Newer hypnotic drugs for the short-term management of insomnia: a systematic review and economic evaluation

Dundar Y, Boland A, Strobl J, Dodd S, Haycox A, Bagust A, Bogg J, Dickson R, Walley T

CRD summary
This review compared zaleplon, zolpidem and zopiclone with benzodiazepines (licensed and used in the UK) for the short-term management of insomnia. The authors concluded that short-acting drugs (Z-drugs) seemed equally effective and safe, but that there was a clear need for further research in this area. The authors suggested interpreting the findings with considerable caution, and their recommendation for further research seems appropriate.

Authors' objectives
To compare the clinical and cost-effectiveness of zaleplon, zolpidem and zopiclone with benzodiazepines for the short-term management of insomnia.

Searching
MEDLINE (from 1966), EMBASE (from 1980), PsycINFO (from 1966) and Web of Science (including Science Citation Index from 1981 and Conference Proceedings Citation Index from 1990) were searched up to March 2003 for articles in any language. The Cochrane Library was searched in 2003, and the Health Technology Assessment and DARE databases were searched between 1994 and 2003. Search terms were reported. Eight psychopharmacological journals were searched between 2002 and June 2003. In addition, reference lists of retrieved articles and pharmaceutical company submissions were manually searched, and internet resources (including industry-supported websites) were inspected.

Study selection
For the clinical effectiveness review, randomised controlled trials (RCTs) that compared newer hypnotics (zaleplon, zolpidem and zopiclone) with each other or with benzodiazepines (licensed and approved for use in the UK) for the short-term treatment of individuals with insomnia were eligible for inclusion. Outcomes of interest were: sleep onset latency, total sleep duration, number of awakenings, sleep quality, rebound insomnia (for all of the previous outcomes) and adverse events. For the extended review on dependency and withdrawals, case-control studies, case series, case reports, cohort studies, and surveys were also eligible.

Included studies were conducted in a range of settings and different countries, with study durations lasting between one night and six weeks. The majority of participants were female and, where reported, their mean age ranged between 30.1 and 73.2 years. The duration of illness ranged from a minimum of two weeks to more than six months. Some studies included patients with prior drug use or concomitant drug use for psychiatric disorders or alcoholism. The majority of studies measured sleep efficacy outcomes using post-sleep questionnaires and sleep diaries, but sleep quality was measured using a variety of rating scales. Crossover trials with less than two nights’ washout were excluded from the analysis.

At least two reviewers independently screened articles for inclusion in the main clinical review, with disagreements resolved by discussion.

Assessment of study quality
At least two reviewers independently assessed the quality of studies included in the main clinical review, based on previously published criteria: randomisation method, allocation concealment, blinding, similar baseline patient characteristics, eligibility criteria specified, reporting of co-interventions, withdrawals (at least 80% patient follow-up), and intention-to-treat analysis. Each criterion was graded as adequately addressed, not adequately addressed, or partially addressed.

Discrepancies were resolved through consensus.
Data extraction

Four reviewers extracted data on outcomes for the main review to calculate odds ratios (ORs) with 95% confidence intervals (CIs) for dichotomous outcomes, and mean differences with 95% confidence intervals for continuous outcomes. Where a decreased score indicated improvement, mean values were negated in order to standardise scores. Where more than one data point was available, data were extracted at baseline and first night after discontinuation of treatment.

For the extended review one reviewer extracted data and this was checked by a second reviewer.

Methods of synthesis

A fixed-effect model was used to pool odds ratios and weighted means differences (WMDs) with 95% confidence intervals for the clinical review, grouped by treatment type. Where meta-analysis was not possible, data were presented as a narrative synthesis.

Results of the review

Twenty-four studies were included in the main review. The authors stated that 3,909 patients were included in the review, but it was difficult to confirm this from the tables as some studies reported the number of patients randomised, while others reported the number of patients analysed. Follow-up ranged between three and 11 days. Only one study reported the method of randomisation and allocation concealment, 15 studies reported that baseline characteristics were adequately or partially comparable (there was a slight discrepancy in the number of studies reported in the text and tables; this review is based on the number from the tables). All studies were blinded to administrators and participants; 15 studies adequately reported reasons for withdrawals (>80%); only four studies used intention-to-treat analysis.

Zolpidem versus nitrazepam: One of two studies reported that zolpidem statistically significantly improved sleep onset latency compared with nitrazepam (68.4% versus 56.4%). One study reported significantly fewer awakenings with zolpidem (p=0.031). Patients receiving zolpidem reported greater improvement in the quality of sleep compared with nitrazepam (66.7% versus 37.5%). There were no statistically significant differences between treatment groups for adverse events or other outcomes.

Zolpidem versus temazepam: One of two studies reported statistically significantly better results for sleep onset latency with zolpidem versus temazepam (p=0.05), and improved sleep quality with zolpidem (p=0.03, one study). There were no statistically significantly different between groups for adverse events or other outcomes.

Zolpidem versus zopiclone: One study showed statistically significantly better results for sleep latency (OR 1.72, 95% CI 1.04 to 2.84), rebound insomnia (OR 0.28, 95% CI 0.13 to 0.60), and adverse events (OR 0.55, 95% CI 0.37 to 0.81) with zolpidem compared to zopiclone. Other outcomes were not statistically significantly different.

Zaleplon versus zolpidem: Two of six studies suggested that zaleplon resulted in shorter sleep onset latency compared with zaleplon, but three studies suggested that sleep duration was significantly less with zaleplon compared with zolpidem. Three of four studies suggested that zolpidem was more likely to result in better sleep quality compared with zaleplon (OR 0.66, 95% CI 0.51 to 0.87). Patients given zaleplon were less likely to experience withdrawal symptoms on the first night compared to patients given zolpidem (OR 0.2, 95% CI 0.13 to 0.72; one study). Zaleplon compared with zolpidem (two studies) was shown to result in statistically significantly less rebound insomnia for sleep onset latency (OR 0.27, 95% CI 0.17 to 0.44; I²=40.9%), sleep duration (OR 0.25, 95% CI 0.15 to 0.41, I²=48%) and number of awakenings (OR 0.34, 95% CI 0.18 to 0.61: I²=55.9%). No other outcomes were statistically significant and there were no differences in the frequency of adverse events.

Zopiclone versus lormetazepam: Zopiclone was significantly less effective in reducing sleep onset latency than lormetazepam (p=0.013; one study), but no other outcomes were significantly different. Adverse events were similar in both groups.

Zopiclone versus nitrazepam (eight studies) and zopiclone versus temazepam (four studies) produced conflicting results.

Sixteen case reports (n=26 patients) were included in the extended review. Withdrawal symptoms were reported by 18 patients and included epileptic seizures, psychomotor agitation, restlessness, anxiety, confusion and sleep disturbances.
Cost information
A separate cost-effectiveness review was undertaken and reported in the review.

Authors' conclusions
The short-acting drugs seemed equally effective and safe with minor differences that may lead a prescriber to favour one over another in different patients. There is a clear need for further research in this area.

CRD commentary
The review question and supporting inclusion criteria were clearly defined. A comprehensive search of the literature was undertaken for the main review. However, only articles in English were included for the extended review, so language bias may have been introduced. The authors acknowledged the potential for publication bias. The authors undertook each step of the main review in duplicate, reducing the potential for reviewer error and bias, but this process was unclear for study selection in the extended review.

Study quality was assessed using appropriate criteria for the main review, but the quality of the RCTs was generally poor. There appeared to be some statistical analysis; it was unclear whether the methods used to synthesise data were appropriate. The authors acknowledged that the comparisons in the review were limited and that only a small subset of studies permitted meta-analysis; many studies did not make or allow direct comparisons. The authors also acknowledged the potential for selective reporting of significant findings for some outcomes, small sample sizes for many studies, short follow-up times, and poor reporting of study details and outcome data.

Given the limitations with the studies, the authors suggested that the findings should be interpreted with considerable caution. The authors' recommendation for further research seems appropriate.

Implications of the review for practice and research

Practice: The authors did not state any implications for practice.

Research: The authors stated that a good quality RCT is needed to allow head-to-head comparisons of some of the key drugs. The RCT should include a placebo arm and last for at least two weeks, and data on sleep outcomes should include quality of life and daytime drowsiness. The authors also stated that further research is needed to examine the effect of intermittent use of hypnotics on tolerance and risk of dependency.

Funding
NIHR Health Technology Assessment Programme on behalf of the National Institute for Health and Clinical Excellence (NICE), project number 02/22/01.

Bibliographic details

PubMedID
15193209

Original Paper URL
http://www.hta.ac.uk/execsumm/summ824.shtml

Additional Data URL

Other publications of related interest
Dundar Y, Dodd S, Strobl J, Boland A, Dickson R, Walley T. Comparative efficacy of newer hypnotic drugs for the

**Indexing Status**

Subject indexing assigned by NLM

**MeSH**

Adult; Aged; Cost-Benefit Analysis; Female; Humans; Hypnotics and Sedatives /administration & dosage /adverse effects /economics /therapeutic use; Male; Middle Aged; Randomized Controlled Trials as Topic; Sleep Initiation and Maintenance Disorders /drug therapy; Treatment Outcome

**AccessionNumber**

12004008558

**Date bibliographic record published**

15/07/2004

**Date abstract record published**

10/11/2010

**Record Status**

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