Cognitive Outcomes of Long-term Benzodiazepine and Related Drug (BDZR) Use in People Living With Mild to Moderate Alzheimer's Disease

JAMDA 21 (2020) 194–200

JAMDA

journal homepage: www.jamda.com

Original Study

Cognitive Outcomes of Long-term Benzodiazepine and Related Drug (BDZR) Use in People Living With Mild to Moderate Alzheimer's Disease: Results From NILVAD

Adam H. Dyer BA, MBBCh, BAO, MSc [a,b,*], Claire Murphy MD [a], Brian Lawlor PhD [b,c], Sean P. Kennelly PhD [a,b], for the NILVAD Study Group

[a] Department of Age-Related Healthcare, Tallaght University Hospital, Dublin, Ireland
[b] Department of Medical Gerontology, School of Medicine, Trinity College Dublin, Dublin, Ireland
[c] Mercer's Institute for Research on Ageing, St James's Hospital, Dublin, Ireland

Keywords:
Dementia
benzodiazepines
cognition
benzodiazepines and related drugs

A B S T R A C T

Objective: Benzodiazepines and related drugs (BDZRs) have been associated with an increased risk of Alzheimer's disease (AD) in later life. Despite this, it remains unclear whether ongoing BDZR use may further accelerate cognitive decline in those diagnosed with mild to moderate AD.
Design: This study was embedded within NILVAD, a randomized controlled trial of nilvadipine in mild to moderate AD. Cognition was measured at baseline and 18 months using the Alzheimer Disease Assessment Scale, Cognitive Subsection (ADAS-Cog). We assessed predictors of long-term BDZR use and analyzed the effect of ongoing BDZR use on ADAS-Cog scores at 18 months. Additionally, the impact of BDZR use on adverse events, incident delirium, and falls over 18-month follow-up was assessed adjusting for relevant covariates.
Setting and Participants: 448 participants with mild to moderate AD recruited from 23 academic centers in 9 European countries.
Results: Overall, 14% (62/448) were prescribed an ongoing BDZR for the study duration. Increasing total number of (non-BDZR) medications was associated with a greater likelihood of BDZR prescription (odds ratio 1.16, 95% confidence interval 1.05-1.29). At 18 months, BDZR use was not associated with greater cognitive decline on the ADAS-Cog controlling for baseline ADAS-Cog scores, age, gender, study arm, and other clinical covariates ($\beta = 1.62, -1.34$ to 4.56). However, ongoing BDZR use was associated with a greater likelihood of adverse events [incidence rate ratio (IRR) 1.19, 1.05-1.34], incident delirium (IRR 2.31, 1.45-3.68), and falls (IRR 1.66, 1.02-2.65) over 18 months that persisted after robust adjustment for covariates.
Conclusions and Implications: This study found no effect of ongoing BDZR use on ADAS-Cog scores in those with mild to moderate AD over 18 months. However, ongoing use of these medications was associated with an increased risk of adverse events, delirium, and falls. Thus, BDZR use should be avoided where possible and deprescribing interventions should be encouraged in older adults with AD.

Benzodiazepines and related drugs (BDZRs) remain one of the most frequently prescribed classes of psychotropic medication in older adults and are commonly used as anxiolytics, sedatives, hypnotics, and anticonvulsants.[1] Long-term use of BDZRs has been found to be associated with an increased risk of dementia and Alzheimer's disease (AD) in several large case-control studies and subsequent meta-analyses.[2–10] The American Geriatrics Society has recommended to avoid all use of BDZRs in older adults, and in particular in those with dementia or cognitive impairment.[11] Despite this, a significant minority of patients with dementia remain on BDZRs.[12–15] However, it is not clear what specific effects ongoing BDZR use has

Funding from the NILVAD study was from the European Commission Framework 7 Programme Health Theme Collaborative Project (grant 279093; PI: Brian Lawlor).
The authors declare no conflicts of interest.
The full author list of the NILVAD Study Group is listed at the end of the article.
* Address correspondence to Adam H. Dyer, BA, MBBCh, BAO, MSc, Department of Age-Related Healthcare, Tallaght University Hospital, Dublin 24, Ireland.
E-mail address: dyera@tcd.ie (A.H. Dyer).

https://doi.org/10.1016/j.jamda.2019.08.006
1525-8610/

on cognitive function in AD, where those affected may be more vulnerable to the adverse cognitive consequences of these drugs.

Few studies have specifically examined cognitive performance (as opposed to AD diagnoses) in adults exposed to BDZRs. In a German study for instance, there was no link between BDZR use and cognitive performance.[16] A further study of more than 5000 participants concluded that although BDZR use was associated with poorer baseline cognition, and overall cognitive decline was similar in those using BDZRs and non-users.[17] Similarly, in the "Three City Study," chronic use was associated with poorer cognitive function, but users did not show an accelerated rate of decline at 7 years.[18] Thus, although lifetime BDZR use appears to be a risk factor for developing AD, the effect of BDZRs on cognitive trajectories is less clear and has not been explored in AD.

BDZRs have many adverse effects beyond those on the central nervous system (CNS). BDZR use has been linked to an increased risk of falls, fractures, and syncope.[19,20] BDZRs are associated with falls owing to their effects on reaction time, effects on balance and gait as well as impaired vision,[19] and have also been linked to an increased fracture risk.[21] Further, BDZRs have also been associated with an increased risk of mortality in older patients (although causality remains difficult to prove).[22]

Although the long-term cognitive effects of BDZRs are unclear from the literature, a significant body of work has demonstrated that BDZR use is associated with an increased risk of delirium, an acute disturbance in cognitive function.[23] This is particularly true for vulnerable older patients on admission to acute hospital settings.[24] Although this has been well assessed in acute hospital environments in unselected older patients, the specific association between BDZRs and delirium in those with a diagnosis of dementia, who may represent a particularly vulnerable group, is less well explored.

The aim of the current study was to evaluate whether ongoing BDZR use was associated with accelerated cognitive decline in mild to moderate AD. To our knowledge, the impact of ongoing long-term BDZR use on cognition in mild to moderate AD has never been assessed. Additionally, we sought to assess if the potential association between BDZRs and accelerated cognitive decline was dependent on APOE $\varepsilon 4$ carrier status, one of the most significant AD risk factors. Further, we aim to explore whether previous associations observed between ongoing BDZR use and both delirium and falls are seen in those with mild to moderate AD, who may represent a particularly vulnerable group.

Methods

This is a longitudinal analysis of data from NILVAD, a Europe-wide, multicenter randomized clinical trial of the antihypertensive nilvadipine in mild to moderate AD. We examined the relationship between ongoing BDZR use and cognitive function at 18-month follow-up in addition to the effect of BDZR use on adverse events, delirium, and falls at 18 months.

Study Design

Participants with mild to moderate AD were recruited from 23 academic centers (universities) across 9 European Countries (France, Greece, the Netherlands, Hungary, Italy, Sweden, the United Kingdom, Ireland, and Germany). The NILVAD trial (Clincaltrials.gov NCT02017340; EudraCT number 2012-002764-27) assigned patients to either nilvadipine 8 mg once daily or placebo for a total duration of 18 months. The full trial protocol in addition to the main trial results has been published elsewhere.[25,26] The full study protocol was granted ethical approval from the appropriate national competent authorities, independent ethics committees, and institutional review boards for all study sites.

Inclusion and Exclusion Criteria

Detailed inclusion and exclusion criteria were published as part of the main study protocol.[25] Briefly, inclusion criteria were men and women aged 50 years or older with a diagnosis of Alzheimer's disease [as per the National Institute of Neurological and Communicative Disorders and Stroke/Alzheimer's Disease Criteria (NINCDS-ADRDA)]. Included patients had a standardized Mini-Mental State Examination (MMSE) score between 12 and 26. Patients were excluded if they had comorbid dementia due to other neurologic disorders, history of significant head trauma, known structural brain abnormalities, or any other condition known to interfere with cognitive function. Patients taking a beta-blocker/calcium channel blocker or with significant cardiovascular disease were excluded (because of the nature of the study drug). Similarly, patients currently (or within the past year) meeting criteria for drug or alcohol abuse or dependence were excluded. Finally, patients with significant renal impairment (estimated glomerular filtration rate <30 mL/min) or severe hepatic impairment (liver cirrhosis) were also excluded.

Medication and Benzodiazepine Use

Medication lists were obtained from patients at baseline and reviewed at each study visit to assess whether patients were continuing to use the same medications. Anatomical Therapeutic Classification (ATC) codes were assigned to each medication. BDZRs were identified by study investigators using the classes N03AE, N05BA, N05CD, and N05CF, which include benzodiazepine drugs and related sedative hypnotics (or "z-drugs").[3,4] For the current study, ongoing BDZR use was defined as the use of 1 of these agents for the entire 18-month duration of the study. We excluded short-term/intermittent BDZR use from the current analysis. Finally, to calculate the total number of non-BDZR medications, BDZR medications were removed from each participant's medication list, and the total number of medications excluding BDZRs calculated.

Cognitive Assessment

Cognitive assessment was performed at baseline and follow-up using the Alzheimer's Disease Assessment Scale, Cognitive Subsection (ADAS-Cog). Change in the ADAS-Cog score over 18 months was the primary cognitive outcome for the current analysis.

Adverse Events, Falls, and Delirium

Given previous evidence for the adverse effects of BDZR use in older patients, we assessed the impact of BDZR use on adverse events, falls, and delirium. The total number of adverse events was calculated for each participant using the main trial adverse events log. This log was updated at each trial visit where new adverse events were reported using the adverse events reporting interview.

Delirium was identified retrospectively by interview at each follow up study visit in relation to all reported adverse events between study visits. This was done using an adapted version of the Family Confusion Assessment Method.[27] Based on this assessment, a trained study assessor concluded whether it was likely or not that the patient had delirium at the time of the adverse event. Incident delirium events were calculated individually for each patient.

Adverse event logs were reviewed in duplicate by 2 gerontology-trained research physicians (A.H.D. and C.M.) in order to identify incident falls over the study period. The number of fall-related events was again summed for each participant to examine the relationship between ongoing BDZR use and incident falls. Records of serious adverse events were also extracted and the relationship between BDZR use and serious adverse events was analyzed based on standard definitions previously detailed.[25]

Other Measures

Baseline demographic and medical history variables were obtained from each patient at initial assessment and included a full medical history, ongoing medical comorbidities, and ongoing medications, as above. Briefly, patients and caregivers were asked for a list of current medical comorbidities, which were cross-checked with medical records. Comorbidities were then coded as per the International Classification of Diseases (ICD) coding. The total number of medical comorbidities was then calculated for each patient. Additionally, variables known to impact on cognition were obtained, such as years since AD diagnosis ("diagnosis duration"), in addition to total years of formal education. Further, AD severity was assessed using the Clinical Dementia Rating—sum of boxes (CDR-sb) scale. This was considered separate from the ADAS-Cog and was a gated co-primary endpoint in the initial trial. We used CDR-sb score as an indicator of overall dementia severity in the current study.

Statistical Analysis

All analysis for the current study was carried out using Stata, version 15.0 (StataCorp, College Station, TX). Statistical significance was considered as $P < .05$.

We reported descriptive statistics as means and standard deviations or as medians with interquartile ranges. We calculated the overall prevalence of BDZR use based on those prescribed a BDZR for the entire 18-month duration of the study as detailed above. For univariate analysis of between-group differences comparing those with ongoing BDZR use to nonusers, we used *t* tests, Wilcoxon rank-sum, and chi-square tests as appropriate. A chi-square statistic was used to assess between-country differences. In order to analyze the predictors of ongoing BDZR use, we used binary logistic regression and presented results as adjusted odds ratios (ORs) with 95% confidence intervals (CIs) and *P* values.

We analyzed the effect of ongoing BDZR use on ADAS-Cog score at 18 months using mixed effects linear regression models with country included as a random effect. In the first instance, we tested this association alone with BDZR use as the independent variable and ADAS-Cog score difference at 18 months as the dependent variable (model 1). This was followed by minimal adjustment for age, baseline ADAS-Cog score, gender, and study group (nilvadipine vs placebo, to control for potential effects of study drug) (model 2). Following this, we adjusted for other AD (diagnosis duration, years of education) and general health covariates (total comorbidities and total number of medications) based on known impact on cognitive function (model 3). Analysis was repeated separately in those with mild and moderate AD (based on MMSE score classification) to assess if the effect of BDZR use on cognitive function varied with AD severity. Results of linear models were reported as coefficients with 95% CIs and the associated *P* value.

In order to analyze any APOE allele–dependent effect of ongoing BDZR use on cognition, we performed a subgroup analysis in those with APOE genotype data available as per the main study protocol.[25] APOE ε4 carrier status was defined as carrying 1 or more APOE ε4 allele. We reran models 1 to 3 above and created an interaction term between APOE ε4 carrier status and ongoing benzodiazepine use. The interaction was tested as the association between the APOE ε4 carrier status × ongoing BDZR use interaction term as the independent variable and the change in ADAS-Cog score at 18 months as the dependent variable.

In order to assess the relationship between BDZR use and adverse events, serious adverse events, falls, and delirium, we used multivariate Poisson regression. We first tested associations unadjusted (model 1). Following this, we adjusted for age, gender, study group, duration of AD, baseline cognition (ADAS-Cog score), and AD severity (CDR-sb score) (model 2). Finally, we adjusted for total number of medications (excluding BDZRs) and total number of medical comorbidities (model 3). Incidence rate ratios were calculated and 95% CIs reported. In each instance where Poisson regression was used, we carried out a negative binomial regression to compare model fit and assess for overdispersion.

Results

Study Participants

Of 448 participants, just under two-thirds (62.28%) were female and mean age was 72.46 years [standard deviation (SD) 8.2]. Median number of years since AD diagnosis was 1.09 years [interquartile range (IQR) 0.47-2.26] and the median years since AD symptom onset was 3.7 years (IQR 2.45-5.42). In terms of cognitive profile, the median MMSE score of included patients at initial assessment was 21 (IQR 18-24) and the mean baseline ADAS-Cog score was 34.08 (SD 10.53). Based on initial MMSE assessment (where MMSE score 10-20 = moderate and >20 = mild), the majority of patients had mild AD (63.53%, n = 284), with the remainder having moderate AD. With regard to dementia severity, the median CDR-sb score was 4.5 (IQR 3-6.5). The overall median number of medications per patient was 5 (IQR 3-7) and the median number of medical comorbidities was 4 (IQR 2-5). Of the 448 who completed the study, 413 (92.19%) had a full ADAS-Cog assessment at 18 months.

Prevalence and Predictors of BDZR Use

Of the 448 participants, 62 (13.84%) were prescribed an ongoing BDZR. Characteristics of patients prescribed an ongoing BDZR vs those not prescribed one are detailed in Table 1 with the appropriate statistics from univariate analysis. Notably, the only significant difference

Table 1
Baseline Characteristics of Those With Ongoing BDZR Use

Characteristic	BDZR Use (n = 62)	No BDZR Use (n = 386)	*P* Value
Age, y, mean (SD)	72.36 (7.9)	72.96 (8.3)	.72
Study Group, % (n) on nilvadipine	61.2 (38)	48.44 (187)	.06
Sex, % (n) female	69.35 (43)	61.19 (236)	.15
Diagnosis duration, y, median (IQR)	1.44 (0.55-2.82)	1.31 (0.54-2.66)	.15
Symptom duration, y, median (IQR)	4.30 (2.49-6.08)	3.64 (2.45-5.32)	.26
Years of formal education, mean (SD)	16.42 (4.12)	16.16 (3.43)	.95
Total (non-BDZR) medications, median (IQR)	6 (4-8)	5 (3-6)	<.001*
Total comorbidities, median (IQR)	4 (2-5)	3 (2-5)	.09
MMSE screen at baseline, median (IQR)	20 (18-24)	21 (18-24)	.52
Initial ADAS-Cog score, mean (SD)	33.75 (10.43)	34.14 (10.56)	.40
Initial CDR-Sb score, median (IQR)	4.75 (4-7)	4.5 (3-6.5)	.09

Univariate analysis of between-group differences at baseline of those prescribed an ongoing BDZR vs those not prescribed an ongoing BDZR. For univariate analysis, *t* tests, Wilcoxon rank-sum tests, and chi-square tests were used as appropriate.
*$P < .05$.

Table 2
Multivariate Analysis of Ongoing BDZR Use

Characteristic	OR (95% CI)	*P* Value
Age, y	0.97 (0.94, 1.01)	.10
Study group	1.61 (0.95, 2.73)	.08
Sex, female	1.43 (0.82, 2.52)	.21
Diagnosis duration, y	1.05 (0.89, 1.26)	.56
Symptom duration, y	1.04 (0.92, 1.17)	.54
Years of formal education	0.98 (0.91, 1.06)	.63
Total (non-BDZR) medications	1.17 (1.06, 1.29)	.002*
Total comorbidities	0.97 (0.94, 1.02)	.82
Initial MMSE score	0.99 (0.95, 1.01)	.85
Initial ADAS-Cog score	0.98 (0.94, 1.02)	.21
Initial CDR-Sb score	1.10 (0.96, 1.26)	.16

Increasing number of overall medications was the only significant predictor of benzodiazepine prescription.
*$P < .05$.

on univariate analysis was a higher number of (non-BDZR) medications in those prescribed a BDZR ($z = 3.75$, $P < .001$, Wilcoxon rank-sum). On logistic regression of ongoing BDZR prescription, the total number of non-BDZRs was associated with an increased likelihood of BDZR use (OR 1.16, 1.05-1.29, $P = .002$). Multivariate analysis are presented in Table 2.

Of those prescribed a BDZR, the most common drugs prescribed were as follows: alprazolam (n = 13; 20.97%), oxazepam (n = 10; 16.13%), zolpidem (n = 9; 14.52%), lorazepam (n = 8; 12.9%), and bromazepam (n = 5; 8.06%). No participant was prescribed multiple ongoing BDZRs. These was a significant difference in ongoing BDZR use by country ($\chi^2 = 27.75$, $P < .001$). Ongoing BDZR use was highest in France (29.63%, 16/54), Ireland (15.69%, 16/102), the Netherlands (14.45%, 11/76), and Italy (14.29%, 7/49), whereas prevalence was lowest in the United Kingdom (2.63%, 2/55), Greece (6.25%, 5/80), and Sweden (6.25%, 1/16). No patient was prescribed an ongoing BDZR in Germany (0%, 0/6), whereas 4 of the 10 patients from Hungary (40%) were prescribed an ongoing BDZR.

Effect of Ongoing BDZR Use on Cognitive Outcomes at 18 Months

Overall, 352 (78.57%) of patients had ADAS-Cog assessment completed at 18 months in addition to full clinical data available. Overall, the mean change in ADAS-Cog score at 18 months for the whole cohort was +9.07 (SD 9.23), indicating a greater dementia severity. The mean ADAS-Cog score at baseline was 32.93 (SD 9.75), and the mean ADAS-Cog score at 18 months was 41.91 (SD 14.56). Of those with ADAS-Cog completed at 18 months, 51 (13.28%) were prescribed a BDZR for the entire 18-month duration of the study. There was no relationship between ongoing BDZR use and the difference in ADAS-Cog scores at 18 months (β = 0.93, −2.05 to 3.92, $P = .54$) (model 1). Similarly, there was no association under either adjusted model (β = 1.84, −1.04 to 4.71, $P = .21$, for model 2; β = 1.61, −1.39 to 4.56, $P = .28$, for model 3) (Table 3). Analysis repeated separately on those with mild vs moderate AD yielded no significant results.

Effect of BDZR Use-APOE ε4 Carrier Status Interaction on ADAS-Cog Score at 18 Months

Of the 352 patients with full follow-up data and ADAS-Cog assessment at 18 months, 275 had APOE genotype available. Unadjusted, there was no association between APOE ε4 carrier status and BDZR use on cognitive outcomes at 18 months measured using the ADAS-Cog (β = 1.24, −6.13 to 8.61, $P = .741$). Further, under both model 1 (β = 0.51, −6.64 to 7.66, $P = .888$) and model 2 (β = 0.51, −6.64 to 7.66, $P = .888$), there was no interaction between APOE ε4 carrier status and ongoing BDZR use on cognition at 18 months.

Effect of Ongoing BDZR Use on Adverse Events, Delirium, and Falls

Of participants enrolled in the study (n = 448), 62 (13.84%) used a BDZR for the study duration. The median number of adverse events in those with ongoing BDZR use was 5 (IQR 2-8), whereas in non-BDZR users the median was 3 (IQR 1-6). The unadjusted IRR for ongoing BDZR use on adverse events was 1.26 (95% CI 1.12-1.42, $P < .001$) (model 1). This association persisted after controlling under both models (IRR 1.26, 95% CI 1.12-1.42, $P < .001$, for model 2; IRR 1.19, 95% CI 1.05-1.34, $P = .006$, for model 3) (see Table 4).

Overall, 64 patients experienced a serious adverse event (14.29%). There was no association between ongoing BDZR use and serious adverse events in either the unadjusted (IRR = 1.14, 0.74-1.74, $P = .56$) (model 1) or adjusted models (IRR 1.24, 0.81-1.91, $P = .338$, for model 2; IRR 1.13, 0.73-1.75, $P = .598$, for model 3) (see Table 4).

Overall, 51 of the study participants (11.38%) experienced incident delirium identified retrospectively by caregiver interview. Two-fifths of these (41.2%; 21/51) experienced more than 1 episode of delirium. Ongoing BDZR use was significantly associated with incident delirium in the unadjusted model (IRR 2.44, 95% CI 1.56-3.81, $P < .001$) (model 1), which persisted under both adjusted models (IRR 2.45, 95% CI 1.55-3.89, $P < .001$, for model 2; IRR 2.31, 95% CI 1.45-3.68, $P < .001$, for model 3) (see Table 4).

In total, 15.2% (68/448) of the participants reported a fall over the study period. A little less than one-third (32.25%, 22/68) reported more than 1 fall. Ongoing BDZR use was associated with incident falls using unadjusted Poisson regression (IRR 1.73, 1.08-2.78, $P = .022$) (model 1). This finding persisted on both minimal (IRR 1.66, 1.03-2.71, $P = .037$) (model 2) and robust adjustment for covariates (IRR 1.66, 1.02-2.65, $P = .041$) (model 3) (see Table 4).

Table 3
Analysis of the Association Between Ongoing BDZR Drug Use and ADAS-Cog Scores at 18 Months

Predictor	Model 1		Model 2		Model 3	
	β Coeff. (95% CI)	*P* Value	β Coeff. (95% CI)	*P* Value	β Coeff. (95% CI)	*P* Value
Ongoing BDZR use	0.31 (−5.48, 6.11)	.92	1.84 (−1.04, 4.71)	.210	1.61 (−1.34, 4.56)	.284
Age			−0.26 (−0.37, −1.44)	<.001*	−0.23 (−0.35, −0.11)	<.001*
Sex, female			−1.35 (−3.28, 0.58)	.170	−1.09 (−3.02, 0.83)	.266
Baseline ADAS-Cog score			0.15 (0.06, 0.25)	.002*	0.19 (0.09, 0.29)	<.001*
Study group			−0.45 (−2.31, 1.40)	.632	−0.42 (−2.24, 1.41)	.655
Years of formal education					0.18 (−0.06, 0.43)	.142
Diagnosis, y					−0.74 (−1.30, −0.17)	.010
Total comorbidities					0.06 (−0.38, 0.50)	.800
Total medications					0.13 (−0.25, 0.52)	.499

Coeff., coefficient.
*$P < .05$.

Table 4
Analysis of the Association Between Ongoing BDZR Use and Adverse Events, Serious Adverse Events, Delirium, and Falls Over 18 Months

Predictor	Model 1		Model 2		Model 3	
	IRR (95% CI)	*P* Value	IRR (95% CI)	*P* Value	IRR (95% CI)	*P* Value
Adverse events						
Ongoing BDZR use	1.26 (1.12, 1.42)	<.001*	1.26 (1.12, 1.42)	<.001*	1.19 (1.05, 1.34)	.006*
Age, y			1.01 (0.99, 1.08)	.11	1.00 (0.99, 1.01)	.86
Sex, female			1.09 (0.99, 1.19)	.06	1.07 (0.96, 1.17)	.19
Study group			0.92 (0.83, 1.00)	.05	0.92 (0.83, 1.01)	.06
AD duration			1.01 (0.98, 1.04)	.60	1.01 (0.98, 1.03)	.72
ADAS-Cog score (baseline)			1.00 (0.99, 1.01)	.21	1.00 (0.99, 1.01)	.23
CDR-Sb score (baseline)			1.00 (0.98, 1.02)	.95	1.01 (0.98, 1.02)	.92
Total comorbidities					1.01 (0.99, 1.03)	.30
Total medications (non-BDZR)					1.07 (1.05, 1.09)	<.001*
Serious adverse events						
Ongoing BDZR use	1.14 (0.74, 1.42)	.566	1.24 (0.81, 1.90)	.34	1.13 (0.73, 1.74)	.60
Age			1.04 (1.02, 1.06)	<.001*	1.03 (1.01, 1.06)	.004*
Sex, female			0.71 (0.52, 0.98)	.04*	0.66 (0.48, 0.91)	.01*
Study group			0.93 (0.84, 1.01)	.06	0.60 (0.43, 1.04)	.06
AD duration			1.02 (0.93, 1.12)	.64	1.03 (0.94, 1.12)	.60
ADAS-Cog score (baseline)			0.99 (0.95, 1.01)	.18	0.99 (0.99, 1.01)	.22
CDR-Sb score (baseline)			1.02 (0.94, 1.10)	.62	1.03 (0.98, 1.02)	.51
Total comorbidities					0.97 (0.89, 1.05)	.44
Total medications (non-BDZR)					1.20 (1.12, 1.27)	<.001*
Delirium						
Ongoing BDZR use	2.44 (1.56, 3.81)	<.001*	2.45 (1.55, 3.88)	<.001*	2.30 (1.45-3.67)	<.001*
Age			1.01 (0.98, 1.03)	.51	1.01 (0.98, 1.03)	.72
Sex, female			0.71 (0.47, 1.08)	.11	0.70 (0.98, 1.03)	.09
Study group			0.86 (0.57, 1.29)	.46	0.86 (0.57, 1.30)	.47
AD duration			0.95 (0.84, 1.06)	.32	0.95 (0.84, 1.06)	.33
ADAS-Cog score (baseline)			1.00 (0.98, 1.02)	.98	1.00 (0.98, 1.02)	.95
CDR-Sb score (baseline)			1.19 (1.09, 1.31)	<.001*	1.20 (1.09, 1.32)	<.001*
Total comorbidities					0.98 (0.88, 1.07)	.61
Total medications (non-BDZR)					1.10 (1.01, 1.21)	.04*
Falls						
Ongoing BDZR use	1.73 (1.08, 2.78)	.022*	1.66 (1.03, 2.71)	.037*	1.66 (1.02, 2.65)	.041*
Age, y			1.06 (1.03, 1.09)	<.001*	1.06 (1.03, 1.09)	<.001*
Sex, female			1.82 (1.15, 2.88)	.01*	1.82 (1.15, 2.87)	.01*
Study group			1.12 (0.75, 1.67)	.57	1.12 (0.75, 1.66)	.57
AD duration			0.99 (0.87, 1.12)	.89	0.99 (0.87, 1.12)	.88
ADAS-Cog score (baseline)			0.97 (0.94, 0.99)	.03*	0.97 (0.94, 0.99)	.03*
CDR-Sb score (baseline)			1.02 (0.9, 1.13)	.76	1.01 (0.92, 1.13)	.77
Total comorbidities					1.01 (0.92, 1.11)	.83
Total medications (non-BDZR)					1.00 (0.92, 1.10)	.95

*$P < .05$.

Discussion

This is the first study to our knowledge to assess the cognitive consequences of ongoing BDZR use in patients with mild to moderate AD. We found no association between ongoing BDZR use and cognitive scores (ADAS-Cog) at 18 months. However, ongoing use of BDZR medication was associated with adverse events, incident delirium, and falls. Thus, consistent with previous literature, these results support avoidance of BDZR drugs (where possible) in older adults with AD.

The prevalence of ongoing BDZR use in the current study is noteworthy, and largely consistent with previous literature. Although issues around dependence may make BDZR discontinuation difficult, guidelines for titrated reductions exist,[19] and discontinuation has been shown to be safe and feasible in older adults.[28,29] BDZR discontinuation has been associated with shorter lengths of hospitalization in older patients who are frail in addition to a decrease in dementia risk posed by BDZR medications.[28,29] A recent review advocates for a stepwise approach to discontinuation in cognitively intact individuals, with a lower threshold for discontinuation in those with dementia.[30]

In the current study, we found no effect of ongoing BDZR use for 18 months on cognitive outcomes in those with mild to moderate dementia. Although there is significant evidence that lifetime BDZR exposure may be a risk factor for AD in later life, no other study to date has examined the cognitive consequences of continuing these medications in those once a diagnosis of AD has been made. Interestingly, our results are consistent with several well-conducted previous studies that have failed to demonstrate an effect on the rate of cognitive decline, even though BDZRs have been associated with poorer cognitive scores.

Strikingly, ongoing BDZR use was associated with overall adverse events, delirium, and falls in the current study. These findings are in keeping with previous studies but are nonetheless highly clinically significant. Our findings are consistent with recommendations such as those from the American Geriatrics Society that BDZR use should be continue to be avoided in older adults and particularly in those with AD.[11] Given that the current study was conducted in those who were able to meet the robust inclusion criteria, it is more than likely that the prevalence of BDZRs in the AD population as a whole is much greater.

An interesting observation from the current study is the significant variance between country BDZR prescribing, varying from, for instance, <3% in the United Kingdom to nearly one-third in France. The reasons for this observation could be numerous. One is differences in national guidelines and practice. However, well-accepted criteria for potentially inappropriate medication use in older patients all discourage the long-term use of BDZR medications in older adults.

This study has several noteworthy strengths. First, the high level of complete follow-up and the high proportion of patients with full

cognitive assessment is a significant strength. In particular, the detailed information available on BDZR use over the 18-month study period in addition to the detailed cognitive assessment that was available enabled us to specifically examine the effects of ongoing BDZR use on cognitive scores at 18 months. Further, the detailed information available on adverse events and delirium obtained from informant interview (using the Family Confusion Assessment Method) enabled us to tease out the deleterious health consequences of ongoing BDZR use in this vulnerable population.

There are some limitations to the current study. Although the study was conducted over 18 months, we cannot rule out that a longer duration of follow-up may yield different results. Delirium occurrence was retrospectively reported by carers rather than directly observed, and given the subtleties of hypoactive presentations of delirium, this may have resulted in an underidentification of delirium by relatives and carers. Despite this, our research question was to assess the impact of ongoing BDZR use on cognition at 18 months, which was quantifiable because of the high fidelity of the available information.

An important limitation of the current study is that a little more than one-fifth of patients did not have an ADAS-Cog assessment completed at 18 months, which may introduce a source of bias. However, this is a common limitation of all longitudinal research studies and clinical trials. Similarly, it is important to highlight that participants included in the current study represent those who met the inclusion criteria, and our findings may have limited applicability to more varied clinical populations. However, in assessing those with mild to moderate AD, we aimed to assess a particularly vulnerable group and our study highlights the adverse effects of ongoing BDZR use in this population.

Conclusion and Implications

The current study found that ongoing BDZR use in those with mild to moderate AD was not associated with accelerated cognitive decline. However, use was significantly associated with adverse events, incident delirium, and falls. Our results add to the mounting evidence of the adverse consequences of ongoing BDZR use in this population and support previous guidelines aimed at discontinuation in older adults, particularly in those with AD.

Acknowledgments

NILVAD Study Group

Brian Lawlor, Mercer's Institute for Research on Ageing, St. James's Hospital and Department of Medical Gerontology, Trinity College, Dublin, Ireland; Ricardo Segurado, CSTAR and School of Public Health, Physiotherapy and Sport Science, University College Dublin (UCD), Dublin, Ireland; Sean Kennelly, Department of Age Related Healthcare, Tallaght Hospital, Dublin 24, and Department of Medical Gerontology, Trinity College Dublin; Marcel G. M. Olde Rikkert, Department of Geriatric Medicine, Radboudumc Alzheimer Center, Donders Institute of Medical Neurosciences, Radboudumc, Nijmegen, the Netherlands; Robert Howard, Division of Psychiatry, University College London and King's College London; Florence Pasquier, CHU Lille, Univ. Lille, DISTALZ Laboratory of Excellence, F-59000 Lille, France; Anne Börjesson-Hanson, Department of Psychiatry and Neurochemistry, Institute of Neuroscience and Physiology, Sahlgrenska Academy, University of Gothenburg; Magda Tsolaki, Papanikolaou General Hospital of Thessaloniki, Greece; Ugo Lucca, Laboratory of Geriatric Neuropsychiatry, IRCCS Istituto di Ricerche Farmacologiche Mario Negri, Milano, Italy; D. William Molloy, University College Cork Centre for Gerontology and Rehabilitation, Cork, Ireland; Robert Coen, Mercer's Institute for Research on Ageing, St. James's Hospital, Dublin, Ireland; Matthias W. Riepe, Department of Geriatrics and Old Age Psychiatry, Psychiatry II, Ulm University at BKH Günzburg, Germany; János Kálmán, Department of Psychiatry, University of Szeged, Hungary; Rose Anne Kenny, Department of Medical Gerontology, Trinity College Dublin (TCD), Dublin, Ireland; Fiona Cregg, Department of Medical Gerontology, Trinity College Dublin (TCD), Dublin, Ireland; Sarah O'Dwyer, Mercer's Institute for Research on Ageing, St. James's Hospital, Dublin, Ireland; Cathal Walsh, Health Research Institute and MACSI, Department of Mathematics and Statistics, University of Limerick, Ireland; Jessica Adams, Department of Old Age Psychiatry, King's College London; Rita Banzi, Laboratory of Geriatric Neuropsychiatry, IRCCS Istituto di Ricerche Farmacologiche Mario Negri, Milano, Italy; Laetitia Breuilh, CHU Lille, Univ. Lille, DISTALZ Laboratory of Excellence, F-59000 Lille, France; Leslie Daly, CSTAR and School of Public Health, Physiotherapy and Sport Science, University College Dublin (UCD), Dublin, Ireland; Suzanne Hendrix, Pentara Corporation, 2180 Claybourne Avenue, Salt Lake City, Utah; Paul Aisen, Department of Neurology, University of Southern California; Siobhan Gaynor, Molecular Medicine Ireland (MMI), Dublin, Ireland; Ali Sheikhi, Health Research Institute and MACSI, Department of Mathematics and Statistics, University of Limerick, Ireland; Diana G. Taekema, Department of Geriatric Medicine, Rijnstate Hospital, Arnhem, the Netherlands; Frans R. Verhey, Department of Psychiatry and Neuropsychology, School of Mental Health and Neuroscience, Alzheimer Center Limburg, Maastricht University, Maastricht, the Netherlands; Raffaello Nemni, IRCCS Don Gnocchi Foundation-University of Milan, Italy; Flavio Nobili, Dept. of Neuroscience (DINOGMI), University of Genoa, and IRCCS AOU Polyclinic, Hospital San Martino, Genoa, Italy; Massimo Franceschi, Neurology Department, Multimedica, Castellanza, Italy; Giovanni Frisoni, Centro San Giovanni di Dio—IRCCS Fatebenefratelli, Brescia, Italy; Orazio Zanetti, Centro San Giovanni di Dio—IRCCS Fatebenefratelli, Brescia, Italy; Anastasia Konsta, Aristotle University of Thessaloniki (AUTH), First Psychiatric Department, Papageorgiou General Hospital, Greece; Orologas Anastasios, Ahepa University General Hospital of Thessaloniki, Greece; Styliani Nenopoulou, Papanikolaou General Hospital of Thessaloniki, Greece; Fani Tsolaki-Tagaraki, Papanikolaou General Hospital of Thessaloniki, Greece; Magdolna Pakaski, Department of Psychiatry, University of Szeged, Hungary; Olivier Dereeper, Centre Hospitalier de Calais, France; Vincent de la Sayette, Centre Hospitalier Universitaire de Caen, France; Olivier Sénéchal, Centre Hospitalier de Lens, France; Isabelle Lavenu, Centre Hospitalier de Béthune, France; Agnès Devendeville, Centre Hospitalier Universitaire d'Amiens, France; Gauthier Calais, Groupement des Hôpitaux de l'Institut Catholique de Lille (GHICL), France; Fiona Crawford, Archer Pharmaceuticals, Sarasota, Florida, and Roskamp Institute, Sarasota, Florida; Michael Mullan, Archer Pharmaceuticals, Sarasota, Florida, and Roskamp Institute, Sarasota, Florida, Pauline Aalten, PhD, Department of Psychiatry and Neuropsychology, School of Mental Health and Neurosciences, Alzheimer Center Limburg, Maastricht University, Maastricht, the Netherlands; Maria A. Berglund, RN, Sahlgrenska University Hospital, Gothenburg, Sweden; Jurgen A. Claassen MD, PhD, Department of Geriatric Medicine, Radboudumc Alzheimer Center, Donders Institute of Medical Neurosciences, Radboudumc, Nijmegen, the Netherlands; Rianne A. De Heus, MSc, Department of Geriatric Medicine, Radboudumc Alzheimer Center, Donders Institute of Medical Neurosciences, Radboudumc, Nijmegen, the Netherlands; Daan L. K. De Jong, MSc, Department of Geriatric Medicine, Radboudumc Alzheimer Center, Donders Institute of Medical Neurosciences, Radboudumc, Nijmegen, the Netherlands; Olivier Godefroy, MD, PhD, Centre Hospitalier Universitaire d'Amiens, France; Siobhan Hutchinson, MD, St. James's Hospital, Dublin, Ireland; Aikaterini Ioannou, MD, 1st Department of Neurology, Ahepa University General Hospital, Aristotle University of Thessaloniki, Greece; Michael Jonsson, MD, PhD, Department of Psychiatry and Neurochemistry, Institute of Neuroscience and Physiology, Sahlgrenska Academy, University of Gothenburg, Sweden; Annette Kent, PhD, Trinity College Dublin (TCD), Dublin, Ireland; Jürgen Kern MD, PhD,

Department of Psychiatry and Neurochemistry, Institute of Neuroscience and Physiology, Sahlgrenska Academy, University of Gothenburg, Sweden; Petros Nemtsas, MD, PhD, 1st Department of Neurology, Ahepa University General Hospital, Aristotle University of Thessaloniki, Greece; Minoa-Kalliopi Panidou, BSc, MA, 1st Department of Neurology, Ahepa University General Hospital, Aristotle University of Thessaloniki, Greece; Laila Abdullah, PhD, Roskamp Institute, Sarasota, Florida; Daniel Paris, PhD, Roskamp Institute, Sarasota, Florida; Angelina M. Santoso, MD, MSc, Department of Geriatric Medicine, Radboudumc Alzheimer Center, Donders Institute of Medical Neurosciences, Radboudumc, Nijmegen, the Netherlands; Gerrita J. van Spijker, MSc, Department of Geriatric Medicine, Radboudumc Alzheimer Center, Donders Institute of Medical Neurosciences, Radboudumc, Nijmegen, the Netherlands; Martha Spiliotou MD, PhD, 1st Department of Neurology, Ahepa University General Hospital, Aristotle University of Thessaloniki, Greece; Georgia Thomoglou, BSc, 1st Department of Neurology, Ahepa University General Hospital, Aristotle University of Thessaloniki, Greece; and Anders Wallin, MD, Department of Psychiatry and Neurochemistry, Institute of Neuroscience and Physiology, Sahlgrenska Academy, University of Gothenburg, Sweden.

References

1. Picton JD, Brackett Marino A, Nealy KL. Benzodiazepine use and cognitive decline in the elderly. Am J Health Syst Pharm 2018;75:e6–e12.
2. Gray SL, Dublin S, Yu O, et al. Benzodiazepine use and risk of incident dementia or cognitive decline: prospective population based study. BMJ 2016;352:i90.
3. Billioti de Gage S, Moride Y, Ducruet T, et al. Benzodiazepine use and risk of Alzheimer's disease: Case-control study. BMJ 2014;349:g5205.
4. Tapianinen V, Taipale H, Tanskanen A. The risk of Alzheimer's Disease associated with benzodiazepines and related drugs: A nested case-control study. Acta Psychiatr Scand 2018;138:91–100.
5. He Q, Chen X, Tang W, et al. Risk of dementia in long-term benzodiazepine users: Evidence from a meta-analysis of observational studies. J Clin Neurol 2019;15:9–19.
6. Zhong GC, Wang Y, Zhang Y, Zhao Y. Association between benzodiazepine use and dementia: A meta-analysis. PloS One 2015;10:e0127836.
7. Gallacher J, Elwood P, Pickering J, et al. Benzodiazepine use and risk of dementia: Evidence from the Caerphilly Prospective Study (CaPS). J Community Health 2012;66:869–873.
8. Wu CS, Wang SC, Chang IS, Lin JM. The association between dementia and long term benzodiazepine in the elderly: Nested case-control study using claims data. Am J Geriatr Psychiatry 2009;17:614–620.
9. Gomm W, vonHolt K, Thome F, et al. Regular benzodiazepine and z-substance use and risk of dementia: An analysis of German Claims data. J Alzheimer's Dis 2016;54:801–808.
10. Imfield P, Bodmer M, Jick SS, Meier CR. Benzodiazepine use and risk of developing Alzheimer's disease or vascular dementia: A case-control analysis. Drug Saf 2015;38:909–919.
11. American Geriatrics Society 2015 Beers Criteria Update Expert Panel. American Geriatrics Society 2015 Updated Beers Criteria for potentially inappropriate medication use in older adults. J Am Geriatr Soc 2015;63:2227–2246.
12. Defrancesco M, Marksteiner J, Fleischacker WW, Blasko I. Use of benzodiazepines in Alzheimer's disease: A systematic review of the literature. Int J Neuropsychopharmacol 2015;18:pyv055.
13. Taipale H, Koponen M, Tanskanen A, et al. Long-term use of benzodiazepines and related drugs among community-dwelling individuals with and without Alzheimer's disease. Int Clin Psychopharmacol 2015;30:202–208.
14. 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;52:84–91.
15. Hessmann P, Zeidler J, Neubauer S, et al. Continuity of treatment with benzodiazepines in dementia patients: An analysis of German health insurance claims data. Int Clinl Psychopharmacol 2018;33:282–289.
16. Grande G, Tramacere I, Vetrano DL, et al. Use of benzodiazepines and cognitive performance in primary care patients with first cognitive complaints. Int Psychogeriatr 2018;30:597–601.
17. Zhang Y, Zhou X, Meranus DH, et al. Benzodiazepine use and cognitive decline in elderly with normal cognition. Alzheimer Dis Asoc Disord 2016;30:113–117.
18. Mura T, Proust-Lima C, Akbaraly T, et al. Chronic use of benzodiazepines and latent cognitive decline in the elderly: Results from the Three-city study. Eur Neuropsychopharmacol 2013;23:212–223.
19. Markota M, Rummans TA, Bostwick JM, Lapid MI. Benzodiazepine use in older adults: Dangers, management, and alternative therapies. Mayo Clin Proc 2016;19:1632–1639.
20. Gerlach LB, Wiechers IR, Maust DT. Prescription benzodiazepine use among older adults: A critical review. Harvard Rev Psychiatry 2018;26:264–273.
21. Saarelainen L, Tolppanen AM, Koponen M, et al. Risk of hip fracture in benzodiazepine users with and without Alzheimer disease. JAMDA 2017;18:87.e15–87.e21.
22. Palmaro A, Dupouy J, Lapeyre-Mestre M. Benzodiazepines and risk of death: Results from two large cohort studies in France and the UK. Eur Neuropsychopharmacol 2015;25:1566–1577.
23. Inouye SK, Charpentier PA. Precipitating factors for delirium in hospitalized elderly persons. Predictive model and inter-relationship with baseline vulnerability. JAMA 1996;275:852–857.
24. Ahmed S, Leurent B, Sampson EL. Risk factors for incident delirium among older people in acute hospital medical units: A systematic review and meta-analysis. Age Ageing 2014;43:326–333.
25. Lawlor B, Kennelly S, O'Dwyer S, et al. NILVAD protocol: A European multicentre double-blind placebo-controlled trial of nilvadipine in mild-to-moderate Alzheimer's disease. BMJ Open 2014;4:e00634.
26. Lawlor B, Segurado R, Kennelly S, et al. Nilvadipine in mild to moderate Alzheimer disease: A randomised controlled trial. PLoS Med 2018;15:e1002660.
27. Steis MR, Evans L, Hirschman KB, et al. Screening for delirium using family caregivers: Convergent validity of the Family Confusion Assessment Method and Interviewer-Rated Confusion Assessment Method. J Am Geriatr Soc 2012;60:2121–2126.
28. Yokoi Y, Misal M, Oh E, et al. Benzodiazepine discontinuation and patient outcome in a chronic geriatric medical/psychiatric unit: A retrospective chart review. Geriatr Gerontol Int 2014;14:388–394.
29. Wu CS, Ting TT, Wang SC, et al. Effect of benzodiazepine discontinuation on dementia risk. Am J Geriatr Psychiatry 2011;19:151–159.
30. Ng BJ, LeCouteur DG, Hilmer SN. Deprescribing benzodiazepines in older patients: Impact of interventions targeting physicians, pharmacists and patients. Drugs Aging 2018;35:493–521.