CHAPTER 15. ANXIETY DISORDERS

15.7 ANXIETY DISORDERS: SOMATIC TREATMENT

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After decades of neglect and controversy, anxiety disorders are increasingly recognized as legitimate medical conditions requiring specific treatment. The unproductive debate over the primacy of biological or psychological factors in the pathophysiology of anxiety is gradually being replaced by a pragmatic approach based on research on the relative contributions of both. A parallel, unbiased approach in treatment research began to examine the merits of combined somatic and psychological treatments in anxiety. Recognition of the role of psychological factors in most medical illnesses is breaking down the artificial barrier between psychiatric and medical conditions. While the stigma of psychiatric illness remains a strong deterrent, the availability of effective treatments, frequently a combination of somatic and psychological, is a powerful incentive for patients to come forward.

To date panic disorder remains the best-researched anxiety disorder. Pharmacological treatment trials in panic disorder outnumber those conducted in other anxiety disorders, and most pharmacological challenge studies were first initiated in panic disorder.

HISTORY

The oldest antianxiety drug is alcohol, and it remains the most frequently used and most easily accessible tranquilizer. Modern medical anxiolysis began with the introduction of paraldehyde and bromides around the turn of the century, followed by the first medical use of barbiturates in 1903. While the availability of a number of safer and more effective anxiolytics today makes them mostly obsolete, paraldehyde remains an old-fashioned treatment for alcohol withdrawal, and certain barbiturates retain

limited use in anesthesiology and addiction medicine. The development of the so-called nonbarbiturate nonbenzodiazepine hypnotic drugs in the 1930s did not address any of the deficiencies of the barbiturates, and in many cases these drugs proved more problematic. Meprobamate (Equanil, Miltown) and tybamate possess very low therapeutic index, methaqualone and methyprylone (Noludar) are highly addicting and can be fatal in overdose, and glutethimide (Doriden) overdose can result in convulsion and fluctuating coma. The synthesis in 1957 of the first benzodiazepine, chlordiazepoxide (Librium), heralded a new era of safe and effective medical management of anxiety. Because of their safety, efficacy, and high therapeutic index, benzodiazepines have for the most part replaced barbiturates and the nonbarbiturate, nonbenzodiazepine type drugs.

The demonstration in the early 1960s that imipramine (Tofranil) controls panic attacks was the first evidence that antidepressant drugs may alleviate anxiety and that this effect may be independent of their antidepressant property. The historic observation that panic attacks were specifically responsive to antidepressants also marked the beginning of a new diagnostic system that differentiates the subtypes of anxiety neuroses on the basis of medication response. Parallel to the work with imipramine in the United States, British investigators found that another class of antidepressants, the monoamine oxidase inhibitors (MAOIs), specifically benefit hysterical patients with phobic symptoms. Since these patients show many features of panic disorder and agoraphobia, tricyclic and tetracyclic drugs and MAOIs quickly became the first-line treatment choice in panic disorder. The pharmacological dissection of the formally homogeneous anxiety neuroses category into distinct anxiety disorders not only changed diagnostic thinking and the treatment of anxiety but also revolutionized psychopharmacology in general. Symptom-specific rather than diagnosis-specific drug development helped refine and create diagnostic categories for all psychiatric conditions.

Of the many subsequently introduced antidepressants with anxiolytic properties, fluoxetine (Prozac) was the next milestone in the pharmacology of anxiety. This first drug in a series of serotonergic agents became the best-selling antidepressant by 1990. The efficacy of serotonergic drugs in the treatment of panic disorder and obsessive-compulsive disorder significantly advanced the treatment of these anxiety disorders and gave rise to new theories implicating the serotonergic system in the neurobiology of anxiety.

In addition to benzodiazepines and several classes of antidepressants currently available anxiolytic agents include β-adrenergic receptor antagonists and the azapyrone buspirone (BuSpar). New drug development targets neurotransmitter systems identified primarily by pharmacological challenges as pertinent to the neurobiology of anxiety. Candidates include partial benzodiazepine agonists and reverse benzodiazepine antagonists, neurosteroids, neuropeptide agonists and antagonists such as cholecystokinin B (CCK-B) antagonists, corticotropin-releasing factor (CRF) antagonists, neuropeptide Y agonists and serotonergic agents acting on specific serotonin receptor subtypes (e.g., serotonin [5-hydroxytryptamine (5-HT)] subtype 1A [5-HT_{1A}] agonists, and 5-HT_2 and 5-HT_3 antagonists). The accelerated drug development process promises highly effective anxiolytic agents with minimal adverse effects in the near future.

GENERAL PRINCIPLES

The general premise of medication use in anxiety disorders is that an underlying neurochemical imbalance is responsible for the disorder, which can be corrected by administration of drugs affecting specific neurotransmitter systems. Another view of medication use in anxiety disorders posits that anxiety disorders result from underlying cognitive, behavioral, or psychodynamic abnormalities and that the role of medications is to allow the patient to participate in appropriate psychotherapeutic work. The evidence is simply not available at present to adjudicate the primacy of one approach over the other. The knowledge base is rapidly evolving, but it will be many years before definitive statements can be made and causal relationships among neurophysiology, psychopathology, drugs, specific psychotherapeutic interventions, and behavioral outcome can be established. However, medication management of most anxiety disorders with or without psychotherapy is one of the most successful treatments in medicine today. Treatment response rates can reach 80 percent in panic disorder, with steadily improving rates for many other anxiety disorders. Nevertheless, a nonpharmacological treatment will almost always be preferable if comparable efficacy can be established. However benign and tolerable they may be, medication use usually entails some adverse effects. Medications may also be contraindicated because of underlying medical conditions or pregnancy.

EVALUATION

Evaluation of the anxious patient for somatic treatment begins with the psychiatric interview. Particular attention is paid to onset, course, symptomatology and comorbidity. While the anxiety disorders represent distinct diagnostic categories, they also frequently present as comorbid conditions in a given patient. Other comorbid conditions include depression, substance use disorders, and personality disorders. Comorbidity usually complicates the management of anxiety disorders and often predicts poorer outcome. The difficulty in making a differential diagnosis in the presence of comorbid depression and anxiety prompted the suggestion to create a separate diagnostic category, mixed anxiety-depressive disorder. Some believe that this new category will discourage rigorous diagnostic thinking; others consider the issue moot from a pharmacological point of view, since most antianxiety medications have antidepressant properties. In sum, establishing the correct diagnosis remains one of the cornerstones of any therapeutic endeavor.

The initial interview should elicit detailed information about prior treatments. In addition to doses, length of treatment period, response, and adverse effects for each agent, the interviewer should ask about prejudices, attitudes, and reservations about taking medications in general. Family history may help in diagnosis, and treatment history of family members can provide important clues about medication response, which also runs in families.

The initial evaluation should include (when appropriate) a thorough physical examination blood tests for chemistry, hematology, and thyroid function; urinalysis; and an electrocardiogram (ECG). If neurological abnormalities are suspected, a neurological examination may need to be supplemented with appropriate brain imaging studies. Prominent nocturnal pathology should be investigated in a sleep

laboratory.

Choosing the Medication When the decision to use medication is made, the psychiatrist frequently faces a dilemma. Scientifically valid recommendations about anxiety management should be based on rigorous double-blind, placebo-controlled trials. However, even when the data are available, the results of controlled trials do not necessarily reflect clinical reality or guide practice. Patients participating in (usually short-term) treatment trials are preselected to meet entry criteria. Natural comorbidity is limited and severity of symptoms is calibrated to ensure sample homogeneity. Elderly, pediatric, and medically ill patients are specifically excluded from most therapeutic trials. Therefore, the bulk of what psychiatrists do in clinical practice remains empirical, and many recommendations are based on expert clinical consensus.

While the choice of medication for a particular patient involves many considerations, treatment algorithms have recently been developed to guide the practitioner. These algorithms consist of decision trees based on numerous, but necessarily limited factors generally applicable to typical patients. In the absence of conclusive evidence for differential efficacy, the choice is usually determined by adverse-effect profiles. These algorithms frequently include combination treatments. Since most of these recommendations are not supported by systematic data, they should be viewed as preliminary, and periodic revisions are imperative. Whenever available, the most salient features of these algorithms are presented for the specific anxiety disorder.

Duration of Treatment Most information on the pharmacological management of anxiety is limited to short-term treatment trials. Long-term trials and follow-ups are rare; sequential treatment research is practically nonexistent. While some studies suggest that longer maintenance treatments lower relapse rates, the optimal length of medication maintenance treatment is still unknown. Since most anxiety disorders are chronic, frequently life-long conditions, treatment should probably be continued indefinitely but perhaps intermittently. In general, the lowest dosage of medication that controls the patient's symptoms should be prescribed. Slow, gradual taper of medication dosage may be attempted after 1 year in symptom-free patients; recurrence should be retreated promptly. The benefit of freedom from adverse effects should be weighed against developing drug resistance. Retreatment with a previously efficacious agent may not produce the same benefits. Frequently, a former drug responder requires several medication trials before an efficacious drug is again found.

Another, possibly related, problem associated with long-term pharmacotherapy of anxiety is drug burnout. *Burnout* refers to patients who, after a few months of response, develop drug resistance while on medication. In these patients, adjusting the dosage up or down may help, but usually one must augment or replace the original medication. Burnout is unrelated to drug tolerance, which is rare in patients suffering from pure anxiety disorders. Even when treated with benzodiazepines, the drug group claimed to be most addicting, patients with anxiety disorders usually continue to respond to stable or decreasing doses.

Treatment Nonresponse Treatment nonresponse should prompt careful reassessment of the target

symptoms, review of adverse effects, discussion of patient expectations, reevaluation of the diagnosis, checking compliance with treatment, identification of comorbid conditions (including personality disorders, substance use, and medical conditions), and potential interactions with concomitant medications (including consideration of pharmacokinetics and pharmacodynamics). The most frequent reason for medication nonresponse remains undermedication (i.e., inadequate dosage or duration). Dosing and length of treatment should be based on valid clinical trials or (in the absence of data) collective clinical experience.

Managing Adverse Effects One of the main reasons for treatment resistance is noncompliance, frequently related to anticipated or actual adverse effects. With the availability of many agents of comparable efficacy, side-effect profiles are increasingly considered in choosing a drug. A less efficacious drug may even be selected because its has a more favorable side-effect profile.

Patients should be well informed about adverse reactions and their management; however, the education and reassurance should match the needs of the patient. An overinclusive presentation may frighten a suggestible patient with anxiety disorder. As an introduction, patients should always be told that most side effects are benign and do not represent clinically significant limitations.

Lower-than-therapeutic starting dosages are generally better tolerated. Even if the initial agitation reaction of panic patients is not expected, a gradual, slow increase gives the anxious patient the best chance to accommodate to adverse reactions. Patients with dry mouth should increase fluid intake, use sugarless gum or candy, and may also try bethanecol (Urecholine). Constipation usually responds to high-bulk diet with plenty of fluid, stool softeners, or milk of magnesia. Avoiding sudden postural changes and using constrictive support hose usually minimizes orthostatic hypotension. If it persists in spite of increased fluid and salt intake, salt tablets, mineralocorticoids, amphetamines, or yohimbine (Yocon) may be tried unless specifically contraindicated. Urinary hesitancy should prompt dosage reduction, and bethanecol may also be tried. In general, anticholinergic side effects are best handled by switching to a less anticholinergic drug. Anticholinergic drugs should not be used in patients with prostatic hypertrophy or narrow-angle glaucoma. Sexual dysfunction is one of the most problematic and resistant adverse effects of drugs with significant serotonergic activity. Dosage reduction is only occasionally helpful. Anorgasmia may respond to bethanecol, cyproheptadine (Periactin), or yohimbine; diminished libido may improve if buspirone (Dulper) or bupropion (Wellbutrin) are added. Sildenfanil (Viagra) is under investigation for use in reversing the adverse sexual effects of SSRIs.

Medication-induced insomnia may improve over time. Switching the dose to the morning should be tried before hypnotic drugs such as a benzodiazepine, zolpidem (Ambien), or trazodone (Desyrel) are added. Sedating drugs should be given at bedtime or in split doses. Patients should be warned that most antidepressants cause photosensitivity. They should also be told that tricyclic and tetracyclic antidepressants may reduce parasympathetic innervation to the heart resulting in decreased beat to beat heart rate variability and potentially increased risks of coronary heart disease and arrhythmia. Antidepressant-induced hypomania may respond to dosage reduction, but if the patient has a history of bipolar disorder, mood stabilizers may be indicated.

Weight gain is one of the most troublesome and limiting adverse effects of antidepressant antianxiety drugs. Tricyclic and tetracyclic drugs with strong anticholinergic profiles and MAOIs are probably the worst offenders, followed by the serotonergic class. Atypical antidepressants such as bupropion, trazodone, and nefazadone (Serzone) are less likely to cause weight gain. If diet and exercise fail, dosage reduction or a switch to a different agent are likely to be more successful.

Antipsychotics As a general rule, antipsychotic medications should not be used for the management of anxiety disorders. However, the new generation of safer, atypical antipsychotics, (i.e., serotonin-dopamine antagonists) appears to have dramatically reduced risks of extrapyramidal side effects and tardive dyskinesia. Antipsychotic drugs may be considered in the treatment of agitation in elderly patients, managing anxiety in patients with organic brain disease, and potentiating antidepressants in patients with refractory obsessive-compulsive disorder with tic disorder or schizotypal personality disorder. Periodic, short-term antipsychotic drug may also be used in patients with histories of multiple substance dependence and those for whom all other alternatives have failed.

Medication Monitoring Duration and frequency of contact between the patient and the medicating doctor vary, depending on many factors (logistics, severity of illness, the patient's response to the medication, and the availability and use of ancillary mental health and medical services), but general guidelines apply. The initial evaluation should last for at least 1 hour. If the patient begins to take medication, a follow-up visit lasting from 20 to 30 minutes should occur within a week or two after the first visit. Another follow-up visit is usually indicated approximately 1 month after the initial evaluation, and if the condition of the patient is stable, monthly visits usually suffice to monitor progress. Face-to-face contact could be less frequent in certain situations, but a visit every 3 months is usually the outside limit. The prescribing physician should always make arrangements for 24-hour coverage and should be available to answer questions on the phone.

PANIC DISORDER WITH OR WITHOUT AGORAPHOBIA

The symptomatic triad of panic disorder consists of panic attacks, usually complicated by anticipatory anxiety and phobic avoidance, or agoraphobia. For a long time the pharmacological approach to panic disorder assumed that blocking panic attacks with medications lead to gradual improvement in both anticipatory anxiety and phobic avoidance. Therefore, panic blockade was the main focus of pharmacotherapy. Response rates to panic blockade alone range from 50 to 80 percent, depending on the definition of response. Since some of these panic-free patients remain avoidant and apprehensive, clinical practice must consider the full spectrum of panic disorder, including anticipatory anxiety, phobia, and comorbid conditions such as mood disorders.

The natural course of panic disorder varies. A significant proportion of these patients have very favorable outcomes, others suffer from long-term disability, and some have an alternating course. To address these problems, the traditional, relatively straightforward, antipanic drug regimens are gradually replaced or modified in clinical practice by complex decision trees, treatment algorithms, drug combinations, and augmentation strategies. The recommendation for refractory cases frequently includes

addition of specific psychotherapeutic techniques as well.

At the time of this writing only five drugs have been approved by the Food and Drug Administration (FDA) to treat panic disorder, but the number of efficacious, off-label antipanic agents are in the dozens. They include high- and low-potency benzodiazepines, selective serotonin reuptake inhibitors (SSRIs), tricyclic and tetracyclic, MAOIs, reversible MAOIs (RIMAs), and novel antidepressants. In explaining the pharmacological options, the clinician should tell the patient about the risks and benefits of these medications. Specifically, the patients should know that most of these medications are equally efficacious and that the choice is usually made on the basis of side effects.

Current consensus is to start treating a patient with uncomplicated panic disorder with low dosages of an SSRI (Table 15.7-1). Even at these low starting dosages many panic patients may experience initial agitation and more-frequent panic attacks. This so-called supersensitivity syndrome is usually limited to the first week or two of treatment. Further dosage reduction, switching to a different compound in the same family, or addition of a high-potency benzodiazepine, such as clonazepam (Klonopin) or alprazolam (Xanax), usually gets the patient through this relatively short period. Dosages can subsequently be increased over several weeks until they reach therapeutic range. For full panic blockade, most patients require dosages equivalent to those used in depression. A therapeutic trial with these agents should last for at least 5 weeks. Panic blockade often leads to improvement in both anticipatory anxiety and phobic avoidance. Preliminary evidence suggests that improvement in phobic avoidance may require higher dosages than panic blockade.

	Starting (mg)	Maintenance (mg)
SSRI		
Paroxetine	5–10	20–60
Fluoxetine	2–5	20–60
Sertraline	12.5–25	50–200
Fluvoxamine	12.5	100–150
Citalopram	10	20–40
Tricyclic antidepressants		
Clomipramine	5–12.5	50–125
Imipramine	10–25	150–300
Desipramine	10–25	150–200
Benzodiazepines		
Alprazolam	0.25–0.5 t.i.d.	0.5–2 t.i.d.
Clonazepam	0.25–0.5 b.i.d.	0.5–2 b.i.d.
Diazepam	2–5 b.i.d.	5–30 b.i.d.
Lorazepam	0.25–0.5 b.i.d.	0.5–2 b.i.d.
MAOIs		
Phenelzine	15 b.i.d.	15–45 b.i.d.
Tranylcypromine	10 b.i.d.	10–30 b.i.d.
RIMAs		
Moclobemide	50	300–600
Brofaromine	50	150–200
Atypical antidepressants		
Venlafaxine	6.25–25	50–150
Nefazodone	50 b.i.d.	100–300 b.i.d.
Other agents		
Valproic acid	125 b.i.d.	500–750 b.i.d.
Inositol	6000 b.i.d.	6000 b.i.d.

Table 15.7-1 Recommended Dosages for Antipanic Drugs (Daily Unless Indicated Otherwise)

Approximately 60 percent of patients respond to this approach. Partial responders can benefit from the addition of a high-potency benzodiazepine or buspirone. Partial responders with tachycardia may try a combination of an SSRI and β-adrenergic receptor antagonists. β-adrenergic receptor antagonists may also alleviate cardiac discomfort associated with mitral valve prolapse. The dosage of β-adrenergic receptor antagonists such as propranolol (Inderal) or atenolol (Tenormin) should be titrated until the heart rate is reduced by 5 to 10 beats per minute. Contraindications to using β-adrenergic receptor antagonists include bradycardia, heart block and asthma. Drug-drug interactions between some SSRIs and some β-adrenergic receptor antagonists should be kept in mind.

Nonresponders should be tapered off the SSRI and offered one of the following options: a second SSRI, venlafaxine (Effexor), a high-potency benzodiazepine, a tricyclic or tetracyclic, or an MAOI. Persistent adverse effects such as weight gain, hypomania, or sexual dysfunction, may also necessitate a switch from an SSRI in otherwise fully responding panic patients, although first an attempt should be made to address these adverse effects.

Originally, one of the most important advantages of SSRI treatment was considered the absence of withdrawal reaction upon discontinuation. However, withdrawal reactions ranging from mild, transient anxiety and insomnia to severe headache, nausea, dizziness, and "electric jolts" lasting for several months have since been reported in up to 86 percent of patients who abruptly discontinue taking SSRIs. Therefore, gradual taper over several weeks is strongly recommended. Anecdotal reports suggest that the addition of benzodiazepines, or trazodone for sleep may alleviate SSRI withdrawal.

MAOIs MAOIs such as phenelzine (Nardil) or tranylcypromine (Parnate) are the most likely to be efficacious in panic disorder, but they present the dilemma of dietary restrictions and the danger of hypertensive reaction, weight gain, orthostatic hypotension, insomnia, and a series of anticholinergic adverse effects. While somewhat less effective, a RIMA, such as moclobemide (Aurorix), is an alternative. After 2 weeks of washout (6 weeks for fluoxetine), the MAOI can be given and the dosage gradually raised to usual antidepressant levels. Comorbid major depressive in disorder in panic disorder patients may respond best to MAOIs. Because of severe withdrawal reactions such as disinhibition, irritability, agitation, insomnia, myoclonic jerks, and occasionally, delirium, thought disorder, cognitive impairment, and mania, gradual taper is strongly recommended before MAOIs are discontinued. The dietary restriction should continue for at least 2 weeks beyond discontinuation.

High-Potency Benzodiazepine High-potency benzodiazepines should be considered if the adverse effects of all other alternatives are unacceptable to the patient, or they may be first-line choices if the patient is unwilling or unable to wait out the 4- to 5-week delay in response associated with most antidepressants. The advantage of switching to a benzodiazepine also includes no wash-out time for the SSRI. In fact, a benzodiazepine can be added to the SSRI during taper. A typical switch would entail adding 0.5 mg of clonazepam twice a day to 40 mg of paroxetine (Paxil). A few days later the paroxetine dose can be lowered to 20 mg, and depending on its sedative effects, clonazepam dosage can be raised to 1 mg twice a day. Every 3 to 4 days the dosage of paroxetine can be halved while clonazepam dosage is adjusted as tolerated.

High-potency benzodiapines and perhaps low-potency benzodiazepines as well are powerful antipanic drugs. Their sedative and habituating potentials are easily managed in most patients and should not significantly diminish their clinical utility. A major advantage of benzodiazepines is their quick onset of action. Most responders benefit within 1 week. Panic patients with prior history of substance use disorder should not be treated with benzodiazepines. Older patients should take significantly lower doses of benzodiazepines because they are more sensitive to sedation and the potential cognitive side effects of benzodiazepines. A history of organic brain disease or significant character pathology may predispose patients to experience disinhibition while taking benzodiazepines.

The serious and clinically limiting problem of withdrawal symptoms from benzodiazepines prompted many studies attempting to alleviate the withdrawal reaction, also referred to as discontinuance syndrome. Studies with clonidine (Catapres), propranolol (Inderal), and carbamazepine (Tegretol) yielded inconsistent results, and substituting other medications such as antidepressants or azapirones that are easier to taper has not been studied sufficiently. Cognitive-behavioral therapy may best counter benzodiazepine withdrawal. The severity of withdrawal is related to the dosage and length of use and to the rate of taper. The rule of lowest efficacious dose for the shortest time needed for improvement should always be observed. Tapering should never exceed a 10 percent dosage reduction every 3 days. Several months of tapering after years of high-dose benzodiazepine use is frequently unavoidable.

Follow-up studies suggest that benzodiazepine-responsive panic patients maintain their gains over several years and do not develop tolerance to the drugs' antianxiety effects. In fact, maintenance dosages of benzodiazepines are frequently lower than dosages during acute treatment. Residual symptoms may require additional treatment. Since use of short-half-life benzodiazepines such as alprazolam may be associated with between-dose rebound anxiety, some clinicians prefer benzodiazepines with longer half-lives, which may also be easier to taper.

Tricyclics and Tetracyclics Switching to a cyclic antidepressant should begin with tapering the SSRI dosage down to the starting dosage. Some clinicians consider it safe to add the tricyclic at low starting dosages while others recommend a drug-free period lasting from 24 hours to 1 week before administering the second drug. The reason for caution is the potential development of the serotonin syndrome, a rare but severe reaction that may occur when two serotonergic drugs are combined. Also, plasma concentrations of tricyclic and tetracyclics may increase due to inhibition of their metabolism by the SSRI.

The first drug ever shown to possess antipanic efficacy is the tricyclic drug imipramine, and many clinicians still consider it the gold standard in panic disorder. Tricyclic and tetracyclic are generally well tolerated. Their clinical utility is clearly limited, however, by anticholinergic and cardiovascular adverse effects and toxicity in overdose. One of the most effective tricyclic drug for panic is clomipramine (Anafranil), which seems to be effective at lower than full antidepressant dosage. A linear relationship may exist between total plasma tricyclic drug concentrations and response rate. In general, agoraphobia may respond to higher dosages than panic attacks alone. Because of the variable nature of the withdrawal reaction upon discontinuation of tricyclic or tetracyclic drugs (somatic distress, sleep disturbance, behavioral activation, cardiac arrhythmias), taper should be tailored to the patient's needs. Halving the original dosage will give an early indication of withdrawal severity.

Secondary Alternatives While controlled data are unavailable, clinicians increasingly turn to venlafaxine (Effexor) as an alternative to SSRIs and tricyclic drugs in the treatment of panic disorder. If such initial adverse effects as nausea and agitation are overcome, venlafaxine is a powerful antipanic agent at a dosage significantly below its antidepressant dosage. Since the safety of combining venlafaxine and an SSRI has not been systematically assessed, the SSRI should be tapered and discontinued before switching to venlafaxine. A potential limitation of venlafaxine is an unusually

severe reaction to taper. Many successfully treated patients complain of nausea, headache, fatigue, dizziness, and gastrointestinal disturbance when trying to reduce the venlafaxine dosage. Anecdotal evidence suggests that the temporary addition of fluoxetine (10 mg a day) may reduce the withdrawal reaction and allow discontinuation of venlafaxine.

Switching to a second SSRI may be justified if the adverse effects of all alternative possibilities are unacceptable to the patient or there is a relative contraindication to using anything but an SSRI. Again, in the absence of controlled data, opinions differ on how to switch between two SSRIs. Since the potential for the serotonin syndrome is even higher than in the case of combining an SSRI and a tricyclic antidepressant, caution is warranted, and most clinicians recommend a drug-free period between two SSRIs.

Buspirone was promoted as a less-sedating alternative to benzodiazepines in the treatment of panic disorder. Buspirone has lower potential for abuse and dependence than benzodiazepines and produces relatively few adverse effects and no withdrawal syndrome. Buspirone does not alter cognitive or psychomotor function, does not interact with alcohol, and is not a muscle relaxant or an anticonvulsant. However, the efficacy of buspirone in panic disorder is disappointing, and with its further handicap of delayed onset of action and the need for multiple dosing, its use is limited to potentiating the efficacy of other antidepressants and countering the adverse sexual effects of SSRIs. Also, buspirone seems even less effective in patients previously exposed to benzodiazepines.

Bupropion, maprotiline (Ludiomil), and trazodone have not been found efficacious for panic disorder in controlled studies, while the anticonvulsants divalproex (Depakote) and gabapentin (Neurontin), the polyol second-messenger precursor inositol, nefazodone, and the calcium channel inhibitor verapamil (Calan, Isoptin) have shown promise as antipanic agents.

While the short-term efficacy of antipanic medications has been established, the question of how long to treat a panic patient who responds to treatment remains open. The results of follow-up studies are mixed. Several reports indicate that most panic patients relapse within 2 months to 2 years after the medication is discontinued. A recent review concludes that following medication discontinuation, only about 30 to 45 percent of the patients remain well, and even remitted patients may display a variety of symptoms. Others find that while occasional panic attacks are quite common, otherwise responding patients rarely revert back to significant phobic avoidance or serious vocational or social disability. Improvement may continue for years following a single course of medication treatment. This favorable outcome may be explained by the heterogeneity of panic disorder, spontaneous learning experience of patients in clinical trials, and concomitant self-monitoring. Given the uncertainty about the optimal duration of treatment, the current recommendation is to continue full-dosage medication for panic-free patients for at least 1 year. Medication taper should be slow, with careful monitoring of symptoms. Distinction should be made among return symptoms, withdrawal, and rebound anxiety.

Since longer duration of illness at baseline predicts poor long-term outcome, all efforts should be made to identify and treat panic patients as early as possible. More-severe phobic avoidance and comorbid

depression and social phobia at baseline also predict poor long-term outcome. Higher depression scores coincide with greater severity of avoidance and disability. The poorer overall outcome in panic disorder patients with comorbid recurrent depression is more likely due to the simultaneous presence of the two conditions. Comorbid depression usually improves in parallel with panic symptoms.

Atypical responses to medications have been reported in panic patients whose first panic attacks were precipitated by cocaine use. These patients respond preferentially to benzodiazepines and anticonvulsants, while tricyclic drugs seem to worsen their anxiety symptoms. This pattern of medication response suggests that cocaine-induced panic attacks may be related to a kindling-like phenomenon.

In a small series of patients with comorbid depression and panic disorder electroconvulsive therapy (ECT) seemed highly effective. None of these patients experienced panic attacks after their fourth ECT treatment until discharge.

GENERALIZED ANXIETY DISORDER

Patients with generalized anxiety disorder suffer from excessive and uncontrollable anxiety and worry for at least 6 months and experience a series of somatic symptoms such as restlessness, irritability, insomnia, and muscle tension. The illness is chronic, with periodic exacerbations and relative quiescence. The relative sparsity of biological data and pharmacotherapy research is due to a number of factors. First, because of their multiple somatic complaints, patients with generalized anxiety disorder are usually seen by generalists and medical specialists other than psychiatrists; generalized anxiety disorder is more likely to be diagnosed as a comorbid condition in psychiatric practices. Second, pharmacotherapy is considered less effective in generalized anxiety disorder than in some other anxiety disorders. Third, the diagnostic features are not clear-cut, and comorbid conditions make the diagnosis difficult.

The efficacy of benzodiazepines in the pharmacological treatment of generalized anxiety disorder gave rise to theories implicating the benzodiazepine–γ-aminobutyric acid (GABA) receptor system in the pathophysiology of generalized anxiety disorder, but evidence exists for the involvement of the serotonergic and noradrenergic systems as well. Benzodiazepines remain the traditional medication choice for patients with generalized anxiety disorder. Data do not support the advantage of any one benzodiazepine over others, and no correlation has been established between clinical response and dosage or plasma concentration. A daily equivalent of 15 to 25 mg of diazepam usually suffices to relieve most symptoms in up to 70 percent of generalized anxiety disorder patients. Both somatic and psychic anxiety symptoms respond within the first week of treatment. Tolerance to the sedative effects of benzodiazepines develops quickly, but the antianxiety effect of a given dosage is well maintained over time in generalized anxiety disorder. However, the relapse rate upon discontinuation of benzodiazepines is high.

Buspirone, the only currently available azapirone, is a potential alternative to benzodiazepine treatment

in generalized anxiety disorder. Response rates between 60 and 80 percent have been reported at dosages ranging from 30 to 60 mg a day in three divided doses. While response rates seem comparable, more patients drop out of buspirone trials than benzodiazepine trials. The relative merits of buspirone and benzodiazepines are further detailed under panic disorder. One notable exception is that generalized anxiety disorder patients exposed to benzodiazepines may still be responsive to buspirone unlike panic patients.

Antidepressants are also effective in generalized anxiety disorder patients. Dosages and response patterns are similar to those observed in panic disorder (Table 15.7-1). Increased initial physiological symptoms and anxiety may be related to adverse effects such as dry mouth, constipation, sedation, and positional hypotension rather than to the hypersensitivity syndrome described in panic disorder.

Isolated (but prominent) symptoms such as palpitation, tremor, and sweating may respond to β-blockers within 1 week of treatment, but the full generalized anxiety disorder picture usually requires the use of benzodiazepines, antidepressants, or buspirone. Controlled studies are unavailable, but clinical experience suggests the benefits of combination treatments for generalized anxiety disorder. For instance, the combination of benzodiazepines or β-adrenergic receptor antagonists with antidepressants could yield a rapid response, and when the antidepressant becomes effective, the benzodiazepine or β-adrenergic receptor antagonists can be tapered off. Several new drugs, currently unavailable in the United States, have also been found promising in recent clinical trials. The only double-blind, placebo-controlled study with the partial benzodiazepine agonist abecarnil showed significant improvement on many measures in patients with generalized anxiety disorder. Tropisetrone, a 5-HT_3 antagonist, has good antianxiety efficacy with few, mild adverse effects, and serazepine, a 5-HT_2 antagonist, also worked well. Gepirone and ipsapirone, two compounds related to buspirone, have demonstrated efficacy comparable to that of buspirone.

Maintenance pharmacotherapy of patients with generalized anxiety disorder should follow the principles given above for long-term treatment of anxiety disorders. Given the fluctuating course of this disorder, periodic discontinuation may be attempted.

OBSESSIVE-COMPULSIVE DISORDER

Patients with OCD suffer from recurrent ruminations, the need for repeated performance of useless stereotyped rituals, or both. The initial assessment of patients with OCD should include a detailed description of type, severity, and onset and identification of target symptoms. Comorbid conditions frequently complicating the treatment of OCD include depression, other anxiety disorders, substance use disorders, schizophrenia, bipolar disorders, and personality disorders. OCD is probably the most difficult anxiety disorder to treat and has the highest rate of nonresponse.

Finding that medications that increase serotonergic transmission in the central nervous system (CNS) are efficacious in OCD revolutionized treatment and suggested that the pathophysiology of OCD is related to changes in serotonin function. Subsequently, a series of these medications such as clomipramine,

fluvoxamine (Luvox), fluoxetine, paroxetine, and sertraline (Zoloft) have been shown in double-blind controlled trials to alleviate the symptoms of OCD. These drugs are used at relatively high daily dosages (clomipramine, 250 mg; fluvoxamine, 300 mg; fluoxetine, 80 mg; paroxetine 60 mg; sertraline, 200 mg a day or more), although recently the high-dosage strategy is being challenged. Some investigators believe that longer duration of treatment rather than higher dosage is required for response. Ten weeks of treatment trial is currently the minimum recommendation, but it is not unusual to have treatment continue for several months before peak efficacy is reached. The average response rate to these agents ranges from 40 to 60 percent, but nonresponders to one drug can respond to another. Therefore, several anti–obsessive-compulsive OCD drugs should be tried sequentially before making conclusions about drug resistance. Recent studies suggest that intravenous pulse loading or gradual infusion of clomipramine may convert oral clomipramine–refractory patients into responders.

Based on meta-analysis of effect sizes in placebo-controlled trials, clomipramine is considered more effective than the SSRIs. However, recent direct comparisons failed to confirm this observation. Also, the potential advantage of clomipramine should be weighed against its more troublesome (primarily anticholinergic) adverse-effect profile.

A significant proportion of OCD patients remain refractory to SSRI monotherapy, which suggests diagnostic heterogeneity and also that the psychophysiology of OCD may involve abnormalities other than serotonin dysregulation. Patients with comorbid chronic tic disorders such as Tourette's disorder may represent a subgroup of OCD and may require the combination of SSRI and an antipsychotic drug such as pimozide (Orap) or haloperidol (Haldol). Addition of a low-dosage antipsychotic to an SSRI may also be justified for comorbid schizotypal personality disorder. In general, however, addition of an antipsychotic should only be considered if all other approaches including trials of several SSRIs and cognitive-behavioral therapy have all failed. Since most of these patients require long-term pharmacotherapy, the potential risk of tardive dyskinesia should be weighed against the benefits. The availability of serotonin-dopamine antagonists, with more-favorable adverse-effect profiles, may change this conservative view.

The presence of neurological abnormalities or abnormal electroencephalogram (EEG) may indicate a need for a trial concomitant use of anticonvulsants such as valproate (Depakene) or carbamazepine, while prominent impulsivity may respond to sympathomimetics (psychostimulants) alone or in combination with other antiobsessional drugs. Earlier case reports of the antiobsessional effects of phenelzine were confirmed in one double-blind trial but not in a subsequent controlled study. The efficacy of phenelzine may be limited to patients with symmetry obsessions. Augmentation strategies to enhance the anti–obsessive-compulsive properties of SSRIs have used lithium (Eskalith), buspirone, pindolol (Visken), fenfluramine, 5-hydroxytryptophan, and L-tryptophan. In the absence of controlled studies confirming their efficacy, the addition of most of these agents cannot be recommended as augmenting strategies with scientific certainty. For example, lithium and buspirone augmentation failed in double-blind controlled trials. Case reports suggest that pindolol (2.5 mg three times a day) may help with comorbid depression but has no additive antiobsessional effect.

Relapse rates are high following medication discontinuation. In one study over 90 percent of the patients relapsed after abrupt discontinuation of clomipramine. Medication maintenance treatment seems to be associated with maintained, and even improved, overall functioning. Dosage titration during maintenance treatment could further improve outcome with few late-emergent adverse events.

The most important predictor of poor outcome in OCD is early onset. The presence of schizotypal, borderline, and avoidant personality disorders, and greater number of personality disorders also predict poorer outcome. Severity and duration of illness, sex, age, and type of symptoms have no predictive value.

Psychosurgery remains the last-resort treatment for intractable OCD. The most frequently performed operation, stereotactic subcaudate tractotomies or capsulotomy, intersects the connections between the frontal lobe and the thalamus and exerts its efficacy on the proposed functional imbalance in OCD between the frontal lobe and other parts of the brain. Stereotactic leukotomy seems to decrease glucose metabolism in the orbital part of the frontal lobe. Cingulotomy resulted in significant improvement in 25 to 30 percent of patients previously unresponsive to medication and behavioral treatments. This rate of improvement seems independent of the changes in anxiety and depression scores. Personality changes following psychosurgery are infrequent, but most patients display lower initiative, drive, and energy levels at follow-up. Capsulotomy can lead to perservative behavioral responses. Striatal lesions may lead to the development of substance use disorders following surgery. Phenytoin (Dilantin) usually controls the symptoms in the few cases when seizure develops following surgery.

The few ECT case studies in intractable OCD show considerable benefits up to a 1-year follow-up and suggest that these benefits are independent of changes in measures of depression. These reports must be viewed with caution until confirmed in controlled trials. Preliminary evidence suggests that plasmapheresis, antibiotics, or both may be indicated in a subgroup of children whose obsessive-compulsive symptoms are associated with a specific autoimmune response in the brain.

SOCIAL PHOBIA

Social phobia is an exaggerated fear of negative evaluations, ranging from specific to generalized types. Some consider avoidant personality disorder to be the most severe form of social phobia. Social phobia is a chronic, disabling condition whose prevalence is being increasingly recognized.

Double-blind, placebo-controlled studies confirmed that the most effective medication for the treatment of generalized social phobia is the MAOI phenelzine. Therapeutic dosages of phenelzine range from 45 to 90 mg a day, with response rates ranging from 50 to 70 percent. Approximately 5 to 6 weeks are needed to assess the efficacy of phenelzine. Responders should continue treatment for at least a year. Dietary restriction and numerous troublesome adverse effects put MAOIs at a significant disadvantage compared with less-efficacious but more acceptable medication choices. For instance, the SSRIs have recently emerged as viable alternatives to phenelzine. Although not subjected to the same rigorous evaluations, the results of controlled trials (fluvoxamine, paroxetine, sertraline), a controlled

discontinuation study (paroxetine), and open-label case reports (citalopram [Celexa]) with SSRIs suggest that their ease of administration and tolerability more than make up for their slightly lower efficacy.

Most clinicians consider SSRIs the first-line treatment choice for patients with generalized social phobia. Since patients with social phobia do not exhibit the supersensitivity syndrome described in panic disorder, SSRI administration can be initiated at usual antidepressant starting dosages (e.g., fluoxetine, 20 mg; paroxetine, 20 mg) and titrated on the basis of clinical response. The benzodiazepines alprazolam and clonazepam also seem efficacious in both generalized and specific social phobias. Their favorable adverse-effect profile and quick onset of action are countered by lower response rates and earlier relapse upon discontinuation than with phenelzine. As in panic disorder, tolerance does not develop to the therapeutic effects of benzodiazepines. Starting and therapeutic dosages for benzodiazepines are the same as those for panic disorder (Table 15.7-1).

Specific social phobias such as fear of public speaking respond moderately well to β-adrenergic receptor antagonists, although the data are mostly anecdotal. Propranolol (20 to 60 mg per dose) counters several of the physiological symptoms of excessive autonomic arousal. Propranolol's short half-life makes it necessary to repeat the effective dose every 2 to 4 hours. If propranolol works but the social phobic situations are unpredictable during the day, a β-adrenergic receptor antagonists with a longer half-life can be tried. Atenolol (Tenormin), 50 to 100 mg before sleep, should control the symptoms for 24 hours. The adverse effects of β-blockers may include sedation, fatigue, dry mouth, gastric cramping, and occasionally confusion and memory problems. Long-term use can lead to depression. Because of the adverse effects and unpredictability of response, the patient is strongly encouraged to test these drugs before the actual event or performance. The utility of β-adrenergic receptor antagonists in generalized social phobia is much more limited. Preliminary evidence supports the use of buspirone as well. Modest response has been noted in patients with social phobia at dosage above 45 mg a day.

Hyperhidrosis (excessive sweating) may be controlled by topical application of aluminum chloride in alcohol (Drysol) while a generalized form of the symptom usually responds to clonidine or terazosin (Hytrin). Ondansetron (Zofran) is the preferred medication for patients with social phobia if the most disabling symptom is nausea or the fear of vomiting. Nausea may also respond to cisapride (Propulsid), but caution should be exercised when prescribed concomitantly with drugs that inhibit cytochrome P450 (CYP) A4 (CYP 3A4). Paruresis a frequent symptom of social phobia, manifesting as the inability to void in public restrooms, usually requires in vivo exposure and relaxation training. Pharmacological approaches have been largely disappointing but a trial of furosemide and bethanechol may be warranted during behavioral treatment.

The RIMA brofaromine (150 mg a day) was found efficacious in a controlled trial. The finding that most patients maintained their gains at a 9-month follow-up assessment suggests that brofaromine could play an important role in the management of social phobia if it becomes available in the United States.

SPECIFIC PHOBIAS

Specific phobias are quite common and only require treatment if they interfere significantly with the functioning. Treatment is usually behavioral exposure. Medications are used occasionally to alleviate the anticipatory anxiety associated with beginning exposure treatment. Low-dose benzodiazepines and β-adrenergic receptor antagonists can be used for this purpose on an as-needed basis.

POSTTRAUMATIC STRESS DISORDER

Patients with posttraumatic stress disorder (PTSD) by definition have experienced a life-threatening trauma. These patients continue to relieve the experience and complain of flashbacks and vivid dreams of the original trauma. Blunted emotions coupled with a wide range of anxiety, mood, and sleep disorders are frequent manifestations of PTSD.

Prior to being assigned to a separate diagnostic entity, trauma survivors were treated according to the most prominent symptom clusters (e.g., anxiety or depression). Consequently, antidepressants and benzodiazepines were the mainstay of pharmacotherapy, with occasional use of antipsychotics for flashbacks and behavioral discontrol. Interpretation of medication trials in PTSD populations is complicated by a number of factors. First, most early medication trials were conducted in war veterans with chronic PTSD and a number of comorbid conditions such as substance use and severe personality disorders. They tended to have undergone several unsuccessful treatment trials and were considered refractory to psychiatric interventions. It has been suggested recently that the results of these earlier trials may not be applicable to well-diagnosed, previously untreated civilian populations. Civilian trauma survivors seem more responsive to pharmacotherapy than veterans. Second, some studies excluded PTSD patients with comorbid depression. Since this strategy eliminated over 50 percent of the otherwise eligible patients, the clinical relevance of these studies may be quite limited. Third, there is no consensus on how to rate improvement in PTSD. Some studies focus on intrusive thoughts; others on avoidance and hyperarousal. The field is in the process of teasing out medication-responsive symptom clusters and perhaps identifying subgroups of PTSD patients. As biological abnormalities are increasingly recognized in the pathophysiology of PTSD, recent pharmacological trials have begun to target neurotransmitter systems thought to be relevant in PTSD.

Currently, the medication treatment of PTSD is mostly based on clinical experience, case studies, open trials, and retrospective chart reviews; comparatively few controlled trials exist. Almost all antidepressants and antianxiety medications have been tried. It is rather unusual to have an agent show no therapeutic benefit in PTSD, but no medication has covered the full spectrum of PTSD symptomatology. Substantial heterogeneity with regard to type and severity of trauma, developmental phase of the patient at the time of the trauma, comorbid conditions, and psychiatric history may explain relative treatment resistance.

Intrusive thoughts, insomnia, recurring dreams and memories may respond to phenelzine at antidepressant dosages (45 to 90 mg a day). Brofaromine, while not yet available in the United States, may be a good alternative to the MAOIs in PTSD; over half of PTSD patients responded to brofaromine

in a double-blind trial. Tricyclic drugs such as amytriptyline (Elavil) or imipramine may improve depressive and anxiety symptoms but have modest effect on intrusive thought. Global improvement is evident even in the absence of prominent depression, but it may not be observable before 8 weeks of treatment. Benzodiazepines, such as alprazolam, have only modest effect on anxiety, and the risk of dependence and abuse potential contraindicate their use in PTSD patients with substance use disorders. Numbing and hyperarousal in civilians but not in veterans, and impulse control, labile affect, and disturbed interpersonal relationships in both populations may respond to fluoxetine in dosages of 60 mg a day and above. Antipanic, low starting dosages of fluoxetine usually circumvent the initial agitation in patients with prominent anxiety; paroxetine may be less activating than fluoxetine in these patients. Fluvoxamine and sertraline reduce hyperarousal, intrusion, and explosiveness. Since SSRIs may be the only medications targeting the full symptom spectrum of PTSD, they are usually considered the first-line pharmacological treatment.

While not considered first-line approaches, clonidine (Catapres) buspirone, and high-dosage propranolol may be used alone or as adjuncts to an SSRI or a tricyclic drug for hyperarousal, nightmares, and flashbacks. Refractory impulsivity and aggressive outbursts in combat veterans may be treated with lithium, carbamazepine, or valproate, alone or in combination with an SSRI. Mood stabilizers have not been tested in civilian PTSD populations.

In the absence of data about optimal duration of pharmacotherapy and relapse upon discontinuation, the recommendations should follow those given for other chronic anxiety and affective disorders. Medication treatment should continue for at least 1 year. Given the considerable uncertainty surrounding the illness, flexibility in tailoring medication combinations according to individual patients is recommended, and psychotherapy should always be part of the management of PTSD.

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Table 15.7-1 Recommended Dosages for Antipanic Drugs (Daily Unless Indicated Otherwise)

	Starting (mg)	Maintenance (mg)
SSRI		
Paroxetine	5–10	20–60
Fluoxetine	2–5	20–60
Sertraline	12.5–25	50–200
Fluvoxamine	12.5	100–150
Citalopram	10	20–40
Tricyclic antidepressants		
Clomipramine	5–12.5	50–125
Imipramine	10–25	150–500
Desipramine	10–25	150–200
Benzodiazepines		
Alprazolam	0.25–0.5 t.i.d.	0.5–2 t.i.d.
Clonazepam	0.25–0.5 b.i.d.	0.5–2 b.i.d.
Diazepam	2–5 b.i.d.	5–30 b.i.d.
Lorazepam	0.25–0.5 b.i.d.	0.5–2 b.i.d.
MAOIs		
Phenelzine	15 b.i.d.	15–45 b.i.d.
Tranylcypromine	10 b.i.d.	10–30 b.i.d.
RIMAs		
Moclobemide	50	300–600
Brofaromine	50	150–200
Atypical antidepressants		
Venlafaxine	6.25–25	50–150
Nefazodone	50 b.i.d.	100–300 b.i.d.
Other agents		
Valproic acid	125 b.i.d.	500–750 b.i.d.
Inositol	6000 b.i.d.	6000 b.i.d.