Associations between Benzodiazepine Use and Neuropsychological Test Scores in Older Adults*

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RÉSUMÉ

Les benzodiazépines sont largement prescrits pour l'anxiété, bien que l'utilisation de cette classe de médicaments fût associée à la dépendance et les changements cognitifs. Cet article décrit une étude dans laquelle j'ai examiné la relation entre une* classe des benzodiazépines disponibles pour l'utilisation et le rendement lié aux tests neuro-psychologiques dans un échantillon de communauté de 1 754 Canadiens âgés de l'Etude canadienne sur la santé et le vieillissement. Les benzodiazépines ont été classés comme ayant une action de courte durée, intermédiare ou longue. À l'aide d'une analyse de régression multiple, et tenant compte de variables démographiques, les associations ont été calculées entre chaque catégorie de benzodiazépine et huit mesures neuro-psychologiques. Les résultats ont révélé des effets différents au sein des classes des trois médicaments; les benzodiazépines avec une courte demi-vie n'etaient associées à aucune mesure neuro-psychologique. Chacune des benzodiazépines à demi-vie intermédiare et à longue demi-vie ont été associée à deux mesures. Afin d'améliorer notre compréhension de la façon dont l'utilisation des benzodiazépines influence la cognition, une concentration accrue sur des domaines spécifiques de la fonction cognitive est requise.

ABSTRACT

Benzodiazepines are widely prescribed for anxiety, although use of this class of medications has been associated with dependency and cognitive changes. This article describes the study in which we investigated the relationship between the class of benzodiazepine available for use and associated performance on neuropsychological tests in a community sample of 1,754 older Canadians from the Canadian Study of Health and Aging. Benzodiazepines were classified as short-, intermediate-, and long-acting. Associations were calculated between each class of benzodiazepine and eight neuropsychological measures, using multiple regression analysis and controlling for demographic variables. Results showed different effects of the co-variates across the three drug classes, and short half-life benzodiazepines were not associated with any neuropsychological measure. Intermediate half-life and long half-life benzodiazepine use were each associated with two measures. Increased focus on specific domains of cognitive function is needed to improve our understanding of how benzodiazepine use influences cognition.

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With the aging of the population, more attention is being paid to chronic health problems that previously were often regarded as inevitable negative consequences of aging. Whereas health promotion efforts have focused on such factors as diet (including salt and fat consumption), exercise, and smoking cessation, less attention has been paid to the health risks associated with the use of prescription medication. Although some of the risks of certain medications on overall cognition are known (Starr et al., 2004), the unintended effects that some medications may have on specific domains of cognition are less widely known. Given their widespread use for anxiety and sleep disorders, benzodiazepines are one class of medication of particular interest. Commonly used in the treatment of anxiety disorders, among other conditions, the effects of benzodiazepines are presumed to occur via actions on the neurotransmitter GABA.

Estimates of usage of benzodiazepines vary with the setting, with community-living older adults showing lower use than residents of aged care facilities. Gray et al. (2006) reported between 5 per cent and 6 per cent of elderly people in the community are benzodiazepine users, whereas Stowell, Chang, Bilt, Stoehr, and Ganguli (2008) gave figures of 5 per cent of men and 10 per cent of women, and Gray, Eggen, Blough, Buchner, and LaCroix (2003) reported a 6.6 per cent incidence and 12 per cent prevalence rate for benzodiazepine use. Egan, Moride, Wolfson, and Monette (2000) reported 20 per cent prevalence for continuous use in the Canadian province of Québec, while Runci, Redman, and O'Connor (2005) reported that approximately 30 per cent of residents in Australian aged care facilities had prescriptions for benzodiazepines. Tannenbaum, Paquette, Hilmer, Holroyd-Leduc, and Carnahan (2012) reviewed the effects of several classes of medication on cognition, including benzodiazepines. They reported consistent negative effects of all classes of benzodiazepines on both amnestic and non-amnestic cognitive functions.

At the same time, there are some indications that usage may be declining, at least in some locales. Mamdani, Rapoport, Shulman, Herrmann, and Rochon (2005) reported a drop in benzodiazepine prescriptions from 1.58 (1993) to 1.43 (2003) per person for mental health conditions in older adults in Ontario. Questions have been raised about the need for high levels of prescriptions for benzodiazepines. Voyer, Cappeliez, Perodeau, and Préville (2005) noted that only one-third of older adult benzodiazepine users had been diagnosed with mental health problems. Furthermore, the rate of usage was not different across new users, users who had stopped taking benzodiazepines, and long-term users. Use of benzodiazepines is certainly not without its risks. Gray et al. (2006) noted increased risk of mobility problems and increased problems with activities of daily living, more so for the use of short half-life benzodiazepines than for the long-acting ones. Additionally, Neutel (1998) noted increased risks for motor vehicle accidents, particularly for new users of benzodiazepines. As well, Verhaeghe, Mets, and Corne (1996) noted that 43 per cent of those arriving at Belgian emergency rooms were using benzodiazepines.

Concerns have also been raised about the cognitive effects of benzodiazepine use. Hogan, Maxwell, Fung, and Ebly (2003) noted that approximately 25 per cent of benzodiazepine users reported adverse outcomes; the proportion was highest among new users. Crowe and Barker (2007) reported negative effects on memory, verbal fluency, cognitive processing speed, and concentration and attention. Such effects were also reported to have occurred in those who had discontinued use of benzodiazepines (Barker, Greenwood, Jackson, & Crowe, 2005), with some improvement in cognition scores occurring following discontinuation, but with substantial residual continued impairment (Barker, Greenwood, Jackson, & Crowe, 2004). Harwood, Kalechstein, and Sultzer (2007) noted increased risk of dementia with benzodiazepine use, while others suggested protective effects and reduced risk with continued use (Llorente, David, Golden, & Silverman, 2000). Harwood et al. (2007) also noted the complication of polypharmacy, with many studies of individuals using benzodiazepines also reporting the use of other medications.

Most of the aforementioned studies of the association between benzodiazepines and cognitive test scores have not differentiated among the various benzodiazepines. The most commonly made distinction has been based on the duration of action, with benzodiazepines usually classified as having short, intermediate, or long half-lives. Results do not always support the distinction. Hanlon et al. (1998) reported that both short and long half-life benzodiazepines were associated with lower scores on a short measure of verbal memory.

The purpose of this study was to assess the effect of the three classes of benzodiazepines on cognitive function (measured through eight neuropsychological tests) in a sample of older Canadians who were either cognitively intact or had some degree of cognitive impairment short of meeting diagnostic criteria for dementia. Previous studies by Egan et al. (2000) and Hogan et al. (2003) on the use of benzodiazepines in this sample of community residents from the Canadian Study of Health and Aging (CSHA) addressed different purposes from this one. Neither of those studies incorporated use of the information from the neuropsychological assessment that was administered as part of the standard diagnostic assessment in the CSHA.

Egan et al. (2000) reported on patterns of continuous benzodiazepine use, while Hogan et al. (2003) reported on the prevalence of benzodiazepine use. We predicted stronger associations of test performance with increased half-life of the prescribed benzodiazepine. Secondary hypotheses were that an increased number of medications taken and a higher number of illnesses would be associated with lower performance on the neuropsychological measures.

Methods

Participants

Benzodiazepine use was reported by 2,914 participants in the Canadian Study of Health and Aging (CSHA; Canadian Study of Health and Aging Working Group, 1994) who underwent a comprehensive clinical assessment consisting of a history and interview with an informant; medical history and examination that included a record of medications being taken; and a detailed neuropsychological assessment. The CSHA Working Group (1994) reported a median of 61 days from the initial screening assessment to the clinical examination. The study nurse recorded medications from pill containers provided during the home visit together with the reports from the informant's memory of the duration of use in months where this information was not available from the pill containers. Up to a maximum of 12 medications were recorded. Of those taking benzodiazepines, 35 people who reported taking two or more benzodiazepines were excluded from further analysis in order to prevent individuals from being in more than one drug group (short half-life plus intermediate half-life in six people, with 29 taking both a short half-life and long half-life benzodiazepine). There were no significant differences between those taking one benzodiazepine and those taking two on any demographic measure or neuropsychological test score.

The CSHA was reviewed by the human research ethics committees at all 18 study centers and approved prior to any data collection. Excluding those diagnosed with dementia, a total of 1,754 older adults remained, 910 with no cognitive impairment (NCI) and 844 with some cognitive impairment but no dementia (CIND; Tuokko, Frerichs, & Kristjansson, 2001). The group with dementia was excluded because of the known cognitive deterioration associated with the diagnosis and the additional variation associated with the stages of dementia present in the sample with dementia. Most participants were female (61.3%). The mean age was 79.6 years (SD = 7.21) with an average of 8.7 years of education (SD = 4.05). The older adults in the study sample were taking zero to 12 prescribed medications, with a mean of 4.2 drugs (SD = 3.04) for a mean of 1.8 illnesses (range 0 to 8, SD = 1.78).

The clinical assessment of the CSHA used the diagnostic criteria of the revised third edition of the American Psychiatric Association's *Diagnostic and Statistical Manual of Mental Disorders* (1987). Diagnosis was made at a consensus conference of those who assessed individuals. Benzodiazepines were classified according to their half-life using the system described by Walop and Semenchuk (2002) that was based upon the Anatomical Therapeutic and Chemical Classification of the World Health Organization.

Procedure

Of interest were the eight domains of cognitive function assessed by the neuropsychological test battery administered during the clinical assessment in the CSHA: abstract reasoning (WAIS Similarities); judgement (WAIS Comprehension); executive function (verbal fluency); language comprehension (Token Test); long- and short-term verbal memory (WAIS Information, Rey Auditory Verbal Learning Test (AVLT) Trial 6, Buschke free recall); and construction (WAIS Block Design). These measures were described in more detail by Tuokko, Kristjansson, and Miller (1995), and were used by Helmes, Ostbye, and Steenhuis (2011) to examine cognitive functioning in individuals with previous head injury. Testing sessions were conducted as they could be scheduled among the other CSHA assessments.

Statistical Analyses

Descriptive statistics for the major demographic variables used were calculated by drug group. Simple one-way analyses of variance were also conducted to explore possible group differences on the unadjusted test scores across the short-, intermediate-, and long half-life benzodiazepines and the group not taking benzodiazepines. Eight separate multiple regression analyses were conducted to evaluate the association between benzodiazepine use and performance on neuropsychological measures. Multiple regression models were developed controlling for gender, age, years of education, and number of illnesses, and of medications taken for each of the eight separate neuropsychological tests with short half-life, intermediate half-life, and long half-life benzodiazepine use as the primary predictors of interest. Duration of benzodiazepine use was considered for inclusion in the analyses, but proved to be missing for enough cases to reduce the sample size. Sample sizes in the tables vary due to missing data.

Results

There were no differences across medication groups for years of education or number of illnesses. Differences were apparent for age (F = 2.23, 3, 1,724 df, p = .005) and for number of drugs (F = 51.2, 3, 1,724 df, $p < .001$).

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The results of Tukey's HSD test, reported in Table 1, indicate differences across medication groups in age and with all benzodiazepine groups taking more medications than the no-benzodiazepine group.

A group of 119 participants took a short half-life benzodiazepine, such as triazolam, for a mean of 9.4 months (*SD* = 29.21, range up to 240 months). An additional 118 participants took an intermediate half-life benzodiazepine, such as alprazolam or temazepam, with a mean duration of use of 6.6 months (*SD* = 26.8 with a range up to 360 months). The most frequently used class (n = 374) was the long half-life benzodiazepines with half-lives of 40 hours or more, such as diazepam or flurazepam, with a mean of 32.9 months (*SD* = 65.00, range up to 480 months). Table 2 reports descriptive statistics for the group not taking benzodiazepines and the users of the three classes of benzodiazepine.

Preliminary analyses showed no gender difference in the use of short half-life benzodiazepines (χ^2 =1.52, 1 *df*, p = .217) or long half-life ones (χ^2 = 2.00, 1 *df*, p = .158). Women were more likely to be using intermediate half-life benzodiazepines than were men (58.1% vs. 37.6%, χ^2 = 5.15, 1 *df*, p = .023). The group taking benzodiazepines had the same number of illnesses (1.8 on average), but were taking more medications than the group not taking benzodiazepines (5.8 vs. 3.7, t = –12.51, 670.3 *df*, p < .001). The simple group comparison analyses were not significant for six of the neuropsychological tests. The one-way analyses were significant for the Token Test (F = 8.40, 3, 1,378 *df*, p < .001) and the WAIS Comprehension score (F = 4.41, 3, 1,442 *df*, p = .009). Tukey's HSD test showed that the group not taking benzodiazepines differed from both the intermediate half-life (p < .001) and long half-life (p = .003) groups on the Token Test. For the Comprehension score, Tukey's HSD test showed the group not taking benzodiazepines differed from the group taking intermediate half-life benzodiazepines (p = .009). Table 3 shows the association of the demographic variables and the three classes of benzodiazepines with the eight neuropsychological measures in the regression analyses.

In the regression analyses, of the eight neuropsychological measures, gender was associated with five: three Wechsler measures, verbal fluency, and Rey AVLT scores. Age was a consistently influential co-variate, being significant for seven of the eight measures, with the exception of the verbal fluency measure. Years of education were associated with all measures. The number of current illnesses was associated with two Wechsler scores, Block Design and Vocabulary, and with the measures of verbal fluency, Token Test, and the Rey AVLT score. The number of prescription drugs taken was associated with four measures: Block Design and Vocabulary from the Wechsler, and verbal fluency and Token Test scores.

The short half-life benzodiazepines were not associated with any neuropsychological measure. Intermediate half-life benzodiazepines showed associations with two neuropsychological measures: the measure of judgement (the Wechsler Comprehension scale), the screening measure of language comprehension (the Token Test). Long half-life benzodiazepine use was associated with test scores on the Token Test and also with a measure of verbal short-term memory, the free recall trial of the Buschke Selective Reminding Test.

Discussion

Benzodiazepine uses varied across only some demographic variables, notably age and number of medications being taken. The group taking short half-life benzodiazepines was somewhat older than the other three groups. While the measure of number of drugs taken did include the use of benzodiazepines, this alone could not account for the magnitude of the differences, from about four drugs to about six drugs (see Table 1). It may be that the use of benzodiazepines is part of a general tendency for prescription of medications, as the benzodiazepine groups did not differ on the numbers of illnesses experienced, which would be the obvious factor in medication prescriptions.

Benzodiazepine use was associated with a reduction in scores for only a few neuropsychological measures,

Table 1: Unadjusted scores on demographic variables for four groups of benzodiazepine users

	Group											
	No Benzodiazepines			Short Half-life			Intermediate Half-life			Long Half-life		
Measure	*Mean*	*SD*	*N*	*Mean*	*SD*	*n*	*Mean*	*SD*	*n*	*Mean*	*SD*	*n*
Age	79.7	7.25	1,346	81.9[a]	6.71	92	78.9[b]	6.82	76	78.9[b]	7.16	240
Education (years)	8.9	4.06	13.26	8.3	3.85	90	8.1	4.02	76	8.3	4.02	236
Number illnesses	1.8	1.71	1,346	2.2	0.81	92	1.9	2.08	76	1.9	0.70	240
Number medications	3.7	2.91	1,346	6.0[a]	3.05	92	5.5[a]	2.70	76	5.8[a]	2.95	240

[a] Different from no medication group; [b] Different from short half-life group.

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Table 2: Unadjusted neuropsychology test score descriptive statistics for four groups of benzodiazepine users

	Group											
	No Benzodiazepines			Short Half-life			Interme-diate Half-life			Long Half-life		
Measure	*Mean*	*SD*	*N*	*Mean*	*SD*	*n*	*Mean*	*SD*	*N*	*Mean*	*SD*	*n*
Vocabulary	4.8	1.40	1,385	4.5	1.34	79	4.4	1.42	68	4.4	1.48	184
Similarities	5.2	3.99	1,375	5.1	3.90	77	4.5	6.34	38	5.1	3.84	184
Comprehension	7.7	3.36	1,369	7.4	3.46	77	6.5[a]	3.12	68	7.4	3.49	184
Block design	7.9	4.72	1,313	8.0	4.54	73	6.8	3.91	63	7.3	4.65	176
Rey AVLT	5.3	3.63	1,150	4.4	3.63	64	5.6	3.52	52	5.3	3.64	138
Buschke recall	11.6	0.87	1,346	11.6	0.81	74	11.5	0.89	64	11.7[a]	0.53	181
Verbal fluency	20.2	10.20	1,271	19.5	9.68	71	18.8	10.27	62	18.7	9.26	174
Token test	34.8	7.94	1,308	34.3	8.54	74	31.2[a]	8.35	61	33.1[a]	8.34	178

[a] group mean differs from no-benzodiazepine group.
***n* = sample size.**
***SD* = standard deviation.**

contrary to our expectations. In partial support of that hypothesis, both intermediate and long half-life classes were associated with lower performance on the measure of language comprehension, the Token Test. This finding was unexpected and has not been reported previously. Intermediate half-life drugs were associated with lower scores on the Wechsler Comprehension test, whereas the long half-life medications were associated with lower scores on the Buschke free recall test. Most of the measures associated with benzodiazepine use are reliant on language, and it is plausible that aspects of language use form a common factor underlying our results. In contrast to these results with limited association of benzodiazepines with scores on memory tests, Hanlon et al. (1998) reported lower scores on memory tests by users of both short- and long half-life benzodiazepines.

Judgement, as reflected in the WAIS Comprehension test, has not previously been reported to be affected by the use of benzodiazepines, but it may have major practical implications. Driving is an activity that relies heavily on judgement and also one that older adults continue as long as possible. At an applied level, Thomas (1998) reported benzodiazepine use to at least double the risk of motor vehicle accidents, with younger persons perhaps showing a greater risk of traffic accidents than older adults (Neutel, 1998), with the use of long half-life benzodiazepines increasing the risk further.

The influence of polypharmacy on cognition was moderate, with four of eight test scores having the number of prescribed medications associated with those scores, partially supporting this hypothesis. This finding would, of course, be partially confounded by the inclusion of benzodiazepines in the total of prescribed medications, which is offset by the statistical control in the regression analyses. Co-variate weights for test performance for the number of chronic illnesses were of the same order of magnitude as the weights for the influence of the number of medications. This suggests that these factors are independent of one another and of approximately the same magnitude.

Not all previous studies have reported negative effects of benzodiazepines on cognition. For instance, McAndrews et al. (2003) noted that benzodiazepine users had greater gains on retesting of two measures – speed of processing and attention – than did controls. Our study included a relatively small and select sample that addressed a more focused issue than the more basic one of differences on initial assessment with medication usage relying upon medications in the home without direct evidence of pill consumption. It is also important to note that participants in the present sample averaged nearly 80 years of age, and many were taking multiple medications. The neuropsychological testing was completed at various times of day and at varied times from that on the day on which medications were recorded. The effective level of benzodiazepines in the participants, therefore, was not controlled as would be the case in experimental studies such as those reviewed by Tannenbaum et al. (2012). It is clear in the present results that some classes of benzodiazepines, notably the longer-acting ones, are more likely to be associated with lower performance on some neuropsychological measures, although the short half-life benzodiazepines did not show any such associations. Other studies have reported minimal increased risk for short half-life benzodiazepines. For example, the use of short half-life benzodiazepines did not increase the risk of unsafe driving actions (Dubois, Bédard, & Weaver, 2008), whereas intermediate half-life and long half-life benzodiazepines did do so.

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Table 3: The relationship between benzodiazepine use and neuropsychological test scores, adjusting for demographic factors of age, education, gender, and number of medical illnesses, and of medications (standardized beta coefficients with 95% confidence limits for unstandardized coefficients)

	Neuropsychological Measure							
Measure	**Vocabulary**	**Similarities**	**Comprehension**	**Block Design**	**Buschke Recall**	**Rey Trial 6**	**Verbal Fluency**	**Token Test**
Gender	–.11* (–.47– –.18)	.03 (–.12–.62)	–.08* (–.90– –.25)	–.07* (–1.1– –0.17)	.04 (–.03–.20)	.16* (.83–1.62)	.12* (1.20–3.22)	.03 (–.29–1.30)
Age	–.14* (–.04– –.02)	–.12* (–.09– –.04)	–.05 (–.05– –.00)	–.16* (–.14– –.07)	–.12* (–.02– –.01)	–.25* (–.16– –.10)	–.01 (–.09–.05)	–.15* (–.22– –.12)
Education	.24* (.07–.10)	.50 (.45–.54)	.45* (.34–.41)	.34* (.35–.46)	.13* (.02–.04)	.22 (.15–.24)	.42* (1.05–1.30)	.40* (.70–.90)
Number illnesses	.10 (.08–.16)	.00 (–.09–.11)	.00 (–.09–.09)	.07 (.05–.30)	.00 (–.03–.03)	.13* (.15–.36)	.07 (.00–.54)	.06 (.04–.47)
Number meds	–.07* (–.01–.01)	–.00 (–.07–.06)	.01 (–.04–.06)	–.08 (–.21–1.12)	–.01 (–.02–.01)	–.04 (–.11–.02)	–.06 (–.39– –.06)	.07* (.04–.47)
Short half-life	.01 (–.27–.34)	.01 (–.68–.94)	–.21 (–.92–.50)	.03 (–.35–1.77)	.02 (–.13–.28)	–.05 (–1.67–.11)	–.01 (–3.07– –1.12)	–.03 (–2.61–.85)
Medium half-life	–.01 (–.38–.28)	–.02 (–1.26–.43)	–.06* (–1.69– –.21)	–.02 (–1.64–.60)	–.00 (–.23–.21)	.01 (–.78–1.12)	–.01 (–3.54–1.12)	–.10 (–5.74–2.00)
Long half-life	–.03 (–.33 –.00)	.01 (–.49–.62)	–.03 (–.73–.23)	–.01 (–.90–.52)	.06 (.02–.29)	.015 (–.56–.67)	–.01 (–2.23–.73)	–.09 (–3.25—.91)
R^2	.116	.260	.216	.153	.035	.143	.190	.197

***Note*: Gender was coded with females numerically higher; CI = confidence interval.**

*** – $p < .05$.**

Participants in the study were primarily independently living community residents who had undergone a comprehensive assessment process verifying absence of dementia, although some cognitive difficulties might still have been present in the CIND group. Such a selection process means that individuals with significant medication-related cognitive problems may have been grouped with the dementia group in the CSHA. There may also be differences across studies due to other explicit or implicit selection factors. In addition, studies such as the present one that rely on reported use of benzodiazepines may deal with groups different from those included in studies such as Préville et al. (2012) that used computer-based prescription records.

Age differences in test performance are well documented, but in this study, the measures used were all raw scores, and only the verbal fluency measure was not associated with age. Education was associated with all measures that were administered, suggesting that test norms for older people should be stratified for this factor in addition to age. These results may also have implications for the study of gender differences. In five of the analyses, gender was associated with performance on neuropsychological measures.

The use of short half-life benzodiazepines, for unknown reasons, was associated with none of the neuropsychological measures. If the cognitive effects of benzodiazepine use are related to their action on the neurotransmitter GABA, then the absence of effects for short half-life types suggests that longer periods of action may be necessary for cognitive effects to become apparent. It is also possible that the duration of cognitive impairment associated with the use of short half-life benzodiazepines is also of comparatively short duration and thus more difficult to detect. Further research will determine if this lack of effects of short half-life benzodiazepines is limited to this particular sample, which differs from most others presented in the literature in that it used a community sample rather than a clinic-based one.

In their recent report of benzodiazepine usage in Québec, Préville et al. (2012) did not report any gender differences in the amount of benzodiazepine prescribed, whereas our data are one step closer to actual use of medications since prescriptions must have been filled in order to have been recorded by the study nurse. At the same time, one of the limitations for our study is that our data cannot be strongly associated with actual use of benzodiazepine that is confirmed by pill counts and blood samples. We acknowledge that this lack of a solid link to actual consumption of benzodiazepines as a limitation to our results. It precludes such analyses as the possible differences in cognitive function associated with intermittent or regular daily use. Participants also varied greatly in terms of how long they had been taking benzodiazepines and so would differ in their tolerance to the drugs. We did not control for this factor, which is a further limitation. We also have not attempted controlling for the effects of other specific drugs or classes of drugs on the association of benzodiazepines with cognitive function. Our results also may not generalize to other countries with a different sociocultural mix and different practices with regard to prescription of medications. Another limitation is that, given the cross-sectional nature of our analysis, it is not possible to fully exclude reverse causation; that is, older adults with certain neuropsychological impairments are more likely to receive prescriptions for benzodiazepines. Our study also did not address issues such as the prescription of benzodiazepines for off-label uses, the frequency of use during the day, and the dosage of benzodiazepines. Nor did we examine the effects of other classes of medication on cognition (Tannenbaum et al., 2012), either individually or in combination with benzodiazepines.

Préville et al. (2012) noted, however, that many such prescriptions for benzodiazepines were unjustified. In addition to the known risks of benzodiazepine use, Billioti de Gage et al. (2012) noted that new use of benzodiazepines by older adults increases the risk of dementia. As well, Neutel (1998) reported increased risk of traffic accidents by new users of benzodiazepines. Both studies also recommended against widespread use of benzodiazepines, which seems particularly relevant for the intermediate- and long half-life classes. In addition, it is clear that continued research is needed to further extend our understanding of differential effects of benzodiazepine use on different cognitive functions. In addition, studies might address the effects of the newer generation of drugs that affect GABA transmission, such as zolpidem, zopiclone, and zaleplon. Further studies might explore the effects of these non-benzodiazepine drugs in common with other drugs associated with causing cognitive deficits, such as antihistamines and early antidepressants (Tannenbaum et al., 2012).

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