Advances In Anxiety Management

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Abstract: Recent developments in neurobiology, diagnostic classification, and drug/psychotherapy trials have increased our ability to manage patients with anxiety disorders. These recent developments, along with epidemiologic surveys showing the high frequency of anxiety disorders in the general population as well as in the primary care population, have reemphasized the importance of anxiety disorders in family practice. This review presents treatment recommendations, including dosage, products, guidelines for monitoring, and discontinuation. Advances in the neurobiology of anxiety are also included. (J Am Bd Fam Pract 1989; 2:37-42.)

Advances in treatment, including medication and psychotherapy, demand accurate classification of anxiety disorders. An accurate diagnosis is important in predicting the natural course and prognosis for individual patients. Table 1 presents the classification scheme for anxiety disorders as outlined in the revised version of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM III-R).[1] Although epidemiologic surveys of anxiety subtypes in family practice populations are sparse, generalized anxiety disorder, adjustment disorder with anxious features, and simple phobias appear to be the most common.[2,3]

Generalized Anxiety

Generalized anxiety is a disorder of excessive anxiety or worry related to two or more life circumstances. Often patients with generalized anxiety can be described as "worry warts" ruminating about finances, family problems, or job difficulties. Such anxiety is nonproductive and does not lead to changes in behavior that would reduce anxiety. An example is the anxious patient who focuses on problems that cannot be changed. By definition, generalized anxiety disorder must also include somatic symptoms (muscle tension, autonomic hyperactivity, and hypervigilance). Initial insomnia is common because the patient is unable to modulate voluntarily worry at bedtime. Generalized anxiety disorder is not diagnosed if it occurs concurrently with depression or is related to primary organic factors, such as hyperthyroidism or excessive caffeine use.

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Adjustment Disorders

Adjustment disorders describe a stress syndrome of maladaptive anxiety to a specific psychosocial stressor. Maladaptive anxiety is medically significant when there is impairment in occupational or social function or the symptoms exceed appropriate reaction to the stressor. Adjustment disorders are short-term reactions lasting no longer than 6 months. Patients with acute medical illness, interpersonal problems, or work difficulties commonly have adjustment disorders with prominent anxiety. For example, a person unable to sleep and with poor concentration during a period of work layoffs may meet criteria for adjustment disorder. Although other persons may be undergoing similar levels of stress, intensity of symptoms, functional impairment, and the request for help from a physician will identify an adjustment disorder with anxiety.

Simple Phobias

Simple phobias appear to be quite common, but often they are mild and infrequently treated by primary care physicians. They include excessive fear of a specific animal, blood, closed spaces, heights, or air travel. Phobias related to health and health care are more commonly encountered by family physicians. They include fear of venipuncture, injections, dental procedures, and irrational fear of illness.

Other Anxiety Disorders

Two anxiety disorders, while less frequently seen by family physicians, are important because of their potential to be quite severe and occasionally disabling. *Panic disorder with or without agoraphobia* may become severe but is highly responsive to

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Table 1. *Relative Prevalence and Severity of Anxiety Disorders.*

Diagnosis	Prevalence	Severity
Panic disorder with or without agoraphobia	++	+++
Generalized anxiety disorder	+++	+
Adjustment disorder with anxious mood	+++	+
Social phobia	+	++
Simple phobia	+++	+
Posttraumatic stress disorder	+	++
Obsessive-compulsive disorder	+	+++

+ = low, ++ = intermediate, +++ = high.

medical treatment. Recurrent and spontaneous panic attacks are discrete periods of acute anxiety usually accompanied by physical symptoms, such as palpitations, chest pain, dizziness, and shortness of breath. These attacks are the hallmark of panic disorder. DSM III-R requires at least four panic attacks in a 4-week period to make a panic disorder diagnosis. Patients often are young women who commonly present with concerns that they are having heart attacks. *Agoraphobia* is a behavioral syndrome that can complicate this disorder. It is characterized by phobic avoidance of crowds, shopping malls, churches, or other places where patients perceive they are separated from sources of security.

Obsessive-compulsive disorder (OCD) is another potentially severe and disabling anxiety condition.[4] In OCD, patients may be tormented by such intrusive thoughts as fear of killing their children, blasphemy, contamination with diseases such as AIDS, or fear of forgetting to turn off appliances and sources of gas or electricity in their homes. These obsessions are often paired with compulsive rituals, e.g., frequent handwashing, counting, touching, and checking behaviors. Obsessive-compulsive disorder often produces clinical depression that can be severe and precipitate contact with a physician. Recent developments in the understanding of OCD have produced more drug research, and several drugs may soon be available to treat this disorder effectively.

Three other anxiety disorders are also recognized. *Social phobia*[5]—an intense fear of embarrassment—and *post-traumatic stress disorder* (PTSD) are less well-defined, and more research is needed to assess their importance to family practice. Additionally, a discrete anxiety disorder, *performance anxiety*, has been described in which patients are symptomatic when they are required to function in front of a large group of people. This disorder may be especially devastating for musicians, actors, and public speakers.

Drug Treatment

Tricyclic Antidepressants

Although best studied for depression, tricyclics play a key role in drug management of primary anxiety disorders.[6-8] Imipramine and desipramine (100 to 300 mg daily) are the tricyclic agents of choice for panic disorder. They have the advantage of requiring no special dietary restrictions as do monoamine oxidase inhibitors, and they can be taken safely for a long time. Disadvantages include anticholinergic side effects and cardiovascular toxicity in overdose. Tricyclics may be helpful for some patients with generalized anxiety disorder, although their use for patients with this condition is less well studied. Adjustment disorder patients with prominent anxious features, including insomnia, may benefit from more sedative antidepressants such as amitriptyline, doxepin, or trazodone. Trazodone has the advantage of a low anticholinergic profile but also the disadvantage of reports of priapism. Preliminary studies of post-traumatic stress disorder have suggested benefits from the same medications that are effective against panic, primarily desipramine and monoamine oxidase inhibitors.[9,10] Although some patients with obsessive-compulsive disorder are benefited by currently available antidepressants, clomipramine appears to be the drug of choice and is currently in FDA trials for release in the United States.

Monoamine Oxidase (MAO) Inhibitors

MAO inhibitors are excellent drugs for anxiety disorders and for mixed anxiety-depression conditions. Phenelzine (45 to 90 mg daily) and tranylcypromine (30 to 60 mg daily) are two commonly used agents of this class. Some efficacy in social phobias has also been shown. Patients considered for MAO inhibitors need to be assessed for their ability to comply with a tyramine-free diet, especially avoiding beer, wines, and cheese. Alcohol abusers should not receive these drugs.

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Benzodiazepines (BZD)

Benzodiazepines are effective drugs for a variety of anxiety conditions and, when used properly, will provide additional help for the anxious patient.[11,12] Diazepam (5 to 30 mg daily) and alprazolam (0.75 to 3.0 mg daily) are examples of long- and short-acting benzodiazepines, each having specific indications. A primary advantage of benzodiazepines is their rapid onset of anxiolytic effect, which can be quite helpful in acutely anxious patients such as those with adjustment disorders. Side effects tend to be minor, and the drugs are usually well tolerated. They probably are best suited for short-term use.

Short-acting benzodiazepines (alprazolam and lorazepam) have been used to manage panic disorder effectively. Their potency offers an advantage because high doses produce less sedation than longer-acting agents, making them useful to control panic attacks. Clonazepam is a high-potency BZD that is also long acting and may be effective for panic disorder. The relative disadvantage of the short-acting agents is their ability to produce withdrawal syndromes. This requires patients to taper the dosage slowly (for example, 0.5 mg per week of alprazolam or lorazepam) in order to discontinue their medication without withdrawal symptoms or rebound anxiety. Alternatively, an equipotent switch to a longer-acting agent with a more rapid taper can be used to discontinue a benzodiazepine. For patients who require long-term use of benzodiazepines, longer-acting agents may have a slight advantage for disorders such as generalized anxiety disorder. They can be used less frequently and will produce fewer withdrawal symptoms on a day-to-day basis. Some panic patients appear to benefit from a combination of benzodiazepine and tricyclic at the beginning of their treatment, with tapering of the benzodiazepine as the tricyclic becomes effective.

The following guidelines may help the clinician use benzodiazepines effectively:

1. Consider nonbenzodiazepine drugs first for the drug-naive patient if possible.
2. Target benzodiazepine use for specific short-term symptoms. A total duration of 2 to 8 weeks' treatment should be agreed upon with the patient before initiation of benzodiazepine treatment.
3. Patients should be screened for potential substance abuse, which includes personal history of alcohol or drug problems, a family history of alcohol or drug abuse, or patients with antisocial personality disorder. Nonbenzodiazepines should be preferred in patients with any risk factor for substance abuse.

Other Drugs

Buspirone (15 to 60 mg daily) represents the first novel class of anxiolytic agents released in the last 25 years. This drug has been targeted for patients with generalized anxiety disorder.[13] It requires several weeks to reduce anxiety and therefore has less to offer for adjustment disorder. This drug may be especially helpful for the generalized anxiety disorder patient with no previous benzodiazepine experience. Little is known about the long-term efficacy of buspirone.

Propranolol, atenolol, and other beta-blocking agents appear to have some effect in social phobia and performance anxiety.[5] Patients with disabling anxiety during performances such as public speaking, recitals, or test taking may be helped with beta-blockers. Beta-blockers appear to work by blocking peripheral anxiety symptoms, e.g., tachycardia and tremulousness, symptoms that can escalate subjective anxiety and impair performance. When using beta-blockers specifically for performance anxiety, the patient should have several practice experiences with the drug before undergoing the performance or test itself. Test doses of propranolol (20 to 40 mg) or atenolol (50 mg) are reasonable starting points.

Duration of Treatment and Discontinuation

The duration of treatment, including decisions to discontinue antianxiety medications, will be patient specific. For patients who experience good-to-excellent improvement in target anxiety symptoms, 4 to 12 months of drug treatment is reasonable. Patients with severe anxiety syndromes receiving nonbenzodiazepines may need longer continuous treatment. When a decision is made to begin a medication taper, a slow gradual reduction (one-fourth dose reduction every 1 to 2 weeks) can be started. During the taper phase, patients will need closer monitoring than during maintenance. Recurrence of symptoms with impairment may necessitate returning to a full dosage or beginning a nondrug intervention program.

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Nondrug Treatment

Nondrug interventions provide opportunity for extending improvement in patients who received medication, as well as providing an alternative to those who do not need medication or refuse to consider medication as an option. Using nondrug interventions for milder cases of generalized anxiety or social phobias may be appropriate. Family physicians can often provide office counseling for anxiety disorders.[14]

An exercise prescription is an appropriate nondrug intervention for many anxiety patients. The focus on exercise helps restructure any feelings of increasing disability related toward the anxiety. Aerobic exercise at 60 to 70 percent of maximum heart rate 4 to 5 times per week can increase self-esteem, lower resting pulse, and reduce autonomic activity. Some panic patients have reported increased anxiety during aerobic exercise, but generalized anxiety disorder patients tolerate exercise well. Several weeks to months may be required for the effects to occur for patients who are not in good physical condition.

Relaxation training also can be helpful for some anxiety disorder patients. The techniques include progressive muscle relaxation, visual imagery, biofeedback, and hypnosis. Because the effects of focused relaxation can occur quickly, adjustment disorders with specific muscle tension symptoms may be appropriate.

Cognitive-behavioral therapy has more research support than all other psychotherapies for treatment of anxiety disorders.[15,16] These therapies usually require weekly visits for 12 to 16 weeks. Simple phobias respond to in-vivo exposure therapy. Social phobia, performance anxiety, and generalized anxiety disorder have received little psychotherapy research attention but theoretically are candidates for cognitive-behavioral therapy. Panic disorder appears to be best treated by a cognitive-behavioral strategy in conjunction with drug therapy. Other therapies besides cognitive-behavior therapy are occasionally indicated. For adjustment disorder patients having prominent symptoms from marital or family problems, focusing on marital or family relations can be important in reducing the symptoms.

Increasing attention has focussed on specific treatment options for specific anxiety disorders.[17-19] Table 2 presents a diagnosis-specific treatment scheme for drug and nondrug interventions. This table is based on clinical experience and the limited research on diagnosis-specific treatment.

Practically speaking, physicians can use the following guidelines in managing the anxiety disorder patient:

1. For most severely ill patients, combination therapy using medication and psychotherapy of the cognitive-behavioral type is the treatment of choice.
2. When cognitive-behavioral therapies are unavailable, drug therapy alone may be tried. If improvement plateaus despite control of anxiety symptoms, consideration should be given to adding a psychotherapy modality such as cognitive-behavioral therapy.
3. Patients best suited for nondrug therapies alone are those with relatively mild symptoms and no impairment. Also, chronic disorders requiring long-term therapy may benefit by a nondrug therapy. If the patient should experience exacerbation of anxiety symptoms during times of exceptional stress, then short-term medication use can be added to psychotherapy for effective long-term management.

Neurobiology

Along with importance of stress as a precipitating and causative factor for anxiety disorders, we are becoming more aware of the brain biochemistry involved with the patient's vulnerability to anxiety. Gamma aminobutryic acid (GABA) appears to be an especially important neurotransmitter in modulating the symptoms of anxiety.[20] Current research supports the role of GABA and a GABA receptor in opening the chloride channels across cell membranes, resulting in a general inhibition of neuronal function. Inhibition appears to reduce subjective anxiety, to facilitate muscle relaxation, and to modify seizure thresholds.

A benzodiazepine receptor has been demonstrated in the brain using positron emission tomography (PET). GABA and benzodiazepines appear to work as a complex at this receptor site with GABA's effects potentiated by the presence of benzodiazepines. It has been suggested that a naturally occurring endogenous benzodiazepine-like substance having antianxiety properties is produced by the central nervous system. Benzodiazepines may mimic the effects of this endogenous substance.

It has been postulated that changes in receptor function as well as levels of GABA or endogenous

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benzodiazepine may alter a person's vulnerability to the psychological and somatic symptoms of anxiety. For example, a relative deficiency of GABA or endogenous benzodiazepine may mediate an increase in subjective anxiety.

Along with progress in brain biochemistry supporting a neurochemical contribution to anxiety, advances in psychiatric genetics have highlighted the familial nature of panic disorder, generalized anxiety disorder, and obsessive-compulsive disorder.[21,22] Family studies of anxiety disorders support the notion of a substantial genetic contribution. Further investigation at the molecular level, using restriction fragment length polymorphisms, is now underway to identify specific chromosomal markers for these disorders. These laboratory techniques, borrowed from molecular genetics, are the same that were used to find the chromosomal markers for Huntington's chorea and Duchenne muscular dystrophy.

Advances in the neurobiology of anxiety have implications for practicing physicians. These include:

1. The biological model of anxiety can be used as supportive evidence that pharmacologic treatment is an appropriate alternative. Explaining this model to patients may encourage some to consider appropriate medication trials.
2. Anxious patients should be viewed as persons with a biological vulnerability that is expressed at a certain level of psychosocial stress.
3. Obtaining an accurate family history of all psychiatric illnesses is now essential for evaluating all patients with a chief complaint of anxiety.

Table 2. *Ratings for Anxiety Modalities by DSM III-R Subtype.*

Modality	DSM III-R Subtype							
	Panic Disorder	Generalized Anxiety Disorder	Adjustment Disorder	Social Phobia	Simple Phobia	PTSD	Performance Anxiety	Obsessive Compulsive
Antidepressants								
Imipramine Desipramine	+++	+	○	○	○	++	○	+
Amitriptyline Nortriptyline	+	+	+	○	○	+	○	+
Doxepin	+	++	+	○	○	+	○	+
Trazodone	○	+	+	○	○	+	○	+
Clomipramine	○	○	○	○	○	○	○	+++
Phenelzine Tranylcypromine	+++	+	○	++	+	++	○	+
Benzodiazepines								
Diazepam Chlordiazepoxide Clonazepam	+	++	+++	○	○	+	○	+
Alprazolam Lorazepam	++	+	+++	○	○	+	○	+
Other drugs								
Buspirone	○	++	○	○	○	○	○	○
Propranolol Atenolol	○	+	○	+	○	○	++	○
Nondrug therapy								
Exercise	+	++	○	○	○	+	○	○
Relaxation	+	++	+	+	○	○	+	○
Cognitive-behavior	++	++	+	+	+++	+	++	+

○ = ineffective or no treatment, + = effective in some patients, ++ = effective in many, +++ = modality (ies) of choice.

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