The skillful practice of psychopharmacology requires a broad knowledge of psychiatry, pharmacology, and medicine. We begin this chapter with an overview of general principles relevant to safe and effective use of psychotropic medications. Subsequent sections cover the major classes of psychotropic medications—antidepressants, antipsychotics, anxiolytics, and mood stabilizers—and the disorders for which they are prescribed. The reader should be aware that this nomenclature is somewhat artificial; for example, many antidepressant medications are also used to treat anxiety disorders.

The authors would like to thank Holly Zboyan, Becky Stager, and Kimberly Cress, M.D., for their invaluable assistance in the preparation of this chapter.

Drug Interactions section contains material developed over many years for other purposes in collaboration with Ann Callahan, Ph.D., and Terence Ketter, M.D.

This work was supported in part by a Young Investigator's Award to Dr. Marangell by the National Alliance for Research on Schizophrenia and Depression.

GENERAL PRINCIPLES

INITIAL EVALUATION

Like all areas of medicine, the art of psychopharmacology rests on proper diagnosis and delineation of medication responses. Before prescribing a psychotropic medication or ECT, a thorough evaluation must be performed with the goals of 1) establishing the diagnosis, course of illness, and target symptoms; 2) deciding whether the diagnosis and target symptoms are likely to respond to medication (for example, dysphoria related to a family problem gener-
effects. This side effect occurs after more prolonged treatment and may be confused with buccolingual tardive dyskinesia (Baldessarini 1988; Deshmukh et al. 1990). It has been found to be present in approximately 4% of patients receiving antipsychotics without concomitant anticholinergics (Yassa and Lal 1986). Like parkinsonian side effects, the rabbit syndrome is treated effectively with anticholinergic drugs.

Akinesia is defined as a behavioral state of diminished spontaneity characterized by decreased gestures, unspontaneous speech, and, particularly, apathy and difficulty with initiating usual activities (Rifkin et al. 1975). Akinesia may appear after several weeks of therapy and is often a subset of the parkinsonism syndrome. Among patients treated with antipsychotic agents, this syndrome may be mistaken for depression. The drugs suggested in Table 27–15 provide effective treatment. Akinesia may also be a manifestation of negative symptoms in a patient with schizophrenia. In this circumstance, use of atypical antipsychotics to improve the negative symptoms should be considered.

Akathisia is an extrapyramidal disorder consisting of a subjective feeling of needing to move, often manifested in an inability to sit still. It is a common reaction that most often occurs shortly after the initiation of antipsychotic medication. After a single oral dose of 5 mg of haloperidol, 40% of patients in one study experienced akathisia; after 1 week of receiving a 10-mg nighttime dose, this rate increased to 75% (van Putten et al. 1984). Unfortunately, akathisia is frequently mistaken for an exacerbation of psychotic symptoms, anxiety, and/or depression. If the dosage of antipsychotic medication is increased, the restlessness continues and eventually worsens. Lowering the dosage may improve the symptoms. Unfortunately, akathisia is among the most treatment resistant of the acute extrapyramidal side effects. In the past, anticholinergic drugs were suggested as the first line of therapy, but they are often ineffective, helping only occasionally when akathisia occurs in combination with other extrapyramidal symptoms, such as rigidity. Benzodiazepines are helpful in some cases.

The treatments of choice for akathisia are the β-adrenergic-blocking drugs, particularly propranolol. Several well-controlled studies have documented that propranolol, in dosages up to 120 mg/day, is an effective treatment for akathisia (Adler et al. 1983, 1989; Lipinski et al. 1984). In general, the lipophilic β-blockers are more effective in treating akathisia than the hydrophilic ones (Dupuis et al. 1987; Reiter et al. 1987; Zubenko et al. 1984). At present there remains a controversy as to whether β-selective drugs effectively treat akathisia, with some negative findings (Zubenko et al. 1984) and some positive reports (Dumon et al. 1992; Dupuis et al. 1987). These drugs avoid the risk of bronchospasm in susceptible patients and, therefore, would be a welcome treatment alternative (Adler et al. 1991; Dumon et al. 1992; Lewis and Lofthouse 1993).

**Tardive disorders.** Tardive dyskinesia (TD) is a disorder characterized by involuntary choreoathetoid movements of the face, trunk, or extremities. The syndrome is usually associated with prolonged exposure to dopamine-receptor-blocking agents, most frequently, antipsychotic drugs. However, use of the drugs such as the antidepressant amoxapine, the antiemetic agents metoclopramide and prochlorperazine, and other drugs with dopamine-receptor-blocking properties also can result in TD. The American Psychiatric Association (APA) Task Force on TD estimated an incidence of 5% per year of exposure among young adults and 30% after 1 year of treatment among elderly patients (American Psychiatric Association 1992). Clozapine seems to carry little or no risk of inducing TD. The incidence of TD in association with the other AAPs has not yet been adequately determined. Preliminary evidence suggests a level of risk for olanzapine between the conventional antipsychotics and clozapine (Tollefson et al. 1997).

The diagnostic features of TD are listed in Table 27–16. These features have been adapted from one of the specific scales developed for the documentation of TD: the Abnormal Involuntary Movement Scale (AIMS). Although this scale is primarily for research use, physicians who prescribe antipsychotic drugs should be familiar with its contents in order to be able to perform a thorough examination for the presence of TD. A procedure for examining a patient for TD can be found in Table 27–17.

An evaluation for abnormal movements should be conducted before treatment begins and every 12 months thereafter. In the mildest stages, the patient may not be aware of the involuntary movements. As the movements become more severe, the patient may become dysfunctional to the point of experiencing difficulty eating or resting. Although the most common form of tardive disorder is the dyskinetic variety, other types have been observed. These include tardive akathisia, tardive dystonia, and tardive tics (Fahn 1985). Tardive dystonia is characterized by frequent contractions of the neck and shoulder muscles, such as seen in torticollis, which emerge with treatment with antipsychotic agents. The patient with tardive akathisia may experience continuous feelings of restlessness.

The most commonly accepted hypothesis of the mechanism for the development of TD is that postsynaptic dopamine receptors develop supersensitivity to dopamine.
the evidence to first exposure to antipsychotic drugs (including drug holidays) is associated with an increased risk, the time since the history of drug holidays (a greater number of drug-free periods associated with an increased risk), the time since the first exposure to antipsychotic drugs (including drug holidays), the presence of brain damage, and the diagnosis (especially the presence of affective disorder).

The issue of informed consent with respect to antipsychotic medications and the risk of TD has been extensively reviewed (Munetz and Roth 1985; Roth 1983). It is usually difficult, if not impossible, to obtain informed consent from a patient with acute psychosis. A general guideline is to inform and educate the family of the patient.

### TABLE 27-16. Clinical features of tardive dyskinesia

<table>
<thead>
<tr>
<th>Category</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>b. Lips and perioral area: involuntary puckering, pouting, smacking.</td>
<td></td>
</tr>
<tr>
<td>d. Tongue: involuntary protrusion, tremor, choreoathetoid movements (i.e., rolling, wormlike movement without displacement from the mouth).</td>
<td></td>
</tr>
<tr>
<td>2. Extremity movements</td>
<td>a. Involuntary movement of upper arms, wrists, hands, fingers: choreic movements (i.e., rapid, objectively purposeless, irregular, spontaneous), athetoid movements (i.e., slow, irregular, complex, serpentine), tremor (i.e., repetitive, regular, rhythmic).</td>
</tr>
<tr>
<td>b. Involuntary movement of lower legs, knees, ankles, toes: lateral knee movement, foot tapping, foot squirming, inversion and eversion of foot.</td>
<td></td>
</tr>
</tbody>
</table>

**Source.** Adapted from the Abnormal Involuntary Movement Scales (AIMS), National Institute of Mental Health 1988 ("AIMS: Abnormal Involuntary Movement Scale" 1988).

### TABLE 27-17. Examination procedure for tardive dyskinesia

<table>
<thead>
<tr>
<th>Step</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Ask patient whether there is anything in his or her mouth (e.g., gum, candy), and if there is, ask him or her to remove it.</td>
<td></td>
</tr>
<tr>
<td>2. Ask patient about the current condition of his or her teeth. Ask patient if he or she wears dentures. Do teeth or dentures bother patient now?</td>
<td></td>
</tr>
<tr>
<td>3. Ask patient whether he or she notices any movements in mouth, face, hands, or feet. If yes, ask him or her to describe them and to assess to what extent they currently bother the patient or interfere with his or her activities.</td>
<td></td>
</tr>
<tr>
<td>4. Have patient sit in chair with hands on knees, legs slightly apart, and feet flat on floor. (Look at entire body for movements while patient is in this position.)</td>
<td></td>
</tr>
<tr>
<td>5. Ask patient to sit with hands hanging unsupported (if male) between legs or (if female and wearing a dress) hanging over knees. (Observe hands and other body areas.)</td>
<td></td>
</tr>
<tr>
<td>6. Ask patient to open mouth. (Observe tongue at rest within mouth.) Do this twice.</td>
<td></td>
</tr>
<tr>
<td>7. Ask patient to protrude tongue. (Observe abnormalities of tongue movement.) Do this twice.</td>
<td></td>
</tr>
<tr>
<td>8. Ask patient to tap thumb, with each finger, as rapidly as possible for 10–15 seconds, separately with right hand, then with left hand. (Observe facial and leg movements.)</td>
<td></td>
</tr>
<tr>
<td>9. Flex and extend patient's left and right arms one at a time. (Note any rigidity.)</td>
<td></td>
</tr>
<tr>
<td>10. Ask patient to stand up. (Observe in profile. Observe all body areas again, hips included.)</td>
<td></td>
</tr>
<tr>
<td>11. Ask patient to extend both arms outstretched in front with palms down. (Observe trunk, legs, and mouth.)</td>
<td></td>
</tr>
<tr>
<td>12. Have patient walk a few paces, turn, and walk back to chair. (Observe hands and gait.) Do this twice.</td>
<td></td>
</tr>
</tbody>
</table>

**Source.** Adapted from the Abnormal Involuntary Movement Scales (AIMS), National Institute of Mental Health 1988 ("AIMS: Abnormal Involuntary Movement Scale" 1988).
about the risks of TD before starting the antipsychotic and to educate the patient gradually about this disorder as soon as possible after agitation and psychosis remit. In many circumstances, true informed consent may not be obtainable from a patient with acute psychosis for several weeks. The psychiatrist also needs to be aware that some states (e.g., California and New Jersey) legally mandate that informed consent be obtained from patients before the initiation of antipsychotic treatment. All such discussions with patients and their families should be documented in the patients' records. Informed consent that is exclusively in the written form has been shown to be less effective in communicating information to the patient than verbal communication combined with written information (Munetz and Roth 1985). The psychiatrist must allocate adequate time to the provision of informed consent consistent with the confusional state and cognitive capabilities of the patient. Further discussion of this area may be found in Chapter 41 of this textbook.

Because antipsychotic medications remain the most effective treatment for most patients with schizophrenia, the case often arises in which a patient develops TD but still requires the medication to function. If discontinuation of the antipsychotic drug is clinically possible, improvement in the TD may be gradual. Worsening of the involuntary movements often occurs initially with tapering of the antipsychotic, a phenomenon referred to as withdrawal dyskinesia. These movements also may be masked temporarily by increasing the dosage of the antipsychotic medication, but the symptoms eventually reemerge, often in a more severe form. However, a 50% reduction in dyskinetic movement is documented in most patients by 18 months after discontinuation of antipsychotic agents (Glazer et al. 1984).

Anticholinergic drugs, often used for the control of EPS in patients taking neuroleptics, have been shown to worsen some forms of TD. Rennanen et al. (1982) and Yassa (1985) reported that TD improved for 9 of 15 patients whose anticholinergic medications had been discontinued. Paradoxically, anticholinergic drugs in high doses have been shown to be of value in the treatment of tardive dystonia (Burke et al. 1982; Fahn 1985).

There is no definitive treatment for TD. Alpha tocopherol (vitamin E) has been shown to be of some benefit, most often for patients who have had TD for less than 5 years (Adler et al. 1993; Akhtar et al. 1993; Dabiri et al. 1994; Egan et al. 1992; Elkashef et al. 1990; Lohr and Caligiuri 1996; Lohr et al. 1987). Vitamin E is a relatively nontoxic antioxidant that may protect neurons from the damaging effects of free radicals, which have been implicated in the etiology of TD. The typical dosage of vitamin E is 1,600 IU/day. In addition to the treatment of existing TD, prophylaxis with vitamin E has been recommended. The most promising treatment for TD is clozapine. In an open trial, Lieberman et al. (1991) found at least 50% improvement in TD among 43% of patients switched from another antipsychotic to clozapine. Severe TD, and especially tardive dystonia, seem to respond best. In view of the risks of agranulocytosis with clozapine treatment (discussed later), this strategy is reserved for patients with severe TD or who are also poorly responsive to other agents. The efficacy of the other AAPs has not been systematically evaluated in this regard, but it is reasonable to attempt to use these agents prior to a clozapine trial. Other medications that have been used with limited benefit include dopamine-depleting agents, GABAergic drugs, low-dose dopamine agonists, and calcium channel blockers.

**Neuroleptic malignant syndrome.** In rare instances, patients taking antipsychotic medications may develop a potentially life-threatening disorder known as neuroleptic malignant syndrome (NMS). Although it occurs most frequently with the use of high-potency conventional antipsychotic drugs, this condition may accompany treatment with any antipsychotic agent, including the AAPs. Patients with NMS typically exhibit marked muscle rigidity, although this feature may be absent with the AAPs. Other salient features include fever, autonomic instability, elevated WBC count (above 15,000/mm³), elevated creatinine phosphokinase (CPK) levels (above 300 U/mL), and delirium. The elevated CPK is due to muscle breakdown, which can lead to myoglobinuria and acute renal failure.

In a large prospective study, Rosebush and Stewart (1989) found that NMS was associated most often with the initiation or increase of antipsychotic medication, and in every case it occurred within 1 month of admission to a psychiatric unit. Episodes that occurred in patients taking stable dosages of antipsychotic medications were almost always associated with antecedent dehydration. Lithium use increases the risk appreciably, as does the presence of a mood disorder. Higher dosages, rapid escalation of dosage, and intramuscular injections of antipsychotics are all associated with the development of NMS (Keck et al. 1989). The keys to treatment after recognition of the syndrome are discontinuation of all medications, thorough medical evaluation, intravenous fluids, antipyretic agents, and cooling blankets. Several medications have been suggested to control NMS. Dantrolene and bromocriptine have received the most attention and are apparently the most successful agents. However, their efficacy over supportive care has not been proved (Guze and Baxter 1985; Levenson
The body of law applied to the practice of psychiatry does not differ from that of medicine in general. Nevertheless, the diagnosis, treatment, and management of patients with psychiatric disorders present not only unique clinical and ethical concerns but unique legal considerations as well. For instance, determinations of a patient's competency, as well as the patient's ability to manage his or her personal affairs, may be required to determine the patient's mental capacity to make health care decisions. Currently, competency determinations are particularly relevant for patients suffering from Alzheimer's disease or dementia related to acquired immunodeficiency syndrome (AIDS). Accordingly, ethical and legal issues such as informed consent, the right to treatment, the right to refuse treatment, substitute decision making, and advance directives are commonly confronted in treating psychiatric patients.

Individuals who have been criminally charged must be legally competent to stand trial. Defendants with psychiatric impairments may not meet the competency standard. Therefore, such persons may require pretrial evaluations of their mental capacity to understand the charges against them and their ability to assist counsel in their own defense. Moreover, depending on the nature and duration of a psychiatric disorder, criminal defendants may seek acquittal or have the charges against them reduced on the basis of the argument that they were legally insane at the time the offense occurred.

Vulnerability to psychiatric malpractice suits has increased, more so in specific areas of psychiatric practice. Table 41-1 reveals the recent malpractice claims experience of the Psychiatrists Purchasing Group, the liability insurer of members of the American Psychiatric Association ("Benefacts" 1996). The increased use of somatic therapies, the assessment and management of violent patients, use of techniques to recover memories of sexual abuse, sexual misconduct, boundary violations, premature discharge of potentially violent patients, and managed care settings all represent areas of heightened liability for the psychiatric practitioner.

The chance of a psychiatrist being sued in the 1980s was 1 in 25 per year ("Benefacts" 1996). Through 1995, however, the odds have increased to about 1 out of every 12 psychiatrists. In some states, psychiatrists are sued at the rate of 1 in 6 every year. Psychiatrists in Massachusetts have moved from 20th to 12th among the most frequently sued specialists within a period of 3 years.

The American Psychiatric Association-sponsored Professional Liability Insurance Program identifies a number of factors to account for the increase in malpractice suits:
Exceeding recommended dosages without clinical indications
• Negligently prescribing multiple drugs (i.e., "polypharmacy")
• Negligently prescribing medication for unapproved uses
• Negligently prescribing "unapproved" medications
• Negligently failing to disclose medication risks

As stated earlier, any physician who prescribes medication has a duty initially to obtain the informed consent of the patient (Table 41-3). Obtaining competent informed consent may be complicated by the fact that some psychiatric patients have a compromised mental capacity for health care decision making due to mental illness. Patients lacking such decision-making capacity require consent for treatment by substitute decision makers (Table 41-4).

Each time a medication is changed and a new drug is introduced, informed consent should be obtained. A failure to inform a patient properly of the risks and consequences of a prescribed medication can be grounds for a malpractice action if the patient is injured as a result (Karasik v. Bird 1984; Moran v. Botsford General Hospital 1984; Wright v. State 1986).

Other areas of negligence involving medication that have resulted in legal action include 1) failure to treat side effects once they have been recognized or should have been recognized, 2) failure to monitor a patient's compliance with prescription limits, 3) failure to prescribe medication or appropriate levels of medication according to the treatment needs of the patient, 4) failure to refer a patient for consultation or treatment by a specialist, and 5) negligent withdrawal from medication.

### Table 41-4. Common consent options for patients lacking the mental capacity for health care decisions

<table>
<thead>
<tr>
<th>Option</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proxy consent of next of kin</td>
</tr>
<tr>
<td>Adjudication of incompetence, appointment of a guardian</td>
</tr>
<tr>
<td>Institutional administrators or committees</td>
</tr>
<tr>
<td>Treatment review panels</td>
</tr>
<tr>
<td>Substituted consent of the court</td>
</tr>
<tr>
<td>Advance directives (living will, durable power of attorney, health care proxy)</td>
</tr>
<tr>
<td>Statutory surrogates (spouse or court-appointed guardian)</td>
</tr>
</tbody>
</table>


The number of psychiatric patients treated with neuroleptics is quite high (H. J. Parry et al. 1973). The risk of developing TD is approximately 4%-7% per year of neuroleptic use (Lohr et al. 1986). These projections are even higher for elderly patients (Kane et al. 1982; Klawans and Barr 1982). As the newer antipsychotic drugs are used more frequently, the risk of developing TD is expected to be lower.

Given these data, the potential for TD litigation is clear. Despite the possibility of a large number of TD-related lawsuits, relatively few psychiatrists have been sued under this cause of action. One reason may be that patients who develop TD may not have the physical and psychological stamina required to pursue litigation.

Cases involving allegations of negligence after a patient develops TD are based on the same legal elements as any other malpractice action. Moreover, the bases for negligence mirror those that have been previously identified with general medication cases. These areas include, but are not limited to, the following:

### Table 41-3. Informed consent: reasonable information to be disclosed

<table>
<thead>
<tr>
<th>Area</th>
<th>Information Provided</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diagnosis</td>
<td>Description of the condition or problem</td>
</tr>
<tr>
<td>Treatment</td>
<td>Nature and purpose of proposed treatment</td>
</tr>
<tr>
<td>Consequences</td>
<td>Risks and benefits of the proposed treatment</td>
</tr>
<tr>
<td>Alternatives</td>
<td>Viable alternatives to the proposed treatment including risks and benefits</td>
</tr>
<tr>
<td>Prognosis</td>
<td>Projected outcome with and without treatment</td>
</tr>
</tbody>
</table>


TARDIVE DYSKINESIA

The development of neuroleptic medications in the mid-1950s dramatically improved the treatment and management of schizophrenic patients. Shortly after the introduction of neuroleptic medications as therapeutic agents, however, researchers and clinicians observed unusual muscle movements in some patients, referred to as tardive dyskinesia (TD).

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Cases involving allegations of negligence after a patient develops TD are based on the same legal elements as any other malpractice action. Moreover, the bases for negligence mirror those that have been previously identified with general medication cases. These areas include, but are not limited to, the following:
Failure to evaluate and monitor a patient properly. Psychiatrists who do not follow patients according to their clinical needs may be subject to legal claims of failure to monitor patients properly.

The defenses and preventive measures applicable to TD-related malpractice claims are consistent with those used in any case alleging negligent drug treatment. Generally speaking, the application of sound clinical practice that is appropriately communicated to the patient and documented in the medical chart serves as an effective foil to any allegations of negligence should TD develop (Frasier v. Department of Health and Human Resources 1986; Radank v. Heyl 1986; Rivera v. NYC Health and Hospitals 1988). Moreover, for the psychiatrist who is treating *chronic aggression* with antipsychotic drugs, it is important to consider the warning by Yudofsky et al. (1987) that

the use of antipsychotic medications in treating chronic aggression involves a substantial risk of the emergence of tardive dyskinesia, because the prevalence of tardive dyskinesia among patients on long-term neuroleptic treatment is about 25% ....

While antipsychotic agents are the treatment of choice for aggression due to psychosis and also may be helpful in the acute short-term management of violence through sedative action, we do not recommend their use in the long-term management of aggression, especially that which is secondary to organic brain syndrome. (p. 400)

### ELECTROCONVULSIVE THERAPY

Although a significant proportion of psychiatrists believe that ECT is a viable treatment for certain mental disorders (O'Connell 1982), it has been estimated that *no more than* 3%-5% of all psychiatric inpatients in the United States receive this treatment (Weiner 1979). It can be expected from these figures that legal actions alleging negligence associated with ECT are likely to be infrequent. The low incidence of ECT-related malpractice suits has corroborated this suspicion (Krouner 1975; Perr 1980). Despite this low malpractice potential, lawsuits involving ECT are occasionally brought. Cases involving ECT-related injuries have represented a variety of circumstances in which negligence has occurred. These cases can be categorized into three groups: pretreatment, treatment, and post-treatment.

#### Pretreatment

Although there is some variation in pre-ECT evaluations, the following procedures recommended by the APA Task Force on Electroconvulsive Therapy (American Psychiatric Association 1990) generally should be performed:
Marcus R: Court rules *right to die* depends on patient's intent. Washington Post, June 26, 1990, p A1, 8
Mishkin B: Determining the capacity for making health care decisions, in Issues in Geriatric Psychiatry (Advances in Psychosomatic Medicine, Vol 19). Edited by Billig N, Rabins PV. Basel, Switzerland, S Karger, 1989, pp 151-166
Perr IN: The clinical considerations of medication refusal. Legal Aspects of Psychiatric Practice 1:5-8, 1984