Clinical Aspects of Chronic Use of Alprazolam and Lorazepam

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Objective: *The authors' goal was to determine the clinical characteristics of persistent users of alprazolam or lorazepam who wished to discontinue their medication.* *Method:* *Long-term users (daily use for more than 3 months) of alprazolam (N=34) or lorazepam (N=97) who entered an outpatient treatment program for discontinuation of benzodiazepines were carefully assessed. Detailed histories of benzodiazepine use were obtained; a structured interview was used to make psychiatric diagnoses based on DSM-III-R criteria.* *Results:* *The majority of patients were using low therapeutic doses of medication (lorazepam: mean=2.7 mg/day; alprazolam: mean=1.2 mg/day) and had either maintained their initial daily dose over time or decreased it. Individuals tended to shift their use of medication from an as-prescribed to an as-needed pattern. Forty-seven percent of the patients were diagnosed with at least one current anxiety disorder, most commonly generalized anxiety. At least one diagnosable personality disorder was found in 45% of the patients, most commonly obsessive-compulsive personality disorder. Patterns of benzodiazepine use were influenced by age, gender, and past history of alcohol dependence.* *Conclusions:* *Long-term users of alprazolam/lorazepam seeking treatment for discontinuation had clinically important past and current psychiatric histories. They used a constant or decreasing dose of medication and made attempts to stop their use. Persistent use of alprazolam/lorazepam for therapeutic purposes did not represent abuse or addiction as the terms are usually understood. A substantial proportion of these patients may be receiving appropriate maintenance therapy for a chronic psychiatric condition.*

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The use of benzodiazepines has attracted considerable attention over the years. This is not surprising in view of the fact that benzodiazepines are the most widely prescribed psychotropic drugs in the world. Furthermore, the resurgence of interest in anxiety disorders in the last decade, their prevalence in the general population (1), and a continuing demand for anxiolytics by both patients and physicians have ensured the sustained scrutiny of this class of drugs. In particular, it is their long-term use that has produced concern in the consumer public and among physicians. The proportion of North Americans using benzodiazepines for more than 1 year has been estimated to be about 1.6% (2).

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Much of this concern centers on the benzodiazepines' liability for abuse and dependence (3). A number of surveys conducted in the United States and Europe have failed to demonstrate any consistent evidence of overprescribing or misuse of benzodiazepines (4). Extensive scientific reviews of both animal and clinical studies have also concluded that benzodiazepines have limited liability for abuse according to traditional criteria and relative to other classes of drugs (5, 6). However, several factors, in particular a failure to distinguish between therapeutic and nontherapeutic use of benzodiazepines, contribute to the continued prominence of this topic as a public health issue. Moreover, most studies have provided limited information on the clinical characteristics of patients who are long-term users, why individuals start to use these drugs, their pattern of medication use, and the natural history of patients' discontinuation of these drugs. Most of the studies of patterns of long-term benzodiazepine use have been restricted to users of the older, longer-half-life benzodiazepines such as diazepam. There are few data on users of the newer, shorter-half-life drugs such as alprazolam and lorazepam, currently the most commonly prescribed benzodiazepines (4, 7, 8).

The major determinants of persistent use have been pre-

TABLE 1. Clinical Characteristics of 131 Long-Term Benzodiazepine Users

Variable	Patients Taking Alprazolam (N=34)[a]		Patients Taking Lorazepam (N=97)[a]	
	N	%	*N*	%
Male sex	20	59	54	56
Employment status				
Employed	26	77	64	66
Unemployed	3	9	13	13
Other	5	14	20	21
Previous psychotropic medications	23	70	57	61
Benzodiazepines	15	46	42	44
Antidepressants	6	18	18	19
Sedatives/hypnotics	2	6	9	9
	Mean	*SD*	*Mean*	*SD*
Total number of standard drinks over 90-day period[b]	44.5	55.5	65.2	91.6
Number of cigarettes per day	5.2	11.1	4.4	8.2
Number of cups of coffee per day	1.5	2.0	1.2	1.7

[a]Total number on which percents are based varies because of missing data for some subjects on some variables.
[b]From the 90-day Timeline Followback Interview (19).

sumed to be primarily pharmacologic, that is, the intrinsic pharmacologic effects of the drug, the dose, and the kinetic properties. More recently, the issue of dependence on benzodiazepines, in particular physiological dependence and its role in persistent use, has been raised. Physiological dependence on benzodiazepines, as evidenced by a withdrawal syndrome, has been well described for high and therapeutic doses (5, 9). It has been reported that withdrawal symptoms are more severe for the benzodiazepines that have a shorter elimination half-life (10). However, a benzodiazepine withdrawal syndrome, resulting from neuroadaptation to the presence of the drug, is often confused with other possible clinical events experienced upon discontinuation, including recurrence of the original symptoms for which the drug was prescribed. Furthermore, a discontinuation syndrome may have little to do with behavioral or psychological dependence (11). A specific relation between withdrawal symptoms and continued self-administration of benzodiazepines has not been established.

We attempted to address some of the questions that figure prominently in the benzodiazepine controversy by systematically evaluating patients presenting to an outpatient treatment program for help in discontinuing their use of alprazolam or lorazepam. The objectives of this investigation were to determine the clinical characteristics of persistent users of alprazolam or lorazepam and the pattern of chronic medication use.

METHOD

The study patients were 131 long-term users (daily use for longer than 3 months) of alprazolam or lorazepam who entered an outpatient treatment program for discontinuation of benzodiazepines. Patients were informed about the treatment research program by referring physicians, newspaper advertisements, or word of mouth. The patients came for treatment primarily because they felt that they no longer required their medication but were having difficulty discontinuing its use on their own, or because they had simply become concerned about the length of time they had used the medication and wanted support in discontinuing it. Since these patients were to participate in a clinical trial of benzodiazepine discontinuation, the study group excluded individuals who were currently using other psychotropic medications: other benzodiazepines, antidepressants, antipsychotics, or anticonvulsants. Patients who met the criteria for current abuse of or dependence on other substances (aside from caffeine and nicotine) were also excluded.

Following a detailed explanation of the evaluation procedures, written informed consent was obtained from the patients. Participants then underwent a comprehensive assessment. Demographic data and a detailed history of benzodiazepine use (12) were collected. Information was obtained about prior psychoactive drug use for symptom control, indications for current use of medication, pattern and duration of medication use, daily dose, drug efficacy, adverse effects from use, attempts to decrease use, and any withdrawal symptoms experienced in so doing. A structured clinical interview for psychiatric diagnoses based on DSM-III-R criteria (Structured Clinical Interview for DSM-III-R [SCID], parts I and II) (13) was conducted. To evaluate symptoms at the time of assessment, the Montgomery and Asberg Depression Rating Scale (14), the Beck Anxiety Inventory (15), the Hopkins Symptom Checklist-90 (HSCL-90) (16), the State-Trait Anxiety Inventory (17), the Clinical Institute Withdrawal Assessment for Benzodiazepines—Revised (18), and the Global Assessment of Functioning Scale (13) were completed. Alcohol consumption was determined with the 90-day Timeline Followback Interview (19). Patients also had a thorough physical examination and provided blood and urine samples for routine biochemistry, hematology, and drug screens for benzodiazepines, alcohol, barbiturates, narcotics, amphetamines, and cannabis.

Data were analyzed with the SAS 6.04 statistical software package (20). Contingency tables were evaluated with chi-square tests (adjusted for continuity in 2×2 tables), and continuous variables were analyzed with two-tailed t tests or one-way analyses of variance. All comparisons were carried out on the complete data set, but with slight variation in the numbers as a result of missing data values. The exploratory nature of the analyses required many statistical comparisons with only a few specific predictions anchored within them. To correct the alpha level for the number of tests would have raised the risk of inappropriately failing to detect potentially interesting relationships.

RESULTS

Thirty-four subjects (mean age=46 years, SD=12) were taking alprazolam, and 97 (mean age=47 years, SD=13) were taking lorazepam. Characteristics of the subjects are summarized in table 1. No significant differences in these variables existed between the group using alprazolam and the group using lorazepam. More men than women presented for treatment. The average alcohol consumption as measured by the 90-day Timeline Followback Interview was low, but with wide variation. The majority of the patients had previously used psychotropic medications, primarily benzodiazepines, for symptom control.

The most frequent indications for use as reported by the patients were anxiety and insomnia (table 2). Alprazolam was prescribed significantly more often than lorazepam for panic attacks. On average, the duration of use was over 3 years, with the lorazepam group having used their medication for significantly longer. This was

likely a reflection of the drug's being on the market longer than alprazolam (lorazepam was marketed in Canada in 1977, alprazolam in 1982). Approximately one-half of the patients reported continued therapeutic effectiveness of the medication throughout the period of use. Most patients had tried to decrease or stop their use on at least one occasion, and all reported symptoms during these discontinuation attempts.

The majority of the patients were using low therapeutic doses of medication. The mean daily dose for lorazepam was 2.7 mg (SD=2.7), with 75% of the patients using doses less than 1.5 mg/day; for alprazolam the mean daily dose was 1.2 mg (SD=1.2), with 50% of the patients using 2 mg/day or less. The alprazolam patients were using significantly higher doses of benzodiazepine as measured by conversion to diazepam-equivalent milligrams (t=2.47, df=125, p=0.02). Most patients had either maintained their initial dose over time or decreased it. Of 33 alprazolam patients, seven (21%) had increased their initial dose, none to more than 5 mg/day; of 86 lorazepam patients, 23 (27%) had increased their dose, two patients to 15 mg/day and the remainder to less than 10 mg/day. Assessment of the pattern of use indicated that patients shifted from initially taking the medication as prescribed to using it on an as-needed basis or to a pattern of both as-prescribed and as-needed use.

Baseline psychiatric symptom levels as assessed by various instruments were low (Montgomery and Asberg Depression Rating Scale mean score=5.6, SD=5.0; Beck Anxiety Inventory mean score=11.7, SD=8.7; State-Trait Anxiety Inventory trait mean score=44.2, SD=12.2; HSCL-90 global severity index mean score=0.81, SD=0.55). The level of general functioning, measured by the Global Assessment of Functioning Scale, was mildly impaired (mean score=69, SD=9). All patients met the DSM-III-R criteria for benzodiazepine dependence as determined by the SCID. The mean total number of diagnostic criteria met out of the nine evaluated was five (SD=1), indicating moderate severity of dependence. The most frequently met criteria were substance taken over a longer period than intended (87%, N=103 of 119), a persistent desire or unsuccessful efforts to cut down or control substance use (95%, N=113 of 119), and characteristic withdrawal symptoms upon reduction of use (89%, N=105 of 118). The least frequently met criteria in both of the drug groups were a great deal of time spent in activities necessary to obtain the substance (7%, N=8 of 119), important social, occupational, or recreational activities reduced because of substance use (6%, N=7 of 119), and frequent intoxication or withdrawal symptoms when expected to fulfill major role obligations (28%, N=33 of 116).

Almost one-half of the individuals (44%, N=51 of 116) had experienced a past major depression, and many (35%, N=41 of 118) had a past history of alcohol abuse/dependence. Current anxiety disorders were prevalent (47%, N=55 of 117), with generalized anxiety disorder the most common (33%, N=39 of 117). An additional 18% of the patients (N=21 of 117) had a past history of anxiety disorder. According to part II of the SCID, 47% of the patients (N=48 of 103) were diagnosed with at least one personality disorder, the most common being obsessive-compulsive (22%, N=23 of 103), followed by borderline, narcissistic, and avoidant.

TABLE 2. Features of Chronic Benzodiazepine Use Among 131 Patients

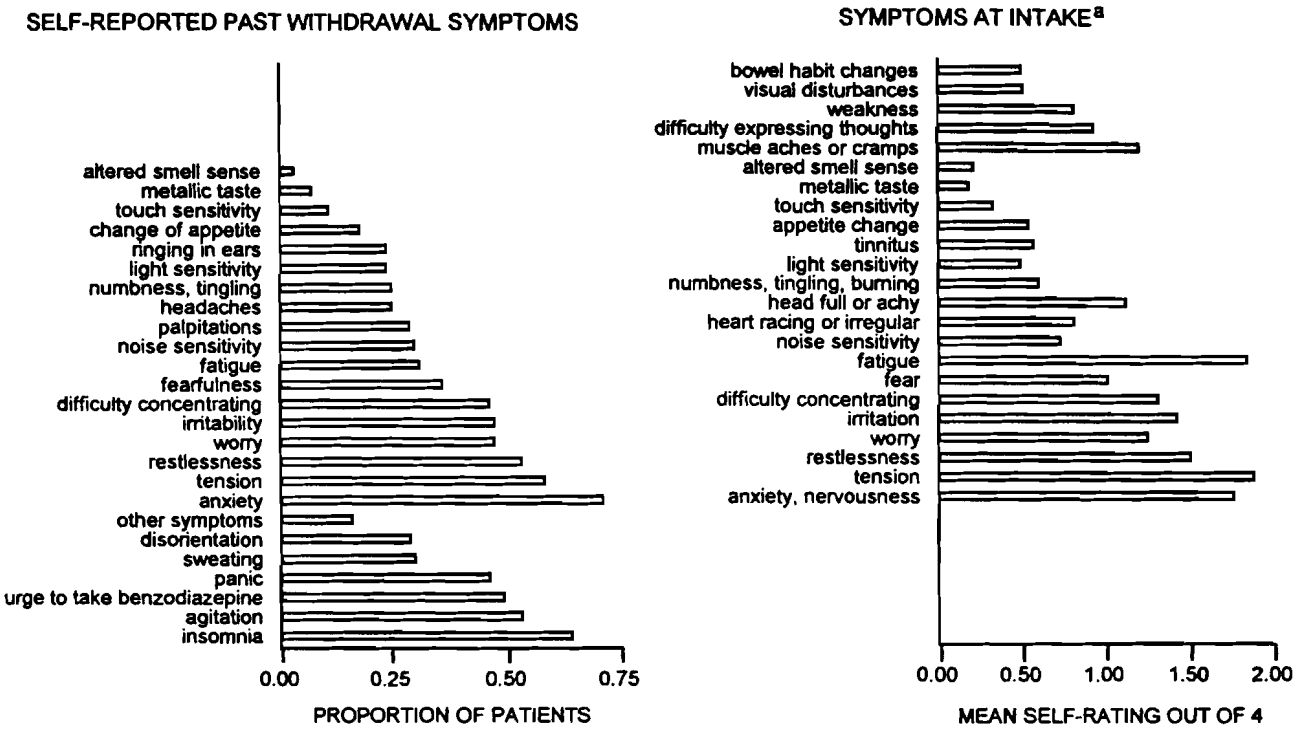
Variable	Patients Taking Alprazolam (N=34)[a]		Patients Taking Lorazepam (N=97)[a]	
	N	%	*N*	%
Reason drug was prescribed				
Panic[b]	12	36	16	17
Anxiety	28	85	71	74
Depression	9	27	12	13
Insomnia	14	42	49	51
Other	4	12	23	24
	Mean	*SD*	*Mean*	*SD*
Current daily dose (mg)	1.2	1.2	2.7	2.7
Current daily dose (diazepam-equivalent mg)	24.2	24.0	13.3	13.7
Duration of drug use (months)[c]	42	26	74	60
	N	%	*N*	%
Effectiveness maintained	18	55	36	38
Tried to stop use[d]	32	97	86	90
Experienced symptoms during discontinuation	32	100	86	100

[a]Total number on which percents are based varies because of missing data for some subjects on some variables.
[b]Significant difference between groups (χ^2=4.51, df=1, p<0.04).
[c]Significant difference between groups (t=4.11, df=121, p=0.0001).
[d]The mean number of attempts to stop was four (SD=5) in the alprazolam group and four (SD=7) in the lorazepam group.

The majority of individuals (91%, N=118 of 129) had made at least one attempt to decrease their dose or stop their use of benzodiazepines, and all who had done so reported experiencing symptoms upon attempting discontinuation. The left side of figure 1 summarizes the various symptoms on a checklist that patients recalled from past withdrawal attempts. The right side of figure 1 shows symptoms acknowledged at the start of baseline monitoring, before tapering of medication began, using the Clinical Institute Withdrawal Assessment for Benzodiazepines—Revised. Among the items common to the two instruments, the most frequently endorsed symptoms were tension, anxiety, worry, irritability, restlessness, and difficulty concentrating.

The data were further analyzed with respect to several key variables reported to be important in influencing patterns of benzodiazepine use: age, gender (unpublished survey by M. Balter, 1991), duration of use (2), and past alcohol dependence (21, 22). When the study group was examined on the basis of age—patients 60 years of age or over (N=24) compared with patients under 60 (N=107)—the older patients reported less prior

FIGURE 1. Symptoms During Past Discontinuation Attempts and Symptoms at a Stable Dose of Medication at Study Intake of Patients Taking Alprazolam (N=34) or Lorazepam (N=97)



[a]Assessed with the Clinical Institute Withdrawal Assessment for Benzodiazepines—Revised.

use of benzodiazepines (30% versus 47%) and antidepressants (0% versus 23%) (χ^2=4.99, df=1, p<0.03), they used lower drug doses (mean=6.9 mg of diazepam equivalents, SD=4.4, versus mean=18.2 mg, SD=18.7; t=5.50, df=124.4, p=0.001), and they had clinically insignificant lower symptom scores on a number of the assessment scales (Montgomery and Asberg Depression Rating Scale, Beck Anxiety Inventory, HSCL-90 depression and phobic anxiety subscales, State-Trait Inventory anxiety scale, and Clinical Institute Withdrawal Assessment for Benzodiazepines—Revised). There were no significant differences in psychiatric diagnoses, although the older age group had the medication prescribed more frequently for insomnia (74% versus 43%; χ^2=5.87, df=1, p<0.02).

Male subjects, who were slightly more numerous in this study (N=74 versus N=57), differed from female subjects on some dimensions. More of the men had used other benzodiazepines for control of symptoms in the past (49% versus 38%) and had past histories of alcohol abuse/dependence (48% versus 22%; χ^2=7.48, df=1, p=0.006) and cannabis abuse/dependence (18% versus 2%; χ^2=6.11, df=1, p=0.01). They were drinking more alcohol at the time of assessment (mean=74 standard drinks in 90 days, SD=95, versus mean=41 standard drinks in 90 days, SD=64; t=2.35, df=122.6, p=0.02), had made more attempts to stop their use of medication (mean number of attempts=6, SD=7, versus mean=4, SD=5; t=2.5, df=107.8, p<0.02), and experienced symptoms (agitation, tension, restlessness) upon discontinuation more frequently than women.

Duration of use of medication influenced a minimal number of variables. Patients who had used their medication for less than 5 years tended to use the drug more often on an as-needed basis only, and more of them had attempted to decrease their dose or stop use (97% versus 85%; χ^2=4.23, df=1, p=0.04). Male subjects were more likely than female subjects to have used their drug for the shorter length of time (60% versus 43%; χ^2=2.95, df=1, p=0.09).

DISCUSSION

Over the past few years, the benzodiazepines have received considerable publicity implying widespread inappropriate use of these drugs (23). Furthermore, the extrapolation has been made that chronic use defines abuse, misuse, or dependence. Most benzodiazepines have been approved for short-term use (4–6 weeks), and there are few studies to document evolving patterns of use among patients over longer periods of time. Other factors that have contributed to the contentious debate about these drugs include confusion in the terminology that is used (i.e., "abuse," "behavioral and psychological dependence," "physical dependence"); marketing of new benzodiazepines every few years, which revives the concern about these drugs; use of

these drugs by some individuals for nonmedical purposes; and inclusion of the benzodiazepines in Schedule IV of the Psychotropic Convention (1971) and of the U.S. Controlled Substances Act. Widely differing belief and value systems, including the unrealistic expectation that there can exist medication without risks, also play an important role. These issues have led to confusion among physicians and patients alike about the use of this class of drugs.

Clearly, there is a need for a better understanding of the clinical implications of chronic benzodiazepine use. We therefore undertook to study more carefully the clinical characteristics of some long-term benzodiazepine users. The group of patients we evaluated was similar in some respects to patients described in earlier studies of older benzodiazepines (24–26). The individuals we assessed were middle-aged and had rather substantial histories of psychotropic medication use, including drugs other than benzodiazepines. However, careful diagnostic evaluation revealed that the majority of our patients had prominent histories of past psychiatric disorders, particularly major depression and alcohol abuse/dependence. Slightly less than one-half the patients suffered from at least one current anxiety disorder, primarily generalized anxiety disorder, and 65% had a lifetime history of any anxiety disorder.

There is accumulating evidence that both generalized anxiety disorder and panic disorder are chronic disorders, with more than one-half of patients relapsing within 5 years of remission after acute treatment (27–33). This has led to the suggestion that maintenance drug therapy may be indicated for some patients (33–36). Maintenance benzodiazepine therapy has demonstrated efficacy in both generalized anxiety disorder (34, 37) and panic disorder (32, 33). However, general acceptance of this recommendation has been limited to a large extent by concerns about physical dependence and by data showing persistent symptoms in patients maintained on benzodiazepines (10, 24, 35, 38). This was not the case in the patients coming to our center for treatment. Their average scores on a number of symptom scales were low. This low level of symptoms suggests either that the patients derived benefit from the medication they were receiving or that these patients in fact did not require medication any longer. The former interpretation is supported by our data showing that a substantial number of patients reported continued efficacy of medication.

Furthermore, in many chronic benzodiazepine users, "state" psychopathology has become confounded with "trait," leading some to suggest that the anxious and depressive psychopathology observed in these patients may be largely characterologic (35). It has been proposed that these traits, subsumed under the terms "neuroticism" and "dependence," may be risk factors for acute benzodiazepine treatment becoming chronic. Forty-five percent of our patients met the DSM-III-R criteria for a personality disorder, and obsessive-compulsive personality disorder was the most common one observed. This finding is of interest in the context of neuroticism being a marker for chronic benzodiazepine use and provides more specific information about the nature of the proposed neuroticism. Importantly, the frequency of personality types in which impulsive behavior is a prominent feature, such as borderline and antisocial personality disorders, was low in contrast to that seen in persons with alcohol and other drug dependence.

It appears reasonable to suggest, therefore, that it is the waxing and waning course of chronic axis I psychiatric disorders and certain personality features that substantially influence duration of use of benzodiazepines. This emphasizes the importance of a correct diagnosis in assessing these patients, particularly if consideration is being given to discontinuing benzodiazepine use. Discontinuation may not be appropriate for some patients unless the drug is replaced with other medication (e.g., antidepressants) or psychotherapeutic interventions are applied.

The pattern of long-term use of alprazolam and lorazepam was characterized by low daily doses, a constant or decreasing dose over the period of use, increasing patient regulation of medication use for symptom control when needed, and attempts to either decrease the dose or stop use of the medication. This pattern of use does not represent abuse, addiction, or drug dependence as usually understood. The core behavioral features commonly associated with addiction, including dose escalation over time and functional impairment because of drug use, were absent in this group of users of benzodiazepines for therapeutic purposes. In the vast majority of cases, even the patients who had in fact increased their doses over time had kept their doses within a therapeutic range, suggesting titration according to symptoms. Similar features of long-term use were found in a large community-based cohort of patients using alprazolam (12). Our findings emphasize the importance of circumspect use of terms such as "abuse" and "dependence." Although all of the patients were diagnosed with benzodiazepine dependence according to the DSM-III-R criteria, the features most often recorded in making this diagnosis were those associated with physical dependence and duration of use. Physical dependence is neither a necessary nor a sufficient criterion for defining drug dependence (39).

Neuroadaptation to varying doses of benzodiazepines has been well documented (9, 10, 40). It has been suggested that withdrawal symptoms lead to persistent use of benzodiazepines (41). Our data indicate that discontinuation symptoms are associated with chronic use, but their role in determining such use is unknown. The fact that our patients acknowledged a considerable number of symptoms on the Clinical Institute Withdrawal Assessment for Benzodiazepines—Revised prior to any drug tapering emphasizes the importance of careful interpretation and monitoring of symptoms before, during, and after benzodiazepine treatment.

In searching for other associations with long-term use, we found that gender appears to play an important role. Earlier studies indicated that females constitute the majority of long-term users (37, 42). We obtained

a similar result in our community survey of persistent alprazolam users (12). However, in the present clinical treatment group, the men slightly outnumbered the women and differed from the women on a number of variables related to the use of benzodiazepines. More men had past histories of use of other benzodiazepines for control of symptoms and of alcohol and cannabis dependence or abuse. In the course of their benzodiazepine use, they had made more attempts to stop taking the medication. They were also drinking more alcohol than the women at the time of assessment, although the amounts were low. These results suggest that the men may have been attempting to self-medicate various symptoms and discomforts with different drugs and that, for males, long-term use of benzodiazepines may be qualitatively different from that for females. A complex interaction of gender, anxiety symptoms, use of various substances to control symptoms, differing subjective responses to these substances, and differing expectations of relief of symptoms may account for these findings. This interaction warrants further investigation, particularly in view of the concern often raised in the literature about the use of benzodiazepines by alcoholics (21, 22) and the potential for their abuse by these patients.

Age was also an important differentiating characteristic in the pattern of use of these drugs. The use of benzodiazepines by the elderly has been viewed as particularly disconcerting. The clinical perception has been that many elderly long-term users continue to receive these drugs because of complaints of insomnia and a reluctance to discontinue them. Our subgroup of patients aged 60 years and over did indeed report a higher frequency of insomnia as the primary indication for use, but their doses of medication were significantly lower than those of the younger patients. Clearly, for older patients, the perceived and observed benefits of ongoing use must be weighed against the potential risks, and many of these patients do in fact engage in such considerations on their own.

There are several limitations to this descriptive study. First, the group of patients evaluated was primarily recruited for their interest in discontinuation, and thus, it was a convenience sample, not a random sample, of long-term benzodiazepine users. This places some restrictions on the generalizations that can be drawn. However, the findings about patterns of use are very similar to those obtained in our community survey of long-term benzodiazepine users (12), individuals who did not wish to stop their use of the drugs. Second, a control group of patients, either long-term users who had successfully discontinued use on their own or a group of unmedicated patients matched for psychiatric diagnosis and presenting for initial treatment, would have clarified which features are indeed characteristic of a chronic benzodiazepine-using population. Such a long-term, prospective follow-up of patients started on benzodiazepine therapy would be ideal.

In conclusion, our findings support the proposition that among users of therapeutic doses of alprazolam and lorazepam, there is minimal evidence of misuse or abuse of these medications. Although physical dependence as measured by the appearance of withdrawal symptoms does occur in many patients, the long-term implications of this phenomenon have not been carefully explored. Similarly, psychological dependence implies only that patients prefer to take the benzodiazepine rather than manage without, and its interpretation is influenced by the objectives of therapy. The overall safety and apparent continued efficacy of these drugs are important considerations when one is treating a subgroup of patients with chronic disabling psychopathology that is unresponsive to alternative medications or interventions. Attempts to restrict the use of this class of drugs have shown that less effective and less safe drugs are resorted to, in response to clinical demand (43, 44). Clearly, there is a need for development of anxiolytic medications with greater efficacy for specific disorders and minimal side effects. However, this does not obviate the fact that some patients appear to derive sustained benefit from long-term treatment with benzodiazepines.

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