Editorials

Benzodiazepine Dependence

Benzodiazepines differ from most abused substances in that there are also licit and legitimate medical indications for their use. This difference has resulted in a tendency on the part of both clinicians and the lay public to confuse the phenomenon of addiction and abuse with that of physical dependence resulting from therapeutic use. A perceived "need" for benzodiazepines to control escalating and disabling symptoms of anxiety, such as panic and phobia, is all too often misinterpreted as the "craving" of an addicted individual. Conversely, individuals with true abuse and addiction often justify their drug craving and abuse as needed pharmacotherapy of an underlying anxiety disorder. After decades of underrecognition of the latter phenomenon, the medical field has become increasingly more aware of and sophisticated in recognizing and treating the addictive disorders. More recently, there has been a complementary increase in awareness that there are definite indications for indefinite benzodiazepine therapy, that individuals receiving benzodiazepines are not necessarily addicts, and that the crucial tasks for clinicians are recognizing and identifying patients who are appropriate candidates for continued therapy and those who are not.

The review paper in this issue of the *Journal* by Landry and colleagues[1] on benzodiazepine dependence and withdrawal goes a long way toward placing the use-abuse dichotomy in perspective by drawing appropriate lines around the contrasting phenomena of therapeutic use versus addiction and withdrawal versus symptom reemergence. In this editorial, my purposes are to provide some particular points of clarification concerning the authors' discussion of the "subacute, prolonged withdrawal syndrome," to discuss the current scientific limitations of our knowledge about treatments for benzodiazepine withdrawal (i.e., what do we know that transcends clinical anecdote and experience?), and to offer some additional recommendations to the overall excellent treatment guidelines that are provided.

The authors' familiarity and experience with the phenomena of addiction, tolerance, and withdrawal might have caused them to underestimate the role of underlying psychiatric illness, principally the anxiety disorders, in the "subacute, prolonged benzodiazepine withdrawal" syndrome. There are no controlled data to support a distinction between more prolonged withdrawal symptoms and anxiety symptom reemergence following benzodiazepine discontinuation. The authors suggest that a prolonged withdrawal syndrome is not a manifestation of relapse because it is not persistent but follows a fluctuating course marked by periodic, paroxysmal "bursts" of symptoms. They suggest that it would be a mistake to turn to psychotropic drugs to alleviate the symptoms.

While this area is certainly controversial and the data needed to clarify the question definitively are unavailable (and perhaps unobtainable because of problems designing a study that would address the area), certain information is well established. First, both panic and generalized anxiety disorders can follow a fluctuating, relapsing-remitting course.[2,3] Symptoms do not always persist. "Bursts" of symptoms after benzodiazepine discontinuation can represent reemergence of underlying panic or anxiety, and anxiety disorders can spontaneously remit after long periods of symptom fluctuation. Second, while withdrawal symptoms often persist well beyond the pharmacokinetic decline in plasma benzodiazepine levels, symptoms usually disappear within 4 weeks.[4] Persistence in labeling continuing symptoms as "withdrawal" can deny patients needed treatment of what might just as likely represent a reemergent anxiety disorder.

Whereas it is probable that some patients with postbenzodiazepine discontinuation relapse have had the relapse at least partly triggered by

Submitted 29 August 1991.

From the Department of Psychiatry and Behavioral Sciences, and the Center for Anxiety and Depression, University of Washington Medical School, Seattle. Address reprint requests to Peter P. Roy-Byrne, M.D., Department of Psychiatry and Behavioral Sciences, RP-10, University of Washington, Seattle, WA 98195.

physiologic benzodiazepine withdrawal, once reinitiated, the underlying anxiety syndrome takes on a life of its own and must be treated. I have personally treated 3 patients in the past 6 months, sent to me with a diagnosis of "low-dose, prolonged withdrawal," whose symptoms remitted following antidepressant treatment. In my opinion, an untreated anxiety disorder is more likely to be present the longer the "withdrawal syndrome" has been going on, and a 60- to 90-day waiting period is much too long. Four weeks after absolute benzodiazepine cessation seems more reasonable to me.

Finally, there are no data to support the authors' suggestion that a *majority* (my emphasis) of patients developing physical dependence on benzodiazepines have personal or family histories of addiction. This statement tends to confuse abuse and therapeutic use by subtly implying that dependence may be a *forme fruste* of addiction.

The authors' excellent treatment section should be supplemented by several caveats. The available evidence does not support the ability of β-blockers to decrease withdrawal symptoms other than palpitations.[5] Hence β-blockers are likely to be helpful only in those rare patients for whom palpitations are a major, disabling part of withdrawal. Although controlled studies provide a crucial foundation for treatment intervention, it must be remembered that in clinical practice a wider range of patients are seen than the restricted, homogeneous populations studied in research. Thus clinical practice must of necessity rely on more than just research studies.

Evidence that a placebo can reduce withdrawal severity[6] suggests that the addition of frequent supportive physician contact to a carefully supervised tapering of medication may be the best general approach to treating benzodiazepine-dependent patients. Applying cognitive-behavioral strategies for anxiety management as part of this support can be extremely helpful.[7] Rate of taper is something that has generally been neglected in the literature. Recent evidence shows that tapering over 12 to 16 weeks markedly reduces the severity of withdrawal seen with 4- to 6-week tapering.[8] Although clinicians continue to switch patients to longer half-life drugs, such as clonazepam or phenobarbital, before reducing the medication, a recent study shows that when a taper is used, withdrawal symptoms are no more frequent or more intense with short half-life benzodiazepines.[3] Nonetheless, switching to a longer half-life drug clearly provides an advantage in selected cases, although routinely doing so is probably unnecessary. The relative advisability of using phenobarbital rather than clonazepam for this purpose has never been subjected to controlled study. In collaboration with Mark Sullivan, M.D., our recent attempt to compare the two drugs in a pain clinic population on multiple medications ran into methodologic difficulties. Nevertheless, the data we were able to collect on two parallel groups of 6 patients suggested that withdrawal symptoms were less intense in those patients receiving clonazepam compared with those receiving phenobarbital.

To provide optimal care for the benzodiazepine-dependent patient, the physician must be able to make an accurate differential diagnosis of the underlying anxiety disorder, which can be quite tricky and requires an advanced level of diagnostic sophistication in many cases. Panic disorder, agitated "masked" depression, and social phobia or anxiety are the most frequently occurring anxiety disorders and often the most underrecognized. These disorders must be distinguished from the dysphoric personality disorder that is likely to improve, not worsen, following several weeks without benzodiazepine medications. In treating benzodiazepine-dependent patients, it is helpful for clinicians to require them to keep some systematic ratings of their major physical and emotional or cognitive symptoms before, during, and after the taper. Such a diary helps document certain symptom fluctuations that are difficult to identify retrospectively, even week by week, and can prevent patients suffering more enduring agitated depressions that wax and wane in severity from retrospectively focusing on isolated "bursts" of anxiety symptoms and insisting that lower level intervening symptoms are absent.

Peter P. Roy-Byrne, M.D.
Seattle, WA

References

1. Landry MJ, Smith DE, McDuff DR, Baughman OL. Benzodiazepine dependence and withdrawal: identification and medical management. J Am Board Fam Pract 1992; 5:167-76.

2. Rickels K, Case WG, Downing RW, Fridman R. One-year follow-up of anxious patients treated with diazepam. J Clin Psychopharmacol 1986; 6:32-6.
3. Noyes R Jr, Reich J, Christianson J, Suelzer M, Pfohl B, Coryell WA. Outcome of panic disorder. Relationship to diagnostic subtypes and comorbidity. Arch Gen Psychiatry 1990; 47:809-18.
4. Schweizer E, Rickels K, Case WG, Greenblatt DJ. Long-term therapeutic use of benzodiazepines: effects of gradual taper. Arch Gen Psychiatry 1990; 47:908-15.
5. Tyrer P, Rutherford D, Huggett T. Benzodiazepine withdrawal symptoms and propranolol. Lancet 1981; 1:520-2.
6. Pecknold JC, McClure DJ, Fleuri D, Chang H. Benzodiazepine withdrawal effects. Prog Neuropsychopharmacol Biol Psychiatry 1982; 6:517-22.
7. Sanchez-Craig M, Kay G, Busto U, Cappell H. Cognitive-beyhavioral treatment for benzodiazepine dependence. Lancet 1986; 1:388.
8. Pecknold JC. Discontinuation studies: short-term and long-term. J Psychiatric Res 1990; 24:80-1.

The Potential Role Of Single-Patient Randomized Controlled Trials (N-Of-1 RCTs) In Clinical Practice

When deciding how patients, as a group, ought to be treated, randomized controlled trials (RCTs) are usually required to establish valid evidence of drug efficacy. As shown by Nuovo and his colleagues in this issue of the *Journal*,[1] however, when deciding on optimal treatment for a given patient, the clinician often cannot rely on the results of such studies. For example, no guidance can be obtained about a treatment when no RCT has been conducted on it. Further, even when a relevant RCT has generated a definite answer, there are two reasons why its result might not apply to an individual patient. First, if the patient does not meet the study's eligibility criteria, extrapolation can be inappropriate; second, even in positive trials not every eligible patient benefits.

Under these circumstances, clinicians typically choose to conduct the time-honored "trial of therapy" in which the patient is given a treatment and the subsequent clinical course determines whether (or which) treatment is judged effective and endorsed. Nevertheless, many elements of these conventional therapeutic trials can mislead the clinicians who conduct them into drawing false-positive conclusions about efficacy. Chief among these conclusions are the placebo effect, the natural history of the illness (which, if self-limited, would have improved if left untreated), the understandably positive expectations of the patient and the clinician about the treatment effect, and the desire of the patient and the clinician not to disappoint one another.[2] Fortunately, such pitfalls can be avoided or minimized if neither the patient nor the clinician knows when active treatment (or which type of treatment) is being administered, and that is why random allocation and double-blinding are key elements of the RCT.

These methodological safeguards of the large-scale RCT now have been applied to the trial of therapy in individual patients. Borrowing from single subject or n-of-1 RCTs developed in psychological research, their therapeutic usefulness (determining the most suitable treatment for a given patient) has repeatedly been demonstrated in medical practice.

In the classical n-of-1 RCT, the patient undergoes several pairs of treatment periods. Each pair includes one period on active or experimental medication and one period on placebo or an alternative drug. The order of the treatment periods is determined by random allocation,[2,3] and both patient and clinician are kept blind. Other n-of-1 RCTs use unconstrained randomization of four or six (or more) planned treatment periods,[4] and phase 2 of the trial reported in this issue by Nuovo and his colleagues is of this sort. Whichever allocation strategy is used, treatment targets (key symptoms, physical signs, or laboratory measurements) are recorded throughout the trial. When the code is broken, treatment effects can be examined by observing the nu-

Submitted 8 August 1991.

From the Department of Medicine, and the Department of Clinical Epidemiology and Biostatistics, McMaster University; the Department of Medicine, St. Joseph's Hospital; and the Department of Medicine, Hamilton Civic Hospitals, Hamilton, Ontario. Address reprint requests to Roman Jaeschke, M.D., Department of Medicine, St. Joseph's Hospital, 50 Charlton Avenue East, Hamilton, Ontario L8N 4A6.