

# Risk for injury in the elderly may vary by benzodiazepine, independent of half-life

Tamblyn R, Abrahamowicz M, Berger R, McLeod P, Bartlett G. A 5-year prospective assessment of the risk associated with individual BDZs and doses in new elderly users. *J Am Geriatr Soc.* 2005;53:233-41.

**Clinical impact ratings:** GIM/FP/GP ★★★★★☆ Geriatrics ★★★★★☆☆

## QUESTION

In older persons, is risk for injury associated with the new use of specific benzodiazepines and drug-specific dose regimens?

## METHODS

**Design:** Prospective cohort study with 5 years of follow-up.

**Setting:** Quebec, Canada.

**Participants:** 253 244 community-dwelling persons ≥ 65 years of age (mean age 73 y, 52% women) who were nonusers of benzodiazepines at the beginning of the observation period. Participants who were institutionalized for the entire follow-up period were excluded.

**Risk factors:** Benzodiazepines with intermediate half-life (HL) (10 h: triazolam, oxazepam, and temazepam), long HL (11 to 47 h: alprazolam, nitrazepam, bromazepam, and lorazepam), and very long HL (48 h: chlordiazepoxide, flurazepam, and diazepam). For each follow-up day, participants were classified as current users of specific benzodiazepines. Each time the exposure status changed (change in drug dosage or change to nonuse), a new record of benzodiazepine use was generated. Fixed covariates included age, sex, and previous injury. Time-dependent covariates were concomitant drug use that might increase or diminish the risk for injury, and comorbid conditions.

**Outcomes:** Injuries (nonvertebral fractures, soft-tissue injuries, and accident-related hospital admissions).

## MAIN RESULTS

69 791 participants (28%) received ≥ 1 benzodiazepine prescription, and 44 753 participants (18%) sustained ≥ 1 injury, of which fractures were the most common (50%). The risk for injury with current use of benzodiazepines compared with nonuse periods in the same patient varied according to the type of benzodiazepine (Table) but did not correlate with HL: Temazepam and oxazepam (intermediate HL), lorazepam (long HL), and flurazepam (very long HL) were associ-

ated with an increased risk for injuries (Table). Higher-dose equivalents of oxazepam, flurazepam, and chlordiazepoxide were associated with the greatest risk for injury.

## CONCLUSION

In older persons, risk for injury was increased with current use of benzodiazepines compared with nonuse periods for some benzodiazepines, a phenomenon explained in part by dose equivalents.

*Source of funding:* Fonds de Recherche en Santé du Québec.

*For correspondence:* Dr. R. Tamblyn, McGill University, Montreal, Quebec, Canada. E-mail: Robyn.tamblyn@mcgill.ca. ■

### Risk for injury associated with current use of benzodiazepines adjusted for past use in older persons\*

Half-life	Benzodiazepine	Mean standardized dose†	Adjusted hazard ratio (95% CI)‡
Intermediate half-life (10 h)	Triazolam	0.92	1.34 (0.95 to 1.90) <sup>§</sup>
	Temazepam	1.04	1.29 (1.01 to 1.65)
	Oxazepam	0.41	1.14 (1.01 to 1.28)
Long half-life (11 to 47 h)	Alprazolam	0.54	1.10 (0.84 to 1.42) <sup>§</sup>
	Nitrazepam	1.29	1.12 (0.77 to 1.63) <sup>§</sup>
	Bromazepam	0.44	1.08 (0.81 to 1.43) <sup>§</sup>
	Lorazepam	0.49	1.15 (1.06 to 1.24)
Very long half-life (48 h)	Chlordiazepoxide	0.65	1.55 (0.83 to 2.90) <sup>§</sup>
	Flurazepam	0.74	1.61 (1.31 to 1.99)
	Diazepam	0.63	1.01 (0.77 to 1.33) <sup>§</sup>

\*CI defined in Glossary. Based on multivariate Cox proportional-hazards models adjusted for time-dependent covariates (concomitant drug use and comorbid conditions).

†Prescribed dose divided by the World Health Organization—recommended daily dose for adults.

‡Estimates risk for injury during periods of use vs nonuse of all patients prescribed a specific benzodiazepine.

§Not significant.

## COMMENTARY

Studies published 15 years ago suggested that benzodiazepines with long elimination HLs increase the risk for hip fracture in older adults, while shorter HL agents do not (1). Since then, research and policy about the hazards of benzodiazepine use have become complex (2). There has been a shift toward the use of agents with shorter HLs (3). The cohort study by Tamblyn and colleagues adds to the growing evidence that short-HL benzodiazepines and newer “nonbenzodiazepine” sedatives may not be any safer than long HL agents (4).

Cohort studies can follow large groups of diverse patients to evaluate uncommon but important outcomes in real-world settings, but they can be vulnerable to the effects of confounding and bias. Unfortunately, randomized trials that adequately assess the harms of benzodiazepine use may never be done. The study by Tamblyn and colleagues builds on previous research and has a number of strengths. The large sample size and long follow-up improve study power, and outcomes have been expanded beyond hip fracture to include other forms of serious injury associated with benzodiazepine use. Modelling has been used to address the time-dependent nature of drug exposure, several sources of bias (detailed in their paper), and coding inaccuracy.

Although debate continues about the relative importance of benzodiazepine HL, some conclusions can be drawn. Higher doses of any benzodiazepine seem to increase the risk for serious injury, and risk appears to be highest soon after treatment is begun. For clinicians, we offer 3 pieces of advice: First, become familiar with and promote non-pharmacologic treatments for insomnia and anxiety (5); second, prescribe benzodiazepines with caution for short, finite periods; and third, avoid benzodiazepines in the hospital since this is a common source of new community prescriptions.

Sudeep S. Gill, MD, MSc, FRCPC  
Paula A. Rochon, MD, MPH, FRCPC  
Institute for Clinical Evaluative Sciences  
Toronto, Ontario, Canada

## References

1. Ray WA, Griffin MR, Downey W. *JAMA.* 1989;262:3303-7.
2. Ming EE. The relationship between BDZs and hip fracture in the elderly. [www.hsph.harvard.edu/organizations/ddil/benzo.html](http://www.hsph.harvard.edu/organizations/ddil/benzo.html).
3. Tu K, Mamdani MM, Hux JE, Tu JB. *J Am Geriatr Soc.* 2001;49:1341-5.
4. Wagner AK, Zhang F, Soumerai SB, et al. *Arch Intern Med.* 2004;164:1567-72.
5. Morin CM, Colecchi C, Stone J, Sood R, Brink D. *JAMA.* 1999;281:991-9.