specific measures utilised and their results are presented in *Table A8* in Appendix 3. Data from non-English papers were not extracted for this component of the review.

Of the 16 studies, one(90) did not include any measures of mood, psychomotor performance, memory or satisfaction with sleep quality. In the remaining 15 studies, 28 questionnaires were used to measure these outcomes.

Studies varied considerably in the level of information provided. The majority of studies (14/16) did not reference or provide enough detail for study methodology. Due to the variations in measurement tools and/or lack of detail, direct comparisons across studies were not possible.

A number of different psychomotor tests were reported in the studies that compared benzodiazepines to the Z-drugs, but most were not described and validated. Details of the exact nature of the test ranged from the measure being cited as a memory test (unspecified), with the scale described as a graphic symbols test (unspecified), to fully specified measures and scales (i.e. Leeds Psychomotor Test). It is possible that the studies incorporated validated tests. However, only two studies provided references for the measures used.(87, 93)

Variation in assessment and variety in the level of information provided make study comparisons difficult. Differences in mood, psychomotor function and memory have been reported. Only one study(104) assessed mood and noted improvements in both zaleplon and zolpidem. None of the studies that directly compared Z-drugs to each other assessed memory or psychomotor performance.

Available data do not provide enough information or appropriate comparisons to allow for valid assessment of the effectiveness of the Z-drugs versus benzodiazepines. An explanation provided by a member of the review panel is that by the time the Z-drugs were developed it was considered unethical to use long-acting benzodiazepine comparators as the negative day time effects were so feared as to make the long-acting drugs almost unusable (Nutt D, University of Bristol, Bristol: personal communication, July 2003).

4.3 Review of dependence and withdrawal

The RCTs included in the main clinical effectiveness review did not provide data related to dependency and withdrawal. The research team extended the search to other study designs that evaluated the use of the non-benzodiazepines. Specifically the team sought to identify any studies reporting the assessment of dependence or withdrawal symptoms following discontinuation of insomnia treatment with the three non-benzodiazepine hypnotics assessed in this review.

4.3.1 Trials and cohort studies

Two RCTs(108, 109) and one open single-group study(110) assessed withdrawal symptoms following zolpidem discontinuation. One open single-group study examined withdrawal following the use of zopiclone.(111) A further paper (112) reports two RCTs investigating the gradual withdrawal of zolpidem or zopiclone after long-term use (minimum 3 months) (see *Table A9* and *Table A10,* in Appendix 3). None of these studies met the inclusion criteria of the main clinical effectiveness review and therefore a formal assessment of their quality was not carried out. No studies assessing withdrawal following zaleplon discontinuation were identified.

4.3.1.1 Zolpidem

Asnis(108) included patients treated for depression with serotonin reuptake inhibitors. A total of 194 patients were randomised to either zolpidem (10 mg) or a placebo for a 4-week treatment phase, after which 153 patients entered a 1-week placebo follow-up period (75 of the zolpidem group). The researchers assessed a potential withdrawal reaction by DSM-IV criteria and reported that no patient in either group experienced more than one symptom constituting criterion B of a sedative/hypnotic withdrawal symptom (Criterion B: autonomic hyperactivity; increased hand tremor; insomnia; nausea and vomiting; transient visual, tactile, or auditory hallucinations or illusions; psychomotor agitation; anxiety; grand mal seizures)(9)

The second trial by Shaw and colleagues(109) compared zolpidem and a placebo in a double-blind RCT involving 80 elderly psychiatric patients aged between 65-85 years. Patients were randomised to two groups on relatively high doses of zolpidem (10 mg and 20 mg) or placebo treatment for a double-blind period of 3 weeks, followed by a 1-week placebo period. The authors report that zolpidem was tolerated without any withdrawal symptoms, but report a small number of adverse events including daytime aggression (1 patient), day time restlessness (1 patient), increased sedation and confusion (1 patient) during the post-treatment phase.

The single-group open study by Maarek(110) tested zolpidem in 96 insomniac patients over 180 days, with the option to carry on for another 180 days. The initial dose was 10 mg but could be adjusted as needed to 20 mg. After the first 180 days, patients could choose to discontinue treatment. Nineteen of the 21 patients who discontinued treatment were followed-up for 20-30 days. Those patients reported no withdrawal symptoms, but there is an indication that at least some of them withdrew from treatment gradually. The method of measurement of withdrawal symptoms was not specified.

Lemoine and colleagues(112) reported two RCTs, one of which involved 193 patients who had received zolpidem (10 mg) for a median of 7.4 months and were thereafter randomised to continue the treatment for 3 further weeks or to be withdrawn gradually over the same time (one week each of full, half, and no dose). Patient files reporting adverse events, dropouts or a score of greater or equal to 3 on the Tyrer(107) benzodiazepine withdrawal symptom questionnaire were reviewed to judge whether events might be related to drug withdrawal. The incidence of such events was 38% and 24% in the withdrawal and continuation group respectively (p=0.049), but no significant difference was found when sleep complaints were excluded. Similarly, the Ashton scale(113) (a list of withdrawal symptoms formalised

into a rating scale) recorded an increase in the withdrawal group, but no change in the continuation group. No difference was recorded between the two groups on the Tyrer questionnaire scores.

4.3.1.2 Zopiclone

The RCT reported by Lemoine and colleagues(112) involved 201 patients who had received zopiclone (7.5 mg) for a median of 9.1 months and were thereafter randomised to continue the treatment for 3 further weeks or to be withdrawn gradually over the same time (one week each of full, half, and no dose). The incidence of events possibly related to drug withdrawal was 38% and 20% in the withdrawal (102 patients) and continuation group (97 patients) respectively (p=0.008). No significant difference was reported when sleep complaints were excluded. Neither the Ashton scale(113) nor the Tyrer(107) questionnaire recorded a significant difference in withdrawal signs between the two groups.

One single-group, open study followed 10 (of originally 11) chronic insomniac patients after 54 nights of treatment with zopiclone (7.5 mg) for a further 2-week withdrawal period on a placebo.(111) EEG recordings and subjective ratings were used to evaluate drug effectiveness. One patient reported significant daytime anxiety and hyperventilation on the first withdrawal day, whereas another patient experienced rebound insomnia, anxiety and general weakness six days after withdrawal.

4.3.2 Case reports

A total of sixteen English-language case reports were identified including eleven on zolpidem (114-124) and five on zopiclone, (125-129) but none on zaleplon (see *Table A11* and *Table A12,* in Appendix 3).

Most reports stem from Western European countries, and two reported cases of zolpidem abuse in the USA. All case studies involved excessive doses of the drugs, which had been gradually increased by patients themselves, at times with the intention of re-enforcing the experienced positive effects of the drug. The maximum dose of zolpidem used by patients ranged from 40 mg per day to 600 mg, that of zopiclone from 22.5 mg to 380 mg per day.

Cases were between 26 and 55 years old, apart from two 67-year-olds, one each on zolpidem and zopiclone (Sikdar(128) does not report the age of six cases). In nine case studies, a history of substance abuse was reported, and in twelve studies patients had a concomitant or previous diagnosis of depression.

Reported withdrawal symptoms from case studies of dependent patients vary across the studies and include epileptic seizures (4 patients on zolpidem, 1 on zopiclone), psychomotor agitation, restlessness, anxiety, confusion, and sleep disturbances. For some patients, no explicit withdrawal symptoms were reported, usually because withdrawal had been managed through gradual dose tapering.

We sought data from the Committee on Safety of Medicines (CSM) related to numbers of cases of dependency reported via the yellow card system. This data is always confounded by several factors – reporting of yellow cards is more common now than in the 1970s when problems with benzodiazepines were greatest, and will

also be influenced by the publicity around adverse effects (dependency on benzodiazepines is more likely to be diagnosed now than in the past, but less likely to be reported since it is well recognised) and changing patterns of use of these drugs – probably fewer long-term users now, although no direct comparative data exist.

The yellow card data shows distortion as a result of these factors – there are, for instance, 40 reports of drug dependency on zopiclone, one on zolpidem and none on zaleplon compared to three on nitrazepam, two on temazepam and one on lormetazepam. The figures clearly underestimate the problem and the relative contributions of each drug to the problem. We did not feel that any more detailed data would add anything useful to this analysis.

4.4 Discussion

The diversity of possible comparisons and the range of outcome markers in the review may be confusing. This is compounded by the fact that outcomes are rarely standardised and even when reported, may differ in exact interpretation. Also the quality of reporting is poor and as a result meta-analysis has been possible on only a small number of studies. It is therefore difficult to interpret the results. The results related to the key outcomes on the data provided from comparisons in the studies are presented in *Table 4C* and summarised in the following text.

Table 4C: Summary of results

Comparison n= of studies	Sleep Latency	Sleep Duration	Number of Awakenings	Quality of Sleep	Adverse Events	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=2)[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) **NDC** (n=4)	**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 improvement, NDC: No direct comparisons. Number of studies is shown in brackets.

[a] In one study nitrazepam resulted in a greater reduction in sleep onset latency on the 5th day (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.

1. *Concerning zolpidem*:

a) Zolpidem with nitrazepam (n=2)

- One study reports statistically significantly fewer awakenings with zolpidem

b) Zolpidem with temazepam (n=2)

- One study reports significantly favourable results for sleep latency and sleep quality in the zolpidem group

c) Zolpidem with zopiclone (n=1)

- Results from the only study in this comparator group suggest a statistically significant difference in favour of zolpidem for sleep latency, rebound insomnia of sleep latency and adverse events

2. *Concerning zopiclone*:

a) Zopiclone with lormetazepam (n=1)

- Only one study in this group reports that lormetazepam results in shorter sleep onset latency than zopiclone

b) Zopiclone with nitrazepam (n=8)

- There is no convincing evidence of any differences in the outcomes measured between zopiclone and nitrazepam (two studies suggest sleep latency is significantly shorter with zopiclone and one study reports significant improvements in sleep quality for zopiclone).
- Results from four studies suggest a statistically significant difference in favour of zopiclone in daytime alertness.

c) Zopiclone with temazepam (n=4)

- There is no convincing evidence of any differences in the outcomes measured between zopiclone and temazepam (only one study reports that rebound insomnia of sleep latency is significantly worse following zopiclone than after temazepam).

3. *Concerning zaleplon*:

Zaleplon with zolpidem (n=6)

- Some evidence suggests that zaleplon results in shorter sleep latency than zolpidem but zolpidem results in longer sleep duration than zaleplon
- Evidence suggests that zolpidem is statistically significantly more likely to improve sleep quality than zaleplon

- Evidence suggests that withdrawal is less likely and rebound insomnia significantly less likely on zaleplon compared to zolpidem

It must be remembered that these comparisons are limited, and that it was possible to undertake meta-analysis with data from only a small subset of the papers included in the review. Many papers did not make direct comparisons between the active treatments and reported only comparisons with placebos: often with insufficient data to allow direct comparisons to be made. Studies frequently reported a statistical difference in endpoints between drugs, but did not report enough data to allow evaluation of the clinical importance of this difference.

There was also evidence of multiple testing of outcomes, with selective reporting of significant findings, which meant that many of the results that were reported might have been spurious. The extent of the multiple testing was not always clear and not accounted for in statistical analysis. A related issue is that of the power of the studies – most were too small to detect any difference between therapies, and none have power calculations which support the size of the study. Issues of the differences between studies designed to show equivalence or difference between therapies do not seem to have been considered.

The very nature of insomnia will have led to skewed data in many of the papers considered. While they were often correctly reported using median data, this made any form of meta-analysis impossible. Other problems included limited availability of data from abstracts,(89, 99, 103) and data that were not normally distributed and comparisons made only with a placebo.(100-102) In some studies, the data was not adequately labelled in the study report(83, 84, 89)and there was excessive use of multiple comparisons.(82, 84, 87, 93) Three studies(93, 97, 98) did not have appropriate wash out periods (e.g. at least a week) so the data must be interpreted with caution.

These factors in part arise from the era in which most of these trials were undertaken (10 studies reported before 1990). The conduct and reporting of trials during that time were less standardised and published studies were not required to meet what are now accepted as standard quality criteria.(130)

The research question provided to the review team was based on an assumption of the effectiveness of each of the groups of drugs – that is the team was asked to compare the effectiveness of the interventions to each other.

The use of indirect comparisons, of drug A to placebo and drug B to placebo (or to some common comparator, e.g. triazolam) to draw comparisons between A and B, has been recommended in cases where either there is no direct comparison or where the comparison depends on limited evidence, such as only one RCT. In the past, there were concerns that indirect comparisons may carry greater bias than direct comparisons, and may overestimate the efficacy of one or other drug. This is the case for naïve or unadjusted comparisons, but Song and colleagues(131) have recently described methods for adjusting such comparisons, which may avoid these problems. In 44 direct and indirect comparisons, they found similar results in all but 3: the

reasons for these discrepancies vary but a key issue was that the studies in the indirect comparisons should be as similar as possible, and this aspect needed careful attention.

Song and colleagues(131) suggest that the results of indirect comparisons can be quantitatively combined to increase the statistical power if there is no discrepancy between the two. Use of such methods might have allowed us to make indirect comparisons between more drugs, in particular between zaleplon and other benzodiazepines. We had concerns however about the quality of many of the placebo controlled or comparator studies on which we would have been dependent, and the quality of their reporting: the direction of their effect would probably have been similar, but the power of these studies would have been small and required an extensive systematic review and meta-analysis for each comparison. There are substantial heterogeneities in the populations studied, many of whom were normal volunteers rather than insomniacs. Nevertheless, this would have been an interesting adjunct to the current study but was not included in the protocol at the time of writing.

The results of this review must be interpreted with considerable caution. Zaleplon gives shorter sleep latency than zolpidem, but shorter duration of sleep. This largely seems to be the result of the pharmacological profile of the drug and in particular its rapid absorption and short half-life in contrast to the other drugs such as zolpidem or zopiclone or even the relatively short acting benzodiazepines (See *Table 2A* in the Background section).

There are some differences between drugs, but it is difficult to quantify these or their clinical importance. Zolpidem may give rise to less rebound insomnia and shorter sleep latency than zopiclone, but not convincingly compared to the benzodiazepines. Zaleplon gives shorter sleep latency than zolpidem, but a shorter duration and quality of sleep, and less rebound. It might seem therefore that zaleplon might be a slightly better drug than zolpidem for patients with problems falling asleep, but not for those who tend to wake during the night or suffer from early morning awakening. In absolute terms however the benefit in sleep latency seems small and therefore the value of zaleplon over zolpidem may be open to question (WHO came to a similar conclusion). Zaleplon has not been adequately compared to the benzodiazepines used in the UK.

There may be differences in the drugs where they arew used outside their licence. This is regrettably common, as will be discussed later. The randomised controlled trials included in this review all used no more than six weeks therapy and, therefore, it is difficult to make comments on the risks of tolerance and dependency. It has been argued that drugs with a shorter half-life may encourage dependency by causing the rapid onset of withdrawal symptoms and so encouraging the patient to continue taking the drug. However, this is probably less likely to be the case for a hypnotic than for an anxiolytic. Although initially heavily marketed as “non-benzodiazepines” at a time when benzodiazepines were under a considerable cloud with increased awareness of their propensity to cause dependency, in practice it seems that drugs like zopiclone and zolpidem may also cause dependency. It is difficult to detect this in randomised controlled trials and we are dependent on case reports. We could find no case control studies to allow us to derive a comparative incidence. There were no case reports found for zaleplon: this may be a reflection of how the drug is licensed, i.e. for use of

no more than 2 weeks (but not necessarily how it is used), to the fact of its short half-life and clearance, or simply because the drug is not long on the market. The SPC (Summary of Product Characteristics)(132) states clearly that zaleplon may also give rise to dependency and should therefore be used with caution and for no longer than the licensed period. This seems to us to be sound advice. Theoretically, a drug with such a short duration of action seems less likely to cause dependency, but there is no firm evidence to substantiate or reject this view.

It is claimed that intermittent use of drugs may also be useful in avoiding dependency: this seems probable and is encouraged, but we found no studies describing this form of use of the drugs within our inclusion criteria. The manufacturers of zolpidem reported such studies and claim its effectiveness is proven in this situation, unlike other drugs. The BNF(51)also recommends this use for benzodiazepines. The use of short acting drugs as "rescue" therapy of a failure to sleep on one or two nights per week is also described but comparative studies are not available.

A final factor to be considered which may decrease the value of the studies included is publication bias. We were unable to identify any ongoing studies which may have shown inconclusive or even unfavourable results to a study sponsor. The vast majority of studies in this area were conducted with pharmaceutical company involvement: such studies in the past have been shown to contain a bias towards the drugs of the sponsor in other therapeutic areas.

5 Results: economic analysis

5.1 Introduction

In this chapter, we explore the published literature on the costs and benefits of hypnotics for the management of insomnia. We begin with the results of a literature search on the economics of different hypnotic drugs for the management of insomnia. As we were unable to identify any cost-effectiveness analyses for inclusion in the review., The next section goes on to describe the significant economic impact of insomnia worldwide from both a health service and societal perspective. Finally, key issues associated with economic evaluation of newer hypnotic drugs for the management of insomnia are summarised and relevant implications for the NHS are discussed.

5.1.1 Review of economic literature

We conducted a systematic search for comparative economic evidence concerning hypnotic drugs. The aim of the review was to identify published cost-effectiveness analyses of newer hypnotic drugs (zaleplon, zolpidem and zopiclone) for the management of insomnia that are based on clinical evidence from drug versus drug randomised controlled trials.

5.1.2 Identification of studies

One reviewer (ABol) examined the titles and abstracts of the 929 papers identified by the electronic search. In addition, another reviewer (YD) looked through all of the articles identified by the clinical effectiveness search strategies in the search for economic studies.

5.1.3 Quantity and quality of research available

No full economic evaluations based on clinical evidence from randomised controlled trials were identified, either between drug groups (Z-drugs versus benzodiazepines) or within drug groups. Although a large number of papers were identified by the cost-effectiveness search strategies only a small number were assessed for inclusion in the review, none of which met the inclusion criteria.

We did identify two studies which looked at the economic evaluation of hypnotics versus other therapies or no therapy for chronic insomnia. One(133) was in the form of an abstract and included a cost utility analysis. The authors compared different therapeutic options (do nothing approach, suggest non-pharmacological therapies, benzodiazepines or non-benzodiazepines medication (i.e. zopiclone) for the management of chronic insomnia in the elderly, based on the published literature and expert opinion. Results appeared to demonstrate that if there is no underlying health problem, non-pharmacological therapies should be the first line of treatment for insomnia. However, gains and savings appear to be small. When non-pharmacological therapies are compared with benzodiazepines for the average patient, the QALY gain was estimated to be 0.37 QALYs, and savings are estimated to be $2781 over 10 years. Unfortunately, it has not been possible to obtain the full version of this paper in order to determine its relevance to the review.

A second paper, a UK Health Technology Assessment report due for publication later this year, investigated psychological treatments in chronic hypnotic drug users. The economic evaluation was based on the results of a randomised controlled trial and concludes that "in routine general practice settings, psychological treatment for insomnia can improve sleep quality, reduce hypnotic drug use and improve health related quality of life at a favourable cost among long-term hypnotic users with chronic sleep difficulties".(134) The authors estimated that the total cost of service provision was approximately £150 per patient. The mean incremental cost per QALY gained at 6 months was around £3,500. The authors claim that the positive benefits associated with this treatment last for at least 12 months if patients comply with their treatment.

Although of considerable importance in relation to the use of hypnotics outside their therapeutic licence, this paper was not a drug versus drug comparison and outside the scope of this review.

Finally, only one intra-Z-drug economic study was identified. Menzin and colleagues(135) compared the costs and benefits (risk of motor vehicle accidents) of zaleplon and zopiclone. The study, part funded by Wyeth-Ayerst Global Health Outcomes Assessment Group, was not based on data comparing the drugs at all, but on data comparing effects of various blood alcohol concentrations on the risk of road accidents, and an extrapolation of the "blood alcohol equivalent" effects of each drug. This extrapolation leads to a conclusion that compared with zaleplon, use of zopiclone over 14 days in France might lead to 503 excess accidents per 100,000 drivers at an extra cost of US$31 per person (at 1996 values). The extrapolations in the Menzin paper(135) seem extreme and improbable. This study was excluded from the economic review of the literature, as it was not based on any direct comparative data. However, further discussion of this study is presented later.

5.1.4 Commentary

Despite the large volume of published pharmacoeconomic evaluations that exist, we were unable to identify any that explored the cost-effectiveness of different hypnotic drugs for the short-term management of insomnia based on RCT data. None of the studies identified by the review process included economic evaluations comparing benzodiazepines with Z-drugs, nor were any found that included intra Z-group drug comparisons. Most of the papers on cost and/or economic issues that were identified tended to focus on the quantification of the public health consequences of insomnia using cost-of-illness analyses. Most of these papers on costs were written for American and Canadian audiences.

5.2 Economic impact of insomnia

It is very difficult to estimate the true costs of insomnia, and estimates vary from country to country and also within countries. There are several reasons for these variations in estimates. First, there are conflicting estimates of how many people suffer from insomnia. Some authors suggest that 5-10 percent of the adult population(136) is affected whilst others suggest that the size of the problem is much bigger. Stoller(20) suggests that insomnia affects approximately one-third of the population and is of global concern. As described in chapter 2, definitions of insomnia

differ from study to study, and this in turn might help explain why the prevalence of insomnia appears to vary from country to country.(136, 137)

Second, some authors argue that insomnia is under-recognised and under-treated.(27) This might be because the individual does not perceive him/herself to be affected by insomnia and therefore does not report the symptoms to the GP. The individual may prefer to self-treat or might not want to be associated with the stigma of insomnia despite having severe symptoms. Disease may also be defined by the availability of treatment – so if benzodiazepines are the only treatment for insomnia, and they are under a cloud, then patients may be relabelled as anxious/depressed rather than primarily insomniac, and treated accordingly. If individuals do not seek out the usual medical treatments to manage their insomnia, e.g. if they do not go to their GP, then they might be using alternative treatments which are not included in the estimated costs of insomnia e.g. anti-histamines or alcohol.(27) Indeed, only 1 in 20 individuals with insomnia are believed to present to health care professionals with insomnia-related symptoms.(28) Finally, another explanation for the under-treatment (and/or non-diagnosis) of insomnia is because health care professionals might not ask patients about it.(29)

Third, the management of insomnia is associated with a range of diverse costs. These costs are often categorised as direct (medical and non-medical), indirect and intangible. The direct costs of insomnia include prescription drugs, over-the-counter remedies, GP consultations, tests and investigations, inpatient and outpatient hospital visits and referrals to hospital specialists. Indirect costs include the cost of lost earnings to the individual from having to take time off work due to sleep related illnesses. Also, workers suffering from insomnia who are able to work might not be as productive as those who do not suffer from insomnia and this has a knock-on effect on the productivity of the workforce. Insomnia is associated with an incalculable cost in terms of human suffering as a result of poor personal and professional relationships.(20) These intangible costs might include the breakdown of marital relationships and impaired intellectual function.

Despite these difficulties, some authors have attempted to estimate the cost impact of insomnia. The role of such burden of illness studies is always debated – health economists would argue that unless there is something that can be changed, there is little point in evaluating it. On the other hand, for health care planners a realisation of where money is spent and where disease needs are can bring about a change in resource allocation, or can promote further research.

Insomnia is said to be the most frequently reported sleep problem in industrialized nations worldwide(138) and to be associated with significant mortality and morbidity.(20) Estimates of the economic impact of insomnia are therefore high in many countries. In 1995, the direct costs of insomnia ("the cost of medical care or self-treatment borne by patients, organised health care providers, insurance companies or by the government") in the US were estimated to be US $13.9 billion.(139) This total cost was made up of substances used to treat insomnia (US $1.97 billion) and health care services (US $11.96 billion). If indirect (reduced productivity) costs are included in the total, then the total annual cost is estimated to be much higher. Another US estimate in 1994 was higher still, at approximately US $100 billion.(20,

140) In France, the total direct cost of insomnia in 1995 was estimated to be approximately US $ 2 billion(141) and included substances used for insomnia, outpatient visits and sleep specialist investigations.

There are no comparable estimates of the direct costs of insomnia in the UK. However, we do know that in 2002 approximately £25 million was spent on zolpidem, zopiclone, zaleplon, nitrazepam, temazepam, loprazolam and lormetazepam.(77)

5.3 Costs of insomnia within the framework of economic evaluation

As in any costing study, when estimating the costs associated with insomnia and hypnotics, it is very important to be explicit about the perspective adopted for the analysis. For example, if the analyst explicitly states that the viewpoint is that of the National Health Service, then the costs of lost productivity due to insomnia related ill health are no longer considered in the calculation of total costs. However if we extend the perspective to that of publicly funded social services, these costs may be included. Definition of the study viewpoint is crucial as the health implications of insomnia and insomnia treatments are wide-ranging and do not fall on one single sector of the economy.

In practice, the total treatment costs of insomnia are often difficult to define and are made up of a number of different items. Many patients are prescribed hypnotics in the short term after only a single GP consultation. Even for long-term users of hypnotics, there are few consultations related to the hypnotic use, as both parties use the repeat prescribing systems to avoid confrontation and discussion of sensitive issues. Drug costs may seem to dominate the costs of insomnia, but the costs of accidents or injuries might also be considered.

Hypnotics can be sometimes prescribed as part of a cognitive–behavioural therapy (CBT) package for insomnia.(134)This package might include all or some of the following: information leaflets, advice on sleep hygiene, stimulus control programme, relaxation techniques and cognitive therapy components. These packages are certainly not inexpensive and cost substantially more than short-term benzodiazepines alone, though they may be cost effective compared to the adverse consequences of long-term benzodiazepines.

Current national guidance focuses on the non-pharmacological treatment of insomnia.(79) The National Service Framework for Mental Health reflects concerns about over-use of hypnotics and states that the “prescribing rates of benzodiazepines should be monitored and reviewed within the local clinical audit programme”.(80) In the report “Medicines and older people: implementing the medicines-related aspects of the NSF for older people”(142) the guidelines, which apply to all other NSFs and vulnerable users, recommend that primary care agencies should both invite patients to ‘come off’ long-term hypnotics and provide support for them to do so.

5.3.1 Costs to the health service

The direct drug treatment costs of insomnia have been outlined above. It is argued that other costs associated with insomnia are typically insomnia-related accidents (e.g. motor vehicle, work-related and catastrophic accidents)(20) Indeed, Leger(143) suggests that 41% - 54% of all motor vehicle accidents are fatigue related. Accidents are not only related to the disease per se, but also to drug treatments for insomnia. In particular, some hypnotics have been linked to motor vehicle accidents,(144, 145), falls in the elderly(146) and deliberate self-harm(147) (see *Table 5A*). In many of these observational studies, there was insufficient use of newer drugs such as zolpidem or zaleplon to make any comment.

A study by Menzin(135) and colleagues discusses the link between zaleplon and zopiclone and motor vehicle accidents but is, as described above, controversial. The attribution of costs to accidents is also controversial, as they are based on strong assumptions (e.g. what proportion of the cost of a car accident is a direct result of sleepiness?).(143) Careful consideration of the techniques used in measuring costs is therefore required.

Table 5A: Selected studies

Study	Outcome	Study details	Included benzodiazepines and non-benzodiazepines
Barbone(144)	Car accident	Case control study	Alprazolam, bromazepam, chlordiazepoxide, clorazepate hydrochloride, diazepam, lorazepam, oxazepam, flunitrazepam, flurazepam, loprazolam, lormetazepam, nitrazepam, temazepam, zopiclone
Menzin(135)	Car accident	Extrapolation from alcohol related accidents	Zaleplon, zopiclone
Neutel(145)	Car accident	Cohort study	Triazolam, flurazepam, lorazepam, diazepam, oxazepam
Neutel(146)	Falls	(i) Descriptive study (ii)Case-cross over study	Benzodiazepines including lorazepam and oxazepam
Neutel(147)	Self-harm	Population based cohort study	Triazolam, flurazepam, lorazepam, diazepam, oxazepam

5.3.2 Costs to society

Similarly, some argue that the highest costs associated with insomnia are the indirect costs incurred by society,(27) either due to lost productivity or to accidents. The balance between lost productivity or accidents due to insomnia(20, 143)or to the treatment of insomnia is however unclear, and gives scope for much speculation.

5.4 Health outcomes of insomnia within the framework of economic evaluation

Not only are there many types of costs associated with insomnia in the literature, there is a vast range of reported health outcomes.(28) In the published literature, health outcomes of interest in the short-term can be divided into (i) sleep efficacy outcomes, (ii) rebound and tolerance outcomes (iii) adverse effects and (iv) withdrawal. Sleep efficacy outcomes include sleep onset latency, total sleep duration, number of awakenings, adverse events and quality of sleep. Rebound and tolerance outcomes are related to sleep onset latency, total sleep duration, number of awakenings and quality of sleep. Non-sleep related adverse effects range from the insignificant, e.g. indigestion, to the significant, e.g. severe allergic reaction. Other important outcomes of interest include morning disposition (e.g. how does the individual feel on

awakening?) and daytime performance (e.g. does the patient feel tired or sleepy during the day?). These outcomes are often labelled as the residual or hangover effects of the drug. Assessment of quality of life is also of interest. Much of the published literature in this area focuses on zopiclone and/or measures the quality of life of insomniacs compared to good sleepers.(31, 32, 148) In the long-term, health outcomes are focussed on dependency and withdrawal symptoms.

In general, in the assessment of health outcomes associated with hypnotics, the systematic review suggests that in terms of most sleep efficacy measures, there are no major differences between any of the drugs. This leaves us to consider what kind of economic evaluation might be most appropriate to compare these drugs.

Cost minimisation analysis (CMA)

CMA requires that the health outcomes of interest be proven identical for the health care interventions under scrutiny. Although the clinical review has not found significant evidence of major differences between drugs, there are some differences: for instance, shorter sleep latency on zaleplon compared to zolpidem, but longer duration of sleep on zolpidem. We believe that to claim equivalence on the basis of the poor data available would be inappropriate. For many of the health outcomes, as the results of the meta-analysis show (see chapter 4), there appear to be no major differences between the drugs. We therefore believe that using a cost minimisation approach to assess the costs and benefits of the newer hypnotics for the management of insomnia is not valid.

Cost effectiveness analysis (CEA)

In order to conduct a CEA, a clear uni-dimensional outcome of interest is a pre-requisite. As discussed, there is no single outcome of interest from the review that would be applicable to all sufferers. Some people might prefer to fall asleep quickly (sleep onset latency) whilst others might prefer to sleep for more than 6.5 hours (total sleep duration). Individuals might be prepared to accept that they will feel a little bit drowsy the next day if they have uninterrupted sleep (no awakenings) whilst others might not. Recent developments in the techniques of economic evaluation have led to the use of discrete choice experiments to examine patient preferences between treatments that have different levels of specified attributes (e.g. insomnia related outcomes might include sleep onset latency and total sleep duration). Use of such methods to evaluate these outcomes could alleviate some of the problems associated with multiple outputs and facilitate cost effectiveness analyses. However, there are no relevant published data for use by the review team at this time. Given the nature of the outcomes associated with benzodiazepines and non-benzodiazepines, a CEA to assess newer hypnotics for the management of insomnia is not recommended.

Cost utility analysis (CUA)

CUA is the only economic evaluation method that combines the effects of health care interventions in terms of both quality and quantity of life. Although it is unlikely that any of the hypnotics will impact directly on length of life, these drugs may affect quality of life to different extents perhaps for different periods of time. For example, zopiclone is reported to improve quality of life as compared with a placebo.(31) Quality of life is a multi-dimensional health outcome that would enable the many different uni-dimensional health outcomes to be combined. CUA is therefore an

appropriate approach to adopt in light of the nature of the health outcomes. However there is no reliable comparative data on changes in quality of life associated with any of the drugs, and therefore no utility values. We found no data to allow us to undertake such a study and the collection of new data was beyond our remit and resources. However, the recent cost utility study(134) conducted as part of the HTA report on cognitive and behavioural therapies may provide a valuable framework for such work in the future.

Cost benefit analysis (CBA)

CBA requires that all costs and benefits be presented in monetary units. Given that many of the health outcomes associated with hypnotics and insomnia are intangible e.g. drowsiness or breakdown of personal relationships, a CBA would be very difficult. However, if time and resources were unconstrained, then this approach would yield both useful and interesting results.

5.5 Conclusion

This chapter has discussed the published literature on the costs and benefits associated with treatments for insomnia. Results of the literature review have indicated that little evidence is available on the economics of different hypnotic drugs for the management of insomnia. While we accept that the burden of disease imposed by insomnia is significant for both individuals and the NHS, the available evidence does not provide a basis on which we can give any firm guidance with regard to the comparative cost-effectiveness of different drugs in this area. Although a large number of papers have been published in this therapeutic area, none were found to provide sufficient evidence to inform our analyses. There is a need for robust clinical data to allow such analyses to be undertaken.

From a longer-term perspective, there is an equal lack of compelling evidence with regard to the comparative value of individual drugs and drug classes and the prevention of drug dependence. While it appears that those suffering from insomnia are more at risk of falls and motor vehicle accidents, again we have no compelling evidence with regard to the extent to which each of the drugs being compared is likely to lead to beneficial changes in the profile of such accidents. In such a data vacuum, it becomes impossible to choose a structure for the economic evaluation. In particular, to use cost minimisation analysis would imply that we had evidence that the drugs or drug classes being compared had been proven to be equivalent. This is not the case. We have identified an absence of evidence of incremental benefit, which is not necessarily equivalent to evidence of an absence of effect. Until the clinical efficacy data comes up with more compelling conclusions, the economic modelling must be placed in abeyance.

6 Economics: response to industry submission

6.1 Critique of industry economic submissions

Our review of the economic evidence on Z-drugs and benzodiazepines for the short-term management of insomnia reveals that no up-to-date evidence of cost-effectiveness exists in the published literature. No economic evaluations of any of the Z-drugs compared to the benzodiazepines were identified by the literature search. However, the industry economic submissions do, to some extent, address the issue of cost-effectiveness. We appraise the economic models as presented in the industry submissions and comment on the underlying model assumptions and parameter values. We did not attempt to build a decision-analytic cost-effectiveness model given the limitations of both the clinical and economic data available to us at this time. Finally, we discuss the relative cost-effectiveness of newer hypnotic drugs for the short-term management of insomnia based on systematic and objective consideration of the clinical and economic evidence base.

6.2 Industry submissions

Submissions to the National Institute for Clinical Excellence were received from the following manufacturers/sponsors:

1. Sanofi-Synthelabo Ltd: zolpidem
2. Wyeth Pharmaceutical: zaleplon

No submissions from the manufacturers/sponsors of zopiclone were received.

The submission from Sanofi-Synthelabo Ltd.(4) explicitly states that no formal short-term cost effectiveness assessment is included within the submission. They do, however, discuss the cost-effectiveness of non-benzodiazepines versus benzodiazepines in the long-term treatment of insomnia within the framework of economic modelling. Sanofi-Synthelabo Ltd.(4) also included a budget impact analysis and explored the potential additional costs to the NHS of using or switching to zolpidem.

The submission from Wyeth(34) includes a short-term cost-effectiveness model which supplements the clinical evidence presented. A formal budget impact analysis was not presented.

6.3 Sanofi-Synthelabo Ltd submission

6.3.1 Short-term model

No formal short-term economic model was presented in the industry submission.

6.3.2 Long-term model

In their discussion of cost-effectiveness issues, the authors allude to a long-term modelling exercise carried out on the issue of dependency risks, but state that there was too much uncertainty concerning these risks to allow any robust results to be generated. In particular the authors highlight the fact that there is a “lack of robust

data on which to establish the probability of dependency and its increased burden to the health care provider" (Sanofi-Synthelabo Ltd submission p.49)(4). We agree with this view.

In addition, the intended scope of the modelling exercise is unclear from the description of the model. However, it appears to have been largely restricted to cost effects, and therefore does not address issues of quality of life and utility effects, nor does it reflect the licensed indications for the use of the drug.

To summarise, given the lack of detailed information regarding this long-term model, it has not been possible to undertake a formal critique of the modelling exercise.

6.4 Wyeth submission

6.4.1 Short-term models

In the Wyeth submission, two short-term cost effectiveness models are presented and discussed. The first deals with road traffic accidents and the second with falls in the elderly.

6.4.1.1 Road traffic accidents model

This is a cost-consequence algorithm which claims that, compared to zaleplon, zopiclone is associated with extra costs because of a risk to drivers from drug-induced drowsiness. The argument that zopiclone compared with zaleplon leads to excess driving accidents is based on the results of a study by Menzin and colleagues(135), the basis of which has already been criticised in chapter 5.

The algorithm is based on the assumption that "zaleplon does not interfere with mental function the day following administration for insomnia" (Wyeth submission p.28)(34), in contrast to zopiclone. However, our results from the review of clinical evidence suggest that there is currently little evidence from published RCTs to prove any statistically significant differences in terms of residual effects between these two drugs. Therefore this assumption and the relationship to drowsiness induced by various blood alcohol concentrations underlying the Wyeth analysis of road traffic accidents must be open to question.

There are therefore reasonable grounds for considering that this issue is not of central concern in estimating cost-effectiveness from the NHS perspective.

6.4.1.2 Falls and hip fractures in the elderly

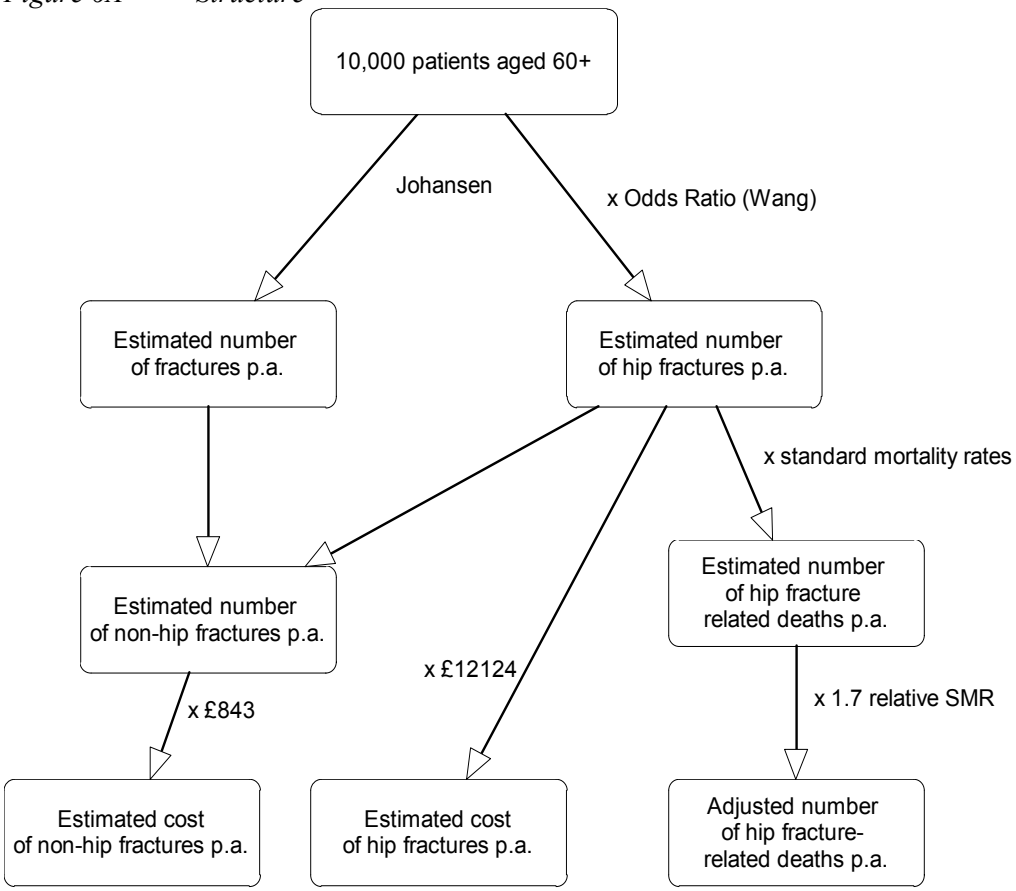
In the submission, the model is described either as 'simple' model or 'simplistic'. The model sets out to calculate the additional cost of hip fractures and additional mortality from using zolpidem, nitrazepam and temazepam versus zaleplon. The economic analysis is based on the use of hypnotic drugs for a one-year period. However, patients do not receive continual therapy, they receive two weeks "on" therapy followed by two weeks "off therapy".

In summary, the weaknesses of the model can be outlined as follows. Firstly, there is a limited conceptual framework offered, and the authors do not provide a

comprehensive description of the model in terms of its scope or perspective. Secondly, the comparisons considered within the model are not stated explicitly or fully described. Finally, the spreadsheets themselves contain errors and some of the key values are inadequately referenced.

As a result, the review team attempted to correct and, in places, rebuild parts of the model in an attempt to obtain more detailed cost effectiveness results.

Figure 6A Structure



The model begins with a representative population of 10,000 people over 60 years old, split into four age bands (60-64, 65-74, 75-84, 85+) for each sex in proportion to their representation in the UK population. These are then multiplied by the annual incidence rates for all fractures and for hip fractures to estimate the annual number of fracture cases (total and hip) to be expected per 10,000 elderly persons. The non-hip fractures are calculated as a simple difference. For scenarios involving zolpidem or benzodiazepines odds ratios from Wang and colleagues(149) are applied in the calculation of the number of hip fractures. The model assumes no increases in hip fractures above baseline in patients taking zaleplon.

Standard age/sex mortality rates are then applied to the number of hip fractures to estimate the expected number of deaths in these patients. These figures are then uplifted by 70% on the basis of excess mortality in 12 months following hip surgery as described in the study by Richmond.(150) The estimated costs of treating hip and

non-hip fractures are calculated using simple averages of £12,124 and £843 respectively.

Spreadsheet Problems

Besides several calculation errors, there appear to be some technical problems and unexplained aspects of the model that could distort the model results.

1. Donaldson(151) and Johansen(152) quote two sources for fracture incidence rates, but chose to use the higher values from Johansen without justification. Use of the lower figures would substantially reduce the claimed differences.
2. The authors employ the Odds Ratios (OR) from Wang's paper(149) as though they were Relative Risk (RR) values. RR is always less than OR and varies depending on the underlying baseline risk level. This means that the excess risk of fractures for benzodiazepines and zolpidem is overstated.
3. Although a source is given for the very large mean cost of treating a hip fracture, none is offered for the mean cost of treating other types of fracture in the elderly (£843) - the differential between these figures may be overstated.
4. In order to verify the mean cost of treating a hip fracture used in the submission, the review team obtained the original article. The mean cost estimated by Dolan and Torgeson (153) includes social costs and these make up approximately 60% of the mean cost of treating a hip fracture. Given that the perspective of the economic analysis is not stated in the Wyeth submission, the review team cannot comment on whether or not it is appropriate to include these costs. In addition, the social costs are largely made up of long-stay hospital care for one year and, in the paper, this is estimated to be twice the cost of long-stay residential care. The review team believe that this assumption leads to an overestimation of costs in the Wyeth submission(34) because recent changes in reimbursement mean that, currently, the cost of long-stay hospital care is approximately 20% more expensive than residential care. This means that the mean cost of a hip fracture used in the submission is likely to be an over-estimate. Also, recent changes to improving patient discharge, with intermediate care and better social support, mean that this scenario is less likely to take place in today's NHS.
5. In calculating the cost of treatment over the course of a year (assuming treatment for 2 weeks out of every 4), the authors assume 4 GP visits per annum for all patients on drug treatments, but consider that patients not assigned drug therapy will not consult their GP again. This seems unreasonable since we must presume that sleep dysfunction continues throughout the period.

Conceptual Issues

Implicitly this model is based on the assumption of equal efficacy between all treatments as far as inducing sleep is concerned. The model is only concerned with minimizing the cost of a single consequence of one adverse effect - falls leading to hip fractures (in some cases with fatal outcome) due to drowsiness. It does not address the important issue of possible drug dependency, and does not attempt to evaluate the utility gains from successful treatment of sleep disturbance. This means that within the original model, it is difficult to calculate meaningful cost effectiveness ratios or

cost utility ratios. Indeed the summary table is unclear, presenting measures and ratios that have little relevance to assessing cost-effectiveness.

Adjusted model

The model has been amended and corrected in several ways to provide more meaningful results (albeit still subject to some of the aforementioned shortcomings). The changes are as follows:

i. All detected calculation or transcription errors have been corrected
ii. Odds Ratios have been replaced by age-related Relative Risks
iii. Patients not on drug therapy are assumed to see their GP twice yearly
iv. Illustrative Quality Adjusted Life Year values have been assigned (a gain of 0.1 in health related quality of life (HRQOL) for 26 weeks of the year for successful therapy, a loss of 0.5 in HRQOL for 13 weeks per hip fracture, and loss of 5 years life-expectancy per death consequent of a hip fracture)
v. Ten pairwise therapy comparisons have been carried out to yield illustrative incremental cost/QALY gained ratios

Results obtained from the adjusted model *based on Wyeth assumptions* are shown in the table below.

Table 6A Results obtained from adjusted Wyeth model (i.e. no inceases in falls on zaleplon but incraeses in falls on other drugs)

Primary therapy	Incremental analysis	A	B	C	D
		Zolpidem	Nitrazepam	Temazepem	No drug
Zaleplon	Inc. cost	-£767,920	-£111,371	-£93,171	+£836,801
	Inc. Qaly	+78.18	+38.54	+38.54	+500.00
	Inc.cost/Qaly	**Dominates**	**Dominates**	**Dominates**	**£1,674**
Zolpidem	Inc. cost		+£656,549	+£674,749	+£1,604,721
	Inc. Qaly		-39.64	-39.64	+421.82
	Inc.cost/Qaly		**Dominated**	**Dominated**	**£3,804**
Nitrazepam	Inc. cost			+£18,200	+£948,172
	Inc. Qaly			0.00	+461.46
	Inc.cost/Qaly			**N/A**	**£2,055**
Temazepem	Inc. cost				+£929,972
	Inc. Qaly				+461.46
	Inc.cost/Qaly				**£2,015**

Therefore if the Wyeth data and assumptions are accepted, the re-analysis suggests that all the drugs of interest in the analysis are similarly cost-effective compared to not treating these elderly patients (see column D), and that the apparent differences between drugs appear to be relatively minor. Based on Wyeth data and assumptions, zaleplon seems to dominate the other therapies ie zaleplon is more effective and less expensive than the comparators (zolpidem, nitrazepam, temazepam and no drug).

Other considerations

The impact of sleep disorders on HRQOL is not considered in any of the Wyeth short-term models. Addressing HRQOL is fundamental to economic assessment, and we have estimated a HRQOL score to allow meaningful comparison between the drugs. Equally, there is no information to indicate the degree of risk/adverse outcome associated with untreated, or imperfectly treated disorder. The other primary concern

is the risk of dependency/withdrawal syndrome. What effect does this have on quality of life, and on health costs?

6.4.2 Long-term model

No formal long-term economic model is presented in the industry submission.

6.5 Conclusion

Sanofi-Synthelabo Ltd did not submit a formal short-term model. Given the authors' explicit recognition of the uncertainty around their long-term model, no formal critique was therefore undertaken by the review group.

Wyeth presented two short-term models and no long-term model. The driving accidents model was not presented in sufficient detail to allow a detailed critique of it to be performed. Critique of the falls model was limited by calculation errors and technical problems, and heavily dependent on assumptions which favour Wyeth's product but which do not seem supported by the clinical analysis in chapter 4.

In summary, careful scrutiny of the models presented has reinforced the view that there is a paucity of clinical and economic evidence available regarding the comparison of benzodiazepine and non-benzodiazepine drugs for the management of short-term insomnia.

7 Budget Impact Analysis

7.1 Introduction

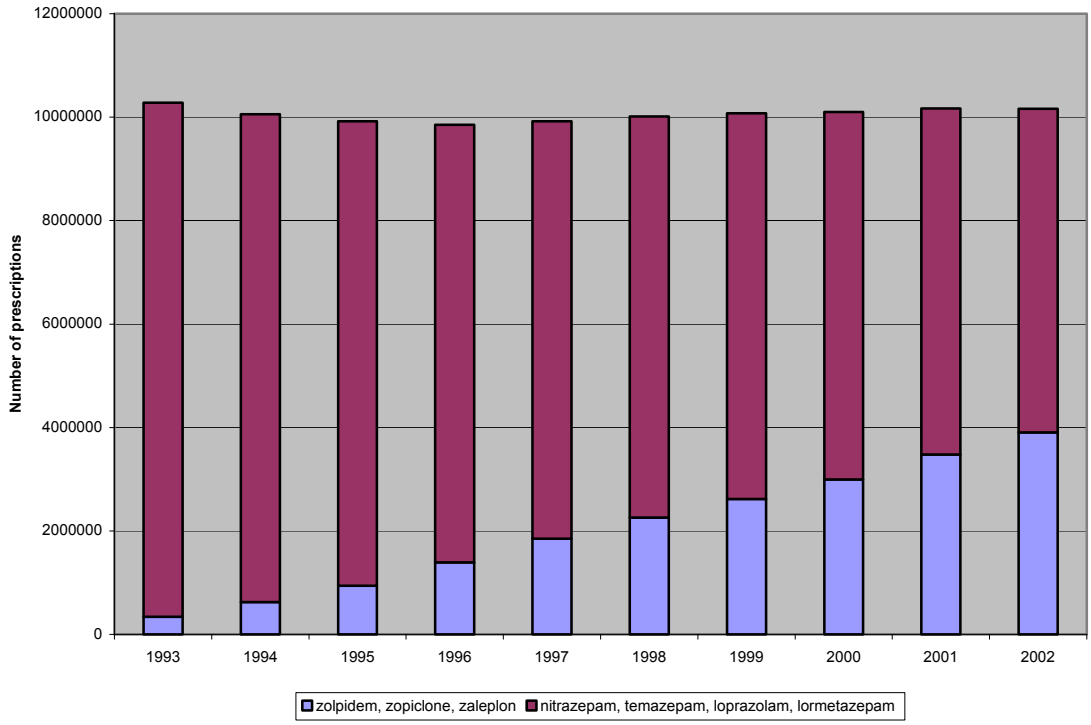
This section describes current trends in the volume of prescriptions and spending on hypnotics in general practice in England during the period 1993-2002. We also project future volumes of prescriptions and spending over the period 2003-2007. Throughout this chapter the benzodiazepine drug group includes nitrazepam, temazepam, loprazolam and lormetazepam. Data on diazepam or lorazepam use have not been included in any of the analyses, since although licensed as hypnotics, they are not defined as hypnotics in the BNF(51) nor widely used for this purpose. The Z-drug group includes zolpidem, zopiclone and zaleplon. This covers the group of drugs defined as "hypnotics" by BNF(51) subsection 4.1.1, with the exception of clomethiazole and choral and its derivatives.

In line with current trends in spending, a budget impact analysis is carried out in order to estimate the costs associated with switching prescribing from benzodiazepines to z-drugs. Again, diazepam and lorazepam are not included in the analysis. A significant proportion of diazepam and lorazepam prescribing is for the treatment of anxiety and to include this data would distort the results of the budget impact analysis. The budget impact analysis is based on data from the Purchasing Price Authority.

7.2 Trends in volume of prescriptions and spending on hypnotics

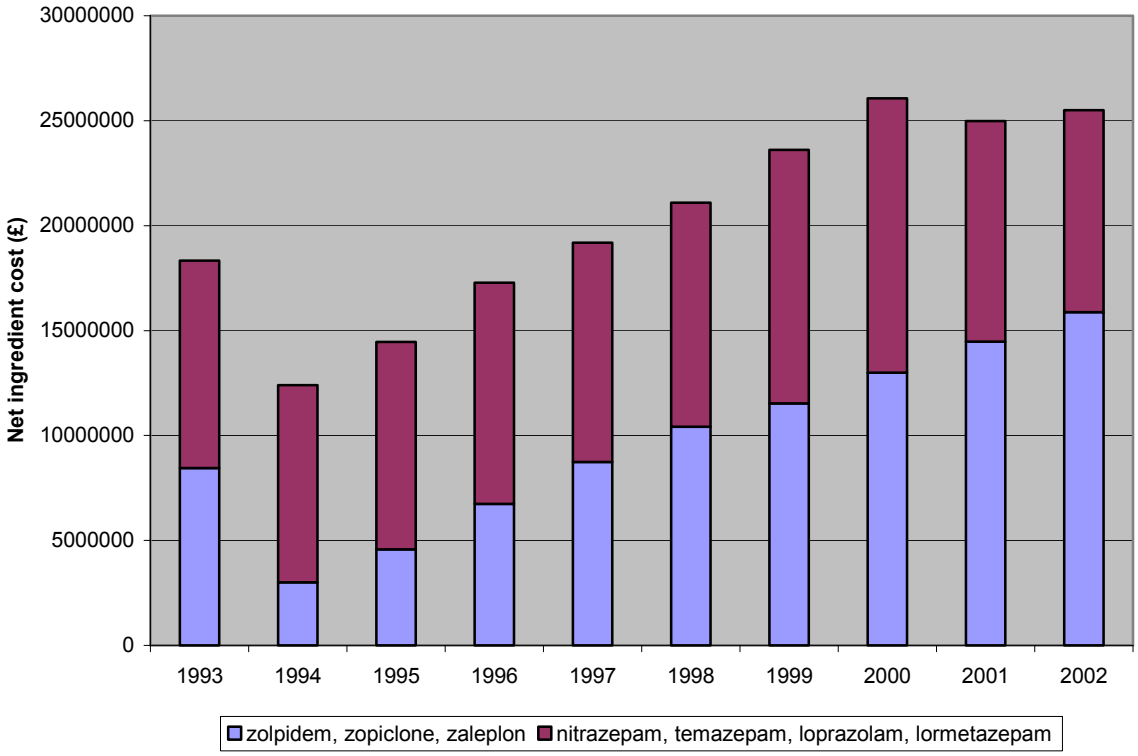
As shown in *Figure 7A*, the total number of prescriptions in general practice in England during the period 1993-2002 has changed little over the whole period with a gradual increase taking place from 1995 onwards. There are approximately 10 million prescriptions issued for hypnotics every year(77). There has been a steady change in the mix of benzodiazepines and Z-drugs within this group. Large numbers of prescriptions for benzodiazepines are still being prescribed, but the volume of benzodiazepine prescribing has fallen substantially over this period. In contrast, there has been a steady rise in the number of Z-drug prescriptions and approximately 4m prescriptions for these newer hypnotics were dispensed in 2002.

Figure 7A: Trends in volume of prescriptions in general practice in England (1993-2002)



The change in the mix of the drugs has lead to an annual increase in total spending on hypnotics over this period. Indeed, total spending on these hypnotics has more than doubled since 1994. *Figure 7B* shows that since 1994, there has been a steady rise in spending on Z-drugs compared with spending on benzodiazepines. Spending on Z-drugs has risen substantially with only £2m being spent in 1994 compared with over £15m being spent in 2002. The dip in total spending on Z-drugs during the period 1993-1994 was due to the company decision to drop the price in the face of a threat by the then Secretary for Health to blacklist zopiclone. At this point, zopiclone made up all spending on Z-drugs, so any change in price had a significant impact on total spend in this group. The more recent dip in the costs for benzodiazepines is due to correction following generic price setting by the Department of Health.

Figure 7B: Trends in spending on hypnotics in general practice in England (1993-2002)



7.3 Current market share

The following table (*Table 7A*) lists current market shares for each of the drugs in 2002 by volume of prescriptions and by total cost to the NHS. Currently the Z-drugs make up 38% of the total market share based on volume of prescriptions. Within the Z-drugs, zopiclone is by far the most frequently prescribed (82%). Temazepam is the most commonly prescribed benzodiazepine (22%) and makes up almost two-thirds of the benzodiazepine market. This percentage has fallen since a change in the regulations in 1995 when temazepam became a controlled drug in an attempt to limit the risk of "non-medical" abuse. As a controlled drug, temazepam carries some of the usual prescribing restrictions.

If current market share is based on spending, using net ingredient cost data, market share of the drugs is reversed. Sixty percent of the total amount spent is on Z-drugs. Within the Z-drugs, zopiclone accounts for 82% of the amount spent. Within the benzodiazepines group, spending on temazepam is approximately 60%.

Table 7A: Current market shares

Hypnotic	Market share %	
	By volume of prescriptions	By spending
Zolpidem	6	10
Zopiclone	32	51
Zaleplon	1	1
All Z-drugs	**38**	**62**
Nitrazepam	17	9
Temazepam	41	22
Loprazolam	2	4
Lormetazepam	2	3
All benzodiazepines	**62**	**38**

7.4 Budget impact analysis

There is a paucity of robust and comparable published evidence on the cost and benefits of the newer hypnotics (zaleplon, zopiclone and zolpidem) for the management of insomnia. Therefore, in this report, the budget impact analysis is simply a pragmatic exercise whose purpose is to highlight the possible financial implications of changes in the mix of benzodiazepine and Z-drug prescriptions. This is a stand-alone exercise and the assumptions therein are not derived from the clinical or economic evidence set out in this report.

In order to carry out a budget impact assessment, accurate information is required on the comparative cost of the hypnotic drugs, total number of prescriptions for each of the drugs and typical length of prescription.

7.4.1 Cost of the drugs

Table 7B presents the list prices of the benzodiazepines and the Z-drugs of interest to this report as quoted in the British National Formulary.(51) Note that zaleplon is licensed only for a 14-day course, unlike the other Z-drugs, which are licensed for up to 28 days, so for comparability of prices, we have used 14 days as the duration although in practice most benzodiazepine prescriptions are for longer (see later).

Table 7B: Cost of the drugs

Product	2002 BNF list price (£) for a 14--day period (defined daily dose)
Zolpidem	2.24 (10mg/day)
Zopiclone	2.24 (7.5mg/day)
Zaleplon	4.04 (10mg/day)
Nitrazepam	0.41 (5mg/day)
Temazepam	0.75 (20mg/day)
Loprazolam	2.23 (1mg/day)
Lormetazepam	0.72 (1mg/day)

List prices as published in the BNF(51) as well as total net ingredient costs from PPA(77) data are used in the budget impact analysis. Total net ingredient costs refer to the total cost of the drug before discounts and does not include any dispensing fees or costs.(154)

7.4.2 Volume of prescriptions

The volume of prescriptions is taken directly from data made available by the Purchasing Price Authority(77)(PPA). In order to estimate cost per prescription for each of the drugs, an estimate of prescription length is required. Two estimates of the length of the prescription are used in the budget impact analysis. As all of the drugs are licensed for short-term use, it seems appropriate to use a uniform 14-day period to estimate the cost of a single prescription for each of the drugs. However, in practice, both benzodiazepines and Z-drugs could be prescribed for more than a 14-day period. In order to estimate the typical length of a prescription for each of the drugs, we used data on the defined daily dose of the drugs (DDD).(155) The DDD is considered a typical adult dose but may not represent the actual prescribed daily dose in any individual country. An estimate of treatment days based on typical usage can then be calculated for each of the drugs (total number of doses/number of prescriptions). Based on this information, the prescription length for each of the drugs is estimated to vary from 16 days to 39 days.

In England, the Average Daily Quantity (ADQ) is reported by the PPA(77) – this is an arbitrary figure based on the average prescribed daily dose and on what preparations are available.(156) For the most part, ADQs are similar to DDDs. We chose not to use the ADQs in our calculations since the ADQ is 5 mg for zolpidem – this would give an unusually long duration of each prescription and is out of keeping with other hypnotics, and so we have used the DDD of 10mg for zolpidem as suggested by the WHO(155). All of our estimated days of average treatment are based on DDD data.

The following table (*Table 7C*) shows the estimated days of treatment based on typical usage as calculated from the PPA dataset(77), and compared to the data provided in the Sanofi-Synthelabo Ltd. submission. The number of days of treatment per prescription with zaleplon is shorter than for other drugs, in keeping with its licence. For nitrazepam, the estimated days of treatment is higher: this suggests that it

is being used at doses higher than its DDD or that prescriptions for chronic users are of extended duration.

Table 7C: Estimated mean days of treatment per prescription

Product	Estimated mean days of treatment per prescription (PPA data)	Estimated mean days of treatment per prescription (Sanofi-Synthelabo)
Zolpidem	22	26
Zopiclone	24	28
Zaleplon	16	17
Nitrazepam	39	36
Temazepam	22	34
Loprazolam	26	36
Lormetazepam	30	35

There is limited data on the actual length of prescriptions issued. Data submitted by Sanofi-Synthelabo Ltd.(4) suggest longer duration of prescription but unfortunately they have been unable to provide further details or describe the methodology used in more detail. In particular, it would have been interesting to define duration of use in new users of hypnotics, and the likelihood of repeat prescriptions, and whether this differed with different drugs.

Sanofi-Synthelabo Ltd. has also calculated the mean number of days of therapy received per year for each type of drug (but unfortunately, cannot provide information on the range nor separate out new users) (*Table 7D*). In general it seems that users of drugs such as nitrazepam or loprazolam are receiving the drug almost permanently. Audit data from one PCT (Gateshead) suggest that nitrazepam and loprazolam account for around 35% of all benzodiazepines/Z-drug prescriptions, and that, depending on the practice, 60-80% of scripts were issued to patients taking the drugs for over two years.

Table 7D: Estimated mean days of treatment per patient per year

Product	Estimated mean days of treatment per patient (Sanofi-Synthelabo)
Zolpidem	111
Zopiclone	145
Zaleplon	51
Nitrazepam	299
Temazepam	215
Loprazolam	290
Lormetazepam	194

The Prescribing Support Unit calculates Specific Therapeutic Area-Prescribing Units (STAR-PUs) for Z-drugs and benzodiazepine hypnotics.(157) These are based on

prescribing patterns and cost in approximately 200 UK practices, and are an approximation of the relative use of the drugs according to patient age. It is possible therefore, knowing the age-sex profile of the practice, to estimate whether it is an above or below average spender or user of these drugs. Data reflect the age/sex profile of hypnotic users, and the relative costs of benzodiazepines and Z-drugs. Analysis shows that hypnotics of all types are predominantly prescribed for older patients, and for women generally more than men (*Tables 7E and 7F*).

Table 7E: STAR(01)-PU Values (hypnotics excluding "Z-drugs")

Age group	Male	Female
0-4	0.0	0.0
5-14	0.0	0.0
15-24	0.1	0.0
25-34	0.3	0.2
35-44	0.3	0.3
45-54	0.4	0.6
55-64	0.5	0.9
65-74	0.7	1.3
75 & over	1.2	1.5

Table 7F: STAR(01)-PU Values ("Z-drugs" only)

Age group	Male	Female
0-4	0.0	0.0
5-14	0.0	0.0
15-24	0.1	0.0
25-34	0.2	0.1
35-44	0.2	0.2
45-54	0.3	0.4
55-64	0.3	0.5
65-74	0.3	0.5
75 & over	0.5	0.7

Finally, data from GPRD(78) define the absolute rates of use of all hypnotics (about 2/3 of total) and anxiolytics (about 1/3 of total) over one year. It is clear that the heaviest use is in the elderly, who are most at risk from adverse effects, and for women more than men.

Table 7G: % of patients prescribed hypnotics or anxiolytics by age and gender

Age group	Male	Female
0-4	0.26	0.2
5-14	0.18	0.19
15-34	1.63	2.23
35-54	3.26	5.54
55-74	5.8	10.8
75+	15.2	22.4
Average	2.2	4.8

7.4.3 Current cost to the NHS

There are a number of ways to estimate the cost of hypnotics to the NHS. Depending on the assumptions made, different estimates of total spending are obtained. The

following table (*Table 7H*) presents the cost to the NHS by drug, based on total net ingredient costs for Z-drugs and benzodiazepines.

Table 7H: Cost to the NHS (2002)

Hypnotic	Total prescriptions (2002)	Cost per prescription per day (£)	Net ingredient cost (£) taken directly from PPA dataset (2002)
Zolpidem	631,710	0.16	2483959
Zopiclone	3,213,805	0.16	13078162
Zaleplon	58,443	0.29	316128
Total z-drugs	3,903,958		15878249
Nitrazepam	1,773,187	0.03	2180660
Temazepam	4,128,277	0.05	5662938
Loprazolam	170,273	0.16	974863
Lormetazepam	184,389	0.05	801395
Total BZDz	6,256,126		9619855
Total	10,160,084		25million

7.4.4 Short-term shift from benzodiazepines to Z-drugs

Current professional advice, e.g. Prodigy(79) favours the prescription of benzodiazepines unless there is a clear clinical reason to favour Z-drugs. However, it is evident from analysis of prescribing patterns that a switch from benzodiazepines to Z-drugs is slowly happening. This may be due to a cohort effect – the large numbers of patients who were given benzodiazepines at the height of their use in the 1970s, and who have been using them ever since, are slowly dying off. Or it may be due to doctor preference to prescribe the newer Z-drugs, either because of their perceived clinical benefits, advertising, or simply because the newer Z-drugs are not benzodiazepines. The following tables illustrate the cost to the NHS of switching prescriptions from benzodiazepines to Z-drugs.

The budget impact analysis recognises that the volume of benzodiazepine prescriptions is decreasing and, following the current trend, will continue to decrease. Following the current trend, it appears likely that the proportion of prescriptions for Z-drugs will continue to rise.

The tables below show the cost of switching from benzodiazepines to Z-drugs. TTtable 7I) using 2002 data, shows, the additional annual cost of switching from benzodiazepines to Z-drugs. In this scenario the reduction in the number of benzodiazepine prescriptions (n=1,251,225) is shared between the Z-drugs according to their 2002 market share of Z-drug prescriptions. Clearly any increase in the number of Z-drug prescriptions is accompanied by substantial increased costs. Additional costs range from £3m to £13m depending on the size of the switch. An important unknown is whether what will change will be simply numbers of prescriptions or length of prescriptions – e.g. will a long prescription for nitrazepam be replaced by a short prescription of zaleplon or other Z-drugs. This seems unlikely.

Table 7I: Additional cost of switching from benzodiazepines to Z-drugs

% switch	Based on a 14-day prescription (£)	Based on estimated average days of treatment (£)
20%	2m	3m
50%	5m	8m
80%	8m	13m

Table 7J using 2002 data, depicts the additional annual cost to the NHS if a reduction in benzodiazepine prescriptions leads to an increase in the number of zolpidem OR zopiclone OR zaleplon prescriptions. For example, if a reduction in 20% (1.2m) of benzodiazepine prescriptions leads to a 1.2m increase in zolpidem prescriptions, then the additional cost to the NHS is £2m or £3m depending on the method used. Clearly the results of the budget analysis must be interpreted in light of the assumptions made; the lowest estimate of total additional cost (£2m) to the NHS is very different from the largest estimate (£17m).

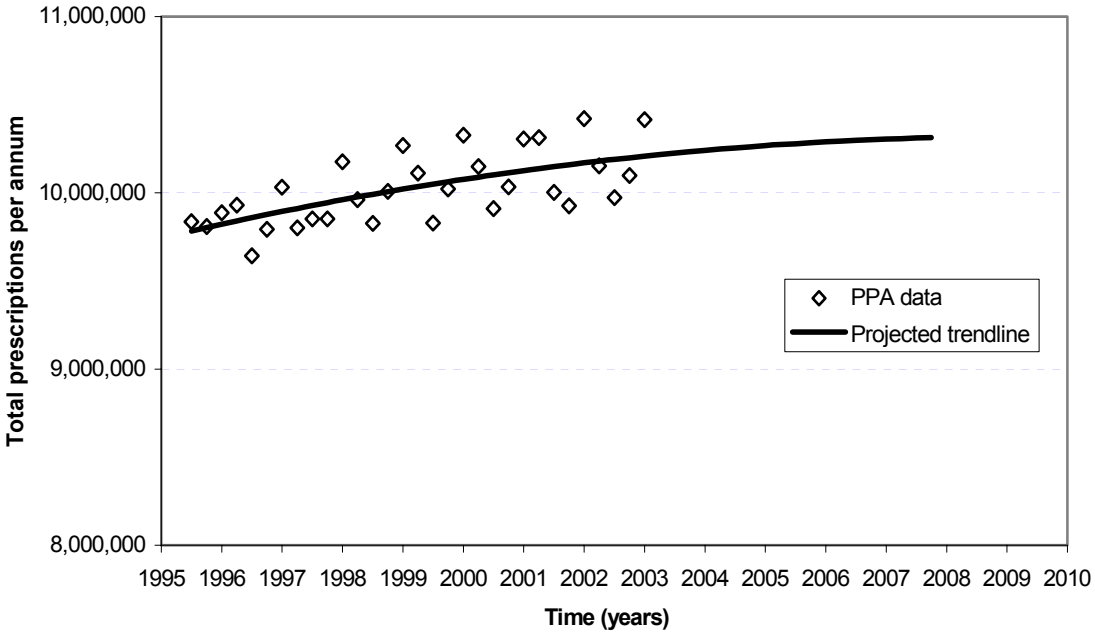
Table 7J: Additional annual cost of switching from benzodiazepines to individual Z-drugs

	Based on a 14-day prescription (£)			Based on estimated treatment days (£)		
	Zolpidem	Zopiclone	Zaleplon	Zolpidem	Zopiclone	Zaleplon
20%	2m	2m	4m	3m	3m	4m
50%	5m	5m	10.5m	7m	8m	10.5m
80%	8m	8m	17m	11m	13m	17m

7.4.5 Long-term shift from benzodiazepines to non-benzodiazepines

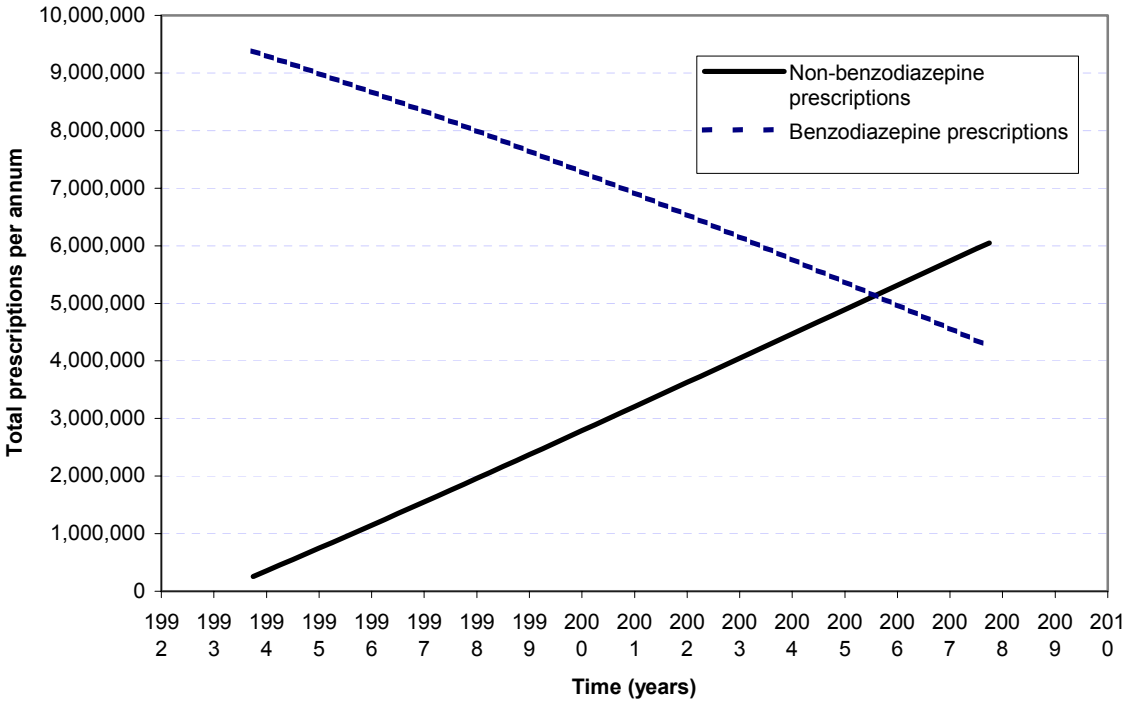
To forecast future NHS expenditure on hypnotics, it is necessary to anticipate the size of future volumes of prescriptions from the perspective of the NHS. In order to do this the trend in historic prescription data from 1995 onwards was modelled using a quadratic function to allow projection of the volume of prescriptions for a five-year period. *Figure 7C* indicates that the total volume of prescriptions for hypnotics is actually projected to increase slightly, reaching almost 10.5m per year by 2008. Each of the data points in the graph below is based on rolling quarterly data.

Figure 7C: Projecting future trends in volumes of prescriptions



On closer analysis it is clear that the number of prescriptions for benzodiazepines may continue to fall and the number of prescriptions for Z-drugs may continue to rise. Given current prescribing patterns, by the end of the year 2005, it may be expected that Z-drug prescribing will overtake that of benzodiazepine.

Figure 7D: Projecting future trends: benzodiazepines versus Z-drugs



As the total volume of hypnotic prescriptions continues to rise, the cost to the NHS will be considerable. Initial estimates of total cost by the year 2007 range from £17m to £33m depending on the method used. Detailed estimates of future spending have not been calculated given the many underlying uncertainties governing this market e.g. potential relative price changes of the drugs, the effect of reducing benzodiazepine prescriptions on the volume of Z-drug prescriptions, availability of new techniques and treatments for insomnia.

7.4.6 Limitations and conclusion

The budget impact analysis clearly shows that any decrease in the volume of benzodiazepine prescribing, if associated with increased prescribing on Z-drugs, will be very costly to the NHS.

In this pragmatic budget impact analysis, a switch from benzodiazepine prescribing to Z-drug prescribing has been used to estimate the likely total cost of hypnotics in the NHS. Although there is no clinical evidence from RCTs to justify this switch, by adopting a pragmatic approach the budget impact analysis has recognised that the number of prescriptions for benzodiazepines is falling and will continue to do so. It is unlikely that a reduction in the number of benzodiazepine prescriptions will lead to savings in the NHS. What is more likely is that the prescriptions for other insomnia treatments will rise. Given current trends in prescribing, it seems appropriate, in the budget impact analysis, to assume that prescriptions for Z-drugs will rise.

However, it may not be the case that a reduction in benzodiazepine prescriptions will only be accompanied by an increase in the number of Z-drugs prescribed. Current guidance is focussed on the non-pharmacological treatment of insomnia and it may be the case that a reduction in the number of benzodiazepine prescriptions is linked to both an increase in prescriptions of Z-drugs and other non-pharmacological treatments. If so, then the budget impact analysis may overestimate or underestimate the total cost of hypnotics in the NHS.

In recognition of the fact that misuse of benzodiazepines is linked to problems of long-term dependency and withdrawal, the National Service Framework for Mental Health(80) recommends that the prescribing of benzodiazepines be audited regularly within a local clinical audit programme. It has been recommended that the following should be audited:

- That new benzodiazepine prescriptions are issued for short-term relief (less than four weeks) of insomnia.
- That advice given about non-drug therapies for insomnia for every new and repeat prescription of benzodiazepines is documented.
- That appropriate advice given about the risk of benzodiazepine use, including the potential for dependence, is documented.

Although not specifically stated, this advice is usually extended to include the Z-drugs, where the evidence of dependency for two of these drugs is not different to that of benzodiazepines. If it is demonstrated that some of the Z-drugs have fewer problems of dependency and withdrawal than benzodiazepines when misused, then it may be the case that increases in initial spending are somewhat off-set in future years;

typical days of treatment will be shorter and fewer individuals will require NHS care to manage their dependency.

One final limitation to the budget impact analysis is that it is carried out from the perspective of the NHS. The impact of insomnia and its treatment has consequences not only for the NHS but also for society as a whole and this must be recognised.

In conclusion, a reduction in the number of benzodiazepine prescriptions, if accompanied by an increase in Z-drug prescribing will be very costly to the NHS. Whether or not the switch from benzodiazepines to Z-drugs is merited on clinical and/or economic grounds is unclear.

8 Conclusions

This review has examined the comparative effectiveness of the newer hypnotics to benzodiazepines in the short-term treatment of insomnia. A key issue is that it does not evaluate the broader question of the appropriateness of using hypnotics in the first place, and of the effectiveness of hypnotics versus placebo or non-pharmacological interventions. Questions also remain about the long-term effectiveness of these drugs when used for periods beyond 4-6 weeks, and their role in a condition which has a variable course and which is typically relapsing. These are vitally important questions, but are outside the remit for this study.

The systematic review identified a relatively small number of studies comparing one hypnotic to another. Most of these studies were old and conducted at a time when the quality of study reporting and publication were lower than they are at present and as a result, many of the studies have been of very poor methodological quality. Furthermore, the studies reported many different outcomes, and it has been difficult to extract and compare data from the studies to address the review question.

A further issue is that the remit of this review was to consider these drugs with respect to their licensed indications. However, it is clear from the prescribing and other data that many of these drugs are prescribed completely outside their current licence. Some of this is historical in origin and represents treatments which were started many years ago. We were unable to obtain data on how many new patients were becoming chronic users of hypnotics, and whether this differed between drugs. Anecdotally, although it still happens, this appears to be far less than in previous years. For instance, the prescribing of nitrazepam is declining, presumably due to a cohort effect as older patients, who were prescribed this drug for many years, gradually die. PCT prescribing advisers report anecdotally (personal communications) that one of the leading sources of chronic prescriptions of hypnotics today are patients seen by consultant psychiatrists rather than a GP; this is borne out by a recent study(158) in a mental health trust which showed that 31% of all patients were prescribed hypnotics, and that 10% of all patients received these for more than 4 weeks. Of all hypnotic prescriptions in this study, 30% were for more than 6 months.

It is therefore striking that the use of hypnotics as a whole has not declined and indeed is increasing slightly. This may be a source of concern for the future, if these drugs continue to be considered inappropriate for widespread or prolonged use.

To summarise the results, there are minor differences between the drugs. Some of these relate to the pharmacology of the drugs; for instance, zaleplon is rapidly absorbed and rapidly cleared – this results in shorter sleep latency, but no extension in duration of sleep compared to zolpidem. The question of which of these is the "better" hypnotic may depend on what aspects of sleep are problematic for the patient – not falling asleep or excessive awakenings. There are therefore trade-offs between different aspects of sleep. Some drugs 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 apparently the worst offenders in this regard.

The lack of any major evidence of difference in terms of clinical effectiveness or utility, or indeed even within well-defined areas such as sleep latency or duration may be due to the poor design on reporting of trials, which undermine attempts to combine results from different studies. Most of the studies were commercially sponsored. Many perceived differences between benzodiazepines and Z-drugs may be the results of the historical time in which they came to the market.

There is however no consistent pattern of superiority of one drug over any other, even within well defined areas. Many of the comparisons between drugs which we would like to have evaluated have never been made, e.g. between zaleplon and many benzodiazepines.

Broad guidance on what constitutes good use of hypnotics has been produced by the BNF.(51) It recommends short term use – no more than 3 weeks, and intermittent dosing is preferable; a rapidly eliminated drug is generally (more) appropriate, and names temazepam, lormetazepam or loprazolam as drugs that fit this description. The Z-drugs are also considered satisfactory.

The question of intermittent use has not been examined in this review: there is evidence to support the use of zolpidem in this way but similar trials do not seem to exist for benzodiazepines or other Z-drugs. It is assumed that such a prescribing pattern should limit the development of tolerance and the risks of dependency but more research on this is needed. There are no comparative studies between drugs in this area.

In summary, the short acting drugs seem equally effective and safe with minor differences that may lead a prescriber to favour one over another in different patients. There is no evidence that one is more cost effective than any other.

A key issue has been the question of drug dependency. This mainly applies when the drug is used outside its licence, and has been difficult to address because of the lack of adequate research in this area. In the past, benzodiazepines were used at higher doses and for prolonged periods and this resulted in large numbers of dependent patients and reports of dependency. By contrast, the newer hypnotics have come on to the market at a later time, when attitudes towards the use of hypnotics and sedatives in general have changed. They are therefore perhaps less likely to be used in the same way and for the same prolonged periods. While there are reports of dependency on these drugs, they are more limited than on benzodiazepines. Some argue that there is a difference in dependency potential among hypnotics when they are used for inappropriately long periods. At present, it may be more appropriate to be on the side of caution, and restrict use of these drugs to the terms of the BNF recommendations, including restriction to use in disabling insomnia.

With regard to other potential adverse effects such as amnesia, next day drowsiness etc, our review has not found any consistent differences between the drugs, in part because of the poor quality of reporting.

Issues raised in the pharmaceutical company submissions involved whether particular drugs might be less likely to lead to falls and to road traffic accidents. There are

described associations between some hypnotics and both of these events. With regard to driving, evidence that long acting drugs such as nitrazepam are more harmful exists, but there is no clear distinction between the shorter acting drugs. Falls, especially in the elderly, may be an issue, but again the evidence in this area to argue that one drug is superior to another is weak.

Much was made in the industry submissions of the improved functioning of individuals during the day as a consequence of the use of the more expensive drugs with shorter half-lives. Again we await further evidence of both the existence of this and its importance. We found limited evidence of statistically significant difference in daytime function, either mental or physical resulting from the use of the different drugs. This is obviously a crucial area for future research which will greatly improve the ability of the economic analysis to undertake a meaningful assessment.

Although we examined the health economics of this area, we found insufficient data to allow us to undertake an economic evaluation. We have reworked one economic evaluation submitted by a company and corrected some of its errors, but point out that this is dependent on a key supposition, i.e. that falls are related to hypnotic use and that one drug will be superior – a contention not so far supported by the trial evidence or indeed by the observational data.

The systematic review provided in this document suggests that an agnostic approach to cost-effectiveness is required at this stage. In the short-term, no systematic evidence is available concerning significant outcome variations between either the different classes of drugs or between individual drugs within each class. Within this short-term horizon, the one element that does vary significantly is the acquisition cost of the individual drugs. In such circumstances, and in the absence of further evidence of their clinical superiority, it seems difficult to justify the use of more expensive drugs and there seems no reason to alter traditional recommendations of choice of drug (i.e. to use short-acting benzodiazepines as first choice).

There are clear research needs in this area: in particular, none of the existing trials adequately compare these medications. We would urge therefore that further consideration should be given to a non-commercially supported formal trial to allow head to head comparison of some of the key drugs in a double blind RCT lasting at least two weeks, and of sufficient size to draw reasonable conclusions. We would also recommend that any such trial should include a placebo arm. It should also collect good quality data around sleep outcomes and in particular quality of life and daytime drowsiness. We do not believe that any formal study of risk of dependency is feasible at present.

Finally the major research issue is perhaps not around the management of short term insomnia, but around the management of long term insomnia: considering the frequency of this symptom and its recurring course, the short term trial of medication and lack of long term follow-up undermine attempts to develop evidence based guidelines for the use of hypnotics in this condition, or indeed for its whole management.

Appendix 1: Search strategies and search results

Table A1: Search for clinical-effectiveness studies: summary

Database	Years	Search strategy	References identified
MEDLINE	1966-2003	See below	244
EMBASE	1980-2003	See below	416
PsychINFO	1966-2003	See below	61
Science Citation Index/Web of Science	1981-2003	((insomnia* or sleep*) and (zaleplon or sonata or zolpidem or stilnoct or zopiclone or zimovane or zileze))	481
Science Citation Index/ ISI Proceedings	1990-2003	As above	37
Cochrane Trials Register	2003 (1)	As above	260
Cochrane Database of Systematic Reviews	2003 (1)	As above	8
HTA*	1994-2003	As above	0
DARE*	1994-2003	As above	5
	Total references identified		**1504**
	Duplicates		**699**
	Total		**805**

** Please note that these databases have retrospective coverage of literature a few years prior to the start dates given. Also, the HTA used to be included as part of the DARE.*

Search Strategy for clinical effectiveness (MEDLINE 1966-2003)

1. randomized controlled trial.pt.
2. randomized controlled trials.sh.
3. random allocation.sh.
4. double blind method.sh.
5. single blind method.sh.
6. clinical trial.pt.
7. clinical trials.sh.
8. controlled clinical trials.sh.
9. (clin$ adj25 trial$).ti,ab.
10. ((singl$ or doubl$ or trial$) adj25 (blind$ or mask$)).ti,ab.
11. random$.ti,ab.
12. research design.sh.
13. exp Evaluation Studies/
14. follow up studies.sh.
15. prospective studies.sh.
16. (control$ or prospective$ or volunteer$).ti,ab.
17. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16
18. animal.sh.
19. human.sh.
20. 18 not (18 and 19)
21. 17 not 20
22. (zaleplon or sonata).af
23. (zolpidem or stilnoct).af
24. (zopiclone or zimovane or zileze).af
25. 22 or 23 or 24
26. exp “Sleep Initiation and Maintenance Disorders”/ or exp SLEEP/
27. (insomnia or sleeplessness).tw
28. 26 or 27
29. 21 and 25 and 28

Search Strategy for clinical effectiveness (EMBASE 1980-2003)

1. randomised controlled trial/
2. controlled study/
3. randomisation/
4. exp double blind procedure/
5. exp single blind procedure/
6. clinical trial/
7. random$.ti,ab.
8. methodology/
9. evaluation/
10. follow up/
11. prospective study/
12. (control$ or prospective$ or volunteer$).ti,ab.
13. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12
14. (zaleplon or sonata).af
15. (zolpidem or stilnoct).af
16. (zopiclone or zimovane or zileze).af
17. 14 or 15 or 16
18. exp insomnia/ or (insomnia or sleeplessness).tw.
19. exp sleep/
20. 18 or 19
21. 13 and 17 and 20
22. limit 21 to human

Search Strategy for clinical effectiveness (PsycINFO 1966-2003)

1. random$ controlled trial.mp.
2. random$.ti.ab.
3. (clin$ adj25 trial$).ti,ab.
4. ((singl$ or doubl$ or trial$) adj25 (blind$ or mask$)).ti,ab.
5. (control$ or prospective$ or volunteer$).ti,ab.
6. (zaleplon or sonata).af
7. (zolpidem or stilnoct).af
8. (zopiclone or zimovane or zileze).af.
9. 1 or 2 or 3 or 4 or 5
10. 6 or 7 or 8
11. exp insomnia/ or (insomnia or sleeplessness).tw.
12. 9 and 10 and 11
13. limit 12 to (human and year=1966-2003)

Table A2: Search strategies for dependency and withdrawal

Database	Years	Search strategy	References Identified
MEDLINE	1966-2003	See below	192
EMBASE	1980-2003	See below	399
PsycINFO	1966-2003	See below	67
	Total references identified		**658**
	Duplicates		**195**
	Total		**463**

Search Strategy for dependency and withdrawal (MEDLINE 1966-2003)

1. withdraw$.mp
2. dependenc$.mp
3. exp drug tolerance
4. tolerance.mp
5. rebound.mp
6. exp substance withdrawal syndrome
7. exp "dependency (Psychology)"
8. (zaleplon or sonata).af
9. (zolpidem or stilnoct).af
10. (zopiclone or zimovane or zileze).af
11. 8 or 9 or 10
12. 1 or 2 or 3 or 4 or 5 or 6 or 7
13. 11 and 12
14. limit to 13 to human

Search Strategy for dependency and withdrawal (EMBASE 1980-2003)

1. withdraw$.mp
2. dependenc$.mp
3. exp drug tolerance
4. tolerance.mp
5. exp withdrawal syndrome/ or exp drug withdrawal
6. rebound.mp
7. (zaleplon or sonata).af
8. (zolpidem or stilnoct).af
9. (zopiclone or zimovane or zileze).af
10. 7 or 8 or 9
11. 1 or 2 or 3 or 4 or 5 or 6
12. 10 and 11
14. limit to 12 to human

Search Strategy for dependency and withdrawal (PsycINFO 1966-2003)

1. withdraw$.mp
2. dependenc$.mp
3. exp drug tolerance
4. tolerance.mp
5. rebound.mp
6. exp drug withdrawal
7. exp drug dependency
8. exp drug tolerance
9. (zaleplon or sonata).af
10. (zolpidem or stilnoct).af
11. (zopiclone or zimovane or zileze).af
12. 9 or 10 or 11
13. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8
14. 12 and 13
15. limit 14 to human

Table A3: Search for cost-effectiveness studies: summary

Database	Years	Search strategy	References identified
MEDLINE	1966-2003	See below	148
EMBASE	1980-2003	See below	440
PsycINFO	1974-2003	See below	38
Science Citation Index/Web of Science	1981-2003	(cost or quality of life) and insomnia	209
Science Citation Index/ ISI Proceedings	1981-2003	(cost or quality of life) and insomnia	26
Cochrane Database of Systematic Reviews	2003 (1)	(cost and insomnia)	46
NHS EED*	1994-2003	(insomnia or sleep)	63
HTA*	1994-2003	(insomnia or sleep)	7
DARE*	1994-2003	(insomnia or sleep)	124
Health Economic Evaluations Database	1995-2003	((benzodiazepine or zaleplon or zolpidem or zopiclone) and cost)	9
	Total references identified		1,100
	Duplicates		171
	New total		**929**

** Please note that these databases have retrospective coverage of literature a few years prior to the start dates given. Also, the HTA used to be included as part of the DARE.*

Medline Cost-effectiveness Search Strategy (1966-2003)

1. benzodiazepine$.mp. or exp benzodiazepines/
2. (zalepon or sonata).af
3. (zolpidem or stilnoct).af
4. (zopiclone or zimovane or zileze).af.
5. exp sleep/
6. insomnia.mp or exp "sleep initiation and maintenance disorders"/
7. (insomnia or sleeplessness).tw
8. cost.mp or exp "Costs and Cost Analysis"/
9. cost$.mp
10. model$.mp
11. economic$.mp. or exp ECONOMICS, NURSING/ or exp ECONOMICS, DENTAL/ or exp ECONOMICS/ or exp ECONOMICS, HOSPITAL/ or exp ECONOMICS, PHARMACEUTICAL/
12. quality of life.mp. or exp Quality of Life/
13. exp Life Expectancy/ or quality adjusted life year.mp. or exp Decision Making/ or exp Quality-Adjusted Life Years/ or exp Cost-Benefit Analysis/ or exp Quality of Life/
14. (1 or 2 or 3 or 4) and (5 or 6 or 7) and (8 or 9 or 10 or 11 or 11 or 12 or 13)

Embase Cost-effectiveness Search Strategy (1980-2003)

1. benzodiazepine$.mp. or exp benzodiazepines/
2. (zalepon or sonata).af
3. (zolpidem or stilnoct).af
4. (zopiclone or zimovane or zileze).af.
5. exp sleep/
6. insomnia.mp or exp "sleep initiation and maintenance disorders"/
7. (insomnia or sleeplessness).tw
8. cost.mp or exp "Costs and Cost Analysis"/
9. cost$.mp
10. model$.mp
11. economic$.mp or exp ECONOMICS/ or exp HEALTH ECONOMICS/
12. quality of life.mp. exp quality of life
13. Health Care Delivery/ or quality adjusted life year.mp. or Cost Effectiveness Analysis/ or Health Status/ or Economics/ or Economic Aspect/ or Quality of Life/ or Cost Benefit Analysis/ or Quality Adjusted Life Year/ or Life Expectancy
14. (1 or 2 or 3 or 4) and (5 or 6 or 7) and (8 or 9 or 10 or 11 or 12 or 13)

PsycINFO Cost-effectiveness Search Strategy (1974-2003)

1. benzodiazepine$.mp. or exp benzodiazepines/
2. (zalepon or sonata).af
3. (zolpidem or stilnoct).af
4. (zopiclone or zimovane or zileze).af.
5. exp sleep/
6. (insomnia or sleeplessness).tw
7. cost.mp or exp "Costs and Cost Analysis"/
8. cost$.mp
9. model$.mp
10. quality of life.mp. or exp Quality of Life/
11. (1 or 2 or 3 or 4) and (5 or 6) and (7 or 8 or 9 or 10)

Appendix 2: Quality assessment checklists

Quality assessment checklist for clinical studies

Studies of clinical effectiveness will be assessed using the following criteria, based on CRD Report No. 4, University of York(81)

- Was the method used to assign participants to the treatment groups really random? (*Computer generated random numbers and random number tables will be accepted as adequate, whilst inadequate approaches will include the use of alternation, case record numbers, birth dates or days of the week*)
- Was the allocation of treatment concealed? (*Concealment will be deemed adequate where randomisation is centralised or pharmacy-controlled, or where the following are used: serially numbered containers, on-site computer-based systems where assignment is unreadable until after allocation, other methods with robust methods to prevent foreknowledge of the allocation sequence to clinicians and patients. Inadequate approaches will include: the use of alternation, case record numbers, days of the week, open random number lists and serially numbered envelopes even if opaque*)
- Was the number of participants who were randomised stated?
- Were details of baseline comparability presented in terms of treatment free interval, disease bulk, number of previous regimens, age, histology and performance status?
- Was baseline comparability achieved for treatment free interval, disease bulk, number of previous regimens, age, histology and performance status?
- Were the eligibility criteria for study entry specified?
- Were any co-interventions identified that may influence the outcomes for each group?
- Were the outcome assessors blinded to the treatment allocation?
- Were the individuals who were administered the intervention blinded to the treatment allocation?
- Were the participants who received the intervention blinded to the treatment allocation?
- Was the success of the blinding procedure assessed?
- Were at least 80% of the participants originally included in the randomisation process, followed up in the final analysis?
- Were the reasons for any withdrawals stated?
- Was an intention to treat analysis included?

Items graded as:

✔ **yes** (item adequately addressed), ✘ **no** (item not adequately addressed), ✔/✘ **partially** (item partially addressed), **NA** not applicable or **NS** not stated.

Quality assessment checklist for cost-effectiveness studies(159)

- Well-defined question
- Comprehensive description of competing alternatives
- Effectiveness established
- All important and relevant costs and consequences for each alternative identified
- Costs and consequences measured accurately
- Costs and consequences valued credibly
- Costs and consequences adjusted for differential timing
- Incremental analysis costs and consequences
- Sensitivity analyses to allow for uncertainty in estimates of costs or consequences
- Study results/discussion include all issues of concern to users

The scores used for each dimension were as follows:

✔	Dimension appropriately addressed
✔/✘	Dimension partially/maybe addressed
N/A	Dimension not applicable

Appendix 3: Clinical data tables

Table A4: Study characteristics

Study name	Interventions Drug & dose n	Study design	Setting	Commercial support	Outcomes	Location & centres	Inclusion criteria	Exclusion criteria	Duration	Follow-up	Other comparators
KAZAMATSURI 1993(86)	Zolpidem 10mg n=73 Nitrazepam 5mg n=74	RCT DB parallel	Majority in-patients	Not stated	Sleep latency, quality of sleep, sleep duration, number of awakenings, feeling on waking up and during day, safety, anxiety	Japan Multicentre	Age 16-70 insomniacs with schizophrenia and manic-depressive psychosis sleep disturbance >3 days/week	Patients in which sleep pattern couldn't be ascertained	1 week	None	None
KUDO 1993(88)	Zolpidem 10mg n=64 Nitrazepam 5mg n=67	RCT DB parallel	Mostly out-patients	Not stated	Sleep latency, quality of sleep, sleep duration, number of awakenings, feeling on waking up and during day, safety, anxiety	Japan Multicentre	Age 16-70 chronic primary insomnia sleep difficulties >3 days/week	Patients in which sleep pattern unclear, inappropriate drug use	1 week	None	None
KERKHOF 1996(89)	Zolpidem 10mg 17 in analysis Temazepam 20mg 13 in analysis	RCT DB parallel	Not stated	Not stated	Polysomnographic parameters, motor activity, subjective estimates of sleep times and sleep quality	The Netherlands Multicentre	Not stated	Not stated	10 nights	11 days	None
LEPPIK 1997(82)	Zolpidem 5mg n=82 Temazepam 15mg n=82	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, no of awakenings, wake time after sleep onset, quality of sleep, morning sleepiness, ability to concentrate	USA Multicentre	Age 60-85 chronic insomnia >3mo, SSL of 30 min, SSD of 4-6/night, impairment of daytime func, deprivation, stable mental and physical health	Mental illness, organic conditions, previous drug use, known allergy, substance abuse, shift workers and individuals with changing sleep schedules	4 weeks	4 days	Triazolam n=85 Placebo n=84

Study name	Interventions Drug & dose n	Study design	Setting	Commercial support	Outcomes	Location & centres	Inclusion criteria	Exclusion criteria	Duration	Follow-up	Other comparators
ANSOMS 1991(83)	Zopiclone 7.5mg n=27 in analysis Lormetazepam 1mg n=25 in analysis *Overall*: n=54	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	Belgium 2 centres	Age 21-55 need daily hypnotic for alcohol withdrawal, sleep latency >30mins, several nocturnal awakenings, waking up too early, trouble during the day because of lack of sleep at night	Mental illness, previous drug use, history of drug abuse, shift workers	5 nights	None	None
AGNOLI 1989(84)	Zopiclone 7.5mg Nitrazepam 5mg *Overall*: n=20	RCT DB cross-over (1 week washout)	Not stated	None reported	Quality of daytime arousal, time of sleep induction, number of nocturnal arousals, quality of sleep, duration of sleep	Italy 3 centres	Age 20-50 generalized anxiety disorder (Hamilton Rating <20), absence of, factors related to onset or persistence of insomnia	Mental illness, organic conditions, concomitant antidepressive, anxiolytic or neuroleptic drug use, effectiveness of placebo.	2 weeks	None	None
ANDERSON 1987(85)	Zopiclone 7.5mg Nitrazepam 5mg *Overall*: n=119 (# per group not reported)	RCT DB parallel	General practice	May & Baker, Ltd., Essex, UK (author)	Sleep latency, nocturnal awakenings, duration of sleep, and quality of sleep, feeling on awakening, adverse events.	UK Multicentre	Age 20-69 unable to fall asleep within 45 minutes, or >2 nocturnal awakenings with difficulty returning to sleep no known cause, or sleeping <6 hours per night.	Mental illness, organic condition, substance abuse, previous drug use, hypersensitivity, night shift workers.	2 weeks	1 week	Placebo n=unknown
JOVANOVIC 1983(90)	Zopiclone 7.5mg n=5 Nitrazepam 5mg n=5	RCT DB parallel	Sleep lab	Rhone-Poulenc Sante, Courbevoie, France (co-author)	Total sleep time, number of awakenings	Germany Single centre	Age 21-49 at least 3 of the following symptoms over at least 2 months without improvement: sleep onset longer than 45 min, sleep duration shorter than 6h, at least 3 nocturnal awakenings, waking up in the morning at least 2h before expected, poor morning conditioning	Acute illness, severe chronic diseases, substance abuse, mental retardation and epilepsy, organic condition (pregnancy), history of drug reaction	14 nights	10 nights (first week on placebo)	None

Study name	Interventions Drug & dose n	Study design	Setting	Commercial support	Outcomes	Location & centres	Inclusion criteria	Exclusion criteria	Duration	Follow-up	Other comparators
KLIMM 1987(87)	Zopiclone 7.5mg Nitrazepam 5mg *Overall*: n=74 (# per group not reported)	RCT DB parallel	Community residence	Rhone-Poulenc-Sante, Courbevoie, France (2 co-authors)	Sleep onset latency, quality of sleep, feeling on awakening, duration of sleep, nocturnal awakenings, condition in the morning, general evaluation	Germany Single centre	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.	Painful conditions, contraindications to benzodiazepines, substance misuse, drug treatment liable to affect metabolism, unable to complete trial or already in other trial, unlikely to cooperate	1 week	None	None
OHTOMO 1 1985(91)	Zopiclone 7.5mg n=54 Nitrazepam 5mg n=74	RCT DB parallel	In and out-patients	Not stated	Sleep latency, number of awakenings, sleep quality, side-effects	Japan Multicentre	Age >60 difficulty with sleeping ≥3 days/week	Mental illness, organic condition, known allergy	1 week	None	None
OHTOMO 2 1985(92)	Zopiclone 5mg n=66 Nitrazepam 5mg n=71	RCT DB parallel	In and out-patients	Not stated	Sleep latency, number of awakenings, sleep quality, side-effects	Japan 14 centres	Age >60 35-81 kg, difficulty with sleeping ≥1 day/week	Mental illness, organic condition, known allergy	1 week	None	None
PULL 1983(93)	Zopiclone 7.5mg Zopiclone 15mg Nitrazepam 5mg Nitrazepam 15mg *Overall:* n=40	RCT DB cross-over(no washout period)	Hospital	Rhone-Poulenc Sante, Courbevoie, France (co-author)	Quality of sleep, including sleep onset latency, total sleep time, number of awakenings, vigilance after awakening, feeling after awakening, memory, side effects,	Luxembourg Single centre	Age 18-65 hospitalised for depression, schizophrenia, alcoholism, stabilised, but suffering from insomnia	Expected hospitalisation <5 days or change in basic treatment, need for psychotropic medication or psychotherapy after 13.00 h, patients expected not to comply with abstinence from certain substances, nonpsychotropic somatic treatment or nonstabilised disorder possibly influencing sleep, pregnancy.	1 night	None	None

Study name	Interventions Drug & dose n	Study design	Setting	Commercial support	Outcomes	Location & centres	Inclusion criteria	Exclusion criteria	Duration	Follow-up	Other comparators
TAMMINEN 1987(94)	Zopiclone 7.5mg n=49 Nitrazepam 5mg n=45 *Overall:* n=130 only 94 included in analysis	RCT DB parallel	Out-patients	Rhone-Poulenc Pharma Norden, Birkerod, Denmark (co-author)	Sleep onset latency, quality of sleep, sleep questionnaire, investigator's global evaluation, general morning condition, working ability, somatic complaints	Finland, Denmark, Norway 7 centres	Age 18-70, insomnia ≥ 3 months, ≥ 2 of the following: latency of sleep onset >30 min, total sleep duration <6.5 hours, nocturnal awakenings >2 per night, time to fall asleep after at least one nocturnal awakening >30 min., awakening >2 hours before scheduled time.	Mental illness, organic condition, known allergy, previous drug use, substance abuse	6 weeks	None	None
NGEN 1990(95)	Zopiclone 7.5mg n=20 Temazepam 20mg n=20	RCT DB parallel	Home-based (unclear)	Acknowledged Rhone Poulenc	Sleep latency, number of awakenings, total sleep duration, psychomotor performance, and physician global assessment.	Malaysia Single centre	Age 18-70 years one of the following symptoms for ≥2 weeks: >45 min. sleep latency, >2 nocturnal awakenings every night without known cause and difficulty returning to sleep, sleep duration <6 hours	Mental illness, organic condition, known allergy, previous drug use, substance abuse, night shift work	2 weeks	None	Placebo n=20
STIP 1999(96)	Zopiclone 7.5mg Temazepam 30mg *Overall:* n=60 (# randomised per group not reported)	RCT DB parallel	Not stated	None stated	Primary: Cognitive functioning Secondary: Anxiety, sleep onset, duration, number of awakenings, quality of sleep, residual effects, memory, attention and concentration	Canada Single centre	Adult patients Primary insomnia or insomnia associated with mild non-psychotic psychiatric disorders (DSM III-R) daytime fatigability, diminished power of concentration and at least two of the following: latency >30 min., sleep duration <5 hours, >2 awakenings per night, early wake up in the morning.	None stated	3 weeks	1 week	Placebo n=15

Study name	Interventions Drug & dose n	Study design	Setting	Commercial support	Outcomes	Location & centres	Inclusion criteria	Exclusion criteria	Duration	Follow-up	Other comparators
Van der KLEIJN 1989(97)	Zopiclone 7.5mg Temazepam 20mg *Overall:* n=60	DB cross-over (2 night washout)	Out-patients	Acknowledged Rhone-Poulenc Pharma	Sleep quality, latency of onset, status after awakening, mood and behaviour during the day, somatic symptoms and side effects	The Netherlands Single centre	Age 18-70 one of the following: latency of sleep onset >30 min, waking too early, several nocturnal awakenings with difficulty in returning to sleep, bothered during day by unsatisfactory sleep.	Non-benzodiazepine hypnotics prior to study, use of psychotropic drugs for the first time or change of such medication, high-dose hypnotic use prior to study, organic conditions, unable to complete questionnaire, substance misuse, mental illness, physical stress situations likely to fluctuate, shift-workers.	5 nights following 2 nights washout	(1 week placebo)	Placebo
WHEATLEY 1985(98)	Zopiclone 7.5mg n=17 Temazepam 20mg n=19 *Overall:* n=36	RCT DB cross-over(no wash out)	Not stated	Acknowledged May & Baker	Sleep latency, nocturnal awakenings, duration, and quality of sleep, state on waking, at work, with others, driving, and side effects.	UK Single centre	Age ≥ 18 difficulty sleeping for ≥ 1 week	Not stated	1 week (no washout between cross-over phases)	None	None
ALLAIN 2001(99)	Zaleplon 10mg Zolpidem 10mg *Overall:*n=53	RCT DB cross-over	General practice	Sanofi-Synthelabo (2 co-authors)	Quality of life, drug preference, diurnal awakeness, quality of sleep onset, quality of sleep, duration of sleep	France (12 general practitioners recruited patients)	Age: not stated Untreated insomnia characterised by difficulties falling asleep, no other criteria mentioned	None specified (except for ban on hypnotic use for 1 week prior to study entry)	2 nights (no information on washout between treatment periods)	None	None
ANCOLI-ISRAEL 1999(102)	Zaleplon 5mg n=166 Zaleplon 10mg n=165 Zolpidem 5mg n=111	RCT DB parallel	Out-patients	Wyeth-Ayerst Research, Radnor, Pa, USA (2 co-authors)	Subjective assessments of sleep latency, total sleep time, number o awakenings, sleep quality, rebound insomnia	USA 35 centres	Age ≥ 65 sleep latency >30 min, awakenings on average per night >3, total sleep time ≤ 6.5 hours	Pre-existing medical condition that would affect the study results, sleep apnea or restless legs syndrome	2 weeks	1 week	Placebo n=107

Study name	Interventions Drug & dose n	Study design	Setting	Commercial support	Outcomes	Location & centres	Inclusion criteria	Exclusion criteria	Duration	Follow-up	Other comparators
ELIE 1997(100)	Zaleplon 5mg n=122 Zaleplon 10mg n=121 Zaleplon 20mg n=124 Zolpidem 10mg n=122	RCT DB parallel	Out-patients	Wyeth-Ayerst Research, Radnor, Pa, USA (2 co-authors)	Sleep latency, sleep maintenance, sleep quality, rebound insomnia, withdrawal effects.	Canada and Europe 39 centres	Age 18-65 primary insomnia or insomnia associated with mild non-psychotic disorders (DSM-III-R), sleep latency ≥30 min, daytime impairment due to sleep disturbance, and either mean sleep duration ≤6.5 hours or prolonged or frequent nocturnal awakenings	Organic conditions, mental illness, previous drug use, substance abuse.	4 weeks	3 days	Placebo n=126
FRY 2000(101)	Zaleplon 5mg n=118 Zaleplon 10mg n=120 Zaleplon 20mg n=121 Zolpidem 10mg n=117	RCT DB parallel	Out-patients	Wyeth-Ayerst Research, Radnor, Pa, USA (co-author)	Primary: Self-reported sleep latency, (SLL) Secondary: Subjective assessments of total sleep time, no. of awakenings, sleep quality, rebound, withdrawal effects, adverse effects	USA 27 centres	Age 16-85 primary insomnia or insomnia associated with mild non-psychotic psychiatric disorders, sleep latency ≥30 min, daytime impairment due to sleep disturbance, average total sleep duration/night ≤6.5, or prolonged or frequent nocturnal awakenings	Transient insomnia, situational insomnia, substance abuse, major mental illness	4 weeks	3 days	Placebo n=119
ZAMMIT 1 2000(103)	Zaleplon 10mg Zolpidem 10mg *Overall:* n=42	RCT DB cross-over	Sleep lab	None reported	Next-day residual sedation, sleep latency, total sleep time	USA Single centre	Age 18-65 objectively verified sleep maintenance insomnia	Pregnancy	2 nights	None	Placebo
ZAMMIT 2 2000(103)	Zaleplon 10mg Zolpidem 10mg *Overall:*n=37	RCT DB cross-over	Sleep lab	None reported	Next-day residual sedation, sleep latency, total sleep time	USA Single centre	Age 18-65 objectively verified sleep maintenance insomnia	Pregnancy	2 nights	None	Placebo

Study name	Interventions Drug & dose n	Study design	Setting	Commercial support	Outcomes	Location & centres	Inclusion criteria	Exclusion criteria	Duration	Follow-up	Other comparators
TSUTSUI 2001(104)	Zolpidem 10mg n=231 Zopiclone 7.5mg n=218	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; sleep quality; physical condition parameters.	Japan 95 centres	Age: not stated Chronic primary insomnia (i.e. experiencing non-restorative sleep or difficulty initiating or maintaining sleep >1mo), sleep difficulties >3 times/week	Mental illness, organic conditions, symptoms interfering with sleep (pain, fever etc.), known allergy, previous drug use, history of drug dependence	2 weeks	1 week	None

Table A5: Participant characteristics *

Study name	Intervention	Age, mean (SD)	Sex (female) %	Duration of illness	Prior drug use	Concomitant drugs	Concomitant disorders(s)
Zolpidem versus Nitrazepam							
KAZAMATSURI 1993(86)	Zolpidem 10mg Nitrazepam 5 mg	10% over 60 years 11% over 60 years	36 36	52% of patients > 6 months; 21% ≤ month	62% 64%	For primary psychiatric disorder	Patients suffer from schizophrenia and manic-depressive psychosis
KUDO 1993(88)	Zolpidem10mg Nitrazepam 5mg	25% over 60 years 31% over 60 years	63 61	27% of patients >6 months; 30% ≤ 1 month			
Zolpidem versus Temazepam							
KERKHOF 1996(89)	Zolpidem 10mg Temazepam 20mg		70				
LEPPIK 1997(82)	Zolpidem 5mg Temazepam 15mg	69 (range 59-85) (total)	63	Chronic insomnia of ≥ 3 months	Use of study medication within 30 days prior to study prohibited, as was regular use of medication that could interfere with assessment of hypnotics, and previous use of zolpidem		
Zopiclone versus Lormetazepam							
ANSOMS 1991(83)	Zopiclone 7.5mg Lormetazepam 1mg	44.2 (8.8) 43.6 (8.1)	37 28		Patients on benzodiazepine tranquillisers or with history of drug abuse before study period excluded		Those in post-alcoholism withdrawal period of ≥ 10 days included
Zopiclone versus Nitrazepam							
AGNOLI 1989(84)	Zopiclone 7.5mg Nitrazepam 5mg	38.2 (9.4)	60	Chronic (mean duration 31.7 days)	Use of benzodiazepines in 8 patients reported		Generalized anxiety disorder (DSM III-R)

Study name	Intervention	Age, mean (SD)	Sex (female) %	Duration of illness	Prior drug use	Concomitant drugs	Concomitant disorders(s)
ANDERSON 1987(85)	Zopiclone 7.5mg Nitrazepam 5mg				Regular medication providing sedation or analgesia and centrally-acting antithypertensives were not permitted		
JOVANOVIC 1983(90)	Zopiclone 7.5mg Nitrazepam 5mg	30.1 (total)	40 60	Minimum 2 months	Drug addiction and previous medication		
KLIMM 1987(87)	Zopiclone 7.5mg Nitrazepam 5mg	73.2 (1.54) (total)	80	Chronic	Regular medications continued unchanged	No psychotropic or centrally active drugs were given during washout period and treatment	71 patients had concomitant diseases including arthritis, circulatory disorders, hypertension and cardiac insufficiency. All were free from severe organic and psychiatric disorders.
OHTOMO 1 1985(91)	Zopiclone 7.5mg Nitrazepam 5mg		57.8				
OHTOMO 2 1985(92)	Zopiclone 5mg Nitrazepam 5mg		56.2				
PULL 1983(93)	Zopiclone 7.5mg Zopiclone 15mg Nitrazepam 5mg Nitrazepam 10mg			26 patients considered as chronic	Patients on hypnotics	Associated psychotropic medication including antidepressants (22 cases), minor tranquillizers (23 cases) and major tranquillizers (7 cases) remained unchanged during trial	Only those hospitalised for depression, schizophrenia, or alcoholism included. The psychiatric episode was stabilized at the beginning of trial.
TAMMINEN 1987(94)	Zopiclone 7.5mg Nitrazepam 5mg	47 (range 26-71) (total)	77	Sleep disturbance of ≥ 3 months	54% of zopiclone and 47% of nitrazepam patients were previously treated with hypnotics (mainly benzodiazepines)		

Study name	Intervention	Age, mean (SD)	Sex (female) %	Duration of illness	Prior drug use	Concomitant drugs	Concomitant disorders(s)
Zopiclone versus Temazepam							
NGEN 1990(95)	Zopiclone 7.5mg Temazepam 20mg	38.4 36.2	60 60	Minimum 2 weeks	Not reported		
STIP 1999(96)	Zopiclone 7.5mg Temazepam 30mg	38.4 (9.9) 42.9 (12.0)	ns ns		Patients having received hypnotics with long-life received lorazepam for 1 week prior to washout		Mild non-psychotic psychiatric disorders (DSM III-R) also included
Van der KLEIJN 1989(97)	Zopiclone 7.5mg Temazepam 20mg	53 (range 23-69) (total)	70		Most patients known regular hypnotic users		
WHEATLEY 1985(98)	Zopiclone 7.5mg Temazepam 20mg	53.2 (12.6) (total)	61	<3 months in 69% of patients	Not reported		
Zaleplon versus Zolpidem							
ALLAIN 2001(99)	Zaleplon 10mg Zolpidem 10mg	52.2 (total)	49		Untreated		
ANCOLI-ISRAEL 1999(102)	Zaleplon 5mg Zaleplon 10mg Zolpidem 5mg	71.51 (5.3) 71.61 (4.84) 72.1 (5.2)	58 58 57		CNS medications, theophylline, corticosteroids, antihistamines, diet pills (discontinued before placebo washout period)		
ELIE 1999(100)	Zaleplon 5mg Zaleplon 10mg Zaleplon 20mg Zolpidem 10mg	42.5 (12.9)) 42.6 (12.5) 42.6 (12.2) 44.3 (12.5)	58 64 70 67		CNS-active medications (discontinued before placebo washout period)		Insomnia associated with mild non-psychotic psychiatric disorders also included

Study name	Intervention	Age, mean (SD)	Sex (female) %	Duration of illness	Prior drug use	Concomitant drugs	Concomitant disorders(s)
FRY 2000(101)	Zaleplon 5mg Zaleplon 10mg Zaleplon 20mg Zolpidem 10mg	43 (12) 40 (10) 41 (13) 42 (11)	69 54 61 54		CNS medications- (discontinued before placebo washout period)		Insomnia associated with mild non-psychotic psychiatric disorders also included
ZAMMIT 1 2000(103)	Zaleplon 10mg Zolpidem 10mg			≥ 1 month			
ZAMMIT 2 2000(103)	Zaleplon 10mg Zolpidem 10mg			≥ 1 month			
Zolpidem versus Zopiclone							
TSUTSUI 2001(104)	Zolpidem 10mg Zopiclone 7.5mg	41.1 (12.6) 43.2 (12.7)	65	Chronic primary insomnia	Zopiclone intake within 3 months prior to study was prohibited, as was hypnotic use in doses exceeding standard single dose	Intake of psychotropic agents necessary for the primary diseases and use of antihistamines, H2 receptor antagonists, xanthines and other drugs reported to induce drowsiness or insomnia allowed provided the dosage unchanged	Psychiatric disorders excluded

* *Blank cells indicate no data reported*

Table A6: 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(86)	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) *%, (amount of time needed to fall asleep)*	366(120) *Mean (SD)*	13.5 (none) 25.7 (1) 45.9 (2-4) 14.9 (5+) *%, (number of awakenings)*		12/79 (15.2)	
KUDO 1993(88)	Zolpidem 10 mg	68.4			66.7	13/79 (16.5)	
	Nitrazepam 5 mg	56.4 *Total improvement (%)*			37.5 *Total improvement (%)*	15/80 (18.8)	
Zolpidem versus Temazepam							
KERKHOF 1996(89)	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*		

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
LEPPIK 1997(82)	Zolpidem 5mg	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 15mg	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(83)	Zopiclone 5mg	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 1mg	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)*	
Zopiclone versus Nitrazepam							
AGNOLI 1989(84)	Zopiclone 7.5mg	Base. 36 (1.5) (n=20) Final 8 (5.7) (n=20)					
	Nitrazepam 5mg	Base. 33 (1.9) (n=20) Final 12 (9.6) (n=20) *Mean (SD), data estimated from graph*					

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
ANDERSON 1987(85)	Zopiclone 7.5mg Nitrazepam 5mg	Base. 42.5 Final 60 Base. 35.5 Final 64 *Data estimated from graph; scale: 0=long, 100=short*			Base. 41.3 Final 67.3 Base. 43.5 Final 65 *Data estimated from graph; scale 0= bad, 100=good*		
JOVANOVIC 1983(90)	Zopiclone 7.5mg Nitrazepam 5mg	Base. 97.8 (n=5) Final 17.5 (n=5) Base. 83.4 (n=5) Final 24.1 (n=5)	Base. 351.8 (n=5) Final 465.7 (n=5) Base. 376.6 (n=5) Final 441.9 (n=5)	Base. 1.5 (n=5) Final 0.1 (n=5) Base. 1.1 (n=5) Final 0.05 (n=5)			
KLIMM 1987(87)	Zopiclone 7.5mg Nitrazepam 5mg	*Change from* Base. 18.2 (48.3) (n=36) *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. 24 (45.6) (n=36) *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 1 1985(91)	Zopiclone 7.5mg Nitrazepam 5mg		10.9 (very effective) 31.3 (effective) 29.7 (little effective) 26.6 (no change) 1.6 (worse) 1.6 (very effective) 26.6(effective) 25.0(little effective) 43.8(no change) 3.1 (worse) *%, (Scale: very effective to worse)*	9.4 (very effective) 25 (effective) 23.4 (little effective) 42.2 (no change) 0 (worse) 7.8 (very effective) 26.6(effective) 28.1(little effective) 37.5(no change) 0 (worse) *%, (Scale: very effective to worse)*	25 (very effective) 31.3 (effective) 18.8 (little effective) 23.4 (no change) 1.6 (worse) 3.1(very effective) 34.4(effective) 32.8(little effective) 29.7(no change) 0 (worse) *%, (Scale: very effective to worse)*	5/64 (7.8) 7/64 (10.9)	

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
OHTOMO 2 1985(92)	Zopiclone 5mg		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 5mg		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(93)	Zopiclone 7.5mg	3.5	2.8	2.93	3.0		
	Zopiclone 15mg	2.8	3.6	2.3	2.4		
	Nitrazepam 5mg	4.2	2.6	2.95	3.5		
	Nitrazepam 10mg	3.2 *Data estimated from graph; scale: smaller score = shorter onset latency*	3.7 *Data estimated from graph; scale: larger score = longer sleep duration*	2.35 *Data estimated from graph; scale: smaller score = fewer awakenings*	2.5 *Data estimated from graph; scale: lower score = better quality of sleep*		
TAMMINEN 1987(94)	Zopiclone 7.5mg	Base. 58 (31.2)(n=49) Final 31.5 (27.2)	Base. 75 Final 37.5	Base. 63.3 Final 18.4	Base. 55.8 (33.7) (n=49) Final 33.8 (24.4)		
	Nitrazepam 5mg	Base. 52.5 (33.7) (n=45) Final 32.7 (29.4) *Mean (SD), Scale: 0 fast, 100 slow.*	Base. 73.3 Final 37.7 *% with duration of sleep < 6.5hrs*	Base. 75.6 Final 24.4 *% with >2 nocturnal awakenings*	Base. 49.9 (30.7) (n=45) Final 34.0 (27.8) *Mean (SD), Scale: 0 good, 100 bad*		

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 Temazepam							
NGEN 1990(95)	Zopiclone 7.5mg Temazepam 20mg	Base. 122.8 (n=13) Final 64.5 (n=13) Base. 50.4 (n=13) Final 26.1 (n=13) *Note: very poorly balanced groups at Base.*	Base. 262.8 (n=13) Final 361.8 (n=13) Base. 295.2 (n=13) Final 337.2 (n=13)	Base. 0.95 (n=13) Final 0.62 (n=13) Base. 2 (n=13) Final 1.28 (n=13)			
STIP 1999(96)	Zopiclone 7.5mg Temazepam 30mg			Base. 4.8 (1.96) (n=19) Final 6.8 (2.05) Base. 5.1 (2.4) (n=16) Final 5.8 (1.96) *Mean (SD), scale (likely) larger score = fewer awakenings*			
Van der KLEIJN 1989(97)	Zopiclone 7.5mg Temazepam 20mg	Base. 2.8 (1.82) (n=53)* Final 3.8 (1.46) Base. 2.8 (1.82) (n=53)* Final 3.7 (1.46) *Mean (SD), data estimated from graph; scale: 1= long, 5= short*			Base. 3.0 (1.31) (n=53) * Final 3.9 (1.46) Base. 3.0 (1.31) (n=53)* Final 3.8 (1.53) *Mean (SD), data estimated from graph; scale: 1= bad, 5=good*	26 17	
WHEATLEY 1985(98)	Zopiclone 7.5mg Temazepam 20mg	Base. 82.9 (n=36) Final 30.8 (n=35) Base. 82.9 (n=36) Final 29.1 (n=32) *Assume n=36 at Base., n=35 on zopiclone and n=32 on temazepam (by calculation from no.(%) given under "Side-effects")*	Base. 300 (n=36) Final 396(n=35) Base. 300 (n=36) Final 396(n=32) *Assume n=36 at Base., n=35 on zopiclone and n=32 on temazepam (by calculation from no.(%) given under "Side-effects")*	Base. 1.9 (n=36) Final 0.75 (n=35) Base. 1.9 (n=36) Final 0.66 (n=32) *Assume n=36 at Base., n=35 on zopiclone and n=32 on temazepam (by calculation from no.(%) given under "Side-effects")*	Base. 2.1 (n=36) Final 0.93 (n=35) Base. 2.1 (n=36) 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"); scale 0 good, 4 bad*	9/35 (26) 5/32 (16) *Side-effects*	

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 2001(99)	Zaleplon 10mg Zolpidem 10mg		480 498				
ANCOLI-ISRAEL 1999(102)	Zaleplon 5mg Zaleplon 10mg Zolpidem 5mg *Medians, estimated from graph*	Base. 75.75 (n=148) Final 38 Base. 62.5 (n=150) Final 31 Base. 58.75 (n=101) Final 42	Base. 290.71 (n=150) Final 325 Base. 316.14 (n=151) Final 348 Base. 308.57 (n=105) Final 360 *Medians, estimated from graph*		82/162 (51) 86/163(53) 72/109 (66) *Number/total (%) with improvement at week 4 in sleep quality from Base./total*	56 59 63 *%, treatment-emergent adverse events*	
ELIE 1999(100)	Zaleplon 5mg Zaleplon 10mg Zaleplon 20mg Zolpidem 10mg *Medians; data extracted from graph*	Base. 66 (n=113) Final 31 Base. 57 (n=112) Final 28.8 Base. 55 (n=116) Final 27.5 Base. 64 (n=115) Final 36.5	Base. 313 (n=113) Final 372 (n=102) Base. 331 (n=112) Final 384 (n=99) Base. 328 (n=116) Final 385 (n=103) Base. 330 (n=115) Final 400 (n=100) *Medians*	Base. 2 (n=112) Final 2 (n=87) Base. 2 (n=111) Final 2 (n=82) Base. 2 (n=114) Final 1 (n=86) Base. 2 (n=114) Final 2 (n=84) *Medians*	66/101 (65.3) 59/100 (59.0) 64/102 (62.7) 66/99 (66.7) *Number with improvement at week 4 in sleep quality from Base./total (%)*	71/121 (59) 87/120 (73) 76/124 (61) 78/122 (64) *Treatment-emergent adverse events*	(8) (9) (10) (16) *(%) with 3+ withdrawal symptoms first night after discontinuation of treatment; data estimated from graph*

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
FRY 2000(101)	Zaleplon 5mg	Base. 69.3 (n=118) Final 45.6 (n=101)	Base. 334.3 (n=118) Final 360.0 (n=101)	Base. 2 (n=115) Final 1.71 (n=90)	49/101 (48.5)	90/118 (76)	1/91 (1.1)
	Zaleplon 10mg	Base. 62.5 (n=119) Final 35.0 (n=102)	Base. 334.3 (n=119) Final 376.3 (n=102)	Base. 1.86 (n=117) Final 1.57 (n=91)	52/102 (51.0)	89/120 (74)	1/83 (1.2)
	Zaleplon 20mg	Base. 61.1 (n=116) Final 30.0 (n=101)	Base. 343.0 (n=116) Final 377.5 (n=101)	Base. 2 (n=114) Final 1.6 (n=90)	57/101 (56.4)	93/117 (79)	2/91 (2.2)
	Zolpidem 10mg	Base. 60.7 (n=115) Final 34.3 (n=98) *Medians*	Base. 334.3 (n=115) Final 392.9 (n=98) *Medians*	Base. 2.14 (n=112) Final 1.67 (n=89) *Medians*	61/98 (62.2) *Number with improvement at week 4 in sleep quality from Base./total (%); data extracted from graph*	96/116 (83) *Treatment-emergent adverse events*	6/85 (7.1) *(%) with 3+ withdrawal symptoms first night after discontinuation of treatment*
ZAMMIT 1 2000(103)	Zaleplon 10mg Zolpidem 10mg						
ZAMMIT 2 2000(103)	Zaleplon 10mg Zolpidem 10mg						
Zolpidem versus Zopiclone							
TSUTSUI 2001(104)	Zolpidem 10mg Zopiclone 7.5mg	179/209 (85.8) 170/219 (77.5) *Number/total (%) with improvement of 1+ scale from Base. (scale 1-5); numbers estimated from percentage*				66/211 (31.3) 102/225 (45.3) *Drug related adverse events*	

Table A7: Outcomes: Rebound insomnia and tolerance

Study name	Interventions	*Rebound insomnia:*				*Tolerance:*			
		Sleep onset latency (min), Mean	**Total sleep duration (min), Mean**	**Number of awakenings Mean**	**Quality of sleep, Mean**	**Sleep onset latency (min), Mean**	**Total sleep duration (min), Mean**	**Number of awakenings, Mean**	**Quality of sleep**
Zolpidem versus Nitrazepam									
KAZAMATSURI 1993(86)	Zolpidem 10 mg Nitrazepam 5 mg								
KUDO 1993(88)	Zolpidem 10 mg Nitrazepam 5 mg								
Zolpidem versus Temazepam									
KERKHOF 1996(89)	Zolpidem 10 mg Temazepam 20 mg								
LEPPIK 1997(82)	Zolpidem 5mg Temazepam 15mg					Initial 44.7 (27.2) (n=82) Final 40.5 (27.2) (n=77) Initial 43.1 (29.2) (n=83) Final 38.0 (26.2) (n=76) *Mean (SD). Skewed variable; therefore not included in MA*	Initial 353.4 (55.2) (n=82) Final 362.8 (64.9) (n=77) Initial 375.0 (63.8) (n=83) Final 375.3 (58.4) (n=76) *Mean (SD). Skewed variable; therefore not included in MA*		

Study name	Interventions	*Rebound insomnia:* Sleep onset latency (min), Mean	*Rebound insomnia:* Total sleep duration (min), Mean	*Rebound insomnia:* Number of awakenings Mean	*Rebound insomnia:* Quality of sleep, Mean	*Tolerance:* Sleep onset latency (min), Mean	*Tolerance:* Total sleep duration (min), Mean	*Tolerance:* Number of awakenings, Mean	*Tolerance:* Quality of sleep
Zopiclone versus Lormetazepam									
ANSOMS 1991(83)	Zopiclone 7.5mg Lormetazepam 1mg								
Zopiclone versus Nitrazepam									
AGNOLI 1989(84)	Zopiclone 7.5mg Nitrazepam 5mg								
ANDERSON 1987(85)	Zopiclone 7.5mg Nitrazepam 5mg	Baseline 42.5 Post-TRT 50 Baseline 35.5 Post-TRT 48 *Data estimated from graph; scale: 0=long, 100=short*			Baseline 41.3 Post-TRT 51.5 Baseline 43.5 Post-TRT 51.3 *Data estimated from graph; scale 0= bad, 100=good*				
JOVANOVIC 1983(90)	Zopiclone 7.5mg Nitrazepam 5mg	Baseline 97.8 (n=5) Post-TRT 49 (n=5) Baseline 83.4 (n=5) Post-TRT 52.6 (n=5) *Post-TRT taken as first 3 nights after treatment*	Baseline 351.8 (n=5) Post-TRT 432.6 (n=5) Baseline 376.6 (n=5) Post-TRT 422.2 (n=5)	Baseline 1.5 (n=5) Post-TRT 0.7 (n=5) Baseline 1.1 (n=5) Post-TRT 0.7 (n=5) *Post-TRT taken as first 3 nights after treatment*					
KLIMM 1987(87)	Zopiclone 7.5mg Nitrazepam 5mg								

Study name	Interventions	*Rebound insomnia:*				*Tolerance:*			
		Sleep onset latency (min), Mean	**Total sleep duration (min), Mean**	**Number of awakenings Mean**	**Quality of sleep, Mean**	**Sleep onset latency (min), Mean**	**Total sleep duration (min), Mean**	**Number of awakenings, Mean**	**Quality of sleep**
OHTOMO 1 1985(91)	Zopiclone 7.5mg Nitrazepam 5mg								
OHTOMO 2 1985(92)	Zopiclone 5mg Nitrazepam 5mg								
PULL 1983(93)	Zopiclone 7.5mg Zopiclone 15mg Nitrazepam 5mg Nitrazepam 10mg								
TAMMINEN 1987(94)	Zopiclone 7.5mg Nitrazepam 5mg					Initial 34.1 (25.9) Final 31.5 (27.2) Initial 35.5 (30.7) Final 32.7 (29.4) *Mean (SD). Scale: 0 fast, 100 slow*			Initial 37.1 (25.2) Final 33.8 (24.4) Initial 27.4 (23.3) Final 34.0 (27.8) *Mean (SD). Scale: 0 good, 100 bad*
Zopiclone versus Temazepam									
NGEN 1990(95)	Zopiclone 7.5mg Temazepam 20mg								

Study name	Interventions	*Rebound insomnia:* Sleep onset latency (min), Mean	*Rebound insomnia:* Total sleep duration (min), Mean	*Rebound insomnia:* Number of awakenings Mean	*Rebound insomnia:* Quality of sleep, Mean	*Tolerance:* Sleep onset latency (min), Mean	*Tolerance:* Total sleep duration (min), Mean	*Tolerance:* Number of awakenings, Mean	*Tolerance:* Quality of sleep
STIP 1999(96)	Zopiclone 7.5mg Temazepam 30mg			Baseline 4.8 (1.96) (n=19) Post-TRT 5.1 (2.27) Baseline 5.1 (2.4) (n=16) Post-TRT 4.4(0.56) SD = 2.24 *Scale unknown as yet; likely that larger score = fewer awakenings*					
Van der KLEIJN 1989(97)	Zopiclone 7.5mg Temazepam 20mg *Notes:*	Baseline 2.8 (1.82) (n=53) Post-TRT 2.0 (1.67) Baseline 2.8 (1.82) (n=53) Post-TRT 2.8 (1.82) *Mean (SD). Data estimated from graph; first night before treatment compared with first night after treatment; scale: 1= long, 5= short*			Baseline 3.0 (1.31) (n=53) Post-TRT 2.0 (0.73) Baseline 3.0 (1.31) (n=53) Post-TRT 2.7 (1.46) *Mean (SD). Data estimated from graph; first night before treatment compared with first night after treatment; scale: 1= bad, 5=good*				
WHEATLEY 1985(98)	Zopiclone 7.5mg Temazepam 20mg								

Study name	Interventions	*Rebound insomnia:* Sleep onset latency (min), Mean	*Rebound insomnia:* Total sleep duration (min), Mean	*Rebound insomnia:* Number of awakenings Mean	*Rebound insomnia:* Quality of sleep, Mean	*Tolerance:* Sleep onset latency (min), Mean	*Tolerance:* Total sleep duration (min), Mean	*Tolerance:* Number of awakenings, Mean	*Tolerance:* Quality of sleep
Zaleplon versus Zolpidem									
ALLAIN 2001(99)	Zolpidem 10mg Zopiclone 10mg								
ANCOLI-ISRAEL 1999(102)	Zaleplon 5mg	(8.5)	(6.5)	(3)					
	Zaleplon 10mg	(9)	(9)	(4.5)					
	Zolpidem 5mg	20/100 (20)	28/104 (27)	(6.5)					
		Number/total (%) with rebound insomnia; data estimated from graph	*Number/total (%) with rebound insomnia; data estimated from graph*	*Total (%) with rebound insomnia; data estimated from graph*					
ELIE 1997(100)	Zaleplon 5mg	5/99 (5)	5/99 (5)	3/61 (5)		Initial 42.5 Final 31	Initial 351 (n=113) Final 372 (n=102)	Initial 2 (n=104) Final 2 (n=87)	Initial 4.1 (n=113) Final 3.8 (n=102)
	Zaleplon 10mg	4/94(4)	3/95 (3)	2/57(4)		Initial 36 Final 28.8	Initial 370 (n=112) Final 384 (n=99)	Initial 2 (n=101) Final 2 (n=82)	Initial 3.9 (n=112) Final 3.7 (n=100)
	Zaleplon 20mg	11/97 (11)	11/99 (11)	3/67 (4)		Initial 33 Final 27.5	Initial 370 (n=116) Final 385 (n=103)	Initial 2 (n=103) Final 1 (n=86)	Initial 3.8 (n=116) Final 3.6 (n=103)
	Zolpidem 10mg	15/92 (16)	15/94 (16)	12/63 (19)		Initial 45 Final 36.5	Initial 379 (n=115) Final 400 (n=100)	Initial 2 (n=100) Final 2 (n=84)	Initial 3.7 (n=115) Final 3.4 (n=100)
	Notes:	*Number/total (%) with rebound insomnia; data estimated from graph*	*Number/total (%) with rebound insomnia; data estimated from graph*	*Number/total (%) with rebound insomnia; data estimated from graph*		*Medians; data estimated from graph*	*Medians*	*Medians*	*Scale: 1=good, 7=bad*

Study name	Interventions	*Rebound insomnia:* Sleep onset latency (min), Mean	*Rebound insomnia:* Total sleep duration (min), Mean	*Rebound insomnia:* Number of awakenings Mean	*Rebound insomnia:* Quality of sleep, Mean	*Tolerance:* Sleep onset latency (min), Mean	*Tolerance:* Total sleep duration (min), Mean	*Tolerance:* Number of awakenings, Mean	*Tolerance:* Quality of sleep
FRY 2000(101)	Zaleplon 5mg	5/95 (5)	5/97 (5)	6/72 (8)		Initial 45.4 Final 45.6 (n=101)	Initial 360 (n=118) Final 360 (n=101)	Initial 1.93 (n=108) Final 1.71 (n=90)	Initial 3.43 (n=118) Final 3.38 (n=101)
	Zaleplon 10mg	4/100 (4)	7/100 (7)	7/64 (11)		Initial 40.7 Final 35.0 (n=102)	Initial 360.6 (n=119) Final 376.3 (n=102)	Initial 1.69 (n=112) Final 1.57 (n=91)	Initial 3.57 (n=119) Final 3.54 (n=102)
	Zaleplon 20mg	8/95 (8)	5/97 (5)	5/72 (7)		Initial 35.7 Final 30.0 (n=101)	Initial 368.6 (n=116) Final 377.5 (n=101)	Initial 1.75 (n=109) Final 1.60 (n=90)	Initial 3.43 (n=116) Final 3.29 (n=101)
	Zolpidem 10mg	23/96 (24)	24/95 (25)	11/69 (16)		Initial 45.7 Final 34.3 (n=98)	Initial 377.1 (n=115) Final 392.9 (n=98)	Initial 1.59 (n=108) Final 1.67 (n=89)	Initial 3.38 (n=115) Final 3.15 (n=98)
		Number/total (%) with rebound insomnia; data estimated from graph	*Number/total (%) with rebound insomnia; data estimated from graph*	*Number/total (%) with rebound insomnia; data estimated from graph*		*Medians*	*Medians*	*Medians*	*Scale: 1=good, 7=bad*
ZAMMIT 1&2 2000(103)	Zolpidem 10mg Zopiclone 10mg								
Zolpidem versus Zopiclone									
TSUTSUI 2001(104)	Zolpidem 10mg Zopiclone 7.5mg	9/191 (4.5) 31/205 (15.4) *Number/total (%) with aggravation of sleep onset latency by 1+ grade at end of follow-up relative to baseline; numbers estimated from percentage*							

Table A8: Overview of studies, measures used and psychomotor, memory, mood and patient satisfaction outcomes

Author	Name of measure	Specific measurement of:	Test type			Reported Findings*
			Memory	*Psycho-motor*	*Mood / Satisfaction*	
Zolpidem Versus Nitrazepam						
KAZAMATSURI 1993(86)	Non-English					
KUDO 1993(88)	Non-English					
Zolpidem Versus Temazepam						
KERKHOF 1996(89)	Groningen Sleep Scale	Quality of sleep				
LEPPIK 1987(82)	Morning Questionnaire (unspecified)	Quality of sleep Ability to concentrate			S	No consistent pattern of differences noted
	Global Impression of Therapy	Sleep quality Sleep improvement Overall feeling			S	
	Global Impression of Treatment					No direct comparisons were made between treatment groups
Zopiclone Versus Lormetazepam						
ANSOMS 1991(83)	Spiegel Sleep Questionnaire	Quality of sleep Morning disposition			S	
	Norris Mood Rating Scale	Mood			M	No significant differences between groups for any of the items
Zopiclone Versus Nitrazepam						
AGNOLI 1989(84)	Hamilton Rating Scale for Anxiety	Anxiety			M	Significant reduction of anxiety levels after zopiclone
	Toulouse-Pieron Attention Test	Attention	Mem			Significant improvement of attentive capacity after zopiclone for some items, some of the time
	Sleep Questionnaire (unspecified)	Sleep quality Daytime arousal			S S	Significantly better quality of daytime arousal after zopiclone

Author	Name of measure	Specific measurement of:	Test type			Reported Findings*
			Memory	*Psycho-motor*	*Mood / Satisfaction*	
ANDERSON 1987(85)	Sleep Questionnaire (unspecified)	Sleep quality			S	
		Morning alertness			S	Zopiclone group more wide awake than nitrazepam group
	Global Assessment of Efficacy					No differences were reported between treatment groups
JOVANOVIC 1983(90)	None	None	-	-	-	-
KLIMM 1987(87)	Sleep Diary (unspecified)	VAS sleep quality			S	
		VAS Alertness on awakening			S	Zopiclone group felt more alert in the morning than nitrazepam group on 2 of 7 active treatment days
	Spiegel Sleep Questionnaire	Quality of sleep			S	
		Morning condition			S	
	Syndrom-Kurztest (SK)	9 sub scales test short-term memory and concentration				No difference between treatment groups on any sub scale of SK test
		1. Object naming				
		2. Object recall				
		3. Read a series of 10 numbers	Mem Mem	P P		
		4. Arrange same numbers in ascending order		P P		
		5. Find missing number using a duplicate set				
		6. Count n times a symbol appears in a list of 126 symbols	Mem Mem	P P		
		7. Interference test – AB to BA substitution				
		8. Object recall of items in test 1	Mem	P		
		9. Object recognition – find test 1 objects from a set of 48	Mem Mem	P P		
OHTOMO 1 and 2 1985(91, 92)	Non-English					

Author	Name of measure	Specific measurement of:	Test type			Reported Findings*
			Memory	*Psycho-motor*	*Mood / Satisfaction*	
PULL 1983(93)	Norris Mood Rating Scale	Mood			M	Calm/excited: Nitrazepam 10mg >calm score Contented/discontented: zopiclone 15mg > contentment score Troubled/tranquil: zopiclone 7.5mg and 10mg and nitrazepam 10mg > tranquil score Tense/relaxed: nitrazepam 10mg and zopiclone 15mg > relaxed score
	Memory Test (unspecified)	Graphic symbols	Mem			No significant differences, tendency in favour of zopiclone
	Vigilance + awakening (unspecified)	Cancellation test		P		No significant differences found between groups
TAMMINEN 1987(94)	Norris Mood Rating Scale	Mood			M	No significant differences between groups in feeling upon awakening
	Psychomotor Tests (unspecified)	Symbol copying		P		No significant difference between treatment groups
		Digit symbol substitution		P		No significant difference between treatment groups
		Tapping rate		P		A trend in favour of zopiclone was found on assessment of tapping rate scores
		Auditory reaction time		P		No significant difference between treatment groups
	Sleep questionnaire (unspecified)	Sleep quality			S	
		VAS working ability			S	
	Investigator's Global Assessment of efficacy					No difference in global assessment of efficacy between treatments
Zopiclone Versus Temazepam						
NGEN 1990(95)	Leeds Psychomotor Tester	Choice reaction time		P		No direct comparisons were made between groups
		Critical flicker fusion		P		
	Cancellation Test (unspecified)	Letter cancellation test		P		

Author	Name of measure	Specific measurement of:	Test type			Reported Findings*
			Memory	*Psycho-motor*	*Mood / Satisfaction*	
STIP 1999(96)	Hamilton Scale for Anxiety	Anxiety			M	No significant difference between groups
	Short-Term Memory (unspecified)	Number recall – increasing complexity	Mem			No significant difference between groups
	Long-Term Memory (unspecified)	Cued recall – word recall	Mem			No significant difference between groups
		Implicit recall – word completion	Mem			No significant difference between groups
		Alertness – visual reaction time	Mem	P		No significant difference between groups
		Sustained attention – visual reaction time	Mem	P		No significant difference between groups
		Divided attention – number recall combined with simultaneous moving target pursuit task	Mem	P		No significant difference between groups
Van Der KLEIJN 1989(97)	Sleep Questionnaire (unspecified)	Sleep quality			S	
	Mood Question (study designed)	Seven questions cited but not specified			M	No significant difference between groups on awakening
WHEATLEY 1985(98)	Patient Questionnaire (unspecified)	Sleep quality			S	
		Feeling on waking			S	No differences between groups
	Life Events (unspecified)	Unspecified			O	Stated that the majority of participants did not report any life events
Zaleplon Versus Zolpidem						
ALLAIN 2001(99)	Sleep questionnaire (LSEQ) Visual Analogue Scale	Sleep quality				
ANCOLI-ISRAEL 1999(102)	Sleep Questionnaire (unspecified)	Sleep quality (question/s unspecified)			S	
ELIE 1999(100)	Sleep Questionnaire (unspecified)	Sleep quality			S	
FRY 2000(101)	Sleep Questionnaire (unspecified)	Sleep quality (question/s unspecified)			S	

Author	Name of measure	Specific measurement of:	Test type			Reported Findings*
			Memory	*Psycho-motor*	*Mood / Satisfaction*	
ZAMMIT 1 and 2 2000(103)	Sleep latency test (SLT) and subjective assessments	Daytime sedation				No direct comparisons reported for next day sedation and psychomotor performance
	Measures of psychomotor performance (not specified)	Psychomotor performance				
Zolpidem Versus Zopiclone						
TSUTSUI 2001(104)	Sleep Questionnaire (unspecified)	Daytime mood (questions unspecified)			M	
		Physical condition (questions unspecified)			S	No direct comparisons reported for daytime physical condition
	Patient Rating of Efficacy (unspecified)	Sleep quality			S	
	Clinical Global Impression Scale					No statistically significant differences reported between treatment groups

* Satisfaction outcomes reported and compared in results section of the report. All significant differences reported at p ≤.05. Any identified trends are reported. Key: Mem – *memory,* S – *self report satisfaction,* M – *self report mood,* O – *other*

Table A9: Dependency and withdrawal review: trials and observational studies – study characteristics

Study name	Intervention/ no of patients	Study design	Number of patients entering withdrawal period	Primary outcomes	Secondary outcomes	Locations & centres	Inclusion criteria	Exclusion criteria	Duration of treatment	Other comparators
ASNIS 1999(108)	Zolpidem 10mg *(94 included in analysis)* *(Overall 194 randomised)*	RCT, DB	75		Hypnotic efficacy, impact on daytime function, quality of life, safety	14 centres, USA and Canada	Age 18-66 yrs, experiencing insomnia and currently treated for a depressive disorder, all pts major depressive disorder, dysthymic disorder or minor depressive disorder (DSM-IV)	HAM-D score >12, history of suicide attempt, psychotropic treatment other than SSRI, insomnia secondary to other conditions (shift work, substance abuse, anxiety disorder)	4 weeks	Placebo *(96 included in analysis)*
LEMOINE 1995(112)	Patients treated for ≥3 months randomised to 3 weeks' continuation of treatment or withdrawal : Zolpidem 10mg (n=193, of which 93 withdrawal) Zopiclone 7.5mg (n=201, of which 102 withdrawal)	2 separate RCTs, DB randomising patients after trial to continuation or gradual withdrawal	Zolpidem 93, zopiclone 102, all on gradual withdrawal (1 week each on full, half, and no dose)		Withdrawal symptoms, withdrawal syndrome (adverse events), quality of sleep	France, Multicentre	Age 18-65 (all patients were included in previous trials involving ≥3 months treatment with the study drug).	History or current episode of depression or psychiatric disorder, severe and evolving physical illness, dementia, alcoholism, drug abuse, acute pain, use of psychotropic drugs within previous 2 weeks, pregnancy or likelihood thereof, breast-feeding	3 weeks following ≥ 3 months treatment in previous trial	None
MAAREK 1992(110)	Zolpidem 10/20mg (10mg in 65% of patients at end of study) (n=96)	Single-group open study	20		Sleep onset latency, number of awakenings, time awake during night, duration of sleep, wake-up time, quality of sleep, feeling on awakening	France, 10 general practitioners	Age >40 years, min. one defined symptom of insomnia	Use of other psychotropic drugs, benzodiazepines, or other hypnotics, malignant disease	180 days	None

Study name	Intervention/ no of patients	Study design	Number of patients entering withdrawal period	Primary outcomes	Secondary outcomes	Locations & centres	Inclusion criteria	Exclusion criteria	Duration of treatment	Other comparators
PECKNOLD 1990(111)	Zopiclone 7.5 mg *(n=11)*	Single-group open study	10		Sleep onset latency, sleep time, wake time, number of awakenings, sleep morphology, psychomotor performance	Canada, number of centres unclear	Sleep problems (defined) for ≥1 month	History of drug abuse or addiction, hypersensitivity to benzodiazepines, psychotic disorder, epilepsy, mental retardation, recent severe head trauma, severe organic illness, pain interfering with sleep, pregnancy, breast feeding, inadequate contraception	54 nights	None
SHAW 1992(109)	Zolpidem 10 mg *(n=40)* Zolpidem 20 mg *(n=40)*	RCT, DB, parallel	Zolpidem 10: 39, zolpidem 20: 36		Sleep onset latency, duration, number of awakenings, total time awake, quality of sleep, status on following morning	England, number of centres unclear	Age 65-85, insomnia ≥ 2 weeks, fulfilling ≥ 2 criteria (defined)	Serious systemic medical condition, transient or situational insomnia, insomnia associated with use of drugs or alcohol, or related to respiratory impairment, history of alcohol abuse, concomitant use of benzodiazepines or hypnotics	21 nights	Placebo *(n=39)*

Table A10: Dependency and withdrawal review: trials and observational studies – patient characteristics and withdrawal symptoms

Study name	Intervention	Age, (Mean) years	Sex and female %	Concomitant treatment	History of substance abuse	Other diagnoses	Previous use of hypnotics	Withdrawal symptoms
ASNIS 1999(108)	Zolpidem 10 mg	41.6	78.9	Fluoxetine, Paroxetine, Sertraline	None	Major depressive disorder, dysthymic disorder or minor depressive disorder	-	No patient had ≥2 of the symptoms of B criterion of sedative/hypnotic withdrawal syndrome (DSM-IV).
LEMOINE 1995(112)	Zolpidem 10 mg, Zopiclone 7.5 mg	Not reported	Not reported	Not reported	Excluded	None reported	Patients had used study drug for a median of 9.1 months (zopiclone) or 7.4 months (zolpidem)	Incidence of events, possibly related to gradual discontinuation of active treatment, was higher in the withdrawal groups than in the treatment group (zolpidem: 38% and 24% respectively; zopiclone: 38% and 20% respectively); if sleep complaints were excluded, no statistical difference remained. No difference in Tyrer questionnaire score; Ashton scale (of withdrawal symptoms) showed significantly more withdrawal symptoms in the zolpidem withdrawal group compared to the zolpidem continuation group (no differences between the two zopiclone groups)
MAAREK 1992(110)	Zolpidem 10/20mg (at end of study 65% of patients used 10mg)	56.8	69.8	None reported	None reported	None reported	79% of patients required hypnotics before study	No report of withdrawal symptoms
PECKNOLD 1990(111)	Zopiclone 7.5 mg	43.9	63.6	None reported	None	None reported	8 patients were taking benzodiazepines within 1 month of entering study	2 patients reported moderate symptoms: anxiety and hyperventilation, anxiety and general weakness (only 9 patients completed withdrawal phase - 1 patient dropped out during withdrawal phase due to rebound insomnia)
SHAW 1992(109)	Zolpidem 10 mg Zolpidem 20 mg	10mg: 74.9 20mg: 72.9	10mg: 77.5 20mg: 57.5	Antipsychotics, antidepressants, treatment of movement disorders, cardiovascular conditions, etc.	None reported	Dementia (50%), Schizophrenia (27%), depression (11%) Majority of patients institutionalised	85% of patients previously on treatment of insomnia	"no withdrawal symptoms" on zolpidem; "adverse events" during follow-up reported: 10mg group: daytime aggression (1 patient) 20mg group: restlessness 5 days after treatment (1 patient), increased sedation and confusion 4 days after treatment (1 patient)

Table A11: Dependency and withdrawal review: case reports – zolpidem

Study name	Intervention (max. daily dose)	Age (years), gender	Location	History of substance/drug abuse	Other diagnoses	Withdrawal symptoms	Notes
ARAGONA 2000(114)	Zolpidem (450-600 mg)	43 F	Italy	Benzodiazepines (Diazepam, flunitrazepam, bromazepam)	None reported	Epileptic seizures	Patient tried to reinforce anxiolytic effect.
BOTLENDER 1997(115)	Zolpidem (140 mg)	53 M	Germany	Benzodiazepines, alcohol, clomethiazole	Idiopathic Parkinson Syndrome, organic delusional syndrome	Restlessness, disturbed sleep, vegetative symptoms	
CAVALLARO 1993(116)	Zolpidem (80 mg)	31 F	Italy	None reported	Major depression	Abstinence phenomena during the day included sweating, tachycardia, tremors, severe anxiety, muscular twitches and myoclonic jerks	*The paper reports a second case of withdrawal symptoms after the drug being described for a personality disorder*
GERICKE 1994(117)	Zolpidem (280 mg)	33 M	Germany	None	Major depression	Generalised tonic-clonic seizure, apathy, drug craving, recurrence of depressive mood	
GOLDEN 2000(118)	Zolpidem (40 mg)	39 M	USA	None reported	Obesity, hypertension	Mild withdrawal syndrome (anxiety, agitation, restlessness, poor concentration, insomnia)	Patient increased dose to combat jet lag
MADRAK 2001(119)	Zolpidem (100 mg)	67 F	USA	Alcohol, barbiturate, benzodiazepine dependence	Depression, anxiety	Tremor, psychomotor agitation, facial flushing, anxiety	Withdrawal symptoms present despite treatment with benzodiazepine
RAVISHANKAR 1998(120)	Zolpidem (200 mg)	55 F	UK	None reported	Depression	Low mood, nightmares, sweating, tremors, panic attacks, confusion	Dose increase because of tolerance to hypnotic effect

Study name	Intervention (max. daily dose)	Age (years), gender	Location	History of substance/drug abuse	Other diagnoses	Withdrawal symptoms	Notes
SAKKAS 1999(121)	Zolpidem (300 mg)	44 F	Greece	Repeated Zolpidem abuse	Depression		No withdrawal symptoms reported on previous discontinuation, patient exhibited “odd” behaviour under effect of zolpidem
SANCHEZ 1996(122)	Zolpidem (300-400 mg)	33 M	Spain	None	None	Rebound insomnia, anxiety, agitation, tremors, and seizures	Patient increased dose because of perceived tolerance.
TRIPODIANAKIS 2003(123)	Zolpidem (600 mg)	43 F	Greece	None	Depression	Epileptic seizures	Patient increased dose as tolerance developed.
VARTZOPOULOS 2000(124)	Zolpidem (400-500mg)	30 F	Greece	Benzodiazepines	Histrionic personality disorder		Dose increases were without marked effect.
	Zolpidem (160-200mg)	26 F		Alcohol	Borderline personality disorder	Confusion, psychomotor agitation	
	Zolpidem (120mg)	33 M		Cannabis	Borderline personality disorder, dysthymia	Craving feelings still on gradual withdrawal	*The paper reports a fourth case of withdrawal symptoms, but it is unclear whether the drug was originally used for insomnia*

Table A12: Dependency and withdrawal review: case reports – zopiclone

Study name	Intervention (max. daily dose)	Age (years), gender	Location	History of substance/drug abuse	Other diagnoses	Withdrawal symptoms	Notes
ARANKO 1991(125)	Zopiclone (90 mg)	36 M	Finland	Nitrazepam, trimipramine, promazine, beer	Major depression and compulsive personality disorder	Grand-mal-type convulsions	
JONES 1998(126)	Zopiclone (22.5 mg)	29 M	Wales	None reported	Pneumothorax	Tachycardia, tremor, sweating, rebound insomnia	
	Zopiclone (30 mg)	26 M		None reported	None reported	Strong craving, anxiety, tremors, sweats, flushes	
	Zopiclone (22.5 mg)	49 F		None reported	Depression	Severe rebound insomnia, anxiety	
	Zopiclone (30 mg)	36 F		Benzodiazepine dependency	Bipolar affective disorder	Sweating, palpitations, tremor, anxiety	
KUNTZE 2002(127)	Zopiclone (337.5 mg)	67 M	Switzerland	None reported	Depressive disorder		Admitted for controlled withdrawal
SIKDAR 1996(128)	Zopiclone (380 mg)	six patients (four M, two F)	England	Temazepam, heroin, cocaine; now on methadone maintenance	Not reported	Rebound insomnia, feeling edgy, very strong craving	Clients reported knowing of "many other" fellow addicts abusing zopiclone
THAKORE 1992(129)	Zopiclone (45 mg)	36 M	Ireland	Alcohol, flurazepam	Depression	Hyperactivity with tachycardia, hand tremor and weakness, panic attacks	

Clinical: Included and Excluded References

Included studies

Study:	*Reference(s)*
	Zolpidem versus Nitrazepam
KAZAMATSURI 1993	Kazamatsuri H, Sato M, Mori A, Toru M, Kaneno S, Murasaki M*, et al.* Clinical evaluation of Zolpidem on insomnia of patients with Schizophrenia and manic-depressive psychosis- double-blind trial in comparison with Nitrazepam. *Rindho Iyaku* 1993;**9**(1):107-36.
KUDO 1993	Kudo Y, Kawakita Y, Saito M, al. e. Clinical efficacy and safety of zolpidem on insomnia: a double-blind comparative study with zolpidem and nitrazepam. *Rinsyoiyaku* 1993;**9**:79-105.
	Zolpidem versus Temazepam
KERKHOF 1996	Kerkhof G, van Vianen BG, Kamphuisen HAC. A comparison of zolpidem and temazepam in psychophysiological insomniacs. *European Neuropsychopharmacology* 1996;**6**(Suppl 4):155-156.
LEPPIK 1997	Leppik IE, Roth Schechter GB, Gray GW, Cohn MA, Owens D. Double-blind, placebo-controlled comparison of zolpidem, triazolam, and temazepam in elderly patients with insomnia. *Drug Development Research* 1997;**40**:230-238. Ochs R, Fillingim J, Cutler N, Leppik I, Lucas E, Cohn M*, et al.* The effect of zolpidem in elderly patients with chronic insomnia. *Sleep Research* 1992;**1**(Suppl 1):164.
	Zopiclone versus Lormetazepam
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