

The harms of benzodiazepines for patients with dementia

Paula A. Rochon MD MPH, Nicholas Vozoris MD MHSC, Sudeep S. Gill MD MSc

■ Cite as: *CMAJ* 2017 April 10;189:E517-8. doi: 10.1503/cmaj.170193

See related article at www.cmaj.ca/lookup/doi/10.1503/cmaj.160126

A wide spectrum of neuropsychiatric symptoms may develop in people with dementia. These symptoms can cause distress to families and caregivers and are challenging for clinicians to manage. Symptoms range from physical aggression to wandering and sleep disturbances. Although a drug therapy that could resolve them without causing new problems would be welcome, no such drug currently exists; serious adverse events often offset the modest benefits of psychotropic drugs in this setting. In the absence of predictably safe and effective drug therapies to manage these challenging behaviours, clinicians are wise to remember the maxim “first do no harm.”

Clinicians usually avoid prescribing benzodiazepines for older people with dementia because these drugs are associated with well-documented harms, including fall-related injuries such as fractures.¹ They are also associated with cognitive worsening,² an adverse event that is especially concerning in vulnerable older individuals who already have cognitive deficits. In a linked research study, Taipale and colleagues³ used Finnish administrative data to explore further the potential harm of benzodiazepines or benzodiazepine-related drugs (the so-called Z-drugs, which include zopiclone and zolpidem) in people with dementia.

Despite known harms, benzodiazepines continue to be used for a variety of conditions, including the management of neuropsychiatric symptoms associated with dementia. Canadian data show that the rate of benzodiazepine use is 15% in the community; the rate increases to more than 30% in long-term care facilities,⁴ where at least half of residents aged 80 years and older have dementia.⁵ A recent study found that women were more likely than men to receive potentially inappropriate prescriptions, particularly for benzodiazepines and other hypnotics.⁶ Another study showed that benzodiazepine therapy was continued chronically in more than 1% of older adults following a hospital admission.⁷

Taipale and colleagues focus on use of benzodiazepines or Z-drugs in patients with newly diagnosed Alzheimer disease living in the community. The authors report that use of these drugs was associated with a modest increased risk in the development of pneumonia severe enough to result in hospital admission or death (adjusted hazard ratio [HR] 1.22, 95% confidence interval

KEY POINTS

- Medications used to manage neuropsychiatric symptoms in frail older individuals with dementia have concerning adverse events.
- Nonpharmacologic approaches to management are preferred.
- For individuals already receiving benzodiazepines or Z-drugs, it is important to review medications regularly.

[CI] 1.05–1.42). The risk of pneumonia appeared highest within the first 30 days of drug use. Although use of benzodiazepines and Z-drugs collectively was associated with a statistically significant increased risk of pneumonia, Z-drug use alone was not (adjusted HR 1.10, 95% CI 0.84–1.44). This lack of statistical significance for the association between Z-drugs and pneumonia may reflect limited power of the study, given the overall modest risk observed.

The findings reported in the linked study suggest that pneumonia should be added to the list of potential harms associated with use of benzodiazepines and Z-drugs in people with dementia. Although a nonsignificant trend for pneumonia in association with use of the Z-drugs was reported, a previous large, population-based study showed that pneumonia risk extended to use of these drugs.⁸ Thus, further study is warranted to determine the comparative safety of benzodiazepines and Z-drugs.

Pneumonia is common in patients with dementia, particularly those with advanced dementia.⁹ There are several mechanisms that support the link between benzodiazepine use and pneumonia. For example, these medications produce sedation (leading to hypoventilation), can reduce pressure in the lower esophageal sphincter (leading to reflux and aspiration), and can suppress immune function, all of which may contribute to pneumonia risk.¹⁰ Benzodiazepine exposure has been associated with pneumonia risk in other populations, including people with chronic obstructive pulmonary disease.¹¹

Taipale and colleagues acknowledge that the association they found between benzodiazepine and Z-drug use and pneumonia was relatively modest. However, there are reasons that this association may have been underestimated in the study. First, the

authors identified only pneumonia severe enough to result in hospital admission or death. They excluded cases of pneumonia that were less severe and treated in outpatient settings or through an emergency department visit. Second, the authors did not include older adults with dementia living in long-term care facilities. Residents in such facilities mainly comprise older women, and a substantial proportion has dementia; this vulnerable group is at particularly high risk of pneumonia. Further valuable insights would be gained through future studies of the association between benzodiazepines and pneumonia that consider a wider spectrum of ways in which pneumonia is diagnosed and managed in a range of care settings. As such, population-level data could provide opportunities to further explore the harms associated with deciding to prescribe benzodiazepines or Z-drugs.

To ensure clinicians “do no harm,” it is important to maximize our use of routinely collected data. Future work could build on the current study by examining potential sex differences related to the use of benzodiazepines and the development of pneumonia. Sex differences should be evaluated for these drugs, given what is known about zolpidem: the US Food and Drug Administration issued a safety announcement indicating that zolpidem products are associated with a risk of next-morning impairment for activities that require complete mental alertness, including driving, particularly among women.¹² As a result, a lower dose of the drug was recommended for women.¹² To our knowledge, sex differences for Z-drugs have not been studied at the population level. If we understood the differences in the way that women and men respond to benzodiazepines and Z-drugs, we could better tailor our prescribing and monitoring practices to minimize harm when these medications are prescribed.

Taipale and colleagues have identified pneumonia as yet another adverse event associated with benzodiazepine and Z-drug use. Their study is a good reminder to clinicians to “first

do no harm” when prescribing these drugs for frail older women and men with dementia. Nonpharmacologic approaches should be the starting point when managing neuropsychiatric symptoms in this patient population, which should help to limit inappropriate use of these drugs. For individuals already receiving benzodiazepines or Z-drugs, this study’s findings underline the importance of regularly reviewing medications and re-evaluating their need.

References

1. Tambllyn R, Abrahamowicz M, du Berger R, et al. A 5-year prospective assessment of the risk associated with individual benzodiazepines and doses in new elderly users. *J Am Geriatr Soc* 2005;53:233-41.
2. American Geriatrics Society 2015 Beers Criteria Update Expert Panel. American Geriatrics Society 2015 Updated Beers criteria for potentially inappropriate medication use in older adults. *J Am Geriatr Soc* 2015;63:2227-46.
3. Taipale H, Tolppanen AM, Koponen M, et al. Risk of pneumonia associated with incident benzodiazepine use among community-dwelling adults with Alzheimer disease. *CMAJ* 2017;189:E519-29.
4. *Drug use among seniors on public drug programs in Canada, 2012*. Ottawa: Canadian Institute for Health Information; 2014.
5. Wong SL, Gilmour H, Ramage-Morin PL. *Health reports: Alzheimer’s disease and other dementias in Canada*. Ottawa: Statistics Canada; modified 2016 May 18.
6. Morgan SG, Weymann D, Pratt B, et al. Sex differences in the risk of receiving potentially inappropriate prescriptions among older adults. *Age Ageing* 2016;45:535-42.
7. Bell CM, Fischer HD, Gill SS, et al. Initiation of benzodiazepines in the elderly after hospitalization. *J Gen Intern Med* 2007;22:1024-9.
8. Obiora E, Hubbard R, Sanders RD, et al. The impact of benzodiazepines on occurrence of pneumonia and mortality from pneumonia: a nested case-control and survival analysis in a population-based cohort. *Thorax* 2013;68:163-70.
9. Givens JL, Jones RN, Shaffer ML, et al. Survival and comfort after treatment of pneumonia in advanced dementia. *Arch Intern Med* 2010;170:1102-7.
10. Vozoris NT. Do benzodiazepines contribute to respiratory problems? *Expert Rev Respir Med* 2014;8:661-3.
11. Vozoris NT, Fischer HD, Wang X, et al. Benzodiazepine drug use and adverse respiratory outcomes among older adults with COPD. *Eur Respir J* 2014;44:332-40.
12. *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)* [safety announcement]. Silver Spring (MD): US Food and Drug Administration; 2013.

Competing interests: None declared.

Affiliations: Women’s College Research Institute (Rochon), Women’s College Hospital; Department of Medicine (Rochon, Vozoris), Institute of Health Policy, Management, and Evaluation (Rochon), University of Toronto; Department of Medicine and Keenan Research Centre in the Li Ka Shing Knowledge Institute (Vozoris), St. Michael’s Hospital, Toronto, Ont.;

Department of Medicine (Gill), Queen’s University; Institute for Clinical Evaluative Sciences (Gill), Kingston, Ont.

Contributors: All of the authors contributed to the conception of the work. Paula Rochon drafted the manuscript. All of the authors revised it critically for important intellectual content, approved the final version to be published, and agreed to act as guarantors of the work.

Acknowledgement: Paula Rochon holds the Retired Teachers of Ontario / Les enseignantes et enseignants retraités de l’Ontario (RTO/ERO) Chair in Geriatric Medicine at the University of Toronto.

This article was solicited and has not been peer reviewed.

Correspondence to: Paula Rochon, paula.rochon@wchospital.ca