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

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Executive summary

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Executive summary

Objectives

To assess the clinical and cost-effectiveness of zaleplon, zolpidem and zopiclone (Z-drugs) compared with 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 10 and 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, 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 considered 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 17 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, variations 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 (one study suggests sleep latency is significantly shorter with zopiclone and another with nitrazepam; 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:
   (a) 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. Although 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 report 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 formal trial to allow head-to-head comparison of some of the key drugs in a double-blind randomised controlled trial lasting at least 2 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.

Publication

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NHS R&D HTA Programme

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The HTA programme commissions research only on topics where it has identified key gaps in the evidence needed by the NHS. Suggestions for topics are actively sought from people working in the NHS, the public, consumer groups and professional bodies such as Royal Colleges and NHS Trusts.

Research suggestions are carefully considered by panels of independent experts (including consumers) whose advice results in a ranked list of recommended research priorities. The HTA Programme then commissions the research team best suited to undertake the work, in the manner most appropriate to find the relevant answers. Some projects may take only months, others need several years to answer the research questions adequately. They may involve synthesising existing evidence or designing a trial to produce new evidence where none currently exists.

Additionally, through its Technology Assessment Report (TAR) call-off contract, the HTA Programme is able to commission bespoke reports, principally for NICE, but also for other policy customers, such as a National Clinical Director. TARs bring together evidence on key aspects of the use of specific technologies and usually have to be completed within a limited time period.

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