

## ACADEMIC HIGHLIGHTS

# Utilizing Benzodiazepines in Clinical Practice: An Evidence-Based Discussion

**T**his ACADEMIC HIGHLIGHTS section of The Journal of Clinical Psychiatry presents the highlights of the meeting "Utilizing Benzodiazepines in Clinical Practice: An Evidence-Based Discussion" held August 16, 2004, in Boston, Mass., and supported by an unrestricted educational grant from Pfizer Inc.

The meeting was chaired by **Jerrold F. Rosenbaum, M.D.**, Department of Psychiatry, Massachusetts General Hospital, Boston. The faculty were **Charles P. O'Brien, M.D., Ph.D.**, Department of Psychiatry, University of Pennsylvania School of Medicine, Philadelphia Department of Veterans Affairs Medical Center, Pa.; **Michael W. Otto, Ph.D.**, Department of Psychiatry, Massachusetts General Hospital, Harvard Medical School, Boston; **Mark H. Pollack, M.D.**, Center for Anxiety and Traumatic Stress Disorders, Massachusetts General Hospital, Harvard Medical School, Boston; **Peter P. Roy-Byrne, M.D.**, Department of Psychiatry and Behavioral Sciences, University of Washington School of Medicine, Seattle; and **Samantha A. Stewart, M.D.**, Massachusetts General Hospital, Boston.

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Chair Jerrold F. Rosenbaum, M.D., began the meeting by citing a recent case report (described herein by Samantha A. Stewart, M.D.) as evidence that the issues and conflicting information surrounding benzodiazepine use in patients with anxiety continue to raise important treatment concerns. Dr. Rosenbaum explained that this meeting was called to review the case and to try to address some of the ongoing questions surrounding benzodiazepine treatment, such as what the effects of benzodiazepines on cognition are and what the abuse potential of these agents is.

## Benzodiazepines: Then and Now

By highlighting issues from presentations he delivered in the 1980s, Dr. Rosenbaum provided an overview of benzodiazepine use. He stated that benzodiazepines were and still are widely used and offer symptomatic relief for some of humankind's most prevalent and distressing conditions. One thing that has changed, Dr. Rosenbaum commented, is pharmacologic alternatives. Tricyclic antidepressants (TCAs), monoamine oxidase inhibitors (MAOIs),  $\beta$ -blockers, azapirones, and sedatives have been replaced with selective serotonin reuptake inhibitors (SSRIs) as primary alternative treatments as of the 1990s. Nonetheless, from a pharmacologic perspective, benzodiazepines remain the most effective acute antianxiety and hypnotic medications compared with other agents.

Dr. Rosenbaum offered that implicit in the antibenzodiazepine sentiment has been a trivialization of anxiety disorders and anxious distress. However, in the 1990s, a panel of experts in the pharmacotherapy of anxiety and de-

pressive disorders<sup>1-4</sup> affirmed with considerable findings that patients who received benzodiazepine treatment were indeed ill, had high levels of psychiatric distress, and generally met criteria for anxiety disorders. Further, in 1999, despite acknowledging some abuse potential (Table 1), this panel of experts recommended the use of benzodiazepines for anxiety disorders, even for long periods.<sup>4</sup>

## Abuse Liability and Physical Dependence

Dr. Rosenbaum explained that 2 major issues surrounding benzodiazepine use continue to be abuse liability, particularly with long-term use, and physical dependence. Dr. Rosenbaum suggested distorted perceptions, such as generalizations from chemically dependent and substance-abusing populations and confusion about the meaning of physical dependence, may have discouraged benzodiazepine use.

Despite public concern over the risk of benzodiazepine abuse and dependence,<sup>5</sup> benzodiazepines remain a com-

**Table 1. Summary of Consensus Among Expert Pharmacotherapists Regarding the Potential for Therapeutic Dose Dependence and Abuse With Benzodiazepine Use<sup>a</sup>**

Benzodiazepines pose a higher risk of dependence and abuse than most potential substitutes but a lower risk than older sedatives and recognized drugs of abuse
There is little consensus about the relative risk of dependence and abuse among the benzodiazepines
Differences among benzodiazepines with shorter and longer half-lives in inducing withdrawal symptoms are much less clear during tapered than during abrupt discontinuation
There is little agreement about the most important factors contributing to withdrawal symptoms and failure to discontinue benzodiazepines
The pharmacologic properties of the medication may be the most important contributors to withdrawal symptoms
The clinical characteristics of the patient may be the most important contributors to failure to discontinue medication

<sup>a</sup>Reprinted with permission from Uhlenhuth et al.<sup>4</sup>

monly used treatment. Psychopharmacologists continue to endorse benzodiazepines as a primary or adjunctive treatment for several anxiety disorders,<sup>4</sup> although other researchers continue to highlight potential risks of benzodiazepine use, especially in patients with comorbid alcohol use disorders<sup>6</sup> and in older patients who are at greater risk for falls. Physical dependence, Dr. Rosenbaum emphasized, implies neither abuse nor loss of benefit but does imply a need for the tapering of treatment at discontinuation. This clinical necessity is not unique to benzodiazepines and is to be considered for all treatments whose effects are associated with receptor adaptation and symptom suppression.

Although experts agree that benzodiazepines pose a higher risk of dependence and abuse than most potential substitutes, they pose a lower risk than older sedatives and recognized drugs of abuse.<sup>4</sup> To put the abuse issue into perspective, Dr. Rosenbaum pointed out that in 1990, the American Psychiatric Association Task Force on Benzodiazepines<sup>7</sup> concluded that benzodiazepines are not drugs of abuse, although benzodiazepine abuse is common among people who are actively abusing alcohol, opiates, cocaine, or sedative hypnotics. At the same time, in response to the perceived addiciveness of benzodiazepines, some states (New York, for example) and countries enacted legislation<sup>8</sup> (the triplicate prescription program) intended to regulate indiscriminate prescribing of benzodiazepines and quell concerns

of the potential for addiction with long-term use. The result was large decreases in benzodiazepine prescriptions, but prescribing of less effective and more dangerous alternatives increased substantially.<sup>9</sup>

### Guidelines for Treating Anxiety Disorders With Benzodiazepines

Dr. Rosenbaum stated that anxiety disorders are not usually cured but rather controlled. He provided the following general clinical principles to help minimize the risk of chronic treatment for acute problems: (1) distinguish acute symptomatic distress driven by recent psychosocial events from Axis I disorder; (2) discuss the goals and limitations of benzodiazepine therapy with the patient, including the meaning of physiologic adaptation and its implication; (3) adopt a dynamic stance to treatment designed to determine the lowest effective dose and a plan for discontinuation; and (4) reevaluate the need for treatment in the short term and over the long term with intermittent structured attempts to taper.

### Conclusion

Dr. Rosenbaum concluded by stating that 20 years ago experts predicted that benzodiazepines would remain a pharmacologic mainstay of clinical anxiety management and that new developments in the pharmacologic modification of the benzodiazepine receptor would one day yield therapeutic strategies to diminish the physical dependence associated with benzodiazepines. These predictions remain to be realized, but progress continues to be made. This ACADEMIC HIGHLIGHTS will clarify the role of benzodiazepine use today.

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## The Effect of Benzodiazepines on Cognition

Dr. Stewart first relayed a case report of a patient she had treated after benzodiazepine overdose (Table 2). She offered that although she was aware of potential problems with tolerance and dependence associated with long-term benzodiazepine use, until treating this patient she was unaware of the extent of the controversy about long-term use and cognitive effects. Therefore, she reviewed the literature on the effects of benzodiazepines on cognition.

### Specific Cognitive Effects

Dr. Stewart stated that benzodiazepine administration has been known to

produce sedation, drowsiness, psychomotor slowing, anterograde amnesia, and difficulties learning new material.<sup>1</sup> Memory loss in particular has been attributed to the sedative effects of benzodiazepines that impair attention. However, different rates of sedation and of amnesia suggest that amnesia in individual patients is a distinct phenomenon within benzodiazepine use, despite the fact that sedation and amnesia are mediated by the same benzodiazepine-receptor subunit.<sup>2</sup>

According to Dr. Stewart, an array of cognitive effects has been described with long-term benzodiazepine use.

Studies<sup>2–7</sup> often attempt to describe highly specific and well-defined areas of decline. Memory changes have variably been described as impaired working memory, explicit memory, or nonverbal memory or alternatively discarded as entirely attributable to sedation or impaired attention or related to peak plasma concentration. The cognitive changes most frequently attributed to long-term benzodiazepine use have been visuospatial deficits and changes in explicit memory; the elderly have specific vulnerability to these cognitive changes.

### Cognitive Effects of Long-Term Benzodiazepine Use

Dr. Stewart referred to a meta-analysis by Barker et al.<sup>8</sup> that investigated whether there is a significant presence of cognitive decline with long-term benzodiazepine use. The final analysis included 13 studies, which the authors acknowledged had varying methodologies that limited their meta-analytic results.

In their review meta-analysis, Barker et al.<sup>8</sup> observed that the duration of benzodiazepine use was between 1 and 34 years, with a mean of 9.9 years. The average dose was the equivalent of 17.2 mg/day of diazepam. Dr. Stewart offered that these data confirm what has long been suspected about benzodiazepine treatment: that many people are using benzodiazepines for substantial lengths of time at substantial doses.

Dr. Stewart reported that the authors<sup>8</sup> measured 12 cognitive domains: visuospatial, attention/concentration, problem solving, general intelligence, psychomotor speed, sensory processing, verbal memory, nonverbal memory, speed of processing, motor control/performance, working memory, and verbal reasoning. Although many of the studies used several batteries to measure more than 1 cognitive function, the authors included only 1 averaged and weighted effect size per cognitive domain from each study. The meta-analytic results

**Table 2. Case Report of Patient With Cognitive Deficits Attributed to Benzodiazepines**

Ms. A was admitted to the Massachusetts General Hospital psychiatric unit after her family found her heavily sedated from having taken 18 mg of lorazepam. She was a white, middle-aged, divorced mother and lawyer who had been profoundly depressed since the loss of her job 2 months earlier. Her family and her new psychiatrist were afraid that this was a suicide attempt, but Ms. A insisted she was just trying to sleep, so every time she roused she took more lorazepam.
A history revealed near lifelong symptoms of anxiety, characterized primarily by an overarching feeling of doom and certainty that the worst was about to happen. As a child, she had loved flying, but after losing her mother in a plane accident and experiencing a later rough flight of her own, she developed a profound phobia of flying. At the same time, her career required that she make frequent short flights, often leaving and returning the same day. It was during this period that she developed the strategy of having 2 drinks and taking several lorazepam tablets before flying.
The benzodiazepine was prescribed by her primary care physician; however, she had begun seeing a psychiatrist 5 years prior during her marital trouble and had had brief trials of both antidepressants and mood stabilizers. At the time of admission, she was taking lorazepam, typically 5 mg, for sleep and flying. She denied increasing the dosage or using the lorazepam other than as prescribed until the presenting events. She had, in fact, recently switched psychiatrists and was attempting to taper her lorazepam use. She currently had prescriptions for 10 mg of zolpidem h.s. and 4 mg of lorazepam h.s.
Her speech was slightly slurred on admission. She was irritable but cooperative. Within 1 day of hospitalization, she was more organized and euthymic, showing no symptoms or signs of withdrawal while taking 3.5 mg of lorazepam and 10 mg of zolpidem. She began taking a selective serotonin reuptake inhibitor, and her dose of lorazepam was tapered to 3 mg with a plan to continue a slow taper to discontinuation. She was educated about cognitive-behavioral therapy (CBT), which she said had previously been recommended by an anxiety disorders clinic.
Basic neuropsychiatric testing showed a surprisingly low IQ score that did not correlate with that of a lawyer. The testing psychologist suggested that Ms. A's alcohol and benzodiazepine use had likely contributed to this cognitive inefficiency, which may interfere with future treatment with CBT. Ms. A and her family adamantly denied alcohol abuse, saying that except for flights, she drank only socially and then rarely more than 2 drinks. Magnetic resonance imaging showed no brain atrophy but did reveal a pituitary microadenoma, which endocrinologists began to treat.

suggested significant decline in all cognitive domains.

Dr. Stewart discussed a second meta-analysis<sup>9</sup> by the same group that researched whether these cognitive changes are reversible upon withdrawal of benzodiazepines. Using the same set of studies except for 1 that did not adequately present follow-up data, Barker et al. assembled an averaged and weighted effect size to represent studies' results as they fit into the same 12 areas of cognitive function.

Dr. Stewart noted that the results of the second meta-analysis<sup>9</sup> were 2-fold. Accumulated data suggested that all areas of cognitive function improved at follow-up testing. However, the data also indicated that improvement never rose to the level of cognitive performance of controls who did not take benzodiazepines. Barker et al. also reported that there was better recovery with younger age.

Dr. Stewart observed that given the cognitive changes reported with benzodiazepine treatment, anatomic or physiologic changes may be demonstrable. However, when Bustos et al.<sup>10</sup> compared computed tomographic imaging changes in patients taking benzodiazepines long-term and in age- and sex-matched controls, no differences in brain atrophy were observed.

## Conclusion

Dr. Stewart concluded that if cognitive decline is indeed a side effect of benzodiazepine use, clinicians may have to be alert to the presence of cognitive changes in their patients.

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## The GABA-Benzodiazepine Receptor Complex in Anxiety

### Molecular Nature

Peter P. Roy-Byrne, M.D., began by explaining that the  $\gamma$ -aminobutyric acid (GABA)-benzodiazepine receptor complex is a pentameric structure with 5 glycoprotein subunits that span a lipid bilayer and form a cylindrical structure with an ion channel in the center (Figure 1). The receptor complex has 2  $\alpha$  subunits alternating with 2  $\beta$  subunits and 1  $\gamma$  subunit. Located at the intersection of the alternating  $\alpha$  and  $\beta$  subunits are the 2 GABA binding sites. The single benzodiazepine binding site is located at the  $\alpha$  and  $\gamma$  intersection, which is consistent with evidence that a  $\gamma$  subunit is necessary for benzodiazepine, but not GABA, action.

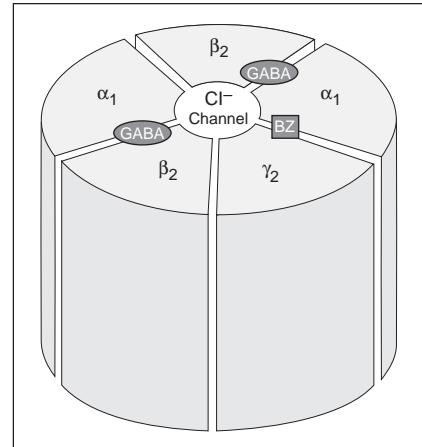
Several molecular families of subunits have been identified in the receptor complex: 6  $\alpha$  isoforms ( $\alpha_{1-6}$ ), 3  $\beta$  isoforms ( $\beta_{1-3}$ ), and 3  $\gamma$  isoforms ( $\gamma_{1-3}$ ), among others. However, most receptor complexes are composed of 2  $\alpha_1$ , 2  $\beta_2$ , and 1  $\gamma_2$  subunits. This receptor subtype is thought to be responsible for the sedative properties of benzodiazepines. Of interest, noted Dr. Roy-Byrne, is that all 3 of these subunits are coded on chromosome 5.

Dr. Roy-Byrne said that differential subunit expression may alter GABA-benzodiazepine receptor function and can occur naturally, which may underlie anxiety proneness, as well as in response to either benzodiazepine treatment or environmental changes.

### Functional and Structural Alterations

Dr. Roy-Byrne discussed research conducted to determine functional differences in the GABA-benzodiazepine receptor complex of patients with anxiety disorders. He and colleagues administered the benzodiazepine agonist diazepam to panic patients and controls and measured changes in saccadic eye movement velocity (SEV).<sup>1</sup> After diazepam administration, controls showed more change in SEV than panic patients, thereby suggesting a reduced sensitivity to benzodiazepines in panic patients. Dr. Roy-Byrne noted that the research finding relevant to Dr. Stewart's patient was that at the highest dose of diazepam, 200 mg/kg, panic patients did not show the cognitive impairment that controls did.

**Figure 1. GABA-Benzodiazepine (BZ) Receptor Complex**



In a similar study by Nutt et al.,<sup>2</sup> the benzodiazepine antagonist flumazenil was given to panic patients and controls. Although as expected flumazenil had no effect in controls, the agent unexpectedly induced panic attacks in panic patients. Subsequent studies<sup>3,4</sup> with flumazenil in panic patients have had mixed results. Nonetheless, the Nutt et al. study<sup>2</sup> was accompanied by a theoretical interpretation that the normal spectrum of GABA-benzodiazepine receptor ligand activity may be altered in anxiety disorders.

Dr. Roy-Byrne explained that under normal conditions the spectrum of ligands for the GABA-benzodiazepine receptor includes full agonist, partial agonist, neutral antagonist, partial inverse agonist, and full inverse agonist activities. In patients with anxiety disorders, the receptor set point is hypothesized to be shifted so that, for example, full agonists act like partial agonists and neutral antagonists act like partial inverse agonists.

According to Dr. Roy-Byrne, the implications of the aforementioned pharmacologic challenges have been confirmed in neuroimaging studies that suggest that patients with anxiety disorders may have either fewer GABA-benzodiazepine receptors<sup>5-7</sup> or reduced levels of the neurotransmitter GABA.<sup>8</sup> Research<sup>9</sup> with mice with  $\gamma_2$  subunit mutation found that the knockout mice had increased anxiety, reduced GABA-benzodiazepine receptor binding in the brain, and reduced sensitivity to benzodiazepines. Dr. Roy-Byrne opined that molecular alteration in the receptor subunits or their isoforms may contribute to anxiety disorders.

### Effects of Chronic Treatment

Dr. Roy-Byrne offered that tolerance to benzodiazepines is assumed to be related to underlying changes in GABA-benzodiazepine subunit expression. Research by Holt and colleagues<sup>10</sup> showed that chronic benzodiazepine treatment differentially altered receptor subunit gene cluster expression in rats. This study focused on 3 subtypes of receptors distin-

guished by their  $\alpha$  subunit isoform. The receptor subtypes with the  $\alpha_1$  isoform had reduced mRNA expression after chronic diazepam or abecarnil treatment. The receptor subtypes with the  $\alpha_2$  and  $\alpha_5$  isoforms had increased mRNA expression with diazepam but not with abecarnil. Because abecarnil is a partial agonist, such a finding suggests that receptor subtypes with  $\alpha_2$  and  $\alpha_5$  isoforms might underlie differences in tolerance and withdrawal thought to be associated with partial benzodiazepine agonists.

Dr. Roy-Byrne and colleagues conducted a study<sup>11</sup> in humans that demonstrated that benzodiazepine tolerance appears to be an exaggeration of the reduced benzodiazepine sensitivity seen in patients with anxiety. Alprazolam-treated panic patients and benzodiazepine-naïve, unmedicated panic patients were given diazepam and then compared on several measures. Among the alprazolam-treated patients, sensitivity to diazepam was widely distributed. Of interest was that the most medication-tolerant patients were the most symptomatic, perhaps indicating that some patients are more prone to develop tolerance and respond poorly to treatment than others.

Dr. Roy-Byrne concluded by saying that still unknown is whether the problems of benzodiazepine tolerance and dependence are related to alterations in the GABA-benzodiazepine receptor complex that precede chronic benzodiazepine treatment or develop as a consequence of it.

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## Efficacy of and Concerns About Benzodiazepines and Their Alternatives for Anxiety Disorders

### Widespread Use of Benzodiazepines

Mark H. Pollack, M.D., commenced by pointing out that contrary to current treatment guidelines for most anxiety disorders, benzodiazepines are widely used for these conditions. For example, the American Psychiatric Association<sup>1</sup> guidelines for managing panic disorder recommend using antidepressants, par-

ticularly SSRIs, for initial medication treatment and recommend using benzodiazepines as only augmenting agents or not at all. However, data from the Harvard Anxiety Research Program<sup>2</sup> show that in the 1990s, benzodiazepines were prescribed more often than any other type of medication, including SSRIs, for panic disorder.

**Table 3. Potential Side Effects of Benzodiazepines**

Sedative, amnestic, and cognitive effects
Psychomotor impairment
Disinhibition
Physiologic dependence
Discontinuation-related symptoms and withdrawal
Abuse liability in predisposed individuals
Negative interaction with alcohol
Lack of efficacy and potential to induce or amplify comorbid depression

When addressing the question of why clinicians continue to prescribe benzodiazepines for anxiety disorders, Dr. Pollack suggested several answers. Benzodiazepines are effective, they have a more rapid onset of action than other anxiolytics, they are well tolerated, and they can be used on a p.r.n. basis for situational anxiety. Also, benzodiazepines may reduce antidepressant-induced activation when given as adjunctive therapy.

### Effectiveness of Benzodiazepines

Dr. Pollack noted that the benzodiazepines, including alprazolam, clonazepam, and diazepam are known for effectively and quickly reducing anxiety symptoms. For example, acute studies of panic disorder<sup>3</sup> and generalized anxiety disorder<sup>4</sup> show that benzodiazepines are more efficacious than placebo and have a quicker onset of action than antidepressants.

Most studies suggest that patients maintain benefits with benzodiazepines over time<sup>5-7</sup> and that doses of the benzodiazepines for the majority of patients either stay the same or tend to decrease.<sup>5-8</sup>

### Concerns About Benzodiazepines

Dr. Pollack suggested that, despite immediate onset and maintained benefit, benzodiazepines are of concern to both clinicians and patients for reasons ranging from side effects to abuse potential (Table 3). He went on to discuss the cognitive effects of long-term benzodiazepine use, which was a

factor in the case presented by Dr. Stewart.

Although a meta-analysis<sup>9</sup> on the effects of long-term benzodiazepine use found cognitive impairment across a variety of measures, the analysis had several limitations such as few studies meeting inclusion criteria, small sample sizes, and wide variety in definition of duration of use and testing for cognitive impairment. In another review of the literature, Deckersbach<sup>10</sup> found that most studies investigating chronic benzodiazepine effects did not exclude patients with significant psychiatric conditions, including anxiety disorders, which could themselves be the cause of the cognitive deficits observed after chronic benzodiazepine use, and that, because patients were not studied prior to benzodiazepine administration, many cognitive deficits may precede treatment.

Dr. Pollack emphasized that a critical issue that has not been adequately addressed in most studies that assess the cognitive effects of long-term benzodiazepine use is the lack of credible controls. Typically, patients receiving benzodiazepines are compared with normal controls rather than untreated anxiety patients or anxiety patients receiving other treatments.

### Alternatives to Benzodiazepines for Anxiety

Dr. Pollack reviewed the psychotropics other than benzodiazepines that have been used to treat anxiety, such as antidepressants and atypical antipsychotics. Antidepressants, including SSRIs, TCAs, and MAOIs, have all been used successfully in the treatment of anxiety, but SSRIs have emerged as the preferred treatment for anxiety disorders across all classes of medication.<sup>11</sup>

According to Dr. Pollack, antipsychotics for anxiolytic use is not a new concept, but the favorable side effect profile of the atypical antipsychotics has rekindled interest in using these agents in anxiety. Research<sup>12</sup> has shown that some atypical antipsychotics are efficacious in obsessive-

compulsive disorder (OCD), posttraumatic stress disorder (PTSD), and generalized anxiety disorder (GAD).

Dr. Pollack also discussed several agents that are forthcoming or under development as anxiety treatments. Pregabalin—not yet commercially available—was described by Dr. Pollack as a potentially credible alternative to benzodiazepines because of its tolerability and speed of onset of anxiolytic effect.<sup>13</sup> Also being researched and developed as potential anxiolytics are GABA  $\alpha_2$  subunit specific agents, which may offer anxiolytic effects without the sedative or amnestic effects; selective GABA reuptake inhibitors such as tiagabine; the anticonvulsant levetiracetam; selective 5-HT<sub>1A</sub> agonists; corticotropin-releasing factor antagonists; substance P (NK1) receptor antagonists; glutaminergic antagonists; and neurotrophic factors.

### Conclusion

Dr. Pollack offered that the popularity of benzodiazepines is perhaps due to clinician and patient experience with these agents as robustly effective anxiolytics. He speculated that until agents with a spectrum of efficacy similar to that of this class are available, benzodiazepines will continue to be widely used to treat anxiety.

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cause dependence is due to the body's adaptation to the effects of the agent. If patients develop a dependence on an agent and then that agent is stopped abruptly, a rebound or withdrawal effect will occur. Dr. O'Brien offered that such outcomes may occur to some extent with virtually anyone who takes a benzodiazepine long-term. However, he reiterated, rebound or withdrawal does not always indicate psychological addiction. Unfortunately, many clinicians may be confused by such a distinction because they think that when a patient has dependence in the physiologic sense, then he or she must be psychologically addicted.

Dr. O'Brien explained that research<sup>3,4</sup> indicates that dose and time are both variables that influence the risk of dependence. The longer the time and the higher the dose, the greater the risk. A study by Rickels et al.<sup>3</sup> found that withdrawal severity was largely determined by treatment duration. Of patients who took diazepam, 15 to 40 mg/day, for less than 8 months, 5% showed withdrawal symptoms, while 43% of patients taking diazepam for more than 8 months showed such symptoms. However, in an 8-week study,<sup>4</sup> 35% of patients taking 2 to 10 mg/day of alprazolam experienced mild-to-moderate withdrawal symptoms but no such symptoms were experienced by placebo-treated patients. On the basis of such results, Dr. O'Brien suggested that how long a clinician treats a patient with a benzodiazepine is a matter of clinical judgment, although in his own practice, he has found that patients are less likely to develop tolerance with intermittent benzodiazepine treatment.

Dr. O'Brien noted that tolerance to some effects of benzodiazepines, like sedation, has led to speculation that tolerance to anxiety effects may also develop. Dr. O'Brien recounted that many United Kingdom experts have explained to him that long-term benzodiazepine treatment is ineffective because of tolerance, and in fact, the Committee on the Review of Medicines in the United Kingdom,<sup>5</sup> citing

## Use and Abuse of Benzodiazepines

Charles P. O'Brien, M.D., Ph.D., acknowledged that in the early 1970s, he and his colleagues began to see both deliberate and unintentional benzodiazepine abuse despite a belief at the time that benzodiazepines had no abuse potential. He reported that today the abuse potential of benzodiazepines is well known and accepted.

### Deliberate Benzodiazepine Abuse

In cases of deliberate abuse, Dr. O'Brien and his colleagues<sup>1</sup> found that people took the agents for the purpose of getting high alone or in combination with other substances. Heroin addicts taking methadone reported that diazepam augmented the effects of methadone. Benzodiazepines were also used to augment the effects of other drugs such as cocaine, alcohol, and heroin.

Dr. O'Brien proposed that several variables (half-life, age of patient, speed of onset and offset, and tolerance) may influence the abuse potential for individual benzodiazepines but qualified such variables by saying that the popularity of an abused drug is rarely based on anything objective. A study<sup>2</sup> that surveyed benzodiazepine use by methadone clients found that diazepam, lorazepam, and alprazolam were among those agents most frequently used, and chlordiazepoxide

and oxazepam were less likely to be used. Dr. O'Brien speculated that the desirability of these agents was related to half-life, i.e., agents with a long half-life were more desirable than agents with a short half-life. He suggested that rapid onset may increase the potential for abuse of agents like diazepam.

### Unintentional Benzodiazepine Abuse

In many cases of unintentional benzodiazepine abuse, patients have been prescribed benzodiazepines as a treatment and then (1) increase their dosage to maintain the drug's effectiveness because they become tolerant to sedating effects of the original dose and/or (2) experience withdrawal symptoms when they try to stop the drug so they continue the drug to avoid the withdrawal effects. Because tolerance and withdrawal are often incorrectly thought of as indicating the presence of addiction, Dr. O'Brien emphasized that it was necessary to make a distinction between physiologic dependence and addiction in cases of unintentional benzodiazepine abuse. According to Dr. O'Brien, dependence is a normal biological response that anyone can develop if he or she takes certain drugs repeatedly. Dependence can even occur with other anxiety agents like β-blockers and antidepressants be-

**Table 4. Symptoms of Benzodiazepine Withdrawal That Differentiate It From Return of Anxiety**

Agitation
Increased sensitivity to lights and sound
Paresthesias and strange sensations
Muscle cramps
Myoclonic jerks
Insomnia
Dizziness
Seizures <sup>a</sup>

<sup>a</sup>More common with benzodiazepines with short half-lives than those with long half-lives.

a lack of evidence that benzodiazepines are efficacious beyond 4 months, recommended benzodiazepines as only short-term treatment. Dr. O'Brien disagreed, however, and cited research<sup>6-8</sup> as well as his own clinical experience as evidence for the efficacy of benzodiazepines in the long-term treatment of anxiety. He also pointed out the results of a study<sup>9</sup> that suggest that tolerance is developed selectively to different benzodiazepine effects. Even after years of treatment, patients with memory impairment due to an acute dose of diazepam did not show tolerance.

Dr. O'Brien reiterated that withdrawal is likely if a patient has developed dependence. Furthermore, because a symptom of withdrawal is anxiety, clinicians and patients may find it difficult to differentiate withdrawal from the return of original anxiety symptoms. He reviewed symptoms of benzodiazepine withdrawal that distinguish it from anxiety recurrence (Table 4). In his practice, he has found carbamazepine, clonidine, and propranolol to be effective for withdrawal symptoms, and others have concurred.<sup>10</sup>

## Conclusion

Dr. O'Brien ended by stating that benzodiazepines are effective treatments and that the number of people treated for anxiety who develop a true addiction syndrome is, in his experience, very small. However, many patients may require detoxification after long-term use.

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## Nonpharmacologic Alternatives: Cognitive-Behavioral Therapy

### Efficacy of Cognitive-Behavioral Therapy in Anxiety Disorders

Michael W. Otto, Ph.D., began by offering that cognitive-behavioral therapy (CBT) is an alternative to pharmacology for the treatment of anxiety disorders. Dr. Otto presented data<sup>1-6</sup> from several meta-analyses that compared CBT with pharmacologic anxiety treatments such as benzodiazepines and antidepressants. Such evidence supports CBT as a viable alternative in the treatment of anxiety and suggests a subtle advantage for CBT over medication in panic disorder,<sup>1,2</sup> PTSD,<sup>3</sup> OCD,<sup>4</sup> and GAD,<sup>6</sup> with the largest advantage for CBT found in PTSD. The only anxiety disorder that suggests a relative advantage for medication over CBT is social anxiety disorder.<sup>5</sup>

Dr. Otto reported that although CBT is thought of as a difficult treatment for patients to complete, that expectation has not been borne out in clinical trials.<sup>1-6</sup> In meta-analytic results, patients treated with CBT had lower dropout rates than patients treated with medications (Table 5). Patients with social anxiety disorder were the exception; dropout rates were about the same in the CBT and antidepressant groups.

### Combining Cognitive-Behavioral Therapy and Pharmacotherapy

According to Dr. Otto, although there is an advantage of combined CBT and medication, this advantage may be lost once the medication is withdrawn.<sup>8,9</sup> He suggested that medication appears to be a powerful context, so that what a patient learns with CBT while taking medication does not necessarily extend to the nonmedication period. For example, animal research<sup>10</sup> has demonstrated that changes in an internal state, like those due to the anxiolytic effect of a benzodiazepine, are a powerful enough context that the safety learned during exposure interventions may occur only within that context. When the internal state is changed, i.e., the benzodiazepine is taken away, anxiety returns.

Similar results were found in a study<sup>11</sup> in which people with a spider phobia were treated with 1 session of exposure-based therapy and then returned for follow-up a week later. At both treatment and follow-up, patients were given caffeine or placebo. Those patients that received caffeine at 1 session and placebo at another session experienced greater return of fear than

**Table 5. Dropout Rates in Controlled Trials as Represented by Mean Percentages in Meta-Analytic Reviews<sup>a</sup>**

Disorder	Dropout Rate (%)
Panic disorder <sup>1,2</sup>	
CBT	5.6
Benzodiazepines	13.1
Non-SSRI antidepressants	25.4
SSRIs	19.9
Posttraumatic stress disorder <sup>3</sup>	
CBT	19.0
Pharmacotherapy	38.0
Obsessive-compulsive disorder <sup>4</sup>	
CBT	16.7
Antidepressants	20.5
Social anxiety disorder <sup>5</sup>	
CBT	10.7
Benzodiazepines	12.0
Antidepressants	10.3
Generalized anxiety disorder <sup>6</sup>	
CBT	10.6
Benzodiazepines	13.1
Antidepressants	33.5

<sup>a</sup>Adapted with permission from Otto et al.<sup>7</sup>  
Abbreviations: CBT = cognitive-behavioral therapy; SSRI = selective serotonin reuptake inhibitor.

those patients that received the same condition at both sessions.

In a randomized, double-blind, placebo-controlled trial<sup>8</sup> in patients with panic disorder, the effects of treatment with the TCA imipramine only, CBT only, placebo only, CBT plus imipramine, and CBT plus placebo were compared. At the end of the 3-month acute treatment, there was no statistically significant difference between response rates for CBT plus imipramine and CBT plus placebo. After 6 months of maintenance treatment, response rates continued to be highest in the CBT plus imipramine and CBT plus placebo groups. Six months after treatment was discontinued, response rates were highest in the CBT plus placebo and CBT only groups. Dr. Otto emphasized that in both combination groups patients were taking a pill, an external context, so the difference in response rates between these 2 groups at the post-discontinuation follow-up suggests that it may have been the change in *internal* context that was most important for the loss of efficacy.

Dr. Otto cited comparable results from a benzodiazepine-exposure

therapy combination study<sup>9</sup> as further evidence that combination treatment offers minor gains in acute treatment but loss of these relative gains after the medication is discontinued.

Dr. Otto proposed that the solution for maintaining the gains of combined treatment is to reapply CBT at the time of medication taper, so that safety learning is reiterated during and after the taper. Studies<sup>12-15</sup> using CBT with benzodiazepine and SSRI taper have shown that treatment gains are maintained when CBT is administered in conjunction with drug taper.

### Cognitive Deficits in Cognitive-Behavioral Therapy

Dr. Otto addressed whether Dr. Stewart's patient was a candidate for CBT, a question that had been raised by the psychologist who had reviewed the patient's neurological tests. Dr. Otto offered that there is evidence that OCD,<sup>16</sup> PTSD,<sup>17</sup> and panic disorder<sup>18,19</sup> are associated with memory deficits, regardless of whether patients are taking benzodiazepines,<sup>20</sup> and it is quite clear that CBT provides a robust response in these patients. Moreover, CBT appears to offer similar acute effects in patients who are and are not already taking medications including benzodiazepines.<sup>21</sup> Hence, concerns about memory effects alone should not deter referral for CBT.

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**Drug names:** alprazolam (*Xanax and others*), carbamazepine (*Epitol, Tegretol, and others*), chlordiazepoxide (*Librium and others*), clonazepam (*Klonopin and others*), clonidine (*Catapres, Duraclon, and others*), diazepam (*Diastat, Valium, and others*), imipramine (*Tofranil and others*), levetiracetam (*Keppra*), lorazepam (*Ativan and others*), oxazepam (*Serax and others*), propranolol (*Inderal, Innopran, and others*), tiagabine (*Gabitril*), zolpidem (*Ambien*).

**Disclosure of off-label usage:** The chair has determined that, to the best of his knowledge, clonidine and propranolol are not approved by the U.S. Food and Drug Administration for the treatment of benzodiazepine withdrawal symptoms.

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