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Long-Term Use of Benzodiazepines in Participants with Comorbid Anxiety and Alcohol Use Disorders

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Abstract

Background—Although the only widely accepted role for benzodiazepines in alcohol dependence is the treatment of withdrawal syndromes, they are frequently prescribed outside of this clinical setting. There is little empirical evidence to guide the rational use of benzodiazepines in the common clinical situation where anxiety disorders are comorbid with alcohol use disorders (AUD). Since January 1989, the Harvard Anxiety Research Program has naturalistically monitored the prospective clinical course of people with anxiety disorders, some of whom had a history of AUD. Earlier research showed that the use of benzodiazepines was not significantly associated with the presence or absence of a history of an AUD over the first year of follow-up. This report extends that investigation.

Methods—Using standard parametric analytic methods, patterns of benzodiazepine use (routinely prescribed medication and as-needed [PRN] use) among participants receiving benzodiazepine treatment was prospectively examined over the course of 12 years. Differences in benzodiazepine usage patterns were examined in each year of follow-up between participants who did ($n = 120$) and did not ($n = 425$) have a new episode of AUD. Using proportional hazards regression analysis, benzodiazepine usage levels were examined as predictors of recovery and recurrence of AUD. Additionally, random-effects regression analyses were used to examine the patterns of benzodiazepine use before and after the onset of a prospectively observed episode of AUD.

Results—Benzodiazepine usage levels remained stable for the full sample over the course of the 12 years. Benzodiazepine use did not distinguish participants who had a new AUD from those who did not. Over the 12 years of follow-up, participants who had an AUD used more PRN medication in years five to eight. This difference reached statistical significance but was not clinically significant. Benzodiazepine usage levels did not predict recovery or recurrence in AUD subjects. Neither the total dose nor the PRN usage of benzodiazepines was significantly associated with the onset of AUD, but when combined into a measure of any benzodiazepine use, a relationship between increased use and the onset of AUD emerged.

Conclusions—For participants in the Harvard Anxiety Research Program with comorbid alcohol dependence and anxiety disorders, there was little association between the use of benzodiazepines and the occurrence of a new AUD. Neither was there a temporal relationship between the use of

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benzodiazepines and the onset of a new AUD. Whether or not this finding extends to a broader patient population or a group of people who present to addictions treatment awaits further investigation.

Keywords

Benzodiazepines; Alcohol Use Disorders; Harvard Anxiety Research Program; Anxiety; Comorbid Alcohol Dependence; Anxiety Disorders

The appropriate use of benzodiazepines for patients with comorbid anxiety disorders and alcohol use disorders (AUD, alcohol dependence or abuse, APA, DSM) continues to engender vigorous debate (Annitto, 1989; Ciraulo, 2000; Hershberg, 1996; Posternak and Mueller, 2001). On one hand, benzodiazepines continue to be standard pharmacotherapy for many anxiety disorders, especially panic disorder, and for patients who need prompt pharmacologic relief of their symptoms during the induction phase of other measures such as selective serotonin reuptake inhibitors (SSRIs) and cognitive-behavioral psychotherapy (APA, 2002; Posternak and Mueller, 2001; Stahl, 2002). On the other hand, benzodiazepines are generally accepted pharmacotherapy only for managing the symptoms of alcohol withdrawal in people with alcohol dependence (APA, 2002). There is no accepted use of benzodiazepines for patients with AUD after detoxification, and their use for patients with comorbid anxiety disorders is at best cautiously advised (APA, 2002; Lejoyeux et al., 1998).

The dilemma of the appropriate prescribing of benzodiazepines to patients with anxiety disorder with AUD has both practical and theoretical value. Anxiety disorders and alcohol use disorders commonly co-occur (Kessler et al., 1997; Kushner et al., 1990; Regier et al., 1998; Swendsen et al., 1998; Swift and Stout, 1992). Among people with any anxiety disorder, 18% have a lifetime history of an AUD. Conversely, 19% of people with any AUD have a lifetime history of an anxiety disorder (Regier, 1990). This co-occurrence needs to be distinguished from the also frequent co-occurrence of anxiety symptoms in people with AUD (Hesselbrock et al., 1985; Kranzler, 1994; Roberts et al., 1999; Schuckit and Hesselbrock, 1994). Each of these common clinical circumstances typically triggers a cascade of diagnostic and therapeutic decisions that often include the use of benzodiazepines. One might argue that the optimal treatment for the anxiety symptoms associated with an active AUD is abstinence from alcohol, since these symptoms are often short-lived. But what role should benzodiazepines play in people with anxiety disorders and AUD, both of which are disabling (Posternak and Mueller, 2001)?

Cross-tolerance with alcohol and the abuse potential of benzodiazepines justify their cautious use. However, there is a dearth of empirical evidence to guide the practicing clinician when making decisions regarding benzodiazepine treatment of patients with anxiety and AUD. Most clinicians can relate personal examples of misadventures with alcoholics who also have anxiety disorders or symptoms, but systematic evidence is lacking (Ciraulo et al., 1988; Posternak and Mueller, 2001). The Harvard/Brown Anxiety Disorders Research Program (HARP) offers a unique opportunity to examine the relationship between benzodiazepine use and AUD in people with anxiety disorders. HARP is a naturalistic, prospective follow-up study of 711 participants with anxiety disorders recruited from clinical settings between 1989 and 1991. Participants were interviewed by telephone or in person at six-month or annual intervals to assess symptoms, psychosocial functioning, and treatment. The study has provided critical information about the longitudinal course of anxiety disorders, revealing them in general to be chronic illnesses (Bruce et al., 2005; Yonkers et al., 2003) associated with significant psychosocial impairment (Massion et al., 1993). Benzodiazepines are more commonly used than selective serotonin reuptake inhibitors in patients with panic disorder, generalized anxiety disorder, and social phobia, and the use of benzodiazepines has slightly decreased over 10 years of follow-up (Bruce et al., 2003).

A previous HARP investigation by Mueller et al. (1996) involved a total of 343 participants who at intake were taking benzodiazepines, 29% of whom had a past or current history of alcohol use disorder (ethanol). When ethanol and nonethanol participants were compared, no significant differences were found in the maximum daily dose or the supplemental (PRN) use of benzodiazepines over the first 12 months of follow-up. Minor differences in pattern of use were apparent when the 12-month period was separated into six-month epochs, but in sum there was little that distinguished the benzodiazepine use of the two groups. In addition, there were no recurrences of AUD observed during the first 12 months of HARP follow-up.

The present study reexamines the relationship between benzodiazepine use patterns and the course of AUD, building on the strength of 12 years of prospectively collected follow-up data. This report tests three hypotheses of the impact of benzodiazepine usage on the course of AUD. First, we hypothesize, based on our earlier findings, that among participants receiving benzodiazepine treatment, there would be no significant difference in benzodiazepine usage patterns between participants who had a new, prospectively observed AUD and those who did not, across the course of the 12 years of the study period. Second, we hypothesize that patterns of benzodiazepine use would not predict recovery for participants who had a prospectively observed episode of an AUD, nor subsequent recurrence for those who have recovered. Third, we hypothesize that benzodiazepine usage would not significantly change at the time of the onset of AUD, nor would benzodiazepine patterns change in the six months after the AUD onset.

METHODS

HARP is a prospective, naturalistic, longitudinal, multicenter study of adults with a current or past history of anxiety disorders. A total of 711 participants entered this study from over 30 clinicians' practices at 11 different clinical treatment facilities in the New England area. These methods are described in detail elsewhere (Keller et al., 1994). Inclusion criteria were a past or current diagnosis of panic disorder with or without agoraphobia, agoraphobia without panic disorder, social anxiety disorder, or generalized anxiety disorder. Insufficient for inclusion but frequently seen as comorbid conditions were diagnoses of simple phobia, posttraumatic stress disorder, obsessive-compulsive disorder, or anxiety disorder not otherwise specified. Participants must have been at least 18 years of age at intake, willing to voluntarily participate in the study, and sign a written consent form. Exclusion criteria were the presence of an organic brain syndrome, a history of schizophrenia, or current psychosis within the last six months before intake.

Intake and Follow-up Assessments

The present data derive from the structured diagnostic interview administered at intake and subsequent follow-up interviews over a period of 12 years. The initial diagnostic evaluation assessed current and lifetime history of relevant psychiatric conditions using a combination of the Structured Clinical Interview for DSM-III-R Non-Affective Disorders, Patient Version (SCID-P), and the Research Diagnostic Criteria (RDC) Schedule for Affective Disorders-Lifetime (SADS-L). Items on the SCID-P and SADS-L were combined to create the 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-Upjohn (LIFE-UP, Keller et al., 1987). The LIFE-UP uses a change-point method to assess the weekly course of disorders using psychiatric status ratings (PSRs) to indicate syndrome severity, document medication use by specific type and dose on a weekly basis, and measure psychosocial functioning monthly. Specifically for AUD, subjects were questioned about whether they consumed any beverage alcohol in the interval since the last research interview. If yes, they

are then systematically asked if they met any of the DSM-III-R criteria for alcohol abuse or dependence during the interval. In this way AUD can be coded as being either active or inactive for each week of the interval. A more detailed description of the HARP intake and follow-up procedures and the reliability of the LIFE-UP can be found in other published reports (Keller et al., 1994; Massion et al., 1993; Warshaw et al., 1994).

Definitions of Recovery and Recurrence

In HARP, AUD are recorded on a three-point PSR scale. A PSR of three indicates the subject met full DSM-III-R diagnostic criteria for alcohol abuse or dependence during the week in question. A PSR of two indicates the subject has residual symptoms of AUD, not meeting full diagnostic criteria. A PSR of one indicates the subject is asymptomatic for AUD. To be considered as having AUD recurrence, a participant must meet diagnostic criteria (PSR of three) for four consecutive weeks. To be considered recovered from AUD, a subject must be asymptomatic (PSR of one) for 26 consecutive weeks. This definition of recovery has been widely used in studies of alcohol use disorders.

Benzodiazepine Use

Based on subject self-report, use and dosage of all medications including benzodiazepines were recorded on a weekly basis throughout follow-up period. For analytical purposes, all benzodiazepine use was standardized by converting reported medications into chlordiazepoxide equivalents by using the same conversion table described in Mueller et al. (1996) (Table 1). Furthermore, we evaluated the amount of benzodiazepine use, based on the total amount of regularly prescribed or administered benzodiazepines as an average daily dose (Benzo Dose) as well as the proportion of weeks the subject reported taking any benzodiazepines on an as-needed basis (PRN). Since the data on the PRN use was documented only as whether or not benzodiazepine medication was received, we are not able to describe the dosing quantities of PRN medications.

Study Group

This report analyzes data on the 545 participants in HARP who were treated with a benzodiazepine during the course of 12 years of follow-up; this represents 77% of the entire study group at intake ($n = 711$). This sample is larger than the original report due to participants who initiated benzodiazepine use after entry into the study. There were no significant clinical or demographic differences between those who were taking a benzodiazepine at intake [$n = 343$; see Mueller et al. (1996) for further details of usage patterns at intake] and those who started taking a benzodiazepine over the course of the following 12 years. The average start of benzodiazepine treatment was 171.6 (SD = 174.7) weeks after intake.

Statistical Methods

Statistical analyses were conducted by using SAS version 8.0 (SAS Institute Inc, 1999), using PROC FREQ, PROC NPARIWAY, PROC PHREG, and PROC GENMOD. Categorical data were compared by using χ^2 and continuous data by Wilcoxon rank sums, since the distributions did not meet the assumptions for parametric analysis. We relied on the determination of effect size (d) for the purposes of interpretation. Cohen (1988) considers $d = 0.20$ “small,” $d = 0.50$ “medium,” and $d = 0.80$ “large.” Cox regression analyses were conducted to calculate the relative hazards of benzodiazepine use as predictors of both recovery and recurrence from AUD. Latent growth analyses using generalized estimating equations procedures were conducted to determine the relationship between benzodiazepine usage patterns and the onset of AUD. For a general introduction to latent growth analysis, see Bryk and Raudenbush (1992). We modeled the benzodiazepine usage over time for the 120 participants who had a prospectively observed new AUD as an interrupted time series to test the hypothesis that there

were benzodiazepine usage changes after AUD onset. These post-AUD changes could take the form of either a change in level at the time of the AUD onset or a progressive change in the following six months (slope) or both. A secular trend term is necessary to rule out the possibility that post-AUD benzodiazepine usage changes might have begun well before AUD onset. There were no constraints on the covariation across time point.

RESULTS

Characteristics of the Study Group

Table 2 presents the clinical and demographic characteristics of this study group at intake, distinguished by whether or not they had development of AUD. The mean age of the study group at intake was 41.2 years, 67% were women, and the large majority had either a high school diploma (53%) or were college graduates (40%). Most engaged in skilled employment (79%), and 60% were married or living with a partner. The most common intake diagnoses were panic disorder with agoraphobia (54%), major depressive disorder (27%), generalized anxiety disorder (27%), and social phobia (24%), and 10% of all subjects had a history of a suicide attempt or gesture.

Of the 711 HARP study participants, 545 reported using benzodiazepines during the 12 years of follow-up, with an average of approximately six years of benzodiazepine treatment ($M = 309.2$ weeks, $SD = 232.2$). Twenty-two percent ($n = 120$) of the sample receiving benzodiazepine treatment had development of AUD during this time period. Patients who had AUD were significantly more likely to be male, have a younger age, and a prior history of a suicide attempt or gesture than those who did not have AUD. Additionally, patients with an intake diagnosis of social phobia and a prior history of AUD were also more likely to have an onset of AUD during the follow-up period. Benzodiazepine treatment, regardless of dosage or PRN usage at intake, was not associated with AUD onset during follow-up. In this study, the mean time to AUD onset for the 120 participants was 160.5 weeks ($SD = 171.5$).

Subjects also received other psychiatric medications. There were no differences between the two AUD groups in the number of weeks during the follow-up period that subjects reported use of SSRIs, anticonvulsants, or antipsychotics. Specifically for the non-AUD group ($n = 425$) and the AUD group ($n = 120$), the following are the respective mean number of weeks for SSRIs (117, $SD = 170$ and 138, $SD = 188$; $df = 1$, $F = 1.42$, $p = 0.23$), anticonvulsants (0.1, $SD = 1.3$ and 0.0; $SD = 0$, $df = 1$, $F = 0.56$, $p = 0.46$), and antipsychotics (1.1, $SD = 12.7$ and 0, $SD = 0$; $df = 1$, $F = 0.84$, $p = 0.36$). No subject reported taking naltrexone.

Course of Benzodiazepine Use

Table 3 shows the summary of benzodiazepine use over the course of the 12 years of follow-up. These data are presented in yearly increments as both the average daily dose and as the number of weeks during the 52-week reporting interval that the subject reported taking any PRN doses. We first examined whether the usage patterns of benzodiazepine increased, decreased, or remained stable for the full sample over the course of the 12 years. The results of random effects regression analyses indicated that benzodiazepine dosage levels remained stable over the course of the 12 years of follow-up ($F = 0.82$, $df = 1$, 4466, $p = 0.62$). In general, patterns of number of weeks of receiving PRN benzodiazepine medications for the total sample were also relatively stable across the 12 years. However, a statistically significant time effect for PRN usage ($F = 2.03$, $df = 1$, 4466, $p = 0.02$) detected an increased mean number of weeks receiving PRN benzodiazepine treatment in years four to 11 in comparison to year one. However, the magnitude of this difference is small, with an average of one additional week per year of PRN usage during years four to 11 in comparison to the baseline levels of mean number of weeks of PRN usage. The percent of participants with any benzodiazepine usage

across the 12 years of the study period remained relatively stable as well; on average, 65% of the sample was receiving benzodiazepine medications annually.

The pattern is somewhat different for subjects, based on whether or not they were AUD or non-AUD (Table 3). With little exception, benzodiazepine use did not distinguish whether or not a subject would have a prospectively observed AUD. Throughout all years, AUD participants generally reported using more benzodiazepine than non-AUD participants, but the majority of differences were small and nonsignificant. The same pattern applies to PRN usage; however, during years five to eight, the differences reach statistical significance. The magnitude of the differences in PRN usage as reflected in effect size, during years five to eight is relatively small: year five ($d = 0.30$), year six ($d = 0.26$), year seven ($d = 0.23$), and year eight ($d = 0.20$). Considering the total number of weeks during follow-up, AUD participants had slightly higher number of weeks using a benzodiazepine ($M = 338.8$, $SD = 229.2$) in comparison to participants without AUD ($M = 300.8$, $SD = 232.6$), but differences were not significant (Wilcoxon $\chi^2 = 2.12$, $DF = 1$, $p = 0.15$).

Benzodiazepine Use as a Predictor of Recovery and Recurrence

Using proportional hazard (Cox) regressions with Efron approximation, a method recommended in analyzing time to event data (Allison, 1995), we examined whether the use of any benzodiazepines the week before recovery and the week before recurrence influenced the course of AUD over the duration of 12 years. Of the 120 AUD participants, 87 (73%) recovered from AUD. Of these 87 participants who recovered, 36 (41%) went on to have another recurrence of AUD. As shown in Table 4, benzodiazepine use carried no predictive value regarding the likelihood of AUD recovery ($RR = 1.31$, 95% $CI = 0.81$ to 2.13) or recurrence ($RR = 0.82$, 95% $CI = 0.46$ to 1.60).

Changes in Benzodiazepine Use Among Participants With Alcohol Use Disorder

Table 5 presents the results of generalized estimating equations analyses that examined benzodiazepine usage patterns six months before and six months after the AUD onset among the 120 participants who prospectively reported this event. Three separate analyses were conducted for benzodiazepine dose, PRN usage, and any benzodiazepine usage. The models used four random effects: 1) intercept (the subject's estimated level at the time of the AUD onset), 2) secular linear trend (linear change in benzodiazepine pattern over time regardless of whether before or after the AUD onset), 3) benzodiazepine use change (a shift in the level of benzodiazepine use in the week of the episode onset), and 4) benzodiazepine slope change (a change in the slope of the benzodiazepine use patterns over time after the AUD onset). This model permits us to examine the use of benzodiazepines at the time of the AUD onset and 6 months after the onset of a prospectively observed AUD. For the dichotomous outcome measures (PRN usage and any benzodiazepine usage), we used methods that specified a binomial distribution with exchangeable log odds ratios. For the continuous outcome measure (benzodiazepine dosage), we found the gamma distribution to best fit the observed data.

In general, benzodiazepine usage patterns had little predictability in relation to AUD onset. There was no relationship between the dose of benzodiazepine and the onset of AUD. For use of any benzodiazepine, however, there was an increase in the log-likelihood of receiving any benzodiazepine at the time of AUD onset (coefficient = 0.38 , $p = 0.04$). Clinically, this translates into a 46% increase in the likelihood of receiving any benzodiazepine at the time of AUD onset. There was a nonsignificant trend ($p = 0.08$) of an increase in the log-likelihood of increased PRN usage in the 26 weeks after the alcohol use disorder onset. Clinically, this translates into 2% increase in the likelihood of increased PRN usage in the 26 weeks after the onset of AUD.

DISCUSSION

In the years since the first report of the use of benzodiazepines among the HARP participants who are at risk to either increase the use of these medications or to have an alcohol use disorder, we continued to collect data on this important clinical issue. The current findings extend the earlier ones, again suggesting that there is little misuse of benzodiazepines in participants who have coexisting anxiety disorders and AUD over 12 years of prospective follow-up. Furthermore, there is little evidence that the intensity (dose, duration) of benzodiazepine use is associated with the onset, recovery, or subsequent recurrence of AUD. Although some measures of benzodiazepine use did reach statistical significance, the magnitude and clinical significance of these differences was small. Subjects who had a prospectively observed episode of SUD were 46% more likely to take any benzodiazepine during the six months after the AUD onset. The use of PRN benzodiazepine and the dose of benzodiazepine were not related to the onset of AUD, but when these measures were collapsed into the measure of any use, a relationship emerged. This is clinically meaningful, but the relationship is not very large. The large number of HARP participants permits us to detect such small differences when subjected to statistical analysis. It is possible that this association is a reflection of an increase in benzodiazepines to treat alcohol withdrawal, but this cannot be determined, since HARP did not collect information pertaining to the attributions for use of medications. However, the magnitude of the increase is very small (0.3 benzodiazepine equivalents), which suggests that this increase does not represent an effort to treat alcohol withdrawal.

Several limitations of this study are relevant. We cannot report on alcohol use because we have no data on quantity or frequency of alcohol use. The LIFE-UP initial SUD probes query subjects about whether or not they drank any beverage alcohol; however, this information is not coded, and subsequent questions focus on the DSM-III-R criteria for AUD. Recovery and recurrence may be too coarse a measure of the activity of AUD when compared with the fine-grained descriptions we have collected on benzodiazepine use. Although other authors have demonstrated the reliability and validity of the LIFE-UP for anxiety and mood disorders, which are the focus of HARP, SUD have not been subjected to the same psychometric study. Nonetheless, we believe the reliability findings can be generalized to include recovery and recurrence of SUD. All HARP participants were recruited into the study by virtue of meeting diagnostic criteria for an anxiety disorder and although they were not excluded if they had an active AUD at intake, none did. Therefore, these findings may not be relevant to the large number of people who have anxiety symptoms in the presence of substance intoxication, withdrawal, or early abstinence. This study population also may not generalize to people who seek out addiction treatment and are subsequently determined to have an anxiety disorder.

However, the clinical and demographic characteristics that distinguish the two groups (AUD and non-AUD), namely, being male, younger, and an intake diagnosis of social phobia, are characteristic of people who have AUD (Regier, 1990), suggesting that this study group may be similar to most populations of people with these diagnoses. Furthermore, it would be expected that a prior history of AUD would predict the occurrence of another episode. The high rate of suicide attempts or gestures in this population is a reminder of the morbid risk anxiety disorders carry, a risk that is further elevated by the co-occurrence of AUD.

The perceived risk of using benzodiazepines in patients with alcohol use disorders has prompted investigators to study the value of buspirone for the treatment of anxiety disorders in patients with comorbid AUD, but buspirone is not consistently effective in these subject groups and is not prompt in its anxiolytic effect (Kranzler, 1994; Malcolm, 1992). Buspirone is relegated to the category of "other agents" in the American Psychiatric Association practice guidelines for the treatment of panic disorder (American Psychiatric Association Work Group on Panic and American Psychiatric Association Steering Committee on Practice, 1998).

However, for patients who have an unacceptable risk to use benzodiazepines or have already had problems, it may represent an additional alternative to SSRIs and cognitive therapy.

Cautious endorsements of the use of benzodiazepines frequently note the risk of physiological dependence of these medications (Ciraulo, 2000). Indeed, the chronic use of benzodiazepines commonly causes physiological dependence and withdrawal syndromes on abrupt discontinuation in people, regardless of a person's personal history of substance use disorders (Rickels et al., 1990; Schweizer et al., 1990). Physiological dependence by itself does not constitute a substance use disorder. It merely guides the patient and their treating physician toward an open discussion of the risks of using this class of medication. The acquisition of a diagnosis of a substance use disorder requires other evidence of adverse consequences of the use of the substance (DSM-IV). An additional risk of using benzodiazepines in patients with AUD is the risk that the cross-tolerance between alcohol and benzodiazepines might lead to an increased rate of recurrence of AUD (Graham et al., 1992).

Our data suggest that for HARP participants, there is little differential risk of benzodiazepine use as a predictor of the onset or subsequent course of an AUD except for the derivative measure of benzodiazepine use, which combined PRN use and dosage level into a single measure of any benzodiazepine use. In fact, the withholding of benzodiazepines in people similar to the participants in this study may unnecessarily deprive them of the benefits of this class of effective medications for anxiety disorders (Ciraulo et al., 1989; Posternak and Mueller, 2001). This prospective, naturalistic follow-up study cannot definitively answer the question of risk of benzodiazepine use in this common clinical situation. The practice of clinical psychiatry would be immeasurably advanced by a carefully designed, randomized, controlled clinical trial assessing the risks and benefits of using benzodiazepines to reduce the morbidity associated with the co-occurrence of AUD and anxiety disorders.

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Table 1

Benzodiazepine Equivalencies

Benzodiazepine	Equivalent Dose (mg)
Alprazolam	0.5
Chlordiazepoxide	10.0
Clonazepam	0.25
Clorazepate	7.5
Diazepam	5.0
Flurazepam	15.0
Lorazepam	1.0
Oxazepam	15.0
Prazepam	10.0
Temazepam	15.0
Triazolam	0.25

Table 2
Intake Demographic and Clinical Characteristics of Study Group

Characteristic	Total <i>n</i> = 545 (100%) <i>n</i> (%)	Non-AUD <i>n</i> = 425 (78%) <i>n</i> (%)	AUD <i>n</i> = 120 (22%) <i>n</i> (%)
Sex ^a			
Men	178 (34)	124 (29)	54 (45)
Women	367 (67)	301 (71)	66 (55)
Age M (SD) ^b	41.2 (12.0)	42.4 (12.1)	36.9 (11.2)
Hospitalized	185 (34)	140 (33)	45 (38)
Suicide attempts/gestures ^c	56 (10)	39 (9)	17 (14)
Education			
College graduate	218 (40)	175 (41)	43 (35)
HS diploma	290 (53)	223 (52)	67 (56)
< HS	37 (7)	27 (6)	10 (8)
Occupation			
Executive	38 (7)	33 (8)	5 (4)
Business manager	125 (23)	98 (23)	27 (23)
Administrator	122 (22)	89 (21)	33 (27)
Clerical	145 (27)	120 (28)	25 (21)
Skilled manual	39 (7)	28 (7)	11 (9)
Machine operator	35 (6)	29 (7)	6 (5)
Unskilled employ	22 (4)	17 (4)	5 (4)
Other	19 (3)	11 (3)	8 (7)
Marital Status			
Married	296 (54)	242 (57)	54 (45)
Living with Partner	29 (6)	19 (4)	10 (8)
Divorced/widowed	83 (15)	64 (15)	19 (16)
Single	137 (25)	100 (24)	37 (31)
Active Anxiety Disorder ^c			
MDD	148 (27)	116 (27)	32 (27)
PD	66 (12)	54 (13)	12 (10)
PDA	292 (54)	225 (53)	67 (56)
OCD	61 (11)	48 (11)	13 (11)
AWOPD	21 (4)	17 (4)	4 (3)
PTSD	44 (8)	36 (8)	8 (7)
GAD	145 (27)	110 (26)	35 (29)
SAD ^d	132 (24)	89 (21)	43 (36)
History of AUD ^e			
No	396 (73)	346 (81)	50 (42)
Yes	149 (27)	79 (19)	70 (58)
Taking any benzodiazepine	395 (72)	314 (74)	81 (68)
Taking PRN benzodiazepine	76 (14)	64 (15)	12 (10)

MDD, major depressive disorder; PD, uncomplicated panic; PDA, panic with agoraphobia; OCD, obsessive compulsive disorder; AWOPD, agoraphobia without panic; PTSD, post traumatic stress disorder; GAD, generalized anxiety disorder; SAD, social phobia.

^a $\chi^2 = 10.65$, $df = 1$, $p < 0.001$.

^b $F = 20.42$, $df = 1$, $p < 0.0001$.

^c Diagnoses are not exclusive.

^d $\chi^2 = 11.31$, $df = 1$, $p < 0.001$.

^e $\chi^2 = 74.41$, $df = 1$, $p < 0.0001$.

Table 3
Summary of Benzodiazepine Dose Characteristics of Study Sample During Followup

Followup Year	Total M (SD)	Non-AUD M(SD)	AUD M (SD)	χ^2	p
1	Average Daily Dose Weeks on PRN % taking any benzodiazepine n 3.3 (4.8) 7.0 (14.9) 69 545	3.3 (4.7) 7.3 (15.0) 71 425	3.3 (5.1) 6.1 (14.6) 65 120	0.0 2.15	0.99 0.14
2	Average Daily Dose Weeks on PRN % taking any benzodiazepine n 3.3 (5.3) 7.1 (16.1) 67 519	3.3 (5.6) 6.8 (15.7) 67 401	3.2 (4.2) 8.3 (17.5) 65 118	0 0.19	0.97 0.66
3	Average Daily Dose Weeks on PRN % taking any benzodiazepine n 3.2 (4.6) 7.8 (17.3) 66 486	3.1 (4.4) 7.4 (16.9) 66 370	3.4 (5.4) 9.1 (18.3) 65 116	0.18 3.63	0.97 0.06
4	Average Daily Dose Weeks on PRN % taking any benzodiazepine n 3.1 (5.5) 8.3 (18.6) 65 449	3.1 (5.6) 7.5 (17.8) 65 340	3.1 (5.1) 11.0 (20.8) 64 109	0.18 3.63	0.97 0.06
5	Average Daily Dose Weeks on PRN % taking any benzodiazepine n 2.9 (4.5) 7.9 (18.1) 63 431	2.8 (4.2) 6.6 (16.6) 64 323	3.0 (5.2) 12.0 (21.6) 63 108	1.01 6.9	0.32 0.009
6	Average Daily Dose Weeks on PRN % taking any benzodiazepine n 2.9 (4.6) 7.9 (18.2) 63 420	2.8 (3.9) 6.7 (17.0) 63 315	3.3 (6.1) 11.4 (20.9) 63 105	0.43 4.47	0.51 0.03
7	Average Daily Dose Weeks on PRN % taking any benzodiazepine n 2.8 (5.2) 7.4 (17.6) 62 408	2.7 (4.0) 6.4 (16.5) 62 306	3.2 (7.9) 10.5 (20.6) 60 102	0.62 4.20	0.43 0.04
8	Average Daily Dose Weeks on PRN % taking any benzodiazepine n 3.1 (5.6) 7.2 (17.3) 64 394	2.8 (4.3) 6.4 (16.5) 65 294	3.7 (8.2) 9.8 (19.4) 63 100	0.02 5.36	0.88 0.02
9	Average Daily Dose Weeks on PRN % taking any benzodiazepine n 2.7 (3.9) 8.4 (18.7) 66 378	2.7 (3.9) 7.7 (18.0) 66 283	2.7 (3.8) 10.3 (20.7) 65 95	0.14 0.96	0.71 0.33
10	Average Daily Dose Weeks on PRN % taking any benzodiazepine n 2.7 (4.2) 8.5 (18.5) 66 356	2.7 (4.0) 7.9 (17.8) 66 264	2.9 (4.7) 10.5 (20.2) 66 92	0.22 1.62	0.64 0.20
11	Average Daily Dose Weeks on PRN % taking any benzodiazepine n 2.6 (4.2) 8.4 (18.2) 66 336	2.5 (3.9) 7.9 (17.8) 66 247	2.9 (4.8) 9.9 (19.4) 64 89	0.10 1.80	0.97 0.18
12	Average Daily Dose Weeks on PRN % taking any benzodiazepine n 2.5 (4.3) 7.3 (16.2) 62 311	2.3 (3.6) 7.1 (15.9) 63 230	2.9 (5.7) 7.8 (17.2) 59 81	0.31 0.02	0.58 0.88

Dose measured in chlordiazepoxide equivalents (see text and Table 1 for details).

Table 4
Proportional Hazards Analyses Examining Course of Benzodiazepine Use as Predictors of AUD Remission and Relapse

	<i>n</i> eligible	<i>n</i> censored	<i>n</i> event	M week of event	χ^2	Hazards ratio	95% CI	<i>p</i>
Recovery	120 ^a	33	87	220	1.22	1.31	0.81–2.13	0.27
Recurrence	87	51	36	337	0.33	0.82	0.46–1.60	0.57

^a of subjects who onset for AUD during followup, 70 had a history of AUD and 50 had no prior history.

Table 5
GEE Analyses Examining Change in Benzodiazepine Use Among AUD Subjects

Variable	Linear Time Trend, Overall		Mean Change Post Onset		Change in Linear Trend Post Onset	
	Coefficient	p	Coefficient	p	Coefficient	p
Benzodiazepine Dose	0.00	0.18	-0.02	0.59	0.00	0.12
Any benzodiazepine	0.00	0.63	+0.38	0.04	0.00	0.98
PRN benzodiazepine	-0.01	0.16	+0.09	0.72	+0.02	0.08