



TITLE: Sleep Medications for Adults Diagnosed with Insomnia: Clinical Evidence and Harms

DATE: 29 April 2013

RESEARCH QUESTIONS

1. What are the clinical harms associated with the use of sleep medications for adults diagnosed with insomnia?
2. What is the clinical evidence regarding the potential for dependence with the use of sleep medications for adults diagnosed with insomnia?

KEY MESSAGE

Five systematic reviews and meta-analyses, 19 randomized controlled trials, and eight observational studies were identified regarding potential harms and dependence with the use of sleep medications for adults diagnosed with insomnia.

METHODS

A limited literature search was conducted on key resources including PubMed, The Cochrane Library (2013, Issue 3), University of York Centre for Reviews and Dissemination (CRD) databases, Canadian and major international health technology agencies, as well as a focused Internet search. Methodological filters were applied to limit retrieval to health technology assessments, systematic reviews, meta-analyses, randomized controlled trials, and non-randomized studies. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between January 1, 2008 and April 24, 2013. Internet links were provided, where available.

RESULTS

Rapid Response reports are organized so that the higher quality evidence is presented first. Therefore, health technology assessment reports, systematic reviews, and meta-analyses are

Disclaimer: The Rapid Response Service is an information service for those involved in planning and providing health care in Canada. Rapid responses are based on a limited literature search and are not comprehensive, systematic reviews. The intent is to provide a list of sources of the best evidence on the topic that CADTH could identify using all reasonable efforts within the time allowed. Rapid responses should be considered along with other types of information and health care considerations. The information included in this response is not intended to replace professional medical advice, nor should it be construed as a recommendation for or against the use of a particular health technology. Readers are also cautioned that a lack of good quality evidence does not necessarily mean a lack of effectiveness particularly in the case of new and emerging health technologies, for which little information can be found, but which may in future prove to be effective. While CADTH has taken care in the preparation of the report to ensure that its contents are accurate, complete and up to date, CADTH does not make any guarantee to that effect. CADTH is not liable for any loss or damages resulting from use of the information in the report.

Copyright: This report contains CADTH copyright material and may contain material in which a third party owns copyright. **This report may be used for the purposes of research or private study only.** It may not be copied, posted on a web site, redistributed by email or stored on an electronic system without the prior written permission of CADTH or applicable copyright owner.

Links: This report may contain links to other information available on the websites of third parties on the Internet. CADTH does not have control over the content of such sites. Use of third party sites is governed by the owners' own terms and conditions.

presented first. These are followed by randomized controlled trials, and non-randomized studies.

Five systematic reviews and meta-analyses, 19 randomized controlled trials, and eight observational studies were identified regarding potential harms and dependence with the use of sleep medications for adults diagnosed with insomnia. No relevant health technology assessments were identified. Additional references of potential interest are provided in the appendix.

Health Technology Assessments

No literature identified.

Systematic Reviews and Meta-analyses

1. Buysse DJ. Insomnia. JAMA. 2013 Feb 20;309(7):706-16.
[PubMed: PM23423416](#)
2. Liu J, Wang LN. Ramelteon in the treatment of chronic insomnia: systematic review and meta-analysis. Int J Clin Pract. 2012 Sep;66(9):867-73.
[PubMed: PM22897464](#)
3. Alessi C, Vitiello MV. Insomnia (primary) in older people. Clin Evid (Online). 2011;2011.
[PubMed: PM22030082](#)
4. Charlson F, Degenhardt L, McLaren J, Hall W, Lynskey M. A systematic review of research examining benzodiazepine-related mortality. Pharmacoepidemiol Drug Saf. 2009 Feb;18(2):93-103.
[PubMed: PM19125401](#)
5. Carson S, McDonagh M, Thakurta S, Yen P. Drug class review: insomnia [Internet]. Portland: Oregon Health & Science University; 2008 Oct [cited 2013 Apr 26]. Available from: <http://www.ncbi.nlm.nih.gov/books/NBK47207/>

Randomized Controlled Trials

6. Roth T, Krystal A, Steinberg FJ, Singh NN, Moline M. Novel sublingual low-dose zolpidem tablet reduces latency to sleep onset following spontaneous middle-of-the-night awakening in insomnia in a randomized, double-blind, placebo-controlled, outpatient study. Sleep. 2013;36(2):189-96.
[PubMed: PM23372266](#)
7. Yan X, Huang S, Ma C, Shen Y, Gu N, Chen H, et al. A randomized, double-blind, double-dummy, multicenter, controlled trial on brotizolam intervention in outpatients with insomnia. Int J Psychiatry Clin Pract. 2013 Feb 22. Epub ahead of print.
[PubMed: PM23025837](#)
8. Lankford A, Rogowski R, Essink B, Ludington E, Heith DH, Roth T. Efficacy and safety of doxepin 6 mg in a four-week outpatient trial of elderly adults with chronic primary insomnia. Sleep Med. 2012 Feb;13(2):133-8.

[PubMed: PM22197474](#)

9. Uchimura N, Kamijo A, Takase T. Effects of eszopiclone on safety, subjective measures of efficacy, and quality of life in elderly and nonelderly Japanese patients with chronic insomnia, both with and without comorbid psychiatric disorders: a 24-week, randomized, double-blind study. *Ann Gen Psychiatry* [Internet]. 2012 [cited 2013 Apr 26];11(1):15. Available from: <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3430596>
[PubMed: PM22731653](#)
10. Huang YS, Hsu SC, Liu SI, Chen CK. A double-blind, randomized, comparative study to evaluate the efficacy and safety of zaleplon versus zolpidem in shortening sleep latency in primary insomnia. *Chang Gung Med J*. 2011 Jan;34(1):50-6.
[PubMed: PM21392474](#)
11. Krystal AD, Lankford A, Durrence HH, Ludington E, Jochelson P, Rogowski R, et al. Efficacy and safety of doxepin 3 and 6 mg in a 35-day sleep laboratory trial in adults with chronic primary insomnia. *Sleep* [Internet]. 2011 Oct [cited 2013 Apr 26];34(10):1433-42. Available from: <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3174845>
[PubMed: PM21966075](#)
12. Uchimura N, Ogawa A, Hamamura M, Hashimoto T, Nagata H, Uchiyama M. Efficacy and safety of ramelteon in Japanese adults with chronic insomnia: a randomized, double-blind, placebo-controlled study. *Expert Rev Neurother*. 2011 Feb;11(2):215-24.
[PubMed: PM21306209](#)
13. Xu Z, Jiang X, Li W, Gao D, Li X, Liu J. Propofol-induced sleep: efficacy and safety in patients with refractory chronic primary insomnia. *Cell Biochem Biophys*. 2011 Jul;60(3):161-6.
[PubMed: PM21107748](#)
14. Ancoli-Israel S, Krystal AD, McCall WV, Schaefer K, Wilson A, Claus R, et al. A 12-week, randomized, double-blind, placebo-controlled study evaluating the effect of eszopiclone 2 mg on sleep/wake function in older adults with primary and comorbid insomnia. *Sleep* [Internet]. 2010 Feb [cited 2013 Apr 26];33(2):225-34. Available from: <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2817909>
[PubMed: PM20175406](#)
15. Krystal AD, Durrence HH, Scharf M, Jochelson P, Rogowski R, Ludington E, et al. Efficacy and safety of doxepin 1 mg and 3 mg in a 12-week sleep laboratory and outpatient trial of elderly subjects with chronic primary insomnia. *Sleep* [Internet]. 2010 Nov [cited 2013 Apr 26];33(11):1553-61. Available from: <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2954705>
[PubMed: PM21102997](#)
16. Roth T, Lines C, Vandormael K, Ceesay P, Anderson D, Snively D. Effect of gaboxadol on patient-reported measures of sleep and waking function in patients with Primary Insomnia: results from two randomized, controlled, 3-month studies. *J Clin Sleep Med* [Internet]. 2010 Feb 15 [cited 2013 Apr 26];6(1):30-9. Available from: <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2823273>

- [PubMed: PM20191935](#)
17. Fava M, Asnis GM, Shrivastava R, Lydiard B, Bastani B, Sheehan D, et al. Zolpidem extended-release improves sleep and next-day symptoms in comorbid insomnia and generalized anxiety disorder. *J Clin Psychopharmacol*. 2009 Jun;29(3):222-30.
[PubMed: PM19440075](#)
 18. Hajak G, Hedner J, Eglin M, Loft H, Storustovu SI, Lutolf S, et al. A 2-week efficacy and safety study of gaboxadol and zolpidem using electronic diaries in primary insomnia outpatients. *Sleep Med*. 2009 Aug;10(7):705-12.
[PubMed: PM19346160](#)
 19. Mayer G, Wang-Weigand S, Roth-Schechter B, Lehmann R, Staner C, Partinen M. Efficacy and safety of 6-month nightly ramelteon administration in adults with chronic primary insomnia. *Sleep* [Internet]. 2009 Mar [cited 2013 Apr 26];32(3):351-60. Available from: <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2647789>
[PubMed: PM19294955](#)
 20. Roth T, Price JM, Amato DA, Rubens RP, Roach JM, Schnitzer TJ. The effect of eszopiclone in patients with insomnia and coexisting rheumatoid arthritis: a pilot study. *Prim Care Companion J Clin Psychiatry* [Internet]. 2009 [cited 2013 Apr 26];11(6):292-301. Available from: <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2805564>
[PubMed: PM20098520](#)
 21. Erman MK, Zammit G, Rubens R, Schaefer K, Wessel T, Amato D, et al. A polysomnographic placebo-controlled evaluation of the efficacy and safety of eszopiclone relative to placebo and zolpidem in the treatment of primary insomnia. *J Clin Sleep Med* [Internet]. 2008 Jun 15 [cited 2013 Apr 26];4(3):229-34. Available from: <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2546455>
[PubMed: PM18595435](#)
 22. Krystal AD, Erman M, Zammit GK, Soubrane C, Roth T, ZOLONG Study Group. Long-term efficacy and safety of zolpidem extended-release 12.5 mg, administered 3 to 7 nights per week for 24 weeks, in patients with chronic primary insomnia: a 6-month, randomized, double-blind, placebo-controlled, parallel-group, multicenter study. *Sleep* [Internet]. 2008 Jan [cited 2013 Apr 26];31(1):79-90. Available from: <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2225552>
[PubMed: PM18220081](#)
 23. Scharf M, Rogowski R, Hull S, Cohn M, Mayleben D, Feldman N, et al. Efficacy and safety of doxepin 1 mg, 3 mg, and 6 mg in elderly patients with primary insomnia: a randomized, double-blind, placebo-controlled crossover study. *J Clin Psychiatry*. 2008 Oct;69(10):1557-64.
[PubMed: PM19192438](#)
 24. Walsh JK, Soubrane C, Roth T. Efficacy and safety of zolpidem extended release in elderly primary insomnia patients. *Am J Geriatr Psychiatry*. 2008 Jan;16(1):44-57.
[PubMed: PM18165461](#)

Non-Randomized Studies

25. Kang DY, Park S, Rhee CW, Kim YJ, Choi NK, Lee J, et al. Zolpidem use and risk of fracture in elderly insomnia patients. *J Prev Med Public Health* [Internet]. 2012 Jul [cited 2013 Apr 26];45(4):219-26. Available from: <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3412984>
[PubMed: PM22880153](#)
26. Kao CH, Sun LM, Liang JA, Chang SN, Sung FC, Muo CH. Relationship of zolpidem and cancer risk: a Taiwanese population-based cohort study. *Mayo Clin Proc* [Internet]. 2012 May [cited 2013 Apr 26];87(5):430-6. Available from: <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3498427>
[PubMed: PM22560522](#)
27. Kripke DF, Langer RD, Kline LE. Hypnotics' association with mortality or cancer: a matched cohort study. *BMJ Open* [Internet]. 2012 [cited 2013 Apr 26];2(1):e000850. Available from: <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3293137>
[PubMed: PM22371848](#)
28. Schaffer CB, Schaffer LC, Miller AR, Hang E, Nordahl TE. Efficacy and safety of nonbenzodiazepine hypnotics for chronic insomnia in patients with bipolar disorder. *J Affect Disord*. 2011 Feb;128(3):305-8.
[PubMed: PM20701978](#)
29. Uchiyama M, Hamamura M, Kuwano T, Nagata H, Hashimoto T, Ogawa A, et al. Long-term safety and efficacy of ramelteon in Japanese patients with chronic insomnia. *Sleep Med*. 2011 Feb;12(2):127-33.
[PubMed: PM21277255](#)
30. Wang LH, Lin HC, Lin CC, Chen YH, Lin HC. Increased risk of adverse pregnancy outcomes in women receiving zolpidem during pregnancy. *Clin Pharmacol Ther*. 2010 Sep;88(3):369-74.
[PubMed: PM20686480](#)
31. Alderman CP, Gilbert AL. A qualitative investigation of long-term zopiclone use and sleep quality among Vietnam war veterans with PTSD. *Ann Pharmacother*. 2009 Oct;43(10):1576-82.
[PubMed: PM19706738](#)
32. Richardson GS, Zammit G, Wang-Weigand S, Zhang J. Safety and subjective sleep effects of ramelteon administration in adults and older adults with chronic primary insomnia: a 1-year, open-label study. *J Clin Psychiatry*. 2009 Apr;70(4):467-76.
[PubMed: PM19284927](#)

PREPARED BY:

Canadian Agency for Drugs and Technologies in Health

Tel: 1-866-898-8439

www.cadth.ca

APPENDIX – FURTHER INFORMATION:**Case Series**

33. Poceta JS. Zolpidem ingestion, automatisms, and sleep driving: a clinical and legal case series. *J Clin Sleep Med* [Internet]. 2011 Dec 15 [cited 2013 Apr 26];7(6):632-8. Available from: <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3227709>
[PubMed: PM22171202](#)

Review Articles

34. Coe HV, Hong IS. Safety of low doses of quetiapine when used for insomnia. *Ann Pharmacother*. 2012 May;46(5):718-22.
[PubMed: PM22510671](#)
35. Zisapel N. Drugs for insomnia. *Expert Opin Emerg Drugs*. 2012 Sep;17(3):299-317.
[PubMed: PM22681198](#)
36. Lader M. Benzodiazepines revisited--will we ever learn? *Addiction*. 2011 Dec;106(12):2086-109.
[PubMed: PM21714826](#)
37. Enato E, Moretti M, Koren G. The fetal safety of benzodiazepines: an updated meta-analysis. *JOGC* [Internet]. 2011 Jan [cited 2013 Apr 26]:46-8. Available from :
http://jogc.org/abstracts/full/201101_DrugsinPregnancy_1.pdf
38. Riemann D, Perlis ML. The treatments of chronic insomnia: a review of benzodiazepine receptor agonists and psychological and behavioral therapies. *Sleep Med Rev*. 2009 Jun;13(3):205-14.
[PubMed: PM19201632](#)
39. Reynoldson JN, Elliott E Sr, Nelson LA. Ramelteon: a novel approach in the treatment of insomnia. *Ann Pharmacother*. 2008 Sep;42(9):1262-71.
[PubMed: PM18648020](#)

Additional References

40. Risk of next-morning impairment after use of insomnia drugs; FDA requires lower recommended doses for certain drugs containing zolpidem (Ambien, Ambien CR, Edluar, and Zolpimist) [Internet]. Silver Spring (MD): U.S. Food and Drug Administration. 2013 [cited 2013 Apr 26]. Available from:
<http://www.fda.gov/downloads/Drugs/DrugSafety/UCM335007.pdf>
41. Evaluating newer sleeping pills used to treat: insomnia. Comparing effectiveness, safety, and price [Internet]. (Consumer Reports Health: Best Buy Drugs). [Yonkers (NY)]: Consumers Union of U.S., Inc.; 2012 Jan [cited 2013 Apr 26]. Available from:
<http://www.consumerreports.org/health/resources/pdf/best-buy-drugs/InsomniaUpdate-FINAL-July2008.pdf>

42. Ben-Hamou M, Marshall NS, Grunstein RR, Saini B, Fois RA. Spontaneous adverse event reports associated with zolpidem in Australia 2001-2008. *J Sleep Res.* 2011 Dec;20(4):559-68.
[PubMed: PM21481053](#)
43. Mattila T, Stoyanova V, Elferink A, Gispen-de Wied C, de Boer A, Wohlfarth T. Insomnia medication: do published studies reflect the complete picture of efficacy and safety? *Eur Neuropsychopharmacol.* 2011 Jul;21(7):500-7.
[PubMed: PM21084176](#)
44. Sleep complaints: whenever possible, avoid the use of sleeping pills. *Prescrire Int.* 2008 Oct;17(97):206-12.
[PubMed: PM19536941](#)
45. Kripke DF. Possibility that certain hypnotics might cause cancer in skin. *J Sleep Res.* 2008 Sep;17(3):245-50.
[PubMed: PM18844818](#)