International Psychogeriatrics (2012), 24:1, 48–54 © International Psychogeriatric Association 2011
doi:10.1017/S1041610211001359

Sedative use and incident cognitive decline among persons aged 75 years and older: a population-based longitudinal study

Franciska Desplenter,[1,2,3] Piia Lavikainen,[1,2] Sirpa Hartikainen,[1,2,4] Raimo Sulkava[5,6] and J. Simon Bell[1,2,7]

[1] *Kuopio Research Centre of Geriatric Care, University of Eastern Finland, Kuopio, Finland*
[2] *Clinical Pharmacology and Geriatric Pharmacotherapy Unit, School of Pharmacy, Faculty of Health Sciences, University of Eastern Finland, Kuopio, Finland*
[3] *Research Centre for Pharmaceutical Care and Pharmaco-economics, Faculty of Pharmaceutical Sciences, Katholieke Universiteit Leuven, Leuven, Belgium*
[4] *Leppävirta Health Centre, Leppävirta, Finland*
[5] *Institute of Public Health and Clinical Nutrition, Department of Geriatrics, University of Eastern Finland, Kuopio, Finland*
[6] *Department of Neurology, Kuopio University Hospital, Kuopio, Finland*
[7] *Quality Use of Medicines and Pharmacy Research Centre, Sansom Institute, School of Pharmacy and Medical Sciences, University of South Australia, Adelaide, Australia*

ABSTRACT

Background: Acute exposure to sedative drugs may induce memory impairment, but there is mixed evidence that long-term sedative use may result in incident cognitive decline. The objective of this study was to investigate the use of sedative drugs and incident cognitive decline in a population-based sample of persons aged 75 years and older.

Methods: The study sample comprised 781 participants in the Geriatric Multidisciplinary Strategy for the Good Care of the Elderly (GeMS) study in Kuopio, Finland. Data on health status, drug use, and sociodemographic factors were elicited during annual nurse interviews from 2004 to 2007. A linear mixed model was used to compare change in Mini-Mental State Examination (MMSE) scores (2005–2007) among users of sedative drugs in 2004 and 2005 (n = 139) to non-users of sedative drugs from 2004 to 2007 (n = 310). The model was adjusted for covariates including age, gender, education, depressive symptoms and antipsychotic use.

Results: Unadjusted mean MMSE scores were 27.50 in 2005, 26.58 in 2006, and 25.95 in 2007 among users of sedative drugs. Unadjusted mean MMSE scores were 28.05 in 2005, 27.61 in 2006, and 27.09 in 2007 among non-users of sedative drugs. Adjusted mean MMSE scores were 0.31 points lower in 2005, 0.62 points lower in 2006, and 0.93 lower in 2007 among users compared to non-users of sedative drugs (P = 0.051).

Conclusions: Sedatives were not associated with statistically significant cognitive decline. However, clinicians should maintain a judicious approach to prescribing sedative drugs given the risk of adverse drug events.

Key-words: psychotropic drugs, Finland, aged, cohort studies, pharmacoepidemiology

Introduction

Older persons are particularly susceptible to adverse drug events (ADEs) due to age-related physiological changes, declining homeostatic reserve, and the influence of comorbid diseases (McLachlan *et al.*, 2009). Age-related changes in pharmacokinetics and pharmacodynamics mean that older persons may be particularly susceptible to ADEs associated with sedative drugs. These ADEs may include daytime drowsiness, depressive symptoms, psychomotor retardation, and falls and fractures (Madhusoodanan and Bogunovic, 2004).

While there is good evidence that acute exposure to sedatives may induce memory impairment, there is mixed evidence that long-term sedative use may result in incident cognitive decline (Barker *et al.*, 2004). Persons at high risk of cognitive decline include those using high doses of sedatives, males, those who consume alcohol, and users of multiple central nervous system (CNS) and/or anticholinergic drugs (Stewart, 2005; Wright

Correspondence should be addressed to: J. Simon Bell, PhD, Associate Professor, Quality Use of Medicines and Pharmacy Research Centre, Sansom Institute, School of Pharmacy and Medical Sciences, University of South Australia, Frome Road, Adelaide, 5000, Australia. Phone: +61 8 8302 2419. Email: simon.bell@unisa.edu.au. Received 19 Apr 2011; revision requested 19 May 2011; revised version received 29 May 2011; accepted 31 May 2011. First published online 16 August 2011.

https://doi.org/10.1017/S1041610211001359 Published online by Cambridge University Press

et al., 2009). A meta-analysis has suggested that cognitive impairment may persist after withdrawal of long-term benzodiazepine treatment (Barker *et al.*, 2004).

There are a range of possible mechanisms for the association between sedative use and incident cognitive decline. First, cognitive effects may result from agonist action at gamma-aminobutyric acid (GABA) receptors (Fastbom *et al.*, 1998). Secondly, benzodiazepine use may precede the development of depressive symptoms, which in turn may be linked to cognitive decline (van Vliet *et al.*, 2009). In addition, the observed association may be due to protopathic bias where benzodiazepines are prescribed for prodromal symptoms of dementia (Lagnaoui *et al.*, 2002).

Relatively few population-based longitudinal studies have investigated the association between sedative use and incident cognitive decline. The objective of this longitudinal study was to prospectively investigate the association between use of sedative drugs and cognitive decline among persons aged 75 years and older.

Methods

Study sample

This study analyzed data from the Geriatric Multidisciplinary Strategy for the Good Care of the Elderly (GeMS) study. The GeMS study was a randomized comparative study which evaluated a model for geriatric assessment, care and rehabilitation between 2004 and 2007 in Kuopio, Finland (Rikala *et al.*, 2011). The study sample (n = 1000) was randomly selected from all persons aged ≥75 years (born before 1 November 1928) living in the city of Kuopio, Finland. Of these 1000 persons, 781 (700 community-dwelling, 81 institutionalized) provided written informed consent to participate (162 persons refused participation, 2 persons had moved residence, and 55 persons died before the scheduled baseline examination) (Figure 1). The study was approved by the Hospital District of Northern Savo ethics committee.

The study group allocation did not impact the evolution of psychotropic drug use (Rikala *et al.*, 2011). Therefore, participants in both the intervention and comparison groups were considered in the present analyses. Persons were excluded from the present analyses based on having a baseline Mini-Mental State Examination (MMSE) score lower than 24 (n = 207). In a second step, persons with dementia based on the DSM-IV criteria at baseline (an additional 27 persons) were excluded from the analyses. This was because persons with dementia and subthreshold levels of dementia may have a different risk of further cognitive decline.

Data collection

Trained nurses conducted annual participant interviews between 2004 and 2007. Participants were interviewed to elicit data on sociodemographic factors, health status and drug use. If a community-dwelling participant was unable to visit the outpatient study clinic the nurse interview took place in the participant's home. Institutionalized participants were interviewed in their place of residence. Participant self-reported drug use was verified from prescription forms and drug packages, and by using medical records from the municipal health center, home nursing service, local hospitals and the Kuopio University Hospital. If a participant was unable to report their drug use, this information was sought from that participant's caregiver.

Drug exposure

The use of prescription and non-prescription drugs was recorded and classified using the Anatomical Therapeutic Chemical (ATC) Classification System. Drug use was categorized as regular if the drug was being taken daily or at regular intervals during the preceding two weeks, or as-needed if there was an irregular pattern of use. This categorization was based on each participant's actual pattern of use rather than the clinician's prescribed or intended pattern of use. Sedative drugs were defined as those belonging to ATC classes N05B and N05C, which included zolpidem and zopiclone.

A participant was defined as a user of sedative drugs if he or she was a regular or as-needed prevalent user of one or more sedative drugs in 2004 and 2005. A participant was considered a non-user of sedative drugs if he or she did not use sedative drugs on a regular or as-needed basis in 2004, 2005, 2006 or 2007. Participants who did not meet the criteria for being a user and non-user of sedative drugs were excluded from the analyses.

Cognitive function

The main outcome measure was change in cognitive function assessed using the 30-item MMSE from 2005 to 2007. The MMSE has been used previously to assess the severity of cognitive impairment and to assess change in cognitive function over time (van Vliet *et al.*, 2009).

Covariates

Covariates were selected on the basis of previous research about cognitive decline in older people. These covariates were sociodemographic

https://doi.org/10.1017/S1041610211001359 Published online by Cambridge University Press

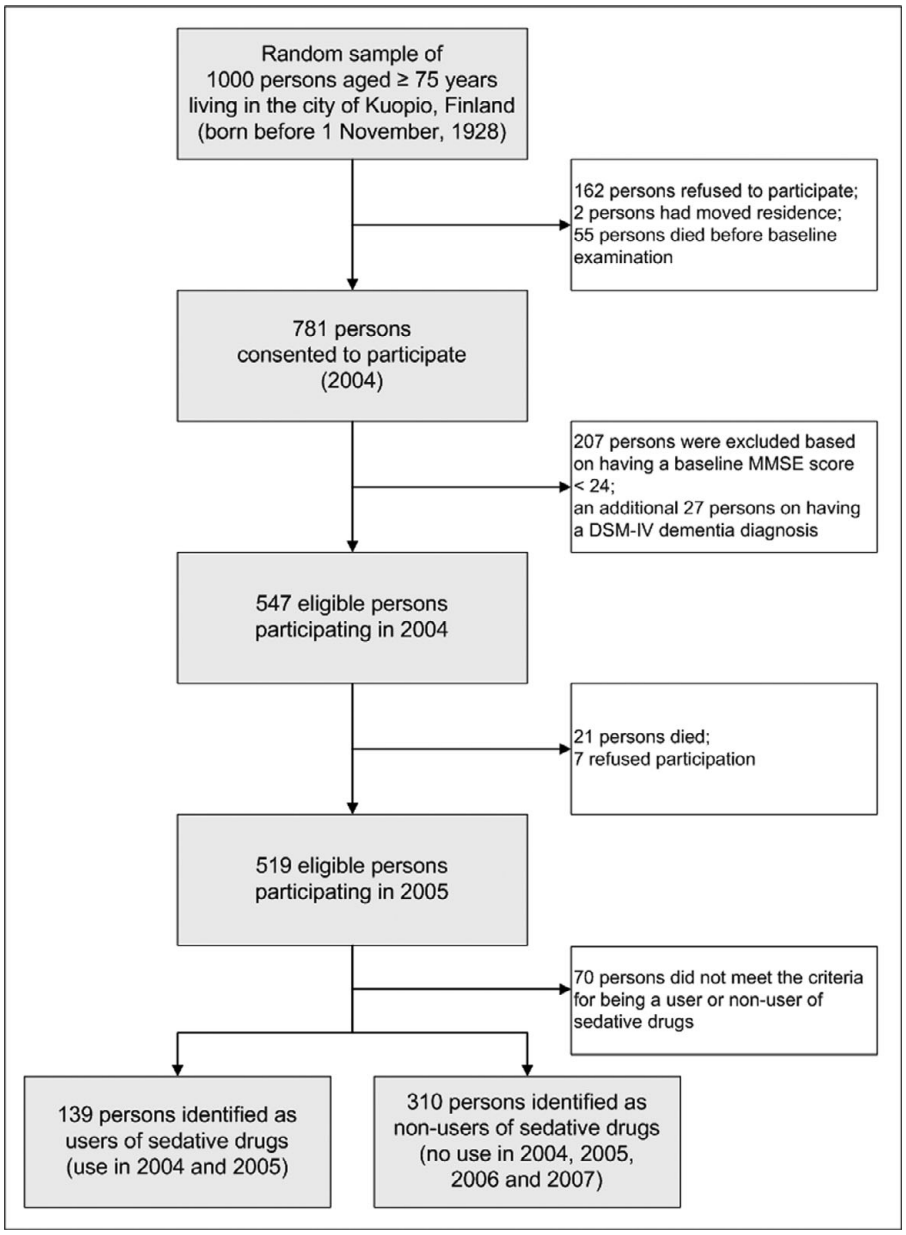


Figure 1. Inclusion and exclusion of participants in the study.

factors, depressive symptoms (yes/no), study group allocation (intervention/comparison group), and concomitant drug use. Sociodemographic factors used as covariates were gender (Azad *et al.*, 2007), age at baseline examination (years) (Kidd, 2008), and educational level (number of years) (Stern, 2006). The presence of depressive symptoms (yes/no) was assessed using the 15-item Geriatric Depression Scale (GDS-15), with scores ≥ 5 considered indicative of depressive symptoms (Paterniti *et al.*, 2002b). Regular or as-needed use of antipsychotic drugs (ATC class N05A) was selected as a covariate because antipsychotics have been associated with deleterious cognitive effects in older persons (Byerly *et al.*, 2001). All analyses were performed using covariate data collected in 2004 prior to the period over which drug exposure was defined.

Statistical analyses

Descriptive statistics were expressed as means and standard deviations for continuous variables, and as proportions for nominal variables. Student's t-tests were used to compare continuous variables, and χ^2 tests for nominal variables. P-values <0.05 were considered statistically significant. A linear mixed model was used to examine change in MMSE scores from 2005 to 2007. Users of sedative drugs in 2004 and 2005 (n = 139) were

https://doi.org/10.1017/S1041610211001359 Published online by Cambridge University Press

Table 1. Descriptive characteristics at baseline (2004) for users and non-users of sedative drugs

CHARACTERISTIC	USERS (N = 139)	NON-USERS (N = 310)	P-VALUE[a]
Male gender, n (%)	26 (18.7)	114 (36.8)	≤0.001
Age (years) (mean ± SD)	81.7 ± 4.7	79.9 ± 3.8	≤0.001
Education (years) (mean ± SD)	8.0 ± 3.6	7.8 ± 3.3	0.620
Community-dwelling, n (%)	138 (99.3)	309 (99.7)	0.559
Living alone, n (%)	89 (64.5)	150 (49.0)	0.002
MMSE (mean ± SD)	27.7 ± 2.0	28.0 ± 1.8	0.160
Depressive symptoms (GDS≥5), n (%)	18 (13.2)	14 (4.6)	0.001
Antidepressant use, n (%)	28 (20.1)	17 (5.5)	≤0.001
Antipsychotic use, n (%)	10 (7.2)	5 (1.6)	0.002

SD = standard deviation; MMSE = Mini-Mental State Examination; GDS = Geriatric Depression Scale.
[a]Student's t-tests were used to compare continuous variables, and χ^2 tests for nominal variables.

compared to non-users of sedative drugs (n = 310) in 2004, 2005, 2006 and 2007. Mixed models are a statistical technique that considers data for drop-outs using a missing-at-random assumption (Verbeke and Molenberghs, 2000). There were no significant differences in MMSE scores between participants and dropouts from 2005–2006 (P = 0.073). However, participants had lower MMSE scores than non-drop-outs from 2006 to 2007 (P<0.001). The mixed model was adjusted for the covariates described in the previous section. Use of antidepressant drugs was not included as a covariate in the final model because it was strongly correlated to the presence of depressive symptoms. The final model included a random slope, random intercept, an auto-regressive covariance matrix, and interaction term between exposure and time. The REML (Restricted Maximum Likelihood) estimation was used (Verbeke and Molenberghs, 2000). Secondary analyses were conducted to compare the adjusted marginal mean MMSE scores among users and non-users of sedative drugs in 2005 and 2007 only. Secondary analyses are recommended when using mixed models with more than two observations to indicate where statistically significant associations exist or do not exist. All analyses were performed using the Statistical Package for the Social Sciences (SPSS) Version 17.0 for Windows (SPSS Inc., Chicago, IL).

Results

The baseline demographic characteristics of the 139 users and 310 non-users are summarized in Table 1. Users of sedative drugs were older (P ≤ 0.001), more likely female (P ≤ 0.001), more likely to live alone (P = 0.002), had a higher prevalence of depressive symptoms (P = 0.001), and were more likely to be concomitant users of antidepressant (P ≤ 0.001) and antipsychotic drugs (P = 0.002) than non-users. However, MMSE scores were not statistically significantly different among users and non-users (P = 0.160). Of the 139 users in 2005, 128 (92.1%) participated in 2006 and 122 (87.8%) participated in 2007. Of the 310 non-users in 2005, 300 (96.8%) participated in 2006 and 291 (93.9%) participated in 2007. The most prevalent regular or as-needed sedative drugs among the 139 users in 2005 were zopiclone (n = 75), temazepam (n = 33) and oxazepam (n = 18).

The unadjusted mean MMSE scores among users of sedative drugs were 27.50 in 2005, 26.58 in 2006, and 25.95 in 2007 (Figure 2). In comparison, the unadjusted mean MMSE scores among non-users of sedatives were 28.05 in 2005, 27.61 in 2006, and 27.09 in 2007. In the final adjusted model, MMSE scores were 0.31 points lower in 2005, 0.62 points lower in 2006, and 0.93 lower in 2007 among users compared to non-users of sedative drugs. The difference in MMSE scores over time (2005–2007) between users and non-users just failed to reach statistical significance (P = 0.051) (Table 2). In secondary analyses, pairwise comparison of the estimated marginal means of MMSE scores obtained in 2005 and 2007 between users and non-users showed an overall difference of 0.69, with a standard error of 0.29 (P = 0.019) when adjusted for all covariates.

Discussion

The main finding of our study was that the association between use of sedative drugs and incident cognitive decline was not statistically significant when assessed using MMSE scores collected from 2005 to 2007. However, in

https://doi.org/10.1017/S1041610211001359 Published online by Cambridge University Press

Table 2. Linear Mixed Model for change in MMSE score (2005–2007) as a function of non-use of sedative drugs in an Finnish population sample aged 75 years and older

EXPLANATORY VARIABLE	PARAMETER ESTIMATE	STANDARD ERROR	P-VALUE
Intercept	35.96	2.55	≤ 0.001
Male gender	0.23	0.25	0.379
Age (years)	−0.11	0.03	≤ 0.001
Education (years)	0.16	0.04	≤ 0.001
Intervention study group	0.19	0.23	0.430
No depressive symptoms	0.13	0.46	0.781
No antipsychotic drug use at baseline	0.40	0.65	0.539
Time	−0.79	0.13	≤ 0.001
No sedative drug use	−0.22	0.44	0.607
No sedative drug use × time	**0.31**	**0.16**	**0.051**

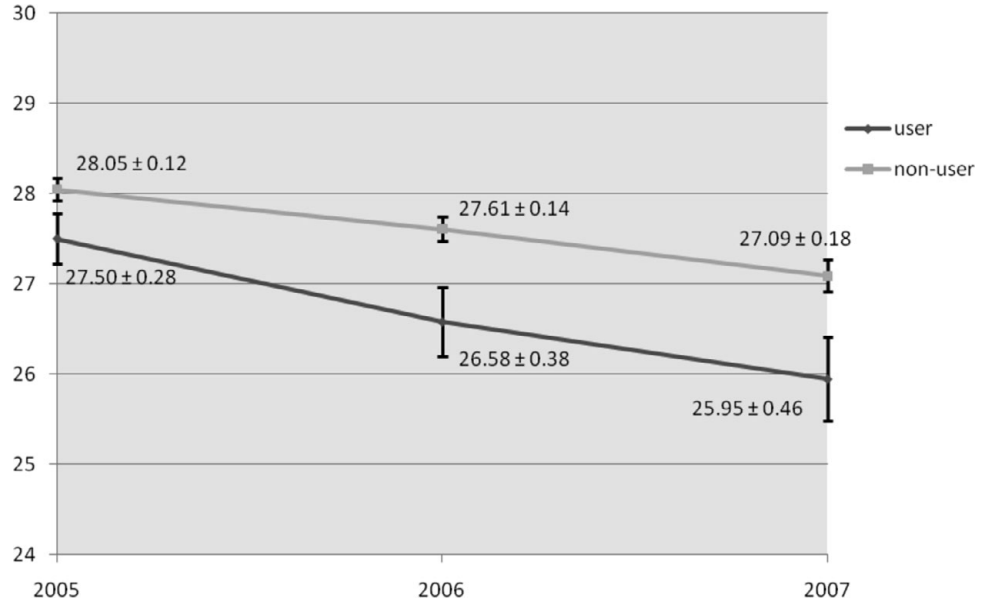


Figure 2. Change in mean MMSE scores (with standard error bars) among users and non-users of sedative drugs.

secondary analyses conducted using only those MMSE scores obtained in 2005 and 2007, use of sedative drugs was associated with statistically significant cognitive decline.

Our findings were consistent with a number of previous studies into the use of benzodiazepines and cognitive decline. Allard *et al.* (2003) reported no association between long-term benzodiazepine use and cognitive decline in a population-based sample of 372 older persons (mean age 76 years) in France. Hanlon *et al.* (1998) reported that current and previous benzodiazepine use was unrelated to level of cognitive functioning among 2765 community-dwelling participants aged 65 years and older. Similarly, van Vliet *et al.* (2009) reported that use of benzodiazepines was not associated with cognitive decline in the Leiden 85+ Study. However, van Vliet *et al.* found that persons who discontinued taking benzodiazepines had a 4.0 point lower MMSE score in the year prior to discontinuation compared to those who continued taking benzodiazepines. This was interpreted as evidence of a "depletion of susceptibles effect" whereby physicians ceased prescribing benzodiazepines to persons with impaired cognitive function (Moride and Abenhaim, 1994). Similarly, Lagnaoui *et al.* (2009) reported a non-significant increased risk of cognitive impairment (odds ratio (OR) 1.5; 95% confidence interval (CI) 0.6–3.4) among former, but not among current benzodiazepine users (OR 1.0; 95% CI 0.5–2.0). We investigated the use of sedative drugs in 2004 and 2005, and incident cognitive decline between 2005 and 2007. However, we cannot exclude the possibility that our non-significant results were also due in part to the "depletion of susceptibles effect".

Our findings were also in contrast to several previous studies. Paterniti *et al.* (2002a) reported an increased risk of dementia among chronic but not episodic users in a four-year longitudinal study of 1398 persons aged from 60 to 70 years. Lagnaoui *et al.* (2002) reported that former use of

https://doi.org/10.1017/S1041610211001359 Published online by Cambridge University Press

benzodiazepines was associated with a significantly increased risk of dementia (OR 2.3; 95% CI 1.2–4.5) among 3777 persons aged 65 years and older. Conversely, two studies have reported a lower risk of cognitive decline among former (Dealberto *et al.*, 1997) and ever (Fastbom *et al.*, 1998) users of benzodiazepines.

Although the incident cognitive decline was not statistically significant between users and non-users of sedative drugs, users of sedative drugs had lower absolute MMSE scores in 2005, 2006 and 2007. This may be partly explained by acute exposure to sedative drugs among participants who continued to use sedatives. In addition, the absolute decline in mean MMSE scores among users of sedative drugs between 2005 and 2007 was 1.55. A decline of more than three MMSE points for a given individual over a 1–4 year period has been described as indicative of "substantial" cognitive deterioration unlikely to have resulted from chance fluctuation (Tangalos *et al.*, 1996).

There are a number of methodological similarities and differences between our study and previous longitudinal studies. Our analyses were adjusted for concomitant use of antipsychotic drugs. This was important because antipsychotic drugs may accelerate the rate of cognitive decline (McShane *et al.*, 1997). Many previous studies have not adjusted for use of other psychotropic drugs (Fastbom *et al.*, 1998; Hanlon *et al.*, 1998; Lagnaoui *et al.*, 2002), or have adjusted for use of psychotropic drugs as a single covariate (Dealberto *et al.*, 1997; Paterniti *et al.*, 2002a). Treating use of other psychotropic drugs as a single covariate may be problematic because antidepressant drugs may be protective against cognitive decline in older persons with depressive symptoms (Mossello *et al.*, 2008). However, like most previous studies, our analyses were not adjusted for concomitant use of anticholinergic, antihypertensive or antidiabetic drugs that may have possible direct or indirect effects on cognition. The use of mixed models meant that we were able to account for persons who dropped out of the study during the two-year follow-up period. This was important because sedative use and cognitive decline have been associated with increased mortality in previous studies (Dewey and Saz, 2001; Belleville, 2010). Despite often considerable attrition rates, most previous analyses have been restricted to subsamples of study participants alive at the end of the follow-up period.

Strengths and limitations

There are a number of additional methodological strengths of our study. First, the longitudinal design meant that we were able to investigate cognitive decline prospectively among users and non-users of sedative drugs in a well-characterized cohort of older persons. Secondly, drug exposure was ascertained though nurse interviews. This method captured actual patterns of drug use rather than prescribed or intended patterns of use. Thirdly, the MMSE is a widely used and validated instrument for assessing cognitive function among older persons. Our study also had a number of methodological limitations. First, sedative use was defined according to prevalent use at consecutive clinical examinations in 2004 and in 2005. For the purpose of the analyses, we assumed that a prevalent user at consecutive clinical examinations was a continuous user between these time points. One year was a relatively short period over which to define long-term use but this period was longer than in many previous epidemiological studies on long-term benzodiazepine use (Lagnaoui *et al.*, 2004; Fortin *et al.*, 2007; Assem-Hilger *et al.*, 2009). Secondly, as with most previous studies, we did not explore the possibility of a dose-response relationship between sedative use and incident cognitive decline. This may have been important because cumulative exposure to CNS drugs has been associated with cognitive decline.

Conclusions

Use of sedative drugs was not associated with a statistically significant incident cognitive decline when assessed using MMSE scores collected from 2005 to 2007. Nevertheless, clinicians should maintain a judicious approach to prescribing sedative drugs given the association with a range of potential ADEs, including incident cognitive decline.

Conflict of interest

None.

Description of authors' roles

FD and JSB drafted the paper. FD and PL conducted the statistical analyses. SH and RS were involved in conducting the GeMS study. All authors revised the paper for important intellectual content, and approved the version of the paper submitted for publication.

Acknowledgments

The authors thank the Social Insurance Institution of Finland and City of Kuopio for supporting the GeMS study. The authors also thank Professor Gert

https://doi.org/10.1017/S1041610211001359 Published online by Cambridge University Press

Laekeman and the K.U. Leuven "Fonds Apotheker en Mevrouw Ysebaert-Devos' for providing a travel grant to Franciska Desplenter.

References

Allard, J., Artero, S. and Ritchie, K. (2003). Consumption of psychotropic medication in the elderly: a re-evaluation of its effect on cognitive performance. *International Journal of Geriatric Psychiatry*, 18, 874–878.

Assem-Hilger, E., Jungwirth, S., Weissgram, S., Kirchmeyr, W., Fischer, P. and Barnas, C. (2009). Benzodiazepine use in the elderly: an indicator for inappropriately treated geriatric depression? *International Journal of Geriatric Psychiatry*, 24, 563–569.

Azad, N. A., Al Bugami, M. and Loy-English, I. (2007). Gender differences in dementia risk factors. *Gender Medicine*, 4, 120–129.

Barker, M. J., Greenwood, K. M., Jackson, M. and Crowe, S. F. (2004). Persistence of cognitive effects after withdrawal from long-term benzodiazepine use: a meta-analysis. *Archives of Clinical Neuropsychology*, 19, 437–454.

Belleville, G. (2010). Mortality hazard associated with anxiolytic and hypnotic drug use in the national population health survey. *Canadian Journal of Psychiatry*, 55, 558–567.

Byerly, M. J., Weber, M. T., Brooks, D. L., Snow, L. R., Worley, M. A. and Lescouflair, E. (2001). Antipsychotic medications and the elderly: effects on cognition and implications for use. *Drugs and Aging*, 18, 45–61.

Dealberto, M. J., McAvay, G. J., Seeman, T. and Berkman, L. (1997). Psychotropic drug use and cognitive decline among older men and women. *International Journal of Geriatric Psychiatry*, 12, 567–574.

Dewey, M. E. and Saz, P. (2001). Dementia, cognitive impairment and mortality in persons aged 65 and over living in the community: a systematic review of the literature. *International Journal of Geriatric Psychiatry*, 16, 751–761.

Fastbom, J., Forsell, Y. and Winblad, B. (1998). Benzodiazepines may have protective effects against Alzheimer disease. *Alzheimer Disease and Associated Disorders*, 12, 14–17.

Fortin, D. *et al.* (2007). Factors associated with long-term benzodiazepine use among elderly women and men in Quebec. *Journal of Women and Aging*, 19, 37–52.

Hanlon, J. T. *et al.* (1998). Benzodiazepine use and cognitive function among community-dwelling elderly. *Clinical Pharmacology and Therapeutics*, 64, 684–692.

Kidd, P. M. (2008). Alzheimer's disease, amnestic mild cognitive impairment, and age-associated memory impairment: current understanding and progress toward integrative prevention. *Alternative Medicine Review*, 13, 85–115.

Lagnaoui, R. *et al.* (2002). Benzodiazepine use and risk of dementia: a nested case-control study. *Journal of Clinical Epidemiology*, 55, 314–318.

Lagnaoui, R. *et al.* (2004). Patterns and correlates of benzodiazepine use in the French general population. *European Journal of Clinical Pharmacology*, 60, 523–529.

Lagnaoui, R. *et al.* (2009). The risk of cognitive impairment in older community-dwelling women after benzodiazepine use. *Age and Ageing*, 39, 226–228.

Madhusoodanan, S. and Bogunovic, O. J. (2004). Safety of benzodiazepines in the geriatric population. *Expert Opinion on Drug Safety*, 3, 485–493.

McLachlan, A. J., Hilmer, S. N. and Le Couteur, D. (2009). Variability in response to medicines in older people: phenotypic and genotypic factors. *Clinical Pharmacology and Therapeutics*, 85, 431–433.

McShane, R., Keene, J., Gedling, K., Fairburn, C., Jacoby, R. and Hope, T. (1997). Do neuroleptic drugs hasten cognitive decline in dementia? Prospective study with necropsy follow up. *BMJ*, 314, 266–270.

Moride, Y. and Abenhaim, L. (1994). Evidence of the depletion of susceptibles effect in non-experimental pharmacoepidemiologic research. *Journal of Clinical Epidemiology*, 47, 731–737.

Mossello, E. *et al.* (2008). Is antidepressant treatment associated with reduced cognitive decline in Alzheimer's disease? *Dementia and Geriatric Cognitive Disorders*, 25, 372–379.

Paterniti, S., Dufouil, C. and Alperovitch, A. (2002). Long-term benzodiazepine use and cognitive decline in the elderly: the Epidemiology of Vascular Aging Study. *Journal of Clinical Psychopharmacology*, 22, 285–293.

Paterniti, S., Verdier-Taillefer, M. H., Dufouil, C. and Alpérovitch, A. (2002). Depressive symptoms and cognitive decline in elderly people: a longitudinal study. *British Journal of Psychiatry*, 181, 406–410.

Rikala, M., Korhonen, M. J., Sulkava, R. and Hartikainen, S. (2011). The effects of medication assessment on psychotropic drug use in the community-dwelling elderly. *International Psychogeriatrics*, 23, 473–484.

Stern, Y. (2006). Cognitive reserve and Alzheimer disease. *Alzheimer Disease and Associated Disorders*, 20 (Suppl. 2), S69–S74.

Stewart, S. A. (2005). The effects of benzodiazepines on cognition. *Journal of Clinical Psychiatry*, 66 (Suppl. 2), 9–13.

Tangalos, E. G. *et al.* (1996). The Mini-Mental State Examination in general medical practice: clinical utility and acceptance. *Mayo Clinic Proceedings*, 71, 829–837.

van Vliet, P., van der Mast, R. C., van den Broek, M., Westendorp, R. G. and de Craen, A. J. (2009). Use of benzodiazepines, depressive symptoms and cognitive function in old age. *International Journal of Geriatric Psychiatry*, 24, 500–508.

Verbeke, G. and Molenberghs, G. (2000). *Linear Mixed Models for Longitudinal Data*. New York: Springer.

Wright, R. M. *et al.* (2009). Effect of central nervous system medication use on decline in cognition in community-dwelling older adults: findings from the Health, Aging And Body Composition Study. *Journal of the American Geriatrics Society*, 57, 243–250.

https://doi.org/10.1017/S1041610211001359 Published online by Cambridge University Press