Received: 20 July 2020 | Revised: 13 October 2020 | Accepted: 27 December 2020

DOI: 10.1002/gps.5494

RESEARCH ARTICLE

International Journal of Geriatric Psychiatry WILEY

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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Funding information
Helse Vest, grant number: 911973

- Benzodiazepines and the combination of benzodiazepines and antidepressants in Alzheimer's disease were associated with greater functional deterioration
- The consumption of antidepressants alone did not show positive or negative significant associations with cognitive or functional decline

1 | INTRODUCTION:

Neurodegenerative disorders, such as dementia, are frequent chronic diseases.[1] Worldwide, around 50 million people have dementia, and there are nearly 10 million new cases every year.[2] Alzheimer's disease (AD) is the most common cause of dementia and contributes to 60%–70% of all cases.[2] Lewy body dementia (LBD) is the second most common type of neurodegenerative dementia and is often underdiagnosed despite showing worse prognosis than AD.[3–5] Functional decline is essential for the diagnosis of dementia and also is one of the most important markers of progression.[6] Functional status depends on several aspects including social, demographic, and health factors. Besides, it is related to morbidity, mortality, and quality of life.[7,8] Thus, it has become an important measurement in the comprehensive geriatric assessment and patient-centered care for older adults.[9] Neuropsychiatric symptoms (NPS) such as depression, anxiety, agitation, and sleep disturbances are very common in dementia[10,11] and have large consequences for quality-of-life, the progression of the disease, and carer burden.[12,13] Psychotropic drugs are commonly prescribed to treat NPS, although with uncertain clinical potency and high risk of adverse effects in older adults with dementia.[14–16] Prescription of such medications is still high, a recent meta-analysis in European nursing homes reported a frequency of use of 44.8% for benzodiazepines (BZD) and 38.3% for antidepressants (ADep).[17] In older adults BZD prescription is associated with adverse events, such as dizziness, syncope, falls, fractures, hospitalizations, delirium, and increased mortality.[18,19] Thus, they should be carefully managed and preferably avoided particularly in individuals with high comorbidity, frailty, and dementia.[14] The evidence regarding the ADep benefits in mood symptoms in people with dementia is mixed and the data are difficult to interpret because of small sample sizes, heterogeneity, and use of multiple outcome measures.[20] But, ADep especially in older adults could also enhance the risk of adverse events, such as falls.[16,21] Despite this, long-term prescription of BZD, alone or in combination with another psychotropic drug such as ADep is common in clinical practice, including in the Nordic countries.[22,23] Previous publications from our group have shown that the risk of using potentially inappropriate medications in older adults with dementia increases with each medication added.[24] Prior research shows that long-term use of BZD combined with tricyclic ADep is related to cognitive deterioration in older adults.[25,26] However, the effect of BZD alone and in combination with ADep (BZD-ADep) on functional decline in people with dementia has been less explored especially in people diagnosed with LBD.

We aim to study the effects of the prescription of BZD and ADep on cognitive and functional decline over 5 years in a mild dementia cohort including subgroups diagnosed with AD and LBD.

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[4,27,28]

Dementia with Lewy bodies (DLB) and Parkinson's Disease Dementia (PDD) groups were combined in an LBD group given pathological and clinical similarities.[6]

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),[29] or DLB[6] and PDD[30] (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.[31]

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).[32] 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 × severity score for the domains. We estimated the frequency × 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, Benzodizepines; 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.[18]

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.[42] BZD induce central nervous system toxicity, generating symptoms such as anterograde amnesia, sedation, drowsiness, motor impairment, inattentiveness, and ataxia.[42] 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[43]

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.[44]

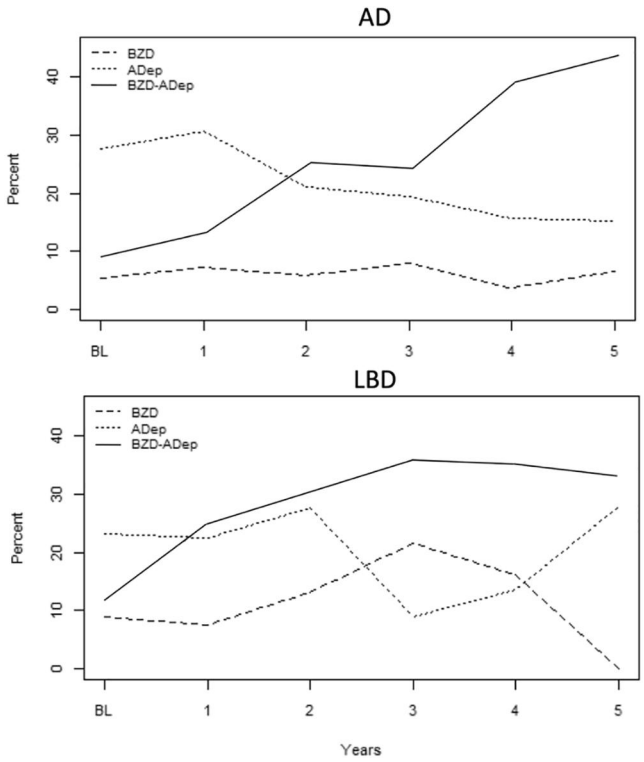

FIGURE 1 Prescription curve of the three groups during the 5 years' follow-up. AD, Alzheimer's disease; ADep, Antidepressants; BZD, benzodiazepines; BZD-ADep, simultaneous consume of benzodiazepines and antidepressants; LBD, Lewy bodies dementia

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.[17,45] This may explain why BZD alone predicted fewer outcomes than BZD-ADep.

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

Functional Decline									
	AD			LBD			Total		
Variables	Estimation	Standard Error	*p*-value	Estimation	Standard Error	*p*-value	Estimation	Standard Error	*p*-value
No adjusted									
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-Adep	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**
$Time^2$	−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**
Adjusted									
BZD	0.226	0.087	**0.0090**	0.011	0.105	0.9150	0.142	0.066	0.0320
ADep	0.076	0.057	0.1870	0.052	0.097	0.5930	0.073	0.050	0.1450
BZD-Adep	0.165	0.058	**0.0050**	0.251	0.089	**0.0050**	0.218	0.049	**0.0000**
Time	0.241	0.034	**0.0000**	0.290	0.058	**0.0000**	0.259	0.030	**0.0000**
$Time^2$	−0.015	0.006	**0.0100**	−0.023	0.011	**0.0300**	−0.020	0.005	**0.0000**
NPI Total	0.004	0.001	**0.0000**	0.006	0.002	**0.0020**	0.005	0.001	**0.0000**
Age	0.011	0.005	**0.0300**	0.014	0.008	0.0810	0.011	0.004	**0.0100**
Sex versus men	−0.181	0.083	**0.0290**	−0.172	0.109	0.1150	−0.253	0.064	**0.0000**
CIRS	0.015	0.016	0.3420	−0.001	0.022	0.9760	0.020	0.013	0.1070
MMSE	−0.037	0.004	**0.0000**	−0.041	0.006	**0.0000**	−0.040	0.003	**0.0000**
Intercept	1.596	0.368	**0.0000**	1.736	0.599	**0.0040**	1.712	0.320	**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.

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-Adep 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,[20,45,46] and with higher rates of prescription.[46,47]

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.[48] Despite this, the use of BZDs in older adults with or without dementia, in nursing homes or living in community is still prevalent,[22,25,47] 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.[26,49,50] Despite this, in our study, we did not find such association. This could be due to the MMSE is language and memory dependent and thus less sensitive to the earliest changes, especially in the LBD patients.[51]

Some ADep, such as tricyclics, have several adverse effects due to their unspecific action on several receptors.[45,52] However, these medications have been progressively replaced by medications with a better safety profile such as selective serotonin reuptake inhibitors. In this study, ADep alone was not found to have any negative effect on cognitive or functional trajectories.

These results suggest that the functional decline in patients with dementia can be exacerbated by the negative effects of BZDs and

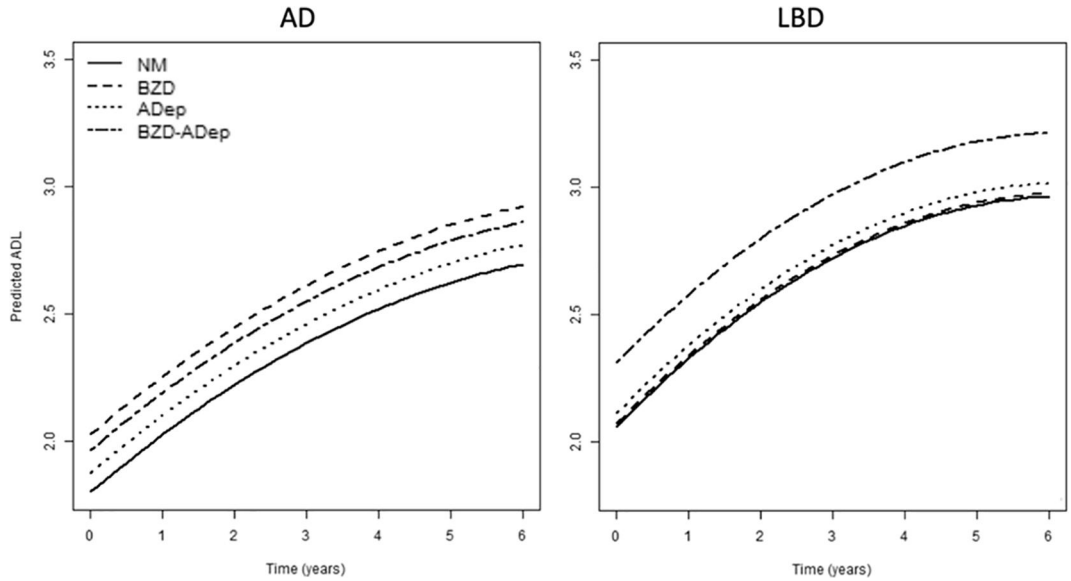

FIGURE 2 Functional trajectories according type of prescription. AD, Alzheimer's disease; ADep, Antidepressants; BZD, benzodiazepines; BZD-ADep, simultaneous consume of benzodiazepines and antidepressants; LBD, Lewy bodies dementia; NM, No BZD or ADep [Correction added on 06 February 2021, after first online publication: The labels in figure 2 were interchanged and have been corrected in this version]

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 (zopiklon = 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.[18,53] There were 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.a. have been correlated with functional and cognitive decline in dementia.[41,54,55] 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.[18,56] The diagnostic procedures were rigorous, and high accuracy has been demonstrated with neuropathological diagnosis.[31] Future studies with larger sample sizes are needed to better understand the effect of psychotropics on function and cognition in people with dementia.

ACKNOWLEDGMENTS

We want to thank all the participants, researchers, and technical staff that have made the DeVest study possible.

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

Cognitive Decline									
	AD			LBD			Total		
Variables	Estimation	Standard Error	*p*-value	Estimation	Standard Error	*p*-value	Estimation	Standard Error	*p*-value
No adjusted									
BZD	0.267	0.676	0.6930	−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**
$Time^2$	−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**
$Time^2$	−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 men	−0.922	0.674	0.1710	−0.628	0.943	0.5050	−0.936	0.526	0.0750
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**	23.674	4.948	**0.0000**	26.794	2.530	**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.

represents independent research supported by the Norwegian government, through hospital owner Helse Vest (Western Norway Regional Health Authority). Also, funded by the National Institute for Health Research (NIHR) Biomedical Research Centre at South London and Maudsley NHS Foundation Trust and King's College London. 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.

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 Disord 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. *J general Intern Med*. 2001;16(11):785-786.
9. Wilberforce M, Challis D, Davies L, Kelly MP, Roberts C, Loynes N. Person-centredness in the care of older adults: a systematic review of questionnaire-based scales and their measurement properties. *BMC Geriatr*. 2016;16(1):63.
10. Bjoerke-Bertheussen BB, Bjoerke-Bertheussen J, Ehrt U, Rongve A, Ballard C, Aarsland D. Neuropsychiatric symptoms in mild dementia with Lewy bodies and Alzheimer's disease. *Dementia Geriatric Cognitive Disord*. 2012;34(1):1-6.
11. Vik-Mo AO, Giil LM, Borda MG, Ballard C, Aarsland D. The individual course of neuropsychiatric symptoms in people with Alzheimer's and Lewy body dementia: 12-year longitudinal cohort study. *Br J Psychiatry*. 2019;216(1):43-48. https://www.cambridge.org/core/journals/the-british-journal-of-psychiatry/article/individual-course-of-neuropsychiatric-symptoms-in-people-with-alzheimers-and-lewy-body-dementia-12year-longitudinal-cohort-study/03170C0BD3CE227967FB7E8D296AC9D0.
12. Rongve A, Vossius C, Nore S, Testad I, Aarsland D. Time until nursing home admission in people with mild dementia: comparison of dementia with Lewy bodies and Alzheimer's dementia. *Int J Geriatr Psychiatry*. 2014;29(4):392-398.
13. Svendsboe E, Terum T, Testad I, et al. Caregiver burden in family carers of people with dementia with Lewy bodies and Alzheimer's disease. *Int J Geriatr Psychiatry*. 2016;31(9):1075-1083.
14. Schmitz A. Benzodiazepines: the time for systematic change is now. *Addiction*. 2020. https://doi.org/10.1111/add.15095.
15. Parikh C. Antidepressants in the elderly: challenges for study design and their interpretation. *Br J Clin Pharmacol*. 2000;49(6):539-547.
16. Ford AH, Almeida OP. Management of depression in patients with dementia: is pharmacological treatment justified? *Drugs Aging*. 2017;34(2):89-95.
17. Hasan 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.
18. Brandt J, Leong C. Benzodiazepines and Z-drugs: an updated review of major adverse outcomes reported on in epidemiologic research. *Drugs R*. 2017;17(4):493-507.
19. Patorno E, Glynn RJ, Levin R, Huybrechts KF. Benzodiazepines and the risk of all-cause mortality in older patients. *Innov Aging*. 2018;2(Suppl 1):852-853.
20. Hessmann P, Dodel R, Baum E, et al. Prescription of benzodiazepines and related drugs in patients with mild cognitive deficits and Alzheimer's disease. *Pharmacopsychiatry*. 2019;52(02):84-91.
21. Alexopoulos GS. Depression in the elderly. *Lancet*. 2005;365(9475):1961-1970.
22. Neutel CI, 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.
23. Fride 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.
24. Oesterhus R, Aarsland D, Soennesyn H, Rongve A, Selbaek G, Kjosavik SR. Potentially inappropriate medications and drug-drug interactions in home-dwelling people with mild dementia. *Int J Geriatr Psychiatry*. 2017;32(2):183-192.
25. 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 NILVAD. *J Am Med Dir Assoc*. 2020;21(2):194-200.
26. 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.
27. 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.
28. Vik-Mo AO, Giil LM, Ballard C, Aarsland D. Course of neuropsychiatric symptoms in dementia: 5-year longitudinal study. *Int J Geriatr Psychiatry*. 2018;33(10):1361-1369.
29. McKhann G, Drachman D, Folstein M, Katzman R, Price D, Stadlan EM. Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA work group under the auspices of department of health and human services Task force on Alzheimer's disease. *Neurology*. 1984;34(7):939-944.
30. 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.
31. Skogseth R, Hortobagyi T, Soennesyn H, et al. Accuracy of clinical diagnosis of dementia with Lewy bodies versus neuropathology. *J Alzheimers Dis*. 2017;59(4):1139-1152.
32. WHO. Collaborating Centre for Drug Statistics Methodology; 2014. https://www.fhi.no/en/hn/drug/who-collaborating-centre-for-drug-statistics-methodology/.
33. Helseinformatikk Norsk. *Ferdigheter I Dagliglivet - RDRS-2. 2020*. https://nhi.no/skjema-og-kalkulatorer/skjema/geriatripleie/ferdigheter-i-dagliglivet-rdrs-2/
34. Linn MW. Rapid disability rating scale-2 (RDRS-2). *Psychopharmacol Bull*. 1988;24(4):799-780.
35. 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.
36. 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.
37. 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.
38. Linn BS, Linn MW, Gurel L. Cumulative illness rating scale. *J Am Geriatr Soc*. 1968;16(5):622-626.
39. 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.
40. Røen I, Selbæk 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.
41. 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.
42. 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/cdsr/doi/10.1002/14651858.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.

How to cite this article: Borda MG, Jaramillo-Jimenez A, Oesterhus R, et al. Benzodiazepines and antidepressants: Effects on cognitive and functional decline in Alzheimer's disease and Lewy body dementia. *Int J Geriatr Psychiatry*. 2021;1–9. https://doi.org/10.1002/gps.5494