Anxiolytics: Past, Present, and Future Agents

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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)*

Anxiety disorders were not studied systematically until the establishment of the DSM-III in 1980. Before DSM-III, anxiety disorders were grouped in the nebulous classification of neurotic disorders. Therefore, a major issue in anxiety disorders is the categorical classification of the disorders. Currently, the categorical syndromes in the anxiety disorders include social anxiety disorder, posttraumatic stress disorder (PTSD), generalized anxiety disorder (GAD), obsessive-compulsive disorder (OCD), and simple phobias. However, controversy exists over which disorders actually comprise the anxiety disorders, with some researchers suggesting that OCD be reclassified as an impulse control disorder. Whether simple phobias should be classified as anxiety disorders has also been questioned; in general, they rarely require treatment and markedly inflate estimates of the prevalence of anxiety disorders as a class.

Another clinically relevant issue in anxiety disorders is the treatment of subsyndromal anxiety symptoms, such as situational anxiety, or anxiety symptoms in the context of other disorders, particularly depression. The literature is replete with studies that show a strong correlation between the severity of anxiety symptoms and the severity of depressive symptoms.[1] Patients with anxiety often score high on the Hamilton Rating Scale for Depression and patients with depression often score high on the Hamilton Rating Scale for Anxiety.

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The frequent categorical (syndromal) comorbidity of anxiety and depression has caused a debate to emerge in the field about the fundamental differences between mood and anxiety disorders, i.e., does a pure anxiety disorder exist? Support for anxiety disorders as independent from mood disorders can be found in epidemiologic and pharmacologic research. Kessler[2] reviewed and evaluated research that suggested GAD was a prodome of other disorders and concluded that GAD was an independent disorder and a major health problem. Pharmacologic data suggest that some classes of agents have antidepressant properties without being anxiolytic; the best example of such an agent would be bupropion. Although bupropion treats the anxiety associated with a major depressive episode, it is not effective in the treatment of, for example, panic disorder or GAD. Additionally, benzodiazepine anxiolytics are ineffective antidepressants but are effective in the treatment of a variety of anxiety disorders.

Researchers have been searching for effective, safe agents to treat anxiety symptoms and disorders for over a century. Many anxiolytics were developed to have fewer side effects than earlier agents. Recently, the empirical approach to anxiolytic development has changed, and agents are now developed to target specific brain neurotransmitter systems such as GABA, which has been posited to play a preeminent role in the pathophysiology of anxiety disorders.

THE HISTORY OF ANXIOLYTICS

Barbiturates

Alcohol was an early anxiolytic as were various bromide preparations and paraldehyde. In 1903, barbital, the first barbiturate, appeared and was followed several years later by phenobarbital. Toxicity and dependence liability issues have relegated barbiturates to infrequent use as anxiolytics today, though many are still available for the treatment of epilepsy and as sedative-hypnotics.

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[3,4] 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.[5] 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.[6] 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.[7] 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.[8] 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.[9–11]

Other Antidepressants

Research into the anxiolytic properties of antidepressants has continued with the intense scrutiny of selec-

Table 1. Potential Treatment Issues With the Use of Anxiolytics

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

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.[12] Fluoxetine is repeatedly effective in the treatment of panic disorder, OCD, and PTSD, though not approved by the FDA for these disorders.[13] Venlafaxine, an SNRI, has FDA approval for GAD and has been shown to be effective in panic disorder, social anxiety disorder, and OCD.[14] The NRI reboxetine, which is not available in the United States, has demonstrated efficacy in panic disorder.[15]

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.[16] 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 α_2 subtype.[17] Tiagabine, the first selective GABA reuptake inhibitor, has been reported to possess anxiolytic activity, at least as an augmenting agent.[18]

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), chlordiazepoxide (Librium and others), clonazepam (Klonopin and others), clorazepate (Gen-Xene, Tranxene, and others), diazepam (Diastat, Valium, and others), fluoxetine (Prozac and others), fluvoxamine (Luvox and others), glutethimide (Cytadren), imipramine (Surmontil, Tofranil, and others), lorazepam (Ativan and others), meprobamate (Equanil, Tranmep, and others), nefazodone (Serzone), oxazepam (Serax and others), paroxetine (Paxil), phenelzine (Nardil), sertraline (Zoloft), tiagabine (Gabatril), 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.

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