CHAPTER 12. SCHIZOPHRENIA

12.8 SCHIZOPHRENIA: SOMATIC TREATMENT

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The somatic treatment of schizophrenia has changed substantially during the 1990s. Until 1990 when clozapine (Clozaril) was introduced in the United States, all available antipsychotic drugs had a similar range of efficacy and were associated with neurological side effects that seriously interfered with their effectiveness. Clozapine was the first of a new generation of antipsychotics that are associated with far fewer extrapyramidal side effects than older drugs and perhaps have better efficacy. Although clozapine's association with agranulocytosis has limited the number of patients who receive it, this agent plays an important role in the treatment of severe psychosis. The introduction of risperidone (Risperdal) in 1994, olanzapine (Zyprexa) in 1996, quetiapine (Seroquel) in 1997, and ziprasidone (Zeldex) in 1998 have given clinicians new alternatives for treating a large number of patients with schizophrenia. The overall impact of these changes on the course of schizophrenia remains to be seen.

HISTORY

The history of somatic therapies in schizophrenia can be divided into two eras: before the discovery of chlorpromazine (Thorazine), the first clearly effective antipsychotic drug, and after. Prior to the introduction of antipsychotics in the early 1950s, several treatments had been administered to individuals with psychotic illness, with results that are difficult to interpret because careful research methods in psychiatry had not been developed. During the late nineteenth and early twentieth century

schizophrenia was believed to deteriorate inevitably into dementia. As a result, patients were frequently hospitalized for long periods. Somatic treatments were used to help control the most severe symptoms of the disorder and to make hospitals safer. Sedating agents such as bromides and barbiturates were used to control agitation, and physical treatments such as hydrotherapy and wet sheet packs were also used for their calming effects. In the early 1920s sleep treatment with barbiturates was introduced. This treatment was based on the observation that symptoms tended to improve following an overdose of barbiturates. The method involved maintaining patients in a highly sedated state for days, during which they would awaken only for necessary activities such as eating and personal hygiene.

Insulin coma treatment was introduced during the 1930s. Patients were administered gradually increasing doses of insulin until a coma occurred. After being monitored for an hour the patient was administered glucose, which terminated the coma. Patients were commonly administered as many as 20 comas. Insulin coma was widely used in the treatment of psychosis, suggesting that it may have been somewhat effective. Unfortunately, it never received adequate research trials, and it remains unclear if the treatment was effective. It was abandoned when antipsychotics were introduced.

Prefrontal lobotomy was proposed as a treatment for serious mental illnesses by Egas Moniz in 1935. The support for this treatment came from animal studies in which frontal lobe extirpations in monkeys resulted in an animal that appeared less easily frustrated. The use of frontal lobotomy was common prior to the introduction of effective antipsychotics, although there is a remarkable lack of controlled studies comparing psychosurgery with other treatments. Although reports suggest that lobotomy may have been effective in reducing severe psychotic symptoms, they also resulted in deteriorations in other areas. Following lobotomies patients frequently demonstrated personality deterioration with impulsive and psychopathic behaviors as well as impaired concept formation and ability to plan. Psychosurgery was abandoned as a treatment for schizophrenia after the introduction of effective antipsychotic medications.

Convulsive therapies were developed after it was observed that some patients improved after a seizure. Drugs such as camphor and metrazol were used initially to induce seizures but were abandoned after Ugo Cerletti and Lucio Bini proposed the use of electrically induced convulsions. In its early days electroconvulsive therapy (ECT) was administered without anesthetics or muscle relaxants. The lack of anesthetics inspired fear in many patients, and the lack of muscle relaxants led to injuries from forceful muscle contractions. ECT administered with anesthesia and muscle relaxants continues to have a role in certain types of schizophrenia.

The first effective antipsychotic medications were probably derived from extracts of the rauwolfia plant. Publications from the 1930s and 1940s suggest that these agents were effective for both hypertension and psychosis. Reserpine (Serpasil) the most potent of the rauwolfia alkaloids, was introduced in the early 1950s and was widely prescribed in the United States and elsewhere for schizophrenia and other psychotic illnesses. Studies comparing reserpine with dopamine receptor antagonists suggested that their efficacies were similar. However, reserpine's adverse effects, particularly depression, led most clinicians to prefer the dopamine receptor antagonists. Thus, reserpine is only rarely used for managing psychosis.

The discovery of the phenothiazine chlorpromazine in the early 1950s may be the most important single contribution to the treatment of psychiatric illness. Laborit, a surgeon in Paris, noticed that administering chlorpromazine to patients prior to surgery resulted in an unusual state in which they seemed less anxious regarding the procedure. In 1952 he convinced Jean Delay and Pierre Deniker and other psychiatrists to administer chlorpromazine to psychotic and excited patients—the effects were extraordinary. Chlorpromazine was effective in reducing hallucinations and delusions as well as excitement. It also caused adverse effects that resembled parkinsonism. The use of chlorpromazine spread rapidly through the psychiatric hospitals in Paris and eventually to the rest of the world. Since chlorpromazine was relatively easy to administer to large numbers of patients, it was partially responsible for a substantial reduction in the number of patients in psychiatric hospitals.

Thioridazine and fluphenazine (Permitil, Proloxin) as well as other classes of drugs such as the butyrophenones (e.g., haloperidol [Haldol]) and the thioxanthenes (e.g., thiothixene [Navan]) were developed after the introduction of chlorpromazine. Although these newer agents differed in their potency and their adverse effect profiles, all had similar effectiveness. Clozapine, the first effective antipsychotic with negligible extrapyramidal effects was discovered in 1958 and first studied in the 1960s. However, in 1976 it was found to be associated with a substantial risk of agranulocytosis, which resulted in delays in its introduction. In 1990 clozapine finally became available in the United States, but its use was restricted to patients who responded poorly to other agents. Risperidone, olanzapine, quetiapine, ziprasidone, and other agents with affinity for both dopamine and serotonin receptors cause minimal extrapyramidal side effects and are not associated with a risk of agranulocytosis. These newer agents are replacing older drugs as the standard treatments for schizophrenia.

PHASES OF TREATMENT IN SCHIZOPHRENIA

Somatic treatment varies depending on the phase of a patient's illness. The acute stage is usually characterized by psychotic symptoms that require immediate clinical attention. These symptoms may represent a first psychotic episode or, more commonly, a relapse in an individual who has experienced multiple episodes. Treatment during this phase focuses on alleviating the most-severe psychotic symptoms. Following the acute phase, which usually lasts from 4 to 8 weeks, patients usually enter a stabilization phase in which acute symptoms have been controlled, but patients remain at risk for relapse if treatment is interrupted or if they are exposed to stress. During this phase, treatment focuses on consolidating therapeutic gains with treatments similar to those used in the acute stage. This phase may last as long as 6 months following recovery from acute symptoms. The third stage is the stable, or maintenance, phase when the illness is in relative remission. The goals during this phase are to prevent psychotic relapse and to assist patients in improving their level of functioning.

FOCUS OF TREATMENT

Patients with schizophrenia can demonstrate large differences in the severity of their psychopathology as well as in the type of symptoms they demonstrate. As a result, treatment strategies should be individualized to the characteristics of each patient's illness. Recent studies indicate that

psychopathology in schizophrenia can be classified into three dimensions: psychotic, negative, and disorganized. Psychotic symptoms include hallucinations, ideas of reference, and delusions. These are symptoms that tend to result in hospitalization and to disrupt the lives of patients. Negative symptoms include decreased motivation, emotional blunting, and impoverished speech and thought; these symptoms are associated with the social and vocational impairments of schizophrenia. Disorganized symptoms include disorganized speech and behavior as well as impairments in attention and information processing; these symptoms are also associated with the social and vocational impairments of schizophrenia.

Antipsychotic drugs are most effective in treating the psychotic dimension. As a result, clinicians adjusted their expectations about the goals of pharmacotherapy in schizophrenia. Although some improvement in the other dimensions often occurred with drug treatment, clinicians were usually satisfied when psychotic symptoms were minimized. These expectations changed following the introduction of clozapine. A proportion of patients who improved with clozapine demonstrated changes in other dimensions as well, including better social and vocational adjustments. Similar improvements have been reported on other serotonin-dopamine antagonists. In addition, other studies (discussed later) suggested that both negative and cognitive symptoms improved with these newer medications.

EFFECTIVENESS OF ANTIPSYCHOTIC MEDICATIONS

A large body of evidence supports the effectiveness of antipsychotics for schizophrenia. Many of these studies were carried out in the 1960s when there was skepticism that these agents were truly antipsychotic rather than more effective tranquilizers. An evaluation of these studies by the 1995 Schizophrenia Patient Outcomes Research Team (PORT) found that about 70 percent of patients treated with an antipsychotic achieved remission. In contrast, only about 25 percent of patients treated with placebo remitted. Most studies compared one or more antipsychotic with either a placebo or an agent such as phenobarbital that served as a control; antipsychotic drugs were found to be more effective than either placebo or tranquilizers.

EFFECTIVENESS OF ECT IN SCHIZOPHRENIA

ECT has been studied in both acute and chronic schizophrenia. Studies in patients with recent-onset schizophrenia indicate that ECT is about as effective as antipsychotic medications and more effective than psychotherapy. Other studies suggest that supplementing antipsychotic medications with ECT is more effective than antipsychotic medications alone. Studies of ECT in chronic schizophrenia have been less promising. Anecdotal reports indicate that ECT is effective in patients who respond poorly to antipsychotic medications. Overall these results suggest that ECT probably has a limited role in schizophrenia. Patients should first receive trials of antipsychotic medications; if these medications are ineffective, acutely ill patients can be treated with ECT. Antipsychotic medications should be administered during and following ECT treatment.

TREATMENT OF ACUTE EPISODES

Indications for Somatic Treatment Nearly all patients with acute psychotic symptoms benefit from an antipsychotic medication. Aside from relieving symptoms, evidence indicates that lengthy delays in initiating drug treatment may alter the long-term course of schizophrenia. This evidence is summarized in a scholarly review by Richard J. Wyatt, who found that treatment delays—usually of 6 months or more—were associated with a greater need for hospital treatment and a worse social and vocational outcome. Many of the studies reviewed by Wyatt have important limitations such as lack of randomization and comparing individuals treated during different decades. However, for ethical reasons a definitive study will never be carried out to determine if withholding treatment worsens the long-term course of schizophrenia so it is probably prudent for clinicians to consider the possibility that untreated psychosis can result in a type of permanent damage.

These data do not mean that all patients need to be treated immediately. In some circumstances the management of a patient may be better if drug treatment is delayed for several days. A brief delay may permit clinicians to make a more thorough diagnostic evaluation and rule out causes of abnormal behavior such as substance abuse, extreme stress, medical illnesses, and other psychiatric illnesses.

Assessment Whenever possible, patients should receive a physical examination with a neurological examination, a mental status examination, and a laboratory evaluation before medications are started. A urine screen for drugs of abuse and blood tests for complete blood count (CBC) electrolytes, glucose, and liver, renal, and thyroid function should be ordered. Other evaluations that should be considered are pregnancy tests in women, electrocardiograms (ECGs) when cardiac disease or age is a factor, and human immunodeficiency virus (HIV) and syphilis tests when relevant. The presence of movement disorders—particularly preexisting tardive dyskinesia—should be assessed because they may influence the selection of an antipsychotic.

Antipsychotics are relatively safe drugs so treatment can usually begin before the results of laboratory tests are known. An exception is clozapine treatment, which should only begin after the patient is known to have a normal CBC. Under emergent conditions—for example, when patients refuse to cooperate with an evaluation—antipsychotics can be administered prior to a medical evaluation.

Selection of an Antipsychotic Drug The introduction of new antipsychotic agents has made the selection of an antipsychotic much more complicated. Prior to the development of the new antipsychotics, all the drugs were equally effective for schizophrenia. Many clinicians believed that different subtypes of schizophrenia responded differently to different antipsychotics. For example, it was proposed that more agitated patients responded better to more-sedating drugs whereas more withdrawn patients responded better to less-sedating agents; however, controlled trials failed to support this. The differences among antipsychotics were confined to their side effects, the available formulations, and, to some extent, their cost. The newer antipsychotics challenged this view, suggesting that certain populations of individuals with schizophrenia were likely to do better on a newer antipsychotic.

Antipsychotic drugs can be categorized into two main groups: the older conventional ones, which have also been called *dopamine receptor antagonists* and the newer second-generation drugs which have been

called *serotonin-dopamine antagonists (SDAs)*, or more broadly, atypical antipsychotics. This textbook uses the terms *dopamine receptor antagonist* and *SDA*, which refer to the theory that the antipsychotic effects of dopamine receptor antagonists result from the blockade of dopamine type 2 (D2) receptors. The SDAs differ in having effects related to their ratio of D_2 and serotonin (5-hydroxytrptamine [5-HT]) type 2A ($5\text{-}HT_{2A}$) antagonism. The dopamine receptor antagonists are further categorized as being low-, mid- or high-potency, with the higher-potency drugs having a greater affinity for D_2 receptors and a greater tendency to cause extrapyramidal side effects. Low-potency drugs are less likely to cause extrapyramidal side effects, but more likely to cause postural hypotension, sedation, and anticholinergic effects.

A number of factors should be considered in selecting an antipsychotic medication. Perhaps the most important consideration should be the patient's prior experience with drug treatment. This includes both the patient's clinical and subjective response. Regarding the subjective response, studies by Theodore Van Putten and others found that a patient's early response to a query such as “How does this medication agree with you?” was a powerful predictor of whether that patient would comply with taking that particular medication. In other words, if the patient has uncomfortable side effects on a medication, compliance is likely to be poor if that medication is prescribed.

Prior to the introduction of the SDAs few options were available for patients who developed extrapyramidal effects. At times, dosage reduction or changing the patient to a lower-potency dopamine receptor antagonist may be helpful. Unfortunately, many patients experience extrapyramidal or other adverse effects at the lowest effective dosage that is clinically effective. The introduction of the SDAs provides an opportunity for treating these individuals with agents that seldom cause extrapyramidal side effects at their effective dosage.

With these factors in mind, clinicians should consider the factors included in Table 12.8-1. In some cases these recommendations are based on incomplete data. For example, it remains unproven that patients with prominent negative or cognitive symptoms will respond better to an SDA than to a dopamine receptor antagonist. Haloperidol is recommended for pregnant patients because more data support its safety and not because it has proved safer than other drugs.

Factors	Considerations
Subjective response	A dyphoric subjective response to a particular drug predicts poor compliance with that drug
Sensitivity to extrapyrimidal adverse effects	A serotonin-dopamine antagonist (SDA)
Tardive dyskinesia	Clozapine or (possibly another SDA)
Poor medication compliance or high risk of relapse	Injectable form of a long-acting antagonist (haloperidol or fluphenazine)
Pregnancy	Probably haloperidol (most data supporting its safety)
Cognitive symptoms	Possibly an SDA
Negative symptoms	Possibly an SDA

Table 12.8-1 Factors Influencing Antipsychotic Drug Selection

An important nonclinical factor is the cost of the drug; the SDAs are much more expensive. However, evidence indicates that the higher drug costs of these agents may be offset by other factors. Studies from the Department of Veterans Affairs and State Hospitals in Connecticut found that patients treated with clozapine required fewer hospital days than patients treated with a conventional dopamine receptor antagonist. As a result, the reduction in hospital days compensated for the higher drug cost associated with clozapine treatment. Similar results from other studies suggest that the higher costs of risperidone and olanzapine may also be partially offset by a reduced need for hospitalization.

In selecting a drug for first-episode patients, clinicians should give a high priority to minimizing adverse effects. Many of these individuals are ambivalent about drug treatment and may discontinue antipsychotics when they experience relatively mild adverse effects. Unpleasant experiences with medications during this initial episode may be frightening to these individuals and may influence their future attitudes toward pharmacotherapy. These considerations may lead to the selection of an SDA or a relatively low dosage of a high-potency dopamine receptor antagonist. A number of studies indicate that both olanzapine and risperidone are effective for first-episode patients.

Route of Administration The decision regarding route of administration is usually straightforward. Under most conditions, patients should be treated with an oral antipsychotic agent. Most antipsychotic drugs have half-lives that permit a single daily dose. Short-acting intramuscular drugs are useful when the patient refuses oral dosing and when a rapid onset is helpful. Intramuscular administration of most antipsychotics results in peak plasma concentrations in about 30 minutes, with clinical effects emerging within 15 to 30 minutes. Most orally administered dopamine receptor antagonists yield a peak plasma concentration 1 to 4 hours following administration.

Antipsychotic medications can also be administered as long-acting injectable compounds. These drugs differ from short-acting compounds in that they have a very gradual onset of action and are eliminated very slowly. This route of administration is helpful for long-term maintenance therapy, but not for acute treatment because clinicians cannot titrate dosage against adverse effects or clinical effects when the onset of clinical effects may occur weeks or months after a drug or dosage change.

Prescribing Antipsychotics Prior to prescribing an antipsychotic drug, clinicians should describe the medication, its target symptoms, and its possible side effects. It is particularly important to describe adverse effects such as akathisia, which can be misinterpreted as agitation under some circumstances. Patients who are severely disturbed may be unable to participate meaningfully in this discussion. However, most patients benefit from information about the goals of treatment and important risks associated with antipsychotic medication. Patients with schizophrenia may be suspicious so it is particularly important to emphasize that they can participate in interpreting medication effects. Because psychotic individuals may be dependent on the help and support of their families, it is frequently helpful to involve one or more family members in decisions about drug treatment.

In some settings and locations patients must give written or verbal consent prior to receiving an antipsychotic medication. This can be a dilemma for patients who are conceptually disorganized and

find it difficult to understand the risks and benefits of drug treatment. Under these circumstances, clinicians should adjust the complexity of the discussion to the patient's state of mind. Thus, it may be appropriate to provide a limited amount of information that focuses on the most common acute adverse effects of the medication when the patient is most seriously impaired. As the patient improves, clinicians may then elaborate on the costs and benefits of medication. For example, detailed discussions about tardive dyskinesia, an adverse effect associated with chronic treatment, may be deferred until the patient has improved and long-term maintenance is being considered.

Psychiatrists must also evaluate whether acutely disturbed patients can participate meaningfully in decisions about their medication. Clinicians should become familiar with local and state laws that affect a patient's right to refuse or accept drug treatment. The most difficult situation is when a patient who desperately needs medication refuses it. Under some conditions, family members who have been educated about schizophrenia may be helpful in convincing patients to accept medication. Every locality has provisions for treating patients against their will under emergency conditions; some areas permit involuntary treatment when certain conditions are met. As patients improve, the great majority eventually accept their own need for medication.

Dosage Selection Finding the best dosage of an antipsychotic is both difficult and important. It is important because these agents, particularly the dopamine receptor antagonists, may cause adverse effects at their effective dosages. Often the clinician must weigh the therapeutic advantages of a particular dosage against uncomfortable or disabling side effects. Figure 12.8-1, from a study by Theodore Van Putten and his colleagues, displays dose-response curves for fluphenazine for both clinical improvement and disabling side effects. These two curves are close together, which indicates that it may be difficult for the clinician to find a dosage that results in clinical improvement without substantial adverse effects.

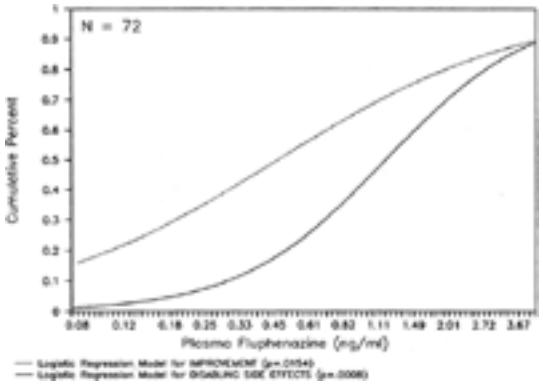

FIGURE 12.8-1 Improvement and disabling side effects as a function of plasma fluphenazine concentration.

Finding the right dosage is difficult because the physician cannot titrate dosage against clinical effects because of the delay between a clinical intervention and the patient's clinical response. Some individuals experience a delay of days or even weeks between the time treatment is started and when the patient eventually responds. These studies are supported by findings indicating that the neurochemical response to an antipsychotic agent is complex and includes an initial blockade of central dopamine receptors, followed by delayed decrease in dopamine turnover.

Although high doses of dopamine receptor antagonists can be associated with extrapyramidal side effects, some patients can tolerate antipsychotics at very high dosages. This is particularly true of nonsedating, high-potency drugs, which has led clinicians to raise the prescribed dosage in hope that higher dosages will lead to greater improvement than moderate dosages. This belief resulted in a substantial increase in the average dosage of antipsychotic drugs prescribed in the United States during the 1970s and 1980s. Many psychiatrists during this period routinely prescribed dosages above 1000 mg a day of chlorpromazine equivalents (20 mg of haloperidol), whereas others reserved high-dosage treatment for patients who remained symptomatic on lower dosages of medication.

A number of dosage comparison studies have failed to support the routine use of higher doses; that is, when groups of patients are assigned to higher dosages (e.g., more than 2000 mg a day of chlorpromazine or 40 mg a day of haloperidol), the rate of improvement and the amount of improvement are no greater than for those assigned to more moderate dosages. Clinicians are sometimes impressed by individuals who require these higher dosages, suggesting that there is a small group of patients who should be treated with high dosages. However, most patients who receive these high dosages are only partial responders to an antipsychotic and have endured dosage increases that were not associated with improvement.

Dosage comparison studies indicate that dosages below 300 mg a day of chlorpromazine (or 5 mg a day of fluphenazine or haloperidol) are likely to be too low for many psychotic patients. At the same time doses above 1000 mg a day of chlorpromazine (or 20 mg a day of fluphenazine or haloperidol) are seldom necessary and may lead to substantial adverse effects.

Only limited data from controlled trials exist to assist clinicians in finding the best dose of clozapine. The mean dose of clozapine prescribed differs between Europe and the United States, with European physicians commonly prescribing less than 300 mg of clozapine daily and clinicians in the United States often prescribing 500 mg or more. These experiences support the practice of treating most clozapine patients with doses in the range of 300 to 500 mg daily. However, adverse effects, particularly sedation and orthostatic hypotension, are often limiting factors that prevent clinicians from reaching a targeted dosage. Although some patients have an optimal response at dosages between 600 and 900 mg daily, the risk of seizures increases substantially in this dosage range. More-recent studies suggest that patients are more likely to respond to clozapine when plasma concentrations are 350 ng/mL or higher, suggesting that measuring plasma concentrations may be useful for poor responders.

Large multicenter trials indicate that risperidone is most effective at 4 to 8 mg daily. Higher doses may lead to extrapyramidal effects without increased effectiveness. In the United States, the average dosage of risperidone prescribed for schizophrenia is slightly more than 4 mg daily. This suggests that a reasonable practice would be to manage patients with schizophrenia with 4 mg of risperidone and increase the dosage if they fail to respond after 4 to 6 weeks.

Most patients with acute schizophrenia can be managed on dosages between 15 and 25 mg daily of

olanzapine. Some individuals respond well to as little as 5 or 10 mg daily. Quetiapine is usually effective when dosages are between 150 and 600 mg daily. Ziprasidone is effective at dosages of 80 to 160 mg daily.

A number of recent findings suggest a reasonable strategy for treating acute schizophrenia. The dose of an antipsychotic that is likely to be effective is the dose that occupies an appropriate number of D_2 receptors. For dopamine receptor antagonists this is approximately 80 percent of receptors. The therapeutic response depends upon processes that occur after these receptors have been occupied for a period of time. This observation is supported by findings from both position emission tomography (PET) scanning and the measurement of plasma homovanillic acid, which suggest that clinical improvement is not associated with the immediate effects of the drug on dopamine receptors, but on processes that occur later. Therefore, the goal in the first days of treatment is to prescribe a drug dosage that occupies an adequate proportion of dopamine receptors and to keep the patient comfortable until the drug is effective. If a patient does not respond in the first week or two, this does not indicate that the current treatment is inadequate. Since most patients on antipsychotic drugs improve during the first 6 weeks, patients should be observed for this interval before a drug is changed. Also, the strategy of using medications on an as-needed basis as a guide to finding the optimal dosage makes very little sense because the immediate and delayed responses to the drug are very different.

A comparison of some antipsychotic drugs is presented in Table 12.8-2.

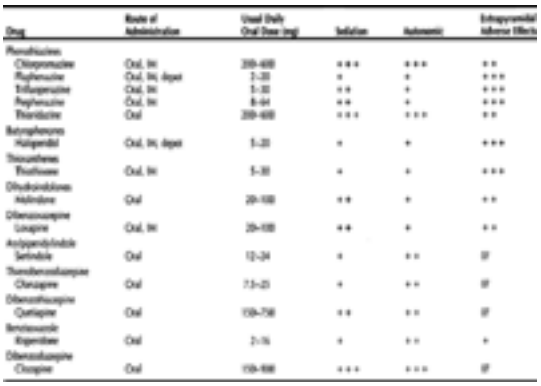

Table 12.8-2 Selected Antipsychotic Drugs

Managing Agitation in Acute Psychosis Agitation in acute schizophrenia can result from disturbing psychotic symptoms such as frightening delusions or suspiciousness or from other causes, including stimulant abuse or extrapyramidal side effects, particularly akathisia. Patients with akathisia can appear agitated when they experience a subjective feeling of motor restlessness. Differentiating akathisia from psychotic agitation can be difficult, particularly when patients cannot describe their internal experience. A trial with an anticholinergic antiparkinson medication or propranolol may be helpful in making the discrimination.

Clinicians have a number of options for managing agitation that results from psychosis. Antipsychotic drugs and benzodiazepines can result in relatively rapid calming when psychotic patients are agitated.

An advantage of an antipsychotic agent is that a single intramuscular injection of a high-potency drug such as haloperidol or fluphenazine can result in calming without excess sedation. Low-potency antipsychotics are often associated with sedation and postural hypotension, particularly when they are administered intramuscularly. The disadvantage of high-potency drugs is that extrapyramidal effects can result from a single injection or, more often, from repeated injections. In younger patients, excessive amounts of injected high-potency drugs can lead to dystonia, which may increase the patient's agitation.

A reasonable intervention for the agitated patient is to treat the agitation with either an intramuscular or oral antipsychotic. If the situation is urgent, intravenous or intramuscular drug administration will lead to more rapid calming. The patient should be started on a regimen of oral antipsychotic the same day. If further treatment of agitation is necessary, benzodiazepines may be administered. Lorazepam (Ativan) has the advantage of reliable absorption when it is administered either orally or intramuscularly. The combination of lorazepam with a high-potency antipsychotic agent has been found to be safer and more effective than large doses of antipsychotics in controlling excitement and motor agitation. Moreover, the use of benzodiazepines may reduce the amount of antipsychotic medication that is needed to control psychotic patients.

MANAGING ADVERSE EFFECTS

Patients frequently experience the adverse effects of an antipsychotic agent before they experience clinical improvement. Whereas a clinical response may be delayed for days or weeks after drugs are started, adverse effects often begin almost immediately. For low-potency drugs, these adverse effects are likely to include sedation, postural hypotension, and anticholinergic effects, whereas high-potency drugs are likely to cause extrapyramidal side effects.

This early onset of adverse effects is important because a patient's interpretation of a drug's effectiveness is often associated with how that drug makes them feel. Moreover, one of the challenges of treating the acutely psychotic is maintaining the trust of individuals who may misinterpret experiences and become suspicious. Warning patients about the potential side effects of medication can lead to prompt management and often improves the trust between patient and clinician. Moreover, minimizing the adverse effects may do long-lasting damage to the patient-clinician relationship because one of the powerful predictors of drug reluctance or drug refusal is an earlier experience of adverse effects.

Extrapyramidal Side Effects The most common form of extrapyramidal side effect is neuroleptic-induced acute akathisia, an adverse effect consisting of a subjective feeling of restlessness along with restless movements, usually in the legs or feet. Patients who experience severe akathisia often pace continuously or move their feet restlessly while they are sitting. Some complain that they are unable to feel comfortable, regardless of what they do. Severe akathisia can make patients feel anxious or irritable, and some reports suggest that severe akathisia can result in aggressive or suicidal acts. Researchers have estimated that 25 to 75 percent of patients treated with a high-potency dopamine receptor antagonist experience akathisia. This adverse effect can be difficult to assess and is frequently misdiagnosed as anxiety or agitation. Akathisia is also thought to be a correlate of poor antipsychotic drug response.

Because patients may experience akathisia as irritability or agitation, asking patients whether they are restless or if they have difficulty sitting still can be helpful in early stages of treatment. At this point, a dosage adjustment, a β-adrenergic receptor antagonist, or an anticholinergic drug may provide considerable relief. Also, patients who have a history of developing severe akathisia that responds poorly to these treatments are likely to do better if they are treated with a new antipsychotic such as clozapine, risperidone, or sertindole.

Neuroleptic-induced acute dystonia is probably the most frightening extrapyramidal side effect. It consists of intermittent or sustained muscular spasms and abnormal postures affecting mainly the musculature of the head and neck, but sometimes the trunk and lower extremities. Common forms of dystonia include abnormal positioning of the neck, impaired swallowing (dysphagia), hypertonic or enlarged tongue, and deviations of the eyes (oculogyric crisis). These reactions usually appear within the first few days of therapy. Dystonias are more likely to occur in younger patients, particularly males in their teens or 20s.

Neuroleptic-induced parkinsonism consists of tremor, muscular rigidity, and a decrease in spontaneous movements, features that resemble the movement disorder in idiopathic parkinsonism. Examination usually reveals a positive glabella tap. This motor disturbance affects about 30 percent of patients who are chronically treated with traditional antipsychotics. The first evidence of drug-induced parkinsonism may be a diminished arm swing or decreased facial expressiveness. Risk factors for antipsychotic-induced parkinsonism include increasing age, dosage, a history of parkinsonism, and underlying basal ganglia damage.

When patients develop neuroleptic-induced parkinsonism, clinicians have a number of alternatives. These include reducing the dosage of the antipsychotic (which is most commonly a dopamine receptor agonist), adding an antiparkinsonism medication, or changing the patient to an SDA that is less likely to cause extrapyramidal adverse effects. The most effective antiparkinsonism medications are the anticholinergic drugs. Although these medications are frequently effective, they also cause their own adverse effects including dry mouth, constipation, blurred vision, and often memory loss. Also, these drugs are often only partially effective, leaving patients with substantial lingering extrapyramidal side effects. Centrally acting β-adrenergic receptor antagonists such as propranolol (Inderal) are frequently effective for treating akathisia; most patients respond to daily dosages between 30 and 90 mg.

Clinicians may consider prescribing prophylactic antiparkinsonism medications for patients who are likely to experience disturbing extrapyramidal effects. These include patients who have a history of extrapyramidal sensitivity or those who are being treated with relatively high dosages of high-potency drugs. Prophylactic antiparkinsonism medications may also be indicated when high-potency drugs are prescribed for young men who tend to have an increased vulnerability for developing dystonias; these patients may also be candidates for the newer drugs.

Some individuals are highly sensitive to extrapyramidal adverse effects at doses that are necessary to control their psychosis. For many of these patients, the adverse effects of the medication may seem

worse than the illness itself. These patients should routinely be treated with an SDA because these agents result in substantially fewer extrapyramidal adverse effects than the dopamine receptor antagonists do. These highly sensitive individuals may actually experience extrapyramidal side effects on an SDA. Risperidone may cause extrapyramidal effects at higher dosages, (e.g., above 6 mg) and olanzapine, quetiapine, and ziprasidone may cause akathisia at their higher dosages.

Tardive Dyskinesia and Other Tardive Syndromes Chronic treatment with an antipsychotic—usually for 6 months or more—can result in movement disorders including neuroleptic-induced tardive dyskinesia and other tardive disorders. Tardive dyskinesias commonly consist of abnormal, involuntary movements of the mouth, tongue, trunk, and extremities. The oral-facial movements occur in about three-fourths of patients with tardive dyskinesia and may include lip smacking, sucking, and puckering as well as facial grimacing. Other movements may include irregular movements of the limbs, particularly choreoathetoid-like movements of the fingers and toes and slow, writhing movements of the trunk. Younger patients with tardive dyskinesia tend to develop slower athetoid movements of the trunk, extremities, and neck.

The abnormal movements of tardive dyskinesia are usually reduced by voluntary movements of the affected areas and are increased by voluntary movements of unaffected areas. The abnormal movements of tardive dyskinesia are usually increased with emotional arousal and absent when the individual is asleep. According to the research criteria in DSM-IV the abnormal movements should be present for at least 4 weeks and patients should have been exposed to an antipsychotic agent for at least 3 months. The onset of the abnormal movements should occur either while the patient is receiving an antipsychotic agent, within 4 weeks of discontinuing an oral agent, or 8 weeks after the withdrawal of a depot antipsychotic drug.

Prevalence surveys indicate that 20 to 30 percent of patients who are chronically treated with a dopamine receptor antagonist exhibit symptoms of tardive dyskinesia. Three to 5 percent of young patients receiving a dopamine receptor antagonist develop tardive dyskinesia each year. The risk in elderly patients is much higher. Although seriously disabling dyskinesia is uncommon, a small proportion of patients have trouble walking, breathing, eating, and talking. Individuals who are more sensitive to acute extrapyramidal effects appear to be more vulnerable to developing tardive dyskinesia. Patients with cognitive disorders and mood disorders may also be more vulnerable to developing tardive dyskinesia than those with schizophrenia.

All dopamine receptor antagonists are associated with a risk of tardive dyskinesia. Evidence from prospective studies indicates that clozapine is associated with a substantially lower risk than dopamine receptor antagonists. Anecdotal evidence indicates that clozapine can decrease abnormal movements in some patients with tardive dyskinesia. At this time it is unclear if the other SDAs are also associated with a lower risk than the dopamine receptor antagonists. The argument has been made that because these drugs are less likely to cause extrapyramidal side effects, they are less likely to cause tardive dyskinesia. For risperidone and olanzapine, prospective studies indicate new cases of tardive dyskinesia develop at a lower rate on these agents than on haloperidol. However, these studies are relatively small and include few cases of tardive dyskinesia. Until these findings are replicated with these agents or other

SDAs, clozapine is the drug of choice for individuals who suffer from disabling tardive dyskinesia.

A Task Force on Tardive Dyskinesia of the American Psychiatric Association recently made a number of recommendations for preventing and managing tardive dyskinesia. These include (1) establishing objective evidence that antipsychotic medications are effective for an individual; (2) using the lowest effective dosage of an antipsychotic drug; (3) prescribing cautiously with children, elderly patients, and patients with mood disorders; (4) examining patients on a regular basis for evidence of tardive dyskinesia; (5) considering alternatives to antipsychotic agents, obtaining informed consent, and also considering dosage reduction in patients who develop tardive dyskinesia; (6) if the tardive dyskinesia worsens consider a number of options, including discontinuing the antipsychotic drug, switching to a different drug, or a trial of clozapine.

Regular monitoring for tardive dyskinesia should be a component of management strategies with antipsychotic drugs. The monitoring should be particularly careful for patients who have an increased risk for tardive dyskinesia, including elderly patients, patients who are sensitive to extrapyramidal side effects, and individuals with affective illness. Routine monitoring should include examination every 3 to 6 months, and high-risk groups should be monitored every 3 months.

A summary of extrapyramidal syndromes is presented in Table 12.8-3.

Table 12.8-3 The Drug-Induced Extrapyramidal Syndromes

Other Adverse Effects Sedation and postural hypotension can be important adverse effects for patients who are being treated with low-potency DRAs, such as chlorpromazine and thioridazine, and clozapine. These effects are often most severe during the initial dosing with these medications, so it may be weeks before patients treated with these medications—particularly clozapine—reach a therapeutic dosage. Although most patients develop tolerance to sedation and postural hypotension, sedation may continue to be a problem. Daytime drowsiness may interfere with such patients attempts to return to community life.

All of the dopamine receptor antagonists as well as risperidone increase prolactin concentrations, which can result in galactorrhea and irregular menses. Evidence suggests that prolactin elevation may impair libido in men and women. Fortunately, clozapine, olanzapine, quetiapine, and ziprasidone do not appear

to elevate prolactin above normal concentrations. As a result, patients who demonstrate these symptoms on a dopamine receptor antagonist or risperidone and have high prolactin concentration should instead be given an agent that does not increase prolactin concentration.

Many antipsychotic drugs cause disturbances in sexual function including ejaculatory or erectile disturbances in men and decreased libido in women; these effects result in a substantial amount of noncompliance in men. Thus clinicians should discuss issues of sexual functioning with patients and intervene when possible. It is unclear if any of the SDAs are associated with a reduced or greater risk of sexual dysfunction than the dopamine receptor antagonists.

Adverse Effects of Clozapine Clozapine has a number of adverse effects that make it a difficult drug to administer. The most serious adverse effect is a risk of agranulocytosis, a potentially fatal condition that occurs in approximately 1 percent of patients treated with clozapine. As a result, patients who receive clozapine in the United States are required to be in a program of weekly blood monitoring for as long as they receive the drug.

Clozapine is also associated with a higher risk of seizures than other antipsychotics. The risk reaches nearly 5 percent at doses over 600 mg. Patients who develop seizures while on clozapine can usually be managed by reducing the dosage and adding an anticonvulsant, usually a form of valproic acid (Depakene) or divalproex (Depakote). Other adverse effects with clozapine include hypersalivation, sedation, tachycardia, weight gain, fever, and postural hypotension.

NEGATIVE AND COGNITIVE SYMPTOMS

Negative symptoms and cognitive impairment are associated with a substantial number of the social and vocational impairments of schizophrenia. This observation has resulted in a reappraisal of the goals of treatment, with a greater emphasis being placed on treatment strategies for decreasing the severity of these impairments. Most of the attention has focused on negative symptoms.

Carpenter has made an important contribution to this area by classifying negative symptoms into primary and secondary categories. *Secondary negative symptoms* are those that may result from other conditions, such as depression or extrapyramidal side effects. The latter are a common cause of secondary negative symptoms, particularly when patients are experiencing akinesia, an adverse effect that can be manifest in decreased speech, decreased motivation, and decreased spontaneous gestures. In addition, positive or psychotic symptoms may result in secondary negative symptoms. A common example is the patient who is withdrawn or uncommunicative as a result of suspiciousness.

The management of secondary negative symptoms begins with the management of the condition that caused these symptoms. For depression this may include the addition of an antidepressant medication; for extrapyramidal effects this may involve the addition of an antiparkinson medication, a dose reduction, or a change to an antipsychotic—usually an SDA—that is associated with less extrapyramidal adverse effects.

If the previously mentioned causes of secondary negative symptoms have been ruled out, the patient is likely to be demonstrating a type of enduring primary negative symptom. Some evidence suggests that the SDAs are more effective in treating negative symptoms than conventional agents. However, it is unclear if these effects are related to a reduction in secondary negative symptoms. Until this issue is decided by adequate controlled studies, it is reasonable for clinicians to consider prescribing an SDA to patients who have substantial negative symptoms.

Patients with schizophrenia frequently suffer from impairments in attention and information processing. These cognitive impairments can also interfere with their social and vocational rehabilitation, even when their psychotic symptoms have been well controlled. As with negative symptoms, cognitive impairments can be due to other causes such as substance abuse or drug effects of medications. The anticholinergic effects of either an antipsychotic or an antiparkinsonism medication such as biperiden (Akineton) or benztropine (Cogentin) can cause cognitive impairments that are difficult to distinguish from symptoms that are part of the schizophrenia. Decreasing the use of anticholinergic medication by changing to drugs that do not require antiparkinsonism medications—particularly SDAs—may be helpful. Evidence also suggests that clozapine, risperidone, olanzapine and other SDAs may be more effective at treating cognitive impairments than dopamine receptor antagonists. For example, a recent study found risperidone effective in improving verbal working memory. Others have reported that clozapine is effective for improving verbal fluency. Olanzapine has resulted in improvements in a number of cognitive measures. If confirmed, these findings will support the practice of treating cognitively impaired patients with schizophrenia with an SDA.

STRATEGIES FOR POOR RESPONDERS

When patients with acute schizophrenia receive an antipsychotic medication approximately 60 percent improve to the extent that they will achieve a complete remission or experience only mild symptoms; the remaining 40 percent of patients improve, but still demonstrate variable levels of positive symptoms that are resistant to the medications. Rather than categorizing patients into responders and nonresponders, it is more accurate to consider the degree to which the illness is improved by medication. Some resistant patients are so severely ill that they require chronic institutionalization; others respond to an antipsychotic drug with substantial suppression of their psychotic symptoms but demonstrate persistent hallucinations or delusions.

Before considering a patient a poor responder to a particular drug one must be certain that they received an adequate trial of the medication. A 6-week trial on an adequate dosage of an antipsychotic agent is considered reasonable for most patients. If patients demonstrate even mild improvement during this period, it may be reasonable to wait because data indicate that patients may improve at a steady rate for 3 to 6 months. It may be also be helpful to confirm that the patient is receiving an adequate amount of the drug by monitoring the plasma concentration. Information about therapeutic plasma concentrations is available for a number of antipsychotic drugs including haloperidol, clozapine, fluphenazine, trifluoperazine (Stelazine), and perphenazine (Trilafon). A very low plasma concentration may indicate that a patient has been noncompliant or, more commonly, only partially compliant. It may also suggest

that the patient is a rapid metabolizer of the drug or that the drug is not being adequately absorbed. Under these conditions increasing the dose may be helpful. If the level is already relatively high, clinicians should consider whether adverse effects may be interfering with therapeutic response.

If the patient is responding poorly, many clinicians will consider raising the dosage above the usual therapeutic level. The use of high dosage in poor medication responders has been studied under a number of circumstances. Nearly all studies found that higher dosages were not associated with greater improvement than conventional dosages, which suggests that changing to another drug is more likely to be helpful than increasing the dosage.

A patient who has responded poorly to a conventional dopamine receptor antagonist is unlikely to do well on another dopamine receptor antagonist. Studies suggest that a poor response to one dopamine receptor antagonist is likely to be followed by a poor response to another; thus, changing to an SDA is more likely to be helpful.

Substantial evidence indicates that clozapine is effective for patients who respond poorly to dopamine receptor antagonists. Double-blind studies comparing clozapine to other antipsychotic agents indicated that clozapine had the clearest advantages over conventional drugs in patients with the most severe psychotic symptoms as well as those who had previously responded poorly to other antipsychotic drugs. The most definitive evidence of clozapine's advantages in this population comes from a multicenter trial reported by John Kane in which clozapine was compared with chlorpromazine. This study was conducted on severely psychotic patients who had failed in trials with at least three antipsychotic drugs. Clozapine was significantly more effective than chlorpromazine in nearly every dimension of psychopathology, including both positive and negative symptoms. This study found that 30 percent of patients treated with clozapine met improvement criteria by the end of the 6-week trial. Studies of longer duration indicate that 60 percent of patients are likely to meet these same improvement criteria when patients are maintained on clozapine for 6 months.

There is also evidence suggesting that risperidone and olanzapine may be helpful when a dopamine receptor antagonist is only partially effective. A Swiss study found that clozapine and risperidone were equally effective in a treatment-resistant population, but risperidone's side effects were more easily tolerated. Another study found that risperidone was somewhat more effective than haloperidol in a similar population and that risperidone was better tolerated. A multicenter comparison of olanzapine and haloperidol in a largely treatment-resistant group of patients found that olanzapine was more effective for both positive and negative symptoms. Taken together these studies support the practice of trying patients on risperidone or olanzapine when they have responded poorly to a dopamine receptor antagonist.

When switching patients from one antipsychotic to another clinicians should be aware that abrupt changes in drugs and dosage can have serious adverse effects in some individuals. For example, abrupt discontinuation or rapid dosage reduction of low-potency antipsychotics such as clozapine or chlorpromazine can lead to withdrawal adverse effects such as nausea or diarrhea. Anecdotal reports

indicate that rapid discontinuation of clozapine can lead to severe psychotic relapse. When treatment is started with some antipsychotics such as clozapine or quetiapine, dosage titration often requires days or even weeks. For individuals who are being changed to treatment with one of these agents, the best strategy usually entails continuing the first agent until the patient is receiving a clinically effective dosage of the second drug. For these reasons, the best methods for switching drugs usually involve a cross-titration in which the patient is gradually changed from one antipsychotic to the other.

MAINTENANCE THERAPY

During the stable or maintenance phase, patients are usually in a relative state of remission, with only minimal psychotic symptoms. The goals during this stage are to prevent patients from suffering psychotic relapse and to assist them to improve their level of functioning. Pharmacotherapy plays an important part in both of these goals. Medications are effective in preventing or delaying psychotic relapse and may also be an important adjunct in managing functional impairments that may interfere with rehabilitation; unfortunately, the adverse effects of medications can undermine these goals.

Drug and Route of Administration for Maintenance Therapy Stable patients maintained on an antipsychotic drug have a much lower relapse rate than patients whose medications are discontinued. Although studies differ, most suggest that 16 to 23 percent of patients a year experience a relapse while receiving medications and 53 to 72 percent relapse without medications. Clinicians are often tempted to discontinue medications in patients who have been well and stable for prolonged periods; unfortunately, these patients also have high relapse rates when their medications are discontinued. Other evidence indicates that patients who experience relapses while they are receiving an antipsychotic drug have milder episodes than patients who relapse on no medication. Donald Johnson has reported that patients whose medications are discontinued are more likely to show dangerous behavior and are more likely to be admitted involuntarily.

These observations about the effectiveness of continuing antipsychotic medication in stable patients have led to the recommendation that most patients with schizophrenia should receive an antipsychotic to prevent relapse. In 1989 the duration of maintenance was considered at an international consensus conference. This consensus group recommended 1 to 2 years of maintenance for patients following a first episode. Although this may be somewhat longer than current practice in many settings, it was recommended because individuals at this stage of their illness may have the most to gain if relapse can be prevented or delayed. First-episode patients may be working or involved in educational programs, both of which can be jeopardized by a second psychotic episode. The consensus conference also recommended that multiepisode patients receive maintenance antipsychotic for at least 5 years. For patients with a history of serious suicide attempts or violent, aggressive behavior, maintenance treatment with neuroleptics may be indicated for longer periods—perhaps indefinitely. The first 3 to 6 months following an acute episode was considered a period of stabilization when patients may not demonstrate acute symptoms but may nevertheless remain more vulnerable to relapse. The consensus conference recommended that following this stabilization period gradual dosage reduction should be implemented at the rate of approximately 20 percent every 6 months until a minimal maintenance dosage level is

reached.

There is also evidence that long-acting depot antipsychotic drugs may be the most effective agents for preventing relapse. A number of double-blind and uncontrolled trials have compared oral and depot treatment. The uncontrolled trials usually compared individuals who were assigned to a depot with those assigned to oral medications; patients assigned to depot medication usually demonstrated much lower rates of relapse. The results are less clear for well-designed double-blind studies. However, these studies tended to use highly selected groups of cooperative patients who were carefully monitored, which would tend to undermine the advantages of depot medications by excluding the patients who were most likely to benefit from this form of treatment: that is, patients with compliance problems. Nevertheless, even under these conditions, in a meta-analysis of six studies Janicak found an advantage in favor of depot treatment.

Dosage Reduction Strategies Concerns about the long-term adverse effects of antipsychotic medications—particularly extrapyramidal effects and tardive dyskinesia—have led to a search for methods of treating patients with the lowest effective dose of medication. One strategy proposes using substantially lower antipsychotic dosages during maintenance treatment than those prescribed for initial short-term treatment. Studies indicate that many patients do well when they are treated with dosages that are approximately 20 percent of an initial treatment dosage. The low dosages were in the range of 4 to 10 mg of fluphenazine decanoate administered every 2 weeks. In 1997 Nina Schooler and her coworkers published the results from the Treatment Strategies in Schizophrenia multicenter study. Their 2-year comparison of low and conventional dosages found that low dosages in this range resulted in relapse rates that were slightly higher than those with conventional dosages but within an acceptable range. Moreover, other studies suggest that lower dosages are associated with milder side effects and better patient compliance.

Another strategy, termed targeted or intermittent therapy, proposes gradually reducing and finally discontinuing the medications in stable patients. Patients are then monitored carefully, and medications are reintroduced if early signs of relapse appear. Controlled trials with this strategy have mostly shown discouraging results. Relapse rates were relatively high as were rates of rehospitalization. These results were confirmed in the Treatment Strategies Study in which rates of rehospitalization were significantly elevated in the targeted treatment group.

Still another strategy combines the features of low- and targeted-dose strategies. In this method patients are treated with the same low doses of a depot drug that were used in the low-dose studies. Patients are monitored for early prodromal signs of relapse, and if these symptoms appear, patients are treated with oral medication. Results suggest that this is an effective strategy for making low-dose treatment safer.

Although the SDAs may be excellent drugs for maintenance treatment, few controlled long-term trials have evaluated their effectiveness. Nevertheless, risperidone, olanzapine, quetiapine, and ziprasidone appear to have important advantages. Concern about adverse effects should be substantially less, which would allow clinicians to treat patients with dosages that should be associated with very low relapse

rates. If findings suggesting that SDAs are associated with a reduced risk of tardive dyskinesia are confirmed, this advantage will provide a compelling reason to select these newer agents. Also, the improved side-effect profile may result in better medication compliance.

The SDAs also have serious adverse effects that are likely to be important concerns during long-term treatment. Some of the newer agents—particularly olanzapine and clozapine—can result in substantial weight gain. Risperidone can cause some extrapyramidal effects and may cause problems related to increased prolactin concentrations such as irregular menstrual periods and galactorrhea. An important disadvantage of the SDAs is the lack of availability of long-acting formulations that are useful for patients who are unreliable pill takers.

INTEGRATING PHARMACOTHERAPY AND PSYCHOSOCIAL TREATMENT

Most patients with schizophrenia will benefit from a combination of pharmacotherapy and psychosocial treatments. Recent improvements in both domains suggest that the overall outcome of this disorder can be improved if patients receive the optimal forms of both treatments at the appropriate stage of their illness. Research studies and clinical experience suggest that psychosocial treatments are probably most effective when patients have recovered from severe psychotic episodes. During the acute psychotic phase clinical management should emphasize maintaining patient cooperativeness and trust. This is particularly important when there is overt suspiciousness or a tendency to misinterpret the intentions of the treatment team. A successful strategy is likely to include clear explanations of the rationale for treatment and possible drug adverse effects. Family members may be important allies in ensuring cooperation, and family psychoeducation programs have been demonstrated to be helpful during this phase.

It is difficult to generalize about the interactions of drugs and psychosocial treatments for stable patients because psychosocial treatments can vary greatly in terms of content and goals. Nevertheless, a number of important treatment principles can be drawn from the literature on combining treatments. The first is that psychosocial treatments are most likely to be effective when patients have been effectively stabilized on drugs. Early studies by Hogarty indicated that psychosocial treatments could actually lead to a worse outcome when outpatients with schizophrenia were treated with a placebo. Other studies indicate that patients are most likely to respond to psychosocial treatments when their condition is stable. For example, a recent study with social skills training found that patients who received pharmacotherapy that minimized the proportion of time that they were in a psychotic state also demonstrated the greatest improvements in social adjustment.

Psychosocial treatments may also improve patient response to pharmacotherapy by improving medication compliance. This was suggested in a study in which patients received a form of family treatment that also encouraged medication compliance. Other studies have indicated that psychosocial treatments—particularly family treatment—may decrease the amount of stress that the patient experiences within the family and that this, in turn, decreases the amount of antipsychotic medication required by the patient.

The introduction of the newer antipsychotics may result in much greater interest in psychosocial interventions. Patients who receive the newer agents may be better candidates for psychosocial treatments when treatment with these agents is associated with improvements in negative and cognitive symptoms as well as reduced adverse effects. Also, patients who improve on clozapine, risperidone, olanzapine, or other drugs may initially appear ready to return to community life. However, these individuals then experience a series of frustrating failures at work, school, or social relationships, which indicate that drug therapy alone may not suffice to prepare them for their new roles.

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Table 12.8-1 Factors Influencing Antipsychotic Drug Selection

Factors	Considerations
Subjective response	A dyphoric subjective response to a particular drug predicts poor compliance with that drug
Sensitivity to extrapyrimidal adverse effects	A serotonin-dopamine antagonist (SDA)
Tardive dyskinesia	Clozapine or (possibly another SDA)
Poor medication compliance or high risk of relapse	Injectable form of a long-acting antagonist (haloperidol or fluphenazine)
Pregnancy	Probably haloperidol (most data supporting its safety)
Cognitive symptoms	Possibly an SDA
Negative symptoms	Possibly an SDA

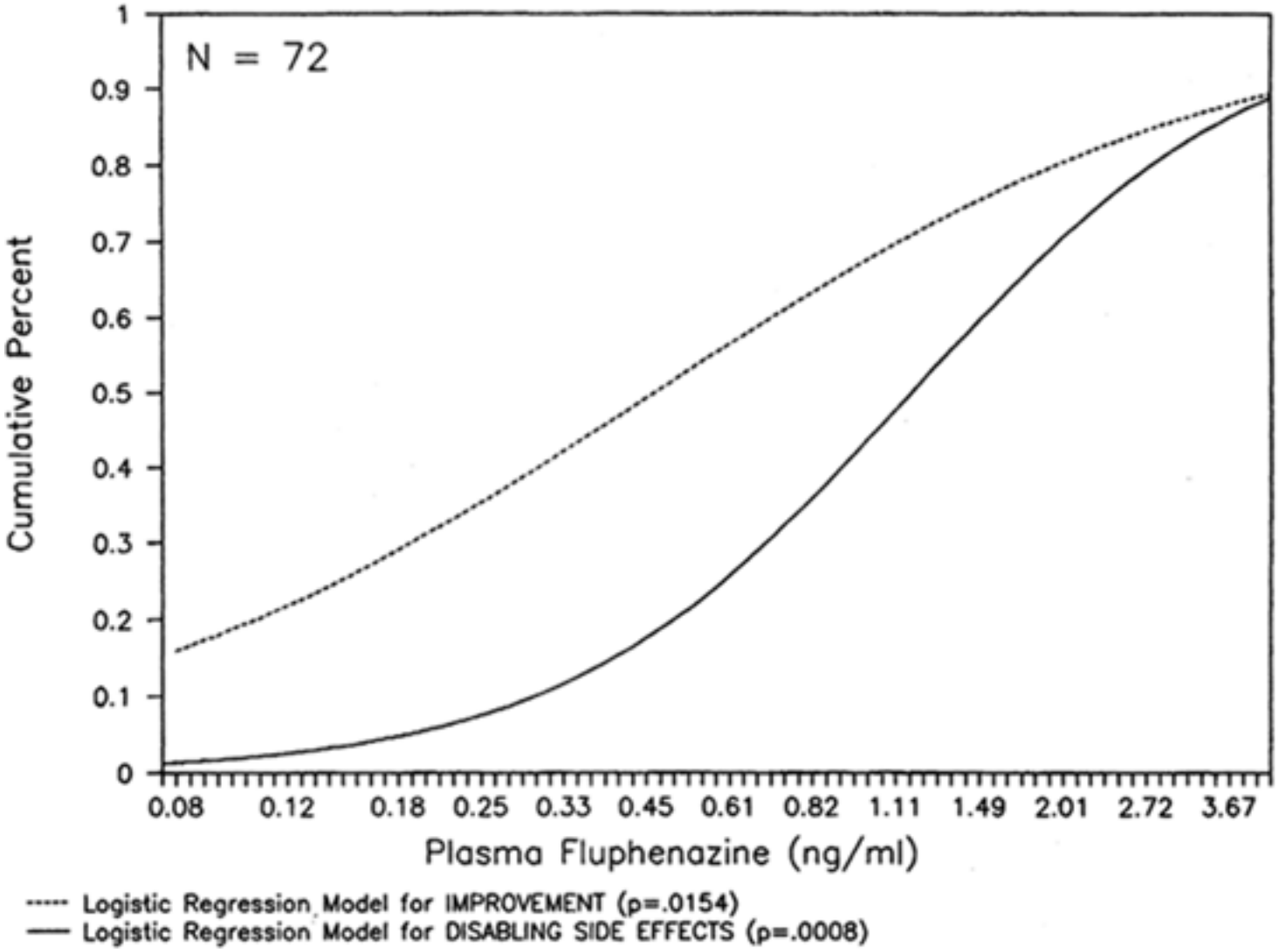

FIGURE 12.8-1 Improvement and disabling side effects as a function of plasma fluphenazine concentration.

Table 12.8-2 Selected Antipsychotic Drugs

Drug	Route of Administration	Usual Daily Oral Dose (mg)	Sedation	Autonomic	Extrapyramidal Adverse Effects
Phenothiazines					
Chlorpromazine	Oral, IM	200–600	+ + +	+ + +	+ +
Fluphenazine	Oral, IM, depot	2–20	+	+	+ + +
Trifluoperazine	Oral, IM	5–30	+ +	+	+ + +
Perphenazine	Oral, IM	8–64	+ +	+	+ + +
Thioridazine	Oral	200–600	+ + +	+ + +	+ +
Butyrophenones					
Haloperidol	Oral, IM, depot	5–20	+	+	+ + +
Thioxanthenes					
Thiothixene	Oral, IM	5–30	+	+	+ + +
Dihydroindolones					
Molindone	Oral	20–100	+ +	+	+ +
Dibenzoxazepine					
Loxapine	Oral, IM	20–100	+ +	+	+ +
Arylpiperidylindole					
Sertindole	Oral	12–24	+	+ +	0?
Thienobenzodiazepine					
Olanzapine	Oral	7.5–25	+	+ +	0?
Dibenzothiazepine					
Quetiapine	Oral	150–750	+ +	+ +	0?
Benzisoxazole					
Risperidone	Oral	2–16	+	+ +	+
Dibenzodiazepine					
Clozapine	Oral	150–900	+ + +	+ + +	0?

Table 12.8-3 The Drug-Induced Extrapyramidal Syndromes

Acute

Drug-induced parkinsonism

A generally mild parkinsonian syndrome that can recapitulate virtually every aspect of the idiopathic form. The most common manifestations are bradykinesia, an increase in muscular tone (appendicular musculature affected more than axial), and a resting tremor. Although the tremor is present less frequently than in the idiopathic variety (about 10–25% of afflicted population), it is indistinguishable from its idiopathic counterpart. It has a regular frequency (3–6 cps), is usually suppressed during volitional action of the involved body part, is exacerbated by stress and anxiety, and classically involves alternating contractions of opposing muscular groups (e.g., pronators and supinators of the forearm). Sialorrhea, seborrhea, and altered righting reflexes also can be present.

Dystonia

This is a sudden-onset, intense, sustained, and uncontrollable muscular contraction. The cephalic musculature is most often affected (jaw, tongue, eyes, and neck) but other areas can be involved (upper extremities and back). It generally develops shortly after the initiation (or reinitiation) of high-potency neuroleptics and occurs during falling plasma neuroleptic levels (8–12 hours after oral dosing).

Akathisia

This neuromotor syndrome consists of an unusual, generally intense, and uniformly uncomfortable sense of internal restlessness most commonly localized to the lower half of the body coupled with pacing behaviors or stereotyped restless movements. It is relieved somewhat during ambulation and is made worse when the patient lies down or is required to sit still. It can occur at any time during neuroleptic treatment (minutes to years after initiating treatment) and follows a waxing and waning course.

Late (tardive)

Tardive dyskinesia

This is an irregular, choreiform movement disorder that can be suppressed volitionally for variable periods by the patient, is generally beyond their awareness, and is exacerbated during distracting maneuvers (e.g., rapid alternating movements of the upper extremities worsen the involuntary bucco-oral choreic movements). Orobuccolingual structures and the distal upper extremities are the most commonly affected, but virtually any voluntary muscle group can be involved. Ninety-five percent of subjects with some type of tardive syndrome will manifest a choreic component.

Tardive dystonia

This is the second most common type of the tardive syndromes. Dystonic movements are slow, variably sustained, and involuntary and may affect the limbs, trunk, neck (e.g., torticollis, spasmodic dysphonia) or face (e.g., Meige's syndrome). Unlike the purely choreic form, tardive dystonia impairs function, is less likely to remit even if the neuroleptics are discontinued (90% still present several years after discontinuation), and can be progressive.

Tardive akathisia

This tardive syndrome is objectively similar to the acute form but exhibits a different treatment response profile (e.g., may be made worse by anticholinergic agents) and is less likely to be coupled with the intense internal sense of restlessness.

Tardive tics

Multiple tic syndromes, ranging from simple invariant motor tics to complex tics with involuntary vocalizations (tardive Gilles de la Tourette's syndrome), can develop after chronic neuroleptic treatment.

Tardive myoclonus

These are brief, nonstereotyped, generally asynchronous muscular jerks. This is the least common of the tardive syndromes.

Other

Neuroleptic malignant syndrome

This unusual but potentially fatal syndrome afflicts less than 1% of subjects chronically treated with neuroleptics. Its protean features are dense muscular rigidity (axial musculature affected more than appendicular and not associated with a parkinsonian tremor), a depressed sensorium, elevated temperature (sometimes to malignant levels), elevated creatinine kinase, and myoglobinuria. Early reports suggested that it had a mortality of 10% to 30%, but with prompt neuroleptic withdrawal and proper supportive care more than 95% now survive. Subsequent rechallenge with neuroleptics is not contraindicated.

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