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Benzodiazepine Use in Community-Dwelling Older Adults: Longitudinal Associations with Mobility, Functioning, and Pain

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Abstract

The aim of the study was to determine the prospective association between baseline benzodiazepine use and mobility, functioning, and pain among urban and rural African-American and non-Hispanic white community-dwelling older adults. From 1999 to 2001, a cohort of 1,000 community-dwelling adults, aged 65 years, representing a random sample of Medicare beneficiaries, stratified by ethnicity, sex, and urban/rural residence were recruited. Benzodiazepine use was assessed at an in-home visit. Every six months thereafter, study outcomes were assessed via telephone for 8.5-years. Mobility was assessed with the Life-Space Assessment. Functioning was quantified with level of difficulty in five basic activities of daily living (ADL: bathing, dressing, transferring, toileting, eating), and six instrumental activities of daily living (shopping, managing money, preparing meals, light and heavy housework, telephone use). Pain was measured by frequency per week and the magnitude of interference with daily tasks. All analytic models were adjusted for relevant covariates and mental health symptoms. After multivariable adjustment, baseline benzodiazepine use was significantly associated with greater difficulty with basic ADL (Estimate = 0.39, 95% CI: 0.04–0.74), and more frequent pain (Estimate = 0.41, 95% CI: 0.09–0.74) in the total sample and declines in mobility among rural residents (Estimate =

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$-0.67, t(5,902) = -1.98, p = .048$), over 8.5 years. Benzodiazepine use was prospectively associated with greater risk for basic ADL difficulties and frequent pain among African-American and non-Hispanic white community-dwelling older adults, and life-space mobility declines among rural-dwellers, independently of relevant covariates. These findings highlight the potential long-term negative impact of benzodiazepine use among community-dwelling older adults.

Keywords

benzodiazepines; mobility; pain; older adults; activities of daily living

1. INTRODUCTION

Benzodiazepines are often prescribed to older adults to target sleep disturbances and psychiatric disorders. However, benzodiazepines confer many risks for older adults such as dependence, rebound anxiety, cognitive impairment, dementia, falls, motor vehicle accidents, and injuries (Berdot et al., 2009; Glass, Lancot, Herrmann, Sproule, & Busto, 2005; Hilmer et al., 2007; Tamblyn, Abrahamowicz, du Berger, McLeod, & Bartlett, 2005; Wu, Wang, Change, & Keh-Ming, 2009). An expert consensus panel concluded that the prescription of all benzodiazepines to older adults should be avoided for treatment of insomnia, agitation, or delirium (The American Geriatrics Society 2012 Beers Criteria Update Expert Panel, 2012). Despite these risks and recommendations, benzodiazepine use remains prevalent (Balkrishnan, Rasu, & Rajagopalan, 2005), frequently prescribed (Martinsson, Fagerberg, Wiklund-Gustin, & Lindholm, 2012), and more commonly used among older adults than in the general population (Blazer, Hybels, Simonsick, & Hanlon, 2000). Prevalence estimates of benzodiazepine use among community-dwelling older adults in the last decade ranged from 4.6% to 25% (Beland et al., 2010; Dublin et al., 2011).

There are documented cross-sectional and longitudinal associations between benzodiazepine use and mobility and physical functioning. Consistently, benzodiazepine use is associated with poor physical performance and mobility limitations across multiple reports (Cao et al., 2008; Gnjdjic et al., 2009; Gray et al., 2002; Gray et al., 2006; Gray et al., 2003; Leveille, LaCroix, Hecht, Grothaus, & Wagner, 1992; Tamblyn et al., 2005). In contrast, results are mixed concerning the relationship between benzodiazepine use and the ability to perform basic activities of daily living (basic ADL: bathing, dressing, transferring, toileting, eating) and instrumental activities of daily living (IADL: shopping, managing money, preparing meals, light housework, heavy housework, telephone use). Of four studies examining sedative-hypnotic medications among older adults, two found decline in basic ADL related to benzodiazepines (Gray et al., 2006; Sarkisian et al., 2000) whereas the other two did not (Gray et al., 2002; Leveille et al., 1992). No known longitudinal studies have analyzed benzodiazepines related to IADL, but one cross-sectional study did reveal poorer ability to engage in IADL was associated with benzodiazepines (Ried, Johnson, & Gettman, 1998).

There are limitations within these previous studies. First, while some investigations have controlled for depressive symptoms, few have controlled for the presence of both depressive and anxiety symptoms (Cao et al., 2008; Gnjdjic et al., 2009; Gray et al., 2002; Gray et al.,

2006; Leveille et al., 1992; Ried et al., 1998; Sarkisian et al., 2000; Tamblyn et al., 2005), which may be primary confounders given they may result in a prescription for benzodiazepines, and are risk factors for physical disability in the elderly (Lenze et al., 2001). Second, the recruited samples lacked generalizability (e.g., only single sex groups (Cao et al., 2008; Gnjidic et al., 2009; Gray et al., 2003; Leveille et al., 1992; Sarkisian et al., 2000), the severely disabled (Cao et al., 2008), or high-functioning older adults were assessed (Gray et al., 2002; Gray et al., 2006; Sarkisian et al., 2000). Third, previous studies often assessed physical functioning from one-time, in-the-lab physical performance assessments rather than extracting a personalized profile of the older adult's typical lifestyle and activity patterns hence limiting the value of these prior analyses (Cao et al., 2008; Gnjidic et al., 2009; Gray et al., 2002; Gray et al., 2006; Gray et al., 2003; Leveille, LaCroix, Hecht, Grothaus, & Wagner, 1992; Ried et al., 1998; Sarkisian et al., 2000; Tamblyn et al., 2005). Fourth, follow-up periods within most prospective studies were relatively short ranging from one to five years (Gray et al., 2002; Gray et al., 2003; Leveille et al., 1992; Sarkisian et al., 2000). Thus, the long-term consequences of benzodiazepines are not fully described. Benzodiazepines confer numerous psychomotor and neuromuscular side effects that over time could plausibly cumulate for greater negative effects. Fifth, there were few reports of benzodiazepine use and functioning among subpopulations e.g., ethnic minority groups and rural-dwelling residents. It is necessary to determine differential risks as a function of these subpopulations because prescription of benzodiazepines is more common among women and non-minority groups, prescription practices can vary by region, and the pharmacokinetics and pharmacodynamics of benzodiazepines may vary by sex and race (Allen, Renner, DeVellis, Helmick, & Jordan, 2008; Franconi, Sanna, Straface, Chessa, & Rosano, 2012; Gleason et al., 1998; Lambert & Norman, 2008; Rasu, Shenolikar, Nahata, & Balkrishnan, 2005). Lastly, long-term consequences of benzodiazepine use on pain among older adults are unknown despite its increase in use with age among persons with pain (Chou, Qaseem, Snow, Casey, & Cross, 2007; Liu, Ye, Watson, & Tepper, 2010). Along with impairments of neuromuscular processing and psychomotor performance, benzodiazepine effects on the central nervous system may also include direct effects on central pain processing or indirect effects through increased risk of falls and injuries that may lead to chronic pain conditions.

To address these research questions, the present investigation determined the prospective relationships between benzodiazepine use and mobility, basic ADL, IADL, as well as pain frequency and interference over 8.5 years in an observational study of community-dwelling older adults balanced by ethnicity (African-American and non-Hispanic whites [NHW]), sex, and residence (urban and rural). We hypothesized that older adults using benzodiazepines at baseline, regardless of the medical indication, would have greater decline in mobility, increased difficulty in basic ADL and IADL, and more frequent pain and greater pain interference after controlling for relevant confounders. We also analyzed these relationships stratified by ethnicity, sex, and residence if significant interactions were noted.

2. MATERIALS & METHODS

2.1. Study Design and Sample

Data were derived from the University of Alabama at Birmingham (UAB) Study of Aging (N=1000), a longitudinal, observational inquiry of factors that influence mobility among community-dwelling older adults 65 years (Allman et al., 2011; Allman, Sawyer, & Roseman, 2006). Participants were selected from a random sample of Medicare beneficiaries residing in five counties of central Alabama from a list provided by the Center of Medicare and Medicaid Services. Recruitment was balanced by the ethnic composition of older adults in central Alabama (African-American and NHW), sex, and residence (two counties classified as urban; three counties as rural). Baseline recruitment took place from 1999–2001. Participants were excluded if they resided in a nursing home or were unable to schedule their own in-home interviews. Of 2,188 participants contacted, 45.7% participants agreed to participate and met eligibility criteria. Participants provided written consent prior to a baseline, in-home interview. General health, cognitive status, medication use, and other sociodemographic and lifestyle factors were assessed at the in-home visit. Cognitive status was assessed with the Mini-Mental State Exams (Folstein, Folstein, & McHugh, 1975) and interviewer observation. All participants were required to be sufficiently cognitively intact to be able to participate in the interviews and provide accurate information. Sufficient cognitive function was defined as the ability to use the telephone, set an appointment for an in-home visit with research staff, and answer initial interview questions by themselves. Mobility, functioning, and pain were assessed via telephone at baseline. Follow-up telephone interviews were conducted at six-month intervals over 8.5 years. Assessments of current mobility, functioning, and pain were conducted at each telephone follow-up.

2.2. Benzodiazepine Exposure

At the baseline in-home assessment, participants reported all medications they were habitually and currently taking by either showing interviewers a medication list or their medication bottles. Indication for each prescription, the type, dosage, frequency and regularity of use were not documented. Benzodiazepines were classified according to the year 2000 edition of the American Hospital Formulary Service Drug Information Pharmacologic-Therapeutic Classification System (McEvoy, 2000).

2.3 Outcome Measures

Life-Space Assessment (LSA)—The UAB Center of Aging developed the LSA to assess usual community mobility among older adults (Baker, Bodner, & Allman, 2003; Peel et al., 2005). The LSA asks participants their level of mobility during the prior four weeks by assessing their movement from the room they sleep within to other areas ranging from the next room to outside their immediate town; the frequency of their movements; and if assistive devices or other persons were used to facilitate their movements. The LSA is a psychometrically valid and reliable measure of mobility that demonstrates concurrent validity with observable physical performance measures (Baker et al., 2003). The test–retest reliability of the scale from the baseline assessment to two-week follow-up was an intra-class correlation coefficient of 0.96 (0.95–0.97). The scale ranges from 0–120 with lower scores denoting poorer mobility.

Basic ADL—Basic ADL were self-reported at each interview, with the question format “Do you have any difficulty performing the task?” to assess eating, dressing, using the toilet, transferring and bathing. A response of “no” was given a value of zero, whereas a response of “yes” was then rated for level of difficulty using a Likert-type scale from 1 = some, 2 = a lot, to 3 = unable to do the task. Scores were summed with higher scores indicating greater difficulty with basic ADL (range: 0–15)(Katz, Ford, Moskowitz, Jackson, & Jaffe, 1963; Peel et al., 2005).

IADL—Were measured with the same question format as basic ADL to assess telephone use, doing light housework, doing heavy housework, preparing meals, shopping, and managing money. Rating and scoring was identical to basic ADL with the exception that scores ranged from 0–18 because six tasks were assessed (Peel et al., 2005).

Pain Frequency—Pain frequency was measured at baseline and months 12, 24, 36, 48, 54, 60, 72, and 90 months. Therefore, the total follow-up period evaluated was 7.5-years. Pain frequency was measured with the question “how frequently over the past four weeks have you experienced pain?” with response choices including ‘not at all,’ ‘less than once a week,’ ‘1-3 times per week,’ ‘4-6 times per week,’ and ‘daily.’ Pain interference was measured using the Medical Outcomes Study SF-12 Scale item “during the past 4 weeks, how much did pain interfere with your normal work (including both work outside the house and housework)?” with response choices including ‘not at all,’ ‘a little bit,’ ‘moderately,’ ‘quite a bit,’ and ‘extremely’ (Ware, Kosinski, & Keller, 1996).

2.4 Control Variables

Multiple covariates were controlled for their probable effects on the outcomes. Sociodemographic information included age, sex, ethnicity (African-American vs. NHW), residence (urban vs. rural), education (categorized as <6th grade, 7-11th grades, high school graduate, some college), and difficulty paying for food, housing, medical care, and/or heating (i.e., not very difficult, somewhat difficult, very difficult). Health behaviors and anthropometric data included body mass index (BMI; measured continuously), smoking status (Never or not within the past year vs. within the past year), and alcohol use (drinks/week). Medical conditions were measured as a comorbidity count based on verified diseases of the Charlson Comorbidity Index without consideration of severity (index range: 0–9)(Charlson, Pompei, Ales, & MacKenzie, 1987). Cognitive status was assessed with the Mini Mental State Exam as a measure of cognitive functioning (Folstein et al., 1975). Depressive symptoms measured with the Geriatric Depression Scale (GDS; scale range: 0–15)(Yesavage et al., 1983), and anxiety symptoms were measured with the Arthritis Impact Measurement Scales 2–Tension Scale (AIMS2; scale range: 5–25; Meenan, Mason, Anderson, Guccione, & Kazis, 1992). The AIMS2 and its subscales have demonstrated acceptable and consistent psychometric properties including test-retest reliability, factor analysis, and validity across age, sex, and education groups (Meenen et al., 1992). The AIMS2–Tension Scale is five-items asking about the frequency of feelings of nervousness and inability to relax on a scale from one to five with response options of ‘always’ (i.e., 1), ‘very often’, ‘sometimes’, ‘almost never’, and ‘never’ (i.e., 5). Lower scores indicate greater levels of tension.

2.5 Statistical Analyses

Descriptive statistics were analyzed to characterize the sample. One-way ANOVA and Chi-square analyses were performed on continuous and categorical variables, respectively, to assess cross-sectional differences in baseline characteristics between benzodiazepine users and non-users. BMI and alcohol use were not distributed normally, therefore Mann Whitney U tests were used to assess group differences.

Mixed effects models assessed differences between groups (benzodiazepine use vs. non-use) on all outcome measures over time (Brown & Prescott, 2006; Little, Milliken, Stroup, Wolfinger, & Schabenberger, 2006). For analysis of LSA scores, a random coefficients model was fitted to model the rate of change over time. This model fits a slope (change in LSA score over the time points) for each group, with individual subjects having random deviations from the group slope. For the remaining outcomes which all had ordinal scales, generalized linear mixed models (covariance pattern model) were fitted to model differences between groups, longitudinally. Basic ADL and IADL were analyzed as ordinal variables due to non-normal distributions. These mixed effects models were employed as they utilize data from all participants (rather than just completers) and minimizes bias and better controls for Type I error in the presence of missing data. Within the models predictor variables were entered sequentially, first with a minimal model including only benzodiazepine use, then sets of covariates as follows: Model 1 included all sociodemographic information; Model 2 included Model 1 variables in addition to health behaviors, BMI, comorbidity count, and MMSE score; and Model 3 included the GDS and AIMS-2-Tension Scale scores. Interaction terms between benzodiazepine use and sex, ethnicity, and residence were also added separately to the fully-adjusted model (Model 3) to ascertain sociodemographic group differences. If interaction terms were statistically significant, then stratified analyses were conducted. Significance was set at $p < 0.05$ within each model. All analyses were performed with SAS version 9.2 (SAS Institute, Inc., Cary, NC) using PROC MIXED for the LSA score and PROC GENMOD for the remaining outcomes.

3. RESULTS

Table 1 shows descriptive characteristics of the sample by benzodiazepine use at the baseline assessment. The average age in the sample was 75.3-years. Ethnicity (African-American and NHW), sex, and region of residence (rural and urban) were approximately balanced at a 50/50 split for each variable. Benzodiazepine use at baseline was 10% (n=100). Baseline covariates and outcomes varied by benzodiazepine use. Benzodiazepine use was significantly related to being older, female, NHW, lower BMI, more anxiety symptoms, lower LSA scores, as well as more comorbidities, depressive symptoms, daily pain, and difficulty with basic ADL. Indication for benzodiazepine use was not documented; however, at baseline assessment, none of the participants using benzodiazepines reported previous diagnoses or current medication use for schizophrenia, psychosis, alcohol abuse, epilepsy or another seizure disorder. Approximately 25.0% (n=25) of benzodiazepine users reported receiving anxiety and/or depression diagnoses in the past.

Over the 8.5-year follow-up, a total of 941 participants with at least one telephone follow-up were included in the analysis. The average length of follow-up was 6.2 (SD = 2.6) years for these individuals. Responders (had at least one telephone follow-up) compared to non-responders (n=59) did not differ by age, ethnicity, education, or in difficulty paying for food, housing, medical care, and/or heating. However, non-responders compared to responders were significantly more likely to be male (66.1% vs. 49.1%, $\chi^2 = 6.4$, $p = .01$) or rural-dwelling (74.6% vs. 50.0%, $\chi^2 = 13.4$, $p < .001$). Considering this was a longitudinal study of older adults, much of the loss of data during follow-up was due to participant death. By the end of the study, 394 participants had died. There were no differences by ethnicity or residence in the number of deaths, but there was a significant difference by gender (Men: 45.9% vs. Women: 32.87%, $p < .001$).

A random coefficients, longitudinal mixed effects model was used to measure the rate of change in LSA over time. Benzodiazepine use was independently associated with LSA in the unadjusted model ($F(1, 12\ 000) = 70.3$, $p < .001$) and it remained significantly associated in Model 1 ($F(1, 12\ 000) = 38.7$, $p < .001$) and Model 2 ($F(1, 12\ 000) = 13.3$, $p < .001$). However in the fully-adjusted model (Model 3), which incorporated mental health measures, the relationship became non-significant ($F(1, 12\ 000) = 2.1$, $p = .13$). When the interaction term for benzodiazepine use and time was added to the Model 3, the relationship between benzodiazepine use with the rate of change in LSA was also non-significant (Estimate = -0.38 , SE = 0.26 , $t(12\ 000) = -1.45$, $p = .15$). However, there was a significant interaction between benzodiazepine use and residence ($F(1, 12\ 000) = 10.4$, $p = .001$). In adjusted, stratified analyses, rural-dwelling participants using benzodiazepines demonstrated an accelerated rate of LSA decline compared to non-users (Estimate = -0.67 , SE = $.34$, $t(5,902) = -1.98$, $p = .048$), whereas there was no relationship among urban-dwelling participants (Estimate = -0.67 , SE = 0.34 , $t(5,868) = 0.19$, $p = .85$). There were no significant interactions between benzodiazepine use and sex or ethnicity.

Table 2 shows the association between benzodiazepine use, basic ADL, and IADL. Benzodiazepine use was associated with greater difficulty in basic ADL at 8.5-year follow-up in the unadjusted model, and remained significant after all covariates and mental health measures were included into the model. There were no significant interactions between basic ADL and sex, ethnicity, and residence. IADL and benzodiazepine use were not significantly related in the full model. Although there was a significant relationship in the unadjusted model indicating greater difficulty in IADL among benzodiazepine users, the association became statistically non-significant in Model 2 once comorbidities, health behaviors, and cognitive functioning were added.

Also in Table 2, pain frequency and interference were significantly related to benzodiazepine use in the unadjusted model, and retained statistical significance in Models 1 and 2. In the fully-adjusted model, benzodiazepine use was prospectively associated with more frequent pain; however, statistical significance was not retained for pain interference. There were no significant interactions between benzodiazepine use and ethnicity, sex, and residence.

4. DISCUSSION

Benzodiazepine use was present in one out of ten participants within a prospective cohort of urban and rural African-American and NHW community-dwelling older adults. At baseline, benzodiazepine use was common among older NHW females and was associated with more physical and mental health problems, basic ADL limitations, and lower mobility.

Independent of mental health symptoms, benzodiazepine use was significantly associated with accelerated decline in mobility among rural-dwelling older adults, and greater basic ADL difficulty and greater pain frequency in the total sample. After adjustment for relevant covariates, benzodiazepine use was not independently related to difficulty in IADL or pain interference.

The present investigation is the first of its kind to evaluate the association of benzodiazepines on the broader continuum of life-space mobility observed among community-dwelling older adults while accounting for mental health symptoms. Rural-dwelling respondents had an accelerated rate of decline in life-space mobility associated with benzodiazepine whereas urban respondents did not demonstrate a relationship. The results for LSA among urban-dwelling older adults are contrary to previous studies that cite benzodiazepine use as an independent predictor of difficulties with physical performance exams (Gray et al., 2002; Gray et al., 2006; Gray et al., 2003; Leveille et al., 1992). Mental health symptoms appeared to account for this loss of a significant association indicating these symptoms, which tend to invoke benzodiazepine prescriptions, contribute more highly to change in LSA, than benzodiazepines. Mental health symptoms, may be more highly associated with LSA among urban-dwelling older adults than in rural-dwelling older adults for various reasons that could not be tested in the present sample. Examples of reasons may include mental health symptoms may affect older adults' choice to travel within their environment in urban settings more than in rural settings, or there may be differences by residence in clinical indicators for prescribing benzodiazepines (i.e., benzodiazepines may be prescribed in response to mental health symptoms more often in urban settings as opposed to rural settings) ... However, in general, we propose that benzodiazepine use may have a cumulative, direct effect on physical movements and coordination over time through its acute sedative effects and impairment of neuromuscular processing and psychomotor performance. As a consequence, the benzodiazepine-user may experience a quickened shrinking of their life space, and also experience significant detrimental effects on mobility-related tasks, reflected by our findings related to basic assessments of ADL. To verify this claim, further inquiry is needed on the dose-response relationship, the frequency and duration of use, and the type of benzodiazepine used as related to life-space mobility over time.

Our results demonstrate that benzodiazepine exposure is related to greater difficulty with basic ADL over time. This result is consistent with two previous studies which found an association with decline in ADL (Gray et al., 2006; Sarkisian et al., 2000), but inconsistent with two other studies that found no association (Gray et al., 2002; Leveille et al., 1992). The studies that found significant associations had larger sample sizes, longer follow-up periods, and sampled older adults from diverse geographical areas (Gleason et al., 1998;

Ried et al., 1998), which indicates these results may be more representative of the general population than the studies reporting no association (Gray et al., 2002; Leveille et al., 1992).

This study is the first to examine the longitudinal association between benzodiazepine use and change in IADL over time. The results indicate the association is not significant after adjustment for physical health indicators and current cognitive functioning, which appears contrary to the results for basic ADL. However, there was greater variability in IADL than ADL and most of the IADL tasks require a minimum level of cognitive functioning to execute over and beyond basic motor functioning. Thus, cognitive status may account for more variability in IADL than benzodiazepines because benzodiazepines may have more unique effects on more heavily motor-dependent tasks than cognitive tasks.

We also found that benzodiazepine use conferred a higher risk for more frequent pain over time but not pain interference. Conceivably the central nervous system effects of benzodiazepines may also alter central pain processing over time. Indeed, γ -aminobutyric acid (GABA), the main neurotransmitter affected by benzodiazepines, serves a role in pain processing. In an animal model, lowering GABA levels within the insula has been found to enhance pain (Jasmin, Rabkin, Granato, Boudah, & Ohara, 2003). However, it is also plausible that pain is a confounder of indication meaning that benzodiazepines are associated with greater frequency of pain because they were prescribed to address pain. Even though benzodiazepines are not a consistent analgesic they are indicated for the treatment of muscle spasms. Furthermore, pain is often associated with mental health symptoms, which are also confounders of indication.

There are multiple strengths to this study including the recruitment of an ethnically diverse sample, oversampling males and African-Americans as well as the inclusion of unhealthy older adults, utilizing an in-home confirmation of current benzodiazepine use, a comprehensive measure of lifestyle-related mobility, and determining the associations while controlling for mental health symptoms. Despite these strengths there are limitations. Medication use was measured primarily as a way to document diagnosed medical conditions; therefore the type, dosage, frequency and regularity of use were not documented at baseline and not monitored during follow-up with the exception of a four-year follow-up visit. The data at this follow-up visit remained limited to the documentation of current benzodiazepine use alone, as estimates of the association by subgroups (i.e., participants who continued vs. discontinued use) were unstable. Because it was unknown whether the medication was discontinued, intermittently, or chronically used, claiming a causal role of benzodiazepine use on functioning over time is not possible. Second, the sample size was relatively small and confined to central Alabama, thus generalizability and making comparisons across sociodemographic groups outside this region are limited. Third, there were unmeasured confounders not included in the analysis that may account for the significant relationships (e.g., sleep disturbance). Fourth, LSA for the past four weeks was measured retrospectively which may be prone to recall bias. Fifth, there were differences in assessment methods between the exposure and outcome variables (in-home vs. telephone interview) which may have altered some of the estimates. Lastly, because basic ADL, IADL, and pain frequency were assessed on an ordinal scale, comparisons between benzodiazepine users and non-users on the rate of change over time were not meaningful.

5. CONCLUSIONS

Despite these limitations, our results illustrate benzodiazepine use is associated with greater long-term risk for limited life-space mobility differentially by residency status, greater difficulty with basic ADL, and more frequent pain. Clinicians should exercise caution when prescribing benzodiazepines to older adults as they may confer risks described in this study as well as in other domains such as falls, fractures and other injuries documented heavily in the extant literature (Glass et al., 2005). If benzodiazepines are prescribed, patients should take them as indicated by their provider and generally should refrain from taking them longer than two to four weeks to reduce risk of physical dependence and other long-term risks indicated from the present results. Further research is needed on findings from the present analysis, such as the assessment of nuances in benzodiazepine use over multiple time points with short-intervals in ethnically and regionally diverse, representative samples. Given the relationship between benzodiazepine use and pain frequency, further research may need to regularly adjust for pain as well as other major confounders of indication.

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Highlights

- Determine prospective association of benzodiazepines on mobility, function and pain
- Sample of 1,000 urban and rural, community-dwelling older adults
- Benzodiazepine use was associated with greater difficulty with basic ADL over 8.5yr
- Benzodiazepine use was associated with more frequent pain over 8.5yr
- Benzodiazepines were related to greater declines in mobility among rural residents

Table 1

Characteristics of the Sample at Baseline and by Benzodiazepine Use.

Characteristic	Whole Sample <i>M(SD)</i> or <i>n</i> (%) (<i>n</i> =1,000)	Benzodiazepine Users <i>M(SD)</i> or <i>n</i> (%) (<i>n</i> =100)	Non-users <i>M(SD)</i> or <i>n</i> (%) (<i>n</i> =900)	χ^2 or <i>t</i> (<i>df</i>) ^a	<i>p</i>
Age	75.3 (6.7)	76.8 (6.6)	75.1 (6.7)	-2.3 (998)	.019
Female Sex	499 (49.9)	65 (65.0)	434 (48.2)	10.1	.001
African-Americans	500 (50)	34 (34.0)	466 (51.8)	11.4	.001
Rural-Dwelling	514 (51.4)	57 (57.0)	457 (50.8)	1.4	.24
Education			7.2		.07
		<6 th grade	17 (17.0)		
		7-11 th grade	41 (41.0)		
		High School Graduate	20 (20.0)		
		>High School	22 (22.0)		
Income Difficulty				2.3	.31
		Not	57 (57.0)		
		Somewhat	30 (30.0)		
		Very	13 (13.0)		
Smoking within the past year				0.1	.75
		130 (13.0)	118 (13.1)		
Alcohol Drinks/Week ^b	1.2 (4.1)	.44 (1.5)	1.2 (4.3)	41,623	.093
Body Mass Index ^b	27.1 (6.9)	25.8(8.0)	27.2 (6.7)	37,943.5	.031
MMSE	25.0 (4.9)	25.2 (4.8)	25.0 (4.9)	-0.4 (998)	.70
CC	2.3 (1.6)	2.9 (1.4)	2.2 (1.6)	-4.6 (998)	<.001
GDS	2.4 (2.3)	3.2 (2.8)	2.3 (2.3)	-3.7 (997)	.002
AIMS2	19.5 (4.1)	16.8 (4.3)	19.8 (4.0)	7.0 (998)	<.001
LSA	64.1 (24.9)	57.4 (22.7)	64.9 (25.1)	2.9 (998)	.004
Basic ADL	1.1 (2.1)	1.7 (2.3)	1.0 (2.0)	-2.6 (117.2)	.01
IADL	2.1 (3.5)	2.8 (3.1)	2.1 (3.4)	-1.8 (872)	.07
Pain Frequency			16.0		.003
		Not at all	14 (14.0)		
		< once per week	11 (11.0)		
		1-3 times per week	13 (13.0)		
		183 (18.3)	170 (18.9)		

Characteristic	Whole Sample M(SD) or n(%) (n=1,000)	Benzodiazepine Users M(SD) or n(%) (n=100)	Non-users M(SD) or n(%) (n=900)	χ^2 or $t(df)^a$	p
Pain Interference	4-6 times per week	56 (5.6)	7 (7.0)	49 (5.4)	.15
	Daily	386 (38.6)	55 (55.0)	331 (36.8)	
	Not at all	413 (41.3)	31 (31.0)	382 (42.4)	
	A little bit	225 (22.5)	22 (22.0)	203 (22.6)	
	Moderately	109 (10.9)	14 (14.0)	95 (10.6)	
	Quite a bit	142 (14.2)	20 (20.0)	122 (13.6)	
	Extremely	111 (11.1)	13 (13.0)	98 (10.9)	

M = mean; SD = standard deviation; MMSE = Mini Mental Status Exam; CC = Charlson Comorbidity Count; GDS = Geriatric Depression Scale; AIMS2 = Arthritis Impact Measurement Scale 2 - Tension subscale; LSA = Life-Space Assessment; ADL = activities of daily living; IADL = instrumental activities of daily living

^a Comparisons between benzodiazepine users vs. non-users were conducted with Chi-square tests for categorical variables and t -tests for continuous variables.

^b Mann Whitney U-tests were performed because the distributions were non-normalized.

Table 2
Generalized Linear Mixed Models for the Relationships between Benzodiazepines, basic ADL, IADL, and Pain Frequency

Models (ref: non-BZD use) ^a	BADL (range: 0-15)			IADL (range: 0-18)			Pain Frequency			Pain Interference		
	Est	95%CI	p	Est	95% CI	p	Est	95% CI	p	Est	95% CI	p
Unadjusted	0.82	0.48–1.17	<.001	0.67	0.28–1.06	<.001	0.78	0.48–1.09	<.001	0.60	0.33–0.89	<.001
Model 1	0.69	0.35–1.02	<.001	0.47	0.07–0.87	.021	0.65	0.33–0.96	<.001	0.49	0.21–0.78	<.001
Model 2	0.56	0.21–0.91	.002	0.30	–0.12–0.72	.16	0.64	0.33–0.95	<.001	0.42	0.14–0.71	.004
Model 3	0.39	0.04–0.74	.031	–0.11	–0.53–0.31	.61	0.41	0.09–0.74	.012	0.16	–0.14–0.45	.29

BADL = basic activities of daily living; IADL = instrumental activities of daily living; Est = estimate of the regression coefficient; CI = confidence interval; ref = reference group; BZD = Benzodiazepine

^aModel 1 = age, sex, ethnicity, education, income difficulty, and region. Model 2 = Model 1 + body mass index, alcoholic drinks per week, smoking status, comorbidity count, and Mini-Mental Status Exam score. Model 3 = Model 2 + Geriatric Depression Scale score, and the Arthritis Impact Measurement Scale 2 – Tension subscale.