# Discussion

# Using Benzodiazepines in Clinical Practice

## UNDERSTANDING BENZODIAZEPINE MECHANISM OF ACTION

**Dr. Stewart:** It seems that benzodiazepines only treat anxiety while the patient is taking them, but my impression from the literature is that antidepressants produce some cumulative changes in the brain if patients comply with treatment [*Malberg JE. J Psychiatry Neurosci 2004;29: 196–205*]. Is it the case that benzodiazepines do not make any permanent changes in anxiety? Can anxiety disorders be cured by benzodiazepines?

**Dr. Rosenbaum:** Patients taking benzodiazepines function better because of the treatment, which has a salient effect on their overall well-being. However, a benzodiazepine is not like an antibiotic that can eliminate an infection within a matter of days.

**Dr. Pollack:** The hope of pharmacologic treatment for an anxiety disorder is to decrease patients' anxiety enough so that they can enter situations they previously avoided. When patients learn that they can enter those situations without losing control, the clinician may sometimes discontinue the benzodiazepine.

**Dr. Rosenbaum:** Is there a theory explaining the mechanism of benzodiazepine-induced anterograde amnesia, which is perhaps the one cognitive effect everyone agrees does occur? Since norepinephrine increases new memory, this amnesia could be caused by a benzodiazepine interfering with norepinephrine, or the interference could be happening in the glutamatergic system. If these neurotransmitter changes were known to cause amnesia, benzodiazepine-induced amnesia might be managed with atomoxetine or memantine.

**Dr. Roy-Byrne:** Anterograde amnesia may result from the benzodiazepine's effect on the glutamatergic system, affecting frontal cortical and hippocampal benzodiazepine receptors that in turn alter the function of glutamate circuits. However, the neuroanatomy and the circuits for memory are still not fully understood.

**Dr. Stewart:** I think that inverse agonists are being tested for promotion of memory.

**Dr. O'Brien:** Dr. Stewart mentioned inverse agonists, and I would like to take the opportunity to remark on this relatively new terminology. An agonist fully interacts with the benzodiazepine receptor, so continuing to increase the dose of a benzodiazepine agonist will eventually cause an overdose. A partial agonist can have high affinity for the receptor, but a full activation of the receptor is prevented, even with increased dose. A pure antagonist completely blocks the interaction between the ligand and the receptor. Many antagonists are turning out to be inverse agonists—that is, agonists in the opposite direction. Thus, a benzodiazepine inverse agonist would cause anxiety instead of sedation.

Nutt and colleagues [*Arch Gen Psychiatry 1990;47: 917–925*] showed that the antagonist flumazenil produced anxiety in patients with anxiety disorders but had no effect in normal subjects. They also found fewer benzodiazepine receptors in patients with anxiety disorders compared with controls. Is there some endogenous antianxiety substance that could explain these findings?

**Dr. Roy-Byrne:** Nutt and colleagues hypothesized that there could be an endogenous benzodiazepine agonist of which patients with anxiety have too little or an endogenous benzodiazepine inverse agonist of which anxiety patients have too much. Alternatively, anxiety patients could have an altered benzodiazepine receptor set-point. Sandler and colleagues [*Prog Clin Biol Res 1985;192: 359–362*] did find elevated levels of tribulin, an anxiogenic ligand, in human urine in states such as panic attacks, alcohol or benzodiazepine withdrawal, and generalized anxiety disorder. So, endogenous substances yet to be found may play a role in anxiety.

**Dr. Rosenbaum:** Given that benzodiazepines appear to bind to receptors differently, that there are different subtypes of receptors, and that there are individual differences in response among patients, do some benzodiazepines work differently than others?

**Dr. Pollack:** The benzodiazepines are different in molecular makeup and in practice. Some people respond better with one than another, for reasons that have yet to be identified.

**Dr. Roy-Byrne:** Is there a reason, other than half-life and potency, that clonazepam is marketed and used as an anticonvulsant?

**Dr. Pollack:** Treatment for seizures, anxiety, and depression seems to be related in that γ-aminobutyric acid (GABA) levels increase when these disorders are managed with medication, be it a non-GABAergic anticonvulsant, benzodiazepine, or selective serotonin reuptake inhibitor (SSRI) *[Bhagwagar Z, et al. Am J Psychiatry 2004;161:368–370].*

**Dr. Rosenbaum:** That makes me recall that alprazolam was initially thought to be a uniquely effective antipanic agent with antidepressant efficacy, but subsequent use as an antidepressant had mixed data [*Petty F, et al. Biol Psychiatry 1995;38:578–591; Birkenhager TK, et al. Int Clin*

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*Psychopharmacol 1995;10:181–195*]. What do you think of benzodiazepine augmentation of SSRIs in depression treatment?

**Dr. Pollack:** Londborg and colleagues [*J Affect Disord 2000;61:73–79*] showed that if clonazepam and fluoxetine were started together, depression response was accelerated. However, a second study [*Smith WT, et al. J Affect Disord 2002;70:251–259*] did not show persistent benefit.

**Dr. Roy-Byrne:** Benzodiazepines have been studied for virtually every anxiety disorder, but has research been conducted on the efficacy of benzodiazepines for a discrete, simple phobia?

**Dr. Pollack:** A study of alprazolam efficacy for fear of flying [*Wilhelm FH, et al. Behav Res Ther 1997;35: 831–841*] found that physiologic activation was increased and the therapeutic effects of exposure were hindered by the agent.

## SIDE EFFECTS OF BENZODIAZEPINES

### Cognitive Effects

**Dr. Rosenbaum:** Ms. A's case [*Stewart SA. J Clin Psychiatry 2005;66(suppl 2):9–13*] suggested that there were enduring cognitive effects from long-term benzodiazepine use. Were these effects clearly attributable to the benzodiazepine?

**Dr. Stewart:** The combination of alcohol and lorazepam was hypothesized to have precipitated this cognitive degeneration.

**Dr. O'Brien:** Did Ms. A have repeat neuropsychiatric testing? Her initial testing was done soon after she had taken a high dose of benzodiazepine combined with an unknown amount of alcohol, both of which might have produced persistent short-term impairment. If she had only an average IQ score, it seems unlikely that she would be able to succeed in law school or get a job with a prestigious law firm.

**Dr. Stewart:** There was no repeat testing. She recovered quickly and left quickly. Ms. A did lose her job under questionable circumstances, so I do not know if she truly was performing at a high level or if the cognitive impairment had been present for a long time. She had a confabulatory style of communicating, possibly indicating she was accustomed to covering up a cognitive problem.

**Dr. O'Brien:** So, perhaps she obtained the job while functioning at a higher level and subsequently experienced cognitive deterioration as a result of the combination of anxiety disorder and improper medication.

**Dr. Stewart:** Yes, although she was still very intoxicated when she arrived at the hospital, and the testing was done only 3 or 4 days after her arrival.

**Dr. Pollack:** How long does short-term cognitive impairment due to alcohol persist?

**Dr. O'Brien:** Cognitive impairment from chronic alcohol use will persist for at least a few weeks after a patient becomes abstinent. Time and money are wasted in treatment programs in which alcoholics are reeducated during and directly after detoxification because, like benzodiazepines, alcohol erases recent memory.

**Dr. Otto:** It is interesting how readily the cognitive deficits were attributed specifically to the benzodiazepine in the case of Ms. A. Some cognitive deficits may be explained by the presence of an anxiety or mood disorder, rather than the medication or even alcohol. I also question the insinuation that someone functioning on an average cognitive level would be mentally unable to complete or benefit from cognitive-behavioral therapy (CBT). The cognitive abilities of participants in clinical studies of CBT efficacy run the spectrum.

**Dr. Rosenbaum:** Dr. Stewart, given the apparent chronicity of Ms. A's benzodiazepine use, were you surprised at how readily she accepted and tolerated taper?

**Dr. Stewart:** Yes. The neuropsychiatric tester seemed to quickly label her a substance abuser, perhaps partially because she acted very hostile when she arrived at the hospital, which created a certain dynamic between her and the hospital staff. However, she did not show symptoms or signs of withdrawal that would indicate that she was as physically dependent as we would have suspected.

### Disinhibition

**Dr. O'Brien:** Can anyone address whether violence is a side effect of benzodiazepines?

**Dr. Rosenbaum:** Benzodiazepines have been said to release behavior that would otherwise be constrained by fear of punishment.

**Dr. Roy-Byrne:** I agree. Disinhibition may be a common property of benzodiazepines, and an aggressive individual who becomes disinhibited might be violent.

**Dr. Pollack:** Violence is not commonly a side effect in clinical trials of benzodiazepines for anxiety disorders.

**Dr. Roy-Byrne:** If violence were a substantive effect, it would appear in clinical trials.

**Dr. Rosenbaum:** I think violence is pretty rare.

**Dr. Roy-Byrne:** However, although such effects are extremely rare, when treating someone with a history of aggressiveness, fighting, and outbursts, I would be reticent to give that patient a disinhibiting substance.

**Dr. Otto:** More minor disinhibition is seen in patients with social phobia. After years of being so inhibited that they were unable to speak up, patients first starting benzodiazepines occasionally overcompensate. They want to say something, and they may find themselves being verbally aggressive until they have a chance to develop a more subtle style.

### Tolerance

**Dr. Roy-Byrne:** Unfortunately, in some cases, a pattern develops in which patients respond to treatment but lose the response after several weeks. Response occurs again at a higher dose, only to be lost after several more weeks of

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treatment. If continual dose elevation is needed, to what maximum dose should physicians go?

**Dr. Pollack:** The limits for benzodiazepine doses are, to a large extent, arbitrary. The pattern you described is often seen as the development of tolerance, when it may actually reflect appropriate dose titration, especially early in treatment.

**Dr. Roy-Byrne:** If this is tolerance, can clinicians assume that if they prescribe a high enough dose, a patient will no longer develop tolerance?

**Dr. Rosenbaum:** There should be a guideline for determining how many times or to what maximum dose clinicians should elevate the dose before deciding that the patient has the capacity to continually adapt to the agent. If a patient adapts to the established maximum dose, the clinician should be prepared to switch to another treatment because further treatment with benzodiazepines may be self-defeating.

**Dr. Pollack:** A patient's improvement is often a result of a reduction in anxiety and an increase in exposure, either self-directed or therapist-directed. Since increased exposure is likely to create more anxiety, patients often need more medication at that point, which may be mistakenly attributed to the development of tolerance.

**Dr. Rosenbaum:** It may appear that increased exposure is causing more anxiety, but it could also be that the patient is experiencing a particularly stressful, transient life event. Raising the dose may unnecessarily create tolerance in order to treat something transient.

**Dr. O'Brien:** Physicians should prevent patients from titrating themselves. Patients may not always know whether the benzodiazepine is working, so sedation often becomes the litmus test. Patients develop a tolerance to sedation, so they may raise the dose as they notice less sedation, unaware that the antianxiety effects may be unaffected. Of course, controversy still exists about whether or not tolerance develops to the anxiolytic effects.

**Dr. Roy-Byrne:** The majority of individuals do not escalate their dose. For the small proportion of patients who do, the question is whether the doses are not holding their anxiolytic effect or if these patients have an underlying addictive diathesis.

**Dr. Pollack:** Because there is no precise way of quantifying what an adequate dose of a benzodiazepine is, it is somewhat arbitrary to say that at a certain dose, abuse is occurring.

**Dr. Rosenbaum:** Benzodiazepines may lose effectiveness in a minority of patients, similar to what occurs with other psychotropics, such as SSRIs and antipsychotics. However, another possibility is that some patients cannot tolerate the anxiety symptoms when experiencing a crisis situation and ask for a higher dose. These patients then become reluctant to experience whatever anxiety symptoms might emerge and continue to escalate dose, thereby setting new plateaus.

## Dependence Versus Addiction

**Dr. Rosenbaum:** Although there is some p.r.n. use of benzodiazepines for sleep disorders and other temporary issues, most people taking benzodiazepines have chronic anxiety disorders and appropriately take these medications long term because benzodiazepines change their lives for the better. Rifkin and colleagues [*Am J Psychiatry 1989; 146:1331–1332*] studied the charts of 2719 outpatients who were prescribed benzodiazepines and found that none of the patients met criteria for benzodiazepine dependence or abuse. Dependence on or addiction to benzodiazepines may be extremely rare.

**Dr. O'Brien:** To meet the criteria for substance dependence in the DSM-IV terminology, there would have to be drug-seeking behavior, forging prescriptions, continuing use despite negative health consequences, and neglecting family and work.

Unintentional dependence is of more immediate concern to clinicians—those patients who are legitimately taking benzodiazepines for an anxiety disorder and, because of tolerance, end up taking higher doses than clinicians are comfortable with. These patients are not trying to get high, and they are usually following their doctors' orders. It is very unusual for someone like that to become an abuser. Some of these patients, however, may have trouble discontinuing benzodiazepines because the body adapts to chronic use. The drug then becomes necessary for continued function, and, if the patient tries to discontinue the benzodiazepine, he or she may feel worse than before taking the medication. Some patients do not discontinue their benzodiazepines, and they function well. As long as these patients' doses are not escalated too much, this situation is acceptable. I do not consider it abuse to continue the drug in a patient who is physically dependent but functioning very well.

Unfortunately, people tend to think of psychiatric illnesses as different from illnesses that affect the lung or the heart. Viewing psychiatric illnesses as true chronic illnesses that require long-term treatment requires a change in mentality.

**Dr. Roy-Byrne:** To believe anxiety disorders are chronic medical illnesses for some patients is to accept that they may need to be treated permanently. No one would argue that an asthmatic who takes long-term medication is addicted, but some think anxiety disorders should be coped with and overcome within a period of time, instead of recognizing anxiety disorders as potentially lifelong illnesses.

**Dr. Rosenbaum:** Still, inhalers for asthma are known to be efficacious over the long term, while uncertainty remains about the continued efficacy of benzodiazepines over the long term.

**Dr. Stewart:** Do some patients continue to take benzodiazepines simply because they feel like they need the medication?

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**Dr. O'Brien:** Needing to take medicine to function normally is a kind of dependence but not an addiction. It is not necessarily bad to have a condition that requires medication, as long as the medication is not impairing the patient and he or she is not trying to get high.

## ALCOHOL AND BENZODIAZEPINES

**Dr. Rosenbaum:** Should benzodiazepines be prescribed for patients with a history of alcohol use?

**Dr. O'Brien:** The APA Task Force [*Salzman C, et al. Benzodiazepine Dependence, Toxicity, and Abuse: A Task Force Report of the American Psychiatric Association. Washington, DC: APA; 1990*] was unanimous that it is best not to prescribe benzodiazepines to a patient with a history of alcohol or other substance abuse. On the other hand, benzodiazepines, such as oxazepam, have been given to alcoholics for many years to detoxify them from alcohol dependence, and few problems with abuse have arisen in that situation, under close supervision.

However, if a patient is an alcoholic, I prefer not to prescribe benzodiazepines. Instead, I would prescribe a medication for alcoholism, like naltrexone. Many clinicians are unaware that such medications exist, but they are effective with some alcoholics [*Volpicelli J, et al. Arch Gen Psychiatry 1992;49:876–880; Kiefer F, et al. Arch Gen Psychiatry 2003;60:92–99*]. Researchers are learning more about the genetics of alcoholism and specific genotypes that may be more amenable to naltrexone treatment because of an endorphin-sensitive form of alcoholism [*Oslin DW, et al. Neuropsychopharmacology 2003;28:1546–1552*]. The U.S. Food and Drug Administration recently approved acamprosate for alcoholism.

Dr. Stewart's patient [*J Clin Psychiatry 2005;66 (suppl 2):9–13*] probably did not meet criteria for alcoholism. Clinicians must, however, warn patients about the dangerous combination of alcohol and benzodiazepines.

**Dr. Rosenbaum:** Is it vital to get the alcohol problem under control before considering a benzodiazepine?

**Dr. O'Brien:** Yes. If clinicians can effectively treat the alcoholism, then they can begin to treat the anxiety disorder.

**Dr. Rosenbaum:** What is the risk of prescribing a benzodiazepine for a patient who continues to use alcohol?

**Dr. O'Brien:** A patient may overdose inadvertently, as it appears happened with Dr. Stewart's patient. Ms. A kept waking up to take more lorazepam, barely cognizant of the fact that she had already taken some. A patient does not have to be suicidal to kill himself or herself when mixing alcohol and benzodiazepines.

**Dr. Stewart:** Is there a disproportionate number of anxiety disorder patients in alcohol-abusing populations?

**Dr. O'Brien:** Yes. In fact, some evidence suggests that chronic alcohol use generates anxiety disorders and vice versa *[Kushner MG, et al. Am J Psychiatry 1999;156: 723–732]*.

**Dr. Otto:** There is a distinction between primary and secondary disorders. Data suggest that panic disorder and generalized anxiety disorder are more likely to follow from pathological alcohol consumption, but social anxiety disorder and agoraphobia seem more likely to precede alcohol problems *[Kushner MG, et al. Am J Psychiatry 1990;147:685–695]*.

**Dr. Rosenbaum:** Sometimes the patient's history can clarify which came first. If a patient says, "I was fine until I had to do presentations at work, and then I found that a drink helped me," then clinicians may assume that anxiety was primary.

## COGNITIVE-BEHAVIORAL THERAPY AND BENZODIAZEPINES

**Dr. Otto:** CBT seeks to increase the emotional tolerance of patients by training them to do nothing in response to anxiety, so p.r.n. use of benzodiazepines may counteract this therapy by conditioning patients to take a pill whenever they get anxious. In CBT, overcoming anxiety should not be contingent on the availability of medication.

**Dr. O'Brien:** I disagree. I believe there is a case to be made for the p.r.n drug. I have found that diazepam is excellent because of its rapid onset. Having a prescription for diazepam p.r.n. gives patients quick relief in a moment of anxiety while enabling them to acquire exposure to an anxiety-provoking situation. I give limited prescriptions that can only be filled at a specific pharmacy, so I know that there is no abuse. The patient's pills over a given time are counted, and the number of pills are gradually decreased. This safety blanket enables patients to get exposure therapy that they would not get without the p.r.n. agent. It also discourages tolerance because the patients are only using the benzodiazepine intermittently.

**Dr. Otto:** Dr. O'Brien gives a nice example of the natural application of stepwise exposure within the context of psychopharmacologic treatment. Some synergistic effects between the benzodiazepine and CBT can be expected. Early in treatment, benzodiazepine plus CBT is acceptable. However, by the end of CBT, I want to know that the patient can function without the benzodiazepine. Otherwise, the patient may seem fine but relapse once he or she terminates the benzodiazepine.

**Dr. Rosenbaum:** What if a patient never discontinues the benzodiazepine and is functioning well?

**Dr. Otto:** Most patients are eventually going to discontinue benzodiazepines on their own or under supervision. Terminating the benzodiazepine within the context of CBT has a better chance of success.

**Dr. Rosenbaum:** Is CBT successful for patients who are born anxious, i.e., those who are inhibited, shy, and

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fearful as children and who develop anxiety disorders as adults? Are those patients able to function without medication?

**Dr. Otto:** Dr. Pollack and I, along with our colleagues [*Am J Psychiatry 1996;153:376–381*], found that adult panic patients with childhood-onset anxiety disorders did not respond to treatment differently from those who did not have childhood anxiety. Furthermore, some patients have made the decision a priori that medication or CBT is the answer and are unwilling to try the other treatment.

## CONCLUSION

**Dr. Stewart:** So, there may be serious negative effects with benzodiazepines over the long term, but the information is not concrete.

**Dr. Otto:** There are some memory costs, but they may pale in comparison to the impairment of an anxiety disorder.

**Dr. Rosenbaum:** With more than 40 years of available benzodiazepine treatments, it is unlikely that there is a serious, previously unknown effect lurking. When in doubt, clinicians should choose to maintain or improve the patient's quality of life whenever possible.

**Dr. Roy-Byrne:** Anxiety does not just cause distress and reduced quality of life but may also have medical effects such as hypertension and heart disease.

**Dr. Otto:** When I consider, for example, a shy person who is about to start college, I think how fortunate that person is that his or her anxiety disorder did not affect the decision to attend college because effective treatment was available.

**Dr. Rosenbaum**: As clinicians, we should use whatever safe treatment is available and effective in ending the anxiety of these patients.

*Drug names*: acamprosate (Campral), alprazolam (Xanax and others), atomoxetine (Strattera), clonazepam (Klonopin and others), diazepam (Valium and others), flumazenil (Romazicon), fluoxetine (Prozac and others), lorazepam (Ativan and others), memantine (Namenda), naltrexone (Revia and others), oxazepam (Serax and others).

*Disclosure of off-label usage:* The chair has determined that, to the best of his knowledge, no investigational information about pharmaceutical agents has been presented in this article that is outside U.S. Food and Drug Administration–approved labeling.

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