



Title: Safety of Zopiclone or Trazodone for Insomnia in Adults

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Context and policy issues:

Insomnia is a common complaint in the general population. It is characterized by difficulty in initiating sleep and/or maintaining sleep (frequent nocturnal awakenings or early morning awakenings).¹ The estimated prevalence of insomnia varies from 10 to 38%.^{2,3} This may be a result of the different definitions, classification systems and diagnostic criteria that were adopted in the epidemiologic surveys.² In Canada, the prevalence was reported as 13.4% or 3.3 million Canadians in 2005.⁴

Hypnotics may provide people who suffer from insomnia relief from symptoms of insomnia. Treatment with benzodiazepines (BZ) at a high dose and/or continuous use may result in a number of undesired effects such as altered sleep architecture, impaired daytime psychomotor performance, anterograde amnesia, rebound insomnia, withdrawal symptoms, tolerance, dependence, abuse potential and respiratory depression.¹ Z-drugs, zopiclone for instance, are another class of hypnotics. They are non-BZ that also act as agonists of the GABA receptor complex. Zopiclone has been licensed as a "hypnotic" since 1996.⁵ Most of the evidence from clinical trials indicated that Z-drugs had a good safety and tolerability profile, such as no significant next-day psychomotor or memory impairment, similar or fewer residual effects, and less frequent /severe rebound insomnia following withdrawal when compared with BZs.¹ Trazodone is a second-generation triazolopyridine antidepressant that possesses significant anxiolytic and sedative activity.⁶ It was approved for the use as antidepressant in 1995 by Health Canada.⁷ Trazodone was demonstrated to be effective in relieving insomnia symptoms in patients with concomitant diseases, such as depression.⁸ The purpose of the current report is to examine the comparative safety of zopiclone and trazodone in treating patients with insomnia.

Research question:

What is the safety in treatment with zopiclone / trazodone in people with insomnia, when compared to benzodiazepines?

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Methods:

A limited literature search was conducted on key health technology assessment resources, including PubMed, The Cochrane Library (Issue 4, 2007), University of York Centre for Reviews and Dissemination (CRD) databases, ECRI, EuroScan, international HTA agencies, and a focused Internet search. Results include articles published between 1992 and December 2007 and are limited to English language publications only. Filters were applied to limit the retrieval to systematic reviews, randomized controlled trials and observational studies. Quality of the included clinical trials was assessed using Jadad scale.⁹ The allocation concealment were also examined.¹⁰

Summary of findings:

Three systematic reviews and one clinical practice guideline that examined the clinical effectiveness of BZs and Z-drugs in patients with insomnia were identified from the literature search.^{2,3,11,12} The Dündar review³ included clinical trials with various study designs; while the others included randomized controlled trials (RCTs) only.^{2,11,12} The dose of zopiclone used in the included primary studies ranged from 5 to 15mg/day, and the treatment duration varied from one night to 6 weeks. Limited results of adverse events were reported in these reports, partly because the harm outcomes were insufficiently assessed in the primary studies.

In the Holbrook review¹¹, 13 RCTs that compared BZs with zopiclone were included; however, data from only 4 of the 13 RCTs was used in adverse events assessment. A summary odds ratio for adverse effects suggested a non-significant trend toward more side effects with the use of BZs (OR 1.5, 95%CI 0.8 - 2.9) when compared with zopiclone. The report of National Institute for Clinical Excellence (NICE)² made a similar statement that no statistically significant difference in the rates of treatment-related adverse events associated with any of the comparisons of Z-drugs vs. BZs. The Dündar review³ reported a non-significant difference in the adverse event rates between BZs and zopiclone, but patients in the nitrazepam group experienced deterioration in sleep quality between weeks 2 and 6, which suggested tolerance to the drug. The Glass review¹² involved people aged ≥ 60 years old exclusively. It compared BZs with Z-drugs (no separate results for zopiclone were reported). It concluded that there was no significant difference in cognitive or psychomotor-type adverse events between the two treatments.

A systematic review explored trazodone's effect in patients with primary insomnia, or insomnia either secondary to depression or induced by antidepressants, and healthy subjects as well.¹³ The dose used in the included studies ranged from 50 to 600mg/day, and the active treatment duration ranged from one night to 6 weeks. The majority of the studies included in this review were small and with limited treatment duration. The review described the common adverse events that related to higher doses of trazodone, and stated that when treating patients with insomnia with lower-than-antidepressant doses, conclusions regarding risks associated with use could not be made.

A summary of the evidence with respect to the comparison between BZs and zopiclone / trazodone can be found in Table 1.

Table 1: Summary of Systematic Reviews / Clinical Practice Guidelines

Author, year Study design	Population, number of trials included	Intervention vs. comparator	Results
Zopiclone			
Holbrook et al., 2000 ¹¹ SR	Pts with insomnia, 45 RCTs compared BZs with placebo or another active agent, while 13 involved ZOP	BZs were compared with placebo or another active agent	There was a non-significant trend toward more AEs with the use of BZs when compared to ZOP.
NICE, 2004 ² CPG	Pts with insomnia, 13 RCTs compared BZs to ZOP	BZs vs. Z-drugs (Zaleplon, zolpidem and ZOP)	No statistically significant differences in the rates of tx-emergent AEs associated with any of the comparisons of Z-drugs vs. BZs. No consistent differences between the Z-drugs and BZs in the incidence of next-day residual effects.
Dündar et al., 2004 ³ SR	Pts with insomnia, 17 studies compared a Z-drug with a BZ, 13 studies compared ZOP to a BZ	BZs vs. Z-drugs or comparison between any two of the Z-drugs	ZOP vs. lormetazepam (1 study): % of pts reported AEs was similar in both groups (26% vs. 28%) ZOP vs. nitrazepam (2 studies): no significant difference between groups on AE rates; tolerance was shown in nitrazepam group, but not in ZOP group ZOP vs. temazepam (2 studies): 26% of pts on ZOP reported AEs compared with 17% on temazepam in one study; while a non-significant difference was reported in terms of AEs in another study The short-acting drugs (ZOP, lormetazepam, and temazepam) are equally safe with minor differences.
Glass et al., 2005 ¹² SR	Pts with insomnia, aged 60 or over, 24 RCTs compared sedative hypnotics to placebo or active comparator, while 3 compared ZOP to BZs	Compared sedative hypnotics to placebo or another active comparator	The most common AEs were drowsiness/fatigue, headache, nightmares, and nausea/gastrointestinal disturbances; studies of Z-drugs vs. BZs found no significant difference in cognitive AEs or psychomotor-type AEs.

Author, year Study design	Population, number of trials included	Intervention vs. comparator	Results
Trazodone			
Mendelson, 2005 ¹³ SR	Pts with insomnia or healthy subjects, 18 studies (RCTs, or non-controlled trials)	TRA vs. placebo or no comparator	Common AEs (at doses of 75- 500mg/day) included drowsiness, dizziness, dry mouth, nausea/vomiting, constipation, headache, hypotension, and blurred vision. Drowsiness and next-day sedation were consistently reported. Hypotension, orthostatic hypotension with syncope, ventricular arrhythmias, cardiac conduction disturbances and exacerbation of ischemic attacks were reported at antidepressant doses (100-600mg/day), while in elderly people orthostatic hypotension was observed when receiving lower doses or concomitant antihypertensive therapy. Priapism was also reported. Tolerance was shown in pts when TRA used >1-3 weeks.

BZ: benzodiazepine; ZOP: zopiclone; SR: systematic review; CPG: clinical practice guideline; RCT: randomized controlled trial; AE: adverse event; pt: patient; tx: treatment; TRA: trazodone

Six RCTs compared zopiclone with BZs were retrieved.¹⁴⁻²⁰ They were all published between 1992 and 1999. The study quality was limited due to unclear allocation concealment, as well as no sufficient description for methods of randomization and blinding. One double-blind RCT, reported in two publications, was considered to have higher quality in that the details of randomization and lost to follow up data were provided, also treatment allocation concealment was considered to be adequate.^{15,16} It involved 1507 patients (aged between 18 and 71 years) with insomnia. Patients took either zopiclone 7.5mg, flunitrazepam 1mg, triazolam 0.25mg or placebo each night for a period of 28 days. Adverse events and rebound insomnia were assessed during the treatment, and in 14 days follow-up period after the discontinuation of zopiclone. Rates of adverse events were similar between zopiclone and BZs, while patients in the zopiclone group reported more bitter taste. Fewer patients experienced rebound insomnia in the zopiclone group in the follow-up period than in placebo, and no significant difference observed between the three active treatment groups.

Rates of adverse events were comparable between zopiclone and BZs in three other RCTs,^{14,18,20} while higher rates were observed in the BZ group in one study.¹⁷ Liu's study reported more severe rebound insomnia and more withdrawal effects (i.e., anxiety, headache and palpitations) in the BZ group.

There was no head-to-head trial identified comparing trazodone to a BZ. Two small RCTs compared trazodone with placebo.^{8,21} They were both considered to have poor quality due to a lack of description of randomization and blinding, and allocation concealment was unclear. Adverse events data was briefly provided in the reports. No severe adverse events reported for the use of trazodone.

A summary of the evidence from RCTs can be found in Table 2 .

Table 2: Summary of Clinical Trials

Author, year	Study design, patients, treatment period	Intervention vs. comparator	Results	Jadad scale score; Allocation concealment
Zopiclone				
Begg et al., 1992 ¹⁴	Double-blind RCT, 88 pts with sleep disorders (taking ≥30 minutes to fall asleep, and/or ≥2 awakenings during the night, and/or total sleep time < 6hrs, 1 week	Midazolam 15mg/night vs. ZOP 7.5mg/night	4 WDAEs: 3 from midazolam group vs. 1 from ZOP group; 40% in midazolam group vs. 31% in ZOP group experienced AEs, no significant difference; no significant difference in severity of AEs between groups; both drugs were associated with some residual daytime sedation. Taste disturbance was peculiar to ZOP, while clumsiness on awakening to midazolam.	1/5; Unclear
Hajak et al., 1994 ¹⁵	Double-blind RCTs, 1507 patients with insomnia, 28 days	ZOP 7.5mg/night, flunitrazepam 1mg/night, triazolam 0.25mg/night, or placebo	Pts in ZOP group reported significantly more bitter/metallic taste, while more speech disorders were reported in triazolam group, and more weakness in legs was reported in flunitrazepam group. Also reported were vertigo, headache, nausea, feeling of weakness, dizziness, vomiting, tiredness, restlessness, and dry mouth. There was no significant difference among the 3 drugs with respect to total AE rates.	3/5; Adequate
Hajak et al., 1998 ¹⁶ (follow-up of Hajak 1994 ¹⁵)	1507 patients with insomnia who had been treated for 28 days (see above), then on day 29 the active drugs and placebo were abruptly withdrawn and the pts were observed for a further period of 14 days	ZOP 7.5mg/night, flunitrazepam 1mg/night, triazolam 0.25mg/night, or placebo	Rebound insomnia rate was significantly lower in pts treated with ZOP than pts of the placebo group. No significant differences between any active tx groups.	3/5; Adequate

Author, year	Study design, patients, treatment period	Intervention vs. comparator	Results	Jadad scale score; Allocation concealment
Moffaert et al., 1995 ¹⁷	Double-blind RCT, 81 pts with insomnia associated with depression, 5 days	ZOP 7.5mg/night vs. flunitrazepam 2mg/night	<p>Number of pts with AEs: from 2 at baseline to 6 in ZOP group, from 5 to 12 in flunitrazepam group.</p> <p>Frequency of AEs was higher in flunitrazepam group, but not significantly. Severity of AEs was similar between 2 groups. Pts with ZOP experienced headache, tremor, hypotension, diarrhea, aggressivity, additional nightmares and anxiety; pts with flunitrazepam experienced nausea, vertigo, drowsiness, sedation, asthenia, concentration difficulties, bad mood, headache, palpitations, stomachache, pyrosis, increased appetite, aggressivity, and increased depression.</p>	1/5; Inadequate
Dehlin et al., 1995 ¹⁸	Double-blind RCT, 102 elderly pts with insomnia, 2 weeks	ZOP 5mg/night vs. flunitrazepam 1mg/night	<p>No serious or unexpected AEs. No WDAE. Numbers of AEs at the end of tx: 23 in ZOP group; 23 in flunitrazepam group.</p> <p>AEs: Vertigo: 10 in ZOP group vs. 4 in flunitrazepam group; depression: 7 vs. 10 respectively; arthralgia: 7 vs. 5 respectively; diarrhea: 2 vs. 6 respectively; headache: 2 vs. 6 respectively. No significant difference detected between groups.</p>	1/5; Inadequate
Liu et al., 1997 ¹⁹	Double-blind crossover RCT, 15 people with insomnia, 14 days	ZOP 7.5mg/night vs. triazolam 0.25mg/night	<p>Rebound insomnia during withdrawal period was more severe in pts with triazolam;</p> <p>Other withdrawal effects: anxiety 4 cases with ZOP, 8 cases with triazolam; headache 1 and 3 respectively, palpitation 1 and 2 respectively, tremor 0 and 2 respectively, and multiple soreness 0 and 1 respectively.</p>	1/5; Adequate

Author, year	Study design, patients, treatment period	Intervention vs. comparator	Results	Jadad scale score; Allocation concealment
Stip et al., 1999 ²⁰	Double-blind RCT, 50 pts with primary insomnia or insomnia associated with mild non-psychotic psychiatric disorders, 3 weeks	ZOP 7.5mg/day vs. temazepam 30mg/day vs. placebo	Temazepam and ZOP have no significant adverse effect on cognitive functions (memory) and daytime alertness during the study period.	1/5; Adequate
Trazodone				
Nierenberg et al., 1994 ²¹	Double-blind crossover RCT, 15 pts with depression-related insomnia, 7-8 days	TRA 50mg/night vs. placebo	1 pt had a prolonged erection with TRA, but no recurrence after decrease in dose	1/5; unclear
Kaynak et al., 2004 ⁸	Double-blind crossover RCT, 12 female pts with insomnia related to antidepressant treatment, 7 days	TRA 100mg vs. placebo	TRA tx: 1 pt reported mild and transient acid indigestion and 2 others had mild daytime sedation in the morning; placebo tx: no AE was mentioned	0/5; unclear

BZ: benzodiazepine; RCT: randomized controlled trial; AE: adverse event; WDAE: withdrawal due to adverse events; pt: patient; tx: treatment

Conclusions and implications for decision or policy making:

The evidence available related to the risk of harm with zopiclone and trazodone treatment in patients with insomnia was limited.

From the 3 systematic reviews and 1 clinical practice guideline, there was no significant difference between BZs and zopiclone with respect to the adverse events rates. Tolerance was implied in one review for BZ. As for trazodone, risks associated with its use for insomnia was not conclusive.

The majority of the RCTs identified were old, had a small sample size, short treatment duration and poor quality. Also, adverse events were insufficiently reported. Most of the RCTs found the similar adverse events rates between BZs and zopiclone; higher rebound insomnia rates and more withdrawal effects were noted for the BZs group. No severe adverse event was reported for trazodone in placebo-controlled studies.

Despite of the lack of compelling evidence, the existing studies suggest similarity in adverse event profile for zopiclone and trazodone when compared to BZs; patients receiving zopiclone may be benefit from less tolerance and fewer withdrawal symptoms. No serious adverse events or treatment-related death was observed.

In clinical practice, besides the effectiveness and harm of certain hypnotics, further concerns surrounding the management of patients with insomnia are: 1) Insomnia can be a result of other co-morbidities (e.g. depression, psychological diseases, pain related to rheumatoid arthritis, etc). Therefore treatment of the underlying cause(s) may help to resolve the insomnia. 2)

Physicians would also need to monitor the use of these drugs to ensure compliance but prevent overuse and reliance. Cost of hypnotics may not be an issue when deciding which drug to use. The cost of a single lowest dose for zopiclone was C\$0.34, which was not very expensive if compared to a commonly prescribed BZ.²²

A potential limitation of this report is that the literature search was restricted to English language publications, and did not consider clinical trial designs other than RCT. On the other hand, more large scale, well-designed clinical trials that evaluate the risk for harm of hypnotics are warranted.

Prepared by:

Stella Chen, MD, MSc, Research Officer
Carolyn Spry, MLIS, Information Specialist
Health Technology Inquiry Service
Email: htis@cadth.ca
Tel: 1-866-898-8439

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