Anxiety Disorders, Comorbid Substance Abuse, and Benzodiazepine Discontinuation: Implications for Treatment

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INTRODUCTION

Comorbidity among various disorders complicates research and practice. Comorbidity among emotional disorders and substance use disorders is a particularly thorny problem due to the dearth of relevant clinical research. This chapter reviews what is known about the comorbidity of substance use and anxiety disorders and presents recent data collected in the context of comorbid anxiety and mood disorders that may have implications for the relationship of anxiety and substance use disorders. The specific case of the relationship of benzodiazepine use to successful outcome of psycho- social treatments and recent developments in successful psychosocial strategies for discontinuing benzodiazepines in anxious patients may provide important information for future studies. This chapter begins with a brief review of data on the co-occurrence of substance use and anxiety disorders.

COMORBIDITY AMONG SUBSTANCE USE AND ANXIETY DISORDERS

A number of studies have reported a high rate of comorbidity among anxiety and substance use disorders. Most of these studies have surveyed alcohol dependence and abuse. Rates of comorbidity have typically been calculated in two different ways. First, the prevalence of anxiety disorders has been examined in alcohol dependence and abuse patient samples. Second, rates of alcohol dependence and abuse have also been examined in samples of outpatients with anxiety disorders.

The majority of surveys have followed the first approach and have found that the lifetime prevalence of clinically significant anxiety disorders in patients with alcohol abuse and dependence ranges from 25 percent to 45 percent for patients with clearly defined anxiety disorders, but may approach 60 percent if one includes identifiable anxiety disorders that are subthreshold in terms of severity (Bowen et

al. 1984; Chambless et al. 1987; Hesselbrock et al. 1985; Mullaney and Trippett 1979; Smail et al. 1984; Cox et al. 1989; Johannessen et al. 1989).

Surveys using the second approach and examining rates of alcohol dependence and abuse in anxiety disorder outpatient samples suggest that approximately 15 percent to 25 percent present with evidence of current or past alcohol abuse or dependence (Bibb and Chambless 1986; Thyer et al. 1986). Himle and Hill (1991) found that the frequency of alcohol abuse or dependence differed among persons with various anxiety disorders. For example, the percentage of alcohol abuse or dependence among those individuals with a principal diagnosis of panic disorder (PD) with agoraphobia (who may also have presented with additional anxiety disorders) was 31.5 percent, as compared to 24.6 percent for obsessive-compulsive disorder and 14.4 percent for a specific phobia. Thus, it would seem that some anxiety disorders confer a higher risk for substance abuse then others.

In any case, there is evidence that patients presenting with these comorbid pictures have more clinically severe conditions than individuals with either condition alone. Thus, there are reasons to examine factors contributing to comorbidity in this subgroup more closely.

One method of examining the possible reasons for the acquisition of comorbid disorders is to ascertain a temporal sequence in their onset. Most studies indicate that anxiety precedes alcohol abuse and dependence. This pattern would seem to confirm the frequent clinical observation that many individuals with anxiety disorders begin to abuse alcohol with the purpose of self-medicating their anxiety disorders. However, Kushner and colleagues (1990) noted that the pattern seems to hold true only for some disorders, such as PD with or without agora-phobia, social phobia, and specific phobia. For some other disorders, particularly generalized anxiety disorder (GAD) and depression, the more prevalent pattern may be the reverse; that is, substance abuse seems to contribute to the onset of GAD and depression. One possible mechanism of action here is that the individual experiences a loss of control over the substance use subsequent to addiction and develops reactive anxiety or depression.

Illicit drug use has also been reported to precipitate anxiety disorders. For example, Aronson and Craig (1986), as well as Louie and colleagues (1989), reported a number of cases in which cocaine use and/or withdrawal from cocaine precipitated panic attacks. In these

cases the resulting panic disorder continued well after the cessation of cocaine use. In fact, as many as 30 percent of patients presenting with PD have reported an onset associated with either licit or illicit drug use (Barlow 1988), with marijuana being one of the more common precipitants. Hyperventilation and other symptoms associated with withdrawal from alcohol have also been reported to trigger long-lasting PD (Weissman 1988). In cases where substance abuse seems to "trigger" anxiety disorders, clinical strategies might target the substance use first before addressing related anxiety on the chance that anxiety, to the extent that it might be related to the substance use, would concurrently remit. These clinical speculations, however, are nothing more than assumptions since little is known about the effects of targeting one disorder when treating additional comorbid disorders in an individual.

COMORBIDITY AMONG ANXIETY AND MOOD DISORDERS: IMPLICATIONS FOR COMORBID SUBSTANCE USE DISORDERS

Research from the author's anxiety disorders research clinic has produced some evidence on the effects of comorbidity among anxiety and mood disorders on treatment outcome, both short and long term. Since these results are somewhat surprising, it is possible that they may have some implications for similar comorbid patterns among anxiety disorders and substance use disorders. One recently analyzed set of data examined the impact of treatment for panic disorder using an effective cognitive-behavioral treatment (Barlow et al. 1989) on the course and outcome of generalized anxiety disorder that was not directly treated (Brown and Barlow 1992). GAD was chosen because it is the most frequently co-occurring diagnosis in patients with a principal diagnosis of PD (Moras et al., submitted). For purposes of this analysis, the comorbid presence of GAD was considered at both a clinical level of severity as well as a subclinical level of severity in which GAD was clearly identifiable but was not considered severe enough to interfere substantially with functioning. As noted in figure 1, of 68 panic disorder patients treated, 32 percent had a clinically significant GAD additional diagnosis at pretreatment, with an additional 9 percent evidencing subthreshold GAD. At posttreatment the rate of GAD above threshold declined to 9 percent, whereas subthreshold GAD increased to 16
percent

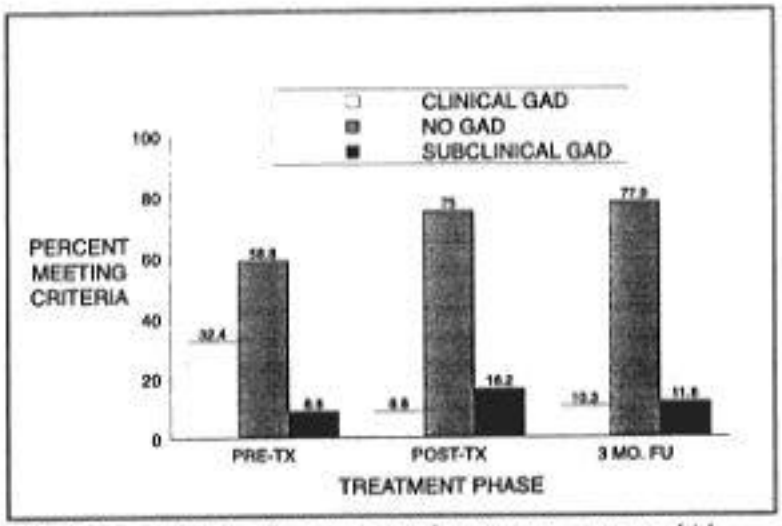

FIGURE 1. *Effects of panic control treatment on comorbid GAD diagnoses in 68 patients with panic disorder.*

KEY: Clinical GAD = Anxiety Disorders Interview Schedule-Revised [ADIS-R] diagnosis of GAD with clinical severity rating of 4 or above on a 0-8 scale; subclinical GAD = ADIS-R diagnosis of GAD with clinical severity rating below 4; PRE-TX = before treatment; POST-TX = after treatment; 3MO.FU = 3-month followup.

because several patients with a clinically significant GAD at pretreatment moved to the subclinical category at posttreatment. These results were relatively stable at a 3-month followup. Thus, in this example, a comorbid disorder improved with successful treatment of the target disorder in spite of the fact that no attempts were made to treat it directly. Of course, one possible reason for these results is that GAD and PD share many symptoms, with GAD often considered to be the "basic" anxiety disorder (Brown et al. 1994). Thus, the success-ful treatment of panic disorder may have "generalized" to symptoms comprising GAD such as anxious arousal and cognitions of future danger.

Now there is more substantial data on the impact of pretreatment and posttreatment comorbidity on outcome of treatment for panic disorder (Brown and Barlow 1995). Analyzing 87 patients with PD who completed active treatment, the investigators first looked at the effect of the presence of additional diagnoses at pretreatment on short-term outcome (i.e., posttreatment and 3-month followup). The

effect of having at least one additional diagnosis was examined on two measures of treatment outcome, high endstate status and panic-free status. Interestingly, patients with at least one additional diagnosis at pretreatment, irrespective of type, did as well at posttreatment and 3-month followup as those patients without an additional diagnosis. The presence of a mood disorder pretreatment did seem to impact somewhat on results at posttreatment, but any effect of mood disorder had disappeared by the 3-month followup; so, those PD patients with or without a mood disorder did equally well. Of more interest here is the question of whether cognitive-behavioral treatment for PD resulted in the reduction of additional diagnoses after treatment, as seemed to be the case for GAD. Fifty-three patients were utilized in these analyses because they had been administered the full assessment battery at pretreatment, 3-month followup, and 24-month followup. Basically, the results, presented in figure 2, reflect a generally improving pattern at 3-month followup in additional diagnoses, followed by a return close to baseline levels in the presence of additional diagnoses at a 2-year followup. Specifically, 39.6 percent of the patients presented with at least one additional diagnosis at pretreatment whereas 30.2 percent of the patients evidenced at least one additional diagnosis at a 2-year followup, despite the fact that these patients maintained or improved upon their treatment gains for PD symptomatology over the same interval. For example, 41.5 percent of patients met high endstate criteria in regard to their PD status at 3-month followup (a category very close to "cured"), whereas this had increased to 62.3 percent at the 2-year followup. Panic-free status remained in the 75 percent range.

Another way of examining these data is to look at the longitudinal course of additional diagnoses. For example, the five patients who were assigned a mood disorder diagnosis at the 2-year followup may or may not have been the same five patients who had a mood disorder diagnosis at pretreatment. The author and colleagues were able to make these longitudinal comparisons on 64 patients who had completed the 2-year followup. The results are presented in figure 3. As is evident in that figure, the continued presence of comorbid diagnoses was associated with poorer treatment outcome for PD at 2 years. Specifically, whereas 76.9 percent of the patients who no longer had any comorbid diagnoses met high end-state criteria, only 33.3 percent of the patients with continued comorbidity met

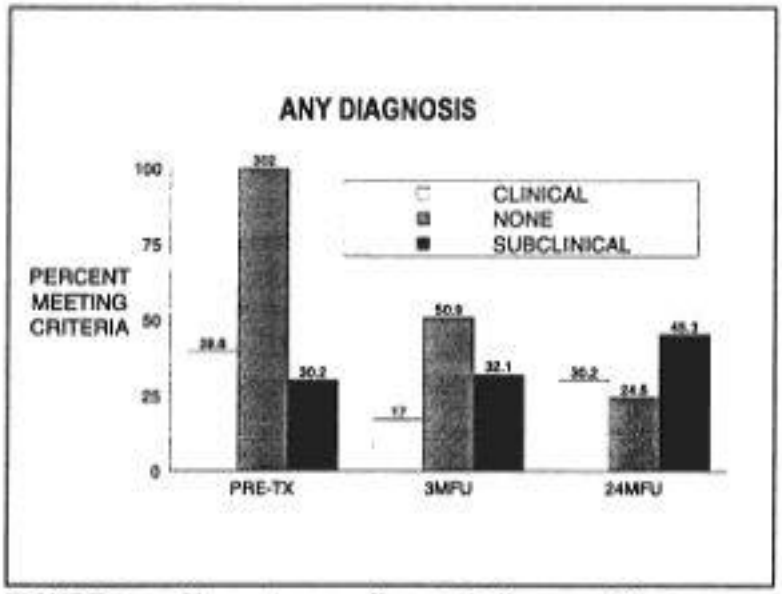

FIGURE 2. *Change in overall comorbidity rate following cognitive-behavioral treatment for PD.*

KEY: ANY DIAGNOSIS = presence of additional diagnosis irrespective of type; PRE-TX = pretreatment; 3MFU = 3-month followup; 24MFU = 24-month followup.

these criteria. Among the 36 patients who had not received any additional diagnoses at pretreatment, 6 (16.7 percent) were assigned a diagnosis other than PD at 24 months, but the remainder continued to be disorder free. Whereas 66.7 percent of the 30 patients who continued to have no comorbid diagnoses at 2 years met high end- state functioning criteria at this assessment point, only one (16.7 percent) of the six patients with a new additional diagnosis met these criteria.

There are two implications of this analysis for comorbidity between anxiety disorders and substance abuse. First, successful treatment of one disorder may only temporarily affect the course of the comorbid disorder when assessed longitudinally. Second, this comorbid disorder should be carefully attended to over the course of a long-term followup.

Furthermore, continued presence of a comorbid disorder bodes poorly for outcome of the original disorder. That is, treatment of the target disorder

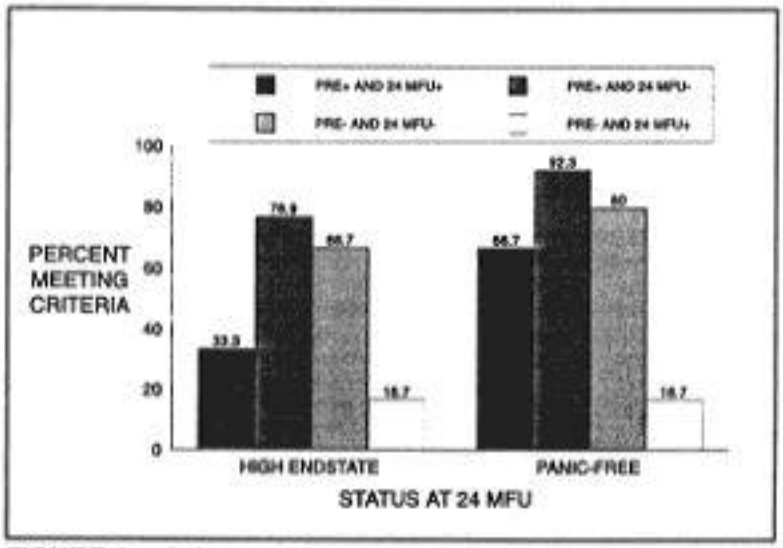

FIGURE 3. *Relation of longitudinal changes in comorbidity to treatment outcome at 24-month followup.*

KEY: PRE+ AND 24MFU+ = comorbidity present at both pretreatment and 24-month followup (24MFU); PRE+ AND 24MFU- = comorbidity present at pretreatment but not present at 24MFU; PRE- AND 24MFU- = comorbidity not present at either pretreatment or 24MFU; PRE- AND 24MFU+ = comorbidity not present at pretreatment but present at 24MFU.

is less successful in the presence of a persisting comorbid disorder. Thus, while existing pretreatment comorbidity does not seem to predict outcome in the target disorder, at least among the anxiety and mood disorders, additional comorbid diagnoses present at pretreatment are not likely to permanently remit, with the possible exception of reactive anxiety or depression. Moreover, the continued presence of an additional diagnosis at 24-month followup is associated with poorer outcome in the target disorder, in this case PD.

It is possible that these results are related to the functional relationship among diagnoses. That is, "reactive" depression and anxiety may permanently remit once the target disorder is treated, whereas more independent comorbid diagnoses may benefit only temporarily from treatment only to reemerge at a later point in time. Clearly, these analyses have to be carried out with comorbid anxiety disorders and substance abuse and dependence while taking into consideration the

temporal sequencing of these disorders in order to determine overall treatment strategies. The author found that, with the exception of generalized anxiety and depression, most anxiety disorders preceded the onset of alcohol abuse problems. On the other hand, the relationship between cocaine and PD in particular seems to reflect the opposite pattern of onset, with cocaine use triggering panic attacks and subsequently chronic PD after remission of cocaine abuse problems in a large proportion of those people suffering from PD. While treatment of PD seems successful whether triggered by drug use or not (Barlow 1988), few have attempted to treat anxiety disorders in the context of comorbid substance abuse. Some have argued that the presence of substance abuse would interfere with the results of many psychosocial treatments for anxiety disorders. This is because these treatments require the patient to experience anxiety in order to effectively learn new coping procedures and to make attributions of success to one's personal experiences. On the other hand, patients abusing alcohol might experience any anxiolytic effects as due to continued alcohol use and make those attributions.

While little data exist to support these arguments either way, some data do exist in another related area, specifically the use of benzodiazepines for anxiety disorders and the relationship of benzodiazepine use to successful psychosocial treatments. Specific problems that arise in this context involve the effects of benzodiazepines on psychosocial treatments for anxiety disorders and difficulties with discontinuing benzodiazepines.

BENZODIAZEPINE USE IN THE ANXIETY DISORDERS: RELATIONSHIP TO PSYCHOSOCIAL TREATMENTS

Benzodiazepines are commonly prescribed for anxiety disorders. Often these drugs are prescribed in low dosages by primary care physicians to control symptoms of anxiety before referring patients on to mental health professionals. For example, medication use in PD patients presenting for psychosocial treatment at two clinics known for psychosocial approaches are presented in table 1. As is evident, the overall percentage of patients on medication at time of presentation is approximately 60 percent, with fully 50 percent taking benzodiazepines. Interestingly, 40 percent of the total sample are taking one drug, the high potency benzodiazepine alprazolam. While these data were collected in the late 1980s, more recent experience at the author’s clinic reflects few substantial changes. Of course, these

TABLE 1. *Medication use of PD patients presenting for psychological treatment.*

	Albany, NY[a]		Philadelphia, PA[b]		Overall	
	N	%	N	%	N	%
N not using medication	29	39	18	46	47	41
N using medication	46	61	21	54	67	59
Benzodiazepines	39	52	18	46	57	50
Alprazolam	33	44	12	31	45	39
Diazepam	4	5	2	5	6	5
Lorazepam	1	1	0	0	1	1
Chlordiazepoxide	1	1	3	8	4	4
Clonazepam	0	0	1	3	1	1
Tricyclic						
Imipramine	8	11	2	5	10	9
Other medication						
Propranolol	5	7	0	0	5	4
Buspar	0	0	1	3	1	1

KEY: a = Phobia and Anxiety Disorders Clinic, State University of New York at Albany. Based on two independent samples collected during 1986-1987 (Sanderson et al. 1990, 1989). b = Center for Cognitive Therapy, University of Pennsylvania. Data were collected during 1988-1989 (Sanderson and Beck 1989).

patients are still symptomatic or they would not be presenting for treatment. Thus, the use of benzodiaze-pines in this context can be analyzed as a predictive factor in assessing response to psychosocial treatment, as well as long-term outcome.

A few studies have examined this question. For example, Wardle and colleagues (1994), in one of the few prospective studies of its kind, examined the effects of very small doses (5 mg) of diazepam on the treatment of agoraphobia by in vivo exposure. The design of this experiment is presented in figure 4.

Specifically, those patients already utilizing drugs (users) or not (nonusers) discontinued drug use and then were introduced to either a placebo or 5 mg of diazepam in a double-blind fashion. They were then assessed once again prior to a course of in vivo exposure for their

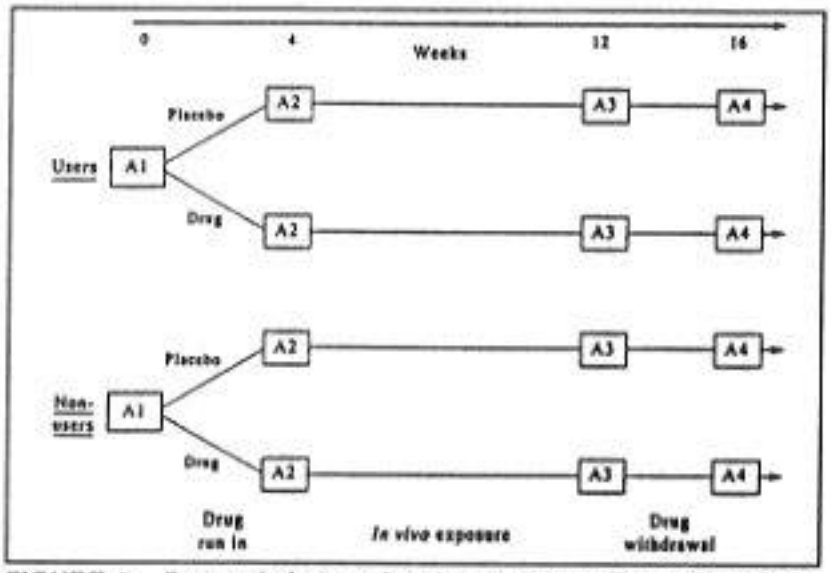

FIGURE 4. *Research design of study examining effects of low doses of benzodiazepines on in vivo exposure treatment of agoraphobia.*

SOURCE: Wardle et al. 1994.

agoraphobia before undergoing an additional assessment at 12 weeks after completion of in vivo exposure. After drug discontinuation they were assessed once again. While no effects were directly evident on measures of agoraphobia at any assessment point, global clinical ratings of improvement were slightly better after treatment for those patients on placebo as opposed to those on diazepam. This finding is potentially significant because of the small and certainly nontherapeutic dose of diazepam utilized in this experiment.

More recently Marks and colleagues (1993) examined the effects of more substantial therapeutic dosages of alprazolam as well as in vivo exposure either alone or in combination in the treatment of PD and agoraphobia. The major set of results demonstrated that patients did relatively well based on assessments immediately following treatment whether in vivo exposure was combined with alprazolam or not, with approximately 70 percent showing substantial clinical benefit. However, subsequent assessment after discontinuation from drug showed a substantially greater relapse in those patients taking alprazolam compared to those patients undergoing in vivo exposure without alprazolam. Thus, alprazolam actually seemed to interfere with the therapeutic effects of in vivo exposure (see figure 5).

Finally, new data from the author's clinic suggest that at both the 3- and 24-month followup, those patients taking small and, in most cases, non-therapeutic doses of medication, mostly benzodiazepines, evidence a poorer outcome on measures of clinical severity than do those patients who are not using drugs even after controlling for initial levels of severity. Specifically, on overall measures of clinical severity from a semistructured interview, the Anxiety Disorders Interview Schedule-Revised (ADIS-R) (DiNardo and Barlow 1988), as well as ratings of fear

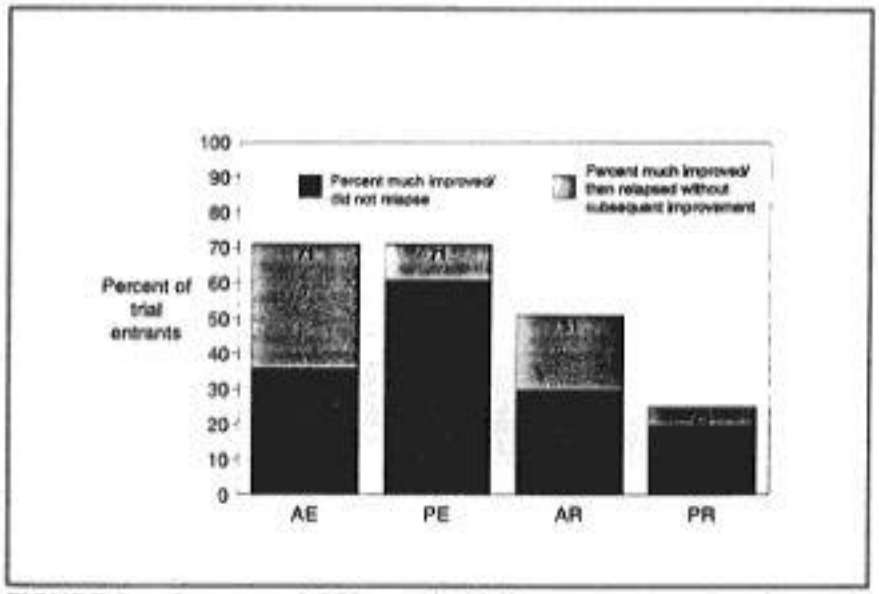

FIGURE 5. *Outcome of CGI at end of followup: percent of trial entrants who became much/very much improved on the assessor-rated CGI at any time and who remained so without major relapse to the end of the study at week 43.*

of panic from this same interview schedule, or scores on the Anxiety Sensitivity Index (Reiss et al. 1986) and subjective symptoms scale, reflecting impairment in functioning, those patients not taking drugs during treatment either did significantly better (from the ASI and ADIS-R–Fear of Panic Measure) or trended better (on the ADIS-R clinical severity and subjective symptoms scale measure) at the 24-month followup. Thus, it seems that benzodiazepine use may interfere with the long-term effects of psychosocial treatment of anxiety disorders (Brown and Barlow 1995).

This is all the more striking since other classes of drugs such as the tricyclic antidepressants do not seem to interfere with psychosocial treatment. If anything, this class of drugs produces a synergistic effect when combined with psychosocial treatment (Barlow and Brown, in press).

Benzodiazepine Discontinuation

Concern over benzodiazepine prescribing practices has been growing in recent years (Roy-Byrne 1991; Tyrer 1988). These concerns focus mostly on the potential for abuse, dependence, cognitive and motor impairment, and difficulties associated with treatment discontinuation (Lader and Petursson 1983). Discontinuation is considered desirable for a number of reasons, including the reluctance of many individuals to undergo long-term treatment; concerns for safety over the long term, particularly in the elderly (Lader and Petursson 1983) or during pregnancy (Laegrid et al. 1987); and the need to reevaluate the necessity of continued antianxiety treatment in patients who have improved or recovered while on benzodiazepines (Rosenbaum 1990). Advantages of high potency benzodiazepines, on the other hand, include rapid onset of anxiolytic effects and more tolerable side effect profiles during acute treatment (Pollack and Rosenbaum 1988).

Attempts at discontinuation from benzodiazepines are associated with the onset of a specific withdrawal syndrome as well as very high relapse (Fyer et al. 1987; Nutt 1990; Noyes et al. 1991). For example, Noyes and colleagues (1988) found that nearly half of the patients treated with benzodiazepines for over 1 year experienced a withdrawal syndrome upon discontinuation of medication. For these and other reasons most patients are unable to complete benzodiazepine medication taper; this is true whether the taper is fast or slow (Pecknold et al. 1988) or whether the benzodiazepines have a long half-life or a short half-life (Rickels et al. 1990; Schweizer et al. 1990).

There is now some evidence that psychosocial treatments and benzodiaze- pines may be combined more effectively if applied sequentially. Some of this evidence comes from studies examining the effects of new brief psychosocial treatments to assist patients in discontinuing from benzodiaze-pines. A number of early case studies and clinical series suggest that a combination of cognitive-behavioral strategies seems successful in assisting discontinuation (e.g., Tyrer et al. 1985; Higgit et al. 1987). More recently, Otto and colleagues have devised a treatment for purposes of benzo-diazepine discontinuation

(Otto et al. 1992, 1993). This approach was adapted from a successful treatment for PD (Barlow and Craske 1994). Spiegel and colleagues at Illinois have carried out a similarly successful effort (Spiegel et al. 1994).

In the Otto and colleagues (1993) study, 33 patients were randomly assigned to one of two taper conditions: a slow taper condition alone or a slow taper condition in conjunction with 10 weeks of group cognitive-behavioral treatment. All patients met criteria for PD with or without agoraphobia. Significantly, more patients receiving the cognitive-behavioral program (13 of 17; 76 percent) successfully discontinued benzodiazepine treatment compared to patients receiving the slow taper alone (4 of 16; 25 percent). Three-month followup evaluation indicated that 77 percent of patients in the cognitive-behavioral program remained benzodiazepine free.

Similarly, Spiegel and colleagues (1994) used an extremely gradual taper of as little as 0.125 mg every 7 days to attempt to discontinue PD patients who had been brought to a panic-free state with alprazolam. Ten patients received supportive therapy and 10 patients a cognitive-behavioral treatment (CBT) program modeled after Barlow and Craske (1994). With this slow taper, 90 percent of the CBT group and 80 percent of the comparison group successfully discontinued, but after 30 months only 40 percent of the comparison group remained off benzodiazepines, the others having resumed because of anxiety and panic symptoms. In contrast, all patients in the cognitive-behavioral group remained off medication. Results are presented in figure 6. These two studies have important implications for possible strategies for combining benzodiazepines and psychosocial treatments, as suggested below.

CONCLUSIONS

Results from all surveys indicate substantial comorbidity between anxiety disorders and substance abuse and dependence. Further analyses are needed to ascertain the functional relationship among these comorbid patterns and the long-term course of comorbidity as a function of treating one or the other disorder. For example, if substance abuse problems are essentially attempts to self-medicate an anxiety disorder, then successful

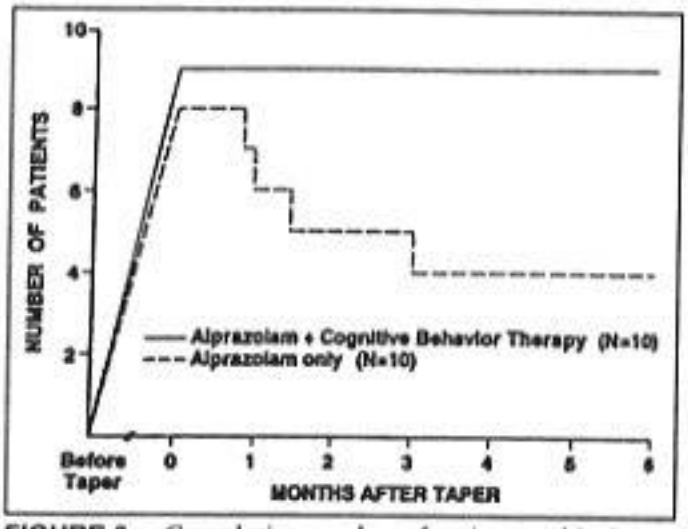

FIGURE 6. *Cumulative number of patients achieving and maintaining drug abstinence in groups receiving alprazolam only and alprazolam plus CBT.*[a]

KEY: a = Significant difference between survival distributions from before taper to after taper to 3 months after taper (Lee-Desu statistic = 4.197, df = 1, $p < 0.5$).

treatment of the anxiety disorder may also ameliorate the substance abuse disorder. On the other hand, if anxiety (or depression) is a reaction to substance abuse, then the initial target of treatment may have to be substance abuse-related issues.

Developing psychosocial approaches to benzodiazepine discontinuation may also have implications for the treatment of comorbid anxiety disorders and substance abuse. Specifically, the fact that patients treated psychosocially do less well over the long term if they are undergoing concurrent benzodiazepine administration may be due to one of several reasons. For example, benzodiazepine administration, insofar as it successfully reduces anxiety, may interfere with the emotional processing and development of coping procedures ongoing in cognitive-behavioral treatments in which confronting some anxiety is a necessary part of treatment. Alternatively, patients may attribute any anxiolytic effects to drugs that they happen to be taking, rather than to the development of their own coping procedures and progress they have made in psycho-social treatment. Arguing against the latter interpretation is the fact that patients concurrently on

other classes of medications, such as tricyclic antidepressants, seem to do as well or better after psychosocial treatment than patients not on tricyclic antidepressants. It may be that on a more fundamental neurobiological level, some classes of drugs are more compatible with psychosocial treatment than others.

In any case, it is also possible that a sequential administration of treatments beginning with high potency benzodiazepines with their quick onset, followed by cognitive-behavioral approaches to not only assist in discontinuing benzodiazepines but also to produce long-term effects, will be a useful treatment strategy (Barlow and Brown, in press; Spiegel et al. 1994). This has yet to be demonstrated.

Finally, for those individuals who began abusing substances in attempts to self-medicate anxiety, it may be that, contrary to current clinical wisdom, administration of psychosocial treatments targeting anxiety will at the same time evidence beneficial effects on substance use. This approach might provide a more reliable long-term strategy not only to assist withdrawal from substances but also to promote long-term maintenance of treatment gains and prevent relapse. Studies evaluating this possibility lie ahead.

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