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This educational activity is eligible for CME credit through February 28, 2007. The latest review of this material was January 2005.

Educational Objective
After studying the ACADEMIC HIGHLIGHTS, you will be able to:

- Describe issues related to long-term benzodiazepine treatment such as cognitive effects, tolerance, and physical dependence

This pretest is designed to facilitate your study of the material.

1. **Abuse of benzodiazepines commonly occurs in patients with anxiety disorders.**
   a. True
   b. False

Pretest answer and Posttest on page 31.

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Benzodiazepines: Revisiting Clinical Issues in Treating Anxiety Disorders

This ACADEMIC HIGHLIGHTS section of The Primary Care Companion to 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. This report was prepared by the CME Institute of Physicians Postgraduate Press, 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.*

*Financial disclosure: In the spirit of full disclosure and in compliance with all ACCME Essential Areas and Policies, the faculty for this CME activity were asked to complete a full disclosure statement. The information received is as follows: **Dr. Rosenbaum** is on the advisory board of Bristol-Myers Squibb, Cyberonics, Eli Lilly, and Forest. **Dr. O'Brien** is a consultant for Alkermes, Johnson & Johnson, and McNeil; has received grant/research support from Pfizer; has received honoraria from Pfizer and GlaxoSmithKline; and has given expert testimony for Purdue Pharma. **Dr. Otto** has been a consultant for Janssen, Pfizer, and Wyeth and has received grant/research support from GlaxoSmithKline. **Dr. Pollack** has received research grants from Cephalon, Forest, GlaxoSmithKline, Janssen, Eli Lilly, Pfizer, UCB Pharma, and Wyeth and is on the speaker programs or advisory boards for Bristol-Myers Squibb, Cephalon, Forest, GlaxoSmithKline, Janssen, Eli Lilly, Novartis, Otsuka, Pfizer, Roche, Solvay, UCB Pharma, and Wyeth. **Dr. Roy-Byrne** has received grant/research support from GlaxoSmithKline, Pfizer, and Forest; is a consultant/advisor for Alza, Cephalon, GlaxoSmithKline, Forest, Eli Lilly, Janssen, Pfizer, Pharmacia, Roche, and Wyeth; and has received honoraria from GlaxoSmithKline, Forest, Novartis, Pfizer, Pharmacia, and Wyeth. **Dr. Stewart** has no significant commercial relationships to disclose relative to her presentation.*

The opinions expressed herein are those of the faculty and do not necessarily reflect the views of the CME provider and publisher or the commercial supporter.

Chair Jerrold F. Rosenbaum, M.D., began the meeting by explaining that he had been asked to be a discussant at a case conference at Massachusetts General Hospital where Samantha A. Stewart, M.D., presented the case of a woman (described herein by Dr. Stewart) who was admitted with cognitive deficits potentially caused by benzodiazepine abuse and dependence—issues that were heavily debated during the 1980s. Dr. Rosenbaum stated that the purpose of the meeting was to address concerns related to benzodiazepine use in clinical practice today.

Decades of Benzodiazepine Use

Historical Perspective

Dr. Rosenbaum remarked that benzodiazepines have been a source of controversy in the psychiatric community for years. They became widely available in the 1960s and have been prescribed to hundreds of millions of people over the past 4 decades. In the 1980s, high-potency benzodiazepines were found to be more effective treatments for panic and anxiety than their predecessors, i.e., tricyclic antidepressants, monoamine oxidase inhibitors, β-blockers, azapirones, and sedatives. The key advantages of benzodiazepines over prior agents include either rapid onset of action or less risk of dependence. The rapid onset with low toxicity and desirable therapeutic actions of benzodiazepines as anxiolytics, sedatives, anticonvulsants, and muscle relaxants have contributed to their continued use in treating anxiety disorders today.

Dr. Rosenbaum blamed unfavorable attitudes toward benzodiazepines in the late 1970s and 1980s on both a trivialization of anxiety as a treatable disorder and the negative perception that benzodiazepine treatment leads to abuse or physical dependence. These perceptions led to undertreatment of anxiety disorders. A review[1] of data from a 1979 survey of patients meeting DSM-III criteria for generalized anxiety disorder (GAD) revealed that only 27% had received treatment in the prior year; 73% went without medication. Dr. Rosenbaum underscored the importance of treating anxiety by stating that severe anxiety has been associated with a high risk of suicide.[2,3] In the 1990s, selective serotonin reuptake inhibitors (SSRIs) became the primary treatments for anxiety disorders and often replaced or were used adjunctively with benzodiazepines.

Abuse Liability and Physical Dependence

Dr. Rosenbaum stated that, except in patients with preexisting chemical dependency, abuse of benzodiazepines is rare. Although experts[4] acknowledged that benzodiazepines pose a higher risk of dependence and abuse than most potential substitutes, they also asserted that they pose a lower risk than older sedatives and recognized drugs of abuse. Dr. Rosenbaum reported that abuse liability, particularly with long-term use, continues to be a major issue surrounding benzodiazepine use.

Dr. Rosenbaum emphasized that physical dependence does not imply abuse or loss of benefit, but rather a need for the tapering of treatment at discontinuation. This clinical necessity is not unique to benzodiazepines and should be considered for all treat-

Table 1. Clinical Principles for Treating Anxiety Disorders With Benzodiazepines

1. Distinguish acute symptomatic distress owing to recent stressors from anxiety disorders
2. Discuss the goals and limitations of benzodiazepine therapy with the patient, including the meaning of physical dependence and its implication
3. Adopt a dynamic stance to treatment designed to determine the lowest effective dose and a plan for discontinuation
4. Reevaluate the need for treatment in the short term and over the long term with intermittent structured attempts to taper the drug

ments that effect receptor adaptation and symptom suppression.

According to Dr. Rosenbaum, anxiety disorders are usually not cured but rather controlled. He provided general clinical principles to help minimize the necessity for chronic treatment for anxiety disorders (Table 1).

Conclusion

Dr. Rosenbaum said that 20 years ago he predicted that benzodiazepines would remain a pharmacologic mainstay of clinical anxiety management, which has proven true, and that new developments in the pharmacologic modification of the γ-aminobutyric acid (GABA)-benzodiazepine receptor may one day yield therapeutic strategies to diminish the physical dependence associated with benzodiazepines. He explained that, from a pharmacologic perspective,[4] benzodiazepines remain the most effective acute antianxiety medications available, despite the perceived risk of abuse or dependence.

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Benzodiazepines: Effect on Cognition

Dr. Stewart presented a case report[1] of a patient who had overdosed on benzodiazepines and whom she treated on a medical psychiatric inpatient unit (Table 2). Dr. Stewart's concern about the cognitive deficit in a formerly high-functioning individual, and whether it was caused by alcohol or benzodiazepines, triggered this expert discussion. Benzodiazepine use has been associated with short-term cognitive effects such as sedation, psychomotor slowing, anterograde amnesia, and difficulties learning new material.[2] Sedation and amnesia are mediated by the same GABA-benzodiazepine receptor subunit, but different rates of sedation and amnesia suggest that amnesia is a distinct phenomenon in individual patients.

Long-Term Benzodiazepine Use

Dr. Stewart cited a meta-analysis[3] that investigated the presence of cognitive decline with long-term benzodiazepine use. Results from the 13 studies included in the meta-analysis

Table 2. Case Report of Patient With Cognitive Deficits Attributed to Benzodiazepines[a]

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.

[a]Reprinted with permission from Stewart.[1]

indicated that many people use benzodiazepines for substantial lengths of time at substantial doses; the duration of benzodiazepine use was between 1 and 34 years (mean 9.9 years), and the average dose equivalent was 17.2 mg/day of diazepam. Results suggested decline in all the cognitive domains measured: 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.

A second meta-analysis by the same group[4] indicated improved cognitive function at follow-up after benzodiazepine discontinuation, but function never rose to the level of cognitive performance of controls who did not take benzodiazepines. Of note, younger patients recovered more than older patients. Dr. Stewart offered that although benzodiazepine-induced cognitive deficits may theoretically cause anatomic or physiologic changes, evidence does not support this theory.[5]

Conclusion

Dr. Stewart concluded by stating that since many patients with anxiety disorders are first seen by primary care physicians,[6] clinicians who prescribe benzodiazepines must maintain a heightened awareness of cognitive changes in their patients.

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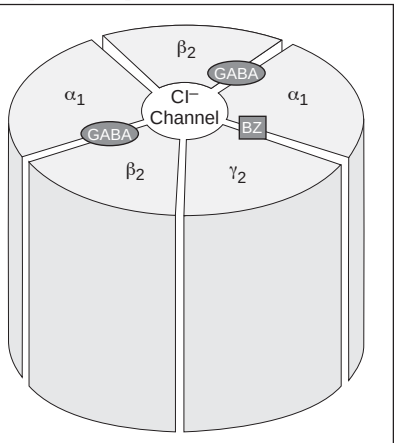
The GABA-Benzodiazepine Receptor Complex in Anxiety

Molecular Nature

Peter P. Roy-Byrne, M.D., began by stating that the pathophysiology of anxiety is currently poorly understood but involves a cascade of neurotransmitters, neuropeptides, receptors, second messengers, and other intracellular signaling mechanisms, as well as changes in gene expression.[1] Dr. Roy-Byrne explained that GABA is one of the most ubiquitous neurotransmitters in the central nervous system (CNS) and operates in over one third of CNS synapses. As the major inhibitory neurotransmitter, GABA stands in dynamic balance with the excitatory neurotransmitter glutamate, and together these systems modulate neuronal excitability. He further explained that the 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).[2] The receptor complex has 2 α subunits alternating with 2 β subunits and 1 γ subunit. Two GABA binding sites are located at the intersection of the alternating α and β subunits. The single benzodiazepine binding site is located at the α and γ intersection, which is consistent with evidence that a γ subunit is necessary for benzodiazepine, but not GABA, action.

Several molecular families of subunits have been identified in the receptor complex, but most receptor complexes are composed of 2 α_1, 2 β_2, and 1 γ_2 subunits, all of which are coded on chromosome 5. Thus, the molecular nature of this receptor complex may relate to disparate sedative, anxiolytic, and amnestic effects of the benzodiazepines.

Figure 1. GABA-Benzodiazepine (BZ) Receptor Complex[a]



[a]Reprinted with permission from Roy-Byrne.[2]

Proneness to anxiety may be related to differential subunit expression and may alter GABA-benzodiazepine receptor function. Altered functioning could occur both naturally and in response to environmental change and administration of benzodiazepine medication.

Reduced Sensitivity in Anxiety Patients

Dr. Roy-Byrne reviewed research that assessed the functional differences in the GABA-benzodiazepine receptor complex of people with anxiety disorders versus those without. In one study,[3] the benzodiazepine agonist diazepam was administered to panic patients and controls. A comparison of saccadic eye movement velocity (SEV) in both cohorts showed that controls had more change in SEV than panic patients. (SEV is a pharmacodynamic measurement that is supposed to be unaffected by anxiety.) At the highest dose of diazepam, 200 mg/kg, controls also showed more cognitive impairment than panic patients.

Citing a similar study that assessed changes in controls and panic patients who received the benzodiazepine antagonist flumazenil,[4] Dr. Roy-Byrne shared that flumazenil had no effect

in controls but induced panic attacks in panic patents. Although subsequent studies[5,6] in panic patients have had mixed results, in theory it appears that the GABA-benzodiazepine receptor ligand may be altered in anxiety disorders.[4] Dr. Roy-Byrne explained that the receptor set point of ligands for the GABA-benzodiazepine receptor in patients with anxiety disorders may be shifted so that, for example, full agonists act like partial agonists and neutral antagonists act like partial inverse agonists.

Patients with anxiety disorders may have either fewer GABA-benzodiazepine receptors or reduced levels of neurotransmitter GABA. These molecular alterations appear to be associated with increased anxiety and reduced sensitivity to benzodiazepines.

Tolerance

Chronic treatment with benzodiazepines may lead to the development of tolerance, which may be associated with the reduced GABA-benzodiazepine sensitivity seen in patients with anxiety. Using the case presented by Dr. Stewart as an example, Dr. Roy-Byrne explained that an individual may develop escalating tolerance to the effects of benzodiazepines, requiring higher and/or more frequent doses. The pattern followed by Ms. A resulted in worsening rather than improvement of symptoms and may have been caused by alterations in the function or structure of the GABA-benzodiazepine receptor.

Conclusion

Dr. Roy-Byrne concluded by stating that an emerging body of evidence suggests that the GABA-benzodiazepine receptor system plays an important role in the modulation and mediation of anxiety disorders. It is still unknown, however, if tolerance and dependence relate to underlying alterations in the receptor complex that either existed prior to chronic benzodiazepine treatment or developed as a consequence of it.

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Benzodiazepines and Alternatives for Anxiety Disorders

Widespread Benzodiazepine Use

Mark H. Pollack, M.D., began by pointing out that despite current treatment guidelines for most anxiety disorders, benzodiazepines continue to be widely used for anxiety disorders. For example, American Psychiatric Association[1] guidelines recommend antidepressants, particularly SSRIs, as first-line treatment for managing panic disorder, whereas benzodiazepines are recommended as augmenting agents or for more acute use. However, benzodiazepines were prescribed more often than any other type of medication, including SSRIs, for panic disorder in the 1990s.[2] Dr. Pollack stated that clinicians continue to prescribe benzodiazepines to their anxious patients because they 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. In addition, benzodiazepines are effective in reducing acute anxiety symptoms associated with panic[3] and GAD.[4]

Dr. Pollack added that not all benzodiazepines have the same effect. Although high-potency and low-potency benzodiazepines appear to have equivalent efficacy,[3,5,6] longer-acting agents, such as clonazepam and alprazolam extended release, require decreased dosing frequency and are associated with less interdose rebound anxiety, peak effects (e.g., sedation, euphoria), abuse potential, and discontinuation-related difficulties with rapid taper (depending on excretion half-life) compared with short-acting agents.[7–9] However, longer-acting agents may have less rapid onset of action and increased accumulation (depending on excretion half-life), which may increase side effect burden, particularly in elderly patients.[10]

Concerns About Benzodiazepine Use

Despite the benefits of benzodiazepines, Dr. Pollack stated that both clinicians and patients are concerned about the potential development of therapeutic tolerance (a loss of efficacy or a need to escalate the dose to maintain benefit) and discontinuation syndromes associated with benzodiazepines. Among potential side effects, Dr. Pollack listed sedation, amnestic effects, psychomotor impairment, and disinhibition, particularly in the young and those with organic brain syndromes or substance abuse histories. Definitive studies are lacking, but some data[11,12] suggest that chronic benzodiazepine use may be associated with cognitive effects, though of uncertain clinical relevance, that cannot be explained by the presence of the anxiety disorder alone.

Most of the available data do not provide evidence for the development of therapeutic tolerance.[7–9] However, Dr. Pollack cautioned that benzodiazepines should not be discontinued suddenly because abrupt discontinuation may trigger the emergence of withdrawal symptomatology or

Table 3. Alternatives to Benzodiazepines for Anxiety

Antidepressants
Buspirone
Psychosocial therapies
Atypical antipsychotics

rebound—a return of the original symptoms (e.g., anxiety or insomnia), but worse than before treatment.[13,14]

Alternatives to Benzodiazepines

Dr. Pollack discussed psychotropic and psychosocial alternatives to benzodiazepines (Table 3). Prescribing antipsychotics for anxiolytic use is not a new concept, but the more favorable side effect profile of the atypical antipsychotics compared with the older typical agents has rekindled interest in using these agents in anxiety.

Dr. Pollack also discussed several agents under investigation in the treatment of anxiety disorders. He stated that pregabalin, a potent ligand for the $\alpha_2\delta$ subunit of voltage-gated calcium channels, may emerge as a credible alternative to benzodiazepines for some patients because of a relatively rapid onset of therapeutic effect.[15] Referring to Dr. Roy-Byrne's explanation of the important role the GABA-benzodiazepine receptor system plays in anxiety, Dr. Pollack said that GABA α_2 subunit-specific agents and selective GABA reuptake inhibitors (e.g., tiagabine) have emerged as intriguing areas of investigation. In addition, the anticonvulsant levetiracetam, selective serotonin agonists, corticotrophin-releasing factor antagonists, substance P (NK1) receptor antagonists, glutaminergic antagonists, and neurotrophic factors are also under study.

Conclusion

Dr. Pollack concluded by stating that benzodiazepines continue to be prescribed because of their robust efficacy for many patients. Clinicians, then, must be cognizant of potential side effects associated with this class. Attempts to find alternatives to currently available agents are fueled by an attempt to improve outcome for patients who are partially better or unresponsive to current therapies.

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Benzodiazepines and Substance Abuse

Charles P. O'Brien, M.D., Ph.D., stated that benzodiazepines are effective anxiolytics, but they carry the risk of abuse. He explained that deliberate abuse occurs when benzodiazepines are used to get high or enhance the effects of other drugs through self-medication. Unintentional abuse occurs when prescribed benzodiazepines are used inappropriately or use is continued after remission of anxiety symptoms.

Deliberate Benzodiazepine Abuse

Dr. O'Brien reported that in the 1970s, some people took benzodiazepines either alone or in combination with other substances, such as alcohol, cocaine, or heroin, for the purpose of getting high.[1] People addicted to heroin and taking methadone, for example, reported that diazepam augmented the effects of methadone. A study[2] that surveyed benzodiazepine use among people taking methadone found that diazepam was the most frequently used, followed by lorazepam and alprazolam, whereas the use of oxazepam or chlordiazepoxide with methadone was relatively low.

Dr. O'Brien said that variables that may lead to abuse include elimination half-life of the agent, the age of the patient, the speed of onset or offset, and the development of tolerance. He added that agents with a rapid onset appear to be more desirable than agents with a gradual onset and long half-life. Dr. O'Brien suggested that the rapid onset of action of diazepam makes it both popular and potentially a greater risk for abuse.

Unintentional Benzodiazepine Abuse

Dr. O'Brien defined prescription misuse as self-medicating by increasing the dose to maintain a drug's effectiveness and/or continuing the drug to avoid withdrawal symptoms. Abuse develops when benzodiazepine use begins during a period of stress and continues despite the absence of the stressor. Some patients who try to stop taking benzodiazepines frequently have trouble sleeping (hypnotic-induced insomnia). Eventually, these patients may have to go through detoxification even though they may have only been taking the medication once a day and not to get high.

Dr. O'Brien emphasized that physiologic dependence is different from tolerance. Pharmacologic dependence is a normal biological response to repeated drug use. However, it is common for tolerance to develop, meaning dose escalation is needed. Rebound or withdrawal symptoms may occur if the medication is abruptly discontinued, but a withdrawal reaction due to dependence does not necessarily mean addiction.

Long-Term Use

Dr. O'Brien reported that, based on his clinical experience, patients continue to benefit from the antianxiety effects of benzodiazepines even after many years of use. He cited a clinical trial[3] that compared memory function before and after administering diazepam (5 mg) or the nonbenzodiazepine anxiolytic buspirone (5 or 10 mg) to chronic benzodiazepine users. The patients were tested before and after a year of treatment, and no tolerance to the memory-impairing effects was noted. Dr. O'Brien cautioned, however, that there is a difference of opinion about tolerance, particularly among British psychiatrists, who indicate that benzodiazepines should not be given over a long period of time.

Dr. O'Brien explained that dose and duration of treatment influence the risk of physical dependence. The longer the time and the higher the dose, the greater the risk. Rickels et al.[4] found that withdrawal severity was determined by treatment duration. Withdrawal symptoms occurred in only 5% of patients who had taken diazepam, 15 to 40 mg/day, for less than 8 months but occurred in 43% of patients who had taken diazepam for more than 8 months. In another study,[5] distinct mild-to-moderate withdrawal symptoms occurred in 35% of patients who had taken alprazolam, 2 to 10 mg/day, when treatment was discontinued after 8 weeks. The authors recommended that treatment duration be a minimum of 6 months, but that medication be tapered over a prolonged period, at least 8 weeks when high doses are employed. Dr. O'Brien stated that duration of benzodiazepine treatment is perhaps a matter of clinical judgment; however, in his own practice, he has treated patients with benzodiazepines on an intermittent basis with good results and a low buildup of tolerance.

Table 4. Symptoms of Benzodiazepine Withdrawal That Differentiate It From Return of Anxiety[a]

Agitation
Increased sensitivity to lights and sound
Paresthesias and strange sensations
Muscle cramps
Myoclonic jerks
Insomnia
Dizziness
Seizures[b]

[a]Reprinted with permission from O'Brien.[6]
[b]More common with benzodiazepines with short half-lives than those with long half-lives.

Withdrawal

Dr. O'Brien listed symptoms common in benzodiazepine withdrawal that help to discern it from the return of the original anxiety disorder (Table 4). He also shared a case report of a woman who had a seizure upon abrupt discontinuation of a relatively high dose of a potent medication with rapid elimination. She had been given alprazolam for a gastrointestinal problem and peptic ulcer-type disorder, and when she was without medication over a weekend, she had a seizure. Thus, withdrawal symptoms can appear fairly rapidly depending on the half-life of the drug but sometimes may appear after a couple of weeks.

Dr. O'Brien stated that the number of people who seek treatment for anxiety and later develop a true abuse or addiction syndrome is, in his experience, small. He also said, however, that the number of people who require detoxification after long-term benzodiazepine use can be surprisingly large.

Conclusion

In considering the case reported by Dr. Stewart, Dr. O'Brien stated that the patient was self-medicating with intermittent doses of benzodiazepines combined with alcohol, probably did not meet criteria for alcoholism, and most likely would benefit from long-term treatment with a benzodiazepine combined with CBT to help manage her various anxiety disorders. He stressed the importance of warning patients about the dangers of mixing alcohol and benzodiazepines and the benefits of involving family members in the treatment plan for the patient. In addition, if a patient presents with both alcohol abuse and anxiety disorders, it is important to treat the alcoholism first and then the anxiety.

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Nonpharmacologic Alternative to Benzodiazepines: CBT

Michael W. Otto, Ph.D., began by stating that cognitive-behavioral therapy (CBT) is an effective first-line strategy for treating anxiety disorders. CBT focuses on helping patients treat their fears by actively relearning a sense of safety in relation to fear cues. Dr. Otto explained that CBT methods vary but typically are comprised of expert information, cognitive restructuring, and exposure therapy. Exposure therapy (using step-by-step, programmed contact with feared situations, events, or sensations) helps patients systematically reacquire a sense of safety based on their own prospective experiences with their fear cues, while cognitive restructuring helps patients eliminate catastrophic thoughts that intensify their anxiety. This occurs in the context of a collaborative focus on helping the patient understand the common patterns that maintain anxiety disorders and applying alternative strategies. Instructing patients to direct their attention to what is objectively occurring during exposure to phobic situations, while at the same time inhibiting subtle avoidance behaviors, appears to enhance exposure outcome.[1–3]

These interventions have been informed by advances in understanding of the etiologic and maintaining factors linked with each anxiety disorder. For example, for panic disorder, research has supported the crucial role of fears of anxiety sensations in cuing panic attacks and motivating avoidance. Accordingly, these fears have been targeted in prevention efforts. For example, in 1 study, individuals at risk for onset of panic disorder were selected and randomly assigned to either a 5-hour workshop or a control condition.[4] Risk for panic onset was defined as having occasional panic attacks as well as elevated fears of anxiety sensations as assessed by the Anxiety Sensitivity Index. Elements of the workshop treatment included education about the nature and etiology of panic and agoraphobia, cognitive restructuring, exposure to feared somatic sensations (interoceptive exposure), and instruction for in vivo exposure to avoided situations. Six-month follow-up data were available for 121 patients who were randomly assigned to this preventive workshop or to a wait list. Results provided clear support for the preventive model: 13.6% of the wait-list group developed panic disorder compared with only 1.8% of those who attended the prevention workshop. These results underscore the type of gains that can be achieved when treatment interventions are closely linked to a well-supported model of the disorder.

Treatment Outcome

Dr. Otto pointed out that, as evaluated across the anxiety disorders, CBT is both effective and well tolerated by patients.[5] He also summarized a series of meta-analytic reviews of the controlled-trial literature for treatment of anxiety disorders. CBT offered equivalent efficacy to medications in treating panic disorder,[6,7] social phobia,[8] OCD,[9] GAD,[10] and posttraumatic stress disorder (PTSD)[11] (where CBT showed the greatest superiority over medications in PTSD). Dr. Otto cautioned that conclusions brought by meta-analytic reviews are broad and raise questions about the equivalence of patients seen across studies; however, results of meta-analytic studies have been supported by the few large, multicenter studies that have directly compared CBT and pharmacotherapy. In short, CBT offers acute outcome that rivals or exceeds pharmacotherapy and also offers strong maintenance of treatment gains.

Context Effects

To further elucidate the benefits and limitations of a learning-based approach to anxiety treatment, Dr. Otto discussed some of the factors influencing the maintenance of treatment gains from CBT.[5] Central to this discussion were studies of the way in which reductions in fears brought about by exposure (extinction) may be specific to the context of exposure.

In multiple animal studies, Bouton[12] showed that the return of fear is likely when that fear was learned in one context, extinguished in another context, and then reassessed in the first context. This work has been extended to the clinic. For example, recent research[13] showed that the return of fear of spiders following initial response to exposure therapy was more likely to occur when follow-up assessment occurred in a context different from the one in which subjects received treatment. Accordingly, to maximize the maintenance of treatment gains, therapists need to ensure that exposure-treatment incorporates multiple contexts (e.g., not just when the patient feels rested, is with a "safe" person, or feels confident).

CBT Plus Medication

Of additional importance are findings indicating that medication appears to be a powerful context; what is learned on medication may fade when patients later discontinue their medication.[14] This effect is strong enough that patients who were treated by CBT only may fare better in the long run than patients who are treated by CBT and medications. This effect is exemplified by a multicenter study of panic disorder where the effects of treatment with imipramine only, CBT only, placebo only, CBT plus imipramine, and CBT plus placebo were compared. Response rates for CBT plus imipramine and CBT plus placebo after 3 months of acute treatment were not significantly different, and after 6 months of maintenance treatment, response rates continued to be highest in these 2 groups. Yet, when pharmacotherapy was subsequently discontinued, patients who had received CBT only maintained their improvement better than patients who had received combined CBT and medication.

This apparent sapping of the strength of CBT upon medication discontinuation can be countered by reinstating CBT at the time of medication taper. Some evidence[15] shows that CBT applied during and after medication discontinuation can help patients maintain their treatment gains despite medication discontinuation. It is this feature of CBT—the ability to aid medication discontinuation while maintaining or extending treatment gains—that is particularly apt for the case presented by Dr. Stewart. Brief treatment with CBT (i.e., 12 sessions) could be used as a strategy to replace benzodiazepine use. In particular, the training provided by CBT to help patients respond differently to anxiety sensations appears to be effective in helping patients cope with benzodiazepine withdrawal while also treating panic disorder.[16]

Conclusion

Dr. Otto also stated that CBT appears to be robust to the memory problems sometimes associated with benzodiazepine treatment, and hence should be considered for Dr. Stewart's patient. Moreover, CBT that focuses on helping patients respond differently to emotional cues also appears to treat tendencies toward self-medication regardless of whether it is specific to anxiety concerns.[17] Dr. Otto concluded by endorsing CBT as an effective strategy for treating anxiety disorders.

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Drug names: *alprazolam (Xanax and others), buspirone (BuSpar and others), chlordiazepoxide (Librium and others), clonazepam (Klonopin and others), diazepam (Valium and others), flumazenil (Romazicon and others), imipramine (Tofranil and others), levetiracetam (Keppra), lorazepam (Ativan and others), methadone (Dolophine, Methadose, and others), oxazepam (Serax and others), tiagabine (Gabitril), zolpidem (Ambien).*

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1. Clinical principles that may minimize the necessity of chronic treatment for anxiety disorders include all of the following *except*:
a. Distinguish acute symptomatic distress owing to recent stressors from an anxiety disorder
b. Discuss the goals and limitations of benzodiazepine therapy with the patient
c. Adopt a treatment plan that allows for dose escalation to the highest dose followed by abrupt discontinuation
d. Reevaluate the need for treatment in the short term and over the long term with intermittent structured attempts to taper

2. Benzodiazepines have been associated with _____ effects such as sedation, psychomotor slowing, anterograde amnesia, and difficulties learning new material.
a. Physical dependence
b. Discontinuation
c. Rebound anxiety
d. Short-term cognitive

3. The γ-aminobutyric (GABA)-benzodiazepine receptor system may play an important role in the modulation and mediation of anxiety disorders.
a. True
b. False

4. Psychotropic alternatives to benzodiazepines for the treatment of anxiety disorders include:
a. Antidepressants, atypical antipsychotics, and buspirone
b. Antidepressants, anticonvulsants, and buspirone
c. Anticonvulsants, typical antipsychotics, and tiagabine
d. Pregabalin, tiagabine, and thioridazine

5. Variables that lead to benzodiazepine abuse include all of the following *except*:
a. Elimination half-life
b. Speed of onset or offset of action
c. Age of the patient
d. Inability to develop tolerance

6. _____ helps patients systematically reacquire a sense of safety based on their own prospective experiences with fear cues.
a. Expert information
b. Cognitive restructuring
c. Exposure therapy
d. Anxiety sensitivity training

Answer to Pretest: 1. b

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