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CHAPTER 20

Psychopharmacology and Electroconvulsive Therapy

The desire to take medicine is perhaps the greatest feature that distinguishes man from animals.

Sir William Osler

THE MODERN treatment era in psychiatry began with the introduction of effective psychotropic medication in the early 1950s. Until that time, the mainstay of treatment was psychotherapy, although prefrontal lobotomy and electroconvulsive therapy (ECT) had been recently introduced—each accompanied by the excitement that any new treatment generates. Their limitations soon became apparent, and after the introduction of antipsychotic and antidepressant medications, lobotomy fell into disuse, and the use of ECT became limited to a relatively small group of patients with severe illnesses, such as major depression.

■ Antipsychotics

Chlorpromazine was introduced in 1952 by the French psychiatrists Jean Delay and Pierre Deniker, after it was recognized that the drug

had powerful calming effects on agitated psychotic patients. Not only were agitated patients calmed, but the new drug seemed to diminish their terrifying hallucinations and troubling delusions. Many antipsychotics have since been developed and marketed, and while they are not curative, improvement can be dramatic. Medication effectiveness is generally sustained over years or even decades.

The antipsychotics can be roughly broken down into two groups. The first group consists of the older, or conventional, antipsychotics. The second group consists of a newer class of drugs, collectively referred to as second-generation antipsychotics (SGAs). They are also known as atypical antipsychotics. The SGAs have rapidly achieved popularity and now account for about 90% of prescriptions for antipsychotic drugs. Both the older antipsychotics and the SGAs ameliorate the symptoms of psychosis, including hallucinations, delusions, bizarre behavior, disordered thinking, and agitation. SGAs tend to have fewer side effects and are better tolerated, but concerns have emerged regarding their potential to induce metabolic side effects, such as impaired glucose tolerance. Although the SGAs were initially seen as more effective than the conventional antipsychotics, this belief is being reappraised in light of recent research. In a large government-funded clinical trial, four SGAs were compared with the conventional antipsychotic perphenazine. There were few differences among the drugs in terms of efficacy or tolerability. The most commonly used antipsychotics are listed in Table 20–1.

Antipsychotic drugs are primarily used to treat schizophrenia and other psychotic disorders, but they are also prescribed to patients with psychotic mood disorders and to patients whose psychoses are medically induced or due to drugs of abuse. Antipsychotics are often used to control aggressive behavior in mentally retarded patients, autistic patients, patients with borderline personality disorder, and patients with delirium or dementia. They also are prescribed to patients with Tourette's disorder to diminish the frequency and severity of vocal and motor tics.

Mechanism of Action

The potency of conventional antipsychotic drugs correlates closely with their affinity for the dopamine 2 (D_2) receptor, blocking the effect of endogenous dopamine at this site. The pharmacological profile of the SGAs differs in that they are weaker D_2 receptor antagonists than conventional antipsychotics, but are potent serotonin type 2A (5-HT_{2A}) receptor antagonists and have significant anticholinergic and antihistaminic activity as

TABLE 20–1. Common antipsychotic agents

Category	Drug (trade name)	Sedation	Orthostatic hypotension	Anticholinergic effects	Extrapyramidal effects	Equivalent dosage, mg	Dosage range, mg/day
Conventional agents							
Phenothiazines							
Aliphatics	Chlorpromazine (Thorazine)	H	H	M	M	100	50–1,200
Piperidines	Thioridazine (Mellaril)	H	H	H	L	95	50–800
Piperazines	Fluphenazine (Prolixin)	L	L	L	VH	2	2–20
	Fluphenazine decanoate	L	L	L	VH	—[a]	12.5–50 mg q 2 wk
	Perphenazine (Trilafon)	L	L	L	H	10	12–64
	Trifluoperazine (Stelazine)	L	L	L	H	5	5–40
Thioxanthenes	Thiothixene (Navane)	L	L	L	H	5	5–60
Butyrophenones	Haloperidol (Haldol)	L	L	L	VH	2	2–60
	Haloperidol decanoate	L	L	L	VH	—[a]	50–250 mg q 4 wk

TABLE 20–1. Common antipsychotic agents *(continued)*

Category	Drug (trade name)	Sedation	Orthostatic hypotension	Anticholinergic effects	Extrapyramidal effects	Equivalent dosage, mg	Dosage range, mg/day
Second-generation (atypical) agents)							
	Aripiprazole (Abilify)	L	VL	L	VL	7.5	10–15
	Asenapine (Saphris)	L	M	L	VL	5	10–20
	Clozapine (Clozaril)	H	H	H	VL	100	200–600
	Iloperidone (Fanapt)	L	M	L	VL	6	12–24
	Olanzapine (Zyprexa)	L	L	M	L	5	15–30
	Quetiapine (Seroquel)	M	L	L	VL	75	300–500
	Paliperidone (Invega)	L	M	L	L	4	3–12
	Risperidone (Risperdal)	L	M	L	L	2	2–6
	Ziprasidone (Geodon)	M	L	VL	L	6	40–160

Note. H = high; L = low; M = moderate; VH = very high; VL = very low.
[a]Long-acting ester; dosage is not directly comparable with that of standard compounds.

well. Central 5-HT_{2A} receptor antagonism is believed to broaden the therapeutic effect of the drug while reducing the incidence of extrapyramidal side effects (EPS) associated with D_2 antagonists.

Antipsychotics appear to exert their influence at mesocortical and mesolimbic dopaminergic pathways. Positron emission tomography (PET) studies show that D_2 receptor occupancy of 65%–70% correlates with maximal antipsychotic efficacy. These studies also show that antipsychotics block these receptors almost immediately, yet full response to the drugs takes weeks to develop. Although all antipsychotics block these receptors, a patient may respond preferentially to one drug but not to another. These observations suggest that antipsychotic drugs have other effects in the central nervous system (CNS) that may actually be responsible for their therapeutic properties, such as an action on second-messenger systems. Although many drug side effects can be linked to their dopamine-blocking properties (e.g., EPS), these drugs also block noradrenergic, cholinergic, and histaminic receptors to differing degrees, accounting for the unique side effect profile of each agent.

Pharmacokinetics

Absorption of orally administered antipsychotics is variable, and peak plasma levels are generally reached in 1–4 hours. Several antipsychotics are also available in an intramuscular preparation, and administration produces effects within 15 minutes. Injectable antipsychotics have much greater bioavailability than oral medication. Metabolism occurs mostly in the liver, largely by oxidation, so that these highly lipid-soluble agents are converted to water-soluble metabolites and excreted in the urine and feces. Excretion of antipsychotics tends to be slow because of drug accumulation in fatty tissue. Most of the conventional antipsychotics are highly protein bound (85%–90%). Nearly all antipsychotics have a half-life of 24 hours or longer and have active metabolites with longer half-lives. Depot formulations have even longer half-lives and may take 3–6 months to reach steady state.

The majority of conventional antipsychotics are metabolized by the cytochrome P450 (CYP) enzyme subfamilies, including 2D6, 1A2, and 3A4. Because of genetic variation, 5%–10% of whites poorly metabolize medications through the CYP2D6 pathway, as do a significant proportion of African Americans. This can result in higher antipsychotic blood levels than anticipated in some patients.

Plasma concentrations can be measured reliably for many antipsychotic drugs, but studies attempting to correlate plasma level with re-

sponse have been inconsistent. Haloperidol and clozapine blood levels appear to correlate with clinical response. With haloperidol, response appears to plateau at about 15 ng/mL, and for that reason higher levels are not recommended. Clozapine levels greater than 350 ng/mL appear to be effective for most patients. The other situations in which plasma levels are useful to obtain include the following:

- When patients' symptoms have not responded to standard dosage
- When antipsychotic medications are combined with drugs that can affect their pharmacokinetics (e.g., carbamazepine)
- When patient compliance needs to be assessed

Use in Acute Psychosis

A high-potency conventional antipsychotic such as haloperidol (5–10 mg/day) or one of the second-generation agents (e.g., risperidone, 4–6 mg/day; olanzapine, 10–20 mg/day; quetiapine, 150–800 mg/day; ziprasidone, 80–160 mg/day) is recommended as an initial choice for the treatment of acute psychosis. Antipsychotic effects generally start early after the drug is started but are cumulative over the ensuing weeks. An adequate trial should last from 4 to 6 weeks. The trial should be extended for another 4–6 weeks when the patient shows a partial response to the initial antipsychotic. If no response occurs after 4–6 weeks, then another drug should be tried. Clozapine is a second-line choice because of its propensity to cause agranulocytosis and the requirement to monitor the white blood cell count.

Highly agitated patients who are out of control require rapid control of their symptoms and should be given frequent, equally spaced doses of an antipsychotic drug. High-potency antipsychotics (e.g., haloperidol) can be given every 30–120 minutes orally or intramuscularly until agitation has subsided. A combination of an antipsychotic and a benzodiazepine may work even better in calming the patient (e.g., haloperidol, 5 mg, plus lorazepam, 2 mg), repeating the doses every 30 minutes until tranquilization is achieved.

Maintenance Treatment

Patients benefiting from short-term treatment with antipsychotic drugs are candidates for long-term maintenance treatment, which has as its goal the sustained control of psychotic symptoms and reduced risk of relapse. The following guidelines regarding relapse prevention were developed at an international conference:

1. Prevention of relapse is more important than risk of side effects because most side effects are reversible, and the consequences of relapse may be irreversible.
2. At least 1–2 years of treatment are recommended following the initial episode because of the high risk of relapse and the possibility of social deterioration from further relapses.
3. At least 5 years of treatment are indicated for multi-episode patients.
4. Chronic, or ongoing, treatment is recommended for patients who pose a danger to themselves or to others.

Research confirms that maintenance treatment with antipsychotics is effective in preventing relapse. When study results are pooled, 30% of those continuing to take medications relapse, compared with 65% of those taking placebo. About 75% of stable patients taken off their medication will relapse within 6–24 months.

Patients with schizoaffective disorder generally receive maintenance treatment with an antipsychotic in combination with a mood stabilizer when the patient has the bipolar type, or an antipsychotic combined with an antidepressant when the patient has the depressed type. Monotherapy with an SGA is a good alternative because these drugs seem to provide both mood stabilization and control of psychotic symptoms. SGAs can also be used for both acute and maintenance treatment of the manic phase of bipolar disorder.

Long-acting antipsychotic preparations are available for patients who are unable to take oral medication on a regular basis or who are noncompliant. There is no universally accepted method for converting a patient from oral to long-acting dosage forms, and dosing with sustained-release formulations must be individualized. A patient can be started on a dosage of 6.25 mg of fluphenazine decanoate intramuscularly every 2 weeks, and the dosage is titrated upward or downward based on the patient's therapeutic response and side effects. For haloperidol, a 400-mg loading dose in the first month, followed by a maintenance dose of 250 mg/month, produces a blood level of 10 ng/mL, and a dose of 150 mg/month produces a blood level between 5 and 6 ng/mL. The SGA risperidone is available in a long-acting injectable preparation (e.g., 25–50 mg every 2 weeks).

Further information about the use of antipsychotics in the treatment of schizophrenia and other psychotic disorders can be found in Chapter 5.

Adverse Effects

Despite their effectiveness in treating psychotic syndromes, antipsychotics have the potential to induce a variety of troublesome side effects. The

severity of these effects differs from drug to drug and corresponds with the drug's ability to affect a particular neurotransmitter system (e.g., dopaminergic, noradrenergic, cholinergic, histaminic). Because of their blockade of 5-HT_{2A} receptors, SGAs are less likely to induce EPS than are conventional antipsychotics. Side effect profiles of the antipsychotics are shown in Table 20–1.

Patients receiving long-term treatment with antipsychotic medication should be regularly monitored for the development of *tardive dyskinesia* (TD), a condition that consists of abnormal involuntary movements usually involving the mouth and tongue. Other parts of the body, including the trunk and extremities, may be affected. TD is thought to result when postsynaptic dopamine receptors develop a supersensitivity to dopamine following prolonged receptor blockade from antipsychotics. Second-generation drugs are much less likely to induce TD, although patients taking them should still be monitored.

The movements of TD are generally mild and tolerable, but about 10% of patients with TD develop a more malignant form of the disorder that can be totally disabling. Elderly patients, women, and patients with mood disorders appear more susceptible to developing TD, and it has a reported incidence of 5% per year of exposure to conventional antipsychotics in young persons and 30% after 1 year of treatment in the elderly.

Patients with TD present special problems because the treatment of choice is to stop the offending drug. Many patients will choose to continue taking the drug regardless of the TD because their lives may be intolerable without medication and the TD may be mild. One option is to switch the patient to an SGA, which will help mask the symptoms and will probably not worsen the TD. Vitamin E (i.e., 1,600 IU/day) may help alleviate the abnormal movements to some extent. If patients do not benefit from a 3-month trial, vitamin E should be discontinued.

Antipsychotic medications are also frequently associated with the development of *pseudoparkinsonism.* This side effect usually takes 3 or more weeks to develop. Patients develop symptoms typical of Parkinson's disease, including tremor, rigidity, and hypokinesia. *Akathisia,* the most common form of EPS, may appear in the first few weeks of antipsychotic treatment. This condition causes subjective feelings of anxiety and tension and objective fidgetiness and agitation. Patients may feel compelled to pace, move around in their chairs, or tap their feet. Treatment for both pseudoparkinsonism and akathisia generally consists of reducing the dosage of the antipsychotic drug whenever possible and/or adding an antiparkinsonian agent to the medication regimen. Akathisia has been treated with β-blockers or amantadine, a drug that

potentiates the release of dopamine in the basal ganglia. Benzodiazepines are also helpful in relieving the symptoms of akathisia. Clonidine has been used successfully to treat akathisia, but it may cause sedation and orthostatic hypotension.

Another potential neurological side effect is the *acute dystonic reaction,* which usually occurs during the first 4 days of treatment with antipsychotics. It is more common in younger persons, cocaine users, and in those treated with intramuscular injections of high-potency antipsychotics. A dystonia is a sustained contraction of the muscles of the neck, mouth, tongue, or occasionally other muscle groups that is subjectively distressing and often painful. Acute dystonias typically respond within 20–30 minutes to intramuscular benztropine (i.e., 1–2 mg) or diphenhydramine (i.e., 25–50 mg). There is little need for a standing dose of an antiparkinsonian agent after the dystonia resolves, because dystonic reactions usually do not recur. Patients beginning a course of a conventional antipsychotic can benefit from 2 weeks of prophylactic benztropine (1–4 mg/day) to help head off a dystonic reaction.

Antipsychotics, particularly low-potency compounds (e.g., chlorpromazine), commonly cause anticholinergic side effects including dry mouth, urinary retention, blurry vision, constipation, and exacerbation of narrow-angle glaucoma. These side effects are best treated by reducing the dosage of the drug or switching to a more potent agent (e.g., haloperidol) or to an SGA. Antiparkinsonian drugs commonly used to treat EPS, such as benztropine, can worsen these side effects. If urinary retention continues to be a problem, bethanechol (i.e., 15 mg three times daily) may help the patient empty his or her bladder. Bulk laxatives will help with constipation.

The most common cardiovascular side effect of the antipsychotics is *orthostatic hypotension,* mediated by α-adrenergic blockade. This side effect is caused more frequently by low-potency compounds (e.g., chlorpromazine). Antipsychotics generally do not cause arrhythmogenic effects when used in standard dosages. Chlorpromazine, thioridazine, pimozide, and the second-generation drugs aripiprazole and iloperidone have been associated with QT_c prolongation, which can be of concern for abnormal cardiac conduction or sudden death. Patients with a history of QT_c prolongation, a recent myocardial infarction, or uncompensated heart failure should avoid these drugs.

Agranulocytosis occurs in 0.8% of patients taking clozapine during the first year of treatment and peaks in incidence at 3 months of treatment. The best preventive measure is to be alert to the appearance of malaise, fever, and sore throat early in the course of therapy. Patients prescribed clozapine must have a baseline white blood cell count of no less than 3,500/mm^3 and an absolute neutrophil count of no less than

2,000 mm^3. Weekly complete blood counts and absolute neutrophil counts must be taken for the first 6 months, every 14 days for another 6 months, and monthly thereafter.

Hyperprolactinemia, often considered an unavoidable consequence of treatment with conventional antipsychotics, can induce amenorrhea, galactorrhea, gynecomastia, and impotence. SGAs are less likely to cause hyperprolactinemia, particularly quetiapine and aripiprazole. If it is not possible to reduce the dosage or change antipsychotics, the addition of bromocriptine (e.g., 2.5–7.5 mg twice daily) may be helpful.

The SGAs have been linked to abnormalities in several *metabolic parameters*, including glucose regulation, lipids, and weight gain. Clozapine and olanzapine appear to be the most likely of the drugs to cause weight gain, followed by risperidone and quetiapine; aripiprazole and ziprasidone are relatively weight neutral. Weight gain associated with long-term antipsychotic treatment can be significant and is a risk factor for diabetes and cardiovascular disease. Weight gain is also a frequent cause for treatment noncompliance. When these medications are prescribed, the American Diabetes Association recommends measuring baseline body mass index (BMI), waist circumference, blood pressure, and fasting glucose and lipid panels. BMI should be followed monthly for 3 months and then measured quarterly. Blood pressure, fasting glucose, and lipid panels should be followed up at 3 months and then yearly.

Other miscellaneous side effects of the antipsychotics include nonspecific skin rashes, retinitis pigmentosa (especially with dosages of thioridazine, >800 mg/day), fever (with clozapine), pigmentary changes in the skin (i.e., blue, gray, or tan), weight gain, cholestatic jaundice (with chlorpromazine), reduced libido, and inhibition of ejaculation (with thioridazine). Low-potency conventional antipsychotics are associated with a risk for seizures, especially at higher dosages (e.g., >1,000 mg/day of chlorpromazine). The drugs are not contraindicated in epilepsy patients as long as they receive adequate treatment with anticonvulsants. All antipsychotics except clozapine are listed as Category C drugs by the U.S. Food and Drug Administration (FDA), meaning that pregnancy risk cannot be ruled out. Clozapine is listed as Category B, meaning that there is no evidence of pregnancy risk in humans.

All conventional antipsychotics have the potential to cause *neuroleptic malignant syndrome* (NMS), a rare idiosyncratic reaction that does not appear to be dose related. SGAs appear to be less likely to induce NMS. Considered a medical emergency, the syndrome is characterized by rigidity, high fever, delirium, and marked autonomic instability. Serum levels of creatinine phosphokinase and of liver enzymes are generally elevated. There is no standard approach to the treatment of NMS. Both

the muscle relaxant dantrolene and the dopamine agonist bromocriptine have been used to treat NMS. Stopping the offending antipsychotic drug and providing supportive care may be as effective. ECT can be used in severe cases not responding to medical management. Once the patient has recovered, antipsychotics can be cautiously reintroduced after a 2-week wait. Selecting an agent from a different antipsychotic class (e.g., chlorpromazine rather than haloperidol, if haloperidol caused the NMS) or switching to an SGA is advisable.

Rational use of antipsychotics

1. A high-potency conventional antipsychotic or one of the SGAs should be given as first-line treatment.
   - SGAs are effective and well tolerated and have less potential to induce EPS.
2. Second-line drug choices include the other conventional antipsychotics.
3. A drug trial should last 4–6 weeks.
   - The trial should be extended when there is a partial response that has not plateaued and shortened when no response occurs or side effects are intolerable or unmanageable.
   - Aripiprazole or ziprasidone may be the better choice in patients at risk for weight gain.
   - Quetiapine or aripiprazole may be favored when low EPS and low prolactin levels are desired.
4. All antipsychotics should be started at a low dosage and gradually increased to fall within a therapeutic range.
   - Evidence suggests that blood levels can help guide dosage adjustments for haloperidol and clozapine.
5. There is little reason to prescribe more than one antipsychotic agent. Using two or more such drugs increases adverse effects and adds little clinical benefit.
6. Because of its risk of agranulocytosis and need for monitoring of the white blood cell count, clozapine should be reserved for patients with treatment-refractory illness.
7. Many patients will benefit from chronic antipsychotic administration.
   - Patients should be carefully monitored for evidence of metabolic abnormalities, including weight gain, glucose dyscontrol, and lipid abnormalities.

■ Antidepressants

Not long after chlorpromazine appeared in the late 1950s, the antidepressant imipramine was synthesized in an attempt by researchers to find additional compounds for the treatment of schizophrenia. It soon became apparent that imipramine had little effect on hallucinations and delusions; instead, it alleviated depression in patients who were both psychotic and depressed. This finding led to the development of the tricyclic antidepressants (TCAs). Modifications of the three-ring chemical structure followed as additional TCAs were produced, including amitriptyline and desipramine.

At about the same time that TCAs were synthesized, the antidepressant properties of monoamine oxidase inhibitors (MAOIs) were discovered. Iproniazid, an antibiotic used to treat tuberculosis, was found to relieve depression in tuberculosis patients. Later work showed that the drug also was effective in relieving depression. No longer used as an antidepressant, iproniazid has been succeeded by more effective MAOIs, including phenelzine and tranylcypromine.

A second and third generation of antidepressants have since been developed, some of which differ structurally from both the TCAs and the MAOIs. In the early 1980s, tetracyclic compounds (also referred to as *heterocyclics*) with a somewhat similar structure and comparable properties were marketed, including maprotiline and amoxapine. Another group of antidepressants, collectively known as the *selective serotonin reuptake inhibitors* (SSRIs), was developed in the late 1980s and early 1990s. Other antidepressants also were introduced but do not fit within any particular grouping, including bupropion, mirtazapine, venlafaxine, and duloxetine. The antidepressants are all thought to work by altering levels of neurotransmitters in the CNS. With minor exceptions, all are equally effective, differing primarily in their adverse effects and potency. A comparison of commonly prescribed antidepressants is presented in Table 20–2.

The primary indication for antidepressants is the acute and maintenance treatment of major depression. The effectiveness of antidepressants is unquestioned, and approximately 65%–70% of patients receiving an antidepressant will respond within 4–6 weeks. In contrast, the placebo response rate in depression ranges from 25% to 40%. Depressed patients with melancholic symptoms (e.g., diurnal variation, psychomotor agitation or retardation, terminal insomnia, pervasive anhedonia) may respond better to antidepressants than do other patients. Secondary depressions (i.e., depressions that follow or complicate other

TABLE 20–2. Commonly used antidepressants

Category	Drug (trade name)	Sedation	Anti-cholinergic effects	Orthostatic hypotension	Sexual dysfunction	GI effects	Activation/ Insomnia	Half-life, h	Target dosage, mg	Dosage range, mg/day
Selective serotonin reuptake inhibitors										
	Citalopram (Celexa)	VL	None	None	VH	H	VL	35	20	10–60
	Escitalopram (Lexapro)	VL	None	None	VH	H	VL	25	10	10–30
	Fluoxetine (Prozac)	None	None	None	VH	H	VH	24–72	20	20–80
	Fluvoxamine (Luvox)	M	None	None	VH	H	L	15	200	100–300
	Paroxetine (Paxil)	L	L	None	VH	H	L	20	20	20–50
	Sertraline (Zoloft)	VL	None	None	VH	VH	M	25	100	50–200

TABLE 20–2. Commonly used antidepressants *(continued)*

Category	Drug (trade name)	Sedation	Anti-cholinergic effects	Orthostatic hypotension	Sexual dysfunction	GI effects	Activation/ Insomnia	Half-life, h	Target dosage, mg	Dosage range, mg/day
Other antidepressants										
	Bupropion (Wellbutrin)	None	None	None	None	M	H	12	300	150–450
	Desvenlafaxine (Pristiq)	L	None	VL	H	VH	M	10	50	50–400
	Duloxetine (Cymbalta)	VL	L	None	VL	H	L	8–17	60	40–60
	Mirtazapine (Remeron)	H	None	None	None	VL	None	20–40	30	15–45
	Nefazodone (Serzone)	H	None	L	None	M	VL	2–4	300	100–600
	Trazodone (Desyrel)	VH	VL	VH	None	M	Yes	6–11	400	300–800
	Venlafaxine (Effexor)	L	None	VL	H	VH	M	3–5	225	75–350

TABLE 20–2. Commonly used antidepressants *(continued)*

Category	Drug (trade name)	Sedation	Anti-cholinergic effects	Orthostatic hypotension	Sexual dysfunction	GI effects	Activation/ Insomnia	Half-life, h	Target dosage, mg	Dosage range, mg/day
Tricyclics										
	Amitriptyline (Elavil)	VH	VH	VH	H	VL	None	9–46	150	50–300
	Clomipramine (Anafranil)	VH	VH	VH	VH	VL	None	23–122	150	50–300
	Desipramine (Norpramin)	M	M	M	H	VL	VL	12–28	150	50–300
	Doxepin (Sinequan, Adapin)	VH	VH	VH	H	VL	None	8–25	200	50–300
	Imipramine (Tofranil)	H	VH	VH	H	VL	None	6–28	200	50–300
	Nortriptyline (Pamelor)	M	M	M	H	VL	None	18–56	100	20–150

TABLE 20–2. Commonly used antidepressants *(continued)*

Category	Drug (trade name)	Sedation	Anti-cholinergic effects	Orthostatic hypotension	Sexual dysfunction	GI effects	Activation/ Insomnia	Half-life, h	Target dosage, mg	Dosage range, mg/day
Monoamine oxidase inhibitors										
	Isocarboxazid (Marplan)	M	L	H	H	VL	L	—[a]	30	10–50
	Phenelzine (Nardil)	L	M	VH	H	VL	L	—[a]	60	15–90
	Tranyl-cypromine (Parnate)	None	M	VH	L	VL	M	—[a]	30–40	20–90

Note. GI = gastrointestinal; H = high; L = low; M = moderate; VH = very high; VL = very low.
[a]Maximal inhibition by monoamine oxidase inhibitors is achieved in 5–10 days.

psychiatric disorders); depressions accompanied by anxiety, somatization, or hypochondriasis; and depressions accompanied by personality disorders (often called *neurotic depression*) respond less well than do depressions without these features. Chronic forms of depression, including dysthymia, also respond to antidepressants, although treatment results are not as robust as those seen in acute forms of depression.

Other disorders that are treated with antidepressants include the depressed phase of bipolar disorder, panic disorder, agoraphobia, obsessive-compulsive disorder (OCD), social phobia, generalized anxiety disorder (GAD), posttraumatic stress disorder (PTSD), bulimia nervosa, and certain childhood conditions (e.g., enuresis, school phobia). Because antidepressants are used to treat a broad range of psychiatric disorders, the term *antidepressant* is a misnomer.

Selective Serotonin Reuptake Inhibitors

The SSRIs have rapidly become the most widely prescribed antidepressants in the United States ever since fluoxetine was introduced in 1988. Six SSRIs are currently marketed: citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, and sertraline. They are structurally dissimilar but share similar pharmacological properties involving their relatively selective serotonin reuptake inhibition. They largely lack the side effects of TCAs caused by blockade of muscarinic, histaminic, and α-adrenergic receptors. For this reason, SSRIs are generally better tolerated than TCAs and are safer in overdose. Also, because they are unlikely to affect seizure threshold or cardiac conduction, SSRIs are safer for patients with epilepsy or cardiac conduction defects.

The SSRIs are remarkably versatile and are used to treat major depression, panic disorder, OCD, social phobia, PTSD, bulimia nervosa, and probably many other disorders as well. However, marketing strategies have led to the following FDA-approved indications in adults:

- Major depression—citalopram, escitalopram, fluoxetine, paroxetine, and sertraline
- Obsessive-compulsive disorder—fluoxetine, fluvoxamine, paroxetine, and sertraline
- Social anxiety disorder—fluoxetine, paroxetine, and sertraline
- Panic disorder—paroxetine and sertraline
- Generalized anxiety disorder—escitalopram and paroxetine
- Posttraumatic stress disorder—paroxetine and sertraline
- Premenstrual dysphoric disorder—fluoxetine and sertraline
- Bulimia nervosa—fluoxetine

All of the SSRIs are metabolized by the liver, but only fluoxetine and sertraline have active metabolites. Fluoxetine has the longest half-life at 2–3 days, and its major metabolite, norfluoxetine, has a half-life of 4–16 days. The other SSRIs have half-lives ranging from 15 to 35 hours. The active metabolite of sertraline, norsertraline, has a half-life of 2–4 days. All are well absorbed from the gut and reach peak plasma levels within 4–8 hours.

The SSRIs share a similar side-effect profile, with only subtle differences among them. Side effects are largely dose related and can include mild nausea, loose bowel movements, anxiety or hyperstimulation (which leads to jitteriness, restlessness, muscle tension, and insomnia), headache, insomnia, sedation, and increased sweating. Patients sometimes report other side effects, including weight gain or weight loss, bruxism, vivid dreams, skin rash, and amotivation.

Sexual dysfunction is relatively common in both men and women treated with SSRIs. These drugs can decrease libido and cause ejaculatory delay or failure in men and anorgasmia in women. For this reason, SSRIs are sometimes prescribed to men to treat premature ejaculation. For persistent complaints of sexual dysfunction, management strategies include lowering the dosage, switching to one of the newer non-SSRI antidepressants (e.g., bupropion, duloxetine), or coadministering another medication as an antidote (e.g., bupropion, 75–300 mg/day, or cyproheptadine, 4–8 mg, taken 1–2 hours before sexual activity). Sildenafil and other medications used to treat male erectile dysfunction also appear to be effective in treating SSRI-related sexual dysfunction.

Adverse effects tend to diminish over time, but they persist in some patients. Fluoxetine is the most likely, and escitalopram the least likely, to induce adverse effects. When hyperstimulation is problematic, it can be managed by lowering the dosage, switching to another SSRI, or switching to one of the newer non-SSRI antidepressants. A β-blocker (e.g., propranolol, 10–30 mg three times daily) can be helpful in treating subjective jitteriness and tremor. Benzodiazepines (e.g., lorazepam, 0.5–1 mg twice daily) can be prescribed to counteract this side effect as well. Because complaints of hyperstimulation tend to diminish over time, adjunctive medications may not be needed long-term. Trazodone (e.g., 50–150 mg at bedtime) can be effective in treating insomnia, although men should be warned of its rare propensity to cause priapism (a sustained, painful erection).

When SSRIs are discontinued, many patients develop a *discontinuation syndrome.* The exception is fluoxetine, which self-tapers because of the long half-life of both the parent compound and its major metabolite. Symptoms include nausea, headache, vivid dreams, irritability, and dizziness. These often begin within days of drug discontinuation and continue for 2 weeks or longer. The symptoms can be minimized by tapering the drug slowly over several weeks. The short-term use of a benzodiazepine is often helpful.

Rare cases of a *serotonin syndrome* have been reported with the use of these drugs, particularly among patients who have concurrently taken two or more drugs that boost CNS serotonin levels. Typical symptoms include lethargy, restlessness, mental confusion, flushing, diaphoresis, tremor, and myoclonic jerks. Untreated, the serotonin syndrome can progress to hyperthermia, hypertonicity, rhabdomyolysis, renal failure, and death. Several deaths have been reported in patients taking a combination of an SSRI and MAOI, presumably as a result of this syndrome. Because of the potential lethality of this combination, when a patient is switched from an SSRI to an MAOI, a sufficient time must pass to ensure that the SSRI has been fully eliminated from the body before initiating treatment with an MAOI. With fluoxetine, this means that about 6 weeks must pass.

The SSRIs each inhibit one or more cytochrome P450 isoenzymes to a substantial degree and have the potential to cause clinically important drug interactions. For that reason, care should be taken when prescribing adjunctive or concurrent medication metabolized through this enzyme system. This means that SSRIs may induce a several-fold increase in the levels of coprescribed drugs that are dependent on the inhibited isoenzymes for their clearance. Fluoxetine, fluvoxamine, and paroxetine are the most likely to cause drug interactions, whereas citalopram and escitalopram have less potential to do so. See Table 20–3 for a description of the SSRIs and the isoenzyme systems inhibited and coadministered drugs affected.

Given their widespread use, the SSRIs are undoubtedly being used during pregnancy and breast-feeding. That said, all of the SSRIs are included in FDA risk Category C (pregnancy risk cannot be ruled out), except for paroxetine, which is in Category D (positive evidence of risk). The evidence base is largest with fluoxetine, which appears to be safe. There is some evidence that paroxetine and sertraline are associated with cardiovascular anomalies. The SSRIs are secreted in breast milk and should probably be avoided in women who are breast-feeding.

TABLE 20–3. Selective serotonin reuptake inhibitors (SSRIs) and other newer antidepressants and potentially important drug interactions

Antidepressant	Enzyme system inhibited	Potential drug interactions
Fluoxetine	2D6	Secondary TCAs, haloperidol, type 1C antiarrhythmics
	2C	Phenytoin, diazepam
	3A4	Carbamazepine, alprazolam, terfenadine
Sertraline	2D6	Secondary TCAs, antipsychotics, type 1C antiarrhythmics
	2C	Tolbutamide, diazepam
	3A4	Carbamazepine
Paroxetine	2D6	Secondary TCAs, antipsychotics, type 1C antiarrhythmics, trazodone
Fluvoxamine	1A2	Theophylline, clozapine, haloperidol, amitriptyline, clomipramine, imipramine, duloxetine
	2C	Diazepam
	3A4	Carbamazepine, alprazolam, terfenadine, astemizole
Nefazodone	3A4	Alprazolam, triazolam, terfenadine, astemizole, carbamazepine
Duloxetine	1A2	Fluvoxamine, theophylline, clozapine, haloperidol, amitriptyline, clomipramine, imipramine
	2D6	Secondary TCAs, antipsychotics, type 1C antiarrhythmics, trazodone

Note. TCAs=tricyclic antidepressants.
Source. Adapted from Nemeroff et al. 1996.

Other Newer Antidepressants

Bupropion

Bupropion has a unique chemical structure similar to that of psychostimulants, which may account for certain shared properties. Because its primary metabolite, hydroxybupropion, inhibits the reuptake of dopamine and norepinephrine, the drug has been called a dopamine-norepinephrine reuptake inhibitor. Bupropion is used for the treatment of major depression but is also FDA approved for the treatment of smoking cessation under the trade name Zyban. An extended-release form of the drug has been approved as a treatment for seasonal affective disorder. Bupropion also has been used to treat attention-deficit/hyperactivity disorder. It is not effective in treating panic disorder, OCD, social phobia, or other anxiety syndromes.

Bupropion is rapidly absorbed following oral administration, and peak concentrations are achieved within 2 hours, or 3 hours after administration of the sustained-release formulation. Elimination is biphasic, with an initial phase of approximately 1.5 hours and a second phase lasting about 14 hours. The biphasic decline for the sustained-release formulation is less pronounced than that of the immediate-release formulation.

Bupropion is relatively well tolerated, having minimal effects on weight gain, cardiac conduction, or sexual functioning. The most common side effects are headache, nausea, anxiety, tremors, insomnia, and increased sweating. These symptoms generally subside with time. Restlessness and tremor can be treated with propranolol (e.g., 10–30 mg three times daily). The patient may benefit from short-term coadministration of a benzodiazepine tranquilizer.

The main disadvantage of bupropion is that the incidence of seizures increases substantially at dosages greater than 450 mg/day. For this reason, the drug is contraindicated in patients with a seizure disorder or an eating disorder that may be associated with a lower seizure threshold. The main risk of overdose is the development of seizures.

Duloxetine

Duloxetine is a potent inhibitor of both serotonin and norepinephrine and for that reason is designated—along with venlafaxine and desvenlafaxine—as a selective serotonin-norepinephrine reuptake inhibitor (SNRI). The drug is FDA approved to treat major depression and generalized anxiety disorder and also is indicated to treat diabetic neuropathic pain and fibromyalgia. Duloxetine is well absorbed from the gut and is

metabolized in the liver mainly through P450 isoenzymes CYP2D6 and CYP1A2. Its major metabolites have minimal pharmacologic activity. The half-life ranges from 8 to 17 hours.

Duloxetine is well tolerated. The most common side effects include insomnia, asthenia, nausea, dry mouth, and constipation. The drug is not associated with weight gain, and rates of sexual dysfunction are low. Duloxetine is metabolized through the CYP isoenzymes, creating a potential for drug interactions (see Table 20–3). Because of reports of hepatotoxicity, the drug should be used with caution in persons with chronic liver disease, or in those with substantial alcohol use. It should not be combined with MAOIs because of the potential for a serotonin syndrome. The drug has been fatal in overdose at doses as low as 1,000 mg.

Mirtazapine

Mirtazapine has a dual mode of action and enhances both serotonergic and noradrenergic neurotransmission but is not a reuptake inhibitor. The drug is also a potent histamine antagonist, a moderate α-adrenergic antagonist, and a moderate antagonist at muscarinic receptors. Mirtazapine is FDA indicated for the treatment of major depression. The drug is well absorbed from the gut and is 85% protein bound. It has a half-life of 20–40 hours. Mirtazapine is well tolerated but may cause somnolence, increased appetite, and weight gain. Because of its long half-life, it needs to be taken only once daily. The drug has little effect on the cardiovascular system and minimally affects sexual functioning. Mirtazapine is unlikely to be associated with cytochrome P450–mediated drug interactions. One potential advantage is its early effect on reducing anxiety symptoms and sleep disturbance.

Somnolence occurs in more than half of the patients receiving mirtazapine, although tolerance develops after the first few weeks of treatment. Rare cases of agranulocytosis have been reported. In these cases, patients recovered after medication discontinuation. Routine laboratory monitoring is not currently recommended because this side effect is rare, but the development of fever, chills, sore throat, or other signs of infection in association with a low white blood cell count warrants close monitoring and discontinuation of the drug. The drug is unlikely to be fatal in overdose. The drug should not be used in combination with an MAOI.

Nefazodone

Nefazodone combines blockade of the 5-HT_2 receptor with weak inhibition of neuronal serotonin reuptake and is structurally similar to trazodone. The drug is indicated for the treatment of major depression. Side effects include nausea, somnolence, dry mouth, dizziness, constipation, asthenia, and blurred vision. The drug is generally well tolerated, and these side effects are considered benign. Nefazodone does not appear to alter seizure threshold, does not cause weight gain, and does not impair sexual functioning. The drug has the potential to inhibit the cytochrome P450 3A3/4 isoenzyme, which can lead to drug-drug interactions when other medications metabolized by that isoenzyme are coadministered. Drawbacks include the need for twice-daily dosing and a slow dosage titration. Nefazodone does not appear to be fatal in overdose. In rare cases, potentially irreversible hepatic failure has been associated with the drug. This led the FDA to issue a black box warning in 2002, and later the trade product Serzone was voluntarily withdrawn from the market. Generic formulations remain available.

Trazodone

Trazodone is a weak inhibitor of serotonin but also blocks 5-HT_2 receptors. The drug is a triazolopyridine derivative that shares the triazolo ring structure with alprazolam, a benzodiazepine. Trazodone is indicated for the treatment of major depression. The drug is readily absorbed from the gastrointestinal tract, reaches peak plasma levels in 1–2 hours, and has a half-life of 6–11 hours. Trazodone is metabolized by the liver, and 75% of its metabolites are excreted in the urine. Adverse effects are partially mediated by α-adrenergic antagonism and antihistaminic activity. The drug should not be coadministered with MAOIs. Concurrent use with antihypertensives may lead to hypotension.

The most common adverse effects are sedation, orthostatic hypotension, dizziness, headache, nausea, and dry mouth. These effects are mostly benign. Trazodone does not block anticholinergic receptors, so urinary retention and constipation are uncommon. The drug has no significant effect on cardiac conduction, although there are reports of increased ventricular irritability in patients with preexisting cardiac conduction defects or ventricular arrhythmias. It is unlikely to be fatal in overdose. Because trazodone is so sedating, it is widely used to treat insomnia (e.g., 50–150 mg at bedtime).

One concern with trazodone is that in rare cases it has been associated with priapism, which can be irreversible and require surgical intervention. Men prescribed trazodone should be warned of this side effect and be advised to report any change in the frequency or firmness of erections. The drug should be immediately discontinued if these changes occur. Immediate medical treatment should be sought for sustained erections.

Venlafaxine and Desvenlafaxine

Both venlafaxine and its primary active metabolite desvenlafaxine are classified as SNRIs and have minimal effect on other neurotransmitter receptors. Venlafaxine has an indication for the treatment of major depression, but its extended-release formulation is FDA approved for the treatment of generalized anxiety disorder, social anxiety disorder, and panic disorder. The drug is rapidly absorbed from the gut and is 98% bioavailable; its half-life is about 4 hours. Desvenlafaxine is marketed in a sustained-release formulation and is indicated for the treatment of major depression. Like the parent compound, desvenlafaxine is well absorbed orally and has a half-life of about 10 hours. Both venlafaxine and desvenlafaxine are metabolized by the liver and are renally excreted.

The side-effect profile of venlafaxine and desvenlafaxine is similar to that of the SSRIs and includes hyperstimulation, sexual dysfunction, and transient withdrawal symptoms. The drugs do not affect cardiac conduction or lower seizure threshold and generally are not associated with sedation or weight gain. Blood pressure monitoring is recommended with the use of either drug because of dose-dependent increases in mean diastolic blood pressure in some patients, particularly those with hypertension. The drugs are unlikely to inhibit cytochrome P450 isoenzymes, so drug-drug interactions are unlikely. Both drugs are contraindicated in patients taking MAOIs because of the risk of serotonin syndrome. The drugs are generally not fatal in overdose. The main drawback with venlafaxine is that it is generally taken twice daily, although the extended-release formulation can be taken once daily.

Tricyclic and Tetracyclic Antidepressants

TCAs are believed to work by blocking the reuptake of both norepinephrine and serotonin at the presynaptic nerve ending. The tertiary amines (e.g., amitriptyline, imipramine, doxepin) primarily block serotonin reuptake, whereas the secondary amines (e.g., desipramine, nortriptyline, protriptyline) mainly block norepinephrine reuptake. Clomipramine is an exception because it is a relatively selective serotonin reuptake inhibitor. All of these drugs also block muscarinic, histaminic, and α-adrenergic receptors. The degree of blockade corresponds with the side effect profile of the agent as shown in Table 20–2. (The tetracyclics maprotiline and amoxapine are rarely used and are not included in the table.)

TCAs are well absorbed orally; they undergo an enterohepatic cycle, and peak plasma levels develop 2–4 hours after ingestion. They are

highly bound to plasma and tissue proteins and are fat soluble. TCAs are metabolized by the liver, and their metabolites are excreted through the kidneys. All TCAs have active metabolites, and there is as much as a tenfold variation in steady-state plasma levels of TCAs among individuals. These differences are primarily caused by individual variations in the way the liver metabolizes the drugs. Their half-lives vary but are generally in the range of 1 day. Steady-state plasma levels are achieved after five half-lives; half-life, in turn, is dependent on metabolism of the drug by hepatic microsomal enzymes. Blood levels tend to be increased by drugs that inhibit the cytochrome P450 system, including chlorpromazine and other antipsychotics, disulfiram, cimetidine, estrogens, methylphenidate, and many of the SSRIs.

The established therapeutic range for imipramine (the total for imipramine plus its metabolite desipramine) is generally thought to be greater than 200 ng/mL. For nortriptyline, the therapeutic range is between 50 and 150 ng/mL. Desipramine plasma levels greater than 125 ng/mL are considered therapeutic. Plasma blood levels can be measured for the other TCAs but are not clinically meaningful. Levels should be obtained 12 hours after the last dose.

There is no reason to routinely obtain plasma levels, particularly when the patient is doing well. Blood levels are helpful in cases of drug overdose but may also be useful when evaluating a patient's failure to respond adequately, significant symptoms of toxicity, or suspected noncompliance; in establishing a therapeutic window; and in setting dosage levels for a patient with significant cardiac or other medical disease (when it is desirable to keep the blood level at the lower range of the therapeutic value).

TCAs commonly cause sedation, orthostatic hypotension, and anticholinergic side effects such as constipation, urinary hesitancy, dry mouth, and visual blurring. Each TCA differs in its propensity to cause these effects. Tertiary amines (e.g., amitriptyline, imipramine, doxepin) tend to cause more pronounced side effects. Tolerance usually develops to anticholinergic side effects and sedation, but TCAs should be used with caution in patients with prostatic enlargement and narrow-angle glaucoma. Elderly patients should have their blood pressure carefully monitored because drug-induced hypotension can lead to falls and resultant fractures.

Antihistaminic effects include sedation and weight gain. α-Adrenergic blockade causes orthostatic hypotension and reflex tachycardia. Miscellaneous side effects of TCAs include tremors, pedal edema, myoclonus, restlessness or hyperstimulation, insomnia, nausea and vomiting, electroencephalographic changes, rashes or allergic reactions, confusion,

and seizures. It is uncertain whether TCAs are teratogenic, but their use in the first trimester of pregnancy should be avoided. Because a metabolite of the tetracyclic amoxapine is an antipsychotic, the drug can induce EPS, including TD.

Cardiovascular side effects tend to be the most worrisome. All TCAs prolong cardiac conduction, much like quinidine or procainamide, and carry the risk of exacerbating existing conduction abnormalities. Patients with low-grade abnormalities such as first-degree atrioventricular block or right bundle branch block should use these medications cautiously, and dosage increases should be accompanied by serial electrocardiograms. Patients with a higher-grade block (e.g., second-degree atrioventricular block) should not take TCAs. As a general rule, an SSRI or one of the newer antidepressants that does not prolong cardiac conduction (e.g., mirtazapine) should be used in patients with cardiac conduction defects.

A withdrawal syndrome occurs in some patients who have been taking high doses of TCAs for weeks or months. Symptoms can begin within days following abrupt discontinuation of the drug and include anxiety, insomnia, headache, myalgia, chills, malaise, and nausea. This syndrome usually can be prevented by a gradual taper of 25–50 mg/week. If this is not possible, small doses of an anticholinergic medication such as diphenhydramine (e.g., 25 mg two to three times daily) may help relieve symptoms.

Monoamine Oxidase Inhibitors

MAOIs inhibit monoamine oxidase (MAO), an enzyme responsible for the degradation of tyramine, serotonin, dopamine, and norepinephrine. Blocking this enzymatic process leads to an increase in CNS levels of these monoamines. Two types of MAO have been identified: MAO-A, which is found in the brain, liver, gut, and sympathetic nerves, and MAO-B, which is found in the brain, liver, and platelets. MAO-A acts primarily on serotonin and norepinephrine, and MAO-B acts primarily on phenylethylamine; both act on dopamine and tyramine. Inhibitors of MAO-A may be more effective as antidepressants.

The four MAOIs commonly used in the United States are isocarboxazid, phenelzine, tranylcypromine, and selegiline. A transdermal patch formulation of selegiline is FDA approved for the treatment of major depression.

MAOIs are readily absorbed when orally administered. They do not have active metabolites, and the drugs are renally excreted. MAOIs irreversibly inhibit MAO, reaching maximum inhibition after 5–10 days.

It is generally thought that platelet MAO activity, which reflects MAO inhibition, needs to be reduced by 80% to achieve an antidepressant response. The body takes approximately 2 weeks after the discontinuation of MAOIs to synthesize enough new MAO to restore its baseline concentrations. Plasma levels are not measured for the MAOIs.

MAOIs are thought to be particularly effective in forms of depression accompanied by significant anxiety. They have been found effective in treating panic disorder and agoraphobia, social phobia, PTSD, and bulimia nervosa. They also are thought to be particularly valuable in the treatment of *atypical depression*. Patients with this condition usually have a mixture of anxiety and depression, along with a reversal of diurnal variation (i.e., worse in the evening), hypersomnia, mood lability, hyperphagia, and a sensation of leaden paralysis.

The MAOIs have minimal anticholinergic and antihistaminic effects. They are potent α-adrenergic blockers, which results in a high frequency of orthostatic hypotension. If severe, this effect can be counteracted by the addition of salt and salt-retaining steroids such as fluorohydrocortisone (Florinef). Elastic support stockings may also be helpful. Other common side effects include sedation or hyperstimulation (e.g., agitation), insomnia, dry mouth, weight gain, edema, and sexual dysfunction.

The most serious side effect results from the concomitant ingestion of an MAOI and substances containing tyramine, leading to severe hypertension and death or stroke in rare cases. Patients taking MAOIs must follow a special low-tyramine diet. Because MAOIs can interact with sympathomimetics (e.g., amphetamines) to produce a hypertensive crisis, patients need to be aware of potential interactions with prescribed and over-the-counter medications. MAOIs also have a potentially lethal interaction with meperidine, the mechanism of which is not fully understood but may have to do with serotonin agonism. Because selegiline primarily affects MAO-B, there is no need to follow a tyramine-free diet when using the 6-mg patch, but at higher doses the diet is recommended. (See Table 20–4 for a list of restricted foods and medications for those prescribed MAOIs.) Patients should be encouraged to carry a list of prohibited foods with them and to wear a medical bracelet indicating that they are taking an MAOI.

When symptoms of the hypertensive crisis occur (e.g., headache, nausea, or vomiting), patients should be instructed to immediately seek medical attention at a medical clinic or hospital emergency department. There, patients can be treated with intravenous phentolamine (e.g., 5 mg). Patients who do not have easy access to medical care should be advised to carry a 10-mg tablet of nifedipine with them; its α-blocking

TABLE 20–4. Dietary instructions for patients taking monoamine oxidase inhibitors (MAOIs)

Foods to avoid

Cheese: all cheeses except cottage cheese, farmer cheese, and cream cheese

Meat and fish: caviar; liver; salami and sausage; smoked, dried, pickled, cured, or preserved meats and fish

Vegetables: overripe avocados, fava beans, sauerkraut

Fruits: overripe fruits, canned figs

Other foods: yeast extracts, fermented products, monosodium glutamate

Beverages: red wine, sherry, liquors

Foods to use in moderation

Chocolate

Coffee

Colas

Tea

Soy sauce

Beer, other wine

Medications to avoid

Over-the-counter pain medications except for plain aspirin, acetaminophen, and ibuprofen

Cold or allergy medications

Nasal decongestants and inhalers

Cough medications; plain guaifenesin elixir may be taken, however

Stimulants and diet pills

Sympathomimetic drugs

Meperidine

Selective serotonin reuptake inhibitors (SSRIs), bupropion, desvenlafaxine, mirtazapine, nefazodone, trazodone, venlafaxine

Source. Adapted from Hyman and Arana 1987; Krishnan 2009.

properties, which act to lower blood pressure when taken sublingually, make it a useful stopgap measure.

All physicians and dentists should be informed when their patients are taking MAOIs, especially when surgery or dental work is indicated, so that drugs that interact adversely with MAOIs can be avoided. It is advisable to wait 2 weeks after discontinuing an MAOI before resuming a normal diet or using a TCA, an SSRI, or another medication that may have an adverse interaction with the MAOI.

Use of Antidepressants

Treatment should begin with one of the SSRIs. Because these drugs are effective, well tolerated, and generally safe in overdose, they have replaced the TCAs as first-line therapy. Most patients will respond to a standard dosage, and frequent dosage adjustments are unnecessary. Patients with a history of cardiac conduction defects should receive one of the SSRIs or another new agent (e.g., bupropion, duloxetine, mirtazapine). Impulsive patients or those with suicidal urges also should receive an SSRI or one of the newer agents because they are unlikely to be fatal in overdose. When a TCA is used, nortriptyline, imipramine, and desipramine are the drugs of choice because meaningful plasma levels can be measured. The TCAs all require close titration, beginning with relatively low dosages. Recommended dosage ranges for the antidepressants are found in Table 20–2.

Patients being treated for their first episode of major depression should be maintained on medication at the same dosage used for acute treatment for at least 4–9 months after achieving remission. When medication is ultimately tapered and discontinued, patients should be carefully monitored to ensure that their remission is stable. Patients with the following characteristics should be considered for chronic maintenance treatment to reduce the risk of relapse:

- Three or more lifetime episodes of major depression
- Double depression (i.e., major depression plus dysthymia)
- Two or more severe episodes of major depression within the past 5 years
- Depressive disorder complicated by comorbid substance use or anxiety disorder
- Age greater than 60 years at onset of major depression

Drug trials generally should last 4–8 weeks. When the patient's symptoms do not respond to an antidepressant after 4 weeks of treatment at the target dosage, the dosage should be increased, or the patient should be switched to another antidepressant, preferably from a different class with a slightly different mechanism of action. When this regimen fails, nonresponders may benefit from the addition of lithium, which will increase the likelihood of response in many patients. Response from lithium augmentation is often evident within a week with relatively low dosages (e.g., 300 mg three times daily). ECT is an option in patients whose depression does not respond to medication.

Other agents have been used to augment the effect of TCAs, including triiodothyronine, tryptophan, methylphenidate, and pindolol, but the effectiveness of these agents in augmenting response has not been adequately studied.

Rational use of antidepressants

1. SSRIs or one of the other newer antidepressants should be used initially, and TCAs and MAOIs should be reserved for nonresponders.
2. Dosages should be adjusted to fall within the recommended range, and each drug trial should last 4–8 weeks.
3. SSRIs generally are given once daily. TCAs can be administered as a single dose, usually at bedtime. MAOIs usually are prescribed twice daily but not at bedtime because they can cause insomnia. Bupropion is administered in two to three divided doses to minimize its risk of causing seizures.
4. Although adverse effects appear within days of starting a drug, therapeutic effects may require 2–4 weeks to become apparent.
   - Improvement should be monitored by following up target symptoms (e.g., mood, sleep, energy, appetite).
5. Patients with heart rhythm disturbances should be given one of the newer antidepressants that do not affect cardiac conduction (e.g., bupropion, mirtazapine, or an SSRI).
6. Antidepressants are usually unnecessary in patients with grief reactions (uncomplicated bereavement) or adjustment disorders with depressed mood, because these disorders are self-limiting.

Rational use of antidepressants *(continued)*

7. When possible, SSRIs should be tapered (except for fluoxetine, which self-tapers) because many patients experience withdrawal symptoms. TCAs also should be tapered slowly because of their tendency to cause withdrawal reactions. No clinically significant withdrawal reaction occurs with MAOIs, but a taper over 5–7 days is sensible.
8. The coadministration of two different antidepressants does not boost efficacy and will only worsen side effects. In rare cases, the combined use of a TCA and an MAOI or a TCA and an SSRI is justified, but these combinations should never be used routinely.
   - MAOIs should not be coadministered with SSRIs or with any of the other new antidepressants.

■ Mood Stabilizers

Lithium carbonate, a naturally occurring salt, became available in 1970. Its first use in medicine (in the form of lithium chloride) was as a salt substitute for people with hypertension who needed a low-sodium diet, but its use was abandoned when it was found to make some people sick. In the late 1940s, Australian psychiatrist John Cade found that lithium calmed agitated psychotic patients. Later, it was discovered that lithium was particularly effective in people with mania. The Danish researcher Mogens Schou observed that lithium was effective in relieving the target symptoms of mania and that it also had a prophylactic effect. Lithium has since been joined by valproate, carbamazepine, and lamotrigine for the treatment of bipolar disorder.

In addition to the mood stabilizers, all of the SGAs (except clozapine) have been approved for the treatment of acute mania; two are indicated for maintenance treatment of bipolar disorder (aripiprazole and olanzapine); and four are indicated for the adjunctive treatment of acute mania in combination with lithium or valproate (aripiprazole, olanzapine, quetiapine, and risperidone). Additionally, both quetiapine and a combined form of olanzapine and fluoxetine (Symbyax) are approved to treat the depressed phase of bipolar disorder. The mood stabilizers are listed in Table 20–5. (Further information about the treatment of bipolar disorder is found in Chapter 6.)

TABLE 20–5. Commonly used mood stabilizers

Drug (trade name)	Therapeutic plasma level	Dosage range, mg/day
Carbamazepine (Tegretol)	6–12 mg/L	400–2,400
Lamotrigine (Lamictal)	N/A	50–200
Lithium carbonate (Eskalith, Lithobid)	0.6–1.2 mEq/L	900–2,400
Valproate (Depakene, Depakote)	50–120 mg/L	500–3,000

Lithium Carbonate

The mechanism of action of lithium is unknown. Lithium has effects on intracellular processes, such as inhibiting the enzyme inositol-1-phosphatase within neurons. The inhibition leads to decreased cellular responses to neurotransmitters that are linked to the phosphatidylinositol second-messenger system.

The onset of action often takes 5–7 days to become apparent. The usual plasma level of lithium for the treatment of acute mania is 0.9–1.4 mEq/L, but some patients do well outside this range. Antipsychotics, which work more quickly, may be preferred when rapid behavioral control is needed, although benzodiazepine-induced sedation may be as effective.

Maintenance dosages may be lower, aiming for a blood level in the range of 0.5–0.7 mEq/L. Lithium has no role in the acute treatment of unipolar major depression but is a first-line treatment for bipolar depression. Lithium is sometimes used to augment the effect of antidepressants in the treatment of major depression.

The most dramatic effect of lithium is in the prophylaxis of manic and depressive episodes in bipolar patients. Lithium appears to work best at reducing the frequency and severity of manic episodes. Although response to lithium tends to remain stable over time, most patients will have breakthrough episodes. Lithium has also been shown to be effective in preventing recurrences of depression in patients with unipolar major depression. It is one of the few drugs demonstrated to reduce suicide attempts and suicides.

Lithium is also used in the treatment of schizoaffective disorder, especially the bipolar subtype. Lithium is sometimes used to treat aggression in patients with dementia, mental retardation, or "acting out" personality disorders (especially the borderline and antisocial types).

Pharmacokinetics of Lithium

Lithium carbonate is administered orally but is available in liquid form as lithium citrate. Lithium is rapidly absorbed from the gut, and peak blood levels are obtained about 2 hours after ingestion. The elimination half-life is about 8–12 hours in manic patients and about 18–36 hours in euthymic patients. (Manic patients are overly active and have a higher glomerular filtration rate and therefore clear lithium from their system more rapidly.) Lithium is not protein bound and does not have metabolites. It is almost entirely excreted through the kidney but may be found in all body fluids (e.g., saliva, semen). Blood plasma levels are checked 12 hours after the last dose is given.

Slow-release preparations are available and are indicated when gastrointestinal toxicity is evident or when twice-daily dosing would enhance compliance. Lithium usually is administered two or three times daily in patients with acute mania. Once-daily dosing with extended-release preparations is recommended in patients receiving the drug prophylactically. Once-daily dosing may offer some protection to the kidneys, although a single large daily dose can cause gastric irritation. Lithium usually is started at 300 mg twice daily in the average patient and is then titrated until a therapeutic blood level is achieved. Dosage may be adjusted every 3–5 days. Levels should be checked monthly for the first 3 months and every 3 months thereafter. Patients receiving chronic lithium administration can be monitored less frequently. Lithium can be safely discontinued without a taper.

Adverse Effects of Lithium

Minor side effects of lithium occur relatively soon after initiating treatment. Thirst or polyuria, tremor, diarrhea, weight gain, and edema are all relatively common side effects but tend to diminish with time. About 5%–15% of the patients undergoing long-term treatment develop clinical signs of hypothyroidism. This side effect is more common in women and tends to occur during the first 6 months of treatment. Hypothyroidism can be managed effectively with thyroid hormone replacement. Baseline thyroid assays should be obtained before starting lithium. Thyroid function should be tested once or twice during the first 6 months of treatment and every 6–12 months thereafter as clinically indicated. Thyroid dysfunction reverses after lithium is discontinued.

Long-term lithium treatment may lead to increased levels of calcium, ionized calcium, and parathyroid hormone. High levels of calcium can cause lethargy, ataxia, and dysphoria, symptoms that may be attributed to depression rather than hypercalcemia.

Lithium is excreted through the kidneys and is reabsorbed in the proximal tubules with sodium and water. When the body has a sodium deficiency, the kidneys compensate by reabsorbing more sodium than normal in the proximal tubules. Lithium is absorbed along with sodium and poses the risk of lithium toxicity with hyponatremia. Thus patients should be instructed to avoid becoming dehydrated from exercise, fever, or other causes of increased sweating. Sodium-depleting diuretics (e.g., thiazides) should be avoided because they may increase lithium levels. The concomitant use of nonsteroidal anti-inflammatory agents should also be avoided because of their potential to raise lithium levels, most likely mediated by their effect on renal prostaglandin synthesis.

Lithium has the potential to cause nephrogenic diabetes insipidus because lithium reduces the ability of the kidneys to concentrate urine. As a result, many lithium-treated patients produce large volumes of dilute urine. This can be clinically significant for some individuals, particularly when output exceeds 4 L/day. Amiloride (e.g., 10–20 mg/day) or hydrochlorothiazide (e.g., 50 mg/day) can be administered to (paradoxically) reduce urine output. A nephrotic syndrome caused by glomerulonephritis occurs in rare cases. This complication typically reverses when lithium is discontinued.

Long-term lithium use can cause a decrease in the glomerular filtration rate; significant decreases are uncommon. The decrease is presumably due to a tubulointerstitial nephropathy, perhaps caused by the patient's cumulative exposure to lithium; therefore, the lowest effective dosage possible should be maintained. Renal function should be assessed every 2–3 months during the first 6 months of treatment and every 6–12 months thereafter as clinically indicated. If proteinuria or an increase in creatinine is evident, additional tests should be performed.

Some patients will develop reversible, nonspecific T-wave changes similar to those seen with hypokalemia. Arrhythmias are uncommon, but sinus node dysfunction has been reported. Some patients develop acne, and those with acne may have an exacerbation. Psoriasis also may be worsened. Lithium has been reported to cause hair loss.

Lithium induces a reversible leukocytosis, with white blood cell counts of 13,000–15,000/mm^3. The increase is usually in neutrophils and represents a step-up of the total body count rather than demargination.

Parkinsonian-like symptoms, such as cogwheeling, hypokinesis, and rigidity, may occur in lithium-treated patients. Cognitive effects, such as distractibility, poor memory, and confusion, also can develop at therapeutic levels of lithium.

Contraindications to Lithium

Patients with a severe renal disease (e.g., glomerulonephritis, pyelonephritis, polycystic kidneys) should not receive lithium because it is renally excreted; dangerous blood levels may result when the kidneys are not functioning normally. In patients who have had myocardial infarction, lithium should be discontinued for at least 10–14 days. If treatment with lithium is necessary during the postinfarct period, low dosages and periodic cardiac monitoring are recommended.

Lithium is contraindicated in the presence of myasthenia gravis because it blocks the release of acetylcholine. Lithium should be given cautiously in the presence of diabetes mellitus, ulcerative colitis, psoriasis, and senile cataracts. Because of the increased incidence of cardiovascular malformations in infants of mothers taking lithium (Ebstein's anomaly), lithium should be discontinued during the first trimester of pregnancy. Because lithium is secreted in breast milk, mothers taking the drug should not breast-feed.

Valproate

Valproate, a simple branched-chain carboxylic acid, is commonly used as an anticonvulsant and is FDA approved for the treatment of acute mania. An extended-release formulation is approved as well for both acute manic and mixed states. It is considered a first-line treatment for bipolar disorder, along with lithium carbonate and carbamazepine. It also is effective for long-term maintenance treatment of bipolar disorder. It appears to reduce recurrences of mania and to increase the length of depression-free intervals.

The mechanism of its action is unknown, although it enhances CNS levels of γ-aminobutyric acid (GABA) by inhibiting its degradation and stimulating its synthesis and release. Valproate is rapidly absorbed after oral ingestion, and its bioavailability is nearly complete. Peak concentrations occur in 1–4 hours; it is rapidly distributed and highly (90%) protein bound.

The half-life of valproate ranges from 8 to 17 hours. The drug is metabolized by the liver, primarily through glucuronide conjugation. Less than 3% is excreted unchanged. Unlike carbamazepine, valproate does not induce its own metabolism. A plasma concentration of about 50–125 μg/mL correlates with acute antimanic response. Valproate may be more effective than lithium in patients with mixed presentations, with irritable mania, with a high number of prior episodes of mania, or with a history of nonresponse to lithium.

Commonly reported side effects include gastrointestinal complaints (e.g., nausea, poor appetite, vomiting, diarrhea), asymptomatic serum hepatic transaminase elevation, tremor, sedation, and weight gain. Less frequent side effects include rashes, hematological abnormalities, and hair loss. Hepatic transaminase elevation can occur and is dose related; it generally subsides spontaneously. A rare but fatal hepatotoxic reaction to valproate has been reported. The enteric-coated form of valproate is generally well tolerated and has a low incidence of gastrointestinal side effects; however, it is more expensive than generic formulations.

Neural tube defects have been reported with the use of valproate during the first trimester of pregnancy; therefore, its use in pregnant women is not recommended. Coma and death have occurred from valproate overdoses.

Before valproate treatment is begun, the patient should have a complete blood count and a liver enzyme measurement; the latter should be done periodically during the first 6 months and then about every 6 months thereafter. The drug is started at 250 mg three times daily and can be increased by 250 mg every 3 days. Serum levels can be obtained after 3–4 days. Most patients will need between 1,250 and 2,500 mg/day.

Carbamazepine

Carbamazepine, an anticonvulsant used to treat complex partial and tonic-clonic seizures, has a structure similar to that of the TCAs. It is used as an alternative to lithium and valproate in the treatment of acute mania and may be effective for maintenance treatment of bipolar disorder. The drug has been approved by the FDA for the treatment of acute manic or mixed episodes of bipolar disorder.

The precise mechanism of action of carbamazepine is unknown, but the drug has a wide range of cellular and intracellular effects in the CNS. Of theoretical interest is its dampening effect on kindling, a process in which repeated biochemical or psychological stressors are thought to result in abnormal excitability of limbic neurons.

When carbamazepine is used to treat mania, there is generally a delay of 5–7 days before its effect is apparent. Carbamazepine can safely be combined with antipsychotics, especially when behavioral control is necessary. It may be more effective in patients who cycle rapidly (i.e., more than four episodes per year) and who tend not to respond well to lithium. The usual custom is to aim for typical anticonvulsant blood levels of 8–12 μg/mL, despite the fact that no dose-response curve has been established.

From 10% to 15% of the patients taking carbamazepine develop a skin rash, which is generally transient. Other common side effects include impaired coordination, drowsiness, dizziness, slurred speech, and ataxia. Many of these symptoms can be avoided by increasing the dosage slowly. A transient leukopenia causing as much as a 25% decrease in the white blood cell count occurs in 10% of patients. A smaller reduction in the white blood cell count may persist in some patients as long as they take the drug, but this is not a reason for discontinuation. Aplastic anemia develops in rare cases.

Carbamazepine is typically started at a dosage of 200 mg twice daily and increased to three times daily after 3–5 days. Most patients will need dosages of 600–1,600 mg/day.

Before starting carbamazepine, the patient should have a complete blood count and an electrocardiogram. The patient should be warned about the drug's rare hematological side effects. Any indication of infection, anemia, or thrombocytopenia (e.g., petechiae) should be investigated and a complete blood count should be obtained, but routine blood monitoring is unnecessary. Because carbamazepine is a vasopressin agonist, it can induce hyponatremia; therefore, convulsions or undue drowsiness should be cause for obtaining serum electrolyte measurements. Carbamazepine has been linked with fetal malformations similar to those seen with phenytoin and therefore should be avoided in pregnant women, especially during the first trimester. Breast-feeding by women taking this drug is not recommended.

Lamotrigine

Lamotrigine, also an anticonvulsant, is FDA approved for the maintenance treatment of bipolar I disorder to delay the time to occurrence of mood episodes. It appears to be most effective in delaying the time to occurrence of depressive episodes and may be effective in the treatment of acute depressive episodes as well. Although its mechanism of action is unclear, it affects CNS neurotransmission by blocking sodium channels. This action inhibits the release of presynaptic glutamate, aspartate, and GABA. The drug also is a weak inhibitor of the serotonin-3 receptor.

The target dosage of lamotrigine is 200 mg/day, achieved through a slow titration (i.e., 25 mg/day for 2 weeks, 50 mg/day for 2 weeks, 100 mg/day for 1 week, then 200 mg/day). The oral bioavailability of the drug is 98%, and peak plasma concentrations occur initially at 1–3 hours, with a secondary peak at 4–6 hours. The drug is about 60% protein bound and is widely distributed in the body. Metabolism is through he-

patic glucuronidation, and none of the metabolites are active. The half-life ranges from 25 to 35 hours.

Lamotrigine is generally well tolerated, and most side effects are minor. In rare cases, the drug can induce the potentially life-threatening Stevens-Johnson syndrome and toxic epidermal necrolysis. Patients should be instructed to discontinue the drug at the first sign of a rash. Rashes are more common in children. Lamotrigine should probably not be combined with valproate because the combination can substantially increase the risk of serious rash, including Stevens-Johnson syndrome. The drug is listed as Category C in terms of pregnancy risk, which indicates that risk cannot be ruled out.

Rational use of mood stabilizers

1. Lithium, valproate, or carbamazepine should be used initially for the treatment of acute mania.
   - Monotherapy with SGAs, which are effective and well tolerated, is an excellent alternative.
   - The combination of lithium and valproate or the combination of a mood stabilizer with one of the SGAs may be effective when monotherapy fails.
2. A clinical trial of lithium, valproate, or carbamazepine should last 3 weeks; at this point, another drug should be added or substituted if there is minimal or inadequate response.
   - Drug nonresponders may respond to electroconvulsive therapy.
3. Lithium may be given as a single dose at bedtime when the amount is less than 1,200 mg. Lithium should be given with food to minimize gastric irritation.
4. Renal function and thyroid indices should be regularly monitored in patients treated with lithium. Hepatic function should be regularly monitored in patients treated with valproate.
5. Lamotrigine may be particularly helpful in preventing the development of depressive episodes in bipolar I patients.

■ Anxiolytics

Anxiolytics are the most widely prescribed class of psychotropic drugs. They include the barbiturates, the nonbarbiturate sedative-hypnotics

TABLE 20–6. Benzodiazepines commonly used as anxiolytics

Drug (trade name)	Rate of onset	Half-life, h	Long-acting metabolite	Equivalent dosage, mg	Dosage range, mg/day
Alprazolam (Xanax)	Fast	6–20	No	0.5	1–4
Chlordiazepoxide (Librium)	Fast	20–100	Yes	10.0	15–60
Clonazepam (Klonopin)	Moderate	30–40	No	0.25	1–6
Diazepam (Valium)	Very fast	30–100	Yes	5.0	5–40
Lorazepam (Ativan)	Fast	10–20	No	1.0	0.5–10
Oxazepam (Serax)	Slow	5–20	No	15.0	30–120

(e.g., meprobamate), the benzodiazepines, and buspirone. Currently, only the benzodiazepines and buspirone can be recommended because of their superior safety record. There is still a strong belief in the general population that these medications are overprescribed by psychiatrists and other physicians. Despite their reputation, benzodiazepines are generally prescribed for short periods, are prescribed for rational indications, and are used appropriately by most patients.

Benzodiazepines

Benzodiazepines constitute an important class of drugs with clear superiority over the barbiturates and nonbarbiturate sedative-hypnotics. Benzodiazepines have been marketed in the United States since 1964. These drugs have a high therapeutic index, little toxicity, and relatively few drug-drug interactions. The benzodiazepines are indicated for the treatment of anxiety syndromes, sleep disturbances, musculoskeletal disorders, seizure disorders, and alcohol withdrawal and for inducing anesthesia. Their approved indications reflect subtle differences among them (e.g., side effects, potency) and in marketing strategy. Commonly used benzodiazepines are compared in Table 20–6.

Benzodiazepines are believed to exert their effects by binding to specific benzodiazepine receptors in the brain. The receptors are intimately

linked to receptors for GABA, a major inhibitory neurotransmitter. By binding to benzodiazepine receptors, the drugs potentiate the actions of GABA, leading to a direct anxiolytic effect on the limbic system.

Indications for Benzodiazepines

Benzodiazepines are useful for the treatment of generalized anxiety disorder, especially when severe. Many patients benefit when their anxiety is acute and problematic; these drugs generally should be given for short periods (e.g., weeks or months). Patients with mild anxiety may not need medication and can be successfully managed with behavioral interventions (e.g., progressive muscle relaxation).

Benzodiazepines have an antipanic effect. Both alprazolam and clonazepam have FDA indications for the treatment of panic disorder but because of their abuse potential are considered second-line treatments after the SSRIs. Similarly, while benzodiazepines are effective in treating social phobia, the SSRIs should be used initially because they do not have an abuse potential.

Anxiety frequently complicates depression. Benzodiazepines are frequently coadministered with an antidepressant because they are more effective in quickly relieving accompanying anxiety than is the antidepressant. When the antidepressant begins to take effect, the benzodiazepine can be withdrawn gradually.

Benzodiazepines are effective in alleviating situational anxiety. These syndromes, called *adjustment disorders with anxiety* in DSM-IV-TR, are characterized by anxiety symptoms (e.g., tremors, palpitations) that occur in response to a stressful event. Adjustment disorders are generally brief, and for that reason, treatment with benzodiazepines is time limited.

Benzodiazepines have established efficacy in the short-term treatment of primary insomnia unrelated to identifiable medical or psychiatric illness. Their use as hypnotic agents is discussed in Chapter 17, which includes a description of the individual drugs, their dosing, and their adverse effects.

Alcohol withdrawal syndromes are commonly treated with benzodiazepines (most often chlordiazepoxide), because benzodiazepines and alcohol are cross-tolerant. The treatment of these syndromes is described in Chapter 9. Other uses of the benzodiazepines include the treatment of akathisia and catatonia and as an adjunct to the treatment of acute agitation and mania.

Pharmacokinetics of Benzodiazepines

Benzodiazepines are rapidly absorbed from the gut and, with the exception of lorazepam, are poorly absorbed intramuscularly. Lorazepam is available for parenteral use, and its versatility contributes to its widespread use in hospitalized patients. Midazolam is a short-acting agent used to induce anesthesia but is not available orally. Benzodiazepines are metabolized chiefly by hepatic oxidation and have active metabolites. Lorazepam, oxazepam, and temazepam are metabolized by glucuronide conjugation and have no active metabolites; they are relatively short acting and are thus the preferred benzodiazepines for elderly patients.

There are differences between single-dose and steady-state kinetics. Rapid-onset drugs tend to be lipophilic, a property that facilitates rapid crossing of the blood-brain barrier. Drugs with longer elimination half-lives accumulate more slowly and take longer to reach steady state. Washout of these drugs is similarly prolonged. Drugs with shorter half-lives reach steady state more rapidly but also have less total accumulation. Drugs with long half-lives tend to have active metabolites.

Because of the differences in metabolism and half-lives, the best therapeutic results are obtained when the needs of the patient and the situation are taken into account. When prescribing, three parameters largely determine drug selection: 1) half-life, 2) presence of metabolites, and 3) route of elimination. For example, in older adults, the clinician should select a benzodiazepine with a short half-life, few metabolites, and renal excretion in order to minimize drug accumulation and adverse side effects.

Adverse Effects of Benzodiazepines

CNS depression is common with benzodiazepines. Symptoms include drowsiness, somnolence, reduced motor coordination, and memory impairment. These may diminish with continued administration or dosage reduction. However, patients should be cautioned not to drive or use machines, especially when starting these drugs.

All benzodiazepines have the potential for abuse and addiction. Because physiological dependence is more likely to occur with longer drug exposure, minimizing the duration of continuous treatment should reduce this risk. Also, benzodiazepines should be prescribed cautiously in patients with histories of alcohol or drug abuse and in patients with unstable personalities (e.g., borderline and antisocial personality disor-

ders). When signs of dependence appear (e.g., drug-seeking behavior, increasing the dosage to get the same effect), the drug should be tapered and discontinued. Patients should be advised to avoid alcohol when taking benzodiazepines because the combination will cause greater CNS depression than either drug alone.

Discontinuation of benzodiazepine therapy after long-term treatment can lead to tremulousness, sweating, sensitivity to light and sound, insomnia, abdominal distress, and systolic hypertension. Serious withdrawal syndromes and seizures are relatively uncommon but are more likely with abrupt discontinuation. Symptom recurrence appears to have a more rapid onset after discontinuation of short-acting benzodiazepines; the effect of drug discontinuation can be minimized by gradually tapering the drug over 1–3 months. Such a slow taper is particularly important for benzodiazepines with short half-lives. When discontinuing short-acting benzodiazepines, it may be helpful to switch the patient to a long-acting drug before initiating a taper (e.g., from alprazolam to clonazepam).

Nearly all benzodiazepines fall into pregnancy risk Category D (positive evidence of risk) or X (contraindicated in pregnancy), mainly on the basis of the occurrence of neonatal toxicity and withdrawal syndromes. For these reasons, their use during pregnancy and breast-feeding should be avoided.

Benzodiazepines can be used safely in medically ill and elderly patients. In general, drugs that do not accumulate (e.g., lorazepam) should be used. Because benzodiazepines can cause respiratory depression, they should not be used in persons with sleep apnea, although small dosages are tolerated even in patients with chronic pulmonary disease. Small dosages are also indicated for the elderly, who are susceptible to the CNS depressant effects of benzodiazepines, which can contribute to memory difficulties and falls.

The least controversial aspect of benzodiazepines is their tremendous index of safety. When they are taken alone, even massive overdoses are rarely fatal.

Buspirone

Buspirone has an FDA indication for the treatment of generalized anxiety disorder. Structurally unlike other anxiolytics, it is a serotonin type 1A (5-HT_{1A}) receptor agonist and does not interact with the benzodiazepine receptor. As such, it does not produce sedation, does not interact with alcohol, and does not pose a risk for abuse. Buspirone is ineffective

in blocking panic attacks, relieving phobias, or diminishing obsessions or compulsions. Buspirone is well absorbed orally and is metabolized by the liver. Its half-life ranges from 2 to 11 hours. Drowsiness, headache, and dizziness are common side effects.

Buspirone's effect on chronic anxiety is equal to that of diazepam, although its effects are not apparent for 1–2 weeks. The usual dosage range is 20–30 mg/day in divided doses. Alternatives to buspirone for the treatment of generalized anxiety disorder include the SNRIs venlafaxine and duloxetine and the SSRIs.

Rational use of anxiolytics

1. The benzodiazepines should be used for limited periods (e.g., weeks to months) to avoid the problem of dependency, because most conditions they are used to treat are self-limiting.
   - Some patients will benefit from long-term benzodiazepine administration; in these situations, patients should be periodically assessed for continuing need.
2. The benzodiazepines have similar clinical efficacy, so the choice of a specific agent depends on its half-life, the presence of metabolites, and the route of administration.
3. Once- or twice-daily dosing of the benzodiazepines is sufficient for most patients.
   - A dose given at bedtime may eliminate the need for a separate hypnotic.
   - Short-acting agents (e.g., alprazolam) are an exception to this recommendation because their dosing interval is determined by their half-lives.
4. Buspirone is not effective on an as-needed (prn) basis and is useful only for the treatment of generalized anxiety disorder.
5. The SNRIs venlafaxine and duloxetine, or one of the SSRIs, are effective alternatives to the benzodiazepines and buspirone in the treatment of generalized anxiety disorder.
   - Because response to these agents takes several weeks, it is important to educate the patient not to expect quick results.

■ Agents Used to Treat Extrapyramidal Syndromes

Anticholinergic agents closely resemble atropine in their ability to block muscarinic receptors, and all are similar in action and efficacy for alleviating antipsychotic-induced EPS, especially pseudoparkinsonism. These drugs are believed to diminish or eliminate EPS by reestablishing dopamine-acetylcholine equilibrium, which they do by blocking acetylcholine in the corpus striatum. An equilibrium of dopaminergic (inhibitory) and cholinergic (excitatory) neuronal activity in the corpus striatum is thought to be necessary for normal motor functioning. Antipsychotic medications cause dopamine reuptake blockage and an absolute decrease in dopamine and thus a relative increase in interneuronal acetylcholine, which results in EPS.

The anticholinergic drug benztropine should be started at a dosage of 1–2 mg/day. Smaller dosages should be used with geriatric patients. The maximum allowable dosage is 6 mg/day of benztropine or its equivalent, because a delirium can occur at higher dosages. Benztropine can be administered once daily, preferably at bedtime because it may cause sedation. The side effects of anticholinergic medications—dry mouth, blurry vision, constipation, and urinary hesitancy—are additive with those of the antipsychotics. Table 20–7 shows common agents used to treat EPS and their dosage ranges.

Intramuscular benztropine (1–2 mg) or diphenhydramine (25–50 mg) works within 20–30 minutes to alleviate acute dystonic reactions. These drugs may be given intravenously as well and relieve dystonia within minutes. Benztropine is the preferred agent because it usually does not cause sedation. Lorazepam (1–2 mg intramuscularly) also seems to work.

Amantadine and propranolol also are used to treat EPS. Amantadine acts to increase CNS concentrations of dopamine by blocking its reuptake and increasing its release from presynaptic fibers. This action is thought to restore the dopamine-acetylcholine balance in the striatum. Amantadine is primarily useful in treating the symptoms of pseudoparkinsonism, such as tremors, rigidity, and hypokinesia. One advantage of amantadine is its lack of anticholinergic effects, so that it can be safely combined with antipsychotics without concern for the development of an anticholinergic delirium. Treatment is initiated at 100 mg/day and increased to 200–300 mg/day. Onset of action occurs within 1 week. Adverse effects include orthostatic hypotension, livedo reticularis, ankle edema, gastrointestinal upset, and visual hallucinations in rare cases.

TABLE 20–7. Common agents used to treat extrapyramidal syndromes

Category	Drug (trade name)	Dosage range, mg/day	Comments
Anticholinergics	Benztropine (Cogentin)	0.5–6	Use 1–2 mg im of benztropine or 25–50 mg im of diphenhydramine for acute dystonia. Anticholinergics tend to work better at relieving the tremor of pseudoparkinsonism than hypokinesia.
	Biperiden (Akineton)	2–6	
	Diphenhydramine (Benadryl)	12.5–150	
	Procyclidine (Kemadrin)	2.5–22.5	
	Trihexyphenidyl (Artane)	1–15	
Dopamine facilitators	Amantadine (Symmetrel)	100–300	Useful in situations in which anticholinergic side effects need to be avoided.
β-Blockers	Propranolol (Inderal)	10–80	Works well for treating akathisia.
α-Agonists	Clonidine (Catapres)	0.2–0.8	May cause orthostatic hypotension; therefore, dosage should be increased slowly. Works well for treating akathisia.

Propranolol and other β-blockers have been used to treat akathisia, which usually is not alleviated with an anticholinergic agent. Propranolol (e.g., 10–20 mg three to four times daily) or another equivalent centrally acting β-blocker seems to work well; its effect is often apparent within days. Discontinuation of the drug will lead to a recurrence of symptoms.

Clonidine, an α_2-receptor agonist, also has been used to treat akathisia. The drug is usually given in divided doses ranging from 0.2 to 0.8 mg/day. Orthostatic hypotension and sedation are the main side effects. Clonidine should be used as a second-line agent for patients unresponsive to propranolol.

In treating any EPS, the clinician should begin by reducing the dosage of the antipsychotic drug whenever possible or switching to an SGA with less potential to cause EPS. When these steps fail, anticholinergics, amantadine, or propranolol can be useful adjuncts. Because EPS are unpleasant and reduce the likelihood that the patient will remain compliant with treatment, drugs used to treat these side effects can make a significant difference in the patient's comfort.

■ Electroconvulsive Therapy

ECT is a procedure in which a controlled electric current is passed through the scalp and selected parts of the brain to induce a grand mal seizure. The procedure was introduced in 1938 in Italy by Ugo Cerletti and Lucio Bini to replace less reliable convulsive therapies that used liquid chemicals. ECT is one of the oldest medical treatments still in regular use, a fact that attests to its safety and efficacy. Its mechanism of action is poorly understood, yet it is known to produce multiple effects on the CNS, including neurotransmitter changes, neuroendocrine effects, and alterations in intracellular signaling pathways.

Indications for Electroconvulsive Therapy

ECT is used almost exclusively for the treatment of mood disorders and is generally reserved for patients who fail one or more trials of antidepressant medication, patients who are at high risk for suicide, and patients who are debilitated by their failure to take in adequate food and fluids. Patients at high risk for suicide and in need of rapid treatment are also candidates for ECT because it tends to work more quickly than antidepressant medication. Some patients will choose to have ECT as a first-line treatment rather than take medication. There is growing evidence that the combination of ECT with antidepressant medication produces an even more robust response than either treatment alone.

Patients receive an index course of 6–12 treatments at a rate of two to three per week, although the precise number is individualized based on response. An index series of treatments can be administered in inpatient or outpatient settings, a determination that the physician and patient (and the patient's family) need to make. Generally, if the treatments are given in the outpatient setting, the patient should not be at risk for suicide, should have supportive family members available to help care for

the patient at home, and should be medically stable. Some patients will be candidates for maintenance (or prophylactic) ECT to keep them from relapsing. Typically, these patients have failed multiple medication trials yet respond favorably to ECT. With prophylactic ECT, a treatment is given anywhere from once per week to once per month depending on the patient. Because mood disorders tend to be chronic or recurrent, maintenance treatment for some will be indefinite.

As many as 80%–90% of patients receiving ECT as a first-line treatment respond favorably, while those who have failed antidepressants have a 50%–60% response rate. Certain depressive symptoms are associated with a good response to ECT, including psychomotor agitation or retardation; nihilistic, somatic, or paranoid delusions; and acute onset of illness. ECT is not generally recommended for patients with chronic forms of depression or patients with serious personality disorders (e.g., borderline personality disorder).

Mania responds well to ECT, although its use is primarily reserved for patients not responding to medication. Similarly, patients with a schizoaffective disorder may benefit when medication has been ineffective. Schizophrenic patients are sometimes treated with ECT, particularly when a superimposed major depression or a catatonic syndrome is present. As a general rule, patients with schizophrenia of relatively brief duration (i.e., less than 18 months) respond better than those with more chronic forms of the illness, yet sometimes even patients with chronic schizophrenia will respond to ECT. Indications for ECT are summarized in Table 20–8.

TABLE 20–8. Indications for electroconvulsive therapy (ECT)

Medication-refractory depression
Suicidal depression
Depression accompanied by refusal to eat or take fluids
Depression during pregnancy
History of positive response to ECT
Catatonic syndromes
Acute forms of schizophrenia
Mania unresponsive to medication
Psychotic or melancholic depression unresponsive to medication

Pre–Electroconvulsive Therapy Workup

Baseline screening should include a physical examination, basic laboratory tests (blood count and electrolytes), and an electrocardiogram. These will help to rule out physical disorders that may complicate ECT, reveal occult arrhythmias that may require monitoring during the procedure, or will uncover electrolyte abnormalities that need correcting prior to ECT such as hypokalemia. A chest X-ray should be obtained in patients with pulmonary disease. Spine films are no longer routinely obtained due to the rarity of fractures with current ECT protocols. Relative contraindications include recent myocardial infarction (i.e., within 1 month), unstable coronary artery disease, uncompensated congestive heart failure, uncontrolled hypertensive cardiovascular disease, and venous thrombosis. Space-occupying brain lesions and other causes of increased intracranial pressure, such as recent intracerebral hemorrhage, unstable aneurysms, or vascular malformations are the only absolute contraindications to ECT. Psychotropic medications may be continued, although benzodiazepines should be reduced to the lowest possible dose (or be discontinued altogether) because they can interfere with the induction of a seizure.

Electroconvulsive Therapy Procedure

ECT sessions are usually scheduled in the morning. The patient's bladder should be emptied, and he or she should not have had food or fluids for at least 6–8 hours before the procedure. The treatment team usually consists of a psychiatrist, an anesthesiologist (or nurse anesthetist), and a specially trained nursing team. The treatment area should have resuscitative equipment available.

Patients are anesthetized with a short-acting anesthetic (e.g., methohexital, etomidate), receive oxygen to prevent hypoxia, receive succinylcholine as a muscle relaxant to attenuate convulsions, and receive atropine or glycopyrrolate to reduce secretions and to prevent bradyarrhythmias. Glycopyrrolate does not cross the blood-brain barrier and may be associated with less postictal confusion than atropine in the elderly. After the patient is anesthetized, electrodes are placed on the scalp.

Two different electrode placements are commonly used. Bilateral placement involves placing the electrode on each side of the head over the parietal lobes. With unilateral placement, one electrode is placed over the right temple and the other is placed at the vertex of the skull. Bilateral placement is associated with a more efficient response while

right unilateral placement is associated with less post-ECT confusion and memory loss.

A brief electrical stimulus is applied after placement of the electrodes. A bidirectional pulse wave is given rather than a continuous sinusoidal waveform commonly used in the past because the pulse wave is associated with less cognitive impairment. Stimulation usually produces a 30- to 90-second tonic-clonic seizure. The seizure is accompanied by a period of bradycardia and a transient drop in blood pressure, followed by tachycardia and a rise in blood pressure. A rise in cerebrospinal fluid pressure parallels the rise in blood pressure. These physiological responses are attenuated by the pre-ECT medications. Minor arrhythmias are frequent but are seldom a problem.

Therapeutic Aspects of Electroconvulsive Therapy

For the treatment to be therapeutic, a seizure must occur. Furthermore, the electrical stimulus must involve sufficient energy. A process called *stimulus dosing* has been developed to deliver the amount of electricity needed to be therapeutic and yet keep the dose to the minimum required to induce a seizure. This will help minimize cognitive impairment. The unit of electrical charge is measured in millicoulombs (mC). Initially, several low doses are given, increasing the charge with each successive stimulation. The dose at which the patient seizes is called the *seizure threshold.* When using bilateral electrode placement, a patient will have a therapeutic response when the dosage is two and one-half times threshold, and about six times threshold when right unilateral placement is used.

Adverse Effects of Electroconvulsive Therapy

Adverse effects during ECT can include brief episodes of hypotension or hypertension, bradyarrhythmias, and tachyarrhythmias; these effects are rarely serious. Fractures were widely reported to occur during ECT-induced seizures in the past but are uncommon now because of the use of muscle relaxants. Other possible adverse effects include prolonged seizures, laryngospasm, and prolonged apnea due to pseudocholinesterase deficiency, a rare genetic disorder. Seizures lasting longer than 2 minutes should be terminated (e.g., with intravenous lorazepam, 1–2 mg). Immediately after treatment, patients experience postictal con-

fusion. Headache, nausea, and muscle pain also may be experienced after ECT.

The most troublesome long-term effect of ECT is memory impairment. Because ECT disrupts new memories that have not been incorporated into long-term memory stores, ECT can cause anterograde and retrograde amnesia that is most dense around the time of treatment. The anterograde component usually clears quickly, but the retrograde amnesia can extend back to months before treatment. It is unclear if the memory loss is due to the ECT or to ongoing depressive symptoms. Not all patients experience amnesia, and modifications in ECT, including unilateral electrode placement, modification of the pulse wave, and the use of low dosages of electricity, help to minimize any memory loss that occurs. All patients should be informed that permanent memory loss may occur.

ECT is generally viewed favorably by patients who have received it. In one study, nearly 80% of the patients believed that they were helped by ECT, and 80% said that they would not be reluctant to have it again. A substantial minority reported approaching the treatment with anxiety, yet more than 80% of the respondents found that it produced no more anxiety than a dental appointment.

■ Self-Assessment Questions

1. What is the presumed mechanism of action of the antipsychotics?
2. What are the common indications for antipsychotics?
3. How are the antipsychotics used in the treatment of acute psychosis? How are they used in maintenance treatment?
4. What are the common extrapyramidal side effects that occur with antipsychotics? Describe the syndromes and discuss their clinical management.
5. What disorders can be treated with antidepressants? Why is the term *antidepressant* a misnomer?
6. What is the putative mechanism of action of the TCAs? Of the MAOIs? Of the SSRIs? Of the other new agents?
7. Are blood levels of TCAs meaningful? When should they be obtained?
8. What are the common side effects of the SSRIs? TCAs? MAOIs?
9. What agent is associated with the occurrence of priapism? Why is this occurrence worrisome?

10. What are the typical plasma level ranges for lithium carbonate for acute treatment of mania? For maintenance treatment?
11. What are the common side effects of lithium? Of valproate? Of carbamazepine?
12. When is lamotrigine used? What are its side effects?
13. What are the commonly used anxiolytics? What are their indications? Contraindications?
14. Describe the adverse effects of anxiolytics. Are they dangerous in overdose?
15. What drugs are commonly used to manage extrapyramidal symptoms in patients receiving antipsychotics?
16. Describe how ECT is administered. What is the purpose of atropine (or glycopyrrolate)? Succinylcholine? Methohexital?
17. What conditions respond well to ECT? What are the adverse effects of ECT?