TECHNOLOGY ASSESSMENT REPORT FOR THE HTA PROGRAMME
FINALISED VERSION: 22 April 2003

Title:
Newer hypnotic drugs for the management of insomnia

A. Details of review team

Rumona Dickson, Ms
Director, LRIG
Liverpool Reviews and Implementation Group (LRIG)
New Medical School
Ashton Street
Liverpool, UK
L69 3GE
Tel: 0 151 794 5682/5541
Fax: 0 151 794 5678
Email: rdickson@liv.ac.uk

Details of other members of the review team

Dundar Y
Boland A
Haycox A
Strobl J
Walley T

B. Full title of research question

A rapid and systematic review 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 management of insomnia.

C. **Clarification of research question and scope**

The review will examine the comparative clinical and cost-effectiveness of drugs used for the short-term management of insomnia.

Clinically, the review will compare the effectiveness of three non-benzodiazepine agents (zaleplon, zolpidem and zopiclone), within their licensed indications, with benzodiazepines that are used in the NHS for the short-term management of insomnia. Flunitrazepam and flurazepam, which hold a UK marketing authorisation but are not approved for use on the NHS, and triazolam, for which marketing authorisation has been withdrawn in the UK, will not be included in the review.

Where data are available, comparisons between any of the three non-benzodiazepine drugs (zaleplon, zolpidem and zopiclone) will be carried out.

In addition, if the evidence allows, the relative incidence of any dependency and effects of withdrawal will be examined.

The evaluation of economic evidence will include quality assessment of published cost minimisation, cost effectiveness, cost utility and cost benefit analyses. Economic models included in the industry submissions will be critiqued as appropriate. If appropriate data are available, an economic model will be developed to estimate the cost effectiveness of the treatment alternatives.

D. **Report Methods**

Search strategy
The following databases will be searched for relevant published literature for the period from 1966 to March 2003.

- CCTR (Cochrane Controlled Trials Register)
- CDSR (Cochrane Database of Systematic Reviews)
- DARE (Database of Abstracts of Reviews of Effectiveness)
- EMBASE
- Health Technology Assessment (HTA) database
- ISI Web of Science- Proceedings (Index to Scientific & Technical Proceedings)
- MEDLINE
- NHS EED (NHS Economic Evaluation Database)
- PsycINFO
- ISI Web of Science- Science Citation Index Expanded

Details of the search strategies used to explore EMBASE and MEDLINE are available in Appendix I.

Depending on the data available within included trials the strategy may be expanded to identify other study designs that evaluate issues related to adverse events (e.g. dependency and withdrawal symptoms).

Research groups identified through searches of the registers listed below will be contacted for information about ongoing trials:

- National Research Register
- Cochrane Library
- CenterWatch Clinical Trials Listing Service (centerwatch.com)
- *meta*Register of Controlled Trials and ISRCTN Register (controlled-trials.com)
- ClinicalTrials.gov – National Institutes of Health database (clinicaltrials.gov)

Bibliographies of previous reviews, retrieved articles and industry submissions made to the National Institute for Clinical Excellence (NICE) will be searched for further studies.

Handsearching of recent issues of neurology/sleep journals that might not yet been indexed in electronic databases covering the period from October 2002 to March 2003 will be conducted. Internet resources (including industry supported websites) will be examined for information on clinical trials and cost data.

Inclusion and exclusion criteria

a. Inclusion criteria

Study design	**Clinical effectiveness:** Randomised Controlled Trials (RCTs)* **Economic evaluation:** Full economic evaluations based on evidence from RCTs that consider both costs and consequences * other study designs, as necessary, to examine dependency and withdrawal
Patient population	Individuals with insomnia
Interventions	Zaleplon, zolpidem and zopiclone
Comparators	Benzodiazepines**
Outcomes	**Clinical:** • sleep latency • sleep duration • number of awakenings • sleep quality • quality of life • daytime alertness • tolerance • abuse potential • adverse effects including dependency and withdrawal **Economic:** • cost per increase in sleep duration • cost per decrease in sleep latency • cost per adverse effect avoided • cost per quality adjusted life year gained

** The BNF (Edition 44) (1) refers the following benzodiazepines for the short-term management of insomnia: diazepam, loprazolam, lorazepam, lormetazepam, nitrazepam, temazepam.

b. Exclusion criteria

RCTs that:

- provide only unplanned, interim findings
- provide data on only a sub-group of the enrolled patients
- are continuing to recruit patients
- include volunteer subjects that do not report symptoms of insomnia in their study population

Comparison of:

- benzodiazepines not currently licensed for use in the management of insomnia in the UK

Quality assessment strategy

All included studies, resulting from our searching, will be assessed for methodological quality. The quality of clinical effectiveness studies will be assessed using criteria based on CRD Report No. 4. (2) Should the broader search strategy related to withdrawal and dependency identify non-randomised controlled trials, quality assessment tools appropriate to that type of study will be used.

Cost effectiveness studies will be quality assessed using criteria updated from the checklist developed by Drummond.(3) Study quality will be evaluated independently by two reviewers. Disagreements will be resolved by consensus and if necessary, a third reviewer will be consulted.

Data extraction strategy

Data from sources located in our search will be extracted as detailed below and will include information listed in Appendix II.

Individual study data relating to study design, findings and quality will be extracted by one reviewer and independently checked for accuracy by a second reviewer. Study details will be extracted on pre-tested data extraction forms. Time permitting, authors of the studies will be contacted for missing data. Data from studies presented in multiple publications will be extracted and reported as a single study with all other relevant publications listed. Data extraction and reporting related to dependency and withdrawal will be narrative and be reported in tables.

Methods of analysis/synthesis

a. Methods of analysis for clinical studies

Individual study data and quality assessment will be summarised in structured tables and as a narrative description. Potential effects of study quality will be discussed.

For binary outcomes, where sufficient data are available, relative treatment effects will be presented in the form of relative risks (RR). For continuous outcomes, mean differences will be calculated. Relative risk data will be pooled only if this makes sense clinically and statistically. Heterogeneity between studies will be assessed by considering differences in the (a) study population, (b) intervention, (c) outcome measures and (d) study quality.

b. Methods of analysis for economic studies

Individual study data and quality assessment will be summarised in structured tables and as a narrative description. All potential effects of study quality will be discussed.

To supplement findings from the economic literature review, additional cost and benefit information from other sources, including the industry submissions, will be collated and presented as appropriate.

Methods for estimating quality of life, costs and cost-effectiveness and/or cost/QALY

a. Cost data

The primary perspective for the analysis of cost information will be the NHS. Cost data will therefore focus on the marginal direct health service costs associated with the drugs.

Quantities of resources used will be identified from consultation with experts, primary data from relevant sources and the reviewed literature. Unit cost data will be extracted from the literature (e.g. Personal Social Services Research Unit and Chartered Institute of Public Finance and Accounting cost databases) or obtained from other relevant sources (drug price lists, NHS reference costs). All cost data will be converted to a single year (2003) in pounds sterling.

Where appropriate costs will be discounted at 6%, the rate recommended in the NICE guidance to manufacturers and sponsors of submissions.(4)

b. Assessment of benefits

A balance sheet will be constructed to list benefits and costs arising from alternative treatment strategies. We anticipate that the main measures of benefit will be prolonged duration of sleep and improved quality of life.

Where appropriate, effectiveness and other measures of benefit will be discounted at 1.5%, the rate recommended in the NICE guidance to manufacturers and sponsors of submissions. (4)

c. Modelling

We will undertake a detailed analysis of the industry model(s), which will include an assessment of strengths and weaknesses and a discussion of the implications of different assumptions.

Our ability to construct an economic model will depend on the data available. If appropriate, the results in terms of costs and effectiveness will be presented in terms of a balance sheet. A formal combination of costs and benefits will also be performed, although the type of economic evaluation will only be chosen in light of the variations in outcome identified from the literature searches.

Ideally, the results would be presented as incremental cost per QALY ratios for each alternative considered. If sufficient data are not available to construct these measures with substantial precision, incremental cost effectiveness analysis or cost minimisation analysis will be undertaken.

d. Sensitivity Analysis

If appropriate, sensitivity analysis will be applied to our model in order to assess the robustness of the results to realistic variations in the levels of the underlying data (e.g. acquisition price of drugs). Where the overall results are sensitive to a particular variable, the sensitivity analysis will analyse the exact nature of the impact of variations.

The results of the evaluation will be used to estimate comparative cost-effectiveness ratios under different treatment scenarios based upon appropriate subgroups of patients.

E. Handling the company submission(s)

The Liverpool Reviews and Implementation Group intends to use the industry dossier:

- As a source of data, looking for studies that meet the inclusion criteria (RCTs/other effectiveness as well as cost-effectiveness, cost utility studies and cost benefit analysis).
- To undertake an analysis of any industry models, including the strengths and weaknesses and the implications of different assumptions. The detail to which this can be undertaken will depend on the number and size of company dossiers submitted.

Any 'commercial in confidence' data taken from the company submission will be underlined in our report.

F. Project Management

a Timetable/milestones:

Submission	Date
Draft protocol	20 February 2003
Finalised protocol	13 March 2003
Progress report	04 June 2003
Complete, near final draft report to external reviewers and NICE Technical Lead	14 July 2003
Final assessment report	13 August 2003

b. Review Advisory Panel

The Group will recruit an Advisory Panel of experts to support the development of the review. Panel members may advise on specific sections of the review: clinical, healthcare policy, health economics, statistics and review methodology.

c. External reviewers

The Technology Assessment Report will be subject to external peer review by at least two experts. These reviewers will be chosen according to academic seniority and content expertise and will be agreed with NCCHTA. We recognise that methodological review will be undertaken by the NICE secretariat and Appraisal Committee, but if the TAR encounters particularly challenging methodological issues we will organise independent methodological reviews. External expert reviewers will see a complete and near final draft of the TAR and will understand that their role is part of external quality assurance. All reviewers are required to sign a copy of the NICE Confidentiality Acknowledgement and Undertaking. We will send external reviewers' signed copies to NCCHTA. Comments from external reviewers and the Technical lead, together with our responses to these will be made available to NCCHTA in strict confidence for editorial review and approval.

d. Competing Interests

No competing interests exist for members of the Review Team.

G. Appendices

I Details of MEDLINE and EMBASE search strategies

a. MEDLINE Search Strategy (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"/
27. exp SLEEP/
28. 26 or 27
29. (insomnia or sleeplessness).tw.
30. 28 or 29
31. 21 and 25 and 30

b. EMBASE Search Strategy (1980-2003)

1. randomized controlled trial/
2. controlled study/
3. randomization/
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

II Details of data extraction

Clinical effectiveness data to be extracted will include, but not be limited to:

Study Details

- Study bibliographic data
- Type of report (abstract, full manuscript, interim report)
- Type of study
- Methodological details of study
- Concomitant drug therapy
- Details of funding

Participants

- Age
- Sex
- Level of disease
- Co-morbidity
- Number recruited or accrued

Results (data for all outcomes specified will be extracted as available)

- Sleep latency
- Duration of sleep
- Number of awakenings after sleep onset
- Quality of sleep
- Quality of life
- Daytime alertness
- Tolerance
- Abuse potential
- Adverse effects including dependency and withdrawal

III Details of quality assessment

a. **Studies of clinical effectiveness** will be assessed using the following criteria, based on CRD Report No. 4 (2)

- 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 will be graded in terms of ✔ **yes** (item adequately addressed), ✘ **no** (item not adequately addressed), ✔/✘ *partially* (item partially addressed), **?** **unclear** or not enough information, **NA** not applicable or **NS** not stated.

b. **Studies of cost effectiveness** will be assessed using the following criteria, which is an updated version of the checklist developed by Drummond (3)

- Study question
- Selection of alternatives
- Form of evaluation
- Effectiveness data
- Costs
- Benefit measurement and valuation
- Decision modelling
- Discounting
- Allowance for uncertainty
- Presentation of results

All items will be graded as either ✔ **yes** (item adequately addressed), ✘ no (item not adequately addressed), **?** **unclear** or not enough information, **NA** not applicable or **NS** not stated.

V. Background

Insomnia can be classified in several different ways: by duration, severity, or co-morbidity. Epidemiological reports on insomnia use differing definitions, classification systems and diagnostic criteria: the Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV), of the American Psychiatric Association (1994), the International Classification of Sleep Disorders - Revised (ICSD-R) of the American Sleep Disorders Association (1997), and the International Classification of Diseases, 10th edition (ICD-10), of the World Health Organization (1992). The definitions vary substantially across the three classification systems.(5) The estimates of population prevalence of insomnia have, unsurprisingly, varied between 10% to nearly 38%.(6) The prevalence of insomnia is reported to be higher in women and insomnia symptoms increase with age.(7) Many patients complaining of insomnia suffer significant co-morbidities, such as depression, other mental diseases, or organic disorders. Thus insomnia may appear as the primary condition or it may be a symptom of an underlying disease.

It is generally recommended that any underlying causes of insomnia be investigated and treated first. The use of non-pharmacological interventions is preferred as first line treatment of insomnia. These include sleep hygiene, relaxation techniques, and cognitive behavioural therapies.

Benzodiazepines have been available for the pharmacological treatment of insomnia since the mid-1960s. A recent meta-analysis of benzodiazepines for insomnia has found these drugs to be associated with increased sleep duration compared to placebo, but also adverse outcomes such as daytime drowsiness and dizziness.(8) The authors were unable to evaluate tolerance effects in their meta-analysis, because randomised trials tend to be of short duration.

The technology

Zaleplon, zolpidem, and zopiclone are non-benzodiazepine hypnotics introduced in the late 1980s and 1990s and are only licensed for short-term use in insomnia in the UK. These drugs were developed with the intention to overcome some of the adverse effects associated with benzodiazepines including tolerance, dependency and withdrawal symptoms.

Zolpidem is an imidazopyridine, which binds selectively to only one (omega-1) receptor subtype of the GABA-A receptor complex, whereas benzodiazepines are less selective. Zopiclone belongs to the cyclopyrrolone group. Zaleplon, the most recently approved drug, is a pyrazolopyrimidine compound and also binds selectively to the omega-1 site of the GABA-A receptor complex.

Current practice in the UK

The British National Formulary 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.(1) In a recently published study conducted in The Netherlands and Sweden, a third of patients prescribed benzodiazepines had continued use after eight years follow-up.(9)

In the second quarter of 2002, the UK Prescription Pricing Authority 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. The three non-benzodiazepine drugs accounted for £3.86 million (NIC) for over 940,000 items, with zopiclone accounting for over 80% of the prescribed items.

The following table includes the hypnotic agents currently listed in the British National Formulary, September 2002(1) for the short-term management of insomnia.

Pharmaceutical agent	Product name	Dose	Cost for 14 days
Zolpidem	Tablets: *Stilnoct*®	10 mg; elderly (or debilitated) 5 mg	£2.24 (at 10 mg/day)
Zaleplon	Capsules: *Sonata*®	10 mg; elderly 5 mg	£4.04 (at 10 mg/day)
Zopiclone	Tablets: *Zimovane*® *Zileze*®	7.5 mg; elderly initially 3.75 mg increased if necessary	£2.24 (at 7.5 mg/day)
Diazepam	Tablets: *Tensium*® *Rimapam*® Oral solution: *Dialar*®	5-15 mg	£0.29 (at 5 mg/day) £3.68 (at 5 mg/day)
Nitrazepam	Tablets: *Remnos*® *Mogadon*® Oral suspension: *Somnite*®	5–10 mg; elderly (or debilitated) 2.5–5 mg	£0.41 (at 5 mg/day) £4.95 (at 5 mg/day)
Lorazepam	Tablets	1-2 mg	£0.62 (at 1 mg/day)
Loprazolam	Tablets	1 mg, increased to 1.5 or 2 mg if required; elderly (or debilitated) 0.5 or 1 mg	£2.23 (at 1 mg/day)
Lormetazepam	Tablets	0.5–1.5 mg; elderly (or debilitated) 500 micrograms	£0.38 (at 0.5 mg/day)
Temazepam	Tablets Oral solution	10–20 mg, exceptional circumstances 30–40 mg; elderly (or debilitated) 10 mg, exceptional circumstances 20 mg	£0.44 (at 10 mg/day) £2.32 (at 10 mg/day)

VI References

1. British National Formulary. British National Formulary. In. No 44, September 2002 ed. London: British Medical Association and Royal Pharmaceutical Society of Great Britain; 2002.
2. Khan K, Ter Riet G, Glanville J, Sowdon A, Kleijnen J. Undertaking systematic reviews of research on effectiveness. CRD guidance for carrying out or commissioning reviews. 2nd Edition. CRD Report 4. York: NHS Centre for Reviews and Dissemination (CRD), University of York. 2000.
3. Drummond M, Stoddart GL and Torrance GW. Methods for the economic evaluation of health care programmes. Oxford: Oxford Medical Publications; 1987.
4. National Institute for Clinical Excellence. Technical guidance for manufacturers and sponsors on making a submission to a technology appraisal. London: National Institute for Clinical Excellence; 2001.
5. Harvey AG. Insomnia: symptom or diagnosis? Clinical Psychological Review 2001;**21**:1037-59.
6. Holbrook AM, Crowther R, Lotter A, Cheng C, King D. The diagnosis and management of insomnia in clinical practice: a practical evidence-based approach. Canadian Medical Association Journal 2000;**162**:216-20.
7. Ohayon MM. Epidemiology of insomnia: what we know and what we still need to learn. Sleep Medicine Reviews 2002;**6**:97-111.
8. Holbrook AM, Crowther R, Lotter A, Cheng C, King D. Meta-analysis of benzodiazepine use in the treatment of insomnia. Canadian Medical Association Journal. 2000;**162**:225-233.
9. van Hulten R, Isacson D, Bakker A, Leufkens H. Comparing patterns of long-term benzodiazepine use between a Dutch and a Swedish community. Pharmacoepidemiology and Drug Safety 2003;**12**:49-53.