Small benefits of Z drugs over placebo for insomnia

A meta-analysis has found that Z drugs reduce the time taken to fall asleep by 22 minutes compared with placebo. However, this result may not be clinically significant and any benefit of Z drugs must be balanced against their well-documented risks.

Overview: Risks associated with the long-term use of hypnotic drugs have been well recognised for many years. These include falls, accidents, cognitive impairment, dependence and withdrawal symptoms. Recently, an observational study (Billioti de Gage et al. 2012) suggested that benzodiazepines and Z drugs (zaleplon, zolpidem and zopiclone) are also associated with an increased risk of dementia (see Eyes on Evidence February 2013).

Current advice: The NICE technology appraisal on zaleplon, zolpidem and zopiclone recommends that when, after due consideration of the use of non-drug measures, hypnotic drug therapy is considered appropriate for the management of severe insomnia interfering with normal daily life, hypnotics should be prescribed for short periods of time only, in strict accordance with their licensed indications.

The technology appraisal also states that there is no compelling evidence of a clinically useful difference between the Z drugs and shorter-acting benzodiazepine hypnotics from the point of view of their effectiveness, adverse effects, or potential for dependence or abuse. Patients who have not responded to one of these hypnotic drugs should not be prescribed any of the others.

New evidence: A meta-analysis has investigated the effectiveness of Z drugs for insomnia using published and unpublished RCTs submitted to the US FDA for regulatory approval (Huedo-Medina et al. 2012). The study included 13 RCTs (n=4,378) comparing a Z drug with placebo for the treatment of primary insomnia. The drugs studied were eszopiclone, the stereoisomer of zopiclone which is not available in the UK, zaleplon and zolpidem. The primary outcomes were the time taken to fall asleep (known as sleep latency) measured by objectively by polysomnograph and subjectively by patients' perceptions.

The meta-analysis found that both Z drugs and placebo statistically significantly reduced sleep latency.

The reductions in subjective sleep latency seen with Z drugs and placebo were 25 minutes (95% CI 20 to 30 minutes) and 19 minutes (95% CI 12 to 27 minutes), respectively. This difference was not significant. For polysomnographic sleep latency, a reduction of 42 minutes (95% CI 23 to 60 minutes) was seen with Z drugs, compared with a reduction of 20 minutes (95% CI 11 to 28 minutes) with placebo. The difference between Z drugs and placebo was 22 minutes (95% CI 11 to 33 minutes) for polysomnographic sleep latency. This result was statistically significant; however, the effect size was small and may not be clinically important. Although this benefit appears small on a population basis, individual patients may respond better or worse than the population average.
Sleep duration is an important outcome for people with insomnia. In these studies this outcome was infrequently reported and was a secondary outcome. Analysis of the secondary study outcomes showed no significant effect of Z drugs. The lack of difference between groups for other sleep measures coupled with the fact that few reports included them meant there was insufficient evidence to show efficacy on these measures.

The authors reported that a strength of this meta-analysis was that it considered studies submitted to the FDA, which must report all data and are therefore less likely to be affected by reporting bias. However the authors also recognised that the included studies were all sponsored by pharmaceutical industry, which may result in sponsorship bias, and thus overestimation of the effects of Z drugs.

**Commentary:** "This is a well conducted meta-analysis with an interesting methodological approach aiming to reduce the effect of publication bias. Objective measures suggest that Z drugs produce a small but significant improvement in sleep latency over placebo, with a non-statistically significant difference found in potentially more clinically relevant measures. When considering prescribing a Z drug it is necessary to balance this relatively small benefit with the well documented risk profile of these agents. The relatively large placebo response adds strength to the argument to prioritise non drug and specifically psychological interventions.

"It is appropriate to continue to follow current guidance for the management of insomnia: to consider Z drugs when first-line non drug interventions are unsuccessful or inappropriate; to prescribe them for short periods (usually up to 2 to 4 weeks only) at the lowest effective dose; and to avoid repeat prescribing. This guidance is reiterated in the hypnotics section of the Key therapeutic topics – Medicines management options for local implementation document, which also advises that various approaches to reducing hypnotic prescribing can achieve success. A consensus statement on Addiction to Medicines was published by the Royal College of General Practitioners and the Royal College of Psychiatrists. It sets out how medical practitioners, specialist services and patients can work together to improve responses for people dependent on prescribed or over-the-counter medicines." – Dr Steve McWilliam, Medical Research Council Clinical Pharmacology & Therapeutics Research Fellow, University of Liverpool

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