Benzodiazepines and antidepressants: Effects on cognitive and functional decline in Alzheimer’s disease and Lewy body dementia

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Abstract

Objectives: We aim to study the effects of the prescription of benzodiazepines and antidepressants on cognitive and functional decline in older adults living with Alzheimer’s disease (AD) and Lewy body dementia (LBD) over a 5-year follow-up.

Methods: This is a longitudinal analysis of a Norwegian cohort study entitled “The Dementia Study of Western Norway” (DemVest). We included 196 patients newly diagnosed with AD (n = 111) and LBD (n = 85), followed annually for 5 years. Three prescription groups were defined: only benzodiazepines (BZD), only antidepressants (ADep), and the combination of benzodiazepines and antidepressants (BZD-ADep). Linear mixed-effects models were conducted to analyze the effect of the defined groups on the outcomes. The outcomes were functional decline, measured by the Rapid Disability Rating Scale—2, and cognition measured with the Mini-Mental State Examination.

Results: Prescription of the combination of benzodiazepines and antidepressants in LBD was associated with faster functional decline. In AD, the prescription of BZD and BZD-ADep was associated with greater functional deterioration. ADep alone did not show positive or negative significant associations with the studied outcomes.

Conclusions: BZD and especially the combination of BZD and ADep are associated with functional decline in AD and LBD and should be used cautiously.

Keywords

activities of daily living, Alzheimer’s disease, Antidepressive Agents, benzodiazepines, cognitive decline, dementia, functional disability, hypnotics and sedatives, Lewy body dementia

Key Points

• Combination of benzodiazepines and antidepressants in Lewy body dementia was associated with faster functional decline

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INTRODUCTION:

Neurodegenerative disorders, such as dementia, are frequent chronic diseases. Worldwide, around 50 million people have dementia, and there are nearly 10 million new cases every year. Alzheimer’s disease (AD) is the most common cause of dementia and contributes to 60%–70% of all cases. Lewy body dementia (LBD) is the second most common type of neurodegenerative dementia and is often under-diagnosed despite showing worse prognosis than AD. Functional decline is essential for the diagnosis of dementia and also is one of the most important markers of progression. Functional status depends on several aspects including social, demographic, and health factors. Besides, it is related to morbidity, mortality, and quality of life. Thus, it has become an important measurement in the comprehensive geriatric assessment and patient-centered care for older adults. Neuropsychiatric symptoms (NPS) such as depression, anxiety, agitation, and sleep disturbances are very common in dementia and have large consequences for quality of life. Thus, it has become an important measurement in the comprehensive geriatric assessment and patient-centered care for older adults.

Neuropsychiatric symptoms (NPS) such as depression, anxiety, agitation, and sleep disturbances are very common in dementia and have large consequences for quality of life. The progression of the disease, and carer burden, is related to morbidity, mortality, and quality of life. Thus, it has become an important measurement in the comprehensive geriatric assessment and patient-centered care for older adults. Neuropsychiatric symptoms (NPS) such as depression, anxiety, agitation, and sleep disturbances are very common in dementia and have large consequences for quality of life.

2 MATERIALS AND METHODS

2.1 Setting and participants

This is a longitudinal analysis of a Norwegian cohort study entitled “The Dementia Study of Western Norway” (DemVest). The DemVest study recruited patients from dementia clinics in Hordaland and Rogaland counties diagnosed with mild dementia. Mild dementia was defined as a Mini-Mental Status Examination (MMSE) score ≥ to 20 or a Clinical Dementia Rating global score = 1. Here we included patients with AD and LBD with complete information regarding medication, activities of daily living (ADL), and cognition, yielding a total of 196 participants (AD = 111; LBD = 85) who were followed annually. The flow of patients during the study period is shown in Appendix 1.

Exclusion criteria were moderate or severe dementia, delirium (four of the screened candidates were excluded due to delirium), previous bipolar or psychotic disorder, terminal illness, or a recently diagnosed major somatic disease, which could significantly impact cognition, function, or study participation. Further information regarding the DemVest study can be found elsewhere. Dementia with Lewy bodies (DLB) and Parkinson’s Disease Dementia (PDD) groups were combined in an LBD group given pathological and clinical similarities.

2.2 Assessments

Dementia Diagnosis was established according to DSM-IV criteria and was further classified as a specific type of dementia when complying with corresponding validated criteria: for AD (according to National Institute of Neurological and Communicative Disorders, Stroke-AD and Related Disorders Association), or DLB and PDD (according to the DLB 2005 consensus criteria and the Movement Disorder Task Force). Pathological diagnosis was ascertained in 56 subjects of the DemVest cohort, providing diagnostic accuracy above 80% when clinical criteria were applied.

2.3 Drug-prescription classification

Drug names and dosages at baseline were retrieved from the patient or family members and were either given orally or based on a written medication list. Information about over-the-counter drugs could not be retrieved. Medications were classified according to the Anatomical Therapeutic Chemical classification system (ATC). The psychotropic drugs of interest were antidepressants (N06A) and benzodiazepines. Many benzodiazepines are classified as anxiolytics (N05B) and...
hypnotics (N05C). Besides, the nonbenzodiazepine medications (N05CF) known as “Z-drugs” also act via GABA receptors. Thus, our defined BZD group consisted of drugs classified in following ATC-groups: N05BA, N05CD, and N05CF. We established three groups as follows: (1) Benzodiazepines (BZD), (2) Antidepressants (ADep), and (3) combination of BZD and ADep (BZD-ADep). Medications were registered in baseline and yearly during the 5 years of the study.

2.4 | Functional decline in ADL

The ADL were evaluated with the first 13 items (those specifically referring to current difficulties in ADL) from the Norwegian version of the Rapid Disability Rating Scale-2 (RDRS-2).33,34 The 13 included items were: (1) Eating, (2) Making simple food (e.g., sandwiches), (3) Cooking dinner and adhere to a diet, (4) Mobilization—inside/outside (with or without aids), (5) Daily personal care (including brushing teeth, combing hair, and maintaining personal hygiene), (6) Bathing/showering, (7) Dressing (including finding clothes), (8) Toilet usage (including occasional clothing and cleaning), (9) Usage of telephone, (10) Buying food and other necessary items, (11) Handling money and paying bills, (12) Having a financial overview plan ahead and writing tax returns, and (13) Taking medications as prescribed. Each item was scored from 1 to 4 (Alone = 1, with some help = 2, with a lot of help = 3 and Can Not perform = 4) and then divided over the number of items. We summarized the total mean score of the aforementioned items yearly, over a 5-year follow-up.35,36 A higher score indicates a higher level of functional decline.

2.5 | Cognitive decline

Cognition was evaluated using the MMSE. It was assessed annually and its trajectory was analyzed during the follow-up as continue variable.37

2.6 | Other variables

Comorbidities at baseline were assessed retrospectively using the Cumulative Illness Rating Scale (CIRS), a systematic scale of comorbidity (higher value indicates more/higher comorbidities).38 Comorbidities were registered based on patient and informant reports. The validated Norwegian Neuropsychiatric Inventory (NPI) was used to interview family or caregivers, and the nursing home version (NPI-Nursing Home) was used after participants were admitted to nursing homes.39,40 All assessments were completed by the informant who had the most day-to-day contact with the patient. The 12 domains of NPI were registered as present or not during the past 4 weeks, and if present, scored according to their frequency 1–4 and severity 1–3 was registered. Here, we report the frequency \( \times \) severity score for the domains. We estimated the frequency \( \times \) severity score at the time of diagnosis and its longitudinal course for 5 years.

2.7 | Statistical analysis

A descriptive analysis was performed by estimating percentages for categorical variables and means and standard deviations for quantitative variables. Random coefficient mixed models were used to analyze the potential longitudinal association of the consumption of BZD and ADep with cognitive and functional decline for (a) AD patients, (b) LBD patients, and (c) all patients. For longitudinal trajectories of decline, time was used in its linear and quadratic forms. The random effects were an intercept and a slope for time to each subject in the study, assuming an unstructured covariance matrix. Time was centered at 3 years, and the rest of the variables were centered at their mean on the baseline. For model selection, Bayesian Information Criterion (BIC) was used, and variables significance was carried out at 0.05. The model for ADL prediction was adjusted for age, sex, comorbidities at baseline (CIRS), and MMSE. The model for MMSE prediction was adjusted by the same variables, and ADL in place of MMSE. Since BZD and ADep are likely used to treat NPS, and these symptoms may lead to worsening cognition and function by themselves, we adjusted for NPS using the NPI.41 We show unadjusted and adjusted models results. MMSE was treated as a left- and right-censored variable, and corrected by a Tobit linear mixed effect model. Statistical analyses were performed using STATA 15®.

3 | RESULTS

The descriptive information of the sample can be found in Table 1. The AD and LBD groups did not differ significantly concerning age or MMSE, but the CIRS and NPI scores were significantly higher in the LBD group compared to AD. At baseline, 6.6% were prescribed BZD alone, 24.5% ADep alone, and 9.7% the combination. Figure 1 shows the prescription curves for the three studied groups during the 5 years’ follow-up.

3.1 | Functional decline

As expected, both AD and LBD showed functional decline during the observation period. Table 2 displays the results of the linear mixed models conducted. After adjustments, in the LBD group, BZD-ADep was associated with faster functional decline (Est. 0.251 SE 0.089 p-value 0.005). For the AD group, faster functional deterioration was associated with BZD prescription alone (Est. 0.226 SE 0.087 p-value 0.009) and BZD-ADep (Est. 0.165 SE 0.058 p-value 0.005). Likewise, for the total sample, greater functional deterioration was associated with BZD prescription alone (Est. 0.142 SE 0.066 p-value 0.032, significant in the AD group only) and BZD-ADep (Est. 0.218 SE 0.049 p-value <0.0001). Predicted trajectories of functional decline can be visualized in Figure 2.


### TABLE 1 Baseline characteristics of the study sample

| Total n (%) or Mean ± SD | LBD | AD | p-value* |
|--------------------------|-----|----|---------|
| Age                      | 75.30 ± 7.36 | 75.42 ± 6.90 | 75.20 ± 7.73 | 0.840 |
| Sex                      | -   | -  | -       | <0.001 |
| Women                    | 77 (39.29) | 38 (44.71) | 81 (72.97) |
| Men                      | 119 (60.71) | 47 (55.29) | 30 (27.03) |
| CIRS                     | 5.83 ± 2.55 | 6.59 ± 2.55 | 5.33 ± 2.44 | 0.001 |
| MMSE                     | 23.67 ± 2.72 | 23.75 ± 3.19 | 23.61 ± 2.32 | 0.720 |
| NPI total                | 19.52 ± 18.08 | 24.07 ± 18.81 | 16.04 ± 16.77 | 0.002 |
| No BZD or ADep           | 107 (54.59) | 44 (51.76) | 63 (56.76) | 0.430 |
| Benzodiazepines          | 13 (6.63) | 7 (8.24) | 6 (5.41) | 0.400 |
| Antidepressants          | 48 (24.49) | 18 (21.18) | 30 (27.03) | 0.490 |
| Combined                 | 19 (9.69) | 9 (10.59) | 10 (9.01) | 0.054 |

Abbreviations: AD, Alzheimer’s disease; ADep, Antidepressants; ADL, Activities of daily living; BZD, Benzodiazepines; CIRS, Cumulative Illness Rating Scale; LBD, Lewy bodies dementia; MMSE, Mini-Mental state examination; NPI total, Total score of the Neuropsychiatric Inventory; Total, AD + DLB.

3.2 | Cognitive decline

The MMSE score declined in both patient groups during the study period. After adjusting for possible confounders, there were no significant associations between the prescription groups and cognition (Table 3).

4 | DISCUSSION

In this study, we found that the prescription of BZD in combination with ADep was associated with a faster functional decline in patients with AD and LBD during a 5-year follow-up. The effect was relatively small but statistically significant. Little has been reported regarding functional prognosis in people diagnosed with dementia, especially in those diagnosed with LBD.

In general, compared with the young, older adults are more sensitive to BZD, including a higher risk for confusion and disorientation. This increased sensitivity is directly related to the accumulation of BZDs and related active metabolites. BZD induce central nervous system toxicity, generating symptoms such as anterograde amnesia, sedation, drowsiness, motor impairment, inattentiveness, and ataxia.

These effects are particularly higher in those living with dementia where there are already processes such as neurodegeneration that predispose to cognitive and functional impairment and other manifestations such as balance problems, delirium, and falls.

There are pharmacodynamic interactions between BZD and antidepressant drugs which may increase the risk for adverse events. For example, ADep such as Fluoxetine or Paroxetine reduces the metabolism of some benzodiazepines.

A recent meta-analysis in adults reported that participants in the combined therapy BZD-ADep presented at least one adverse effect more often than participants who received antidepressants alone.

It should be noted that in older adults, the risk of adverse effects increases with the addition of a new medication, and even more when both medications affect the same body system. This may explain why BZD alone predicted fewer outcomes than BZD-ADep.
Besides, the rate of BZD-ADep prescriptions was higher than BZD prescriptions alone, and it increased over time.

Thus, we speculate that the observed effects in this study on functional decline are due to a sum of the BZD adverse effects, the interaction BZD-Addep effect, and neurodegeneration. The effect of BZD alone was found only in the AD group, indicating that AD patients may be more susceptible to BZD’s side effects than LBD, but, the sample size of the LBD group was smaller than the AD group.

Previous studies of BZD plus ADep use have found a high probability of combined use when one of the drugs have already been prescribed, and with higher rates of prescription. Commonly these medications are prescribed without a clear indication based on formal diagnosis, lack of a comprehensive geriatric assessment, and inadequate adherence to updated recommendations for prescription in older adults with dementia. Research and consensus panels have concluded that the prescription of all benzodiazepines to older adults should be avoided for the treatment of insomnia, agitation, or delirium. Despite this, the use of BZDs in older adults with or without dementia, in nursing homes or living in community is still prevalent, and tends to increase with the progression of dementia. In this study, the number of people consuming BZD-ADep had increased from 9.69% in baseline to 39.39% in year 5.

Previous studies have reported BZD prescription as a possible risk factor for dementia, as well as associations between BZD prescription and greater cognitive decline.

Table 2: Association between medication group and functional decline across 5 years follow-up in AD and LBD

| Variables | AD     | LBD     | Total    |
|-----------|--------|---------|----------|
|           | Estimation | Standard Error | p-value | Estimation | Standard Error | p-value | Estimation | Standard Error | p-value |
| BZD       | 0.233  | 0.093  | 0.0120 | 0.110  | 0.102  | 0.2810 | 0.207  | 0.069  | 0.0030 |
| ADep      | 0.136  | 0.061  | 0.0270 | −0.036 | 0.096  | 0.7070 | 0.074  | 0.054  | 0.1700 |
| BZD-Addep | 0.252  | 0.062  | 0.0000 | 0.275  | 0.087  | 0.0020 | 0.280  | 0.052  | 0.0000 |
| Time      | 0.316  | 0.036  | 0.0000 | 0.454  | 0.053  | 0.0000 | 0.369  | 0.030  | 0.0000 |
| Time²     | −0.007 | 0.006  | 0.2420 | −0.027 | 0.010  | 0.0090 | −0.015 | 0.005  | 0.0060 |
| Intercept | 1.544  | 0.067  | 0.0000 | 1.838  | 0.090  | 0.0000 | 1.671  | 0.055  | 0.0000 |

Notes: Females given as frequencies and (percentages), otherwise mean ± standard deviations. Time was evaluated with its quadratic and linear term. Differences in gender assessed by Pearson’s Chi-square test, all other by Student’s T-test. Linear mixed models, NPI measured longitudinally and its association with the functional trajectory.

Abbreviations: AD, Alzheimer’s disease; ADep, Antidepressants; ADL, Activities of daily living; BZD, Benzodizepines; CIRS, Cumulative Illness Rating Scale; LBD, Lewy bodies dementia; MMSE, Mini-mental state examination; NPI total, Total score of the Neuropsychiatric Inventory.

p values < 0.05 are printed in bold.
their combination with ADep. These adverse effects are independent of neurodegeneration and can impair physical and mental functioning leading to delirium, low blood pressure, falls, fractures, dependence, hospitalizations. However, although we think this is the most likely explanation, we cannot exclude the possibility of causality in the opposite direction, that is, that antidepressants and BZD are prescribed due to functional decline.

We are aware that our research may have a potential recruitment bias because of referrals of primary care patients, which may have led to an increased number of patients with complicated dementia. However, GPs were encouraged to refer any patients with suspected dementia, and patients were included from psychiatric, neurologic, and geriatric clinics. Also confounding bias might be present in that medication use is potentially associated with mortality, which was the main reason for dropout in the study.

We did not differentiate between the type of antidepressant, considering that tricyclics have a high rate of adverse effects. However, in this study, the prescription of tricyclic ADep was found at baseline only in one person. Likewise, for BZDs, all “Z” drugs were put in this category (38.2% of the subjects consumed non-benzodiazepine hypnotics (zopiclone = 12, zolpidem = 1). There is a perception that nonbenzodiazepine hypnotics are safer than benzodiazepines, however recent studies suggest that this is inaccurate; they tend to have a quicker onset and shorter duration of action but produce similar side effects. There was a high dropout rate and an expected high mortality, particularly in LBD, which may have confounded the observed course of the studied outcomes. Furthermore, fewer subjects consuming only BZD compared with BZD-ADep, and thus statistical power was higher for the BZD-ADep group. Initially, we aimed to study the effect of antipsychotics as well, but this was not possible due to the low numbers (nine prescriptions in total at baseline). Additionally, the specific indications for prescriptions could not be determined. We are aware that the indication for the prescription could influence the outcome. For example, depression, anxiety, sleep disorders, delusions, hallucinations i.e. have been correlated with functional and cognitive decline in dementia. However, we adjusted for total NPI to try to control this interaction. Finally, the co-prescription of other drugs was not considered as a co-variable. This may have influenced the findings.

This study has several strengths, including long follow-up time, yearly assessments with structured instruments, and high completeness of data. Outside of attrition because of death and dropouts, persistency and reoccurrence analysis was achieved for mild to severe dementia because of these advantages. There are few long-term studies assessing medication and daily functioning including LBD patients. The diagnostic procedures were rigorous, and high accuracy has been demonstrated with neuropathological diagnosis. Future studies with larger sample sizes are needed to better understand the effect of psychotropics on function and cognition in people with dementia.

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ETHICS STATEMENT
This study was approved by the regional ethics committee (approval code: 2010/633) and the Norwegian authorities for the collection of medical data. All data was handled and kept following national health and data privacy protocols. All participants signed an informed consent form before inclusion in the study. This paper
TABLE 3 Association between medication group and cognitive decline across 5 years follow-up in AD and LBD

| Variables     | AD          | LBD          | Total         |
|---------------|-------------|--------------|---------------|
|               | Estimation  | Standard Error | p-value | Estimation  | Standard Error | p-value | Estimation  | Standard Error | p-value |
| No adjusted   |             |               |           |             |               |         |             |               |         |
| BZD           | 0.267       | 0.676         | 0.693     | -1.889      | 0.804         | 0.0190   | -0.865      | 0.520         | 0.0960   |
| ADep          | 0.080       | 0.403         | 0.8420    | 0.718       | 0.633         | 0.2570   | 0.238       | 0.350         | 0.4960   |
| BZD-Adep      | -0.627      | 0.456         | 0.1700    | -1.330      | 0.645         | 0.0390   | -0.948      | 0.379         | 0.0120   |
| Time          | -1.449      | 0.292         | 0.0000    | -2.297      | 0.499         | 0.0000   | -1.834      | 0.263         | 0.0000   |
| Time²         | -0.349      | 0.046         | 0.0000    | -0.349      | 0.085         | 0.0000   | -0.341      | 0.041         | 0.0000   |
| Intercept     | 23.552      | 0.324         | 0.0000    | 24.033      | 0.453         | 0.0000   | 23.767      | 0.272         | 0.0000   |
| Adjusted      |             |               |           |             |               |         |             |               |         |
| BZD           | 0.415       | 0.733         | 0.5710    | -1.416      | 0.964         | 0.1420   | -0.387      | 0.584         | 0.5080   |
| ADep          | 0.167       | 0.459         | 0.7160    | 0.810       | 0.783         | 0.3010   | 0.323       | 0.405         | 0.4250   |
| BZD-Adep      | -0.191      | 0.509         | 0.7080    | -0.520      | 0.781         | 0.5050   | -0.389      | 0.433         | 0.3690   |
| Time          | -0.964      | 0.342         | 0.0050    | -1.039      | 0.591         | 0.0790   | -1.000      | 0.304         | 0.0010   |
| Time²         | -0.314      | 0.052         | 0.0000    | -0.365      | 0.104         | 0.0000   | -0.324      | 0.048         | 0.0000   |
| NPI Total     | -0.025      | 0.010         | 0.0090    | 0.007       | 0.016         | 0.6690   | -0.014      | 0.009         | 0.1050   |
| Age           | 0.012       | 0.040         | 0.7660    | 0.064       | 0.070         | 0.3610   | 0.016       | 0.036         | 0.6650   |
| Sex versus    | -0.922      | 0.674         | 0.1710    | -0.628      | 0.943         | 0.5050   | -0.936      | 0.526         | 0.0750   |
| men           |             |               |           |             |               |         |             |               |         |
| CIRS          | -0.019      | 0.131         | 0.8820    | 0.149       | 0.187         | 0.4260   | 0.108       | 0.108         | 0.3160   |
| ADL           | -1.876      | 0.396         | 0.0000    | -2.900      | 0.550         | 0.0000   | -2.388      | 0.321         | 0.0000   |
| Intercept     | 26.830      | 2.814         | 0.0000    | 26.764      | 4.948         | 0.0000   | 26.794      | 2.720         | 0.0000   |

Notes: Females given as frequencies and (percentages), otherwise mean ± standard deviations. Time was evaluated with its quadratic and linear term. Differences in gender assessed by Pearson's Chi-square test, all other by Student's T-test. Linear mixed models, NPI measured longitudinally and its association with the functional trajectory.
Abbreviations: AD, Alzheimer's disease; ADep, Antidepressants; ADL, Activities of daily living; BZD, Benzodizepines; CIRS, Cumulative Illness Rating Scale; LBD, Lewy bodies dementia; MMSE, Mini-mental state examination; NPI total, Total score of the Neuropsychiatric Inventory. p values < 0.05 are printed in bold.

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CONFLICTS OF INTEREST
The authors have no conflicts of interest to declare. The funders had no role in the design of the study; in the collection, analyses, or interpretation of data; in the writing of the manuscript, or in the decision to publish the results. The views expressed are those of the author(s) and not necessarily those of the NHS, the NIHR, or the Department of Health and Social Care.

DATA AVAILABILITY STATEMENT
The data that support the findings of this study are available from the corresponding author upon reasonable request.

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REFERENCES
1. Orgeta V, Mukadam N, Sommerlad A, Livingston G. The lancet commission on dementia prevention, intervention, and care: a call for action. Ir J Psychol Med. 2019;36(2):85-88.
2. Alzheimer’s Association. Alzheimer’s Disease facts and figures. Alzheimers Dement. 2020;16(2):391-.
3. Mueller C, Ballard C, Corbett A, Aarsland D. The prognosis of dementia with Lewy bodies. Lancet Neurol. 2017;16(5):390-398.
4. Rongve A, Soennesyn H, Skogseth R, et al. Cognitive decline in dementia with Lewy bodies: a 5-year prospective cohort study. BMJ Open. 2016;6:e010357.

5. Borda MG, Soennesyn H, Steves CJ, Osland Vik-Mo A, Pérez-Zepeda MU, Aarsland D. Frailty in older adults with mild dementia: dementia with Lewy bodies and Alzheimer’s disease. Dementia Geriatric Cognitive Disorder Extra. 2019;9(1):176-183.

6. McKeith IG, Boeve BF, Dickson DW, et al. Diagnosis and management of dementia with Lewy bodies: fourth consensus report of the DLB Consortium. Neurology. 2017;89(1):88-100.

7. Reuben DB, Rubenstein LV, Hirsch SH, Hays RD. Value of functional status as a predictor of mortality: results of a prospective study. Am J Med. 1992;93(6):663-669.

8. Bierman AS. Functional status: the six vital sign.

9. Reuben DB, Rubenstein LV, Hirsch SH, Hays RD. Value of functional status as a predictor of mortality: results of a prospective study. Am J Med. 1992;93(6):663-669.

10. Bjerke ...

11. Vik ...

12. Rongve A, Soennesyn H, Skogseth R, et al. Cognitive decline in dementia with Lewy bodies and Alzheimer’s disease. J Neurol Neurosurg Psychiatry. 2014;85:320-325.

13. Hasen SS, Zaidi STR, Nirwan JS, et al. Use of central nervous system (CNS) medicines in aged care homes: a systematic review and meta-analysis. J Clin Med. 2019;8(9):1292.

14. Brandt J, Leong C. Benzodiazepines and Z-drugs: an updated review of major adverse outcomes reported on in epidemiologic research. Drugs. 2017;17(4):493-507.

15. Patoine E, Glynn R, Levin R, Huybrechts KF. Benzodiazepines and the risk of all-cause mortality in older patients. Innov Aging. 2018; 2(Suppl 1):852-853.

16. Hessmann P, Dodel R, Baum E, et al. Prescription of benzodiazepines and related drugs in patients with mild cognitive deficits and Alzheimer’s disease. Pharmaceuticals. 2019;52(02):84-91.

17. Alexopoulos GS. Depression in the elderly. Lancet. 2005;365(9475): 1961-1970.

18. Neutel CJ, Skurtveit S, Berg C. What is the point of guidelines? Benzodiazepine and z-hypnotic use by an elderly population. Sleep Med. 2012;13(7):893-897.

19. Frde Tvete I, Bjørner T, Skomedal T. Risk factors for excessive benzodiazepine use in a working age population: a Nationwide 5-year survey in Norway. Scand J Prim Health Care. 2015;33(4):252-259.

20. Oesterhus R, Aarsland D, Soennesyn H, Rongve A, Selbaek G, Kjøs-
vik SR. Potentially inappropriate medications and drug-drug interactions in home-dwelling people with mild dementia. Int J Geriatr Psychiatry. 2017;32(2):183-192.

21. Dyer AH, Murphy C, Lawlor B, Kennelly SP. Cognitive outcomes of long-term benzodiazepine and related drug (BDZR) use in people living with mild to moderate Alzheimer’s disease: results from NILDAD. J Am Med Dir Assoc. 2020;21(2):194-200.

22. Baek YH, Lee H, Kim WJ, et al. Uncertain association between benzodiazepine use and the risk of dementia: a cohort study. J Am Med Dir Assoc. 2020;21(2):201-211.e202.

23. Aarsland D, Rongve A, Nore SP, et al. Frequency and case identification of dementia with Lewy bodies using the revised consensus criteria. Dement Geriatr Cogn Disord. 2008;26(5):445-452.

24. Vik-Mo AO, Gill LM, Ballard C, Aarsland D. Course of neuropsychiatric symptoms in dementia: 5-year longitudinal study. Int J Geriatr Psychiatry. 2018;33(10):1361-1369.

25. McKhann G, Drachman D, Folstein M, Katzman R, Price D, Stadlan EM. Clinical diagnosis of Alzheimer’s disease: report of the NINCDS-ADRSA work group under the auspices of department of health and human services Task force on Alzheimer’s disease. Neurology. 1984; 34(7):939-944.

26. Emre M, Aarsland D, Brown R, et al. Clinical diagnostic criteria for dementia associated with Parkinson’s disease. Mov Disord. 2007; 22(12):1689-1707. quiz 1837.

27. Skogseth R, Hortobagyi T, Soennesyn H, et al. Accuracy of clinical diagnosis of dementia with Lewy bodies versus neuropsychiatry. J Alzheimers Dis. 2017;59(4):1139-1152.

28. WHO. Collaborating Centre for Drug Statistics Methodology; 2014. https://www.hfi.no/en/hn/drug-who-collaborating-centre-for-drug-statistics-methodology/

29. Helseinformatikk Norsk. Ferdigheter I Dagliglivet - RDRS-2. 2020. https://nhi.no/skjema-og-kalkulatorer/skjema/geriatripleie/ferdigheter-i-dagliglivet-rdrs-2/

30. Linn MW. Rapid disability rating scale-2 (RDRS-2). Psychopharmacol Bull. 1988;24(4):799-780.

31. Borda MG, Aarsland D, Tovar-Rios DA, et al. Neuropsychiatric symptoms and functional decline in Alzheimer’s disease and Lewy body dementia. J Am Geriatr Soc. 2020.

32. Borda MG, Jaramillo-Jimenez A, Tovar-Rios DA, et al. Hippocampal subfields and decline in activities of daily living in Alzheimer’s disease and dementia with Lewy bodies. Neurodegener Dis Manag. 2020.

33. Folstein MF, Folstein SE, McHugh PR. Mini-Mental State” A practical method for grading the cognitive state of patients for the clinician. J Psychiatric Res. 1975;12:189-198.

34. Linn BS, Linn MW, Gurel L. Cumulative illness rating scale. J Am Geriatr Soc. 1968;16(5):622-626.

35. Cummings JL, Mega M, Gray K, Rosenberg-Thompson S, Carusi DA, Gornbein J. The Neuropsychiatric Inventory: comprehensive assessment of psychopathology in dementia. Neurology. 1994;44(12): 2308-2314.

36. Raen I, Selbaek G, Kirkevold Ø, Engedal K, Lerdal A, Bergh S. The reliability and validity of the Norwegian version of the quality of life in late-stage dementia scale. Dement Geriatr Cogn Disord. 2015; 40(3-4):233-242.

37. Scarmeas N, Brandt J, Albert M, et al. Delusions and hallucinations are associated with worse outcome in Alzheimer disease. Arch Neurol. 2005;62(10):1601-1608.

38. Griffin CE, 3rd, Kaye AM, Bueno FR, Kaye AD. Benzodiazepine pharmacology and central nervous system-mediated effects. Ochsner J. 2013;13(2):214-223.
43. Martin P. Coadministration benzodiazepine and antidepressant drugs: the state of art. *Encephale*. 2006;32(5 Pt 1):753-766.

44. Ogawa Y, Takeshima N, Hayasaka Y, et al. Antidepressants plus benzodiazepines for adults with major depression. *Cochrane Database Syst Rev*. 2019;6(6):1-65. https://www.cochranelibrary.com/cdruo/co/14651858.CD001026.pub2/full

45. Fulone I, Silva MT, Lopes LC. Long-term benzodiazepine use in patients taking antidepressants in a public health setting in Brazil: a cross-sectional study. *BMJ Open*. 2018;8(4):e018956.

46. Demyttenaere K, Bonnewyn A, Bruffaerts R, et al. Clinical factors influencing the prescription of antidepressants and benzodiazepines: results from the European study of the epidemiology of mental disorders (ESEMeD). *J Affect Disord*. 2008;110(1-2):84-93.

47. Tien SC, Chan HY, Hsu CC. The factors associated with inappropriate prescription patterns of benzodiazepines and related drugs among patients with dementia. *Psychogeriatrics*. 2020;20(4):447-457. https://onlinelibrary.wiley.com/doi/full/10.1111/psyg.12527

48. American geriatrics society 2015 updated beers criteria for potentially inappropriate medication use in older adults. *J Am Geriatr Soc*. 2015;63(11):2227-2246. https://agsjournals.onlinelibrary.wiley.com/doi/abs/10.1111/jgs.13702

49. Billioti de Gage S, Pariente A, Bégaud B. Is there really a link between benzodiazepine use and the risk of dementia? *Expert Opin Drug Saf*. 2015;14(5):733-747.

50. Pariente A, de Gage SB, Moore N, Bégaud B. The benzodiazepine-dementia disorders link: current state of knowledge. *CNS Drugs*. 2016;30(1):1-7.

51. Mitchell A. Cognitive Screening Instruments: A Practical Approach. In: The mini-mental state examination (MMSE): update on its diagnostic accuracy and clinical utility for cognitive disorders. Cham, Switzerland: Springer International Publishing; 2016. https://doi.org/10.1007/978-3-319-44775-9

52. Kok RM, Reynolds CF, 3rd. Management of depression in older adults: a review. *JAMA*. 2017;317(20):2114-2122.

53. Nishtala PS, Chyou T-y. Zopiclone use and risk of fractures in older people: population-based study. *J Am Med Dir Assoc*. 2017;18(4):368.e361-368.e368.

54. You SC, Walsh CM, Chiodo LA, Ketelle R, Miller BL, Kramer JH. Neuropsychiatric symptoms predict functional status in Alzheimer’s disease. *J Alzheimers Dis*. 2015;48(3):863-869.

55. Mallo SC, Patten SB, Ismail Z, et al. Does the neuropsychiatric inventory predict progression from mild cognitive impairment to dementia? A systematic review and meta-analysis. *Ageing Res Rev*. 2020;58:101004.

56. Tseng LY, Huang ST, Peng LN, Chen LK, Hsiao FY. Benzodiazepines, z-hypnotics, and risk of dementia: special considerations of half-lives and concomitant use. *Neurotherapeutics*. 2020;17(1):156-164.

**SUPPORTING INFORMATION**

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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