Use of Benzodiazepines and Selective Serotonin Reuptake Inhibitors in Middle-Aged and Older Adults With Anxiety Disorders

A Longitudinal and Prospective Study

Carlos Israel Pérez Benitez, Ph.D., Kevin Smith, Ph.D., Russell G. Vasile, M.D., Richard Renne, Ph.D., Maria Orlando Edelen, Ph.D., Martin B. Keller, M.D.

Objective: The purpose of this study was to examine the use of benzodiazepines (BZs) and selective serotonin reuptake inhibitors/selective norepinephrine reuptake inhibitors (SSRIs/SNRIs) over nine years of follow-up in middle-aged and older adults with diagnoses of panic disorder with or without agoraphobia, social phobia, or generalized anxiety disorder. Setting and Participants: Participants in this study were enrolled in the Harvard/Brown Anxiety Research Project (HARP). HARP is a naturalistic, longitudinal, multisite study of adults with anxiety disorders who are recruited from psychiatric settings. The analytic sample consisted of 51 participants with anxiety disorders who were 55 to 70 years old at baseline and a younger cohort of 211 participants added for comparative analysis. Design: The authors examined patterns of medication use (BZs and SSRIs/SNRIs) in participants with anxiety disorders as they aged, by assessing the proportion of participants taking these medications using generalized estimating equation modeling. Measurements: The present data were derived from the structured diagnostic interview administered at enrollment using a combination of the Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders, Third Edition–R Non-Affective Disorder, Patient Version, Research Diagnostic Criteria Schedule for Affective Disorders–Lifetime, and subsequent follow-up interviews over a nine-year period using the Longitudinal Interval Follow-up Evaluation–Pharmacal & Upjohn to assess the weekly course of disorders to indicate syndrome severity and document medication use by specific type and dose on a weekly basis. Results: Findings showed that rates of BZ use were high among both the older (53% at baseline) and the younger (57.4%) age groups and did not significantly decrease over time, after controlling for time in episode of their anxiety disorders. There was a statistically significant increase in SSRIs/SNRIs use over time in both groups. At the beginning of the study, 18% of the older group and 21% of the younger group were using SSRIs/SNRIs, however, at the

Received February 23, 2007; revised June 26, 2007; accepted July 18, 2007. From the Department of Psychiatry and Human Behavior, Brown University (CHP, KS, RR, MOE, MB), Providence, Rhode Island; and the Department of Psychiatry, Beth Israel Deaconess Medical Center–Harvard Medical School (RGG), Boston, Massachusetts. Send correspondence and reprint requests to Carlos Israel Perez Benitez, Ph.D., Department of Psychiatry and Human Behavior, Brown University, Box G-14, Regional Medical Center Building, Providence, RI 02912. E-mail: carlos_perez-benitez@brown.edu

© 2008 American Association for Geriatric Psychiatry

Am J Geriatr Psychiatry 16:1, January 2008
Anxiety disorders in the geriatric age group have been the subject of growing interest in the geriatric literature. Anxiety disorders are some of the most commonly occurring psychiatric disorders in older adults, with prevalence rates ranging from 5.5% in the United States to 10% in the Netherlands. Of the anxiety disorders, generalized anxiety disorder (GAD) is the most common, followed by phobic disorders.

Psychopharmacologic approaches continue to be the most frequent treatment for these disorders in older and younger adults. Benzodiazepines (BZs), in particular, have long been the most prescribed class of medication for treating anxiety. Epidemiologic and longitudinal studies suggest that rates of BZ use among older adults range from 10% to 32%. Two longitudinal studies have reported high rates of BZ use among those older adults with a diagnosis of an anxiety disorder. The Berlin Aging Study reported that BZs were used by 19% of the total sample and by 33% of study participants with an anxiety disorder diagnosis, while the Longitudinal Aging Study Amsterdam (LASA) showed that 43% of the study participants with persistent anxiety disorders were using BZs, while antidepressant use remained very low. A limitation of the LASA was that medication use was assessed at study onset and conclusion but not yearly over the six years of follow-up. Attrition rates were high, and the sample size of study participants with full diagnostic criteria for anxiety disorders was very small, limiting the scope of findings.

Although studies such as the LASA and Berlin Aging Study have provided essential information about patterns of medication use, more detailed information is needed about patterns of use over time. To our knowledge, no longitudinal study of older adults has been conducted with patients recruited from psychiatric settings. Given the need for evidence-based guidelines for the longitudinal use of BZs in the treatment of anxiety disorders, it would be useful to empirically define the actual naturalistic use of BZs over time in a population undergoing clinical treatment. Once the naturalistic BZ use characteristics are understood, hypotheses may be generated as to why such patterns of use have evolved. In addition, careful naturalistic longitudinal studies, such as the current study, can serve to generate hypotheses that may shape future prospective clinical trials that could influence evidence-based clinical guidelines.

Long-term use of BZs in older adults can be associated with dependency, significant withdrawal symptoms, unwanted sedative effects, coordination difficulties, and cognitive impairment. Selective serotonin reuptake inhibitors (SSRIs) and venlafaxine have a low risk of dependency and are relatively safe in overdose, although SSRIs take longer than BZs to have an anxiolytic effect and may have side effects that contribute to difficulty with long-term patient compliance. To our knowledge, there are no double-blind, controlled, “head to head” studies available that document the relative efficacy of SSRIs versus BZs in adult participants. There is a particular paucity of efficacy studies of any kind involving older adult patients. Clinical experience has suggested that SSRI/selective norepinephrine reuptake inhibitor (SNRI) antidepressants are well tol-

Key Words: longitudinal course, anxiety disorders, antianxiety agents
erated and have efficacy similar to that of BZs in treating persisting anxiety disorders, in both older and younger patients. Our investigation is unique in that it provides longitudinal data regarding the use of these medications in a naturalistic clinical follow-up study of adults as they age.

The purpose of the current study was to examine the use of BZs and SSRIs over time in older adults with anxiety disorders who were enrolled in the Harvard/Brown Anxiety Research Project (HARP). The prospective and longitudinal nature of HARP allows for tracking the clinical course of anxiety disorders, along with treatment utilization, over time. Previous reports using the present sample found that the frequency of BZ use remained relatively constant and BZs were the most common class of medications prescribed for patients with a diagnosis of panic disorder, social phobia, or GAD. However, these studies were not designed to differentiate the pattern of medication use as patients become older. The present study examines patterns of medication use (BZs and SSRIs) in patients with anxiety disorders as they age, by assessing the proportion of patients taking these medications. On the basis of previous findings from cross-sectional and longitudinal studies of geriatric populations that documented a high frequency of BZ use, we sought to address the following question: is there any change over time in the pattern of BZ and SSRI/SNRI use among adults diagnosed with anxiety disorders as they age?

**METHODS**

**Participants**

HARP is a prospective, naturalistic, longitudinal, multicenter study of 711 adults with a history of anxiety disorders. Participants enrolled in this study from over 30 clinicians’ practices at 11 different clinical treatment facilities in the New England area. The methods are described in detail elsewhere. After complete description of the study to participants, written informed consent was obtained. Inclusion criteria were that participants must have been at least 18 years of age at enrollment with a past or current diagnosis of panic disorder with or without agoraphobia, agoraphobia without panic disorder, social anxiety disorder, or GAD. Insufficient for inclusion but frequently seen as comorbid conditions were diagnoses of simple phobia, posttraumatic stress disorder, obsessive–compulsive disorder, and anxiety disorder not otherwise specified. Exclusion criteria were the presence of an organic brain syndrome, history of schizophrenia, and current psychosis within the last six months before enrollment. The present study is based on data for a total of 386 participants who met criteria for panic disorder with or without agoraphobia, agoraphobia without panic disorder, social anxiety disorder, or GAD at enrollment and who fell within one of the two age ranges defined for this study. Of these eligible participants, 262 had nine years of complete follow-up data. The current sample included 51 study participants who were 55 to 70 years old at baseline (older adults) and a younger cohort of 211 adults who were 30 to 45 years old at baseline (younger adults). (The “older adults” group is younger than samples in traditional studies of late-life disorders because it includes patients in the middle or older adulthood age range at intake. This age range was chosen to increase the sample size required for the analyses [48% of adults were in the 55- to 60-year age range], considering that HARP was not specifically designed for the geriatric population. We also wanted to be consistent with the LASA study that used a similar longitudinal design and population [older adults with anxiety disorder starting at age 55], and finally, by keeping the similar age band (15 years) for each group would facilitate interpretation of findings.)

**Intake and Follow-Up Assessments**

The present data were derived from the structured diagnostic interview administered at enrollment and subsequent follow-up interviews over a nine-year period. The initial diagnostic evaluation assessed current and lifetime history of relevant psychiatric conditions using a combination of the Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders, Third Edition–R Non-Affective Disorder, Patient Version and the Research Diagnostic Criteria Schedule for Affective Disorders–Lifetime. Items on the Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders, Third Edition–R Non-Affective Disorder, Patient Version and Research Diagnostic Criteria Schedule for Affec-
tive Disorders–Lifetime were combined to create "SCALUP," a structured interview used to assess diagnoses at intake (available from M.B. Keller on request). Follow-up interviews were conducted at six-month intervals for the first two years and annually thereafter using the Longitudinal Interval Follow-up Evaluation–Pharmacia & Upjohn, which is a structured interview that uses a change-point method to assess the weekly course of disorders to indicate syndrome severity, document medication use by specific type and dose on a weekly basis, and measure monthly psychosocial functioning. The Longitudinal Interval Follow-up Evaluation–Pharmacia & Upjohn assesses psychopathology with a six-point psychiatric status rating (PSR) scale that is scored for each week of the follow-up interval. The PSR scales for each disorder are described elsewhere. Three studies have been conducted analyzing the reliability and validity of the Longitudinal Interval Follow-up Evaluation–Pharmacia & Upjohn. One of these analyses found that the interrater reliability of the anxiety disorder PSRs and the other instruments was good to excellent (intraclass correlation coefficient range: 0.64–0.99). The long-term test–retest substudy conducted to assess the reliability of using subjects' retrospective recall to assess PSRs over one year found very good to excellent reliability (intraclass correlation coefficient range: 0.89–1.00) for the anxiety disorders, except for panic (intraclass correlation coefficient range: 0.62–0.80). There is also evidence of the external validity of the PSRs when compared with other psychosocial measures.

Information regarding pharmacologic treatment was collected from the participants every 6 to 12 months for each week of the interval and included medication type, average daily dose, and whether participants were taking them on a prn (as circumstances may require) basis. On the basis of subject self-report, use and dosage of all medications, including BZs and SSRls/SNRls, were recorded on a weekly basis throughout follow-up period. For the current study, medication use taken on a prn basis was not included.

Statistical Analyses

We used SAS version 8.3 (SAS Institute, Cary, NC) to analyze Generalized Estimating Equation (GEE) models with binary outcome measures. GEE analysis is a method similar to repeated-measures analysis of variance but provides more flexibility to account for nonnormal outcome data. As a first step, we examined BZ and SSRI use rates over time for the older group only. These models included a main effect for time and controlled for severity with a time-varying covariate indicating the amount of time during the year the respondent was "in episode." Our second set of analyses utilized data from both age groups to allow for time-trend comparisons. In addition to controlling for severity, these models specified main effects for age group and time as well as their interaction. We did not control for demographic variables such as sex and education because we were more interested in trends within groups. Significance of all model coefficients was evaluated using the $\chi^2$ test; $p < 0.05$ was significant.

RESULTS

Compared with ineligible participants ($N = 325$), eligible participants ($N = 386$) had higher rates of being married (47% versus 56%, respectively; $\chi^2 (1) = 5.25$, $p = 0.022$). They did not differ in age, sex, educational level, and employment status. Of the eligible participants, 262 (68%) had nine years of completed follow-up data. Of those who did not have nine years of completed follow-up data (32%), 69 refused to participate, 30 were not located, 13 died, 1 was too ill to be interviewed, and 11 were still active in the study but for less than nine years. There were not significant differences between participants with and those without completed follow-up data in regard to demographic variables, number of comorbid disorders (anxiety and depression), or lifetime substance use disorders. The older group included 51 participants with an average age of 61 years ($SD = 4.6$) at baseline, and the younger group included 211 participants with an average age of 38 years ($SD = 4.4$) at baseline. Women were predominant in both groups (59% of older group and 67% of younger group), and most participants were white (100% and 98.3%, respectively). In the older group, $54\%$ reported being married, $47\%$ had at least some college education, and $37\%$ had full-time employment. In the younger group, $58\%$ were married, $72\%$ had at least some

Am J Geriatr Psychiatry 16:1, January 2008

Reproduced with permission of the copyright owner. Further reproduction prohibited without permission.
college education, and 56% had full-time employment. The younger cohort had significantly higher rates of employment (χ² (1) = 6.04, p = 0.014) and higher levels of education (χ² (1) = 11.62, p < 0.001) than the older group. Other demographic variables and number of comorbid disorders were not significantly different.

An inspection of endorsed anxiety disorders in both groups (Table 1) showed a high level of comorbidity with other anxiety disorders (range: 3%-34%) as well as with major depression (range: 2%-22%) and substance disorders (range: 2%-24%) at the time of the initial assessment and during the nine-year follow-up. Over time, the most commonly occurring comorbid disorders were GAD and panic disorder with agoraphobia for both groups. Regarding medications taken on a regular basis (those on a prn basis were excluded) at some point during the study period, the most reported BZ types were alprazolam (39% of the older group versus 47% of the younger group), clonazepam (20% versus 43%, respectively), diazepam (16% versus 6%, respectively), and lorazepam (12% versus 12%, respectively). Among the SSRI/SNRI group, participants reported more commonly taking fluoxetine (32% of the older group versus 41% of the younger group), sertraline (18% versus 20%, respectively), paroxetine (6% versus 20%, respectively), and venlafaxine (2% versus 10%, respectively).

Our primary goal was to examine the rate of BZ and SSRI/SNRI use among a population of middle-aged and older adults as it related to the age of the patient. GEE analysis of data from the older group alone revealed no significant time effect of the number of participants using BZs. Although not significantly different, there was a small decline of BZ users over time. At the beginning of the study, 53% of the 51 older group adults were using BZs in comparison with Years 3 (48%), 5 (41%), 7 (45%), and 9 (41%) of the follow-up period. In a similar analysis modeling SSRI/SNRI use, the number of participants using SSRIs/SNRIs increased over time: Years 1 (18%), 3 (14%), 5 (22%), 7 (30%), and 9 (35%). However, this change was not statistically significant.

To determine if this pattern of BZ and SSRI/SNRI use was exclusive to this age group, we conducted additional analyses to establish a comparison with younger participants from the same HARP sample. Figure 1 depicts the rates of BZ and SSRI/SNRI use among older and younger adults over the nine-year period.

### TABLE 1. Comorbid Disorders by Group During the Nine-Year Follow-Up Period

<table>
<thead>
<tr>
<th>Group</th>
<th>Younger Adults (N = 211) by Comorbid Anxiety Disorder</th>
<th>Older Adults (N = 51) by Comorbid Anxiety Disorder</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>GAD</td>
<td>SP</td>
</tr>
<tr>
<td>SP</td>
<td>53 (25)</td>
<td></td>
</tr>
<tr>
<td>PD</td>
<td>12 (6)</td>
<td>6 (3)</td>
</tr>
<tr>
<td>PDA</td>
<td>71 (34)</td>
<td>40 (19)</td>
</tr>
<tr>
<td>Major depressive disorder</td>
<td>32 (15)</td>
<td>21 (10)</td>
</tr>
<tr>
<td>Substance abuse/dependence</td>
<td>40 (19)</td>
<td>34 (16)</td>
</tr>
</tbody>
</table>

*Note: Data are number (%) of study participants. GAD: generalized anxiety disorder; SP: social phobia; PD: panic disorder; PDA: panic disorder with agoraphobia.

*These patients developed agoraphobia during the clinical course of their PD.
BZ and SSRI Use in Middle-Aged and Older Adults With Anxiety Disorders

period and the proportion of participants in anxiety episodes. GEE analysis revealed no significant group, time, or interaction effects of BZ use. When we examined SSRI/SNRIs use, GEE analysis revealed a main effect of time ($\chi^2 = 20.0$, $p < 0.001$), after controlling for proportion of time in anxiety episodes. Specifically, as shown in Figure 1, the percentage of SSRI/SNRIs users in both groups significantly increased from Year 1 to Year 9 ($\beta = 0.94$, $Z = 2.10$, $p = 0.035$). Although not statistically significant ($\chi^2 (1) = 3.11$, $p = 0.078$), the rate of SSRI/SNRIs use among the older group was lower than that among the younger group. At the beginning of the study, 18% of the older group and 21% of the younger group were using SSRIs/SNRIs, while at the end of this study, the rates increased to 35% and 43%, respectively.

With respect to patterns of SSRI/SNRIs use, we found that both groups showed a significant increase in use of these medications over time. However, only 35% of the older group was taking SSRIs/SNRIs at the end of the study. Previous reports using HARP data with mixed-age samples also found low to moderate rates of use of these medications. In one study, participants with panic disorder had only a moderate increase in SSRI use (from 13.3% at enrollment to 32.9% at the 10-year follow-up), but approximately two-thirds of SSRI users were BZ users as well. These findings suggest that there is still a gap between the new pharmacologic treatment guidelines for the management of anxiety disorder and the underutilization of these medications in clinical practice. In other countries, studies have found much lower rates of medication use among older adult groups. For example, researchers of the LASA, conducted in the Netherlands, reported that only 7% of their elderly sample with anxiety disorders were using BZs at baseline and throughout the six years of follow-up. The underutilization of SSRIs/SNRIs is likely in part related to medication side effects and possibly influenced by concerns regarding the need for careful clinical monitoring of participants taking these agents.

Our study found that SSRI/SNRIs treatment is still underutilized in older adults with panic disorder, panic disorder with agoraphobia, social phobia, and GAD despite the fact that the relative safety of these medications in the geriatric population has been established and they are considered the primary therapeutic option for these conditions. The use of SSRI/SNRIs in elderly adults with anxiety disorders is highlighted by the absence of evidence-based research supporting alternative psychopharmacologic treatments for these disorders and the potential risks of treating elderly anxious/aged dementia patients with atypical antipsychotic medications. Other studies suggest that effective psychological treatments of anxiety-related disorders are also underutilized.

One limitation of the current study is that it relied solely on participants' self-report of the type and frequency of medications used. Not having additional sources to corroborate participants' information such as medical or pharmacy records may have influenced the accuracy of the data. The age range chosen for the older group did not allow exploring...
medication patterns in participants older than 70 years, who should be part of future studies. Due to the limited sample size, it was not possible to conduct a separate analysis of medication use by specific anxiety disorders. Other useful information about medication combinations, target symptoms, and treatment history were not investigated in the present study.

The attrition rate was relatively high (30%), which was expected for a longitudinal study that included older people. However, participants lost during the follow-up period did not differ from those participants who remained in the study with regard to demographic variables and comorbid psychiatric disorders. Another limitation is that the HARP sample was drawn from the New England area, with most of the participants being white. It is unknown if these results are applicable to other geographic areas in the country and to other ethnic groups. To understand the clinical course of anxiety disorders in other ethnic groups, at the time of this writing, HARP has recruited 200 Hispanic and African American participants with anxiety disorders and is currently following them up. Previous studies found unequal rates of BZ use in different geographic regions of the United States.

The pattern of utilization of medications described in this study raises interesting questions not only about whether administrative, social, and/or financial factors influence medication utilization but also about patterns of side effects and efficacy issues. All these topics need further study. Thus, this study defined what was happening in real life practice but did not address why it happened. Future studies may clarify the factors contributing to the treatment pattern of high rates of persistent use of BZs and relatively lower rates of utilization of SSRIs/SNRIs among populations of patients with anxiety disorders. Further studies are required to enhance our understanding of evidence-based treatment of anxiety disorders in older adults.

This work was supported in part by Wyeth-Ayerst Laboratories, through its Global Research Program on Anxiety and Depression, and by a grant from the National Institute of Mental Health (MH51415).

RGV is a member of the Speaker’s Bureau of Pfizer, Forest, and Wyeth Pharmaceuticals. In the past two years, MBK has been a consultant and received honoraria from the following companies: Collegium, Cypress Bioscience, Cyberonics, Eli Lilly, Forest Laboratories, Janssen, Organon, Otsuka, Pfizer, Pharmacia, Sepracor, Vela Pharmaceuticals, and Wyeth Pharmaceuticals. He has received grants for his research from Eli Lilly, Pfizer, and Wyeth Pharmaceuticals. He has served on the advisory boards for Abbott Laboratories, Bristol-Myers Squibb, Cyberonics, Cypress Bioscience, Eli Lilly, Forest Laboratories, GlaxoSmithKline, Janssen, Novartis, Organon, Pfizer, Sepracor, and Wyeth Pharmaceuticals. He is not a major stockholder of any pharmaceutical or medical company. CIPB, KS, MOE, and RR have no competing interests.

The Harvard/Brown Anxiety Research Project is conducted with the participation of the following investigators: M. B. Keller, M.D. (Chairperson); M. T. Shea, Ph.D. (VA Hospital, Providence–Brown Medical School, Providence, RI); J. Eisen, M.D., K. Phillips, M.D., R. Stout, Ph.D., R. Reine, Ph.D., T. Mueller, M.D., C. Zlotnick, Ph.D. (Butler Hospital–Brown Medical School); R. B. Weisberg, Ph.D., M.G. Warshaw, M.S.S., M.A. (Brown Medical School); R. M. Goisman, M.D. (Massachusetts Mental Health Center–Harvard Medical School, Boston, MA); A. Massion, M.D. (University of Massachusetts Medical Center, Boston, MA); M. E. Rogers, M.D. (Brigham and Women’s Hospital–Harvard Medical School); C. Salzman, M.D. (Massachusetts Mental Health Center–Harvard Medical School); G. Steeke, Ph.D. (Boston University School of Social Work, Boston, MA); K. Yonkers, M.D. (Yale University School of Medicine, New Haven, CT); I. Goldenberg, Psy.D., G. Malyka, M.D., F. Rodriguez-Villa, M.D. (McLean Hospital–Harvard Medical School); R. Vasile, M.D. (Beth Israel Deaconess Medical Center–Harvard Medical School); and E. Fierman, M.D. (Beth Israel Hospital). Additional contributions were made by the following investigators: P. Alexander, M.D., A. Gordon, M.D., S. Rasmussen, M.D. (Butler Hospital–Brown Medical School); J. Curran, M.D., J. Cole, M.D. (McLean Hospital–Harvard Medical School); J. Ellison, M.D., M.P.H. (Harvard Pilgrim Health Care–Harvard Medical School); R. Hirschfeld, Ph.D. (University of Texas, Galveston, TX); J. Hooley, D.Phil. (Harvard University); P. Lazzari, Ph.D. (Stanford University, Stanford, CA); J. Perry, M.D. (Jewish General Hospital–McGill University School of Medicine, Montreal, Quebec, Canada); L. Peterson (Midwest Medical Group, Rockport, ME); J. Reich, M.D., M.P.H., J. Rice, Ph.D. (Renard Hospital–Washington University School of Medicine, St. Louis, MO); H. Samuelson, M.A. (Brigham and Women’s Hospital); D. Shera, M.S. (Harvard School of Public Health); N. Weinshenker, M.D. (New Jersey Medical School); and M. Weismann, Ph.D. (Columbia University, New York, NY).
BZ and SSRI Use in Middle-Aged and Older Adults With Anxiety Disorders

The authors thank K. White, M.D., Holly Ramsawh, Ph.D., and Caroline Greavig-Ardlo for reviewing drafts of this article.

References


