Anxiolytics: Past, Present, and Future Agents

Charles B. Nemeroff, M.D., Ph.D.

Although anxiety disorders were classified as neurotic disorders and not systematically studied before DSM-III, researchers and clinicians have been searching for effective, safe agents to treat anxiety symptoms and disorders for over a century. In that time, barbiturates, benzodiazepines, and many classes of antidepressants have been used as anxiolytics, all with side effect profiles that made them less than optimal treatments for anxiety. The recognition of the role of GABA in anxiety disorders has led researchers to develop anxiolytics that target GABA. The long-sought-after class of anxiolytics that are both effective and safe may be found in the new research being conducted with agents that selectively target GABA receptors and their subtypes. (J Clin Psychiatry 2003;64[suppl 3]:3–6)

From the Department of Psychiatry and Behavioral Sciences, Emory University School of Medicine, Atlanta, Ga.

This article is derived from the teleconference “The Role of GABA in Neuropsychiatric Disorders: A Review of GABA agents,” which was held April 3, 2002, and supported by an unrestricted educational grant from Cephalon, Inc.

Corresponding author and reprints: Charles B. Nemeroff, M.D., Ph.D., Emory University School of Medicine, Dept. of Psychiatry and Behavioral Sciences, 1639 Pierce Dr., Suite 4000, WMB Bldg., Atlanta, GA 30322 (e-mail: cnemero@emory.edu).
Side effects of barbiturates include oversedation and impaired mental performance. At high doses, barbiturates cause anesthesia, coma, and death. Tolerance to barbiturates can develop within a few weeks after initiation of treatment, which may lead to increased doses to maintain the desired pharmacologic effect. In fact, patients who have been treated with barbiturates for years must be considered drug dependent. Withdrawal symptoms may occur if barbiturates are stopped abruptly and range from minor—anxiety—to severe—seizures and death.

Nonbarbiturates

Little changed in the anxiolytic field until 1950 when meprobamate was synthesized. Meprobamate became the first nonbarbiturate agent to be used extensively in the treatment of anxiety. At the time, this agent and others such as glutethimide, methaqualone, and methyprylon were thought to be a major breakthrough but, like barbiturates, turned out to be highly addicting and fatal in overdose.

Benzodiazepines

The first benzodiazepine, chlordiazepoxide, appeared in the late 1950s. A few years later, the related compound diazepam was introduced with 3 to 10 times the potency of chlordiazepoxide and, arguably, a broader spectrum of activity. The development of benzodiazepine derivatives has continued since then, and many, such as oxazepam, clorazepate, lorazepam, alprazolam, and clonazepam, are currently used in the treatment of anxiety.

Psychological and physical dependence may occur with chronic benzodiazepine treatment. If abruptly discontinued, withdrawal symptoms, such as anxiety, agitation, restlessness, and tension, result. Other side effects of benzodiazepines include sedation and psychomotor impairment. Several drugs, particularly cytochrome P450 3A4 inhibitors, such as nefazodone, exert significant drug-drug interactions with benzodiazepines by markedly increasing their plasma concentrations. In contrast, antacids decrease the effect of benzodiazepines.

Such a side effect profile has led to the suggestion that benzodiazepines be replaced as the first-line treatment for anxiety despite their effectiveness as anxiolytics. However, research into the mechanism of action of benzodiazepines on the γ-aminobutyric acid-A (GABA-A) complex has narrowed the anxiolytic action of benzodiazepines to specific α subunits of the GABA-A complex. Currently in development are agents that have the anxiolytic, but not the sedative-hypnotic, effects of older benzodiazepines.

Tricyclic and Monoamine Oxidase Inhibitor Antidepressants

The next stage in the development of the treatment of anxiety disorders was the recognition that some antidepressants had anxiolytic properties. The benefits of the tricyclic antidepressant (TCA) imipramine on panic attacks were noted as early as the 1960s. Monoamine oxidase inhibitor (MAOI) antidepressants were also found to be effective anxiolytics. However, like other anxiolytic agents, TCAs and MAOIs possess a less-than-optimal side effect profile. In addition to the drawback of delayed onset of action (3 to 5 weeks or longer), both classes have been reported to cause orthostatic hypotension and weight gain. TCAs may be fatal if taken in overdose and have a number of drug-drug interactions, particularly with drugs that act as cytochrome P450 2D6 inhibitors. The side effects associated with MAOIs may be more severe than those of other antidepressants, one of which is the risk of a drug-food or drug-drug interaction that causes severe headaches and stroke because of increased tyramine levels.

The discovery that antidepressants may be effective treatment for anxiety was an advance in the therapy of anxiety disorders that led some investigators to further study novel antidepressants, while other investigators developed the azapirone class of anxiolytics.

Azapirones

The azapirone class is small, with only a few agents in existence and only 1, buspirone, has been marketed. Buspirone represents the first available nonsedative, nonbenzodiazepine anxiolytic. The side effect profile of buspirone is much improved relative to other anxiolytics. Buspirone is devoid of the problems of sedation, psychomotor impairment, abuse, dependence, and withdrawal, and it is not lethal in overdose. However, the efficacy of buspirone has remained an issue. It is certainly ineffective for the treatment of panic disorder. In an 8-week double-blind placebo-controlled study, Sheehan et al. compared the efficacy of buspirone with that of the benzodiazepine alprazolam in panic disorder. Of the 101 patients meeting DSM-III-R criteria for panic disorder, 85 completed the study. Alprazolam was superior to buspirone and placebo in producing rapid and sustained improvement in panic attacks, anxiety, phobias, and disability.

Even in GAD, much of the debate about buspirone’s efficacy has centered on the agent’s use in patients who had previously received benzodiazepine treatment. Some reports suggested that patients with a history of benzodiazepine treatment who were then treated with buspirone showed less improvement than benzodiazepine-naive patients treated with buspirone. Recently, in a double-blind, placebo-controlled study, venlafaxine was shown to be more effective in the treatment of GAD compared with placebo, but buspirone was no more effective than placebo. Many clinicians view buspirone as a relatively weak anxiolytic, but it has been shown to be effective in the treatment of GAD in several controlled trials.

Other Antidepressants

Research into the anxiolytic properties of antidepressants has continued with the intense scrutiny of sele-
Table 1. Potential Treatment Issues With the Use of Anxiolytics

<table>
<thead>
<tr>
<th>Class</th>
<th>Treatment Issue</th>
</tr>
</thead>
<tbody>
<tr>
<td>Barbiturates, eg, phenobarbital</td>
<td>Oversedation, impaired mental performance, dependence, withdrawal, anesthesia in overdose, coma in overdose, fatal in overdose</td>
</tr>
<tr>
<td>Nonbarbiturates, eg, meperidine</td>
<td>Dependence, fatal in overdose</td>
</tr>
<tr>
<td>Benzodiazepines, eg, alprazolam</td>
<td>Dependence, withdrawal, sedation, psychomotor impairment, drug-drug interactions</td>
</tr>
<tr>
<td>Tricyclic antidepressants, eg, imipramine</td>
<td>Orthostatic hypotension, weight gain, drug-drug interactions, fatal in overdose</td>
</tr>
<tr>
<td>Monoamine oxidase inhibitor antidepressants, eg, phenelzine</td>
<td>Orthostatic hypotension, weight gain, drug-food interactions, drug-drug interactions</td>
</tr>
<tr>
<td>Azapirones, eg, buspirone</td>
<td>Lack of efficacy in panic disorder and severe anxiety disorders</td>
</tr>
<tr>
<td>Other antidepressants</td>
<td></td>
</tr>
<tr>
<td>Selective serotonin reuptake inhibitors, eg, paroxetine</td>
<td>Discontinuation syndrome on abrupt termination of therapy, delayed onset of action, sexual dysfunction</td>
</tr>
<tr>
<td>Serotonin-norepinephrine reuptake inhibitors, eg, venlafaxine</td>
<td>Same as selective serotonin reuptake inhibitors</td>
</tr>
<tr>
<td>Norepinephrine reuptake inhibitors, eg, reboxetine</td>
<td>Same as selective serotonin reuptake inhibitors, questionable efficacy</td>
</tr>
</tbody>
</table>

tive serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), and norepinephrine reuptake inhibitors (NRIs). Several SSRIs have been approved by the U.S. Food and Drug Administration (FDA) for the treatment of anxiety disorders or in controlled studies have been found to be effective in the treatment of anxiety disorders. Paroxetine has been approved for PTSD, GAD, panic disorder, OCD, and social anxiety disorder. Sertraline has been approved for the treatment of PTSD, panic disorder, and OCD. Fluvoxamine has been approved for OCD and shows efficacy in social anxiety disorder as well. Fluoxetine is repeatedly effective in the treatment of panic disorder, OCD, and PTSD, though not approved by the FDA for these disorders. Venlafaxine, an SNRI, has FDA approval for GAD and has been shown to be effective in panic disorder, social anxiety disorder, and OCD. The NRI reboxetine, which is not available in the United States, has demonstrated efficacy in panic disorder.

Although these antidepressants have side effects profiles that are benign when compared with the side effect profiles of TCAs and MAOIs, these treatments are not without their shortcomings. Discontinuation syndromes have been reported with many antidepressants when treatment was abruptly terminated. Delayed onset of action and sexual dysfunction, as well as a substantial population of patients who do not respond, are other major issues with the use of SSRIs, SNRIs, and NRIs that make them less than-optimal treatments.

THE FUTURE OF ANXIOLYTICS

Researchers have hypothesized that anxiety disorders are caused by abnormalities in GABA neurotransmission in the central nervous system and that anxiety may be alleviated or reduced by agents that target these abnormalities. That barbiturates and benzodiazepines potentiate GABA-mediated inhibitory processes in the brain and are effective treatments for anxiety support this hypothesis. The recognition of the role of GABA in anxiety disorders has led to the development of anxiolytics that target GABA. Hopefully, these new agents will have the benefits of the old agents, i.e., rapid-acting and anxiolytic properties, without the negative side effects associated with the old agents (Table 1). Anxiolytic, but not sedative-hypnotic, properties have been observed in agents still in development that activate the GABA-A $\alpha_1$ subtype. Tiagabine, the first selective GABA reuptake inhibitor, has been reported to possess anxiolytic activity, at least as an augmenting agent.

CONCLUSION

The development of anxiolytics has been propelled by the desire to identify agents that are both effective and safe in the treatment of anxiety. Although their mechanism of action was unknown at the time of drug development, barbiturates and benzodiazepines, 2 of the most effective treatments for anxiety symptoms, act upon GABA receptors. Therefore, the long-sought-after class of anxiolytics may be found in the new research being conducted with agents that selectively target GABA systems and their receptor subtypes.

Drug names: alprazolam (Xanax and others), bupropion (Wellbutrin and others), buspirone (BuSpar and others), clorazepate (Gen-Xene, Tranxene, and others), diazepam (Diastat, Valium, and others), fluoxetine (Prozac and others), fluvoxamine (Luvox and others), glutationamide (Cytadren), imipramine (Surmontil, Tofranil, and others), lorazepam (Ativan and others), meperidine (Equanil, Tranmep, and others), nefazodone (Serzone), oxazepam (Serax and others), paroxetine (Paxil), phencelinze (Nardil), sertraline (Zoloft), tiagabine (Gabitril), venlafaxine (Effexor).

Disclosure of off-label usage: The author 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.

REFERENCES

by specific gamma-aminobutyric acid (GABA) receptor subtypes. Nature 1999; 401:796–800
18. Gruener D. Tiagabine as an augmenting agent for the treatment of anxiety. Presented at the 22nd National Conference of the Anxiety Disorders Association of America; March 21–24, 2002; Austin, Tex.