Chapter 16
The Pharmacological Management of Stress Reactions

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The use of drug therapies in the management of acute stress reactions and chronic stress-related disorders has emerged as understanding of the pathophysiology of these conditions has become better understood. The general approach to treatment has evolved from the use of predominantly rapid-acting sedative agents for the treatment of acute anxiety attacks, to the more frequent use of agents to control the underlying anxiety disorder.

With most psychiatric conditions, conservative strategies for treatment should be employed before more restrictive interventions, such as drug therapies, are used. In the case of stress arousal, relaxation therapies that promote the development of the client's own response mechanisms should be attempted if his or her condition is responsive to such techniques. Cognitive-behavioral therapies, structured breathing, neuromuscular relaxation, and clinical hypnosis (see Chaps. 8, 11, 12, and 13) are generally preferred over drug therapy in situations where clients respond to these treatments, because these methods avoid the potential dependency problems and adverse effects of pharmacological agents.

However, there are instances in which drug therapy is appropriate for treatment of excessive stress. Drug therapy is a useful adjunct for the treatment of panic attacks associated with panic disorder and social phobia, increased arousal and traumatic recall associated with PTSD, and anxiety and compulsive behaviors associated with obsessive–compulsive disorder (OCD).

The present chapter reviews the major classes of pharmacological agents used in the treatment of pathological stress arousal states. Indications and target symptoms (i.e., the undesired physiological states that may be reversible with treatment) are discussed, along with potential problems associated with these agents—adverse effects, dependency liabilities, and drug interactions. We begin with a basic discussion of psychotropic drug pharmacology.

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Pharmacology

Psychotropic drugs exert various effects in the CNS. Most currently available psychotropic medications modulate the activity of neurotransmitters in the brain. Neurotransmitters are small molecules or peptides that carry signals between neurons, i.e., across synapses, the gaps between adjacent nerve cells. Receptors located on pre- and postsynaptic neuronal membranes are the targets for the activity of neurotransmitters and certain drugs.

Norepinephrine (NE), for example, is a monoamine neurotransmitter that has important functions in both the central and peripheral nervous systems. In the brain, several noradrenergic neuronal tracts have been identified, most of which originate in the locus ceruleus. These noradrenergic pathways modulate mood, attention, energy, motor movements, and autonomic functions such as blood pressure control and perspiration. Peripherally, norepinephrine plays a major role in the somatic manifestations of the acute stress response. Elevations in heart rate and urinary retention are mediated by noradrenergic projections from the spinal cord.

Serotonin (5-HT) is an abundant neurotransmitter derived from the dietary amino acid tryptophan. Cell bodies for the serotonergic neurons in the brain are concentrated in the raphe nuclei. Projections from the raphe nuclei are involved in the regulation of mood, motor activity, appetite, sleep, and sexual functioning. Anxiety and panic are also regulated by CNS serotonergic projections. Serotonin release is controlled, in part, by its interactions with norepinephrine, which can either enhance or inhibit serotonin release through interconnecting pathways in the brain stem and the cortex.

Gamma-aminobutyric acid (GABA) is an amino acid derivative that serves as the major inhibitory neurotransmitter in the CNS. It has several functions associated with CNS inhibition, including anxiolytic activity, anticonvulsant activity, sleep promotion, and muscle relaxation. Upon ligand signaling to the GABA-ergic neuron, a very rapid neuronal inhibition is produced. The operation of this mechanism may play an important role in mediating the sensation of anxiety and the initiation of the relaxation response.

Many specific biochemical abnormalities have been identified in psychiatric illnesses. For example, an excess of dopamine neurotransmission in the mesolimbic tract has been correlated with the presence of positive symptoms (e.g., hallucinations and delusions) in patients with schizophrenia. Major depression is felt to be due, in part, to a relative deficiency of serotonin, norepinephrine, and dopamine. Similarly, anxiety states have been associated with an excess of norepinephrine discharge in the locus ceruleus and a relative deficiency of GABA neurotransmission. It is important to note, however, that the identification of these neurotransmitter abnormalities does not necessarily suggest any underlying pathology. In fact, most mental illnesses develop as a result of a combination of genetic, neurodevelopmental, environmental, and social factors.

Current drug therapy, while not always addressing the underlying causes for these mental illnesses, can symptomatically treat these disorders through its effects

on the various neurotransmitter systems. There are several mechanisms by which drugs can modulate neurotransmission in the CNS:

- Direct agonist activity at pre- and postsynaptic receptors.
- Facilitation of the release of stored neurotransmitters.
- Inhibition of presynaptic neurotransmitter reuptake.
- Inhibition of enzymatic neurotransmitter degradation.
- Inhibition of neurotransmitter synthesis and storage.
- Alteration of feedback mechanisms modulating neurotransmitter release.
- Alteration of receptor or ion channel binding sites, leading to facilitation or inhibition of neurotransmission.

With the exception of the sedatives–hypnotics, and stimulant treatments used for attention deficit/hyperactivity disorder, therapeutic effects of psychotropic drug therapy generally occur after several weeks of continuous dosing. Changes in synaptic neurotransmitter concentration tend to lead to altered sensitivity and concentrations of the postsynaptic receptors. These changes occur over the course of several weeks, resulting in the delay in clinical response. Since adverse effects of psychotropic agents are usually most severe at the onset of therapy, a delayed therapeutic response significantly compromises patient adherence to treatment. This is an especially significant consideration when dealing with manifestations of excessive stress, when the patient needs immediate relief from the discomfort associated with the disorder and has little tolerance for side effects. Fortunately, there are many agents available, and while not being optimal for long-term treatment, they can provide a faster onset of symptom resolution.

Many CNS depressants, including sedatives–hypnotics, have a more direct mechanism of action, leading to a more immediate therapeutic effect. While this type of pharmacological profile maybe more desirable to patients, problems with dependence and adverse effects associated with CNS depression make the agents most useful for short-term intervention.

The following sections of this chapter review the classes of drugs used in the treatment of disorders characterized by excessive stress. The mechanisms of action, indications, adverse effects, expected therapeutic outcomes, and relevant drug interactions are described. Our objective is to provide a basic familiarity with the concepts and the role of drug treatment for stress.

Benzodiazepines

The benzodiazepines are a widely used class of medications for the treatment of anxiety disorders and stress reactions. This class of drugs includes diazepam (Valium®), lorazepam (Ativan®), oxazepam (Serax®), alprazolam (Xanax®), clorazepate (Tranxene®), and chlordiazepoxide (Librium®).

Other drugs in this class that are used primarily for sleep disturbances include triazolam (Halcion®), flurazepam (Dalmane®), estazolam (ProSom®), and temazepam

Table 16.1 Comparative characteristics of benzodiazepines

Drug	Dosage range (mg/day)	Duration of action ($t_{1/2}$) in hours	Onset of action (oral absorption)
Alprazolam (Xanax®)	0.25–4.0	12–15	Intermediate
Clonazepam (Klonopin®)	0.5–12.0	18–50	Intermediate
Clorazepate (Tranxene®)	7.5–60.0	Metabolite-dependent Desmethyldiazepam (30–200) Oxazepam (3–21)	Fast
Chlordiazepoxide (Librium®)	10–100	5–30 Demoxepam (14–95) Desmethylchlordiazepoxide (18)	Intermediate
Diazepam (Valium®)	5–60	20–50 Desmethyldiazepam (30–200) 3-Hydroxydiazepam (5–20) Oxazepam (3–21)	Fastest
Lorazepam (Ativan®)	2–16	10–20	Intermediate
Oxazepam (Serax®)	15–60	3–21	Intermediate

(Restoril®). Other related sedative anxiolytic drugs, including the barbituates, meprobamate, chloral hydrate, gluthethimide and ethchlorvynol, are older agents with significant toxicity profiles that are no longer widely used.

The benzodiazepines are all identical in their mechanism of action, and the only differences among them lie in their pharmacokinetic properties (absorption, metabolism, and elimination half-life) (Grimsley, 1995). Table 16.1 lists pharmacokinetic differences and usual therapeutic doses. The benzodiazepines work by enhancing GABA in the brain. These agents have four therapeutic effects—antianxiety, sedative–hypnotic, muscle relaxant, and anticonvulsant. Typically, sedative effects are seen at lower doses. Anxiolytic, muscle relaxant, and anticonvulsant effects are seen at moderate doses. At high doses, benzodiazepines can be used to induce sleep.

In the treatment of anxiety, benzodiazepines are most appropriately used for the treatment of acute panic attacks and to treat residual symptoms not controlled with other agents, such as antidepressants (American Psychiatric Association, 2004, 2009). Certain longer acting benzodiazepines (e.g., clonazepam, diazepam) are approved for long-term use in the prevention of anxiety symptoms such as those seen in panic disorder and generalized anxiety disorder. However, chronic use may lead to tolerance, the phenomenon whereby a certain fixed dose loses its effectiveness over time. Patients may try to counteract this by increasing their own dose, potentially leading to physical dependence, addiction, and abuse. Continued use of the drugs may also result in more difficult withdrawal (discussed below).

Choice of agents depends on the clinical state of the individual for whom they are prescribed. Benzodiazepines with shorter half-lives, such as lorazepam, alprazolam, and oxazepam, may be most useful for persons requiring limited treatment for acute anxiety due to a stressful situation. Those with longer half-lives, such as diazepam, clonazepam, clorazepate, and chlordiazepoxide, may be better for persons requiring longer therapy for chronic anxiety. Shorter-acting agents may also be preferred for

the elderly or those with impaired liver function. These individuals would be more prone to adverse effects from drug accumulation, such as over sedation (American Geriatrics Society, 2012; Hamilton, Gallagher, Ryan, Byrne, & O'Mahony, 2011).

Side effects of the benzodiazepines include sedation, confusion, amnesia, unsteady gait, and lethargy. They are relatively safe on overdose except when combined with other CNS-depressant drugs such as alcohol or other sedatives–hypnotics. The most serious problem with benzodiazepine therapy can be serious withdrawal reactions, the result of physical dependence. Physical dependence may occur after 4–6 months with usual doses or more rapidly, 2–3 weeks, with high doses (Brown, Rakel, Wells, Downs, & Akiskal, 1993). Withdrawal symptoms are frequently the opposite of the usual therapeutic effects of the benzodiazepines. Psychological symptoms include irritability, insomnia, feelings of apprehension, and dysphoria. Physical symptoms may include tremor, palpitations, dizziness, muscle spasm, and sweating. Perceptual symptoms include hypersensitivity to sound, light, and touch, and depersonalization. In severe situations, seizures may occur. Withdrawal symptoms can be minimized by using a slow taper (i.e., a gradual dose reduction over 4–16 weeks, depending on the starting dose and duration of therapy). Adjunctive therapy may be needed, such as beta-blocking agents or sedating antidepressants. Benzodiazepines should never be discontinued abruptly unless serious side effects warrant the risk of withdrawal.

Antidepressants

Antidepressant agents are so named because drugs possessing the common pharmacology of these agents are traditionally used in the treatment of depressive disorders. All currently available antidepressants facilitate neurotransmission of serotonin, norepinephrine, and/or dopamine. However, the exact neuronal targets (e.g., enzymes, reuptake pumps, and autoreceptors) differ from class to class. It is interesting to note, however, that despite the wide array of mechanisms of action of the antidepressants, no agent or class of drugs has been shown to be more consistently efficacious in the treatment of depression. Drug choice is based on presenting symptoms and adverse effect profile, among other clinical factors. However, in the treatment of anxiety states, the pharmacological profiles of the agents determine the spectrum of disorders for which the drugs are likely to be effective.

Antidepressant-associated increases in serotonin (5-HT) and norepinephrine (NE) neurotransmission may have effects other than their direct benefits in affective and somatic manifestations of depression and anxiety. Increasing evidence suggests that by increasing NE and 5-HT neurotransmission in the neurons of the hippocampus, the nerve damage induced by chronic stress can be reversed. The expression of neurotrophic factors that serve to promote neuronal survival and growth in the CNS is decreased during stress. Antidepressant treatment may reverse these changes by upregulating neurotrophic-factor expression (Duman, Malberg, & Thome, 1999; Hellweg, Ziegenhorn, Heuser, & Deuschle, 2008).

The antidepressant drugs are classified by pharmacological mechanism or chemical structure (see Table 16.2). The monoamine oxidase inhibitors (MAOIs) and the tricyclics were the first classes of antidepressants developed. The selective serotonin reuptake inhibitors (SSRIs) and various other agents with novel mechanisms of action were later introduced to address the tolerability issues of the earlier drugs, and have supplanted the older agents as the drugs of choice for stress-related conditions.

Monoamine Oxidase Inhibitors (MAOIs)

Phenylzine (Nardil®) and tranylcypromine (Parnate®) work by irreversibly inhibiting the enzyme that degrades monoamine neurotransmitters. As a result, the concentration of NE and other catecholamines is increased in the synaptic cleft, thereby facilitating neurotransmission.

The benefits of MAOI therapy in the treatment of depression and stress-related disorders are significant. These agents are considered to be very effective in the prevention of panic attacks associated with panic and social anxiety disorder. In clinical trials, 60–70% of patients with panic and social anxiety disorder show significant decreases in the frequency of panic attacks after 8–12 weeks of MAOI therapy (Spiegel, Wiegel, Baker, & Greene, 2000).

However, due to significant food and drug interactions associated with treatment, MAOIs are not currently employed as first- or second-line agents. By irreversibly inhibiting monoamine oxidase, MAOIs subject the patient to a prolonged inability to metabolize tyramine, an amino acid found in aged cheeses, red wines, and cured meats. Elevated levels of tyramine can cause a life-threatening syndrome of elevated blood pressure, palpitations, and hyperthermia. These effects may be avoided by adopting a diet with very low levels of tyramine and avoiding the use of drugs with sympathomimetic effects (e.g., over-the-counter decongestants); however, most clinicians prefer to first use drugs with a better safety profile, avoiding these concerns, unless absolutely necessary.

Tricyclic Antidepressants (TCAs)

The TCAs are a fairly large group of structurally and pharmacologically similar drugs. The therapeutic effects of these agents are thought to be due to their activity as inhibitors of presynaptic NE and 5-HT reuptake. A variety of other receptor effects that differ from drug to drug impact clinical utility and adverse effect profiles.

The TCAs have been found to be consistently effective for panic disorder and generalized anxiety disorder. Imipramine (Tofranil®) has been shown to have efficacy comparable to that of alprazolam in suppressing panic attacks associated with panic disorder. In generalized anxiety disorder, imipramine has been shown to

Table 16.2 Trade name, usual dosage, and indicated uses of antidepressants

Generic name	Trade name	Usual daily dosage (in mg)	Indications	
MAO inhibitors				
Phenelzine	Nardil	45–90	MDD, PD	Used only as last-line agents due to drug interactions
Tranylcypromine	Parnate	20–50	MDD, PD	
TCAs and related agents				
Amitriptyline	Elavil	100–300	MDD, PD, pain	May have severe anticholinergic and cardiovascular side effects
Amoxapine	Asendin	200–600	Insomnia, enuresis	
Desipramine	Norpramin	100–300		
Doxepin	Sunequan	100–300		
Imipramine	Tofranil	100–300		
Maprtiline	Ludiomil	150–225		
Nortriptyline	Pamelor	50–200		
Protriptyline	Vivactil	20–60		
Trimipramine	Surmontil	100–300		
Clomipramine	Anafranil	100–250	OCD	Higher risk of seizures
SSRIs				
Citalopram	Celexa	20–40	MDD	Lower doses effective for
Fluoxetine	Prozac	Oct-80	MDD, PD, OCD	Depressive disorders; higher
Fluvoxamine	Luvox	100–300	OCD, SP	Doses generally needed for
Paroxetine	Paxil	20–60	MDD, OCD, GAD, PD, PTSD, SP	Anxiety disorders
Sertraline	Zoloft	50–200	MDD, OCD, PD, SP, PTSD	
Escitalopram	Lexapro	5–20	MDD, GAD	
Others				
Mirtazapine	Remeron	15–45	MDD	Sedating effects only at lower doses
Nefazodone	Serzone	300–600	MDD	
Trazadone	Desyrel	200–600	MDD	Used primarily as a hypnotic
Venlafaxine	Effexor	75–375	MDD, GAD, PD	

Note: MDD major depressive disorder, *PD* panic disorder, *OCD* obsessive compulsive disorder, *SP* social phobia, *PTSD* posttraumatic stress disorder, *GAD* generalized anxiety disorder

significantly improve symptoms in 60–70% of patients, again, comparable to the response seen with benzodiazepines (Spiegel et al., 2000). However, for all disorders, the effects may only be seen after 3–4 weeks of continuous treatment and tend to disappear after drug discontinuation. Clomipramine (Anafranil®), nortriptyline (Pamelor®), desipramine (Norpramin®), and other agents in this class may produce similar effects at therapeutic doses.

In the treatment of OCD, clomipramine has a level of efficacy not seen with other TCAs. This is thought to be due to this agent's more potent effects in inhibiting serotonin reuptake. About half of clomipramine-treated patients demonstrate moderate improvement (35% reduction in symptoms) in obsessive thoughts and compulsive behaviors (Spiegel et al., 2000).

Several significant liabilities with TCA therapy severely limit their utility. They are associated with anticholinergic side effects such as constipation, urinary retention, and blurred vision. Many of these agents are very sedating due to antihistamine effects. Small doses of amitriptyline (Elavil®) and doxepin (Sinequan®) are used as adjuncts for sleep disorders.

TCAs may cause cardiovascular effects such as arrhythmias and postural hypotension. There are also the risks of seizures, weight gain, light sensitivity, and cognitive impairment associated with TCA therapy. Because of these effects, these agents are usually an alternative to the newer, safer drugs for nonresponders.

Selective Serotonin Reuptake Inhibitors (SSRIs)

The selective serotonin reuptake inhibitors, fluoxetine (Prozac®), fluvoxamine (Luvox®), citalopram (Celexa®), paroxetine (Paxil®), sertraline (Zoloft®), and escitalopram (Lexapro®) are a structurally heterogeneous group of compounds that primarily exert their effects as inhibitors of presynaptic serotonin reuptake. Their relative lack of noradrenergic activity does not seem to reduce their antidepressant efficacy significantly. However, these agents have significant advantages in that their relative absence of anticholinergic and antihistaminic effects provides improved tolerability profiles.

The SSRIs have been shown to have a broad spectrum of activity in the treatment of anxiety disorders and other psychiatric conditions (Kent, Coplan, & Gorman, 1998). Drugs in this class have been approved for use in panic disorder, social phobia, OCD, and PTSD. In most cases, the SSRIs are considered the drugs of choice for these disorders (American Psychiatric Association, 2004, 2009). In panic disorder and social phobia, the SSRIs have shown consistent reductions in frequency of panic attacks after 10–12 weeks of treatment. As with clomipramine, SSRI therapy can reduce the symptoms of obsessions and compulsions associated with OCD. In PTSD, SSRIs have displayed benefits in reducing avoidance, arousal, and depressive symptoms. These agents have also been used to treat eating disorders, impulse control disorders, and premenstrual dysphoric disorder.

It appears that the efficacy for the treatment of anxiety disorders may be similar for all SSRIs. However, there are subtle differences between them. When choosing from among the SSRIs the clinician should consider the drugs' CNS-activating properties and the potential for drug interactions. Side effects include jitteriness (a significant problem for people with anxiety disorders), GI discomfort, sexual dysfunction, tremors, and headaches. Fluvoxamine and fluoxetine tend to have a high rate of CNS-activating effects. Paroxetine, less activating than the other agents in the class, does exhibit mild anticholinergic effects not seen with the other SSRIs. Fluvoxamine and fluoxetine exert potent inhibitory effects on the liver metabolism of many drugs, including many benzodiazepines. Citalopram and escitalopram appear to be relatively free of liver enzyme inhibitory effects.

Other Antidepressants

Venlafaxine (Effexor®) an inhibitor of NE, 5-HT, and dopamine reuptake, is an accepted treatment for generalized anxiety disorder. It can reduce the constant symptoms of anxiety associated with this disorder within the first few weeks of treatment. It is associated with dose-related increases in blood pressure, GI discomfort, and sexual dysfunction.

Nefazodone (Serozone®), a 5-HT–NE reuptake inhibitor, may be useful in the treatment of some anxiety disorders due to its antagonist activity at serotonin 5-HT2 receptors. Antagonism of this receptor subtype confers advantages not seen with other serotonin reuptake inhibitors. Nefazodone is associated with fewer acute anxiety symptoms and less sexual dysfunction than the SSRIs and venlafaxine. Typical side effects include sedation and postural hypotension. Less frequently, it has been associated with liver toxicity, which has caused the use of this drug to decline significantly.

Mirtazapine (Remeron®) is a facilitator of NE and serotonin neurotransmission that shares the 5-HT2 blockade profile with nefazodone. This agent has been found in small studies to be effective for phobic anxiety and post-traumatic stress. Mirtazapine may cause excessive sedation, weight gain, and postural hypotension.

Buspirone

Buspirone (BuSpar®), an anxiolytic, is structurally unrelated to benzodiazepines and antidepressants. It functions as a treatment for generalized anxiety in certain patients but is largely ineffective for most anxiety disorder subtypes, including panic disorders. It is a partial agonist at serotonin type 5-HT1A receptors. Anxiolytic effects of this agent are thought to be due to long-term adaptations that take place with neurotransmitter receptors (Stahl, 2000). Buspirone therefore requires continuous therapy for several weeks to achieve complete resolution of generalized anxiety.

As a chronic therapy, buspirone has advantages over traditional sedatives–hypnotics that clinicians may find useful. Unlike the benzodiazepines, buspirone is not associated

with CNS depression, dependence, and withdrawal symptoms upon discontinuation. This profile may make buspirone useful for the elderly and for individuals with a substance abuse history. However, anxiety sufferers may not be able to tolerate the 2- to 4-week latency to clinical effect. Indeed, patients with generalized anxiety disorder who have a history with benzodiazepine treatment tend not to be affected by buspirone therapy (Schweitzer, Rickels, & Lucky, 1986). Adverse effects of buspirone are mild and include headache, nausea, dizziness, and insomnia.

Antipsychotic Medications

Antipsychotic medications are primarily used for individuals that suffer from psychotic syndromes such as schizophrenia. Many of the newer (second-generation antipsychotic agents) also carry indications for bipolar disorder, both manic and depressed state, irritability associated with autism and other disorders. First-generation antipsychotics include agents such as haloperidol, thioridazine, chlorpromazine, thiothixene mesoridazine, and others. Newer or second-generation (sometimes also called "atypical") antipsychotic medications include risperidone (Risperdal®), olanzapine (Zyprexa®), clozapine (Clozaril®), quetiapine (Seroquel®), ziprasidone (Geodon®), aripiprazole (Abilify®), paliperidone (Invega®), iloperidone (Fanapt®), asenapine (Saphris®), and lurasidone (Latuda®). The older antipsychotic agents are largely ineffective in treating anxiety- or stress-related disorders (Grimsley, 1995). Their use is discouraged for treatment of anxiety disorders due to potentially serious side effects, such as tardive dyskinesia, sedation, cognitive difficulties, blood problems (clozapine), decreased blood pressure, and extrapyramidal symptoms (parkinsonian symptoms).

Several of the second-generation antipsychotics have been studied in clinical trials. Randomized controlled trials have been performed with quietiapine, risperidone, and olanzapine (Lorenz, Jackson, & Saitz, 2010). Open-label trials have been conducted with aripiprazole and ziprasidone. In a placebo-controlled trial, people receiving olanzapine added to a fluoxetine regimen showed a greater reduction in anxiety scores than those that received placebo. The results suggest there may be a therapeutic effect; however, the patients on olanzapine gained more than 10 pounds on average in 6 weeks. Quietiapine has also been systematically studied in anxiety, and positive results occurred in two studies. There are data to support the use of quietiapine in patients with anxiety disorders, particularly those with severe or treatment refractory anxiety. Studies with risperidone showed some improvement in patients with treatment refractory generalized anxiety. However, more work needs to be done to establish its place in therapy. The open-label trials with aripiprazole showed improvement in anxiety rating scales for the treatment of refractory generalized anxiety. These trials had significant limitations in that they had a small number of patients and were not placebo controlled. Further study is warranted (Lorenz 2010).

Atypical antipsychotic medications may be useful in patients with treatment refractory generalized anxiety or those with comorbid psychotic disorders.

They remain second- or third-line agents and should be reserved for those patients for whom other treatments have failed. These agents may also cause significant adverse such as weight gain, hyperglycemia, and hyperlipidemia.

Miscellaneous Agents

Beta-Adrenergic Blocking Agents

This group of medications includes popranolol (Inderal®), metoprolol (Lopressor®), nadolol (Corgard®), and atenolol (Tenormin®). By directly counteracting the increased adrenergic tone seen with stress, these agents are used to treat physical manifestations such as tremor and increased heart rate. They are not as effective as the benzodiazepines at treating anxiety. Beta-adrenergic blocking agents are effective in treating the acute physical reactions to a stressful event such as stage fright and public speaking. These drugs do not alter consciousness.

Beta-adrenergic agents should be used with caution in people who have asthma, since they can exacerbate the disorder. They should also be avoided in people with diabetes, since they can mask a hypoglycemic event. Side effects of the beta-adrenergic blocking agents include lethargy, sedation, low blood pressure, decreased heart rate, dizziness, tiredness, insomnia, and depression in susceptible individuals with chronic use (Grimsley, 1995).

Antihistamines

Antihistamines have also been used. The most commonly used antihistamines are dephenhydramine (Benadryl®) and hydroxyzine (Vistaril, Atarax®). These agents do not have anxiolytic effects and both possess significant sedative properties. There is no evidence that they are useful in primary anxiety disorders, but they may be useful in periodic and short-term use for insomnia. These agents also have potent anticholinergic effects and can cause side effects such as confusion, constipation, cognitive impairment, and nausea. Elderly patients, especially those who have dementia or are medically ill, are particularly susceptible to these side effects (American Geriatrics Society, 2012).

Barbiturates and Non-barbiturate Sedative–Hypnotics

Barbiturates such as phenobarbital should be used very sparingly, if at all, due to their side effects and abuse potential. These drugs are profoundly sedating and cause

cognitive difficulty. They are also potentially lethal in overdose. Non-barbiturates include meprobamate (Miltown®, Equanil), glutethimide (Doriden®), and ethchlorvynol (Placidyl®). The primary effect of these drugs is also sedation, and these agents are potentially lethal in overdose and may be no more effective than placebo in treating anxiety due to stressful events.

Summary

The armamentarium of available pharmacological agents for the treatment of stress-related syndromes and anxiety disorders is evolving as safer alternatives to the CNS-depressant drugs become available. Let us review some of the main points covered in this chapter:

- Symptomatic improvement of the symptoms of acute stress can be addressed with a short-term course of CNS depressants, such as benzodiazepines. Use of benzodiazepines for longer term therapy has the liabilities of development of tolerance, dependence, and withdrawal symptoms. However, the benzodiazepines do represent a significant improvement in drug safety over barbiturates and non-barbiturate sedative–hypnotics.
- Situational anxiety may respond to as-needed treatment with beta-adrenergic blocking agents. These drugs directly antagonize the NE-mediated peripheral manifestations of the stress response.
- Antihistamines may also be used episodically for sedation.
- Over the long term, most anxiety disorders are most appropriately treated with antidepressant drugs. Because these agents work by inducing long-term alterations in neurotransmitter receptor function and sensitivity, response may take several weeks of continuous treatment. However, improvements in the safety profiles of the newer antidepressants make these agents viable choices in the treatment of anxiety disorders.

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