NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

GUIDANCE EXECUTIVE (GE)

Review of TA77: Zaleplon, zolpidem and zopiclone for the management of insomnia

This guidance was issued in April 2004
The review date for this guidance is April 2010

Recommendation

- A review of the guidance should be transferred to the 'static guidance list', and this proposal should be subject to consultation.

Consideration of options for recommendation:

Options	Comment
A review of the guidance should be planned into the appraisal work programme.	The new evidence on the 'Z drugs' found whilst preparing the review proposal is unlikely to have a substantive effect on the recommendations of TA77. We therefore believe that a review of TA77 at present would be a poor use of NICE resources. We have identified several RCTs on hypnotic drugs that are currently in development, however the anticipated launch dates of these products are not until 2011/2012. We therefore believe that any insomnia drugs currently in the pipeline would be best dealt with by the NICE Topic Selection team in the usual manner.
The decision to review the guidance should be deferred [to a specified date].	We recommend that this guidance be transferred to the static list, where it can be monitored for changes and reconsidered if suitable evidence materialises.
A review of the guidance should be combined with a review of a related technology and conducted at the scheduled time for the review of the related technology.	There are no other insomnia topics on the current NICE work programme.
A review of the guidance should be combined with a new appraisal that has recently been referred to the Institute.	No suitable new appraisal was found

A review of the guidance should be incorporated into an on-going clinical guideline.	No suitable guideline was found. [redacted]
A review of the guidance should be transferred to the 'static guidance list'.	**The new evidence found whilst preparing the review proposal is unlikely to have a substantive effect on the conclusions of TA77. We therefore recommend that this appraisal is transferred to the static list, where it can be monitored on an ongoing basis.**

Original remit(s)

To appraise the clinical and cost effectiveness of the use of zaleplon, zolpidem and zopiclone in the management of short-term insomnia, compared with medicines in the benzodiazepine class.

Current guidance

1.1 When, after due consideration of the use of nonpharmacological measures, hypnotic drug therapy is considered appropriate for the management of severe insomnia interfering with normal daily life, it is recommended that hypnotics should be prescribed for short periods of time only, in strict accordance with their licensed indications.

1.2 It is recommended that, because of the lack of compelling evidence to distinguish between zaleplon, zolpidem, zopiclone or the shorter-acting benzodiazepine hypnotics, the drug with the lowest purchase cost (taking into account daily required dose and product price per dose) should be prescribed.

1.3 It is recommended that switching from one of these hypnotics to another should only occur if a patient experiences adverse effects considered to be directly related to a specific agent. These are the only circumstances in which the drugs with the higher acquisition costs are recommended.

1.4 Patients who have not responded to one of these hypnotic drugs should not be prescribed any of the others.

Relevant Institute work

Published

None found

In topic selection

[redacted]

Safety information

15/3/2007: The FDA requested that all manufacturers of sedative/hypnotic drugs strengthen their product labelling to include stronger language concerning potential risks. This follows a review of the available post-marketing adverse event information for these products, including zolpidem, flurazepam, eszopiclone, secobarbital, temazepam, and zaleplon. (Source: NeLM)

Details of new indications

None found for zaleplon, zolpidem or zopiclone.

Details of new products

Drug (manufacturer)	Details
Almorexant (Actelion)	Phase III UK launch planned Q4 2012
Esmirtazapine (Schering Plough)	Phase III
Indiplon (Pfizer)	Phase III UK launch planned Q1 2011
Melatonin (Lundbeck)	Launched June 2008
MK4305 (Merck)	Phase III
Tasimelteon (Vanda Pharmaceuticals)	Phase III UK launch planned Q1 2012
Almorexant (Actelion)	Phase III
Actelion (Eisai)	Phase III
Ramelteon (Takeda)	Phase III

On-going trials

Trial name and contact	Details
Characteristics of Sleep Patterns in Young Adults With and Without Insomnia	Phase IV Ongoing Primary completion date: May 2008
A Multicentre, Randomised, Double-Blind, Double-Dummy, Placebo-Controlled Study to Evaluate the Safety and Efficacy of Ramelteon Compared to Placebo With Zopiclone as a Reference Arm in Adults With Chronic Insomnia	Phase III Currently recruiting

Proposed Timing for updating the guidance

If the guidance is to be updated as an appraisal, it would be scheduled into the work programme accordingly.

New evidence

The search strategy from the original assessment report was re-run on the Cochrane Library, Medline, Medline In-Process and Embase. References from 2003 onwards were reviewed.

Implementation

A submission from Implementation is attached at the end of this paper.

Equality and diversity issues

No equality and diversity issues have been identified.

Appraisals comment:

Current guidance TA77 recommends that, because of the lack of compelling evidence to distinguish between zaleplon, zolpidem, zopiclone or the shorter-acting benzodiazepine hypnotics, the drug with the lowest purchase cost (taking into account daily required dose and product price per dose) should be prescribed. The committee in the current guidance recommended that further research should include the impact of hypnotics and any resultant improvement in sleep quality, on daytime functioning and health-related quality of life (HRQOL). None of the new RCTs have addressed these issues.

Literature searches identified a number of randomised and non-randomised controlled trials since the publication of TA77. However, the evidence base for zaleplon, zolpidem, zopiclone, does not appear to have substantially changed since guidance was published. In particular, there have been no RCTs that address the recommendations for future research or tackle issues with the evidence base that the Committee considered in the original guidance.

The Institute has not issued any new guidance in the area since the publication of TA77 in 2003 [redacted]. In April 2007 it was decided following consultation with stakeholders that the decision to review TA77 should be deferred to 2010 because of a lack of change to the evidence base that would have a material effect on the original guidance. It was noted that there have been a number of developments in the wider field of hypnotic drugs, and these new hypnotics could be considered separately as an STA or could be appraised in a wider appraisal of all newer hypnotics as an MTA or in a clinical guideline.

Summary

The new evidence on the 'Z drugs' found whilst preparing the review proposal is unlikely to have a substantive effect on the recommendations of TA77. It is recommended that this appraisal be transferred to the static list, where it can be monitored on an ongoing basis. Particular focus should be given to incorporating TA77 it into a potential clinical guideline on drugs for insomnia, if possible.

GE paper sign off: Frances Sutcliffe, 26th May 2010.

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NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

IMPLEMENTATION DIRECTORATE

Guidance Executive Review

Technology appraisal 77: Insomnia - newer hypnotic (Zaleplon, zolpidem and zopiclone)

1. NICE implementation uptake report

NICE implementation uptake reports provide information on national trends and activity associated with technologies recommended in NICE guidance.

1.1 **NICE implementation uptake report: insomnia - newer hypnotic drugs.** Available from: http://www.nice.org.uk/media/640/85/TA77NICEImplUptake.pdf

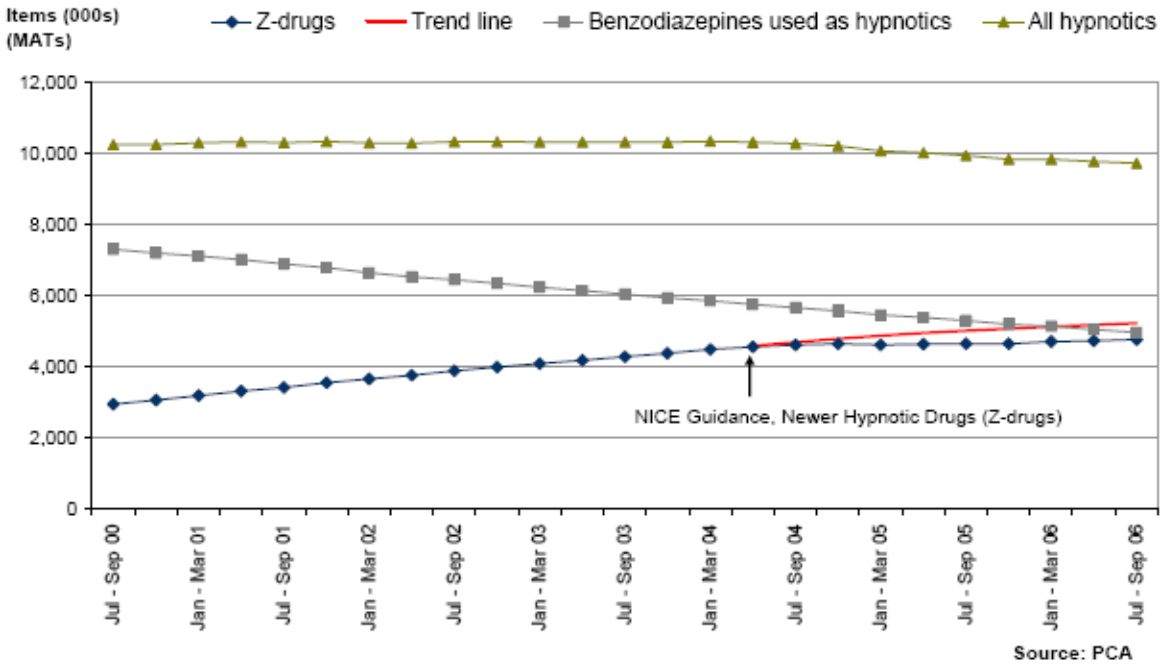
Overview

The long term downward trend in prescribing of benzodiazepines used as hypnotics continues, with a corresponding shift towards prescribing of Z-drugs. Both trends pre-date the publication of the NICE guidance.

However, the guidance anticipated a possible “reduction in the prescribing of hypnotics” and the rate of increase in the prescribing of Z-drugs stabilised following publication of the guidance (figure 1).

National prescriptions data indicate a slight shift towards shorter treatment duration.

Figure 1 Drugs for the treatment of insomnia dispensed in the community in England



2. External literature

2.1 ERNIE

2.1.1 Siriwardena AN, Qureshi Z, Gibson S et al. (2006) GPs' attitudes to benzodiazepine and 'Z-drug' prescribing: a barrier to implementation of evidence and guidance on hypnotics British Journal of General Practice 56 (533): 964-967

Description: This study was a postal questionnaire survey of 84 GPs in a single primary care trust to assess practitioner's beliefs about hypnotics prescribing. The survey reported that responders rated Z-drugs as more effective than benzodiazepines in terms of total sleep time, tolerance, addiction, dependence, daytime sleepiness and road traffic accidents. The study concluded that attitudes were not consistent with current evidence and NICE guidance.

2.2.2 NHS Information Centre for Health and Social Care (2009) Use of NICE appraised medicines in the NHS in England-Experimental Statistics

Description: Estimated numbers of eligible patients were derived from NICE costing templates. Data for Zaleplon, zolpidem and zopiclone was obtained from: Prescription Cost Analysis database (PCA), Prescription and Cost system (ePACT), Hospital Pharmacy Audit Index. The NICE costing template expected an annual number of 558.4 thousand patients. The observed use in 2008 was 115,854.8 thousand defined daily doses, a ratio of 7.4 to 1.