Title

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Journal

Journal of Geriatric Psychiatry and Neurology, 28(4)

ISSN

0891-9887

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Publication Date

2015-12-01

DOI

10.1177/0891988715598227

Peer reviewed

HHS Public Access

Author manuscript

J Geriatr Psychiatry Neurol. Author manuscript; available in PMC 2016 June 29.

Published in final edited form as:

J Geriatr Psychiatry Neurol. 2015 December ; 28(4): 281–287. doi:10.1177/0891988715598227.

The Association between Benzodiazepine Use and Depression Outcomes in Older Veterans

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Abstract

Benzodiazepines (BZDs) are commonly prescribed to older adults with depression, but it is unknown whether they improve antidepressant (AD) adherence or depressive symptoms. We followed 297 older veterans diagnosed with depression and provided a new AD medication prospectively for four months. Data includes validated self-report measures and VA pharmacy records. At initial assessment, 20.5% of participants were prescribed a BZD. Those with a BZD prescription at baseline were significantly more likely than those without to have a personality disorder, schizophrenia spectrum disorder, or other anxiety disorder, and higher depressive symptom and anxiety symptom scale scores on average. In adjusted regressions, BZD use was not

Previous presentation: Portions of this work were presented at the American Association for Geriatric Psychiatry's annual meeting in Orlando, Florida between March 14th – 17th 2014

No Disclosures to Report

significantly associated with AD adherence, any improvement in depressive symptoms, or a 50% reduction in depressive symptoms. Our results suggest BZD use concurrent with AD treatment does not significantly improve depressive outcomes in older veterans.

Keywords

benzodiazepines; antidepressants; adherence; depression; veterans

Despite concerns about the potential for side effects and toxicity, benzodiazepines (BZDs) are commonly used in the elderly[–]. Overall estimates of BZD use in the elderly range from approximately 9 to 25% of the community dwelling population[–]. While guidelines recommend that BZD prescriptions be intermittent, brief and for acute symptom relief, continuous use remains high in older adults[–]. Primary care physicians are the main prescribers of these medications, noting quick efficacy and high patient satisfaction.

Although BZDs are most often prescribed for anxiety and insomnia, in primary care, they are often prescribed to patients with depression. The group of patients with depression prescribed BZDs may be heterogeneous, including both those with untreated or undiagnosed depression[,], as well as those for whom anxiolytics are being used adjunctively with antidepressants (ADs). In the latter group, clinicians may prescribe BZDs to provide immediate relief given that AD's beneficial effects may not occur for several weeks as well as to counteract early AD treatment side effects like anxiety.

Further, some studies have suggested that co-prescribing a BZD with an antidepressant reduces the likelihood of treatment dropout due to side effects and results in greater improvement in depressive symptoms. Furukawa, Streiner, Young, Kinoshita found in a meta-analysis that a mixed-age sample on a combined AD and BZD treatment were less likely to drop out of treatment than individuals only on an AD treatment. Similarly Pfeiffer, Ganoczy, Zivin, Valenstein found that a mixed-age sample of Veterans receiving a BZD were more likely to receive guideline-concordant AD treatment (continuous AD use over the 90 day acute treatment phase) than individuals on ADs alone. Furukawa, Streiner, Young examined randomized control trials of adults taking ADs with BZDs compared with ADs alone and found that individuals with a combined treatment approach had greater reductions in depressive symptoms at 1 and 4 weeks, but not at 6 or 12 weeks. There is more limited data in older adults. Among older adults specifically, Simon, Ludman found similar improvement in depressive symptoms at two-month follow-up regardless of whether subjects had continued or discontinued BZDs that they were taking at baseline. Questions remain regarding the efficacy of benzodiazepine treatment in improving depressive symptoms among older adults who are at particular risk for side effects (such as balance problems/falls and impaired concentration/memory) in taking these medications.

The current study builds on previous research by examining depressive symptom improvement in older veterans who were prescribed a new AD for depression and then followed from the early antidepressant treatment stage for four months in correspondence with the acute treatment phase for depression. In line with previous research[,], we first examined whether BZD use was associated with adherence to an AD regimen in older

veterans. Secondly, we examined whether BZD use at the baseline early treatment interview was associated with improvement in depressive symptoms four months later among older veterans.

Methods

Sample

Our sample was drawn from a study which focused on examining predictors of AD adherence, such as anxiety, among older veterans. The sample included veterans age 60 or older who were diagnosed with depression and provided a new AD medication prescription at one of three VA medical centers in southern Michigan. A patient was considered a new user of an antidepressant if they had not been prescribed one within the previous six months, and if the provider clearly indicated in the chart notes an intention to specifically address depressive symptoms. Participants were screened and given the baseline, early treatment interview as soon as possible following the receipt of their AD prescription (mean time to baseline was 47.8 days, SD= 11.9). This time lag reflects the time it took to identify eligible patients from new AD fills, screen their charts for eligibility, mail a letter of informed consent and then contact them by phone to request their participation. The consent form then had to be mailed back by the participant prior to conducting the initial interview. Consistent with prior work by Kales, Nease Jr, Sirey, Zivin, Kim, Kavanagh, Lynn, Chiang, Neighbors, Valenstein, Blow, participants were subsequently excluded if they were found to have cognitive impairment using the Six-Item Screener and/or if their depression was not viewed to be clinically significant (i.e. having a Patient Health Questionnaire [PHQ-9] score of less than 5). There were 137 patients that were screened but did not participate. Of these, 69 patients refused participation and 68 were ineligible. Eight were ineligible for not having severe enough depression and seven for having cognitive impairment.

Participants were followed up four months after the baseline early treatment interview at the approximate conclusion of the acute treatment phase. The acute treatment phase tends to carry increased risk for treatment dropout, discontinuation of prescribed medications, and suicide[–]. The study was approved by the Institutional Review boards of both the VA Ann Arbor Healthcare System and the University of Michigan Medical School. All participants provided written consent prior to their participation and all interviews were conducted by trained research assistants. No participants were lost to follow-up or drop-out.

Measures

Depressive symptoms—A four month follow-up score on the validated, shortened version of the Patient Health Questionnaire (PHQ-9) depression scale was used as the primary outcome measure. Participants were asked how bothered they have been by problems in the past two weeks such as “feeling down, depressed, or hopeless” and “trouble concentrating on things, such as reading the newspaper or watching television.” Responses are on a Likert scale from zero signifying “not at all” to three signifying “everyday” and are summed for a scale range of 0 to 27 with a higher score indicating greater depressed mood. We considered improvement in depressive symptoms in two ways based on change in PHQ-9 score from baseline to four month treatment follow-up. First, symptoms were

defined dichotomously as improved (PHQ-9 score decreased), or not improved (stable or worsening/increasing score). Second, clinically significant improvement was defined as showing at least a 50% reduction in PHQ-9 score from initial assessment to four month follow-up and a score of less than 10, and as "still depressed" if showing less than 50% reduction. This cut-point was based on prior validation studies and supporting work[–]. For example, an individual with a baseline PHQ-9 score of 10 must improve to a score of 5 or lower to be considered as improving to a clinically significant extent.

Medication adherence and use—Prescribed AD and BZD medications were attained from pharmacy data from VA administrative databases. AD adherence was assessed using the validated self-report measure from the Brief Medication Questionnaire (BMQ) asking participants about their consistency in taking their daily medication in the week leading up to the interview. This measure has been previously shown to be significantly associated with pharmacy refill records. Consistent with prior work, which deems a medication possession ratio of less than 80% to be insufficient, we dichotomized adhering versus not adhering at the four months follow-up treatment stage such that participants who missed two or more daily doses in a given week were classified as non-adherent. Additionally, participants who never began their AD medication (whether by not taking or not filling the prescription) were also considered to be non-adherent. BZD use was assessed as prescribed versus not at initial assessment, determined from objective pharmacy data at the VA.

Control variables—Demographic characteristics included age, race, gender, marital status and level of education. Clinical variables included measures of perceived global functioning (SF-12), instrumental activities of daily living (IADLs), the Anxiety Sensitivity Index-Revised (ASI-R), and the Hospital Anxiety and Depression Scale- anxiety subscale (HADS-A). Psychiatric and medical diagnoses in the year prior to the baseline interview were obtained from the problem summary list of participants' electronic medical records and used to calculate participants' medical illness burden (Charlson Comorbidity Index [CMI]). Participants were categorized as having none, one, or more than one co-morbid illness. Dichotomous (yes = 1, no = 0) reports of previous AD use, current substance abuse, sedative hypnotic drug use (e.x. trazodone, olanzapine), other anxiety diagnoses (e.x. panic disorder, obsessive compulsive disorder), post-traumatic stress disorder (PTSD), and delirium were also included individually as controls. Cognitive executive functioning was assessed using the Wechsler Memory Scale- Letter-Number Sequencing subscale (WMS-III). The specific care site (Ann Arbor, Battle Creek, or Detroit) and the setting of the provider who made the AD treatment recommendation (either primary care or psychiatric care) were also obtained from the participant's electronic medical records and used as variables in the analysis. All control variables were assessed at the initial interview. We further controlled for lag time between receipt of the AD treatment recommendation and the baseline, early treatment interview assessment of the PHQ-9.

Statistical Analysis

We first examined descriptive statistics of the baseline, early treatment characteristics as well as depression outcomes at 4 months post-initial assessment for the study sample and by BZD use versus non-use at baseline (Table 1). Next, logistic regression models were fit to

examine whether BZD use was associated with AD adherence. Finally, logistic regression analyses examined whether BZD use was associated with depressive symptom improvement over the acute treatment phase. All analyses were adjusted for the control variables as listed previously and repeated using two different definitions of symptom improvement. Multiple imputation with SAS (SAS Institute INC, Cary NC) was used in cases of missing values on control variables and/or outcome variables (5.4% or n = 16 with missing values in either outcome or control variables)[9]. All estimates are based on summary estimates from five imputed data sets.

Results

The analytical sample included 297 veterans who were 64.9 years of age on average (range 60–86), 97.3% male and 79.1% Caucasian. BZD use was seen in 20.5% of participants at initial assessment and 25.6% of participants at any point from initial assessment through follow-up, and 71.7% of participants self-reported adherence to their prescribed AD treatment at 4 month follow-up. Out of 61 benzodiazepine users, 17 (27.9%) were new users at the time of receiving their AD. Only three participants did not initiate their AD medication/fill their initial prescription. Out of the 84 non-adhering participants at 4 month follow-up, 32 (38%) took their AD but less than 80%.

Table 1 shows baseline descriptive statistics by those using a BZD versus not using at baseline. Statistically significant differences at $p<.05$ are noted between patients with and without a BZD prescription at baseline. Those with a BZD prescription at baseline were significantly more likely than those without to have a Schizophrenia spectrum disorder (1.6 vs. 0.0%), Personality disorder (4.9 vs. 0.0%), or other Anxiety disorder (44.3 vs. 13.1%). Individuals with a BZD prescription also had significantly higher baseline depressive symptoms (PHQ-9 mean: 14.2 vs. 12.1) and anxiety symptoms (HADS-A mean: 9.9 vs. 8.4) on average.

Our first research question considered BZDs' association with AD adherence. Using logistic regression analyses, we found that BZD use did not have a significant association with AD adherence (OR: 0.82; 95% CI: 0.37, 1.83). Next logistic regression models examining the odds of improvement in depressive symptoms over the acute treatment period showed that a BZD prescription at baseline did not have a significant association with any improvement (OR: 0.86; 95% CI: 0.40, 1.87; $p = 0.71$) or a 50% reduction (OR: 1.53; 95% CI: 0.56, 4.20; $p = 0.41$) on the PHQ-9.

Conclusions

BZD use was common in our sample; approximately 1 in 5 of the older adults beginning a new AD treatment was also prescribed a BZD at baseline. Our participants reported rate of adherence (72%) was in line with other studies of AD adherence which show almost 30% (24.7–28.6%) of individuals to be non-adherent to their prescribed treatment[–]. In contrast with prior mixed-age studies[9], BZD use was not significantly associated with AD adherence among the older veterans in the study. Additionally, adjusting for a variety of demographic

and clinical variables in the logistic regression analyses, we found that BZD use did not have a significant association with depressive symptom improvement.

A substantial proportion of individuals not taking a BZD were taking a sedative hypnotic medication (17.17% at baseline and 22.22% at any point between initial assessment and follow-up). However, this did not dilute the BZD effect as sedative drug use was not a significant covariate, nor did results change with or without sedative drug use included as a covariate in the models. Further, as the majority of our participants taking a BZD were doing so at the baseline, early treatment assessment of our study, this was our primary focus. However, we also considered a model with a more inclusive definition of BZD use at any point from initial assessment to follow-up and found the BZD effect on improvement of PHQ-9 score remained insignificant. Finally, as previously mentioned we imputed outcomes for participants who had missing data per standard imputation procedures[,]. Out of 297 total participants, when we ran the models with only the 289 who had complete outcome data, our results and conclusions did not change.

It may be that BZDs are useful for certain subpopulations of patients such as those with a comorbid anxiety disorder. As seen in Table 1, individuals with a BZD were significantly more likely to report an anxiety disorder (44.3% versus 13.1% among those with no BZD prescription). Individuals with a BZD prescription were also more likely to have a personality or schizophrenia spectrum disorder and greater severity of depressive and anxiety symptoms at baseline. Future studies may consider whether BZD use contributes to depressive symptom improvement and/or AD adherence specifically in individuals with comorbid mental health conditions such as depression and anxiety.

BZDs carry known side-effects including risk for falls and hip fractures, cognitive impairment, and car accidents that are common particularly among older adults[–]. Furthermore, a recent observational study by Weich, Pearce, Croft, Singh, Crome, Bashford, Frisher found that BZDs and other anti-anxiety medications were significantly associated with higher mortality, with individuals taking these drugs at approximately twice the risk for death. This result was found even after controlling for demographic variables, other drug use, and a number of psychiatric illnesses. Given that BZDs were not significantly associated with improvement in depressive symptoms or AD adherence over the acute treatment period and that BZDs can have adverse consequences for older adults, BZDs should be prescribed with caution and monitored closely to ensure that the prescribed treatment regimen is achieving the desired result.

The strengths of the study include an older adult, male sample and inclusion of a wide array of mental and physical health control variables. However a number of potential limitations of our study should also be considered. First, as our sample was recruited from VA clinics, the sample is almost entirely composed of men which reduces its' generalizability to older women. Using the VA as a unique data source, however, allowed us to extend previous work on BZD use that predominantly examined women, to a primarily older male sample[,]. Additionally, the sample size may be underpowered to detect a BZD effect. Further, there was some lag time between prescription of the AD and the baseline, early treatment interview where depressive symptoms were measured which was necessary to identify the

new prescription and contact the participant for interview. Potential for null findings due to depressive symptom change occurring prior to the initial assessment is possible. However, we controlled for this lag time in our models, and a t-test showed that there was not a significant difference in lag time by AD adherence rating ($t(295)=0.76$, $p=0.45$). Additionally, both a Pearson correlation and ANOVA test found that depressive symptom severity was not associated with lag time from prescription to initial assessment (continuous PHQ total score: $r=-0.03$, $p=0.64$; PHQ total classified into 5 severity categories: $F=0.37$, $p=0.83$). We do not have data on BZD adherence or length of use. We were only able to ascertain whether participants had a prescription for a BZD at baseline from VA pharmacy data. While we examined BZD use as a predictor of AD adherence, future studies may consider adherence to both antidepressants and benzodiazepiness as well as length of use.

Further, confounding by indication may be occurring whereby individuals who were taking a BZD before being prescribed a new AD may be different from those not taking a BZD in both health characteristics and comorbid psychiatric illnesses. Therefore it may be challenging to see a benefit of co-prescribing. Our study design and sample size do not fully allow us to address this issue. However, if co-prescription of a BZD were related to treatment adherence and therefore more improvement in depressive symptoms, it can be tested for by the interaction of BZD use by AD adherence on depressive symptom improvement. This interaction was tested and not found to be significant and therefore not included in the final models. Finally our study of medication adherence does rely on objective self-report; however, even a more objective Medication Event Monitoring System (MEMS) may not be fully accurate. A recent meta-analysis found the BMQ measure to be validated against the MEMS in various populations with moderate to high correlations between the two measures. Despite limitations, our study added to existing literature by focusing on the critical treatment time period of initiating a new AD treatment and considered these associations in an understudied group, older males.

In conclusion, results suggest that BZD use was not significantly associated with adherence to a new AD regimen or improvement in depressive symptoms over the acute treatment period. Future research should consider dose and length of BZD treatment, BZD adherence, and other service utilization and how they are associated with depression outcomes in older adults beginning a new AD treatment, particularly in subpopulations with comorbid depression and anxiety. Randomized control trials and larger scale studies that examine individuals with major depressive disorder who are receiving a new AD and BZD at the same time are warranted to help answer these questions. A better understanding of provider and patient characteristics that distinguish between individuals receiving an AD and BZD versus an AD alone may be useful to explore. This may be a next step in helping prescribers determine whether BZD use is recommended in addition to a new AD treatment, and what a recommended course of BZD treatment may be for older adults with depression. While prior mixed-age studies, have found that individuals prescribed a BZD were more likely to adhere to the AD prescription than AD users alone, our study among older adults does not find a significant added benefit of BZD use to adherence or depressive symptoms outcomes over the acute treatment period. Presently prescribers should balance the possible benefits of BZD use with the high risk of side effects for older adults.

Acknowledgments

Funding: Support for this work provided by the VA grant "Modifiable Determinants of Antidepressant Adherence Among Older Veterans, IIR-04-104" and the University of Michigan Program for Positive Aging, Helen C. Kales, MD, Director. Additional funding support from Department of Veterans Affairs, HSR&D Merit Award, Grant # IIR 10-176, "Risk of death among Veterans with depression;" Principal Investigator: Kara Zivin. Dr. Leggett is funded by a National Institute of Mental Health (T32 MH073553) Geriatric Mental Health Services Fellowship.

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Table 1

Subjects' characteristics at baseline

	Total (N=297)	Patients with Benzodiazepine (N=61)	Patients without Benzodiazepine (N=236)
Site of recruitment *			
Ann Arbor	44.1	27.9	48.3
Battle Creek	29.3	44.3	25.4
Detroit	26.6	27.9	26.3
Health care provider *			
Primary care physician	45.4	31.1	49.2
Psychiatrist	54.6	68.9	50.8
Gender			
Female	2.7	3.3	2.5
Male	97.3	96.7	97.5
Race			
Black	17.5	8.2	19.9
White	79.1	88.5	76.7
Others	3.4	3.3	3.4
Age (mean=64.9, range 60–86) *			
60–64	69.7	67.2	70.3
65–74	18.9	27.9	16.5
75–86	11.4	4.9	13.1
Education			
High school or below	41.1	41.0	41.1
Some college or above	58.9	59.0	58.9
Marital status			
With partner/spouse	57.6	47.5	60.2
Without partner/spouse	42.4	52.5	39.8
With prior depression treatment	62.6	75.4	59.3
Delirium	4.0	1.6	4.7
Schizophrenia spectrum disorders *	0.3	1.6	0.0
Bipolar I disorder	0.7	1.6	0.4
Bipolar II disorder	0.3	0.0	0.4
Parkinson's disease	0.3	0.0	0.4
Any substance abuse	17.5	11.5	19.1
Alcohol abuse	13.8	8.2	15.3
Drug abuse	8.1	6.6	8.5
Post traumatic stress disorder diagnosis	36.4	44.3	34.3
Other anxiety disorder *	19.5	44.3	13.1
Personality disorder *	1.0	4.9	0.0
Charlson's comorbidity index			

	Total (N=297)	Patients with Benzodiazepine (N=61)	Patients without Benzodiazepine (N=236)
0	37.4	41.0	36.4
1	27.6	21.3	29.2
>1	35.0	37.7	34.3
Adherence to AD in 4 months	71.7	72.1	71.6
PHQ reduced in 4 months	53.9	59.1	52.5
PHQ reduced at least 50% in 4 months	17.8	18.0	17.8
Means			
Physical component summary of SF12 (PCS)	36.7	37.3	36.6
Mental component summary of SF12 (MCS) *	37.8	35.1	38.5
Patient Health Questionnaire (PHQ-9) *	12.5	14.2	12.1
Patient Health Questionnaire (PHQ-9) in 4 months	11.6	12.9	11.3
Geriatric Depression Scale (GDS-15)	7.6	8.3	7.4
Geriatric Depression Scale (GDS-15) in 4 months	7.6	8.0	7.4
Hospital anxiety depression scale, anxiety subscale (HADS-A) *	8.7	9.9	8.4
Anxiety sensitivity index (ASI)	53.4	53.9	53.2
Instrumental activities of daily living scale (IADL Total)	7.5	7.1	7.6
Weschler LNS *	7.9	6.9	8.1

All characteristics are baseline characteristics unless otherwise noted. None of the patients had dementia, Huntington's disease, other psychoses, or HIV without AIDS.

Charlson's comorbidity index is a composite score based on the presence of myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular disease, chronic obstructive pulmonary disease, dementia, rheumatologic disease, peptic ulcer disease, cirrhosis, hepatic failure, diabetes mellitus, diabetes mellitus with complications, hemiplegia, chronic renal disease, malignant neoplasm, leukemia, lymphomas, metastatic solid tumor, HIV without AIDS, and AIDS.

* $p<0.05$ for statistical significance between patients with and without benzodiazepine.