



TITLE: Sleep Medications for the Treatment or Prevention of Delirium: Clinical Effectiveness and Guidelines

DATE: 09 December 2016

RESEARCH QUESTIONS

1. What is the clinical effectiveness of sleep medications in older adults for the prevention and treatment of delirium?
2. What are the evidence-based guidelines regarding the use of sleep medications in older adults for the prevention and treatment of delirium?

KEY FINDINGS

One systematic review, three randomized controlled trials (RCTs), one non-randomized study, and one evidence-based guideline were identified regarding sleep medications in older adults for the prevention and treatment of delirium.

METHODS

A limited literature search was conducted on key resources including PubMed, The Cochrane Library, 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, non-randomized studies, and guidelines. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between January 1, 2011 and November 28, 2016. Internet links were provided, where available.

The summary of findings was prepared from the abstracts of the relevant information. Please note that data contained in abstracts may not always be an accurate reflection of the data contained within the full article.

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SELECTION CRITERIA

One reviewer screened citations and selected studies based on the inclusion criteria presented in Table 1.

Population	Older adults (age 65 years or older) with delirium; hospital (including acute care, ICU/critical care, surgical) or long-term care setting
Intervention	Sleep medications/sleep agents/hypnotics and sedatives (e.g., benzodiazapines [e.g., clonazepam, diazepam, temazepam), estazolam, alprazolam, and lorazepam], melatonin, ramelteon, non-benzodiazepine sleep agents [e.g., zopiclone, zolpidem])
Comparator	None required
Outcomes	Q1: clinical effectiveness; harms Q2: evidence-based guidelines
Study Designs	Health technology assessments, systematic reviews, meta-analyses, randomized controlled trials, non-randomized studies, evidence-based guidelines

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

One systematic review, three randomized controlled trials (RCTs), one non-randomized study, and one evidence-based guideline were identified regarding sleep medications in older adults for the prevention and treatment of delirium. No relevant health technology assessments were identified.

Additional references of potential interest are provided in the appendix.

OVERALL SUMMARY OF FINDINGS

One systematic review¹ examined the use of melatonin for the prevention of delirium. In elderly patients, the use of melatonin resulted in a decreased incidence of delirium as compared to a control group; however, the difference was not statistically significant. A subgroup analysis indicated that melatonin resulted in a significant decrease in delirium for elderly patients in medical wards.

Two RCTs^{2,4} examined the effect of melatonin on delirium for patients 65 years of age and older in hospital. One study found there was no difference in delirium² while the other determined that melatonin use was associated with a lower risk of delirium.⁴ One RCT³ compared the use of ramelteon with placebo for the prevention of delirium in patients in the intensive care unit who were aged 65 or older. There was a significantly lower risk of delirium observed in the patients who received ramelteon versus those who received placebo. One non-randomized study⁵ examined the use of ramelteon for patients 70 years of age or older after lung cancer surgery. There was a non-significant trend towards reduced delirium observed in the ramelteon group.

One guideline, produced in 2014, was identified from the Canadian Coalition for Seniors' Mental Health⁶ regarding the assessment and treatment of delirium. The guideline indicates that there is insufficient evidence to recommend either short-term melatonin or ramelteon therapy to reduce delirium in older inpatients.

REFERENCES SUMMARIZED

Health Technology Assessments

No literature identified.

Systematic Reviews and Meta-analyses

1. Chen S, Shi L, Liang F, Xu L, Desislava D, Wu Q, et al. Exogenous melatonin for delirium prevention: a meta-analysis of randomized controlled trials. *Mol Neurobiol*. 2016 Aug;53(6):4046-53.
[PubMed: PM26189834](#)

Randomized Controlled Trials

2. de Jonghe A, van Munster BC, Goslings JC, Kloen P, van Rees C, Wolvius R, et al. Effect of melatonin on incidence of delirium among patients with hip fracture: a multicentre, double-blind randomized controlled trial. *CMAJ [Internet]*. 2014 Oct 7 [cited 2016 Dec 8];186(14):E547-E556. Available from:
<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4188685>
[PubMed: PM25183726](#)
3. Hatta K, Kishi Y, Wada K, Takeuchi T, Odawara T, Usui C, et al. Preventive effects of ramelteon on delirium: a randomized placebo-controlled trial. *JAMA Psychiatry*. 2014 Apr;71(4):397-403.
[PubMed: PM24554232](#)
4. Al-Aama T, Brymer C, Gutmanis I, Woolmore-Goodwin SM, Esbaugh J, Dasgupta M. Melatonin decreases delirium in elderly patients: a randomized, placebo-controlled trial. *Int J Geriatr Psychiatry*. 2011 Jul;26(7):687-94.
[PubMed: PM20845391](#)

Non-Randomized Studies

5. Miyata R, Omasa M, Fujimoto R, Ishikawa H, Aoki M. Efficacy of Ramelteon for delirium after lung cancer surgery. *Interact Cardiovasc Thorac Surg*. 2016 Sep 13.
[PubMed: PM27624354](#)

Guidelines and Recommendations

6. Gage L, Hogan DB. 2014 CCSMH guideline update: the assessment and treatment of delirium [Internet]. Toronto: Canadian Coalition for Seniors' Mental Health; 2014. [cited 2016 Dec 8]. Available from: <http://ccsmh.ca/wp-content/uploads/2016/03/2014-ccsmh-Guideline-Update-Delirium.pdf>
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APPENDIX – FURTHER INFORMATION:

Previous CADTH Reports

7. Treatment of older adults with insomnia, agitation, or delirium with benzodiazepines: a review of the clinical effectiveness and guidelines [Internet]. Ottawa: Canadian Agency for Drugs and Technologies in Health; 2016 Jan 14. [cited 2016 Dec 8]. (CADTH Rapid Response Reports). Available from: <https://www.cadth.ca/sites/default/files/pdf/htis/jan-2016/RC0744%20Sedatives%20in%20older%20adults%20Final.pdf>
PubMed: [PM26889523](#)

Clinical Practice Guidelines – Methodology Not Specified

8. Hatch L, Richardson N, Tarmey N. Sedation and delirium in critical care [Internet]. Portsmouth (United Kingdom): Academic Department of Critical Care, Queen Alexandra Hospital Portsmouth; 2014 Jan 17. [cited 2016 Dec 8]. Available from: <http://www.wessexics.com/resources/Sedationdelirium.pdf>
See: Last box, page 4
9. Pharmacologic guidelines for the management of acute agitation in delirium and dementia [Internet]. Columbus (Ohio): Ohio Health; 2012 Jul. [cited 2016 Dec 8]. Available from: https://www.hopewestco.org/files/Delirium_Agitation_Management_Guideline_in_Dementia_Parkinsons.pdf

Review Articles

10. Fruetel K, Herrmann N, Holroyd-Leduc JM, Lam R, McMillan J, Morais J, et al. Choosing Wisely Canada: geriatrics. CGS J CME [Internet]. 2016 May [cited 2016 Dec 8];6(1). Available from: <http://www.canadiangeriatrics.ca/default/assets/File/CHOOSING%20WISELY%20CANADA-%20GERIATRICS.pdf>
11. Tremblay P, Gold S. Prevention of post-operative delirium in the elderly using pharmacological agents. Can Geriatr J [Internet]. 2016 Sep [cited 2016 Dec 8];19(3):113-26. Available from: <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC5038927>
PubMed: [PM27729950](#)
12. Chakraborti D, Tampi DJ, Tampi RR. Melatonin and melatonin agonist for delirium in the elderly patients. Am J Alzheimers Dis Other Demen. 2015 Mar;30(2):119-29.
PubMed: [PM24946785](#)
13. Gosch M, Nicholas JA. Pharmacologic prevention of postoperative delirium. Z Gerontol Geriatr. 2014 Feb;47(2):105-9.
PubMed: [PM24619041](#)
14. Rathier MO, Baker WL. A review of recent clinical trials and guidelines on the prevention and management of delirium in hospitalized older patients. Hosp Pract (1995). 2011 Oct;39(4):96-106.
PubMed: [PM22056829](#)