

PRACTICE GUIDELINE FOR THE Treatment of Patients With Schizophrenia Second Edition

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Originally published in February 2004. This guideline is more than 5 years old and has not yet been updated to ensure that it reflects current knowledge and practice. In accordance with national standards, including those of the Agency for Healthcare Research and Quality's National Guideline Clearinghouse (<http://www.guideline.gov/>), this guideline can no longer be assumed to be current.

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STATEMENT OF INTENT

The American Psychiatric Association (APA) Practice Guidelines are not intended to be construed or to serve as a standard of medical care. Standards of medical care are determined on the basis of all clinical data available for an individual patient and are subject to change as scientific knowledge and technology advance and practice patterns evolve. These parameters of practice should be considered guidelines only. Adherence to them will not ensure a successful outcome for every individual, nor should they be interpreted as including all proper methods of care or excluding other acceptable methods of care aimed at the same results. The ultimate judgment regarding a particular clinical procedure or treatment plan must be made by the psychiatrist in light of the clinical data presented by the patient and the diagnostic and treatment options available.

This practice guideline has been developed by psychiatrists who are in active clinical practice. In addition, some contributors are primarily involved in research or other academic endeavors. It is possible that through such activities some contributors, including work group members and reviewers, have received income related to treatments discussed in this guideline. A number of mechanisms are in place to minimize the potential for producing biased recommendations due to conflicts of interest. Work group members are selected on the basis of their expertise and integrity. Any work group member or reviewer who has a potential conflict of interest that may bias (or appear to bias) his or her work is asked to disclose this to the Steering Committee on Practice Guidelines and the work group. Iterative guideline drafts are reviewed by the Steering Committee, other experts, allied organizations, APA members, and the APA Assembly and Board of Trustees; substantial revisions address or integrate the comments of these multiple reviewers. The development of the APA practice guidelines is not financially supported by any commercial organization.

More detail about mechanisms in place to minimize bias is provided in a document available from the APA Department of Quality Improvement and Psychiatric Services, "APA Guideline Development Process."

This practice guideline was approved in December 2003 and published in February 2004.

GUIDE TO USING THIS PRACTICE GUIDELINE

The *Practice Guideline for the Treatment of Patients With Schizophrenia, Second Edition*, consists of three parts (Parts A, B, and C) and many sections, not all of which will be equally useful for all readers. The following guide is designed to help readers find the sections that will be most useful to them.

Part A, “Treatment Recommendations for Patients With Schizophrenia,” is published as a supplement to the *American Journal of Psychiatry* and contains general and specific treatment recommendations. Section I summarizes the key recommendations of the guideline and codes each recommendation according to the degree of clinical confidence with which the recommendation is made. Section II is a guide to the formulation and implementation of a treatment plan for the individual patient. Section II.F, “Clinical Features Influencing the Treatment Plan,” discusses a range of clinical considerations that could alter the general recommendations discussed in Section II. Section III describes treatment settings and housing options and provides guidance on choice of setting.

Part B, “Background Information and Review of Available Evidence,” and Part C, “Future Research Directions,” are not included in the *American Journal of Psychiatry* supplement but are provided with Part A in the complete guideline, which is available in print format from American Psychiatric Publishing, Inc., and online through the American Psychiatric Association (<http://www.psych.org>). Part B provides an overview of schizophrenia, including general information on its natural history, course, and epidemiology. It also provides a structured review and synthesis of the evidence that underlies the recommendations made in Part A. Part C draws from the previous sections and summarizes areas for which more research data are needed to guide clinical decisions.

To share feedback on this or other published APA practice guidelines, a form is available at http://www.psych.org/psych_pract/pg/reviewform.cfm.

DEVELOPMENT PROCESS

This practice guideline was developed under the auspices of the Steering Committee on Practice Guidelines. The development process is detailed in a document available from the APA Department of Quality Improvement and Psychiatric Services: the “APA Guideline Development Process.” Key features of this process include the following:

- A comprehensive literature review.
- Development of evidence tables.
- Initial drafting of the guideline by a work group that included psychiatrists with clinical and research expertise in schizophrenia.
- Production of multiple revised drafts with widespread review; four organizations and 62 individuals submitted significant comments.
- Approval by the APA Assembly and Board of Trustees.
- Planned revisions at regular intervals.

Relevant literature was identified through a computerized search of PubMed for the period from 1994 to 2002. Using the keywords schizophrenia OR schizoaffective, a total of 20,009 citations were found. Limiting the search by using the keywords antipsychotic agents, antipsychotic, tranquilizing agents, aripiprazole, olanzapine, ziprasidone, quetiapine, risperidone, clozapine, glycine, beta receptor blockers, antidepressive agents, antidepressant, divalproex, valproic acid, lithium, carbamazepine, benzodiazepines, electroconvulsive therapy, community treatment, psychoeducation, family education, skills training, social support, rehabilitation, case management, community support, supported employment, sheltered workshop, family therapy, family intervention, psychosocial adjustment, cognitive behavior, cognitive training, cognitive therapy, counseling, psychotherapy, group therapy, interpersonal therapy, individual therapy, first break, first episode, new onset, early treatment, and early detection resulted in 8,609 citations. After limiting these references to clinical trials and meta-analyses published in English that included abstracts, 1,272 articles were screened by using title and abstract information. The Cochrane Database of Systematic Reviews was also searched by using the keyword schizophrenia. Additional, less formal literature searches were conducted by APA staff and individual members of the work group on schizophrenia. Sources of funding were considered when the work group reviewed the literature but are not identified in this document. When reading source articles referenced in this guideline, readers are advised to consider the sources of funding for the studies.

This document represents a synthesis of current scientific knowledge and rational clinical practice on the treatment of patients with schizophrenia. It strives to be as free as possible of bias toward any theoretical approach to treatment. In order for the reader to appreciate the evidence base behind the guideline recommendations and the weight that should be given to each recommendation, the summary of treatment recommendations is keyed according to the level of confidence with which each recommendation is made. Each rating of clinical confidence considers the strength of the available evidence and is based on the best available data. When evidence is limited, the level of confidence also incorporates clinical consensus with regard to a particular clinical decision. In the listing of cited references, each reference is followed by a letter code in brackets that indicates the nature of the supporting evidence.

PART A:

TREATMENT RECOMMENDATIONS FOR PATIENTS WITH SCHIZOPHRENIA

I. EXECUTIVE SUMMARY

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► A. CODING SYSTEM

Each recommendation is identified as falling into one of three categories of endorsement, indicated by a bracketed Roman numeral following the statement. The three categories represent varying levels of clinical confidence regarding the recommendation:

- [I] Recommended with substantial clinical confidence.
- [II] Recommended with moderate clinical confidence.
- [III] May be recommended on the basis of individual circumstances.

► B. FORMULATION AND IMPLEMENTATION OF A TREATMENT PLAN

Because schizophrenia is a chronic illness that influences virtually all aspects of life of affected persons, treatment planning has three goals: 1) reduce or eliminate symptoms, 2) maximize quality of life and adaptive functioning, and 3) promote and maintain recovery from the debilitating effects of illness to the maximum extent possible. Accurate diagnosis has enormous implications for short- and long-term treatment planning, and it is essential to note that diagnosis is a process rather than a one-time event. As new information becomes available about the patient and his or her symptoms, the patient's diagnosis should be reevaluated, and, if necessary, the treatment plan changed.

Once a diagnosis has been established, it is critical to identify the targets of each treatment, to have outcome measures that gauge the effect of treatment, and to have realistic expectations about the degrees of improvement that constitute successful treatment [I]. Targets of treatment, and hence of assessment, may include positive and negative symptoms, depression, suicidal ideation and behaviors, substance use disorders, medical comorbidities, posttraumatic stress disorder (PTSD), and a range of potential community adjustment problems, including homelessness, social isolation, unemployment, victimization, and involvement in the criminal justice system [I].

After the initial assessment of the patient's diagnosis and clinical and psychosocial circumstances, a treatment plan must be formulated and implemented. This formulation involves the selection of the treatment modalities, the specific type(s) of treatment, and the treatment setting. Periodic reevaluation of the diagnosis and the treatment plan is essential to good clinical practice and should be iterative and evolve over the course of the patient's association with the clinician [I].

► **C. ESTABLISHING A THERAPEUTIC ALLIANCE**

A supportive therapeutic alliance allows the psychiatrist to gain essential information about the patient and allows the patient to develop trust in the psychiatrist and a desire to cooperate with treatment. Identifying the patient's goals and aspirations and relating these to treatment outcomes fosters the therapeutic relationship as well as treatment adherence [II]. The clinician may also identify practical barriers to the patient's ability to participate in treatment, such as cognitive impairments or disorganization and inadequate social resources. Engagement of the family and other significant support persons, with the patient's permission, is recommended to further strengthen the therapeutic effort [I]. The social circumstances of the patient can have profound effects on adherence and response to treatment. Living situation, family involvement, sources and amount of income, legal status, and relationships with significant others (including children) are all areas that may be periodically explored by mental health care clinicians [II]. The psychiatrist can work with team members, the patient, and the family to ensure that such services are coordinated and that referrals for additional services are made when appropriate. The family's needs can be addressed and an alliance with family members can be facilitated by providing families with information about community resources and about patient and family organizations such as the National Alliance for the Mentally Ill (NAMI) [II].

Many patients with schizophrenia require, and should receive, a variety of treatments, often from multiple clinicians. It is therefore incumbent on clinicians to coordinate their work and prioritize their efforts. Because an accurate history of past and current treatments and responses to them is a key ingredient to treatment planning, excellent documentation is paramount [I]. Especially critical, for example, is information about prior treatment efforts and clinical response.

► **D. ACUTE PHASE TREATMENT**

The goals of treatment during the acute phase of treatment, defined by an acute psychotic episode, are to prevent harm, control disturbed behavior, reduce the severity of psychosis and associated symptoms (e.g., agitation, aggression, negative symptoms, affective symptoms), determine and address the factors that led to the occurrence of the acute episode, effect a rapid return to the best level of functioning, develop an alliance with the patient and family, formulate short- and long-term treatment plans, and connect the patient with appropriate aftercare in the community. Efforts to engage and collaborate with family members and other natural caregivers are often successful during the crisis of an acute psychotic episode, whether it is the first episode or a relapse, and are strongly recommended [I]. Family members are often under significant stress during this time. Also, family members and other caregivers are often needed to provide support to the patient while he or she is recovering from an acute episode.

It is recommended that every patient have as thorough an initial evaluation as his or her clinical status allows, including complete psychiatric and general medical histories and physical and mental status examinations [I]. Interviews of family members or other persons knowledgeable about the patient may be conducted routinely, unless the patient refuses to grant permission, especially since many patients are unable to provide a reliable history at the first interview [I]. The most common contributors to symptom relapse are antipsychotic medication nonadherence, substance use, and stressful life events, although relapses are not uncommon as a result of the natural course of the illness despite continuing treatment. If nonadherence is suspected, it is recommended that the reasons for it be evaluated and considered in the treatment plan. General medical health as well as medical conditions that could contribute to symptom exacerbation can be evaluated by medical history, physical and neurological examination, and appropriate laboratory, electrophysiological, and radiological assessments [I]. Measurement of body weight and vital signs (heart rate, blood pressure, temperature) is also recommended [II]. Other laboratory

tests to be considered to evaluate health status include a CBC; measurements of blood electrolytes, glucose, cholesterol, and triglycerides; tests of liver, renal, and thyroid function; a syphilis test; and when indicated and permissible, determination of HIV status and a test for hepatitis C [II]. Routine evaluation of substance use with a toxicology screen is also recommended as part of the medical evaluation [I]. A pregnancy test should be strongly considered for women with childbearing potential [II]. In patients for whom the clinical picture is unclear or where there are abnormal findings from a routine examination, more detailed studies (e.g., screening for heavy metal toxins, EEG, magnetic resonance imaging [MRI] scan, or computed tomography [CT] scan) may be indicated [II].

It is important to pay special attention to the presence of suicidal potential and the presence of command hallucinations and take precautions whenever there is any question about a patient's suicidal intent, since prior suicide attempts, current depressed mood, and suicidal ideation can be predictive of a subsequent suicide attempt in schizophrenia [I]. Similar evaluations are recommended in considering the likelihood of dangerous or aggressive behavior and whether the person will harm someone else or engage in other forms of violence [I].

It is recommended that pharmacological treatment be initiated promptly, provided it will not interfere with diagnostic assessment, because acute psychotic exacerbations are associated with emotional distress, disruption to the patient's life, and a substantial risk of dangerous behaviors to self, others, or property [I]. Before the patient begins treatment with antipsychotic medication, it is suggested that the treating physician, as is feasible, discuss the potential risks and benefits of the medication with the patient [I]. The selection of an antipsychotic medication is frequently guided by the patient's previous experience with antipsychotics, including the degree of symptom response, past experience of side effects, and preferred route of medication administration. In choosing among these medications, the psychiatrist may consider the patient's past responses to treatment, the medication's side effect profile (including subjective responses, such as a dysphoric response to a medication), the patient's preferences for a particular medication based on past experience, the intended route of administration, the presence of comorbid medical conditions, and potential interactions with other prescribed medications [I]. Finally, while most patients prefer oral medication, patients with recurrent relapses related to nonadherence are candidates for a long-acting injectable antipsychotic medication, as are patients who prefer this mode of administration [II].

The recommended dose is that which is both effective and not likely to cause side effects that are subjectively difficult to tolerate, since the experience of unpleasant side effects may affect long-term adherence [I]. The dose may be titrated as quickly as tolerated to the target therapeutic dose of the antipsychotic medication, and unless there is evidence that the patient is having uncomfortable side effects, monitoring of the patient's clinical status for 2–4 weeks is warranted to evaluate the patient's response to the treatment [II]. During these weeks it is often important for physicians to be patient and avoid the temptation to prematurely escalate the dose for patients who are responding slowly [I]. If the patient is not improving, it may be helpful to establish whether the lack of response can be explained by medication nonadherence, rapid medication metabolism, or poor absorption [II].

Adjunctive medications are also commonly prescribed for comorbid conditions in the acute phase. Benzodiazepines may be used to treat catatonia as well as to manage both anxiety and agitation until the antipsychotic has had time to be therapeutically effective [II]. Antidepressants can be considered for treating comorbid major depression or obsessive-compulsive disorder, although vigilance to protect against the risk of exacerbation of psychosis with some antidepressants is important [II]. Mood stabilizers and beta-blockers may be considered for reducing the severity of recurrent hostility and aggression [II]. Careful attention must be paid to potential drug-drug interactions, especially those related to metabolism by cytochrome P450 enzymes [I].

Psychosocial interventions in the acute phase are aimed at reducing overstimulating or stressful relationships, environments, or life events and at promoting relaxation or reduced arousal through simple, clear, coherent communications and expectations; a structured and predictable environment; low performance requirements; and tolerant, nondemanding, supportive relationships with the psychiatrist and other members of the treatment team. Providing information to the patient and the family on the nature and management of the illness that is appropriate to the patient's capacity to assimilate information is recommended [II]. Patients can be encouraged to collaborate with the psychiatrist in selecting and adjusting the medication and other treatments provided [II].

The acute phase is also the best time for the psychiatrist to initiate a relationship with family members, who tend to be particularly concerned about the patient's disorder, disability, and prognosis during the acute phase and during hospitalization [I]. Educational meetings, "survival workshops" that teach the family how to cope with schizophrenia, and referrals to local chapters of patient and family organizations such as NAMI may be helpful and are recommended [III]. Family members may be under considerable stress, particularly if the patient has been exhibiting dangerous or unstable behavior.

► **E. STABILIZATION PHASE**

During the stabilization phase, the goals of treatment are to reduce stress on the patient and provide support to minimize the likelihood of relapse, enhance the patient's adaptation to life in the community, facilitate continued reduction in symptoms and consolidation of remission, and promote the process of recovery. If the patient has improved with a particular medication regimen, continuation of that regimen and monitoring are recommended for at least 6 months [I]. Premature lowering of dose or discontinuation of medication during this phase may lead to a recurrence of symptoms and possible relapse. It is also critical to assess continuing side effects that may have been present in the acute phase and to adjust pharmacotherapy accordingly to minimize adverse side effects that may otherwise lead to medication nonadherence and relapse [I].

Psychosocial interventions remain supportive but may be less structured and directive than in the acute phase [III]. Education about the course and outcome of the illness and about factors that influence the course and outcome, including treatment adherence, can begin in this phase for patients and continue for family members [II].

It is important that there be no gaps in service delivery, because patients are particularly vulnerable to relapse after an acute episode and need support in resuming their normal life and activities in the community [I]. For hospitalized patients, it is frequently beneficial to arrange an appointment with an outpatient psychiatrist and, for patients who will reside in a community residence, to arrange a visit before discharge [II]. Adjustment to life in the community for patients can be facilitated through realistic goal setting without undue pressure to perform at high levels vocationally and socially, since unduly ambitious expectations can be stressful and can increase the risk of relapse [I]. While it is critical not to place premature demands on the patient regarding engagement in community-based activities and rehabilitation services, it is equally critical to maintain a level of momentum aimed at improving community functioning in order to instill a sense of hope and progress for the patient and family [I].

► **F. STABLE PHASE**

The goals of treatment during the stable phase are to ensure that symptom remission or control is sustained, that the patient is maintaining or improving his or her level of functioning and quality of life, that increases in symptoms or relapses are effectively treated, and that monitoring for adverse treatment effects continues. Regular monitoring for adverse effects is recom-

mended [I]. If the patient agrees, it is helpful to maintain strong ties with persons who interact with the patient frequently and would therefore be most likely to notice any resurgence of symptoms and the occurrence of life stresses and events that may increase the risk of relapse or impede continuing functional recovery [II]. For most persons with schizophrenia in the stable phase, psychosocial interventions are recommended as a useful adjunctive treatment to pharmacological treatment and may improve outcomes [I].

Antipsychotic medications substantially reduce the risk of relapse in the stable phase of illness and are strongly recommended [I]. Deciding on the dose of an antipsychotic medication during the stable phase is complicated by the fact that there is no reliable strategy available to identify the minimum effective dose to prevent relapse. For most patients treated with first-generation antipsychotics, a dose is recommended that is around the “extrapyramidal symptom (EPS) threshold” (i.e., the dose that will induce extrapyramidal side effects with minimal rigidity detectable on physical examination), since studies indicate that higher doses are usually not more efficacious and increase the risk of subjectively intolerable side effects [II]. Lower doses of first-generation antipsychotic medications may be associated with improved adherence and better subjective state and perhaps ultimately better functioning. Second-generation antipsychotics can generally be administered at doses that are therapeutic yet well below the “EPS threshold.” The advantages of decreasing antipsychotic doses to minimize side effects can be weighed against the disadvantage of a somewhat greater risk of relapse and more frequent exacerbations of schizophrenic symptoms. In general, it is more important to prevent relapse and maintain the stability of the patient [III].

The available antipsychotic medications are associated with differential risk of a variety of side effects, including neurological, metabolic, sexual, endocrine, sedative, and cardiovascular side effects. Monitoring of side effects based on the side effect profile of the prescribed antipsychotic is warranted. During the stable phase of treatment it is important to routinely monitor all patients treated with antipsychotics for extrapyramidal side effects and the development of tardive dyskinesia [I]. Because of the risk of weight gain associated with many antipsychotics, regular measurement of weight and body mass index (BMI) is recommended [I]. Routine monitoring for obesity-related health problems (e.g., high blood pressure, lipid abnormalities, and clinical symptoms of diabetes) and consideration of appropriate interventions are recommended particularly for patients with BMI in the overweight and obese ranges [II]. Clinicians may consider regular monitoring of fasting glucose or hemoglobin A1c levels to detect emerging diabetes, since patients often have multiple risk factors for diabetes, especially patients with obesity [I].

Antipsychotic treatment often results in substantial improvement or even remission of positive symptoms. However, most patients remain functionally impaired because of negative symptoms, cognitive deficits, and limited social function. It is important to evaluate whether residual negative symptoms are in fact secondary to a parkinsonian syndrome or untreated major depression, since interventions are available to address these causes of negative symptoms [II].

Most patients who develop schizophrenia and related psychotic disorders are at very high risk of relapse in the absence of antipsychotic treatment. Unfortunately, there is no reliable indicator to differentiate the minority who will not from the majority who will relapse with drug discontinuation. It is important to discuss with the patient the risks of relapse versus the long-term potential risks of maintenance treatment with the prescribed antipsychotic [I]. If a decision is made to discontinue antipsychotic medication, additional precautions to minimize the risk of a psychotic relapse are warranted. Educating the patient and family members about early signs of relapse, advising them to develop plans for action should these signs appear, and encouraging the patient to attend outpatient visits on a regular basis are warranted [I]. Indefinite maintenance antipsychotic medication is recommended for patients who have had multiple prior episodes or two episodes within 5 years [I]. In patients for whom antipsychotic medications have been prescribed, monitoring for signs and symptoms of impending or actual relapse is recommended [I].

Adjunctive medications are commonly prescribed for comorbid conditions of patients in the stable phase. Comorbid major depression and obsessive-compulsive disorder may respond to antidepressant medications [II]. Mood stabilizers may also address prominent mood lability [II]. Benzodiazepines may be helpful for managing anxiety and insomnia during the stable phase of treatment [II].

In assessing treatment resistance or partial response, it is important to carefully evaluate whether the patient has had an adequate trial of an antipsychotic medication, including whether the dose is adequate and whether the patient has been taking the medication as prescribed. An initial trial of 4–6 weeks generally is needed to determine if the patient will have any symptomatic response, and symptoms can continue to improve over 6 months or even longer periods of antipsychotic treatment [II]. Given clozapine's superior efficacy, a clozapine trial should be considered for a patient who has had no response or partial and suboptimal response to two trials of antipsychotic medication (at least one second-generation agent) or for a patient with persistent suicidal ideation or behavior that has not responded to other treatments [I].

A number of psychosocial treatments have demonstrated effectiveness during the stable phase. They include family intervention [I], supported employment [I], assertive community treatment [I], skills training [II], and cognitive behaviorally oriented psychotherapy [II]. In the same way that psychopharmacological management must be individually tailored to the needs and preferences of the patient, so too should the selection of psychosocial treatments [I]. The selection of appropriate psychosocial treatments is guided by the circumstances of the individual patient's needs and social context [II].

Interventions that educate family members about schizophrenia are needed to provide support and offer training in effective problem solving and communication, reduce symptom relapse, and contribute to improved patient functioning and family well-being [I]. The Program for Assertive Community Treatment (PACT) is a specific model of community-based care that is needed to treat patients who are at high risk for hospital readmission and who cannot be maintained by more usual community-based treatment [I]. Persons with schizophrenia who have residual psychotic symptoms while receiving adequate pharmacotherapy also may be offered cognitive behaviorally oriented psychotherapy [II].

Supported employment is an approach to improve vocational functioning among persons with various types of disabilities, including schizophrenia, and should be made available [I]. The evidence-based supported employment programs that have been found effective include the key elements of services focused on competitive employment, eligibility based on the consumer's choice, rapid job search, integration of rehabilitation and mental health care, attention to the consumer's preferences, and time-unlimited and individualized support.

Social skills training may be helpful in addressing functional impairments with social skills or activities of daily living [II]. The key elements of this intervention include behaviorally based instruction, modeling, corrective feedback, and contingent social reinforcement.

Treatment programs need to combine medications with a range of psychosocial services to reduce the need for crisis-oriented hospitalizations and emergency department visits and enable greater recovery [I].

► **G. OTHER SPECIFIC TREATMENT ISSUES**

1. First episode

It is important to treat schizophrenia in its initial episode as soon as possible [II]. When a patient presents with a first-episode psychosis, close observation and documentation of the signs and symptoms over time are important because first episodes of psychosis can be polymorphic and evolve into a variety of specific disorders (e.g., schizophreniform disorder, bipolar disorder, schizoaffective disorder) [I]. Furthermore, in persons who meet the criteria for being prodromally

symptomatic and at risk for psychosis in the near future, careful assessment and frequent monitoring are recommended until symptoms remit spontaneously, evolve into schizophrenia, or evolve into another diagnosable and treatable mental disorder [III]. The majority of first-episode patients are responsive to treatment, with more than 70% achieving remission of psychotic signs and symptoms within 3–4 months and 83% achieving stable remission at the end of 1 year. First-episode patients are generally more sensitive to the therapeutic effects and side effects of medications and often require lower doses than patients with chronic schizophrenia. Minimizing risk of relapse in a remitted patient is a high priority, given the potential clinical, social, and vocational costs of relapse [I]. Family members are especially in need of education and support at the time of the patient's first episode [I].

2. Negative symptoms

Treatment of negative symptoms begins with assessing the patient for syndromes that can cause the appearance of secondary negative symptoms [I]. The treatment of such secondary negative symptoms consists of treating their cause, e.g., antipsychotics for primary positive symptoms, antidepressants for depression, anxiolytics for anxiety disorders, or antiparkinsonian agents or antipsychotic dose reduction for extrapyramidal side effects [III]. If negative symptoms persist, they are presumed to be primary negative symptoms of the deficit state. There are no treatments with proven efficacy for primary negative symptoms.

3. Substance use disorders

Nearly one-half of patients with schizophrenia have comorbid substance use disorders, excluding nicotine abuse/dependence, which itself exceeds 50% in prevalence in this group. The goals of treatment for patients with schizophrenia who also have a substance use disorder are the same as those for treatment of patients with schizophrenia without comorbidity but with the addition of the goals for the treatment of substance use disorders, e.g., harm reduction, abstinence, relapse prevention, and rehabilitation. A comprehensive integrated treatment model is recommended in which the same clinicians or team of clinicians provide treatment for schizophrenia as well as treatment of substance use disorders [III]. This form of treatment features assertive outreach, case management, family interventions, housing, rehabilitation, and pharmacotherapy. It also includes behavioral interventions for those who are trying to attain or maintain abstinence and a stage-wise motivational approach for patients who do not recognize the need for treatment of a substance use disorder.

4. Depression

Depressive symptoms are common at all phases of schizophrenia. A careful differential diagnosis that considers the contributions of side effects of antipsychotic medications, demoralization, the negative symptoms of schizophrenia, and substance intoxication or withdrawal is recommended [I]. Depressive symptoms that occur during the acute psychotic phase usually improve as patients recover from the psychosis. There is also evidence to suggest that depressive symptoms are reduced by antipsychotic treatment, with comparison trials finding that second-generation antipsychotics may have greater efficacy for depressive symptoms than first-generation antipsychotics [II]. Antidepressants may be added as an adjunct to antipsychotics when the depressive symptoms meet the syndromal criteria for major depressive disorder or are severe, causing significant distress or interfering with function [II].

5. Suicidal and aggressive behaviors

Suicide is the leading cause of premature death among patients with schizophrenia. Some risk factors for suicide among patients with schizophrenia are the same as those for the general pop-

ulation: male gender, white race, single marital status, social isolation, unemployment, a family history of suicide, previous suicide attempts, substance use disorders, depression or hopelessness, and a significant recent adverse life event. Specific demographic risk factors for suicide among persons with schizophrenia are young age, high socioeconomic status background, high IQ with a high level of premorbid scholastic achievement, high aspirations and expectations, early age at onset/first hospitalization, a chronic and deteriorating course with many relapses, and greater insight into the illness.

Despite identification of these risk factors, it is not possible to predict whether an individual patient will attempt suicide or die by suicide. It is important to consider suicide risk at all stages of the illness and to perform an initial suicide risk assessment and regular evaluation of suicide risk as part of each patient's psychiatric evaluation [I]. There is evidence to suggest that both first- and second-generation antipsychotic medications may reduce the risk of suicide. However, clozapine is the most extensively studied and has been shown to reduce the rates of suicide [II] and persistent suicidal behavior [I].

During a hospitalization, use of suicide precautions and careful monitoring over time for suicidal patients are essential [I]. Upon discharge, the patient and the family members may be advised to look for warning signs and to initiate specific contingency plans if suicidal ideation recurs [I]. After a recent discharge from the hospital, a higher frequency of outpatient visits is recommended, and the number of visits may need to be increased during times of personal crisis, significant environmental changes, heightened distress, or deepening depression during the course of illness [III].

A minority of patients with schizophrenia have an increased risk for aggressive behavior. The risk for aggressive behavior increases with comorbid alcohol abuse, substance abuse, antisocial personality, or neurological impairment. Identifying risk factors for aggressive behavior and assessment of dangerousness are part of a standard psychiatric evaluation [I].

► H. TREATMENT SETTINGS AND HOUSING OPTIONS

Patients with schizophrenia may receive care in a variety of settings. In general, patients should be cared for in the least restrictive setting that is likely to be safe and to allow for effective treatment [I]. Indications for hospitalization usually include the patient's being considered to pose a serious threat of harm to self or others or being unable to care for self and needing constant supervision or support [I]. Other possible indications for hospitalization include general medical or psychiatric problems that make outpatient treatment unsafe or ineffective [III] or new onset of psychosis [III]. Efforts should be made to hospitalize such patients voluntarily [I].

Treatment programs that emphasize highly structured behavioral techniques, including a token economy, point systems, and skills training that can improve patients' functioning, are recommended for patients with treatment-resistant schizophrenia who require long-term hospitalization [I].

When it is uncertain whether the patient needs to be hospitalized, alternative treatment in the community, such as day hospitalization, home care, family crisis therapy, crisis residential care, or assertive community treatment, should be considered [III]. Day hospitalization can be used as an immediate alternative to inpatient care for acutely psychotic patients or used to continue stabilization after a brief hospital stay [III].

Day treatment programs can be used to provide ongoing supportive care for marginally adjusted patients with schizophrenia in the later part of the stabilization phase and the stable phase of illness, and such programs are usually not time-limited [III]. The goals are to provide structure, support, and treatment to help prevent relapse and to maintain and gradually improve the patient's social functioning [III].

II. FORMULATION AND IMPLEMENTATION OF A TREATMENT PLAN

Because schizophrenia is a chronic illness that affects virtually all aspects of life of affected persons, treatment planning has three goals: 1) reduce or eliminate symptoms, 2) maximize quality of life and adaptive functioning, and 3) enable recovery by assisting patients in attaining personal life goals (e.g., in work, housing, and relationships). For purposes of presentation throughout this guideline, the course of treatment for persons with schizophrenia is divided into three phases: acute, stabilization, and stable. The acute phase begins with a new onset or acute exacerbation of symptoms and spans the period until these symptoms are reduced to a level considered to be the patient's expected "baseline." The stabilization period follows the acute phase and constitutes a time-limited transition to continuing treatment in the stable phase. Combined, the acute and stabilization phases generally span approximately 6 months. The stable phase represents a prolonged period of treatment and rehabilitation during which symptoms are under adequate control and the focus is on improving functioning and recovery. While these distinctions may be somewhat arbitrary, they provide a useful framework for discussion of treatment.

Many of the advances in the treatment of schizophrenia over the past two decades have come from recognition of the complexities of the manifestations and the different stages of the illness. These insights into the multiple components of psychopathology in schizophrenia and into the role of family, social, and other environmental factors in influencing both psychopathology and adaptation have resulted in development of a wide range of treatments that target specific aspects of the illness. Recognition of the different stages of the illness has led to various approaches in treatment planning, treatment selection, and drug dosing. Fragmentation of services and treatments has long been a problem in delivering comprehensive care to persons with schizophrenia. This fragmentation is determined by several factors, including the use of many different treatment settings, the necessary involvement of several professional disciplines, and the use of multiple funding streams, coupled with inadequate insurance coverage and the decline in funding for public and private mental health services, to mention just a few. It is critical, under these circumstances, that there be an overarching treatment plan that serves the short- and long-term needs of the patient and that is periodically modified as clinical circumstances change and new knowledge about treatments becomes available.

► A. PSYCHIATRIC MANAGEMENT

This section is an overview of key issues in the psychiatric management of patients with schizophrenia. It highlights areas that research has shown to be important in affecting the course of illness and success of treatment. These issues arise in the management of all psychiatric illnesses. This section notes the particular ways in which they occur in the treatment of patients with schizophrenia.

1. Assessing symptoms and establishing a diagnosis

Effective and appropriate treatments are based on accurate, relevant diagnostic and clinical assessments. In the case of schizophrenia, the diagnosis has major implications for short- and long-term treatment planning. (See Part B, Section IV.A, "Clinical Features," for a description of the characteristic symptoms of schizophrenia and the DSM-IV-TR criteria for diagnosis of

the illness.) It is beyond the scope of this guideline to discuss the differential diagnosis of psychotic disorders and their evaluation. However, it is important to note that diagnosis is a process rather than a one-time event. As new information becomes available about the patient and his or her symptoms, the patient's diagnosis should be reevaluated and, if necessary, the treatment plan changed.

Proper diagnosis, while essential, is insufficient to adequately guide treatment of schizophrenia. Treatments are directed at the manifestations and sequelae of schizophrenia. It is critical to identify the targets of each treatment, to have outcome measures that gauge the effect of treatment, and to have realistic expectations about the degrees of improvement that constitute successful treatment. Depression, suicide, homelessness, substance use disorders, medical comorbidities, social isolation, joblessness, criminal victimization, past sexual or physical abuse, and involvement in the criminal justice system are all far more common among persons with schizophrenia, particularly in the chronic stages of the illness, than in the general population. In addition to the core symptoms of schizophrenia, these areas need careful assessment and, as warranted, appropriate interventions.

A number of objective, quantitative rating scales to monitor clinical status in schizophrenia are available, as described in the American Psychiatric Association's (APA's) *Handbook of Psychiatric Measures* (1). They include the Structured Clinical Interview for DSM-IV (2) for establishing diagnosis, the Abnormal Involuntary Movement Scale (3) for monitoring tardive dyskinesia and other abnormal movements, and the Brief Psychiatric Rating Scale (BPRS) (4–6) and the Positive and Negative Syndrome Scale (PANSS) (7) for monitoring psychopathology. Other brief structured assessments are also available (8, 9). There are several reasons that use of rating scales is important. First, rating scales provide a record that documents the patient's response to treatment. This record is of particular value when the treatment is nonstandard (e.g., combination of antipsychotics) or expensive. Second, the ratings can be compared with the patient's, family members', and clinician's impressions of treatment effects and over time can clarify the longitudinal course of the patient's illness. This process can help temper excessive optimism when new treatments are begun and can provide useful information about the actual effects of prior treatments. Third, use of anchored scales with criteria to assess the severity and frequency of symptoms helps patients become more informed self-observers. Finally, use of the rating scales over time ensures that information about the same areas is collected at each administration and helps avoid omission of key elements of information needed to guide treatment.

2. Developing a plan of treatment

After the assessment of the patient's diagnosis and clinical and psychosocial circumstances, a treatment plan must be formulated and implemented. This process involves the selection of the treatment modalities, specific type(s) of treatment, and treatment setting. Depending on the acuity of the clinical situation and because information about the patient's history and from the clinical evaluation may only gradually become available, this process can be iterative and evolve over the course of the patient's association with the clinician. Indeed, formulation and periodic reevaluation of the treatment plan at different phases of implementation and stages of illness are essential to good clinical practice. This process is described in greater detail in the subsequent sections on the various phases of illness, treatment settings, and types of treatments.

3. Developing a therapeutic alliance and promoting treatment adherence

It is essential for the psychiatrist who is treating the patient to establish and maintain a supportive therapeutic alliance, which forms the foundation on which treatment is conducted (10). Such an alliance allows the psychiatrist to gain essential information about the patient and allows the patient to develop trust in the psychiatrist and a desire to collaborate in treatment.

To facilitate this process, continuity of care with the same psychiatrist over time is recommended, allowing the psychiatrist to learn more about the patient as a person and the individual vicissitudes of the disorder over time. However, while continuity is desirable, it does not ensure quality, and continuity of inadequate treatment can be highly problematic.

Research indicates that specific attention in the therapeutic relationship to identifying the patient's goals and aspirations and relating them to treatment outcomes increases treatment adherence (11). Moreover, evidence supports the conclusion that the most effective medication adherence strategies focus on the patient's attitudes and behaviors with respect to medication rather than taking a general psychoeducational approach (12).

Not uncommonly, patients with schizophrenia stop taking medications, miss clinic appointments, fail to report essential information to their psychiatrists, and otherwise choose to not participate in recommended treatments. To address partial or full treatment nonadherence, the clinician should first assess contributing factors. Potential factors can be broadly conceptualized under the health belief model, which assumes adherence behavior is dynamic and influenced by a patient's beliefs about need for treatment, the potential risks and benefits of treatment, barriers to treatment, and social support for adhering to treatment (13). Frequent causes of poor adherence are lack of insight (14), breakdown of the therapeutic alliance, discrimination associated with the illness, cultural beliefs, failure to understand the need to take daily medication even in the stable phase, cognitive impairment (15, 16), and experience of unpleasant medication side effects such as akathisia (17, 18). Most patients have some ambivalence about taking antipsychotic medications, all of which can be associated with unpleasant and, rarely, dangerous side effects. Even patients with good insight into their symptoms or illness may not perceive their prescribed medication as potentially or actually helpful. Patients who do experience troublesome or serious side effects may decide that these effects outweigh the benefits of medication. Finally, people important to the patient, including family and friends, may discourage the patient from taking medication or participating in other aspects of treatment.

Once the reasons for incomplete adherence are understood, clinical interventions can be implemented to address them. For example, encouraging the patient to report side effects and attempting to diminish or eliminate them can significantly improve medication adherence. Also, it is important for patients who are relatively asymptomatic in the stable phase to understand that medication may be prophylactic in preventing relapse (19, 20). If a patient stops taking medication during the stable phase, he or she may feel better, with less sedation or other side effects. As a result, the patient may come to the false conclusion that the medication is not necessary or does not have benefits. As will be described in later sections, psychotherapeutic techniques based on motivational interviewing and cognitive behavior techniques may enhance insight and treatment adherence. In situations in which patients choose not to adhere to prescribed psychosocial interventions, a careful review of the patient's perceptions of the goals of the treatment and its likelihood for success is recommended.

The clinician may also help to identify practical barriers to adherence, such as cognitive impairments or disorganization that interferes with a willing patient's regular taking of medication or participation in treatment. Use of simple aids, such as a pillbox placed in a prominent location in the home and a watch with an alarm, can enhance adherence. Family members and significant others can also be involved, for example, by helping the patient fill the pillbox and by regularly monitoring adherence. Patients without health care insurance may have difficulty affording even generic antipsychotics or basic psychosocial services. The clinician may help with access to medications by suggesting and completing the physician's sections of the application for patients' assistance programs offered by most pharmaceutical companies. Some patients may not have transportation to the pharmacy or to physician appointments and other treatment services. For patients who are parents, lack of child care may also pose a barrier to attending appointments.

For some patients, medication with a longer elimination half-life or long-acting injectable medications are options that may improve treatment adherence or minimize nonadherence. It is also important to note that the half-lives of oral antipsychotic medications vary widely. For patients who are prone to forget doses or are intermittently nonadherent to treatment, drugs with slower rates of metabolism may be used preferentially.

When a patient does not appear for appointments or is nonadherent in other ways, assertive outreach, including telephone calls and home visits, when appropriate, may be very helpful in reengaging the patient in treatment. This outreach can be carried out by the psychiatrist or other designated team member (e.g., of an assertive community treatment team), when available, in consultation with the psychiatrist. For some patients, nonadherence with care is frequent and is associated with repeated cycles of decompensation and rehospitalization. Particularly for patients who pose ongoing risks to self or others as a result of nonadherence, many states now have programs available for mandatory outpatient treatment (sometimes referred to as outpatient commitment). Although some have questioned whether mandatory outpatient treatment increases patients' reluctance to seek help voluntarily (21–23), a growing body of evidence suggests that a number of benefits may occur with mandatory outpatient treatment for appropriately selected patients when it incorporates intensive individualized outpatient services for an extended period of time. In addition to enhanced adherence, most (24–27) but not all (28) studies show mandatory outpatient treatment to be associated with benefits, including reductions in substance use and abuse, decreases in violent incidents, reductions in the likelihood of being criminally victimized, and improvements in quality of life in appropriately targeted patients. Thus, for a small subgroup of patients with repeated relapses and rehospitalizations associated with nonadherence, mandatory outpatient treatment can be a useful approach to improved adherence and enhanced outcomes (29).

4. Providing patient and family education and therapies

Working with patients to recognize early symptoms of relapse can result in preventing full-blown illness exacerbations (30). Family education about the nature of the illness and coping strategies can markedly diminish relapses and improve quality of life for patients (31). For general educational purposes, a variety of useful written materials about schizophrenia is available. The interventions that have been shown to be effective, however, involve face-to-face interactions in individual or group sessions for a total of at least 9–12 months, with the availability of crisis intervention and problem-solving tasks as a central element of the therapy.

5. Treating comorbid conditions

As already noted, a number of psychiatric, social, and other medical conditions occur far more frequently in persons with schizophrenia than in the general population. Periodic assessment of these conditions by the treatment team is important. Commonly co-occurring major depression, substance use disorders, and PTSD are usually identifiable through clinical examinations and discussions with the patient and significant others, combined with longitudinal observation of the patient's behavior patterns. Each of these conditions deserves attention and possibly treatment in its own right, with such treatment concurrent with that for schizophrenia. Substance use disorders, in particular, complicate assessment and treatment of schizophrenia, but delaying treatment of the psychotic disorder until the substance use disorder is under control is not recommended, as untreated psychosis is likely to be associated with increased substance use (32).

Section II.F.3, "Concurrent General Medical Conditions," discusses nonpsychiatric medical conditions that are commonly comorbid with schizophrenia. Certain illnesses, such as diabetes, are more common in persons with schizophrenia and have also been associated with some second-generation antipsychotic medications. Nicotine dependence is also common among persons with schizophrenia and contributes to the increased risk of physical illnesses (33, 34). It is important that patients have access to primary care clinicians who can work with the psychia-

trist to diagnose and treat concurrent general medical conditions and that the psychiatrist maintain competence in screening for common medical conditions and for providing ongoing monitoring and treatment of common medical conditions in conjunction with primary care clinicians.

6. Attending to the patient's social circumstances and functioning

The social circumstances and functioning of the patient can have profound effects on adherence and response to treatment. The patient's living situation, family involvement, sources and amount of income, legal status, and relationships with significant others (including children) can both produce stress and be protective; thus, all are areas where periodic exploration by mental health care clinicians is warranted. A frequently neglected aspect of social assessment is the parenting role of patients with children (35, 36). The patient's sexuality is also often not adequately assessed, not only from the standpoint of adverse medication effects, but in terms of sexual relations and practices.

Depending on the nature of the problem in the patient's social circumstances, other mental health professionals may need to be involved in achieving its resolution. The psychiatrist can work with team members, the patient, and the family to ensure that such services are coordinated and that referrals for additional services are made when appropriate. It is important that disability income support is secured when indicated.

7. Integrating treatments from multiple clinicians

Many patients with schizophrenia require a variety of treatments, often from multiple clinicians. This requirement creates the potential for fragmentation of treatment efforts for patients who frequently have problems with planning and organizing. In many settings integration of treatments is best accomplished through designation of treatment teams, led by a psychiatrist or other skilled mental health professional, that meet periodically to review progress and goals and to identify obstacles to improvement. So-called case management, which provides the patient assistance in gaining access to community services and resources, is often useful to facilitate integration of treatments. Either several members of a team or one person can be assigned to be the case manager, ensuring that the patient receives coordinated, continuous, and comprehensive services. For example, the case manager may accompany the patient to a welfare agency, visit the patient's home if a clinical appointment is missed, or convene a meeting of workers from different agencies serving the patient to formulate an overall treatment plan in conjunction with the psychiatrist. There are a variety of educational and organizational approaches to building teams and programs that facilitate the goal of integrated treatment (37, 38).

8. Documenting treatment

Whether treated in the private or public sector, most persons with schizophrenia will have many different practitioners over the course of their illness. These transitions result from changes in treatment venues (inpatient, outpatient, assertive community treatment, etc.), program availability, insurance, the patient's locale, and clinic personnel. Because an accurate history of past and current treatments and responses to them is a key ingredient to treatment planning, excellent documentation is paramount. Especially critical, for example, is information about prior medication trials, including doses, length of time at specific doses, side effects, and clinical response. Despite the importance of an accurate history, studies of the adequacy of documentation (39) and clinical experience illustrate the extraordinary difficulty encountered in efforts to piece together a coherent story from the medical records of most patients with schizophrenia. Although actual chart documentation is the responsibility of the individual practitioner, it is typically the employing or contracting organization that is in the best position to facilitate good documentation and to effect periodic overviews of treatment. Appropriate documentation of assessment of competency, informed consent for treatment, and release of information also deserve careful attention by the clinician and the treatment organization.

Within the organization there are at least two major issues in information management. From the standpoint of information collection, the organization and its practitioners need to agree on the critical elements of information to obtain and the frequency with which they should be obtained. Recording of information may occur contemporaneously with collection or immediately thereafter. Labor-saving forms (paper or computer-based) may help in prompting data collection and easing its recording. Once information is collected, the ability to gain access to the information is essential. Thus, the organization will want to develop plans so that medical records will be available whenever and wherever the patient is seen. In addition, if the patient's care is transferred from one practitioner to another (e.g., outpatient to inpatient), necessary information will need to be transferred to the new practitioner ahead of or along with the patient. Release of a patient's information will generally require the patient's consent and should conform to applicable regulations and policies (e.g., state law, the Health Insurance Portability and Accountability Act, and *Principles of Medical Ethics: With Annotations Especially Applicable to Psychiatry* [40]).

► **B. ACUTE PHASE**

The goals of treatment during the acute phase of a psychotic exacerbation are to prevent harm, control disturbed behavior, reduce the severity of psychosis and associated symptoms (e.g., agitation, aggression, negative symptoms, affective symptoms), determine and address the factors that led to the occurrence of the acute episode, effect a rapid return to the best level of functioning, develop an alliance with the patient and family, formulate short- and long-term treatment plans, and connect the patient with appropriate aftercare in the community. It is especially important to address the anxiety, fear, and dysphoria commonly associated with an acute episode. Efforts to engage and collaborate with family members and other natural caregivers are often successful during the crisis of an acute psychotic episode, whether it is the first episode or a relapse. Also, family members and other caregivers are often needed to provide support to the patient while he or she is recovering from an acute episode. The main therapeutic challenge for the clinician is to select and “titrate” the doses of both pharmacological and psychosocial interventions in accordance with the symptoms and sociobehavioral functioning of the patient (41). It is important to emphasize that acute-phase treatment is often but no longer necessarily associated with hospitalization. With the growth of managed care restricting the use of hospitalization and the development of alternative community-based programs, acute-phase treatment frequently occurs outside of the hospital.

1. Assessment in the acute phase

A thorough initial workup, including complete psychiatric and general medical histories and physical and mental status examinations, is recommended for all patients, as allowed by the patient's clinical status. Interviews of family members or other persons knowledgeable about the patient should be conducted routinely unless the patient refuses to grant permission, especially since many patients are unable to provide a reliable history at the first interview. In emergency circumstances, as when a patient's safety is at risk, it may be necessary and permissible to speak with others without the patient's consent.

When a patient is in an acute psychotic state, acutely agitated, or both, it may be impossible to perform an adequate evaluation at the time of the initial contact. With the patient's consent, the psychiatrist may begin treatment with an appropriate medication and perform the necessary evaluations as the patient's condition improves and permits. For acutely psychotic or agitated patients who lack the capacity or are unwilling to agree to receive medication, state regulations on involuntary treatment should be followed.

Some of the most common contributors to symptom relapse are antipsychotic medication nonadherence, substance use, and stressful life events (42–47). Medication adherence may be

assessed by the patient's report, the reports of family members or other caregivers, pill counts, prescription refill counts, and, for some medications, antipsychotic blood levels. Attention needs to be given to potential drug-drug interactions that may affect blood levels and hence toxicity and adherence. Useful guides for determining potential adverse drug interactions related to the cytochrome P450 enzyme system are now available (48, 49). The reason for nonadherence should also be evaluated and considered in the treatment plan.

General medical health as well as medical conditions that could contribute to symptom exacerbation can be evaluated by medical history; physical and neurological examination; and appropriate laboratory, electrophysiological, and radiological assessments. Substance use should be routinely evaluated as part of the medical history and with a urine toxicology screen. It is important to realize that many drugs of abuse, including most designer drugs and hallucinogens, are not detected by urine toxicology screens; if use of such substances is suspected, a blood toxicology screen can detect some of them. Withdrawal from alcohol or some other substances can present as worsening psychosis, and the possibility of withdrawal should be evaluated by medical history and vital sign monitoring in all patients with acute exacerbation of symptoms. (The results of toxicology screens will usually be negative, since risk of withdrawal is often highest several days after abstinence from chronic abuse.) Body weight and vital signs (heart rate, blood pressure, temperature) should be measured. A CT or MRI scan may provide helpful information, particularly in assessing patients with a new onset of psychosis or with an atypical clinical presentation. Although imaging studies cannot establish a diagnosis of schizophrenia, specific findings from a CT or MRI scan (e.g., ventricular enlargement, diminished cortical volume) may enhance the confidence of the diagnosis and provide information that is relevant to treatment planning and prognosis. Given the subtle nature of the neuropathological findings in schizophrenia, MRI is preferred over CT.

Table 1 delineates suggested laboratory tests for evaluating health status, including studies that may be indicated when the clinical picture is unclear or when there are abnormal findings on routine examination, as well as suggested methods to monitor for side effects of treatment.

These tests may detect occult disease that is contributing to psychosis and also determine if there are comorbid medical conditions that might affect medication selection, such as impaired liver or renal function. Tests to assess other general medical needs of patients should also be considered (e.g., gynecological examination, mammogram, and rectal examination) (54). The U.S. Preventive Services Task Force has reviewed the evidence of effectiveness and developed recommendations for clinical preventive services (<http://www.ahcpr.gov/clinic/uspstfix.htm>).

It is also important that special precautions be taken in the presence of suicidal ideation or intent or a suicide plan, including an assessment of risk factors such as prior attempts, depressed mood, and suicidal ideation, which are the best predictors of a subsequent suicide attempt in schizophrenia (55, 56). Other predictors of suicide that also warrant close attention include the presence of command hallucinations, hopelessness, anxiety, extrapyramidal side effects, and an alcohol or other substance use disorder. Similar evaluations are necessary in considering the likelihood of dangerous or aggressive behavior and whether the person will harm someone else or engage in other forms of violence (57). The coexistence of substance use (58) significantly increases the risk of violent behavior. Because past behavior best predicts future behavior, family members and friends are often helpful in determining the risk of a patient's harming self or others and in assessing the patient's ability for self-care.

2. Psychiatric management in the acute phase

Psychosocial interventions in the acute phase are aimed at reducing overstimulating or stressful relationships, environments, or life events and at promoting relaxation or reduced arousal through simple, clear, coherent communication and expectations; a structured and predictable environment; low performance requirements; and tolerant, nondemanding, supportive relationships with the psychiatrist and other members of the treatment team.

TABLE 1. Suggested Physical and Laboratory Assessments for Patients With Schizophrenia

Assessment	Initial or Baseline	Follow-Up
Assessments to monitor physical status and detect concomitant physical conditions		
Vital signs	Pulse, blood pressure, temperature	Pulse, blood pressure, temperature, as clinically indicated, particularly as medication doses are titrated
Body weight and height	Body weight, height, and body mass index (BMI) ^a	BMI every visit for 6 months and at least quarterly thereafter ^b
Hematology	CBC	CBC, if clinically indicated, including assessment of patients treated with clozapine
Blood chemistries	Electrolytes Renal function tests (BUN/creatinine ratio) Liver function tests Thyroid function tests	Annually and as clinically indicated
Infectious diseases	Test for syphilis Tests for hepatitis C and HIV, if clinically indicated	
Pregnancy	Consider pregnancy test for women of childbearing potential	
Toxicology	Drug toxicology screen, heavy metal screen, if clinically indicated	Drug toxicology screen, if clinically indicated
Imaging/EEG	EEG, brain imaging (CT or MRI, with MRI being preferred), if clinically indicated	
Assessments related to other specific side effects of treatment ^c		
Diabetes ^d	Screening for diabetes risk factors ^e ; fasting blood glucose ^f	Fasting blood glucose or hemoglobin A1c at 4 months after initiating a new treatment and annually thereafter ^f
Hyperlipidemia	Lipid panel ^g	At least every 5 years
QTc prolongation	ECG and serum potassium before treatment with thioridazine, mesoridazine, or pimozide; ECG before treatment with ziprasidone in the presence of cardiac risk factors ^h	ECG with significant change in dose of thioridazine, mesoridazine, pimozide, and, in the presence of cardiac risk factors, ziprasidone or addition of other medications that can affect QTc interval
Hyperprolactinemia	Screening for symptoms of hyperprolactinemia ⁱ Prolactin level, if indicated on the basis of clinical history	Screening for symptoms of hyperprolactinemia at each visit until stable, then yearly if treated with an antipsychotic known to increase prolactin ⁱ Prolactin level, if indicated on the basis of clinical history
Extrapyramidal side effects, including akathisia	Clinical assessment of extrapyramidal side effects	Clinical assessment of extrapyramidal side effects weekly during acute treatment until antipsychotic dose is stable for at least 2 weeks, then at each clinical visit during stable phase
Tardive dyskinesia	Clinical assessment of abnormal involuntary movements	Clinical assessment of abnormal involuntary movements every 6 months in patients taking first-generation antipsychotics and every 12 months in those taking second-generation antipsychotics In patients at increased risk, assessment should be done every 3 months and every 6 months with treatment using first- and second-generation antipsychotics, respectively ^j

TABLE 1. Suggested Physical and Laboratory Assessments for Patients With Schizophrenia (continued)

Assessment	Initial or Baseline	Follow-Up
Cataracts	Clinical history to assess for changes in distance vision or blurred vision; ocular examination including slit-lamp examination for patients treated with antipsychotics associated with an increased risk of cataracts	Annual clinical history to assess for visual changes; ocular examination every 2 years for patients under age 40 and every year for patients over age 40

^aBMI may be calculated by using the formula weight in kg/(height in m)² or the formula 703 × weight in lb/(height in inches)² or by using a BMI table available from the National Institute of Diabetes and Digestive and Kidney Diseases (<http://www.niddk.nih.gov/health/nutrit/pubs/statobes.htm#table>). A person with a BMI >25 to 29.9 is considered overweight, and one with a BMI of 30 or higher is considered obese. As an alternative to BMI, waist size can be used as an indicator of risk (>35 inches for women and >40 inches for men).

^bExcept for patients with a BMI of <18.5, an increase in BMI of 1 BMI unit would suggest a need for intervention by monitoring weight more closely, engaging the patient in a weight management program, using an adjunctive treatment to reduce weight, or changing the antipsychotic medication.

^cAlthough this practice guideline recommends that patients treated with antipsychotic medications be monitored for physical conditions and side effects on a regular basis, there are no absolute criteria for frequency of monitoring. Occurrence of conditions and side effects may be influenced by the patient's history, preexisting conditions, and use of other medications in addition to antipsychotic agents. Thus, decisions about monitoring patients for physical conditions, specific side effects, or abnormalities in laboratory test results will necessarily depend on the clinical circumstances. In general, baseline assessments related to physical conditions and specific medication-related side effects will be done at the time of initiating or changing antipsychotic medications or when adding other medications that contribute to these side effects. Information in this section of the table is adapted from the recommendations of the October 2002 Mount Sinai Conference on Health Monitoring of Patients With Schizophrenia (50).

^dThe U.S. Food and Drug Administration has requested all manufacturers of second-generation (atypical) antipsychotic medications to include a warning in their product labeling regarding hyperglycemia and diabetes mellitus. Although precise risk estimates for hyperglycemia-related adverse events are not available for each agent, epidemiological studies suggested an increased risk of treatment-emergent adverse events with second-generation antipsychotics. In some patients, this hyperglycemia was extreme and/or associated with ketoacidosis, hyperosmolar coma, or death.

^eFactors that indicate an increased risk for undiagnosed diabetes include a BMI greater than 25, a first-degree relative with diabetes, habitual physical inactivity, being a member of a high-risk ethnic population (African American, Hispanic American, Native American, Asian American, Pacific Islander), having delivered a baby heavier than 9 lbs or having had gestational diabetes, hypertension, a high-density lipoprotein cholesterol level <35 mg/dl and/or a triglyceride level >250 mg/dl, history of abnormal findings on the glucose tolerance test or an abnormal level of fasting blood glucose, and history of vascular disease (51). Symptoms of possible diabetes include frequent urination, excessive thirst, extreme hunger, unusual weight loss, increased fatigue, irritability, and blurry vision.

^fAs an alternative to measurement of fasting blood glucose, a hemoglobin A1c level may be obtained. An abnormal value (fasting blood glucose >110 mg/dl or hemoglobin A1c >6.1%) suggests a need for medical consultation. More frequent monitoring may be indicated in the presence of weight change, symptoms of diabetes, or a random measure of blood glucose >200 mg/dl.

^gAdditional information on screening of patients for possible lipid disorders can be found in the guidelines of the National Cholesterol Education Program (52) and the U.S. Preventive Services Task Force (53).

^hIn this context, cardiac risk factors include known heart disease, a personal history of syncope, a family history of sudden death at an early age (under age 40, especially if both parents had sudden death), or prolonged QTc syndrome.

ⁱChanges in libido, menstrual changes, or galactorrhea in women; changes in libido or in erectile or ejaculatory function in men.

^jPatients at increased risk for developing abnormal involuntary movements include elderly patients and patients who experience acute dystonic reactions, other clinically significant extrapyramidal side effects, or akathisia.

The patient should be provided information on the nature and management of the illness that is appropriate to his or her ability to assimilate information. The patient should also be encouraged to collaborate with the psychiatrist in selecting and adjusting the medication and other treatments provided. Ordinarily, a hospitalized patient should be provided with some information about the disorder and the medications being used to treat it, including their benefits and side effects. As described in Section II.A.3, “Developing a Therapeutic Alliance and Promoting Treatment Adherence,” the psychiatrist must realize that the degree of acceptance of medication and information about it will vary according to the patient’s cognitive capacity, the extent of the patient’s insight, and efforts made by the psychiatrist to engage the patient and the patient’s family members in a collaborative treatment relationship.

The acute phase is also the best time for the psychiatrist to initiate a relationship with family members, who tend to be particularly concerned about the patient’s disorder, disability, and prognosis during this phase and during hospitalization. Educational meetings, “survival workshops” that teach the family how to cope with schizophrenia, and referrals to the local chapter of NAMI may be helpful. The NAMI web site (<http://www.nami.org>) offers a wealth of useful information. Manuals, workbooks, and videotapes are also available to aid families in this process (59–64). Active efforts to involve relatives in treatment planning and implementation are often a critical component of treatment.

3. Use of antipsychotic medications in the acute phase

Treatment with antipsychotic medication is indicated for nearly all episodes of acute psychosis in patients with schizophrenia. In this guideline the term “antipsychotic” refers to several classes of medications (Table 2). These include the first-generation antipsychotic medications and the second-generation (sometimes referred to as “atypical”) agents clozapine, risperidone, olanzapine, quetiapine, ziprasidone, and aripiprazole.

Pharmacological treatment should be initiated as soon as is clinically feasible, because acute psychotic exacerbations are associated with emotional distress, disruption to the patient’s life, and a substantial risk of behaviors that are dangerous to self, others, or property (57, 68, 69). There are limited circumstances where it may be appropriate to delay treatment, for example, for patients who require more extensive or prolonged diagnostic evaluation, who refuse medications, or who may experience a rapid recovery because substance use or acute stress reactions are thought to be the potential cause of the symptom exacerbation.

Before treatment with antipsychotic medication is begun, baseline laboratory studies may be indicated, if they have not already been obtained as a part of the initial assessment (Table 1). In addition, the treating physician should, as is feasible, discuss the potential risks and benefits of the medication with the patient. The depth of this discussion will, of course, be determined by the patient’s condition. Even with agitated patients and patients with thought disorder, however, the therapeutic alliance will be enhanced if the patient and physician can identify target symptoms (e.g., anxiety, poor sleep, and, for patients with insight, hallucinations and delusions) that are subjectively distressing and that antipsychotics can ameliorate. Acute side effects such as orthostatic hypotension, dizziness, and extrapyramidal side effects, including dystonic reactions, insomnia, or sedation, should be discussed at this stage, leaving discussion of long-term side effects to when the acute episode is resolving. Mentioning the possibility of acute side effects helps patients to identify and report their occurrence and also may help maintain a therapeutic alliance. To the extent possible, it is important to minimize acute side effects of antipsychotic medications, such as dystonia, that can significantly influence a patient’s willingness to accept and continue pharmacological treatment. Patients with schizophrenia often have attentional and other cognitive impairments that may be more severe during an acute illness exacerbation, and so it is often helpful to return to the topic of identifying target symptoms and risk of acute side effects multiple times during the course of hospitalization.

TABLE 2. Commonly Used Antipsychotic Medications

Antipsychotic Medication	Recommended Dose Range (mg/day)^a	Chlorpromazine Equivalents (mg/day)^b	Half-Life (hours)^c
First-generation agents			
<i>Phenothiazines</i>			
Chlorpromazine	300–1000	100	6
Fluphenazine	5–20	2	33
Mesoridazine	150–400	50	36
Perphenazine	16–64	10	10
Thioridazine	300–800	100	24
Trifluoperazine	15–50	5	24
<i>Butyrophenone</i>			
Haloperidol	5–20	2	21
<i>Others</i>			
Loxapine	30–100	10	4
Molindone	30–100	10	24
Thiothixene	15–50	5	34
Second-generation agents			
Aripiprazole	10–30		75
Clozapine	150–600		12
Olanzapine	10–30		33
Quetiapine	300–800		6
Risperidone	2–8		24
Ziprasidone	120–200		7

^aDose range recommendations are adapted from the 2003 Schizophrenia Patient Outcome Research Team recommendations (65).

^bChlorpromazine equivalents represent the approximate dose equivalent to 100 mg of chlorpromazine (relative potency). Chlorpromazine equivalents are not relevant to the second-generation antipsychotics; therefore, no chlorpromazine equivalents are indicated for these agents (66).

^cThe half-life of a drug is the amount of time required for the plasma drug concentration to decrease by one-half; half-life can be used to determine the appropriate dosing interval (67). The half-life of a drug does not include the half-life of its active metabolites.

Rapid initiation of emergency treatment is needed when an acutely psychotic patient is exhibiting aggressive behaviors toward self, others, or objects. When the patient is in an emergency department, inpatient unit, or other acute treatment facility, existing therapeutic protocols usually define the appropriate response. Most of these protocols recognize that the patient is usually frightened and confused and that the first intervention involves staff members talking to the patient in an attempt to calm him or her. Attempts to restrain the patient should be done only by a team trained in safe restraint procedures to minimize risk of harm to patients or staff (70). Antipsychotics and benzodiazepines are often helpful in reducing the patient's level of agitation (71). If the patient will take oral medication, rapidly dissolving forms of olanzapine and risperidone can be used for quicker effect and to reduce nonadherence. If a patient refuses oral medication, most states allow for emergency administration despite the patient's objection. Short-acting parenteral formulations of first- and second-generation antipsychotic agents (e.g., haloperidol, ziprasidone, and olanzapine), with or without a parenteral benzodiazepine (e.g., lorazepam), are available for emergency administration in acutely agitated patients (72–79). Use of rapidly dissolving oral formulations of second-generation agents (e.g., olanzapine, risperidone) or oral concentrate formulations (e.g., risperidone, haloperidol) may also be useful for

TABLE 3. Choice of Medication in the Acute Phase of Schizophrenia

Patient Profile	Consider Medication From			
	Group 1: First-Generation Agents	Group 2: Risperidone, Olanzapine, Quetiapine, Ziprasidone, or Aripiprazole	Group 3: Clozapine	Group 4: Long-Acting Injectable Antipsychotic Agents
First episode		Yes		
Persistent suicidal ideation or behavior			Yes	
Persistent hostility and aggressive behavior			Yes	
Tardive dyskinesia		Yes; all group 2 drugs may not be equal in their lower or no tardive dyskinesia liability	Yes	
History of sensitivity to extrapyramidal side effects		Yes, except higher doses of risperidone		
History of sensitivity to prolactin elevation		Yes, except risperidone		
History of sensitivity to weight gain, hyperglycemia, or hyperlipidemia		Ziprasidone or aripiprazole		
Repeated nonadherence to pharmacological treatment				Yes

acute agitation. Other medications, such as droperidol, can be used in selected clinical situations of extreme emergency or in highly agitated patients (80). However, if droperidol is used, its potential for cardiac rhythm disturbances must be considered, as indicated in its labeling by a black-box warning for QTc prolongation.

In nonemergency circumstances in which the patient is refusing medication, the physician may have limited options. When a patient refuses medication, it is often helpful to enlist family members as allies in helping the patient to accept medication. Often, patients can be helped to accept pharmacological treatment over time and with psychotherapeutic interactions that are aimed toward identifying subjectively distressing symptoms that have previously responded to treatment (12). Clinicians are encouraged to make greater use of the option of advance directives by patients in states where this option is available. Advance directives allow competent patients to state their preferences about treatment choices in the event of future decompensation and acute incapacity to make decisions. Depending on prevailing state laws, when treatment measures instituted on the basis of an advance directive fail, pharmacological treatment may be administered involuntarily even in the absence of acute dangerousness (81). In other instances, depending on state laws, a judicial hearing may need to be sought for permission to treat a patient who lacks capacity.

The process for determining pharmacological treatment in the acute phase is shown in Table 3 and Figure 1.

The selection of an antipsychotic medication is frequently guided by the patient's previous experience with antipsychotics, including the degree of symptom response, the side effect profile (including past experience of side effects such as dysphoria), and the patient's preferences for a particular medication, including the route of administration. The second-generation antipsychotics should be considered as first-line medications for patients in the acute phase of schizophrenia, mainly because of the decreased risk of extrapyramidal side effects and tardive dyskinesia (82–85), with the understanding that there continues to be debate over the relative

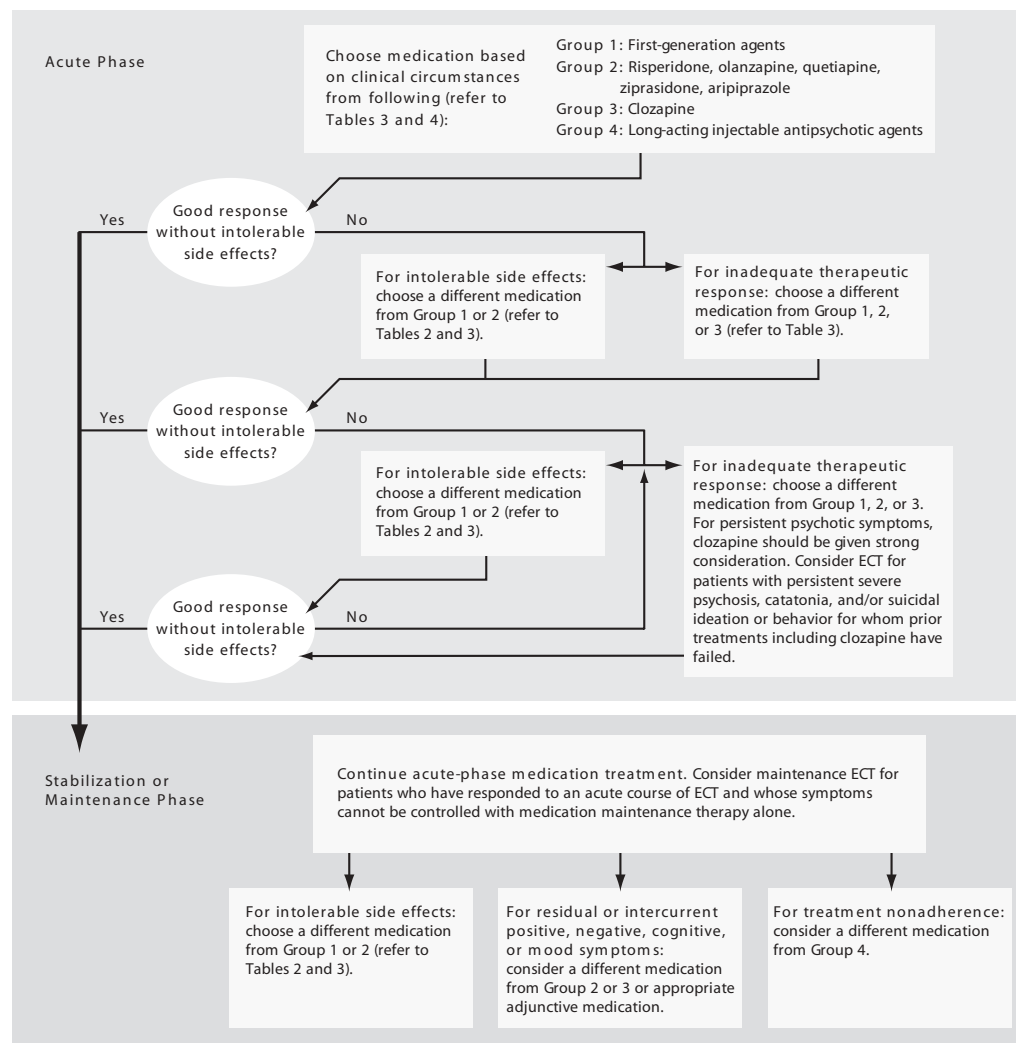


FIGURE 1. Somatic Treatment of Schizophrenia.

advantages, disadvantages, and cost-effectiveness of first- and second-generation agents (86–89). For patients who have been treated successfully in the past or who prefer first-generation agents, these medications are clinically useful and for specific patients may be the first choice. With the possible exception of clozapine for patients with treatment-resistant symptoms, antipsychotics generally have similar efficacy in treating the positive symptoms of schizophrenia, although there is emerging evidence and ongoing debate that second-generation antipsychotics may have superior efficacy in treating global psychopathology and cognitive, negative, and mood symptoms. To date, there is no definitive evidence that one second-generation antipsychotic will have superior efficacy compared with another, although in an individual patient there may be clinically meaningful differences in response (89). A patient's past history of side effects can guide antipsychotic drug selection, since there is considerable difference in side effect profiles among the available antipsychotics. Table 4 lists the relative frequency of some adverse effects associated with selected antipsychotic medications. Strategies for the monitoring

TABLE 4. Selected Side Effects of Commonly Used Antipsychotic Medications^a

Medication	Extrapyramidal Side Effects/ Tardive Dyskinesia				Glucose Abnormalities	Lipid Abnormalities	QTc Prolongation	Sedation	Hypotension	Anticholinergic Side Effects
	Prolactin Elevation	Weight Gain								
Thioridazine	+	++	+	+?	+?	+++	++	++	++	++
Perphenazine	++	++	+	+?	+?	0	+	+	0	0
Haloperidol	+++	+++	+	0	0	0	++	0	0	0
Clozapine ^b	0 ^c	0	+++	+++	+++	0	+++	+++	+++	+++
Risperidone	+	+++	++	++	++	+	+	+	0	0
Olanzapine	0 ^c	0	+++	+++	+++	0	+	+	++	++
Quetiapine ^d	0 ^c	0	++	++	++	0	++	++	0	0
Ziprasidone	0 ^c	+	0	0	0	++	0	0	0	0
Aripiprazole ^e	0 ^c	0	0	0	0	0	+	0	0	0

^a0=No risk or rarely causes side effects at therapeutic dose. +=Mild or occasionally causes side effects at therapeutic dose. ++=Sometimes causes side effects at therapeutic dose. +++=Frequently causes side effects at therapeutic dose. ?=Data too limited to rate with confidence. Table adapted from Tandon (90) with permission of Current Medicine, Inc.

^bAlso causes agranulocytosis, seizures, and myocarditis.

^cPossible exception of akathisia.

^dAlso carries warning about potential development of cataracts.

^eAlso causes nausea and headache.

and clinical management of selected side effects of antipsychotic medications are outlined in Table 1 and discussed in detail in Part B, Section V.A.1, “Antipsychotic Medications.”

While many patients prefer oral medication, patients with recurrent relapses related to partial or full nonadherence are candidates for a long-acting injectable antipsychotic medication, as are patients who prefer the injectable formulation (91). If a long-acting injectable medication is indicated, the oral form of the same medication (i.e., fluphenazine, haloperidol, and risperidone in the United States) is the logical choice for initial treatment during the acute phase. The transition from oral to long-acting injectable medication can begin during the acute phase; however, the long-acting injectable agents are not usually prescribed for acute psychotic episodes because these medications can take months to reach a stable steady state and are eliminated very slowly (92). As a result, the psychiatrist has relatively little control over the amount of medication the patient is receiving, and it is difficult to titrate the dose to control side effects and therapeutic effects. There may, however, be circumstances when it is useful to prescribe long-acting medications during acute treatment. For example, if a patient experiences an exacerbation of psychotic symptoms while receiving long-acting injectable medications, it may be useful to continue the long-acting injectable medication while temporarily supplementing it with oral medication (92).

Determining the optimal dose of antipsychotic medication in the acute phase is complicated by the fact that there is usually a delay between initiation of treatment and full therapeutic response. Patients may take between 2 and 4 weeks to show an initial response (93) and up to 6 months or longer to show full or optimal response. It is important to select a dose that is both effective and not likely to cause side effects that are subjectively difficult to tolerate, since the experience of unpleasant side effects may affect long-term adherence (see Section II.A.3, “Developing a Therapeutic Alliance and Promoting Treatment Adherence”). Some common early side effects such as sedation, postural hypotension, acute dystonia, or nausea will typically improve or resolve after the first several days or weeks of treatment, and patients can be encouraged to tolerate or temporarily manage these short-term effects. Other side effects, notably

akathisia and parkinsonism, are likely to persist with long-term treatment. In general, the optimal dose (range) of medication is that which produces maximal therapeutic effects and minimal side effects. The optimal dose of first-generation antipsychotics (Table 2) is, for most patients, at the “EPS threshold,” the dose that will induce extrapyramidal side effects and where a physical examination of the patient shows minimal rigidity (94). Evidence suggests that doses above this threshold increase risk of extrapyramidal and other side effects without enhancing efficacy (95–97). Second-generation antipsychotics can generally be administered at doses that are therapeutic yet well below the “EPS threshold.” The target dose (Table 2) usually falls within the therapeutic dose range specified by the manufacturer and in the package labeling approved by the U.S. Food and Drug Administration (FDA). In clinical practice, however, doses of several second-generation drugs, including olanzapine, quetiapine, and ziprasidone, have extended above their recommended ranges. In determining the target dose, the psychiatrist should consider the patient’s past history of response and dose needs, clinical condition, and severity of symptoms. Doses should be titrated as quickly as tolerated to the target therapeutic dose (generally sedation, orthostatic hypotension, and tachycardia are the side effects that limit the rate of increase), and unless there is evidence that the patient is having uncomfortable side effects, the patient’s clinical status ideally should then be monitored for 2–4 weeks before increasing the dose or changing medications. During these weeks it is often important for the physician to be patient and avoid the temptation to prematurely escalate the dose for patients who are responding slowly. Rapid escalation can create the false impression of enhanced efficacy when time is often an important factor, and higher doses may actually be detrimental.

If the patient is not improving, consider whether the lack of response can be explained by medication nonadherence, rapid medication metabolism, or poor absorption. If the patient has been treated with one of the medications for which there are adequate data on blood level relationships with clinical response (e.g., clozapine, haloperidol), determination of the plasma concentration may be helpful. If nonadherence is a problem, behavioral tailoring (i.e., fitting taking medication into one’s daily routine) (30), motivational interviewing, and other psychotherapeutic techniques may be useful in helping the patient develop an understanding of the potential benefits of medication (12, 98). In addition, surreptitious nonadherence (i.e., “cheeking”) may be addressed by use of a liquid (e.g., risperidone, haloperidol), a quick-dissolving tablet (e.g., olanzapine, risperidone), or a short-acting intramuscular form (e.g., ziprasidone, haloperidol).

If the patient is adhering to treatment and has an adequate plasma concentration of medication but is not responding to the treatment, alternative treatments should be considered. If the patient is able to tolerate a higher dose of antipsychotic medication without significant side effects, raising the dose for a finite period, such as 2–4 weeks, can be tried, although the incremental efficacy of higher doses has not been well established. If dose adjustment does not result in an adequate response, a different antipsychotic medication should be considered.

4. Use of adjunctive medications in the acute phase

Other psychoactive medications are commonly added to antipsychotic medications in the acute phase to treat comorbid conditions or associated symptoms (e.g., agitation, aggression, affective symptoms), to address sleep disturbances, and to treat antipsychotic drug side effects. Therapeutic approaches to treatment resistance and residual symptoms are discussed in Section II.E, “Special Issues in Caring for Patients With Treatment-Resistant Illness.”

Adjunctive medications are also commonly prescribed for residual symptoms and comorbid conditions during the acute phase. For example, benzodiazepines may be helpful in treating catatonia as well as in managing both anxiety and agitation. The most agitated patients may benefit from addition of an oral or a parenteral benzodiazepine to the antipsychotic medication. Lorazepam has the advantage of reliable absorption when it is administered either orally or parenterally (99). There is some evidence that mood stabilizers and beta-blockers may be

TABLE 5. Selected Medications for Treating Extrapyramidal Side Effects

Generic Name	Dose (mg/day)	Elimination Half-Life (hours)	Target Extrapyramidal Side Effects
Benztropine mesylate ^a	0.5–6.0	24	Akathisia, dystonia, parkinsonism
Trihexyphenidyl hydrochloride	1–15	4	Akathisia, dystonia, parkinsonism
Amantadine	100–300	10–14	Akathisia, parkinsonism
Propranolol	30–90	3–4	Akathisia
Lorazepam ^a	1–6	12	Akathisia
Diphenhydramine ^a	25–50	4–8	Akathisia, dystonia, parkinsonism

Sources. *Drug Information for the Health Care Professional* (104, p. 290) and DRUGDEX (105).

^aAvailable in oral or parenteral forms.

effective in reducing the severity of recurrent hostility and aggression (100–102). Major depression and obsessive-compulsive disorder are common comorbid conditions in patients with schizophrenia and may respond to an antidepressant. However, some antidepressants (those that inhibit catecholamine reuptake) can potentially sustain or exacerbate psychotic symptoms in some patients (103). Careful attention must be paid to potential drug-drug interactions, especially those related to the cytochrome P450 enzymes (48, 49).

Sleep disturbances are common in the acute phase, and while controlled studies are lacking, there is anecdotal evidence that a sedating antidepressant (e.g., trazodone, mirtazapine) or a benzodiazepine sedative-hypnotic may be helpful.

Medications can be used to treat extrapyramidal side effects (Table 5) and other side effects of antipsychotic medications that are described in detail in Part B, Section V.A.1, “Antipsychotic Medications.” Decisions to use medications to treat side effects are driven by the severity and degree of distress associated with the side effect and by consideration of other potential strategies, including lowering the dose of the antipsychotic medication or switching to a different antipsychotic medication. The following factors should be considered in decisions regarding the prophylactic use of antiparkinsonian medications in acute-phase treatment: the propensity of the antipsychotic medication to cause extrapyramidal side effects, the patient’s preferences, the patient’s prior history of extrapyramidal side effects, other risk factors for extrapyramidal side effects (especially dystonia), and risk factors for and potential consequences of anticholinergic side effects.

5. Use of ECT and other somatic therapies in the acute phase

ECT in combination with antipsychotic medications may be considered for patients with schizophrenia or schizoaffective disorder with severe psychotic symptoms that have not responded to treatment with antipsychotic agents. The efficacy of acute treatment with ECT in patients with schizophrenia has been described in a number of controlled trials as well as in multiple case series and uncontrolled studies (106–108). The greatest therapeutic benefits appear to occur when ECT is administered concomitantly with antipsychotic medications. The majority of studies, including several randomized studies, have shown benefit from ECT combined with first-generation antipsychotic agents (109–126). More recent findings also suggest benefit from combined treatment with ECT and second-generation antipsychotic medications (127–135). However, given the clear benefits of clozapine in patients with treatment-resistant psychotic symptoms, a trial of clozapine will generally be indicated before acute treatment with ECT.

Clinical experience, as well as evidence from case series and open prospective trials, suggests that ECT should also be considered for patients with prominent catatonic features that have not responded to an acute trial of lorazepam (136–143). For patients with schizophrenia and comorbid depression, ECT may also be beneficial if depressive symptoms are resistant to treat-

ment or if features such as suicidal ideation and behaviors or inanition, which necessitate a rapid therapeutic response, are present.

For additional details on the assessment of patients before ECT, the informed consent process, the technical aspects of ECT administration, and the side effects associated with treatment, the reader is referred to APA's *The Practice of Electroconvulsive Therapy: Recommendations for Treatment, Training, and Privileging: A Task Force Report of the American Psychiatric Association* (107).

Although it has been suggested that repetitive transcranial magnetic stimulation (rTMS) may share beneficial features of ECT (144, 145) and several recent studies with rTMS have shown promising results in decreasing auditory hallucinations (146–148), rTMS does not have an FDA indication for the treatment of psychosis, and additional research is needed before recommending its use in clinical practice.

► C. STABILIZATION PHASE

During the stabilization phase, the aims of treatment are to sustain symptom remission or control, minimize stress on the patient, provide support to minimize the likelihood of relapse, enhance the patient's adaptation to life in the community, facilitate the continued reduction in symptoms and consolidation of remission, and promote the process of recovery.

Controlled trials provide relatively little guidance for medication treatment during this phase. If the patient has achieved an adequate therapeutic response with minimal side effects or toxicity with a particular medication regimen, he or she should be monitored while taking the same medication and dose for the next 6 months. Premature lowering of dose or discontinuation of medication during this phase may lead to a relatively rapid relapse. However, it is also critical to assess continuing side effects that may have been present in the acute phase and to adjust pharmacotherapy accordingly to minimize adverse side effects that may otherwise lead to medication nonadherence and relapse. Moreover, any adjunctive medications that have been used in the acute phase should be evaluated for continuation.

Psychotherapeutic interventions remain supportive but may be less structured and directive than in the acute phase. Education about the course and outcome of the illness and about factors that influence the course and outcome, including treatment adherence, can begin in this phase for patients and continue for family members. Educational programs during this phase have been effective in teaching a wide range of patients with schizophrenia the skills of medication self-management (e.g., the benefits of maintenance antipsychotic medication, how to cope with side effects) and symptom self-management (e.g., how to identify early warning signs of relapse, develop a relapse prevention plan, and refuse illicit drugs and alcohol), as well as strategies for interacting with health care providers (149–152).

It is important that there be no gaps in service delivery, because patients are vulnerable to relapse and need support in adjusting to community life. Not uncommonly, problems in continuity of care arise when patients are discharged from hospitals to community care. It is imperative to arrange for linkage of services between hospital and community treatment before the patient is discharged from the hospital. Short lengths of hospital stay create challenges for adequately linking inpatient to outpatient care, but to the extent possible, patients should have input into selecting their postdischarge follow-up residential and treatment plans. It is frequently beneficial to arrange an appointment with an outpatient psychiatrist and, for patients who will reside in a community residence, to arrange a visit before discharge (153, 154). After discharge, patients should be helped to adjust to life in the community through realistic goal setting without undue pressure to perform at high levels vocationally and socially, since unduly ambitious expectations on the part of therapists (20), family members (155), or others, as well as an overly stimulating treatment environment (156), can be stressful to patients and can increase the risk of relapse. These principles also apply in the stable phase. Efforts should be made to actively involve family members in the treatment process. Other psychosocial treatments,

discussed below in Section II.D, “Stable Phase,” may be initiated during this phase depending on the patient’s level of recovery and motivation. While it is critical not to place premature demands on the patient regarding engagement in community-based activities and rehabilitation services, it is equally critical to maintain a level of momentum aimed at improving community functioning in order to instill a sense of hope and progress for the patient and family. These efforts set the stage for continuing treatments during the stable phase.

► **D. STABLE PHASE**

Treatment during the stable phase is designed to sustain symptom remission or control, minimize the risk and consequences of relapse, and optimize functioning and the process of recovery.

1. Assessment in the stable phase

Ongoing monitoring and assessment during the stable phase are necessary to determine whether the patient might benefit from alterations in the treatment program. Ongoing assessment allows patients and those who interact with them to describe any changes in symptoms or functioning and raise questions about specific symptoms and side effects.

Monitoring for adverse effects should be done regularly (Table 1). Clinicians should inquire about the course of any side effects that developed in the acute or stabilization phases (e.g., sexual side effects, sedation). Monitoring for other potential adverse effects should be guided by the particular medications chosen (see Part B, Section V.A.1, “Antipsychotic Medications”).

If the patient agrees, it is helpful to maintain strong ties with persons who interact with the patient frequently and would therefore be most likely to notice any resurgence of symptoms and the occurrence of life stresses and events that may increase the risk of relapse or impede continuing functional recovery. However, the frequency of assessments by the psychiatrist or other members of the treatment team depends on the specific nature of the treatment and expected fluctuations of the illness. Frequency of contacts may range from every few weeks for patients who are doing well and are stabilized to as often as every day for those who are going through highly stressful changes in their lives.

2. Psychosocial treatments in the stable phase

For most persons with schizophrenia in the stable phase, treatment programs that combine medications with a range of psychosocial services are associated with improved outcomes. Knowledge and research regarding how best to combine treatments to optimize outcome are scarce. Nonetheless, provision of such packages of services likely reduces the need for crisis-oriented care hospitalizations and emergency department visits and enables greater recovery.

A number of psychosocial treatments have demonstrated effectiveness. These treatments include family interventions (31, 157, 158), supported employment (159–162), assertive community treatment (163–166), social skills training (167–169), and cognitive behaviorally oriented psychotherapy (158, 170). An evidence-based practices project sponsored by the Substance Abuse and Mental Health Services Administration (SAMHSA) is developing resource kits on family interventions, assertive community treatment, and supported employment (draft versions available at http://www.mentalhealthpractices.org/pdf_files/fpe_pcs.pdf; http://www.mentalhealthpractices.org/pdf_files/act_c.pdf; http://www.mentalhealthpractices.org/pdf_files/se_mhpl.pdf).

In the same way that psychopharmacological management must be individually tailored to the needs and preferences of the patient, so too should the selection of psychosocial treatments. The selection of appropriate and effective psychosocial treatments needs to be driven by the circumstances of the individual patient’s needs and his or her social context. At the very least, all persons with schizophrenia should be provided with education about their illness. Beyond needing illness education, most patients will also benefit from at least some of the recommended psychosocial interventions. However, since patients’ clinical and social needs will vary at differ-

ent points in their illness course and since some psychosocial treatments share treatment components, it would be rare for all of these psychosocial interventions to be utilized during any one phase of illness for an individual patient.

a) Prevention of relapse and reduction of symptom severity

A major goal during the stable phase is to prevent relapse and reduce the severity of residual symptoms. Certain psychosocial interventions have demonstrated effectiveness in this regard. They include family education and support, assertive community treatment, and cognitive therapy.

Interventions that educate families about schizophrenia, provide support, and offer training in effective problem solving and communication have been subjected to numerous randomized clinical trials (171, 172). The data strongly and consistently support the value of such interventions in reducing symptom relapse, and there is some evidence that these interventions contribute to improved patient functioning and family well-being. Randomized clinical trials have reported 2-year relapse rates for patients receiving family “psychoeducation” programs in combination with medication that are 50% lower than those for patients receiving medication alone (173–180). Further, a recent study found psychoeducational programs using multiple family groups to be more effective and less expensive than individual family psychoeducational interventions for Caucasians, though not for African Americans (178). On the basis of the evidence, persons with schizophrenia and their families who have ongoing contact with each other should be offered a family intervention, the key elements of which include a duration of at least 9 months, illness education, crisis intervention, emotional support, and training in how to cope with illness symptoms and related problems.

PACT is a specific model of community-based care. Its origin is an experiment in Madison, Wisconsin, in the 1970s in which the multidisciplinary inpatient team of the state hospital was moved into the community (181, 182). The team took with it all of the functions of an inpatient team: interdisciplinary teamwork, 24-hour/7-days-per-week coverage, comprehensive treatment planning, ongoing responsibility, staff continuity, and small caseloads. PACT is designed to treat patients who are at high risk for hospital readmission and who cannot be maintained by more usual community-based treatment as well as for patients with severe psychosocial impairment who need extensive assistance to live in the community. Randomized trials comparing PACT to other community-based care have consistently shown that PACT substantially reduces utilization of inpatient services and promotes continuity of outpatient care (183, 184). Patients’ satisfaction with this model is generally high, and family advocacy groups, such as NAMI in the United States, strongly support its use and dissemination.

Results are less consistent regarding the effect of PACT on other outcomes, although at least some studies have shown enhancement of clinical status, functioning, and quality of life. Cost-effectiveness studies support its value in the treatment of high-risk patients. Studies also indicate that a particular PACT program’s effectiveness is related to the fidelity with which it is implemented, that is, the degree to which the program adheres to the original PACT model.

Controlled studies of cognitive behavior psychotherapy have reported benefits in reducing the severity of persistent psychotic symptoms (170). Most of the studies have been performed with individual cognitive behavior therapy of at least several months’ duration; in some studies, group cognitive behavior therapy and/or therapy of a shorter duration has been used. In all of the studies clinicians who provided cognitive behavior therapy received specialized training in the approach. In addition, the key elements of this intervention include a shared understanding of the illness between the patient and therapist, identification of target symptoms, and the development of specific cognitive and behavioral strategies to cope with these symptoms. Therefore, based on the available evidence, persons with schizophrenia who have residual psychotic symptoms while receiving adequate pharmacotherapy may benefit from cognitive behaviorally oriented psychotherapy.

A variety of other approaches to counseling individual patients to help them cope better with their illness are used, although research in this area remains limited. In general, counseling

that emphasizes illness education, support, and problem solving is most appropriate. A notable prototype of this approach is personal therapy, as developed by Hogarty and colleagues (185–187). Personal therapy is an individualized long-term psychosocial intervention provided to patients on a weekly to biweekly frequency within the larger framework of a treatment program that provides pharmacotherapy, family work (when a family is available), and multiple levels of support, both material and psychological. The approach is carefully tailored to the patient's phase of recovery from an acute episode and the patient's residual level of severity, disability, and vulnerability to relapse.

b) Negative symptoms

During the stable phase, negative symptoms (e.g., affective flattening, alogia, avolition) may be primary and represent a core feature of schizophrenia, or they may be secondary to psychotic symptoms, a depressive syndrome, medication side effects (e.g., dysphoria), or environmental deprivation. The effectiveness of psychosocial treatments for reducing negative symptoms is not well studied. Furthermore, most research (for both psychosocial and pharmacological treatments) does not distinguish between primary and secondary negative symptoms. Thus, the generic term “negative symptoms” is used to summarize these findings. Some studies of cognitive behavior therapy report improvements in residual negative symptoms. In a review of three studies, Rector and Beck (188) reported a large aggregated effect size favoring cognitive behavior therapy over supportive therapy for reducing negative symptoms. Also, one study of family psychoeducation reported an improvement in negative symptoms with this intervention (189).

c) Improving functional status and quality of life

A primary treatment goal during the stable phase is to enable the patient to continue the recovery process and to achieve the goals of improved functioning and quality of life. To the degree to which active positive symptoms impair functional capacity, medications that reduce positive symptoms may improve functioning. However, research indicates consistently that positive symptoms show a low correspondence with functional impairments among patients with schizophrenia (190). Rather, it is the negative symptoms and cognitive impairments that are more predictive of functional impairment (191). Because available medications have at best only modest effects on these illness dimensions, it is not surprising that there is scant evidence that medications improve functional status beyond that achieved through reduction of impairing positive symptoms. Consequently, certain psychosocial and rehabilitative interventions are essential to consider in the stable phase to enhance functional status.

Supported employment is an approach to improve vocational functioning among persons with various types of disabilities, including schizophrenia (192). The evidence-based supported employment programs that have been found effective include the key elements of individualized job development, rapid placement emphasizing competitive employment, ongoing job supports, and integration of vocational and mental health services. Randomized trials have consistently demonstrated the effectiveness of supported employment in helping persons with schizophrenia to achieve competitive employment (193, 194). Employment outcomes related to the duration of employment and to the amount of earnings also favor supported employment over traditional vocational services. Further, there is no evidence that engagement in supported employment leads to stress, increased symptoms, or other negative outcome (159). Evidence is inconsistent about the relationship between clinical and demographic variables and successful vocational performance; therefore, it is recommended that any person with schizophrenia who expresses an interest in work should be offered supported employment. Promoting job retention is a continuing challenge even for supported employment. Studies have found that persons with schizophrenia experience considerable difficulties retaining jobs achieved through supported employment (162, 194). This problem appears to be related to neurocognitive impairments (195), among other factors.

Social skills training has been found helpful in addressing functional impairments in social skills or activities of daily living. The key elements of this intervention include behaviorally based instruction, modeling, corrective feedback, and contingent social reinforcement. Clinic-based skills training should be supplemented with practice and training in the patient's day-to-day environment. The results of controlled trials indicate the benefit of skills training in improving illness knowledge, social skills, and symptom and medication management when offered with adequate pharmacotherapy (167). Evidence is strongest for the benefit of skills training in increasing the acquisition of skills assessed by situationally specific measures.

d) Patient and self-help treatment organizations

Peer support is social-emotional and sometimes instrumental support that is mutually offered or provided by persons having a mental health condition, i.e., mental health consumers, to others sharing a similar mental health condition to bring about a desired social or personal change (196). The oldest and most widely available type of peer support is self-help groups. Based largely on uncontrolled studies of self-help groups for persons with severe mental illness, Davidson et al. (197) concluded that self-help groups seem to improve symptoms and increase participants' social networks and quality of life. Additional studies of self-help groups have demonstrated other positive outcomes, including reductions in hospitalizations, improved coping, greater acceptance of the illness, improved medication adherence and illness management, improved daily functioning, lower levels of worry, and higher satisfaction with health (198–200, unpublished 1989 manuscript of M. Kennedy).

Within the realm of consumer-provided or -delivered services are consumer-run or -operated services, consumer partnership services, and consumer employees. Consumer-run or -operated services are services that are planned, operated, administered, and evaluated by consumers (201, 202). Those service programs that are not freestanding legal entities but share control of the operation of the program with nonconsumers are categorized as consumer partnerships. Consumer employees are persons who fill positions designated for consumers as well as consumers who are hired into traditional mental health positions. Reviews of peer support/consumer-provided services specifically for persons with severe mental illness have generated positive results, but the findings are somewhat tentative, given the infancy of the research area (197, 203, 204). Such services have been associated with reduced hospitalizations, reduced use of crisis services, improved social functioning, reduced substance use, and improved quality of life (205–209).

3. Use of antipsychotic medications in the stable phase

Once a patient reaches the stable or maintenance phase of treatment, it is important for the physician to develop a long-term treatment management plan that minimizes the risk of relapse, monitors for and minimizes the severity of side effects, and to the extent possible addresses residual symptoms.

Antipsychotics can reduce the risk of relapse in the stable phase of illness to less than 30% per year (210–215). Without maintenance treatment, 60%–70% of patients relapse within 1 year, and almost 90% relapse within 2 years. Strategies can be used to increase the likelihood that patients will adhere to prescribed medication regimens. Such strategies are described in Section II. A.3, “Developing a Therapeutic Alliance and Promoting Treatment Adherence.”

Deciding on the dose of an antipsychotic medication during the stable phase is complicated by the fact that there is no reliable strategy available to identify the minimum effective dose to prevent relapse. Although higher doses are often more effective at reducing relapse risk than lower doses, higher doses often cause greater side effects and lessen subjective tolerability; therefore, clinicians should attempt to treat at a dose that minimizes side effects but is still in the effective range of a particular drug (refer to Table 2). For most patients treated with first-generation antipsychotics, clinicians should use a dose around the “EPS threshold” (94), since studies indicate that higher doses are usually not more efficacious and increase risk of subjec-

tively intolerable side effects (95–97). Lower doses of first-generation antipsychotic medications may be associated with improved adherence and better subjective state and perhaps ultimately better functioning. Second-generation antipsychotics can generally be administered at doses that are therapeutic but will not induce extrapyramidal side effects. The advantages of decreasing antipsychotics to the “minimal effective dose” should be weighed against a somewhat greater risk of relapse and more frequent exacerbations of schizophrenic symptoms (216). Recent evidence suggests potentially greater efficacy in relapse prevention for the second-generation antipsychotic drugs (215, 217); however, whether this result is due to better efficacy or some other factor such as greater treatment adherence or reduced side effects is unclear.

The available antipsychotics are associated with differential risk of a variety of adverse effects, including neurological, metabolic, sexual, endocrine, sedative, and cardiovascular effects (Table 4). A suggested approach to monitoring of side effects is detailed in Table 1 and should be based on the side effect profile of the prescribed antipsychotic as detailed in Part B, Section V.A.1, “Antipsychotic Medications.”

Antipsychotic treatment often results in substantial improvement or even remission of positive symptoms. However, most patients remain functionally impaired because of negative symptoms, cognitive deficits, and impaired social function. It is important to evaluate whether residual negative symptoms are in fact secondary to a parkinsonian syndrome or an untreated major depressive syndrome, since interventions are available to address these negative symptoms. There are few proven treatment options for residual positive symptoms, primary negative symptoms, cognitive deficits, or social impairments (see Section II.E, “Special Issues in Caring for Patients With Treatment-Resistant Illness”).

Most patients who develop schizophrenia and related psychotic disorders (schizoaffective disorder and schizophreniform disorder) are at very high risk of relapse in the absence of antipsychotic treatment. Emerging evidence suggests this may even be true for first-episode patients; some studies (46, 218) have shown that more than 80% of such patients who do not receive antipsychotic treatment experience some recurrence of symptoms in the 5 years after remission. Unfortunately, there is no reliable indicator to differentiate the minority who will not relapse from the majority who will relapse. Antipsychotics are highly effective in the prevention of relapse in remitted first-episode patients. One-year relapse risk varies from 0% to 46% of patients who are prescribed antipsychotics (210–213). Adherence to maintenance antipsychotic medication likely has an influence on effectiveness and may contribute to varying relapse rates. The most prudent treatment options that clinicians may discuss with remitted first- or multi-episode patients include either 1) indefinite antipsychotic maintenance medication or 2) medication discontinuation (after at least 1 year of symptom remission or optimal response while taking medication) with close follow-up and with a plan to reinstitute antipsychotic treatment on symptom recurrence. However, evidence indicates that sustained treatment is associated with fewer relapses than is targeted intermittent treatment (219). In addition, intermittent treatment strategies appear to increase rather than decrease the risk of tardive dyskinesia. Clinicians should engage patients in a discussion of the long-term potential risks of maintenance treatment with the prescribed antipsychotic (see Part B, Section V.A.1, “Antipsychotic Medications”) versus the risks of relapse (e.g., the effect of relapse on social and vocational functioning, the risk of dangerous behaviors with relapse, and the risk of developing chronic treatment-resistant symptoms). If a decision is made to discontinue antipsychotic medication, the discontinuation should be gradual (e.g., reducing the dose by 10% per month). Additional precautions should be taken to minimize the risk of a psychotic relapse. The physician should educate the patient and the family about early signs of relapse, advise them to develop plans for action should these signs appear, and suggest that the patient continue to be seen by a physician on a regular basis.

Indefinite maintenance antipsychotic medication is recommended for patients who have had multiple prior episodes or two episodes within 5 years. Patients taking antipsychotic medication should also be monitored for signs and symptoms of impending or actual relapse, since even in

adherent patients the risk of relapse in chronic schizophrenia is about 30% per year. The treatment program should be organized to respond quickly when a patient, family member, or friend reports any symptoms that could indicate an impending or actual relapse. Early intervention using supportive therapeutic techniques and increasing medication as indicated can be very helpful in reducing the likelihood of relapse and hospitalization (220). During prodromal episodes, patients and family members should be seen more frequently for treatment, monitoring, and support, and assertive outreach, including home visits, should be used when indicated.

4. Use of adjunctive medications in the stable phase

Other psychoactive medications are commonly added to antipsychotic medications in the stable phase to treat comorbid conditions, aggression, anxiety, or other mood symptoms; to augment the antipsychotic effects of the primary drug; and to treat side effects. Other medications that may address treatment-resistant and residual psychotic symptoms are discussed in Section II.E, “Special Issues in Caring for Patients With Treatment-Resistant Illness.”

Adjunctive medications are commonly prescribed for comorbid conditions. For example, major depression and obsessive-compulsive disorder are common comorbid conditions in patients with schizophrenia and may respond to antidepressant medications (221–223). However, some antidepressants (those that inhibit catecholamine reuptake) can potentially sustain or exacerbate psychotic symptoms in some patients (103). Benzodiazepines may be helpful for managing anxiety during the stable phase of treatment (224), although risk of dependence and abuse exists with chronic use of this class of medication. There is some evidence that mood stabilizers and beta-blockers (100–102) may be effective in reducing the severity of recurrent hostility and aggression. Mood stabilizers may also address prominent mood lability. As mentioned previously, attention must be given to potential drug interactions, especially related to metabolism by the cytochrome P450 enzymes (48, 49).

Patients treated with first-generation antipsychotics may require the long-term use of medications for treatment of extrapyramidal side effects (Table 5). Although the study findings are not consistent, there is some evidence that vitamin E may reduce the risk of development of tardive dyskinesia (225, 226). Given the low risk of side effects associated with vitamin E, patients may be advised to take 400–800 I.U. daily as prophylaxis.

Many other medications may be used to treat or reduce the risk of various antipsychotic side effects. These medications are discussed with each specific antipsychotic in Part B, Section V.A.1, “Antipsychotic Medications.”

5. Use of ECT in the stable phase

Clinical observations (227, 228) and a single randomized clinical trial (229) suggest that maintenance ECT may be helpful for some patients who have responded to acute treatment with ECT but for whom pharmacological prophylaxis alone has been ineffective or cannot be tolerated. The frequency of treatments varies from patient to patient and depends on the degree of clinical response and side effects of treatment (107). As with acute treatment with ECT, available evidence suggests that treatment with antipsychotics should continue during the maintenance ECT course (229).

E. SPECIAL ISSUES IN CARING FOR PATIENTS WITH TREATMENT-RESISTANT ILLNESS

About 10%–30% of patients have little or no response to antipsychotic medications, and up to an additional 30% of patients have partial responses to treatment, meaning that they exhibit improvement in psychopathology but continue to have mild to severe residual hallucinations or de-

lusions. Even if a patient's positive symptoms respond or remit with antipsychotic treatment, other residual symptoms, including negative symptoms and cognitive impairment, often persist. Treatment resistance is defined as little or no symptomatic response to multiple (at least two) antipsychotic trials of an adequate duration (at least 6 weeks) and dose (therapeutic range).

Treatment may be completely or partially unsuccessful for a variety of reasons. The patient may receive a suboptimal dose of antipsychotic, either because an inadequate dose has been prescribed or because the patient does not take some or all of the prescribed antipsychotic. The prescribed antipsychotic may be partially or fully ineffective in treating acute symptoms or in preventing relapse. Substance use may also cause or contribute to treatment resistance.

In assessing treatment resistance, clinicians should carefully evaluate whether the patient has had an adequate trial of an antipsychotic, including whether the dose is adequate and whether the patient has been taking the medication as prescribed. Strategies for improving adherence are described in Section II.A.3, "Developing a Therapeutic Alliance and Promoting Treatment Adherence."

Even when patients are taking antipsychotics, suboptimal treatment response and residual symptoms are common. There are considerable differences between patients in responsiveness to available antipsychotics. However, currently there is no reliable strategy to predict response or risk of side effects with one agent compared with another. Thus, adequate trials of multiple antipsychotics are often needed before antipsychotic treatment is optimized. Complicating the evaluation of treatment response is the fact that there is some time delay between initiation of treatment and full clinical response. An initial trial of 2–4 weeks generally is needed to determine if the patient will have any symptomatic response, and symptoms can continue to improve for up to 6 months (230, 231).

Because of clozapine's superior efficacy, a trial of clozapine should be considered for a patient with a clinically inadequate response to antipsychotic treatment or for a patient with suicidal ideation or behavior (55). Besides clozapine, there are limited options for the many patients who have severe and significant residual symptoms even after antipsychotic monotherapy has been optimized, and none have proven benefits. Various augmentation strategies that have limited or no evidence supporting their efficacy are often used. However, clinicians may consider a time-limited trial of an agent to determine if it offers any benefit to an individual patient. To avoid risking side effects and potential drug interactions, it is important that the actual efficacy of adjunctive medications is carefully evaluated and that adjunctive medications that do not produce clinical benefits are discontinued. Depending on the type of residual symptom (e.g., positive, negative, cognitive, or mood symptoms; aggressive behavior), augmentation strategies include adding another antipsychotic (232–234), anticonvulsants (102, 235–237), benzodiazepines (224), *N*-methyl-D-aspartate (NMDA) receptor allosteric agonists (e.g., D-serine [238], glycine [239–242], D-cycloserine [243–246]), and cholinergic agonists (247–249). ECT has demonstrated benefits in patients with treatment-resistant symptoms (106–108). Cognitive behavior therapy techniques may have value in improving positive symptoms with low risk of side effects (98). In addition, cognitive remediation is under investigation as a therapeutic strategy to reduce the severity of cognitive deficits (250).

► F. CLINICAL FEATURES INFLUENCING THE TREATMENT PLAN

1. Psychiatric features

a) First episode

Active psychosis is dangerous to a person's safety; disrupts capacity to function, life, and reputation; and if persistent for too long can negatively affect prognosis (251). In contrast, early treatment may result in a significant reduction in morbidity and better quality of life for pa-

tients and families (252–256). Approximately 25 studies have examined this phenomenon; about two-thirds have shown a significant association between earlier treatment and better outcome on one or more measures, and none has shown a significant association between delayed treatment and better outcome on any measure (257). Despite the benefits of early treatment, there is usually a delay of 1–2 years between the onset of psychotic symptoms and the time the patient first receives adequate psychiatric treatment (252, 258–261). Thus, once psychosis is evident, it should be treated immediately.

In some persons, particularly those with a family history of schizophrenia or other factors influencing risk, prodromal symptoms may be apparent before the development of a full schizophrenia syndrome. Although empirical evidence on long-term outcome is limited, antipsychotic medication treatment may also be helpful in some persons with prodromal symptoms (262–264).

When a patient presents with a first episode of psychosis, close observation and documentation of the signs and symptoms over time are important because initial psychotic episodes can be polymorphic and evolve into a variety of specific disorders (e.g., schizophreniform disorder, bipolar disorder, schizoaffective disorder). There is controversy over whether first-episode patients should be treated as outpatients or in the hospital. Inpatient care offers both risks and protections. On the one hand, the experience of a first psychiatric hospitalization, especially in a closed setting with many chronically ill patients, can be frightening and produce its own trauma (265). On the other hand, the nature and severity of a first episode are often unknown, unpredictable, and require more than “usual” surveillance. A hospital setting also allows for careful monitoring of the psychotic symptoms as well as any side effects, including acute dystonia, akathisia, or neuroleptic malignant syndrome (266), that may arise from treatment with antipsychotic medications.

Patients with first-episode psychosis are comparatively more treatment responsive than patients with multiple episodes of psychosis but, at the same time, are quite sensitive to side effects (267–270). Up to the early 1990s, drug treatment for a first episode of psychosis was limited to first-generation antipsychotic medications that could cause severe sedation and extrapyramidal side effects. The second-generation antipsychotic medications have less propensity to cause extrapyramidal side effects, and patients are hence less likely to need concomitant anticholinergic agents (271–273).

More than 70% of first-episode patients achieve a full remission of psychotic signs and symptoms within 3–4 months, with 83% achieving stable remission at the end of 1 year (274). Studies also reveal that first-episode patients often respond to low doses of antipsychotic medications (275–279). However, predictors of poor treatment response include male gender, pre- or perinatal injury, more severe hallucinations and delusions, attentional impairments, poor premorbid function, longer duration of untreated psychosis (280), the development of extrapyramidal side effects (281), and high levels of expressed emotion in the patient’s family (282–289).

Not uncommonly, symptoms of schizophrenia have their onset before adulthood, and aspects of treatment may differ in children and adolescents. For more information on treating children and adolescents, readers are referred to the American Academy of Child and Adolescent Psychiatry’s *Practice Parameter for the Assessment and Treatment of Children and Adolescents With Schizophrenia* (290).

Once remission of psychotic symptoms is achieved, a high priority should be placed on minimizing risk of relapse, given its potential clinical, social, and vocational costs. In particular, recurrent episodes are associated with increasing risk of chronic residual symptoms and evidence of anatomical neuroprogression (257, 280, 291–293). Patients, their families, and treating clinicians often hope that symptom remission indicates that the disease will not become chronic, although this is true only for a minority (about 10%–20%) of patients (46, 218, 294). Thus, clinicians should candidly discuss the high risk of relapse and factors that may minimize relapse risk. Although there is very little study of factors that act to maintain recovery in remitted first-episode patients, evidence suggests that antipsychotics are highly effective in prevention of re-

lapse. In patients for whom antipsychotics are prescribed, 1-year relapse risk varies from 0% to 46%, with relapse rates of patients who discontinue taking medication being up to five times higher than rates for those who continue treatment (46, 210–213). Since adherence to maintenance medication treatment likely influences effectiveness, it may contribute to the varying relapse rates found in these studies.

In arriving at a plan of treatment with remitted first-episode patients, clinicians should engage patients in discussion of the long-term potential risks of maintenance treatment with the prescribed antipsychotic versus risks of relapse (e.g., effect of relapse on social and vocational function, risk of dangerous behaviors with relapse, and risk of developing chronic treatment-resistant symptoms). Prudent treatment options that clinicians may discuss with remitted patients include either 1) indefinite antipsychotic maintenance medication (295) or 2) medication discontinuation with close follow-up and a plan of antipsychotic reinstitution with symptom recurrence. Medications should never be stopped abruptly, as rebound psychosis may result and may be misinterpreted as a reoccurrence. In addition to maintenance antipsychotic medication, other potential strategies to maintain recovery in remitted first-episode patients include enhancing stress management and eliminating exposure to cannabinoids and psychostimulants (296).

b) Subtypes and deficit symptoms

According to DSM-IV-TR, the classic subtypes of schizophrenia are paranoid, disorganized, catatonic, undifferentiated, and residual. There are at present no treatment strategies specific to the various subtypes, with the exception of the use of benzodiazepines for catatonia. The deficit/nondeficit categorization, or the deficit syndrome, is also important to recognize, although there are also no specific treatments (297). The negative symptoms of schizophrenia may be classified as primary or secondary. Negative symptoms may be primary and represent a core feature of schizophrenia, or they may be secondary to positive psychotic symptoms (e.g., paranoid withdrawal), medication side effects (e.g., dysphoria), depressive symptoms (e.g., anhedonia), anxiety symptoms (e.g., social phobia), demoralization, or environmental deprivation (e.g., in chronic institutionalization). Deficit schizophrenia is heavily loaded with enduring primary negative symptoms such as affective flattening, avolition, and alogia.

The prevalence of deficit states in first-episode schizophrenia has been estimated to be between 4% and 10% (298). Negative symptoms are already present in the prodromal phase (299–301), and the prevalence increases with the length of the schizophrenic illness (302–306). Male patients have been found to experience more negative symptoms than female patients (307–309). Patients with deficit schizophrenia are also found to have poorer premorbid adjustment during childhood and early adolescence. They exhibit more impairment in general cognitive abilities and have problems in sequencing of complex motor acts, which suggests frontoparietal dysfunction (310).

Treatment of negative symptoms begins with assessing the patient for factors that can cause the appearance of secondary negative symptoms (311). The treatment of such secondary negative symptoms consists of treating their cause, e.g., antipsychotics for primary positive symptoms, antidepressants for depression, anxiolytics for anxiety disorders, or antiparkinsonian agents or antipsychotic dose reduction for extrapyramidal side effects. If negative symptoms persist after such treatment, they are presumed to be primary negative symptoms of the deficit state (312).

There are no treatments with proven efficacy for primary negative symptoms. Clozapine was reported to be effective for negative symptoms in earlier short-term trials (313), but subsequent longer-term studies challenged such claims (314, 315), although clozapine treatment was associated with significant improvement in social and occupational functioning (314). The second-generation antipsychotic medications have been reported to be useful against negative symptoms (316–322), but this improvement may be accounted for by their having less propensity to cause extrapyramidal side effects (323).

c) Substance use disorders

More than one-third of patients with schizophrenia spectrum disorders also have a substance use disorder, and people with schizophrenia show six times the risk of developing a substance use disorder than do persons in the general population (324). Other research finds that between 20% and 65% of people with schizophrenia experience comorbid substance use disorders (325–328). A recent Australian study found the 6-month and lifetime prevalence of substance abuse or dependence among people with schizophrenia to be 26.8% and 59.8%, respectively (329).

Substance abuse in schizophrenia has been associated with male gender, single marital status, less education, earlier age at onset of schizophrenia and at first hospital admission, frequent and longer periods of hospitalization, more pronounced psychotic symptoms, more severe cerebral gray matter volume deficits, and negative consequences such as poor treatment adherence, depressive symptoms, suicide, violence, legal problems, incarceration, severe financial problems, family burden, housing instability, and increased risk of HIV infection (327, 330–332) and hepatitis infection, particularly hepatitis C infection (333). Substance abuse has been associated with precipitation of schizophrenia at an earlier age (334–340), and in some studies amphetamine abuse has been associated with an earlier age of onset (341). Alcohol and a variety of other substances have also been associated with symptom relapses in schizophrenia (342). Nicotine, alcohol, cannabis, and cocaine have been found to be the most commonly abused substances. Patients may also abuse prescribed medications such as benzodiazepines and anti-parkinsonian agents.

The goals of treatment for patients with schizophrenia who also have a substance use disorder are the same as those for treatment of schizophrenia without comorbidity but with the addition of the goals for treatment of substance use disorders, e.g., harm reduction, abstinence, relapse prevention, and rehabilitation (343).

Evaluation of the patient with schizophrenia should always include a comprehensive inquiry into possible substance use. Self-report is often unreliable; corroborating evidence from all sources such as family members, friends, community-based case managers, and treatment personnel should be sought (330, 344). Screening instruments for substance use disorders developed for the general population, such as the Alcohol Use Disorders Identification Test (AUDIT) (345), can be used, but screening instruments specifically for patients with severe mental illnesses, such as the Dartmouth Assessment of Lifestyle Instrument (346), have been developed and may have greater sensitivity for detecting substance use disorders in people with schizophrenia. Laboratory investigations such as urine and blood toxicology for abused substances and liver function tests should be carried out. Many patients with schizophrenia do not develop the full physiological dependence syndrome associated with dependence on alcohol or other substances (330). However, even use of low levels of alcohol or other substances by patients with schizophrenia can have untoward consequences. Psychiatrists should therefore attend carefully to the presence of alcohol or other substance use and be familiar with the potential negative consequences described earlier. The rates of current substance use will likely be higher in acute settings such as the emergency department, and thus the index of suspicion and effort devoted to assessment of substance use should be especially high in such settings.

Traditionally, patients with schizophrenia and comorbid substance use disorders were treated in separate programs, either sequentially or in parallel, for the two types of disorder. Since the mid-1980s, a comprehensive integrated treatment model has been adopted to provide continuous outpatient treatment interventions and support over long periods of time (months to years), enabling patients to acquire the skills they need to manage both illnesses and to pursue functional goals. In this model, the same clinicians or teams of clinicians provide treatment both for substance use disorders and for other mental disorders. This form of treatment features assertive outreach, case management, family interventions, housing, rehabilitation, and pharmacotherapy. It also includes a stage-wise motivational approach for patients who do not recognize the need for treatment of substance use disorders and behavioral interventions for those

who are trying to attain or maintain abstinence. The interventions have been associated with reduced substance use and attainment of remission (347–350).

Initially, many patients need interventions to build motivation rather than to achieve abstinence. Special efforts are made to help them recognize that their substance use is interfering with their ability to pursue personal goals and to nurture their desire to reduce and eliminate their substance use (161, 349). Such efforts represent examples of interventions during the second (persuasion) stage in a four-stage dual-diagnosis treatment model based on readiness for change; the other treatment stages are engagement, active treatment, and relapse prevention (351). Studies show that treatment programs with these characteristics can be effective in reducing substance use and in decreasing the frequency and severity of psychotic decompensations (332, 352–354). Collaboration with family members is often helpful for both the patients and the family members (64, 171, 355, 356).

In practice, treatment of substance use disorders is commonly conducted by means of a group therapy approach, usually after patients have achieved stabilization of their schizophrenic symptoms. The therapeutic approach should be an integrated one that takes into account patients' cognitive deficits and limited tolerance for stress. Generally, groups should emphasize support, psychoeducation, and skills training (344, 352, 357). The length and frequency of group sessions should be regulated according to the attention span and interactive tolerance of the patients. Therapists should be active in keeping the group structured and focused and should limit the amount of stress by avoiding the direct confrontation of patients that is common to traditional treatment programs for persons with substance use disorders. Patients should understand that they have two complex chronic disorders that together lead to a poorer prognosis than each would have separately. Patients who have not yet attained complete abstinence should be accepted into treatment, with abstinence as a treatment goal (344, 352, 358). Patients who do not view abstinence as a treatment goal may still be successfully engaged in treatment that is aimed at achieving abstinence (359). Community-based self-help and support groups such as Alcoholics Anonymous or Narcotics Anonymous can be important in the recovery of patients with substance use disorders. Such connections are, however, more effective once patients are actively pursuing abstinence (349).

Antipsychotic medications remain the mainstay of pharmacological treatment for patients with comorbid substance use disorders. They are used in the usual doses, but patients should be informed that side effects such as sedation and incoordination can be aggravated when combining antipsychotic medication with alcohol or other substances. First-generation antipsychotic medications and clozapine also have the potential to lower the seizure threshold and infrequently may precipitate seizures during alcohol or benzodiazepine withdrawal. Dysphoria associated with first-generation antipsychotic medications may precipitate or worsen the substance use (360). On the other hand, studies have demonstrated that clozapine use is associated with reductions in the use of nicotine, alcohol, cannabis, and cocaine (361–363). In some clinical trials, second-generation antipsychotics such as risperidone and olanzapine have also been shown to be effective for reducing craving in cocaine dependence (364).

There is suggestive evidence from a case series of 30 patients with schizophrenia and other severe mental illnesses and alcoholism that disulfiram in moderate doses can be used safely and is associated with clinical benefits in alcohol outcomes over 1–3 years (365). However, for patients with schizophrenia who abuse alcohol, disulfiram may pose some risk since it can precipitate psychosis at high doses (358, 366). It also has harmful physical effects when taken with alcohol, and thus it is recommended only for patients who are motivated and who have previously shown good judgment, treatment adherence, and reality testing.

d) Depressive symptoms

Depressive symptoms are common in all phases of schizophrenia (367). The proportion of patients with schizophrenia who also manifest depression ranges from 7% to 75% (368). Depres-

sion may occur in the prodromal phase (300, 301), in the first episode (369–371), during the early course (372, 373), and after remission, and it may be superimposed on the symptoms of residual schizophrenia (“postpsychotic depression”) (374) or may occur in a prodrome to a psychotic relapse (375–379).

When patients with schizophrenia present with depressive features, important differential diagnostic possibilities need to be considered (368, 380). These include side effects of antipsychotic medications (including medication-induced dysphoria, akinesia, and akathisia), demoralization, and the primary negative symptoms of schizophrenia. Concurrent abuse or the sudden withdrawal of substances such as cannabis, cocaine, narcotics, alcohol, nicotine, and caffeine can also lead to depression. When the depressive symptoms are present at a syndromal level during the acute phase of the schizophrenic illness, the possibility of schizoaffective disorder should be considered.

Depressive symptoms that occur during the acute psychotic phase usually improve as the patient recovers from the psychosis. There is also evidence to suggest that depressive symptoms are reduced by antipsychotic treatment, with comparison trials finding that second-generation antipsychotics may have greater efficacy for depressive symptoms than first-generation antipsychotics (381, 382). However, there is also evidence to suggest that this apparent antidepressant effect may be related to the lower likelihood of neurological side effects with second-generation antipsychotics (222, 368, 383, 384). The approach hence is first to treat the psychosis.

If antipsychotic medication-induced dysphoria is suspected, then antipsychotic dose reduction may be effective. Alternatively, the clinician may switch the patient’s medication to an antipsychotic with a lower risk of inducing extrapyramidal symptoms (Table 4). There is no evidence that medications that treat the motor symptoms of extrapyramidal side effects (e.g., benztropine, amantadine) (Table 5) are effective for the treatment of neuroleptic-induced dysphoria.

Antidepressants are added as an adjunct to antipsychotics when the depressive symptoms meet the syndromal criteria for major depressive disorder, are severe and causing significant distress (e.g., when accompanied by suicidal ideation), or are interfering with function. Tricyclic antidepressants have been extensively studied in the treatment of postpsychotic depression (103, 385). Antidepressants, including the selective serotonin reuptake inhibitors (SSRIs) and dual reuptake inhibitors, have also been found to be useful in the treatment of depression in schizophrenia (368, 384). However, very few studies have examined the effects of antidepressants in patients treated with second-generation antipsychotic medications, making it difficult to evaluate the current utility of adjunctive antidepressant agents. When prescribed, antidepressants are used in the same doses that are used for treatment of major depressive disorder. There are, however, potential pharmacokinetic interactions with certain antipsychotic medications; for example, the SSRIs (such as fluoxetine, paroxetine, and fluvoxamine) are inhibitors of cytochrome P450 enzymes and thereby increase antipsychotic plasma levels. Similarly, the blood levels of some antidepressants may be elevated by the concomitant administration of antipsychotic medications.

e) Risk of suicide

Suicide is the leading cause of premature death among persons with schizophrenia (386, 387). Compared to the general population, persons with schizophrenia are nine times more likely to die by suicide (388). Up to 30% of patients with schizophrenia attempt suicide (389), and between 4% and 10% die by suicide (390–394). The estimated rate of suicidal behavior among persons with schizophrenia is between 20% and 40% (395, 396).

Some risk factors for suicide in schizophrenia are the same as those for the general population, including being male, white, single, socially isolated, and unemployed; having a positive family history of suicide; previous suicide attempts; having a substance use disorder; being depressed or hopeless; and having a significant recent adverse life event. Specific risk factors for suicide among persons with schizophrenia are young age, high socioeconomic status back-

ground, high IQ with a high level of premorbid scholastic achievement, high aspirations and expectations, an early age at onset of illness/first hospitalization, a chronic and deteriorating course with many relapses, and greater insight into the illness (391, 397–401). A change in the environment, such as a hospital admission and discharge, may trigger suicidal behavior (402, 403). Suicide is more common within the first 6 years of the initial hospitalization and also during periods of remission after 5–10 years of illness. Other risk factors include severe depressive and psychotic symptoms, with an increase in the patient's paranoid behavior (395, 404–406). Suicidal ideation has also been shown to be predictive of suicide over the subsequent 2–4 weeks (407). As patients do not often report suicidal ideation spontaneously, clinicians are encouraged to ask patients about suicidal ideas whenever there is suggestion that they could be present (e.g., in the presence of depression or severe stress). Treatment-related factors associated with suicide include inadequate antipsychotic treatment, nonadherence to the medication regimen, and lack of response to medication (408). In several case reports, suicide has also been noted among patients with akathisia (409, 410).

Despite identification of these risk factors, it is not possible to predict whether an individual patient will attempt suicide or will die by suicide. Suicide thus must be considered at all stages of the illness, and suicide risk must be assessed initially and regularly as part of each patient's psychiatric evaluation. The patient's desire to die may be more important than the lethality of the methods used (403). Additional information may be obtained from close family members and treating therapists. Patients should be admitted to a secure inpatient unit if they are judged to be at substantial risk for suicide.

It is important to maximize the treatment of both psychosis and depression. There is suggestive evidence that both first- and second-generation antipsychotic medications may reduce the risk of suicide (411). However, clozapine is the most extensively studied and has been shown to have the greatest therapeutic effect on suicidal behavior, possibly reducing the suicide rate by as much as 75%–85% (55, 398, 399, 412). For these reasons, clozapine should be preferentially considered for patients with a history of chronic and persistent suicidal ideation or behaviors.

During the initial hospitalization, suicide precautions should be instituted, and the patient must be closely monitored to prevent escape. There should also be minimal use of ward transfers. Suicide risk should be examined carefully before a patient is granted any privileges and again before the patient is finally discharged from the hospital. The patient and the patient's family members should be advised to look for warning signs and to initiate specific contingency plans if suicidal ideation recurs. In outpatients, the frequency of visits should be higher after a recent discharge from the hospital and may need to be increased in times of personal crisis, significant environmental changes, heightened distress, or deepening depression during the course of illness.

For additional information, readers are directed to APA's *Practice Guideline for the Assessment and Treatment of Patients With Suicidal Behaviors* (56).

f) Aggressive behavior

Although only a minority of patients with schizophrenia are violent, evidence does suggest that schizophrenia is associated with an increase in the risk of aggressive behavior (413–419). Sociodemographic risk factors for aggression in schizophrenia are male gender; being poor, unskilled, uneducated, or unmarried; and having a history of prior arrests or a prior history of violence (420). The risk for aggressive behavior increases with comorbid alcohol abuse, substance abuse, antisocial personality, or neurological impairment (421–427). Violent patients with schizophrenia have more positive symptoms and bizarre behaviors and may act on their delusions, especially if the delusions are distressing and the patient can find evidence to support them (428–430). Patients who experience command hallucinations to harm others are also more likely to be violent (431).

Identifying risk factors for violence and assessment of dangerousness are parts of a standard psychiatric evaluation, which should be conducted in an environment that is safe for both the patient and clinician (432). It is important to determine if use of alcohol or other substances, including use of amphetamines or other stimulants, is causing or contributing to aggressive behavior. Severe akathisia associated with prescribed medications may also cause or contribute to aggressive behavior. It is important to inquire about thoughts of violence and determine the persons to whom these thoughts are directed. Parents, for example, are frequent targets of violence when it occurs (433). When a patient is found to pose a serious threat to others (e.g., having homicidal ideation with imminent plans), the psychiatrist should consider hospitalizing the patient and must exercise his or her own best judgment, in accord with the legal requirements of the jurisdiction, to protect those people from foreseeable harm (54, 434).

If the patient is acutely aggressive, the clinician can try to calm the patient by distraction or “talking down” techniques. If restraint or seclusion is needed, it should be done with adequate numbers of well-trained professional staff (70). When sedation is indicated and the patient is unwilling to accept oral medication, intramuscular injection of a first-generation antipsychotic agent (5 mg of haloperidol) (75) or second-generation agent (e.g., ziprasidone) (76–79) can be given, with or without a concomitant dose of 1–2 mg of oral or intramuscular lorazepam (72–74). Other medications, such as 5 mg i.m. of droperidol, can be used in selected clinical situations of extreme emergency or in highly agitated patients (80, 435). However, if droperidol is used, its potential for cardiac rhythm disturbances must be considered, as indicated in its labeling by a black-box warning for QTc prolongation. After seclusion, restraint, or sedation, the mental status and vital signs of the patient should be monitored regularly. Release from seclusion or restraint can proceed in a graded fashion, as risk of harm to self or others diminishes (432).

Limit setting and behavioral approaches have been employed for the management of persistently violent patients (432, 436). Antipsychotic medications remain the mainstay of management (421, 437), with good evidence for clozapine in particular (438–440). Other agents have been used, including mood stabilizers (lithium, valproate), SSRIs (such as citalopram), benzodiazepines, and β -adrenergic blocking agents (propranolol, nadolol), but empirical evidence is lacking.

It is common for patients with schizophrenia in the community to stop taking their medications. Patients who are more likely to be violent with psychotic relapses are of particular concern and may be primary candidates for mandatory outpatient treatment programs (441) (see Section II.A.3, “Developing a Therapeutic Alliance and Promoting Treatment Adherence”).

g) Psychosis-induced polydipsia

Polydipsia is compulsive water drinking, usually in excess of 3 liters per day. It can be complicated by water intoxication, i.e., severe hyponatremia (serum sodium <120 mmol/liter), which is potentially fatal, as the associated cerebral edema can result in delirium, seizures, coma, and death. About 20%–25% of chronically ill inpatients have primary polydipsia, and as many as 10% have a history of water intoxication (442–445).

The pathophysiology of the water imbalance is still unclear. It occurs most commonly in the most severely ill patients with schizophrenia and thus has been termed “psychosis-induced polydipsia.” Polydipsia and water intoxication are associated with long hospitalization, high doses of antipsychotic medications, moderate doses of anticholinergic medications, and heavy smoking (442, 444). Development of hyponatremia has also been associated with use of diuretics, SSRIs and venlafaxine (446, 447), tricyclic antidepressants, and calcium antagonists (448). Polydipsia has also been known to occur prior to the introduction of antipsychotic medications (449).

The approach to psychosis-induced polydipsia is to control both the psychosis and water intake after excluding possible underlying medical causes of polydipsia, such as diabetes mellitus, diabetes insipidus, chronic renal failure, malignancy, pulmonary disease, hypocalcemia, and hypokalemia. Acute management involves water restriction and sodium replacement to prevent seizures. Clozapine appears to be effective, albeit in studies with small sample sizes

(450–452). The second-generation antipsychotics have also been examined for their role in the long-term management of the condition (453, 454). Various other medications, including demeclocycline (455, 456), naltrexone (457), enalapril (458), clonidine (458, 459), and propranolol (460), have also been used in some case studies.

2. Demographic and psychosocial variables

a) Homelessness

By current estimates, as many as 800,000 Americans are homeless on any given night; an estimated one-fourth of these people have serious mental illnesses, and more than one-half have an alcohol and/or drug problem (461). Schizophrenia is a risk factor for homelessness, as is infectious disease, alcohol and other substance use, depression, and social isolation (462, 463). Comprehensive reviews have suggested that the rate of schizophrenia in homeless persons has ranged from 2% to 45%. Methodologically superior studies have produced estimates of 4%–16%, with a weighted average prevalence of 11% (464). Factors that have been noted to contribute to the magnitude of homelessness among patients with schizophrenia include deinstitutionalization (465), limitations of public funding, problems in service integration, and lack of low-cost housing (466). Substance use disorders contribute substantially to homelessness among patients with schizophrenia. Many housing programs do not accept patients with schizophrenia who use alcohol or other substances, and treatment for substance use disorders is often lacking for these individuals (466). In addition, the illness of schizophrenia may directly predispose persons to housing difficulties through withdrawal, disorganization, and disruptive behaviors (467).

Homeless mentally ill persons are likely to have multiple impairments. Most lack basic health care, income, and any social support network. Only slightly more than one-half of the homeless persons with schizophrenia have been found to be currently receiving psychiatric treatment (464). Homeless persons with schizophrenia have been found to have elevated rates of victimization (468) and to have mortality rates that are three to four times higher than the expected rate (469). Further, a large study of mentally ill homeless veterans found that a majority of homeless veterans contacted through a national outreach program did not receive medical services within 6 months of program entry (470). Medical treatment is thus a great challenge for this population.

Given the level of need of this population, services should include provision of appropriate housing, access to medical services, treatment of substance use disorders, income support and benefits, and rehabilitation and employment assistance (466). Such services must be comprehensive, continuous, accessible, and individualized (467). A number of controlled studies have demonstrated the effectiveness of such treatment models for reducing homelessness and improving psychiatric outcomes (164, 471). The Center for Mental Health Services conducted a multisite 5-year demonstration program called Access to Community Care and Effective Services and Supports (ACCESS) to test the effect of the integration of fragmented services in treating homeless persons with serious mental illness. This study involved 18 sites in nine states from 1993 to 1998, and treatment outcomes were studied at both the system and patient levels. All project sites conducted extensive outreach efforts to engage homeless persons and provided a comprehensive range of services, including mental health treatment, medications, substance use disorder treatment or referral, job placement, housing support, social support, and primary health care. Patients served in the ACCESS program showed improved housing stability and reductions in substance use and minor criminal incidents, as well as increased use of psychiatric outpatient care, although integration of treatment did not influence these outcomes. The provision of direct community services and outreach appeared to be most important.

Clinical care of homeless mentally ill patients involves three basic stages: 1) engagement, 2) intensive care, and 3) ongoing rehabilitation (472). In introducing services into the community, psychiatrists must be prepared to work with homeless patients in nonclinical environments,

including streets, shelters, subways, bus terminals, and other public spaces. In discussing outreach to homeless patients with schizophrenia, Goldfinger (467) stressed the importance of engagement. Homeless patients with schizophrenia are often fearful and distrustful of the mental health system, and they can require a combination of patience, persistence, and understanding. Depending on the needs and wants of a particular patient, the provision of food, clothing, medical attention, or simply company can be indispensable in developing a therapeutic relationship. As noted by Goldfinger (467), such provisions document one's concern, demonstrate one's reliability, and acknowledge the importance of the needs of the homeless person with schizophrenia. To engage the homeless person with schizophrenia, active outreach is usually necessary and is often performed by case managers. In particular, street outreach to homeless persons with serious mental illness is justified, as they have been found to be more severely impaired, to have more basic service needs, to be less motivated to seek treatment, and to take longer to engage than those contacted in other settings. The ACCESS program found that patients engaged from the street showed improvement on nearly all outcome measures that was equivalent to that of enrolled patients who were contacted in shelters and other service agencies (473).

Despite appropriate outreach efforts, some homeless persons with mental illness are so impaired that they remain unable to recognize their basic needs or avoid personal dangers. One program developed to address the treatment needs of this population was the Homeless Emergency Liaison Project (Project HELP), in which a mobile treatment team arranged for involuntary psychiatric emergency department evaluation of high-risk homeless patients (474). Involuntary hospitalization resulted from 93% of such evaluations, and 80% of all patients received the diagnosis of schizophrenia. At 2-year follow-up of 298 patients initially evaluated during the project, only 12% were found to be back living on the streets.

b) Cultural factors

Cultural factors are known to affect the course, diagnosis, and treatment of schizophrenia (475). There is a robust pattern of evidence that race has a substantial effect on whether persons with substantively similar symptoms receive a diagnosis of an affective disorder or a schizophrenia spectrum psychotic disorder. Compared with Caucasians, African Americans, especially men, are less likely to receive a diagnosis of a mood disorder and more likely to receive a diagnosis of schizophrenia (476–479). African Americans with schizophrenia are also less likely to receive a diagnosis of a comorbid affective or anxiety disorder (480, 481). While it is possible that such differences may reflect actual illness variation among racial/ethnic groups, there is growing evidence that cultural differences in symptom and personal presentation, help seeking, interpretation of symptoms and clinical judgments by (usually Caucasian) clinicians, and treatment referral are likely causing race-linked biases in diagnosis and therefore in treatment (e.g., see references 482–486). Additional possible causes or contributors to this pattern of disparity include low levels of cultural competence among clinicians, unbalanced research samples, inaccurate or biased pathology assessment tools, and the failure of researchers to control for socioeconomic status, education, and urbanicity (487, 488). These remarkably consistent findings suggest that clinicians should be mindful of the extent to which cultural factors influence their diagnostic approach.

c) Race

Once patients receive a diagnosis, substantial data suggest that race affects the type of pharmacological treatment they receive. For example, the Schizophrenia Patient Outcomes Research Team (PORT) (65) showed that among patients for whom psychotropic medications at doses outside the recommended range were prescribed, patients from racial/ethnic minority groups (especially African Americans) were much more likely than Caucasian patients to receive doses above recommended levels. The same patients were also more likely to receive prophylactic antiparkinsonian agents, suggesting increased rates of adverse side effects related to higher doses.

Prescription of higher doses of antipsychotic medications to African American patients has also been noted in several other reports (489–493).

However, in another PORT study, among patients with schizophrenia who were also experiencing significant depression, Caucasian patients were significantly more likely to receive adjunctive medications (494). In addition, there is growing evidence that racial/ethnic minority patients with psychotic disorders are less likely than Caucasian patients to receive second-generation antipsychotics and more likely to receive long-acting injectable agents (495–498). Other research suggests that these gaps may be decreasing over time but are still persistent and may be related to differential prescribing patterns in private versus managed health care (496, 499).

There is clearly a need for more research to describe and understand the differences in patterns of treatment by race and ethnicity. Most of the published research focuses on African Americans; the needs and treatments of other cultural groups also require attention. The observed phenomena provide little guidance about whether the care delivered is appropriate. In the meantime, the strength and consistency of these findings suggest that clinicians should consider the extent to which a patient's race and/or ethnicity are playing a role in the treatment and should ensure that care is being individualized and optimized.

To some extent, differences in drug dosing or side effect risk may be related to genetically based differences in drug metabolism. For example, the activity of the enzyme encoded by the CYP2D6 gene is very low or absent in 5%–8% of Caucasians but only 2%–5% of African Americans and Asians. Low activity of the enzyme encoded by the CYP2D6 gene may dramatically affect the metabolism of many drugs, increasing serum levels (500). There is also suggestive evidence that up to one-third of African Americans possess genetic polymorphisms of other enzymes that metabolize psychotropic agents, resulting in altered metabolism and potential for enhanced medication side effects. Ethnic factors may also confer a susceptibility to medication side effects in certain persons. For example, patients of Jewish descent have been noted to be at greater risk for clozapine-induced agranulocytosis than other patients with schizophrenia (501) and therefore may require close monitoring during clozapine treatment.

d) Gender

There are numerous gender differences in the presentation and course of schizophrenia (502–505). Men with schizophrenia have been noted to have a younger age at onset, a poorer premorbid history, more negative symptoms, a greater likelihood of having the deficit syndrome (306, 309), and a poorer overall course than women with schizophrenia (503, 506). Compared with men, women are more likely to have affective symptoms, auditory hallucinations, and persecutory delusions, but they have a better overall course and better outcomes than men, as evidenced by better social and occupational functioning, fewer hospitalizations, and less substance use and antisocial behavior (504, 505, 507). While such differences may be biologically mediated, psychosocial factors, including family and societal expectations, may also affect outcome. Haas and colleagues (507) noted that social and occupational role demands may result in unrealistic family expectations of men with schizophrenia, and this issue should be dealt with in treatment.

There are also gender differences in both response to and adverse effects of treatments for schizophrenia. Most of this research has been conducted with first-generation antipsychotic medications. Women exhibit more rapid responses to antipsychotic medications and a greater degree of improvement in both first-episode and multi-episode schizophrenia (504). It has also been observed that even after body weight is considered, women require lower antipsychotic doses (508, 509) than men, although there is suggestive evidence that postmenopausal women may require higher doses (504). Although women may show greater responsivity to antipsychotics, they also experience more neurological side effects, including acute dystonia, parkinsonism, akathisia, and tardive dyskinesia (504). Women also develop higher serum prolactin levels in response to both first-generation antipsychotics and risperidone, compared with men (504), and therefore women may be more prone to the sexual side effects of the medications. Finally, although studies of gen-

der differences in response to psychosocial treatments are sparse, there is some evidence to suggest that social skills training may be more effective for male patients, whereas inpatient family interventions have shown greater success in families of female patients (504, 505).

e) Pregnancy

Treatment of the pregnant or lactating patient with schizophrenia must consider two issues: 1) risks of various psychotropic medications to the fetus, newborn, and breast-fed infant, and 2) adequacy of prenatal care. A general reference on medications in pregnancy and lactation is the text by Briggs et al. (510).

Controlled studies of psychotropic drug risks during pregnancy are, for obvious ethical reasons, not done. Knowledge of the risks of these agents comes from animal studies and from uncontrolled exposures in humans. Nonetheless, there is a body of information that can help guide clinicians' and patients' decision making about the use of psychotropic agents during pregnancy and lactation. Risks do vary from drug to drug and from drug class to drug class. In addition, two periods of high risk to the fetus or newborn are identifiable: teratogenic risk is highest in the first trimester, and withdrawal risk is highest at the time of birth. Only with planned pregnancies is management of first trimester psychotropic drug exposure under full control of the doctor and patient. Drug withdrawal risk at the time of parturition may be more predictable and manageable, depending on the drug(s) involved and the circumstances of delivery.

There are substantial data on fetal exposure to first-generation antipsychotic medications, with relatively little evidence of harmful effects, especially with high-potency agents (511–513). Much less information is available regarding fetal exposure to second-generation antipsychotic medications. Koren et al. (514) found that pregnant women with schizophrenia taking second-generation antipsychotic medications were frequently obese and had inadequate intake of folic acid, putting their offspring at increased risk for neural tube defects. Such an outcome would be an indirect rather than a direct effect of these medications. A limited number of reports of treatment with olanzapine during pregnancy and lactation showed that olanzapine did not appear to increase the risk of harm (515). A case report of clozapine treatment during pregnancy described development of gestational diabetes, possibly exacerbated by clozapine, but no fetal abnormalities (516). Pregnancy can be a period of decreased symptoms for women with schizophrenia, but relapses are frequent in the postpartum period (517). Thus, the clinical risks of not using antipsychotic medications may be somewhat less during pregnancy but are greater thereafter.

Compared with antipsychotic medications, mood stabilizers and benzodiazepines are much more closely associated with fetal malformations and behavioral effects (511, 513, 518). Thus, their risk/benefit ratio is different, and the need for their continuation during pregnancy and breast-feeding requires strong clinical justification.

A number of studies have shown that pregnant women with schizophrenia receive relatively poor prenatal care. These women have more obstetric complications, and their offspring are more likely to have adverse outcomes, such as low birth weight and stillbirth (519–522). There are many contributing factors to the relatively poor prenatal care and outcomes, such as low socioeconomic status, high rates of smoking and substance use disorders, and obesity. For the clinician treating a pregnant woman with schizophrenia, it is particularly important to insist on early involvement of an obstetrician who can help reduce the risks of the pregnancy and with whom risks and benefits of pharmacological treatment options can be discussed.

f) Psychosocial stressors

A variety of psychosocial stressors can precipitate the initial development or recurrence of symptoms in a vulnerable person (304, 523–526). Stressors include stressful life events (e.g., interpersonal loss, leaving home, military service), sociocultural stress (e.g., poverty, homelessness, fragmented social network), or a distressing emotional climate (e.g., hostile and critical attitudes and overprotection by others in one's living situation or high levels of expressed emotion) (282–289). While schizophrenia can emerge or worsen in the absence of environmental

influences, attention to stressors frequently helps to prevent relapse and/or maximize healthy functioning. Sometimes the stress is internal, and knowledge of developmental vulnerabilities can assist in identifying and assisting with this variety of stress. Treatment strategies include preventing the development or accumulation of stressors and helping the patient develop coping strategies that keep tension levels within manageable bounds.

g) Schizophrenia in later life

With the overall increase in longevity, the number of older patients with schizophrenia is expected to increase rapidly over the next three decades (527). Among middle-aged and elderly persons with schizophrenia, approximately 80% have early-onset schizophrenia (528), with the remaining 20% including persons with late-onset schizophrenia (onset after age 40) and very-late-onset schizophrenia-like psychosis (onset after age 60) (DSM-IV, 529). The rate of aging-associated cognitive decline in older patients with schizophrenia is similar to that in age-comparable normal persons, although, as with younger patients, they have greater overall cognitive impairment (530, 531). The approach to the treatment of older persons with schizophrenia is similar to that of younger patients (532) and involves combining pharmacotherapies with psychosocial interventions.

Several age-related physiological changes may influence the approach to pharmacotherapy. These physiological changes include reduced cardiac output (and concomitant reduction in renal and hepatic blood flow, relative to younger persons), reduced glomerular filtration rate, possible reduction in hepatic metabolism, and increased fat content. These changes may alter the absorption, distribution, metabolism, and excretion of medications and may result in prolonged drug effects and greater sensitivity to medications, in terms of both therapeutic response and side effects (533). Age-related changes in receptor-site activity may further influence response to drugs in elderly patients. In general, recommended starting doses in older patients are one-quarter to one-half of the usual adult starting dose (529) (see Table 2).

The presence of concomitant medical illness or the use of multiple medications frequently complicates the treatment of older patients. In addition, age-related sensory deficits and cognitive impairment may interfere with patients' adherence to prescribed medication regimens. Elderly patients may unintentionally take incorrect doses of medications or follow erroneous dosing schedules.

Several important considerations bear on the use of antipsychotics in elderly patients. The cumulative annual incidence of tardive dyskinesia with first-generation antipsychotic medications has been found to be sixfold higher in later life than in younger adults (i.e., about 30% in later life) (534). Other side effects of particular concern in elderly patients include sedation, anticholinergic effects, and postural hypotension. Second-generation antipsychotics are generally recommended over first-generation agents because of their significantly lower risk of inducing extrapyramidal symptoms and tardive dyskinesia in older persons (534–538). However, the second-generation agents have other clinically significant and common side effects (Table 4), most notably sedation and orthostatic hypotension. Elderly patients with low cardiac output are especially vulnerable to hypotension and cardiac arrhythmia. The anticholinergic side effects of antipsychotic drugs in the presence of the age-related decrease in cholinergic function can contribute to problems such as urinary retention, confusion, and constipation or fecal impaction in the elderly patient. In some cases, elderly patients who are frail or poorly nourished may benefit from medication-induced weight gain; however, weight gain may also aggravate preexisting cardiovascular disease or osteoarthritis in this population. Elevated prolactin levels may also compromise bone-mineral density and increase osteoporosis.

Depression is not only common but also functionally disruptive in older persons with schizophrenia (539). In such instances, an antidepressant may need to be added to the treatment regimen. A wide variety of antidepressants are commonly used, although no comprehensive comparative trials in this population have been published. One small study found citalopram to be both useful and relatively safe in older patients with psychosis (540).

Psychosocial treatments are also recommended for a majority of individuals. Psychosocial evaluation may reveal a precipitating stress, such as a death in the family or a move to unfamiliar surroundings, that may explain a sudden change in the elderly person's behavior. Recent work has evaluated the benefits of integrated cognitive behavioral and social skills training (CBSST) in groups of older patients with schizophrenia (541). Results of a small randomized, controlled pilot study comparing CBSST plus pharmacotherapy to pharmacotherapy alone demonstrated the feasibility and acceptability by patients of CBSST and some improvement in psychopathology with CBSST in older patients with schizophrenia (541). Another pilot study showed the usefulness of functional adaptation skills training (542) in improving daily functioning in older patients with schizophrenia.

3. Concurrent general medical conditions

Patients with schizophrenia and related severe and persistent mental illness suffer disproportionately from a variety of comorbidities, including cardiovascular disease, respiratory disease, diabetes, infectious diseases (e.g., HIV), and substance use disorders (including nicotine, alcohol, and other substances) (543–554). A consequence of this excess comorbidity is an increased non-suicide-related mortality rate in this population (34, 388, 555). The increased frequencies of the various comorbid conditions are determined by multiple factors, including associations with schizophrenia itself (e.g., diabetes, smoking), life style (e.g., smoking, substance use, obesity, lack of exercise), environment (e.g., poverty, institutionalization), and medications (e.g., extrapyramidal syndromes, tardive dyskinesia, hyperprolactinemia, weight gain, hyperglycemia, hyperlipidemia, and cardiac arrhythmias). Thus, treatment selection and clinical management of patients with schizophrenia must consider the patient's past medical history and general medical status of the patient in determining the treatment plan. Patients should be evaluated in terms of their medical history and baseline assessments and then monitored with the relevant measures at appropriate intervals or when the patient's medical condition warrants or when a change in medication that could affect their medical condition is made, as indicated in Table 1. In the event that the patient's comorbid medical condition is affected adversely by a therapeutic agent (including an antipsychotic drug), management strategies may include helping the patient tolerate the adverse effect, treating the comorbid condition, or considering a change in the psychotropic medication to an alternative with less potential to induce side effects.

Patients with dementia and elderly patients are at very high risk of tardive dyskinesia. In addition, patients with dementia, Parkinson's disease, or other disorders associated with structural brain pathology are at increased risk of worsening of extrapyramidal side effects. Similarly, patients with psychosis and mental retardation are at increased risk for extrapyramidal side effects and tardive dyskinesia (556, 557). Thus, in these groups of patients, second-generation antipsychotics and particularly those with minimal or no risk of extrapyramidal effects (e.g., quetiapine) are recommended (558, 559). Furthermore, when such patients are treated with antipsychotic drugs, they must be monitored for side effects, and the increased risk of extrapyramidal side effects and tardive dyskinesia must be weighed against potential therapeutic benefits.

For patients with preexisting osteopenia or osteoporosis, an antipsychotic with minimal to no effects on prolactin should be prescribed. If a drug that increases prolactin is clinically indicated, then the relative safety of the antipsychotic should be discussed with the physician treating the bone demineralization. Female patients with menstrual or fertility problems should be evaluated for abnormalities in prolactin secretion, and non-prolactin-elevating medications should be considered as indicated. In addition, for women with breast cancer, antipsychotics with prolactin-elevating effects should be avoided or prescribed only after consultation with the patient's oncologist. In such instances, aripiprazole, which partially suppresses prolactin release, may be specifically indicated. However, in lactating mothers, suppression of prolactin may be detrimental, and the potential for this effect should be considered.

Obese patients and patients who have or may be at risk for diabetes and cardiovascular disease should be assessed before beginning treatment with antipsychotic drugs. Additional assessments are indicated at appropriate intervals thereafter or when warranted by a change in the patient's medical condition or medication regimen (see Table 1). Treatment selection should weigh the expected benefits of antipsychotic therapy against its potential to exacerbate or contribute to the development of specific medical conditions.

Patients with prolonged QT syndrome, bradycardia, certain electrolyte disturbances, heart failure, or recent myocardial infarction and patients who are taking drugs that prolong the QT interval should not be treated with an antipsychotic that could further prolong the QT interval or increase the risk of the arrhythmia torsades de pointes. These antipsychotics include thioridazine, droperidol, and ziprasidone. Pimozide also may prolong the QT interval.

Medications with low affinity for α -adrenergic receptors should be prescribed for patients who are vulnerable to orthostatic hypotension, including elderly patients, patients with peripheral vascular disease or compromised cardiovascular status, and other severely debilitated patients.

For patients with acute angle-closure glaucoma, severe constipation (or at risk for fecal obstruction), history of a paralytic ileus, urinary retention, prostate hypertrophy, or delirium/dementia, antipsychotics with little or no antagonism for cholinergic receptors should be prescribed.

Patients with severe dementia may be at increased risk of stroke when treated with risperidone. Clinicians treating psychosis in patients with dementia should refer to up-to-date FDA guidelines when considering the safety of risperidone in this population.

Clozapine should not be prescribed for patients with neutropenia ($<1500/\text{mm}^3$) or low white blood cell (WBC) count ($<3000/\text{mm}^3$) or a history of such sensitivities to prior medications.

III. TREATMENT SETTINGS AND HOUSING OPTIONS

► A. CHOICE OF TREATMENT SETTING OR HOUSING

Patients with schizophrenia may receive care in a variety of settings. Choice of setting may be guided by a number of factors, summarized in Table 6. In general, patients should be cared for in the least restrictive setting that is likely to be safe and to allow for effective treatment.

► B. COMMON TREATMENT SETTINGS

1. Hospitals

Treatment in the hospital has the advantage of providing a safe, structured, and supervised environment and reducing stress in both patients and family members. It allows the psychiatrist to closely monitor the level of the patient's symptoms, the patient's level of functioning and reactions to treatment, and side effects of treatment.

Hospitalization is usually indicated for patients who are considered to pose a serious threat of harm to themselves or others or who are so severely disorganized or under the influence of delusions or hallucinations that they are unable to care for themselves and need constant supervision or support. Other possible indications for hospitalization include general medical or psychiatric problems that make outpatient treatment unsafe or ineffective (e.g., if a patient's psychiatric status continues to deteriorate despite optimal care in the community). Patients who cannot be adequately cared for in nonhospital settings should be hospitalized voluntarily if possible. If patients decline voluntary status, they can be hospitalized involuntarily if their condition meets the criteria for involuntary admission of the local jurisdiction.

Alternative treatment settings should be considered when it is uncertain whether the patient needs to be hospitalized or when the patient does not need formal hospitalization but requires

TABLE 6. Factors Affecting Choice of Treatment Setting or Housing

Availability of the setting or housing
The patient's clinical condition
• Need for protection from harm to self or others • Need for external structure and support • Ability to cooperate with treatment
Patient's and family's preference
Requirements of the treatment plan
• Need for a particular treatment or a particular intensity of treatment that may be available only in certain settings • Need for a specific treatment for a comorbid psychiatric or other general medical condition
Characteristics of the setting
• Degrees of support, structure, and restrictiveness • Ability to protect patient from harm to self or others • Availability of different treatment capacities, including general medical care and rehabilitation services • Availability of psychosocial supports to facilitate the patient's receipt of treatment and to provide critical information to the psychiatrist about the patient's clinical status and response to treatments • Capacity to care for severely agitated or psychotic patients • Hours of operation • Overall milieu and treatment philosophy
Patient's current environment or circumstances
• Family functioning • Available social supports

more intensive services than can be expected in a typical outpatient setting (560). Alternative treatment settings in the community may include day or partial hospitalization, home care, family crisis therapy, crisis residential care, and assertive community treatment (see Part B, Section V.C.1.a, "Program for Assertive Community Treatment [PACT]"). A recent meta-analysis has shown that such alternatives to hospitalization for acutely ill patients can sometimes be at least as effective and sometimes more effective than hospitalization in terms of reducing loss to follow-up, reducing family burden, and increasing the patient's and family's satisfaction while being cost-neutral (561). These crisis intervention programs typically provide medication and a mobile multidisciplinary team that is available outside of traditional office hours. Other studies have demonstrated that crisis intervention can be associated with reduced symptoms, preserved role functioning, and reduced hospital readmission rates (181, 562–570).

Patients may be moved from one level of care to another on the basis of the factors summarized in Table 6, with an ongoing assessment of their readiness and ability to benefit from a different level of care. The choice of residence must be guided by the availability of housing and accompanying psychiatric support programs as well as by the patient's and family's preferences and resources.

Since a major aim of acute hospitalization is to facilitate rapid resolution of acute symptoms through the provision of a safe, nonstressful therapeutic environment, the hospital milieu should be organized to help achieve this goal. In consideration of the severe symptoms and cognitive impairment in acute schizophrenia, the hospital milieu should be highly structured; staff members should be clearly identifiable and should always wear name tags, whether they wear uniforms or street clothes; calendars and clocks should be in evidence on the ward; and ward schedules should be posted in order to provide a clear-cut external structure for the patients, who often have disorganized and impaired reality testing (571).

For acutely ill patients whose psychotic symptoms respond rapidly to antipsychotic medication, a brief hospitalization followed by day hospitalization when indicated has been shown to be as effective as or more effective than longer-term hospitalization, with no increase in rehospitalization rate and better maintenance of role functioning and less family burden at 1- and 2-year follow-up (571, 572). A number of randomized controlled studies have compared shorter and longer lengths of hospitalization. In the United States the shortest average duration of hospitalization studied was 11 days, which was compared with an average stay of 60 days for the control group (572), while in England, Hirsch et al. (573) compared outcomes for an average stay of 9 days with those for an average stay of 14 days. Other studies examined the effects of shorter and longer hospitalizations, but the general conclusion from all of the studies was that longer hospitalization conferred no additional benefit over shorter hospitalization in such areas as symptom improvement, community adjustment, and readmission rate (574–584). Brief hospitalization allows for effective treatment in the least restrictive environment but is optimal only when there is a system of community care in place and patients adhere to follow-up treatment. Thus, when there is no longer a clear-cut need for the patient to remain in the hospital and community treatment is available and accessible, the psychiatrist should consider discharging the patient from the hospital. On the other hand, if adequate community treatment and support resources are not in place, patients should not be discharged until they have achieved sufficient remission to enable them to function in the community without such supports.

2. Long-term hospitalization

Before the introduction of clozapine, 10%–20% of persons with schizophrenia remained severely psychotic with grossly impaired functioning despite optimal pharmacological and conventional care (585). The degree to which this percentage has been decreased by the availability of clozapine and other agents is unclear, but there remains a group of patients who require long-term, supervised hospitalization for their safety and protection, as well as for the protection of the family and community (586–588).

The organization of the long-stay hospital ward, the training and duties of its personnel, and the quality of care provided vary greatly and determine the therapeutic value of the hospital experience (589, 590). Studies have suggested that patients with treatment-resistant schizophrenia who require long-term hospitalization profit most from treatment programs that emphasize highly structured behavioral techniques, including a token economy, point systems, and skills training that can improve patients' functioning (591, 592). Paradoxically, despite its demonstrated efficacy, the token economy is not often used in clinical settings (593, 594). Obstacles to its implementation include resistance by staff members who hold to traditional custodial methods, increased costs (for the reinforcers backing up the tokens), lack of support from administrators, and inadequate training of clinical staff (595).

3. Crisis residential programs

The treatment of patients outside of large institutions is a fundamental objective of community psychiatry, and this objective creates the need for adequate community-based acute care as part of the comprehensive array of services needed to support persons with serious mental illness in the community. In many mental health systems, acute-care episodes involving hospitalization are the single largest cost element in the array of services needed to provide community care. Crisis residential facilities are homes in neighborhoods that are staffed and organized to accept and treat patients with serious mental illness in lieu of voluntary psychiatric admission. Crisis residential programs 1) provide short-term monitoring and crisis intervention in a residential, nonhospital setting as an alternative to inpatient care; 2) are staffed 24 hours per day/7 days per week; and 3) support patients in maintaining continuity with their outpatient caregivers and social networks during an acute-care episode. Crisis residential models have been studied as alternatives to hospitalization for patients with serious mental illness who 1) are willing to ac-

cept voluntary treatment, 2) do not require emergent medical assessment for an unstable medical condition, and 3) do not require acute substance detoxification. The findings of three randomized controlled trials indicate that crisis residential programs can deliver clinical outcomes comparable to those of hospital care at significantly less cost. In addition, crisis residential models have been successfully integrated into mental health systems in demonstration projects in a wide range of communities throughout the United States and overseas. Crisis residential models of acute care comport with community mental health practice that values the provision of needed care in the least restrictive or most integrated setting (596–600).

4. Day hospitalization or partial hospitalization

Day hospitalization can be used as an immediate alternative to inpatient care for acutely psychotic patients or to continue stabilization after a brief hospital stay. The day hospital should be staffed in a manner similar to the staffing of the day shift for an acute inpatient service, with close coordination with and involvement of family members and/or supervised residence staff. Brief overnight stays on inpatient units should be available for patients who demonstrate severe exacerbation of symptoms. As with all alternatives to inpatient care for acutely ill patients, the patient should not be considered at risk of harming self or others, should have the capacity to cooperate at least minimally in treatment, should have a significant other willing to provide care (a crisis residence can perform the same function), and should have access to appropriate community treatment resources. Treatment alternatives such as day hospitalization have the potential advantages of less disruption of the patient's life, treatment in a less restrictive and more integrated environment, and avoidance of the stigma attached to psychiatric hospitalization.

Controlled studies have shown that day hospitalization is at least as effective as acute inpatient care, and in some studies more effective, in such measures as decreasing symptoms and the rehospitalization rate and better preserving role functioning (562, 563, 573, 601–609). Meta-analyses have shown that day hospitalization has been associated with reductions in overall days of inpatient care, more rapid resolution of symptoms, and decreased overall costs with no increase in burden to family members. Social functioning did not differ across treatment settings (562, 563, 597, 598, 604, 606, 608, 610–614). The Cochrane review (609) combined data from nine studies involving acutely ill patients, the majority of whom had a diagnosis of schizophrenia. The review found that, at the most pessimistic estimate, day hospital treatment was feasible for 23% (N=2,268, 95% CI=21%–25%) of those currently admitted to inpatient care.

5. Day treatment

Generally, day treatment programs are used to provide ongoing supportive care for marginally adjusted patients with schizophrenia in the later part of the stabilization phase and the stable phase of illness. Such programs, which are usually not time limited, provide structure, support, and treatment programs to help prevent relapse and to maintain and gradually improve the patient's social functioning. Long-term day treatment attendance was thought to improve engagement (615), improve clinical outcome (615), and reduce readmission rates (616, 617). However, a Cochrane review found that there was no evidence that day care centers were better or worse than outpatient care in their effects on any clinical or social outcome variable (609). There was some evidence that day treatment might be more expensive than outpatient care (156, 618, 619).

However, the development of effective models of vocational rehabilitation and social skills training, as discussed in Part B, Sections V.C.1.c, “Supported Employment” and V.C.1.e, “Social Skills Training,” respectively, renders some of the previous research on day treatment as a “setting” of care to be less relevant than research on the types of programs that should be provided to patients with schizophrenia who are in the stable phase of illness and in need of recovery-oriented services. At this point in the development of psychosocial services, the effectiveness of day programs is likely to be a function of the quality of the programming patients receive while they attend. Thus, when planning for treatment in the stable phase of

illness, the clinician should carefully evaluate the available programming and help the patient implement a plan based on the patient's preferences and needs and on the availability of services that are recovery focused and consistent with evidence-based practices.

6. Housing

The advent of community-based care has produced a challenge regarding the housing of persons with severe mental illness and its connection to psychiatric care. Other than living with family, choices include hostels, group homes, therapeutic communities, and supported independent tenancies. Increasingly, people with severe mental illness are choosing to live as independently as possible in self-contained accommodations because sharing accommodation with other residents who also have mental illness can seem like living in an institution (620). Two essential paradigms have been promoted. In the transitional housing paradigm, patients live in housing that is directly connected to psychiatric treatment. The acceptance of treatment is often a contingency of using such housing. The underlying assumption is that patients "transition" through housing with decreasing levels of supervision as their mental status improves. A second paradigm is that of supported housing. In this paradigm, housing is not directly connected to treatment. Housing is typically in independent units, and mental health services are provided as needed in order to support patients in retaining their housing. Therefore, in a transitional housing model, a patient who is experiencing a relapse or worsening of symptoms would be moved to a housing setting with a higher level of supervision. In a supported housing model, such a patient would simply receive increased psychiatric services in his or her home, to facilitate housing stability.

The type of supported housing available to people with mental disorders seems to be dependent on the local availability of resources (621).

According to Budson (622), the most common types of residential facilities used currently include:

- *Transitional halfway houses.* A transitional halfway house is defined as a residential facility providing room and board and promoting socialization until suitable housing is available (623). It is used as a transitional facility between the hospital and the community for recovering patients.
- *Long-term group residences.* These facilities have on-site staff and are used for chronically functionally disabled persons. The length of stay is indefinite, in contrast to the length of stay in a halfway house, which is usually 6–8 months.
- *Cooperative apartments.* No on-site staff persons are present in cooperative apartments, but staff members make regular visits for oversight and guidance of residents.
- *Intensive-care or crisis community residences.* These facilities can be used to help prevent hospitalization or shorten the length of hospitalization. Usually, there are on-site nursing personnel and counseling staff.
- *Foster or family care.* Some patients are placed in foster or family care in private homes. There is a concern that in some situations only a custodial function may be provided (624). Close supervision of foster families is necessary to ensure that patients are living in a therapeutic environment.
- *Board-and-care homes.* These facilities are generally proprietary rooming houses. As with family care, close monitoring and supervision are necessary, since some of these facilities provide substandard environments for patients.
- *Nursing homes.* Nursing homes are suitable for some geriatric or chronically medically disabled patients, but they have been used inappropriately for other long-term patients to facilitate discharge, mainly from state hospitals. Various investigators have suggested that more developed activity programs and psychiatric supervision are needed to prevent declines in nursing home residents' social functioning and self-care.

Research on the merits of different housing programs and arrangements is inconclusive. For example, Friedrich et al. (625) examined housing preferences of persons with severe mental illness living in three types of community residences by surveying both patients and family members. Although a larger proportion of family members than patients preferred housing with more support, for both groups, current and preferred residence were consistent. For patients living independently, social isolation was perceived as a problem by patients and family members. The authors concluded that although supported housing works well for some persons, a continued need exists for an array of housing options with varying levels of structure. In contrast, a 10-site Scandinavian study (626) found that independent housing was related to a better quality of life concerning living situation and a better social network regarding availability and adequacy of emotional relations.

Dedicated programs whereby people with severe mental illness are located within one site or building with assistance from professional workers have the potential for great benefit, as they provide a safe haven for people in need of stability and support. This potential benefit, however, may be provided at the risk of increasing patients' dependence on professionals and prolonging exclusion from the community. Whether or not the benefits outweigh the risks can be only a matter of opinion in the absence of reliable evidence. Thus, there is an urgent need to investigate the effects of supported housing on people with severe mental illness within a randomized trial (627).

Newman (628) critically reviewed studies of the relationship between housing attributes and serious mental illness. Three studies found no effect of improved housing adequacy on housing satisfaction in addition to that provided by case management. Three studies found that fewer housing occupants led to better outcomes. The strongest finding from the literature on housing as a variable and as an outcome was that living in independent housing was associated with greater satisfaction with the housing and the neighborhood. However, given the methodological weaknesses of these studies, Newman pointed out the critical need for a coherent agenda built around key hypotheses and for a uniform set of measures of housing as a variable and as an outcome.

7. Correctional settings

The number of persons with schizophrenia incarcerated in prisons and jails in the United States has grown dramatically over the past two decades, paralleling the increase in incarceration among the general population (629). Generally, the rates of schizophrenia in correctional settings have been found to be significantly higher than in the general community population (630), with 1.8%–4.4% of incarcerated persons meeting the diagnostic criteria for schizophrenia (631). Consequently, screening of newly arrived detainees and inmates by correctional officers or health care staff members is important in identifying persons with schizophrenia or other psychotic disorders who will require more in-depth psychiatric assessment and treatment (632).

Since suicide is common in jails and prisons (633) and since newly incarcerated persons are at increased risk for suicide (56), screening of incarcerated persons with schizophrenia should include questions about suicidal thoughts and suicide attempts. Periodic reassessment is recommended since persons with schizophrenia may develop suicidal ideas or become more symptomatic while in a jail or prison. This worsening of symptoms can result from a number of factors, including stress related to incarceration, removal from support systems, and inadequate mental health services within the correctional setting (632).

For detainees and inmates who are identified as having schizophrenia or other serious mental illnesses, a variety of levels of mental health care may exist in the correctional system, including “outpatient” care, specialized housing, and “inpatient” care. In fact, correctional facilities are constitutionally required to provide adequate treatment to incarcerated persons with serious mental illnesses such as schizophrenia. Minimum standards for an acceptable treatment program were established in *Ruiz v. Estelle* (634) and include screening and evaluation; treatment be-

yond simple segregation and supervision; the use of adequate numbers of competent mental health professionals; individualized treatment; accurate, complete, and confidential medical record keeping; appropriate supervision of use of psychiatric medications; and identification, treatment, and supervision of inmates at risk for suicide. These minimum standards have been endorsed and expanded by other organizations, including APA (632).

Since jails are local facilities used for the confinement of persons awaiting trial or those convicted of minor crimes, mental health treatment of jail inmates is often limited by the short length of stay and small size of the facility. Treatment generally emphasizes prescription of psychotropic medications or crisis intervention services, which may include transfer to special housing units, special observation, and brief psychotherapy. Some longer-term psychotherapies may be available to inmates whose pretrial confinements or sentences are of a greater duration. The essential mental health services for a jail population include access to inpatient psychiatric beds; mental health care coverage that is available 7 days a week; availability of a full range of psychotropic medications that are prescribed and monitored by a psychiatrist; appropriate nursing coverage in any medical health area, including mental health; and procedures developed and monitored by psychiatrists and nurses to ensure that psychotropic medications are distributed by qualified medical personnel, whenever possible (635).

Prisons are generally under state or federal control and are used to confine persons serving longer sentences. Consequently, prison mental health systems generally provide a more comprehensive system of mental health care to persons with schizophrenia than would be available in a jail setting. In particular, the importance of a chronic care program for inmates with serious mental illness has become increasingly recognized as an essential component of prison mental health systems. These programs are often known as residential treatment units, intermediate care units, supportive living units, special needs units, psychiatric services units, or protective environments for the seriously mentally ill. Inmates appropriate for these units generally have had significant difficulty functioning in a general population environment because of symptoms related to their serious mental disorders. These units typically are designed to house 30–50 inmates per housing unit, which allows staffing to be done in a cost-effective fashion (635). A psychosocial rehabilitation approach is a frequently used treatment model. For short-term detainees and inmates, such treatments should focus on symptom management, adjustment to the correctional setting, planning for upcoming release, and reintegration into the home community. For long-term inmates, the primary foci should be symptom management, relapse prevention, and adjustment to incarceration.

If incarcerated persons with schizophrenia refuse treatment, administrative processes may permit mandated treatment to protect the safety of the person and others. For example, in all jurisdictions, emergency treatment can be instituted if psychosis results in paranoia and threats to other inmates, to staff, or to the person him- or herself. Some jurisdictions include administrative protocols for nonemergency treatment of inmates who refuse to accept medications (e.g., protocols established by *Washington v. Harper* [636]). Thus, clinicians practicing in correctional settings should become familiar with local and state law and with institutional policy on involuntary treatment.

While incarcerated, inmates with schizophrenia may show symptoms of withdrawal, disorganization, and/or disruptive behavior, which may be associated with disciplinary infractions. These infractions, in turn, may lead the inmate with schizophrenia to be placed in a locked-down setting within units that are often called “administrative segregation” or “disciplinary segregation” (637). Such units have been conceptualized as having three main characteristics: social isolation, sensory deprivation, and confinement (638). Each of these elements can vary significantly, but inmates typically spend an average of 23 hours per day in a cell, have limited human interaction and minimal or no access to programs, and are maintained in an environment that is designed to exert maximum control over the person. Inmates’ responses to the segregation experience differ, and relevant scientific literature is sparse (639). Nonetheless, mental

health clinicians working in such facilities frequently report that inmates without preexisting serious mental disorders develop irritability, anxiety, and other dysphoric symptoms when housed in these units for long periods of time (640). Difficulties in providing appropriate and adequate access to mental health care and treatment are especially problematic in any segregation environment and are related to logistical issues that frequently include inadequate office space and limited access to inmates because of security issues (641). In addition, because of their inherently punitive structure, such units typically provide very little support, access to relevant treatment modalities, or therapeutic milieu. Consequently, persons with schizophrenia should generally not be placed in a 23-hour/day lockdown for behaviors that directly result from the schizophrenia, because such an intervention is likely to exacerbate rather than reduce the symptoms of schizophrenia as well as increase rather than reduce disruptive behaviors (632, 642).

Before release from a correctional facility, inmates with schizophrenia should be assisted in finding a source for needed care in the community. In addition, attention should be paid to the housing and financial needs of inmates nearing release. On leaving the correctional facility, inmates should be provided with enough medication to allow them time to consult a physician and obtain a new supply.

PART B:

BACKGROUND INFORMATION AND REVIEW OF AVAILABLE EVIDENCE

IV. DISEASE DEFINITION, NATURAL HISTORY AND COURSE, AND EPIDEMIOLOGY

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► A. CLINICAL FEATURES

Table 7 presents DSM-IV-TR diagnostic criteria for schizophrenia, which is a major psychotic disorder. Its essential features consist of characteristic signs and symptoms that have been present for a significant length of time during a 1-month period (or for a shorter time if successfully treated), with some signs of the disorder persisting for at least 6 months. No single symptom is pathognomonic of schizophrenia. Rather, the symptoms may involve multiple psychological realms, such as perception (hallucinations), ideation, reality testing (delusions), thought processes (loose associations), feeling (flatness, inappropriate affect), behavior (catatonia, disorganization), attention, concentration, motivation (avolition, impaired intention and planning), and judgment. These psychological and behavioral characteristics are associated with a variety of impairments in occupational or social functioning. Although there can be marked deterioration with impairments in multiple domains of functioning (e.g., learning, self-care, working, interpersonal relationships, and living skills), the disorder is noted for great heterogeneity across persons and variability within persons over time. It is also associated with a recurrent and progressive course (280, 643). Persons with schizophrenia also suffer disproportionately from an increased incidence of general medical illness (644) and increased mortality (34, 645–653), especially from suicide, which occurs in up to 10% of patients (643, 654–657).

TABLE 7. DSM-IV-TR Diagnostic Criteria for Schizophrenia

-
- A. *Characteristic symptoms:* Two (or more) of the following, each present for a significant portion of time during a 1-month period (or less if successfully treated):
1. delusions
 2. hallucinations
 3. disorganized speech (e.g., frequent derailment or incoherence)
 4. grossly disorganized or catatonic behavior
 5. negative symptoms, i.e., affective flattening, alogia, or avolition
- Note:* Only one Criterion A symptom is required if delusions are bizarre or hallucinations consist of a voice keeping up a running commentary on the person's behavior or thoughts, or two or more voices conversing with each other.
- B. *Social/occupational dysfunction:* For a significant portion of the time since the onset of the disturbance, one or more major areas of functioning, such as work, interpersonal relations, or self-care, are markedly below the level achieved prior to the onset (or when the onset is in childhood or adolescence, failure to achieve expected level of interpersonal, academic, or occupational achievement).
- C. *Duration:* Continuous signs of the disturbance persist for at least 6 months. This 6-month period must include at least 1 month of symptoms (or less if successfully treated) that meet Criterion A (i.e., active-phase symptoms) and may include periods of prodromal or residual symptoms. During these prodromal or residual periods, the signs of the disturbance may be manifested by only negative symptoms or two or more symptoms listed in Criterion A present in an attenuated form (e.g., odd beliefs, unusual perceptual experiences).
- D. *Schizoaffective and Mood Disorder exclusion:* Schizoaffective Disorder and Mood Disorder With Psychotic Features have been ruled out because either (1) no Major Depressive, Manic, or Mixed Episodes have occurred concurrently with the active-phase symptoms; or (2) if mood episodes have occurred during active-phase symptoms, their total duration has been brief relative to the duration of the active and residual periods.
- E. *Substance/general medical condition exclusion:* The disturbance is not due to the direct physiological effects of a substance (e.g., a drug of abuse, a medication) or a general medical condition.
- F. *Relationship to a Pervasive Developmental Disorder:* If there is a history of Autistic Disorder or another Pervasive Developmental Disorder, the additional diagnosis of Schizophrenia is made only if prominent delusions or hallucinations are also present for at least a month (or less if successfully treated).

Classification of longitudinal course (can be applied only after at least 1 year has elapsed since the initial onset of active-phase symptoms):

Episodic With Interepisode Residual Symptoms (episodes are defined by the reemergence of prominent psychotic symptoms); also specify if: With Prominent Negative Symptoms

Episodic With No Interepisode Residual Symptoms

Continuous (prominent psychotic symptoms are present throughout the period of observation); also specify if: With Prominent Negative Symptoms

Single Episode In Partial Remission; also specify if: With Prominent Negative Symptoms

Single Episode In Full Remission Other or Unspecified Pattern

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The characteristic symptoms of schizophrenia have often been conceptualized as falling into two broad categories—positive and negative symptoms. A third category of disorganized symptoms has recently been added because statistical analyses show it to be a dimension independent of the positive symptom category, under which it was previously included. The positive symptoms include delusions and hallucinations. Disorganized symptoms include disorganized speech (658) (thought disorder), disorganized behavior, and poor attention. Negative symptoms include restricted range and intensity of emotional expression (affective flattening), reduced thought and speech productivity (alogia), anhedonia, and decreased initiation of goal-directed behavior (avolition) (659). Negative symptoms may be primary and represent a core feature of schizophrenia, or they may be secondary to psychotic symptoms, a depressive syndrome, medication side effects (e.g., dysphoria), or environmental deprivation.

According to DSM-IV-TR, subtypes of schizophrenia are defined by the predominant symptoms at the time of the most recent evaluation and therefore may change over time. These subtypes include paranoid type, in which preoccupation with delusions or auditory hallucinations is prominent; disorganized type, in which disorganized speech and behavior and flat or inappropriate affect are prominent; catatonic type, in which characteristic motor symptoms are prominent; undifferentiated type, which is a nonspecific category used when none of the other subtype features are predominant; and residual type, in which there is an absence of prominent positive symptoms but continuing evidence of disturbance (e.g., negative symptoms or positive symptoms in an attenuated form) (660). Although the prognostic and treatment implications of these subtypes vary, the disorganized type tends to be the most severe and the paranoid type to be the least severe (661).

Other mental disorders and general medical conditions may be comorbid with schizophrenia. Along with general medical conditions, the most common comorbid disorder appears to be substance use disorder. Commonly abused substances include alcohol (327); stimulants such as cocaine and amphetamines (662–664); nicotine, cannabis, phencyclidine (PCP); and LSD (665–667). Such comorbidities can worsen the illness course and complicate treatment (331, 668–670). Individuals with schizophrenia may also experience symptoms of other mental disorders, especially depression but also obsessive and compulsive symptoms, somatic concerns, dissociative symptoms, and other mood or anxiety symptoms. Whether symptoms alone are present or whether criteria for comorbid diagnoses are met, these features can significantly worsen prognosis (671) and often require specific attention and treatment planning. General medical conditions are often present, and persons with schizophrenia may be at special risk for those associated with poor self-care or institutionalization (e.g., tuberculosis, hepatitis), substance use (e.g., emphysema and other cigarette-related pathology, HIV-related disease), and antipsychotic-induced movement disorders. Some persons with schizophrenia develop psychosis-induced polydipsia, which can lead to water intoxication and hyponatremia.

► **B. NATURAL HISTORY AND COURSE**

Schizophrenia can be viewed as a disorder that develops in phases: premorbid, prodromal, and psychotic (252, 257, 259, 260, 672). The premorbid phase encompasses a period of normative function, although the person may experience events that contribute to the development of the subsequent illness, including complications in pregnancy and delivery during the prenatal and perinatal periods and trauma and family stress during childhood and adolescence (673).

The prodromal phase involves a change from premorbid functioning and extends up to the time of the onset of frank psychotic symptoms. It may last only weeks or months, but the average length of the prodromal phase is between 2 and 5 years (252, 260, 674). During the prodromal phase the person experiences substantial functional impairment and nonspecific symptoms such as sleep disturbance, anxiety, irritability, depressed mood, poor concentration, fatigue, and be-

havioral deficits such as deterioration in role functioning and social withdrawal (675, 676). Positive symptoms such as perceptual abnormalities, ideas of reference, and suspiciousness develop late in the prodromal phase and herald the imminent onset of psychosis (677).

The first psychotic episode may be abrupt or insidious in its onset. In most Western countries, 1–2 years elapse on average between the onset of the first psychotic symptoms and the first adequate treatment, defined as the duration of untreated psychosis (252, 259–261, 678). This time period has been found to be significantly longer in men than in women (261).

The psychotic phase progresses through an acute phase, a recovery or stabilization phase, and a stable phase. The acute phase refers to the presence of florid psychotic features such as delusions, hallucinations, formal thought disorder, and disorganized thinking. Negative symptoms often become more severe, and patients are usually not able to care for themselves appropriately. The stabilization (recovery) phase refers to a period of 6–18 months after acute treatment. During the stable phase, negative and residual positive symptoms that may be present are relatively consistent in magnitude and usually less severe than in the acute phase. Some patients may be asymptomatic whereas others experience nonpsychotic symptoms such as tension, anxiety, depression, or insomnia.

The period after recovery from a first episode of schizophrenia and extending for up to the subsequent 5 years is known as the early course. If patients experience further deterioration in symptoms and/or function, it is most likely to occur during this time, because by 5–10 years after onset most patients experience a plateau in their level of illness and function (257, 643). This phase has also been termed “the critical period” (679) because most follow-up studies have shown that up to 80% of patients will have relapsed within this 5-year period (46). Before relapse occurs, there is usually a prodromal period in which nonpsychotic symptoms, followed by emotional disturbance and then frank psychotic symptoms develop over a period of about 4 weeks (680–682).

The long-term outcome of schizophrenia varies along a continuum between reasonable recovery and total incapacity. About 10%–15% of persons with the disorder are free of further episodes (683), but the majority display exacerbations and remissions in the context of experiencing clinical deterioration, and about 10%–15% remain chronically severely psychotic (643, 684).

Several demographic and clinical variables have value in predicting long-term outcome. For example, better outcomes are associated, on average, with female gender, family history of affective disorder, lack of family history of schizophrenia, good premorbid social and academic functioning, higher IQ, married marital status, later age of onset (685), acute onset with precipitating stress, fewer prior episodes (both number and length), a phasic pattern of episodes and remissions, advancing age, minimal comorbidity, paranoid subtype, and symptoms that are predominantly positive (delusions, hallucinations) and not disorganized (thought disorder, disorganized behavior) or negative (flat affect, avolition) (282, 303, 304, 502, 523, 660, 661, 683, 686–692). It appears that the course is influenced by cultural factors and societal complexity, with better outcomes in developing countries (689).

The excessive mortality of patients with schizophrenia has been reported to be two to four times that of the general population (34, 551, 656, 693–696). About 4%–10% of persons with schizophrenia die by suicide, and the rates are highest among males in the early course of the disorder and in industrialized countries (387, 390, 697). Severe psychotic symptoms, depression, comorbid substance use disorder, and adverse life events increase the risk of suicide in persons with schizophrenia (395, 698). Other major causes of death also include unnatural causes, such as accidents and traumatic injuries, and medical conditions, such as cardiovascular disorders and respiratory and infectious diseases (387).

► C. EPIDEMIOLOGY

The lifetime morbidity risk for schizophrenia (i.e., the proportion of a population meeting the criteria for schizophrenia at any time during life provided they live through the entire age range

of risk) is estimated to be 1.0% (699, 700) and appears to be the same for men and women up to age 60 years (701, 702).

The incidence of schizophrenia appears to be stable across countries and cultures and over time (701), although there is some controversy on this point, with some studies showing significant variability (703). In the World Health Organization (WHO) Determinants of Outcome Study, the median annual incidence of schizophrenia across eight participating WHO sites was 0.22 per 1,000 population (704). Earlier reports of declining incidence of schizophrenia over time have not been confirmed (699, 700, 702).

The Epidemiologic Catchment Area study in the United States reported a lifetime prevalence rate of schizophrenia of 1.5% (705). Studies of representative community samples assessed by structured diagnostic interviews in the United States yield estimates of the lifetime prevalence for schizophrenia of 0.7% (706).

Among persons age 65 years and older, the prevalence is probably 1% (528, 707, 708). There are, however, controversies about whether early-onset and late-onset schizophrenia are different or similar disorders.

About 20%–40% of patients experience their first psychotic symptoms before age 20 years (709). For men, the peak incidence of onset of schizophrenia has been determined to be between ages 15 and 25 years; for women, between ages 25 and 35 years (710). The WHO's Determinants of Outcome Study found a mean gender difference in age at onset of 3.4 years (711). Some studies (711–713), but not all (714), have demonstrated this earlier mean age of onset in men across cultures. However, this finding may not be evident in familial schizophrenia (715, 716). Women display a second peak of onset after age 40–45 years, just before menopause (674, 717–719).

Men experience more negative symptoms and women more affective symptoms (309), although acute psychotic symptoms, either in type or severity, do not differ between the two genders (508, 720). The prevalence of negative (deficit) states in first-episode schizophrenia has been estimated to be between 4% and 10% (298) and increases with the length of the schizophrenic illness (302–306, 661).

More than 80% of patients with schizophrenia have parents who do not have the disorder (721). However, the risk of having schizophrenia is greater in persons whose parents have the disorder; the lifetime risk is 13% for a child with one parent with schizophrenia and 35%–40% for a child with two affected parents (722). The risk increases with the number of affected relatives. Twin studies have found a concordance rate among monozygotic twins of about 50%, compared to 9% for dizygotic twins and siblings (721, 723).

Many studies (724–729), but not all (730–732), have reported an association between obstetric complications that involved fetal hypoxic brain damage and a subsequent increase in risk for schizophrenia. Such complications include viral infection during pregnancy (733–738); first-trimester maternal starvation (739); rhesus incompatibility (740, 741); and maternal preeclampsia (741–743), anemia (741, 743), and diabetes (743). Patients with an early onset of schizophrenia were more likely to have a history of birth complications than those with later onsets (744, 745). Persons born in the winter months are also at a higher risk (746–748).

Substance use has been associated with precipitation of symptoms of schizophrenia (334–340, 667, 749, 750). The mean age at onset of schizophrenia as well as the age at first admission was lower in patients who had a history of substance use and higher in patients without such a history (341, 751).

Recent studies examining immigration and schizophrenia have shown an increase of the disorder in second-generation African Caribbean immigrants in the United Kingdom (752–754). Other risk factors have been associated with an increased risk for schizophrenia (691, 702). They include single marital status, a lower socioeconomic class (525), being raised in an urban environment (755, 756), environmental stress (525), and advanced paternal age (757, 758).

Schizophrenia is by far the most costly mental illness (759) and has been estimated to account for 2.5% of annual health care expenditures in the United States (760). The cost of schizophrenia for American society was estimated to be \$32.5 billion in 1990; by 1995, the cost was estimated to have escalated to \$65 billion (761). Indirect costs to the patients, their families, other caregivers, and society must also be considered (762). In a British study, the annual indirect costs incurred through productivity loss by patients were estimated to be at least four times the direct costs (763).

V. REVIEW AND SYNTHESIS OF AVAILABLE EVIDENCE

► A. PHARMACOLOGICAL TREATMENTS

This section is organized by medication. For each medication or medication class, the available data regarding efficacy are reviewed. Short-term efficacy has generally been measured by reductions in psychopathology (positive, negative, affective, and general symptoms) among treated patients during 6- to 12-week medication trials. An advantage of studies that measure psychopathological changes is that they clearly demonstrate how well a medication can achieve a reduction in the target symptoms. Less clear is how such reductions in symptoms relate to improvements in patients' functioning. Acute and long-term efficacy have also been assessed by examining effects on cognitive function as measured by neurocognitive test performance (764–766), which in turn has been related to patients' functional capacity and performance (767).

Long-term efficacy has usually been measured by reductions in either relapse or rehospitalization rates among treated patients and by levels of persisting or residual symptoms and general outcome over the course of several years. The utility of relapse rates depends on the measure that is used. Relapse rates based on symptom reemergence have varied markedly from study to study, partly because different criteria for the types and severity of symptoms have been used to define relapse. Rehospitalization rates, which may also be used to determine rates of relapse, offer the advantage of reflecting both symptoms and functioning. However, rehospitalization rates are affected by other clinical and nonclinical determinants. Thus, they tend to be more conservative estimates of relapse (occurring at a rate of 1%–10% per month after discontinuation of therapy) than are rates of reemergence of psychotic symptoms (5%–20% per month) (99). More recently, long-term efficacy has been measured in terms of quality of life, health service utilization, and social and vocational function (768–771). In addition, these measures of outcome have been used to define the level of recovery of patients.

1. Antipsychotic medications

In this guideline the term “antipsychotic” refers to multiple medications (Table 2), including the first-generation antipsychotic medications and the second-generation agents clozapine, risperidone, olanzapine, quetiapine, ziprasidone, and aripiprazole. In addition to having therapeutic effects, both first- and second-generation antipsychotic agents can cause a broad spectrum of side effects. Side effects of medications are a crucial aspect of treatment because they often determine medication choice and are a primary reason for medication discontinuation.

Side effects can complicate and undermine antipsychotic treatment in various ways. The side effects themselves may cause or worsen symptoms associated with schizophrenia, including negative, positive, and cognitive symptoms and agitation (772). In addition, these side effects

may contribute to risk for other medical disorders (50, 773). Finally, these side effects often are subjectively difficult to tolerate and may affect the patient's quality of life and willingness to take the medication (17).

Most side effects of antipsychotic treatment result from actions on neurotransmitter systems and anatomic regions beyond those involved in mediating the intended therapeutic effects of the medication. Among the antipsychotic medications, differences in the risk of specific side effects are often predictable from the potencies and receptor binding profiles of the various agents. Some side effects result from receptor-mediated effects within the central nervous system (e.g., extrapyramidal side effects, hyperprolactinemia, sedation) or outside the central nervous system (e.g., constipation, hypotension), whereas other side effects are of unclear pathophysiology (e.g., weight gain, hyperglycemia). Side effects that are similar across several classes of agents, including both first- and second-generation antipsychotics, are discussed in Section V.A.1.c, "Shared Side Effects of Antipsychotic Medications." These shared side effects include neurological effects (i.e., acute and chronic extrapyramidal effects, neuroleptic malignant syndrome), sedation, cardiovascular effects (i.e., hypotension, tachycardia, and conduction abnormalities), anticholinergic and antiadrenergic effects, weight gain and glucose and lipid metabolic abnormalities, and sexual dysfunction. Side effects unique to particular agents are discussed in the respective sections concerning those agents, as are other unique implementation issues. Suggested approaches for monitoring and clinical management of the side effects of antipsychotic medications are outlined in Table 1.

a) First-generation agents

First-generation antipsychotic agents effect their therapeutic action, as well as their extrapyramidal side effects, primarily by blocking dopamine, subtype 2 (D₂), receptors in mesolimbocortical and nigrostriatal areas of the brain (774).

(1) Efficacy in the acute phase

The evidence supporting the effectiveness of first-generation antipsychotic medications in reducing psychotic symptoms in acute schizophrenia comes from studies carried out in the 1960s (775, 776) as well as numerous subsequent clinical trials (99, 777). Each of these studies compared one or more antipsychotic medications with either placebo or a sedative agent, such as phenobarbital (778), that served as a control. Nearly all of these studies found that the antipsychotic medication was superior for treating schizophrenia. These studies demonstrated the efficacy of first-generation antipsychotic medications for every subtype and subgroup of patients with schizophrenia. Moreover, in reviews of studies that compared more than one first-generation antipsychotic medication, Klein and Davis (779) and Davis et al. (777) found that, with the exception of mepazine and promazine, all of these agents were equally effective, although there were differences in dose, potency, and side effects of the different drugs.

First-generation antipsychotic medications are effective in diminishing most symptoms of schizophrenia. In a review of five large studies comparing an antipsychotic to placebo, Klein and Davis (779) found that patients who received an antipsychotic demonstrated decreases in positive symptoms, such as hallucinations, uncooperativeness, hostility, and paranoid ideation. Patients also showed improvement in thought disorder, blunted affect, withdrawal-retardation, and autistic behavior.

These findings—along with decades of clinical experience with these agents—indicate that first-generation antipsychotic treatment can reduce the positive symptoms (hallucinations, delusions, bizarre behaviors) and secondarily reduce the negative symptoms (apathy, affective blunting, alogia, avolition) associated with schizophrenic psychosis (297). In placebo-controlled comparisons (99, 776), approximately 60% of patients treated with first-generation antipsychotic medication for 6 weeks improved to the extent that they achieved complete remission or experienced only mild symptoms, compared to only 20% of patients treated with

placebo. Forty percent of medication-treated patients continued to show moderate to severe psychotic symptoms, compared to 80% of placebo-treated patients. Eight percent of medication-treated patients showed no improvement or worsening, compared to nearly one-half of placebo-treated patients. A patient's prior history of a medication response is a fairly reliable predictor of how the patient will respond to a subsequent trial (780, 781).

Since the advent of second-generation antipsychotic medications, research on first-generation agents has reduced considerably. In recent years, randomized, controlled studies of the efficacy of first-generation agents for acute treatment have focused on dosing strategies and defining the most effective dose range to maximize symptom response and minimize side effects. These studies have consistently found that modest doses of first-generation agents (typically defined in haloperidol doses of less than 10 mg/day or plasma levels <18 ng/ml) are as efficacious or more efficacious than higher doses (782–784). Moderate doses of first-generation agents have been reported to improve comorbid depression (369, 785, 786), whereas higher doses are associated with greater risk of extrapyramidal side effects and dysphoria (785, 787) and may be especially problematic for patients with frontal lobe dysfunction (788).

(2) Efficacy in the stabilization and stable phases

Empirical research provides relatively little guidance for psychiatrists who are making decisions about medication and dosage during the stabilization phase. The use of first-generation antipsychotic medications during this phase is based on the clinical observation that patients relapse abruptly when medications are discontinued during this phase of treatment.

A large number of studies (789, 790) have compared relapse rates for stabilized patients who continued taking a first-generation antipsychotic medication and for those whose regimen was changed to placebo. During the first year only about 30% of those continuing to take medications relapsed, compared with about 65% of those taking placebo. Even when adherence with medication treatment was ensured by the use of long-acting injectable medications, as many as 24% of patients relapsed in a year (791). Hogarty et al. (792) found that among outpatients maintained with antipsychotic medications for 2–3 years who had been stable and judged to be at low risk of relapse, 66% relapsed in the year after medication withdrawal. Studies in which the medications of well-stabilized patients were discontinued indicate that 75% of patients relapse within 6–24 months (790). Among patients who have experienced a first episode of schizophrenia, a number of carefully designed double-blind studies indicate that 40%–60% of patients relapse if they are untreated during the year after recovery from this initial episode (211, 212, 218).

A critical issue during the stable treatment phase is adherence to the medication regimen. One strategy for improving adherence with first-generation agents is use of the long-acting injectable formulation. Studies with long-acting antipsychotics show a dose-response relationship in prophylactic efficacy, although there is a tradeoff in the relationship between dose and relapse rate on the one hand and side effects on the other (793, 794). The higher the dose used, the lower the relapse rate but the higher the rate of side effects, whereas the reverse is seen with lower doses. Although a small number of randomized trials have assessed the effectiveness of more modest doses of long-acting injectable medications than those typically used in clinical practice, evidence on this question remains inconclusive. Inderbitzen et al. (795) found no loss of clinical effectiveness when the average dose of patients already receiving long-acting injectable fluphenazine was cut gradually by 50% over a 5-month period (from an average of 23 mg every 2 weeks to 11.5 mg every 2 weeks). Similarly, Carpenter et al. (796) found a regimen of 25 mg of fluphenazine decanoate every 6 weeks to be equally effective as the same dose administered every 2 weeks. However, Schooler et al. (219) compared three medication strategies using fluphenazine decanoate: a continuous moderate dose (12.5–50 mg every 2 weeks); a continuous low dose (2.5–10 mg every 2 weeks); and targeted, early intervention (fluphenazine only when the patient was experiencing symptoms). They found that both continuous low-dose

and targeted treatment increased the use of rescue medication and the rate of relapse, while only targeted treatment increased the rate of rehospitalization.

(3) Shared side effects

Side effects of first-generation antipsychotic medications typically vary with the potency of the agent. High-potency first-generation antipsychotics are associated with a high risk of extrapyramidal effects, a moderate risk of sedation, a low risk of orthostatic hypotension and tachycardia, and a low risk of anticholinergic and antiadrenergic effects. In contrast, low-potency first-generation antipsychotic agents are associated with a lower risk of extrapyramidal effects, a high risk of sedation, a high risk of orthostatic hypotension and tachycardia, and a high risk of anticholinergic and antiadrenergic effects. Although other side effects also vary with the specific medication, in general, the first-generation antipsychotic medications are associated with a moderate risk of weight gain, a low risk of metabolic effects, and a high risk of sexual side effects. With certain agents (thioridazine, mesoridazine, pimozide), a moderate risk of cardiac conduction abnormalities is also present. Neuroleptic malignant syndrome occurs rarely but is likely to be more often observed with first-generation agents (especially high-potency agents) than with second-generation antipsychotic medications. Details on the nature and management of each of these side effects are provided in Section V.A.1.c, “Shared Side Effects of Antipsychotic Medications.”

(4) Other side effects

Other side effects include seizures, allergic reactions, and dermatological, hepatic, ophthalmological, and hematological effects.

Seizures

First-generation antipsychotic medications can lower the seizure threshold and result in the development of generalized tonic-clonic seizures (797). The low-potency first-generation antipsychotic medications confer the greatest risk. The frequency of seizures with low-potency antipsychotic medications is dose related, with higher doses associated with greater risk. At usual dose ranges, the seizure rates are below 1% for all first-generation antipsychotic medications, although patients with a history of an idiopathic or medication-induced seizure have a higher risk.

Allergic and dermatological effects

Cutaneous allergic reactions occur infrequently with first-generation antipsychotic medications. Medication discontinuation or administration of an antihistamine is usually effective in reversing these symptoms. Rarely, thioridazine is associated with hyperpigmentation of the skin. Photosensitivity also occurs infrequently and is most common with the low-potency phenothiazine medications; patients should be instructed to avoid excessive sunlight and use sunscreen (99).

Hepatic effects

Also occurring with this class of medications are elevation of liver enzyme levels and cholestatic jaundice. Jaundice has been noted to occur in 0.1%–0.5% of patients taking chlorpromazine (99). This side effect usually occurs within the first month after the initiation of treatment and generally requires discontinuation of treatment. However, given the relative infrequency of antipsychotic-induced jaundice, other etiologies for jaundice should be evaluated before the cause is judged to be antipsychotic medication.

Ophthalmological effects

Pigmentary retinopathies and corneal opacities can occur with chronic administration of the low-potency medications thioridazine and chlorpromazine, particularly at high doses (e.g., more than 800 mg/day of thioridazine). For this reason, patients maintained with these medications should have periodic ophthalmological examinations (approximately every 2 years for

patients with a cumulative treatment of more than 10 years), and a maximum dose of 800 mg/day of thioridazine is recommended (797). With the increased use of high-potency medications in the past two decades, there has been virtually no reporting of this side effect (777).

Hematological effects

Hematological effects, including inhibition of leukopoiesis, can occur with use of first-generation antipsychotic medications. Such effects include benign leukopenia and the more serious agranulocytosis. The best data exist for chlorpromazine, with which benign leukopenia occurs in up to 10% of patients and agranulocytosis occurs in 0.32% of patients (797).

(5) Implementation

Issues in implementation of treatment with first-generation antipsychotic medications include route of administration, dosage strategy, and medication interactions.

Route of administration

First-generation antipsychotic medications can be administered in oral forms, as short-acting intramuscular preparations, or as long-acting injectable preparations. Short-acting intramuscular medications reach a peak concentration 30–60 minutes after the medication is administered, whereas oral medications reach a peak in 2–3 hours (798). As a result, the calming effect of the first-generation antipsychotic may begin more quickly when the medication is administered parenterally. However, this calming effect on agitation is different from the true antipsychotic effect of these medications, which may require several days or weeks (779). It is also worth noting that oral concentrates are typically better and more rapidly absorbed than pill preparations and often approximate intramuscular administration in their time to peak serum concentrations.

A single or twice-daily dose of an oral preparation will result in steady-state blood levels in 2–5 days (798). Long-acting injectable first-generation antipsychotic medications (fluphenazine decanoate or enanthate and haloperidol decanoate in the United States) may require up to 3–6 months to reach a steady state (92). As a result, they are seldom used alone during acute treatment, when the psychiatrist is adjusting the dose in accordance with therapeutic effects and side effects.

The advantage of long-acting injectable medications has been best demonstrated in studies such as those conducted by Johnson (799) under conditions that resemble most closely those in community clinics. In these studies, patients with histories of poor adherence were included in the study population and the amount of contact between patients and staff was limited. In the larger, more carefully controlled investigations (791, 800), patients with serious adherence problems—that is, the patients most likely to benefit from treatment with long-acting injectable medications—were commonly not included. Thus, a study by Hogarty et al. (800) showed a reduction in relapse associated with fluphenazine decanoate compared to oral fluphenazine only after 2 years of follow-up, as the effect of the drug on nonadherence and subsequent relapse took time to develop in a study population that was relatively stable and adherent at baseline.

Long-acting injectable medications are thought to be especially helpful in the stabilization and stable phases. Janicak et al. (99) examined six studies that compared the risk of psychotic relapse in patients who were randomly assigned to receive either oral or long-acting injectable medication. The longest of those studies (800) lasted 2 years and showed a relapse rate of 65% for patients taking oral medication and a rate of 40% for patients taking long-acting injectable medication. Although the remaining five studies, all of which lasted 1 year or less, had variable results, a meta-analysis of all six studies showed a significantly lower relapse rate in patients who received long-acting injectable medication ($p < 0.0002$) (99).

Dosage strategy

The effective dose of a first-generation antipsychotic medication is closely related to its affinity for dopamine receptors (particularly D₂ receptors) and its tendency to cause extrapyramidal side

effects (801, 802). Thus, high-potency medications have a greater affinity for dopamine receptors than do low-potency medications, and a much lower dose of high-potency medications is required to treat psychosis. This relationship can be expressed in terms of dose equivalence (e.g., 100 mg of chlorpromazine has an antipsychotic effect that is similar to that of 2 mg of haloperidol). The dose equivalencies of commonly prescribed medications are listed in Table 2.

High-potency first-generation antipsychotic medications, such as haloperidol and fluphenazine, are more commonly prescribed than low-potency compounds (803). Although these medications have a greater tendency to cause extrapyramidal side effects than the low-potency medications, such as chlorpromazine and thioridazine, their side effects are easier to manage than the sedation and orthostatic hypotension associated with low-potency agents. High-potency medications can more safely be administered intramuscularly, since they seldom cause hypotension. In addition, because of sedation, orthostatic hypotension, and lethargy, the dose of a low-potency medication should be increased gradually, whereas an adequate dose of a high-potency medication can usually be achieved within a day or two. Finding the optimal dose of a first-generation antipsychotic is complicated by a number of factors. Patients with schizophrenia demonstrate large differences in the dose of first-generation antipsychotic they can tolerate and the dose required for an antipsychotic effect. A patient's age may influence the appropriate dose; elderly patients are more sensitive to both the therapeutic and adverse effects of first-generation antipsychotics. In addition, in studies in which dose is not fixed, it is difficult to determine dose by assessing antipsychotic effectiveness, since it may take many days at a therapeutic dose before there is an appreciable decrease in psychosis (778, 780).

A number of studies (reviewed by Davis et al. [777] and by Baldessarini et al. [95]) provide guidance about the usual doses required for acute treatment. Results of 19 controlled trials suggested that daily doses below 250 mg of chlorpromazine (or 5 mg of haloperidol or fluphenazine) are less adequate for many acutely psychotic patients than are moderate doses, between 300 and 600 mg of chlorpromazine. In the studies, response was typically measured by improvement in the score on the excitement, agitation, or psychosis subscale of the BPRS (6), and the proportions of patients responding to low doses after 1 and 2–10 days were 38% and 50%, respectively; these rates compared unfavorably with the improvement rates of 61% and 56% among patients taking moderate doses for similar periods (95). Davis et al. (777) came to similar conclusions. They found that daily doses between 540 and 940 mg of chlorpromazine were optimal. The findings of clinical trials involve groups of patients; some patients have optimal responses at doses above or below these optimal ranges. Psychiatrists have treated acutely psychotic patients with high doses of high-potency first-generation antipsychotic medications during the first days of treatment. This treatment is based on the belief that higher doses result in a more rapid improvement than that resulting from moderate doses (804). However, studies have revealed that high daily doses (more than 800 mg of chlorpromazine equivalents daily) were no more effective, or faster acting, on average than were moderate doses (500–700 mg/day) (95). After 1 day, 50% of the patients treated with high doses responded, compared to 61% of those who received moderate doses. After 2–10 days, high-dose treatment led to a slightly worse outcome: only 38% of those receiving high doses but 56% of those receiving moderate doses were improved. These studies indicate that higher doses are no more effective for acute treatment than normal doses, but higher doses are associated with a greater incidence of side effects.

Controlled trials have provided similar information regarding the effect of medication dose on outcome during the maintenance phase. In 33 randomized trials in which high doses (mean, 5200 mg/day of chlorpromazine equivalents) were compared to low doses (mean, 400 mg/day) during maintenance treatment, the lower doses were more effective in improving clinical state in more than two-thirds of the trials (95). In addition, in 95% of the studies the higher doses resulted in greater neurological side effects. Studies of doses of less than 200 mg/day of chlorpromazine equivalents tended to show that such doses were less effective than higher doses. An international consensus conference (294) made the reasonable recommendation of a reduction

in first-generation antipsychotic dose of approximately 20% every 6 months until a minimal maintenance dose is reached. A minimal dose was considered to be as low as 2.5 mg of oral fluphenazine or haloperidol daily, 50 mg of haloperidol decanoate every 4 weeks, or 5 mg of fluphenazine decanoate every 2 weeks.

Concerns about the side effects of first-generation antipsychotic medications during maintenance treatment and the risk of tardive dyskinesia led to several studies that focused on methods for treating patients with the lowest effective maintenance dose. A number of investigators (19, 805–807) have studied gradual reductions in the amounts of medication given to stabilized patients until the medications are completely discontinued. Each patient was followed closely until there were signs of the beginning of a relapse. At that time, the patient's medication was reinstituted. To make this strategy work, patients and their families were trained to detect the early signs of impending psychotic breakdown. This approach used antipsychotic medications only intermittently to target symptom exacerbations and to avert anticipated exacerbations. Studies of the efficacy of this "targeted medication approach" have produced mixed results, and this approach is not recommended because of the substantial increase in the risk of relapse (19, 219, 805, 806).

Another strategy involves using much lower doses of a long-acting injectable first-generation antipsychotic than are usually prescribed. Several groups have compared low doses to moderate and high doses of fluphenazine decanoate. Initially, studies found that patients receiving very low doses (mean=2.5 mg every 2 weeks) were significantly more likely to relapse over the course of 1 year than were patients receiving standard doses (12.5–50.0 mg every 2 weeks) (56% versus 7%) (794). A subsequent study demonstrated that patients given a slightly higher dose (2.5–10.0 mg every 2 weeks) showed a nonsignificant difference in relapse after 1 year, compared with patients given standard doses (24% versus 14%) (808). Another study found no significant difference in relapse after 1 year between patients who received low doses (mean=5 mg every 2 weeks) and those who received standard doses (25–50 mg every 2 weeks) but did detect a significant difference in relapse rates after 2 years between the low-dose group and the standard-dose group (70% versus 35%) (793). Other studies, however, reported no difference in relapse rates after 2 years between patients who received low doses (mean=3.8 mg every 2 weeks) and those who received standard doses (25 mg every 2 weeks) (809). However, Schooler et al. (219) found that low-dose fluphenazine decanoate (2.5–10 mg every 2 weeks) increased the relapse rate and the use of rescue medication, compared to a continuous moderate dose (12.5–50 mg every 2 weeks). Collectively, these studies indicate that doses of fluphenazine decanoate as low as 5–10 mg every 2 weeks have been shown to be clinically effective, and some patients may respond to even lower doses, but the risk of relapse can increase significantly with these lower doses. However, consideration should be given to judicious reduction in the long-acting injectable dose over time, especially for patients with adverse side effects, in order to evaluate the optimal dose.

In considering the use of low-dose, long-acting injectable first-generation antipsychotics, the beneficial side effect profile associated with the use of lower doses should also be taken into account. Kane et al. (794) found that low-dose users had fewer early signs of tardive dyskinesia after 1 year than did standard-dose users. In a study by Marder et al. (793), lower doses were associated with significantly less discomfort (as measured with the SCL-90-R [810]), psychomotor retardation, and akathisia after 2 years. Hogarty et al. (809) reported that patients receiving minimal doses had less muscle rigidity, akathisia, and other side effects at 1 year and had greater improvements in instrumental and interpersonal role performances at 2 years.

First-generation antipsychotic medications have a very high therapeutic index for life-threatening side effects (780). Consequently, overdoses rarely are fatal unless they are complicated by preexisting medical problems or concurrent ingestion of alcohol or other medications. Symptoms of overdose are generally characterized by exaggerations of the adverse effects, with respiratory depression and hypotension presenting the greatest danger. Treatment is symptomatic and supportive and includes 1) ensuring airway patency and maintenance of respiration;

- 2) orally administering activated charcoal to decrease absorption and considering gastric lavage;
- 3) maintaining blood pressure with intravenous fluids and vasopressor agents; and 4) administering anticholinergic agents if needed to counteract extrapyramidal signs (811).

Medication interactions

A number of medication interactions can have clinically important effects for patients who are treated with antipsychotic medications (48, 49, 812). Certain heterocyclic antidepressants, most SSRIs, some beta-blockers, and cimetidine may increase antipsychotic plasma levels and increase side effects. On the other hand, barbiturates and carbamazepine decrease plasma levels through effects on cytochrome P450 enzymes.

b) Second-generation agents

The medications discussed in this section are referred to as second-generation antipsychotics primarily because the doses that are effective against the psychopathology of schizophrenia do not cause extrapyramidal side effects. Their therapeutic effects are attributed to central antagonism of both serotonin and dopamine receptors and also possibly to relatively loose binding to D₂ receptors (813–815).

Clozapine

Clozapine is a second-generation antipsychotic with antagonist activity at numerous receptors, including dopamine (D₁, D₂, D₃, D₄, D₅), serotonin (5-HT_{1A}, 5-HT_{2A}, 5-HT_{2C}), muscarinic (M₁, M₂, M₃, M₅), α_1 - and α_2 -adrenergic, and histamine (H₁) receptors (816–818). Clozapine is an agonist at muscarinic (M₄) receptors (819). Clozapine is also distinguished from other antipsychotic medications by its greater efficacy in treating positive symptoms in patients with treatment-resistant illness and by the absence of extrapyramidal side effects. However, it is associated with several serious and potentially fatal adverse effects, including agranulocytosis in 0.5%–1% of patients, seizures in about 2% of patients, and rare occurrences of myocarditis and cardiomyopathy.

Efficacy of clozapine

Clozapine has demonstrated superior efficacy for the treatment of general psychopathology in patients with treatment-resistant schizophrenia, compared to the first-generation antipsychotics haloperidol and chlorpromazine in six of eight published double-blind randomized trials (313, 314, 769, 820–824). A meta-analysis pooled the results of five of these studies that categorically defined subjects as “responders” based on clinically meaningful improvement in psychopathology and found that clozapine-treated patients were 2.5 times more likely to meet response criteria than those treated with a first-generation antipsychotic ($p=0.001$) (87). Clozapine also has demonstrated efficacy in reducing the frequency of suicidal ideation and suicide attempts in a randomized 2-year study of 980 patients with schizophrenia or schizoaffective disorder at high risk for suicide because of previous or current suicidal ideation or behavior (55). In this study patients were randomly assigned to receive either clozapine or olanzapine. Fewer patients who received clozapine attempted suicide (34 subjects), compared to patients who received olanzapine (55 subjects) ($p=0.03$), and a 24% reduction in risk of suicidal behaviors was found. In light of this evidence, clozapine should be preferentially considered for patients with a history of chronic and persistent suicidal ideation or behaviors. In addition, several studies suggest that clozapine may reduce the severity of hostility and aggression in patients with treatment-resistant symptoms (57, 314, 440, 821, 825–827). Open-label and double-blind studies of clozapine have produced inconsistent results with regard to effects on cognition, with some measures showing improvement and others showing no changes or even decrements in performance (828–840).

There is also preliminary evidence from open-label observational studies that clozapine may reduce risk of relapse in patients with treatment-resistant schizophrenia (841–845). Although these studies are encouraging, they are limited since some included only clozapine responders,

while others did not include a comparison group. These studies are supported by the results of a large randomized open trial, in which significantly fewer hospital readmissions were observed for patients treated with clozapine, compared to those treated with usual care in a state hospital system over a 2-year period (822). The only double-blind study that measured readmission rates over a 1-year period failed to show a difference between haloperidol and clozapine for patients with treatment-resistant schizophrenia, although patients treated with clozapine stayed fewer days in the hospital (769). Taken together, the evidence is suggestive that treatment with clozapine is associated with reduced rates of relapse and rehospitalization in patients with treatment-resistant schizophrenia.

Studies of other populations, including patients with first-episode schizophrenia (846) and patients with treatment-responsive schizophrenia or schizoaffective disorder (847), demonstrate only limited or inconsistent superior efficacy for clozapine. In addition, studies comparing clozapine to other second-generation antipsychotics generally show comparable efficacy of clozapine with other second-generation antipsychotics (87, 381, 820, 848). However, since relatively low doses of clozapine were used in these studies, the results must be interpreted with caution.

In summary, a clozapine trial should be considered for patients who have shown a poor response to other antipsychotic medications. Clozapine may also be considered for patients with a history of chronic and persistent suicidal ideation or behaviors. In addition, clozapine may also be considered for patients with persistent hostility and aggression, given that superior efficacy of clozapine has been demonstrated in these patient populations.

Shared side effects of clozapine

Clozapine is associated with a very low risk of acute and chronic extrapyramidal side effects, a high risk of sedation, a high risk of orthostatic hypotension and tachycardia, a low risk of cardiac conduction abnormalities, a high risk of anticholinergic effects, a high risk of weight gain and metabolic abnormalities, and a low risk of prolactin elevation and sexual side effects. Neuroleptic malignant syndrome occurs rarely with clozapine. Details on the nature and management of each of these side effects are provided in Section V.A.1.c, “Shared Side Effects of Antipsychotic Medications.”

Other side effects of clozapine

Sialorrhea and drooling occur relatively frequently and are most likely due to decreased saliva clearance related to impaired swallowing mechanisms (849), or possibly as a result of muscarinic cholinergic antagonist activity at the M₄ receptor or to α -adrenergic agonist activity (850). Interventions include use of a towel on the pillow at night to reduce discomfort. While there is little systematic information about pharmacological interventions, case reports suggest potential improvement with antimuscarinic agents and α receptor agonists (851–853). However, since clozapine also exhibits significant anticholinergic properties, use of agents with added anticholinergic effects must be approached with extreme caution to avoid potential adverse effects such as constipation or cognitive impairment.

Fever (>38°C) may occur during the first few weeks of treatment (854, 855). Generally a clozapine-associated fever is self-limiting and responds to supportive measures. However, fever is a symptom of neuroleptic malignant syndrome, agranulocytosis, and cardiomyopathy, and the presence of fever warrants evaluation for these potentially life-threatening complications of clozapine treatment.

The risk of agranulocytosis (defined as an absolute neutrophil count less than 500/mm³) has been estimated at 1.3% of patients per year of treatment with clozapine (99, 854, 856). The risk is highest in the first 6 months of treatment, and therefore weekly WBC and neutrophil monitoring is required. After 6 months, monitoring may occur every 2 weeks, as the risk of agranulocytosis appears to diminish considerably (an estimated rate of three cases per 1,000 patients). WBC counts must remain above 3000/mm³ during clozapine treatment, and absolute neutrophil counts must remain above 1500/mm³.

In the United States through 1989 there were 149 cases of agranulocytosis, with 48 (32%) fatalities. With the advent of systematic monitoring, fatalities have been greatly reduced (857–859). Between 1989 and 1997, among the 150,409 patients treated with clozapine who were included in the patient registry maintained by the U.S. manufacturer of the drug, 585 cases of agranulocytosis, with nine fatalities, were reported. Thus, awareness of agranulocytosis and the monitoring system have decreased the reported rate of clozapine-induced agranulocytosis to less than 0.5%.

Reports of myocarditis, with resultant cardiomyopathy and fatal heart failure, associated with clozapine use suggest a 17- to 322-fold elevation in risk in clozapine-treated patients. The absolute risk is estimated to range from 1 per 500 treated patients (860) to 1 per 10,000 treated patients (861). An immune mechanism mediated by immunoglobulin E antibodies is suspected because of reports of associated eosinophilia. Most but not all cases have occurred early in treatment, suggesting that the risk of myocarditis may be less after the first few months.

Clozapine is also associated with a dose-related risk of seizures (854). The overall seizure rate is 2.8%; with low-dose treatment (<300 mg/day) the risk is 1%, with medium doses (300–599 mg/day) the risk is 2.7%, and with high doses (>599 mg/day) the risk is 4.4%. The seizure risk for clozapine is also related to rapid increases in dose. Therefore, the rate of titration should not exceed the guidelines described in the subsequent section on implementation of treatment with clozapine.

In addition, there are case reports associating clozapine treatment with several other rare but potentially serious adverse events, including pancreatitis (862, 863), deep vein thrombosis (864, 865), pulmonary embolism, hepatitis (866, 867), and eosinophilia (863). Because of the small number of reports, the causal relationship with clozapine is unclear.

Implementation of treatment with clozapine

Before initiating treatment with clozapine, a complete blood count (CBC) with differential should be performed and the patient's general and cardiovascular health status should be evaluated. The cardiovascular side effects of clozapine should be considered in planning treatment for patients with preexisting heart disease. Treatment should be initiated at a low dose (12.5–25 mg once or twice daily) and increased gradually (by no more than 25–50 mg/day) as tolerated until a target dose is reached. Because of the risk of marked hypotension, sedation, and seizures with rapid dose escalation, dose titration should not occur more rapidly. During dose titration the patient's cardiovascular status, including orthostatic pulse, blood pressure, and subjective complaints of dizziness, should be monitored. Since the side effects of clozapine in the initial and dose-adjustment phases may be severe in some patients, admission to the hospital may be justifiable (e.g., for unstable patients who require rapid dose increases to a therapeutic level, patients with a limited social support system, or patients prone to orthostatic hypotension or seizures).

Adequate safety monitoring during treatment is important to minimize the risk of adverse events. The clozapine package label states that WBC and neutrophil counts should be evaluated before treatment is initiated, weekly during the first 6 months of treatment and at least every 2 weeks after 6 months of treatment (854). Clozapine treatment should not be initiated if the initial WBC count is $<3500/\text{mm}^3$, if the patient has a history of a myeloproliferative disorder, or if the patient has a history of clozapine-induced agranulocytosis or granulocytopenia.

With maintenance treatment, patients should be advised to report any sign of infection immediately (e.g., sore throat, fever, weakness, lethargy). A WBC count $<2000/\text{mm}^3$ or absolute neutrophil count (ANC) $<1000/\text{mm}^3$ indicates impending or actual agranulocytosis, and the clinician should stop clozapine treatment immediately, check WBC and differential counts daily, monitor for signs of infection, and consider bone marrow aspiration and protective isolation if granulopoiesis is deficient. A WBC count of $2000\text{--}3000/\text{mm}^3$ or ANC of $1000\text{--}1500/\text{mm}^3$ indicates high risk of or impending agranulocytosis, and the clinician should stop clozapine

treatment immediately, check the WBC and differential counts daily, and monitor for signs of infection. Clozapine may be resumed if no infection is present, the WBC count rises to >3000 , and the ANC is >1500 (resume checking WBC count twice a week until it is >3500). If the WBC count is $3000\text{--}3500/\text{mm}^3$, if it falls to $3000/\text{mm}^3$ over 1–3 weeks, or if immature WBC forms are present, repeat the WBC count with a differential count. If the subsequent WBC count is $3000\text{--}3500/\text{mm}^3$ and the ANC is $>1500/\text{mm}^3$, repeat the WBC count with a differential count twice a week until the WBC count is $>3500/\text{mm}^3$.

Agranulocytosis is usually reversible if clozapine is discontinued immediately (868). When agranulocytosis develops, clozapine should be immediately discontinued, and patients should be given intensive treatment for the secondary complications, e.g., sepsis. Granulocyte colony stimulating factor has been used to accelerate granulopoietic function and shorten recovery time (869). Lithium has also been considered as a possible treatment for leukopenia or to prevent the development of agranulocytosis in patients who may be susceptible to this adverse effect (870, 871).

Although there have been reports of successful clozapine rechallenge after leukopenia, the risk of recurrence remains high (872). A rechallenge with clozapine should not be undertaken in patients with confirmed cases of agranulocytosis ($\text{ANC} < 500/\text{mm}^3$), as recurrence is almost certain (872). Clinically, rechallenge should only be considered for patients whose WBC count remained greater than $2000/\text{mm}^3$, whose absolute neutrophil count remained greater than $1500/\text{mm}^3$, and for whom trials with multiple other antipsychotics had failed but a good clinical response to clozapine was shown.

In addition, patients should be monitored for weight gain, glucose abnormalities, and hyperlipidemias that may occur during treatment with clozapine. Table 1 outlines suggested monitoring and clinical management of such adverse effects. Patients should also be monitored for other potentially life-threatening adverse effects of clozapine, including fever and other signs of myocarditis. Patients should be advised to report any signs of myocarditis (e.g., fever, fatigue, chest pain, palpitations, tachycardia, respiratory distress, peripheral edema). Immediate clinical evaluation is warranted, and a cardiovascular evaluation is needed if these symptoms are not explained by other causes. A cardiac evaluation is thus recommended for clozapine-treated patients who experience unexplained fever, fatigue, chest pain, palpitations, tachycardia, hypotension, narrowed pulse pressure, respiratory distress, peripheral edema, ST-T wave abnormalities or arrhythmias as shown by ECG, or hypereosinophilia as shown by a CBC, especially if these symptoms are experienced during the first few months of treatment (873).

Controlled trials provide only limited guidance regarding the optimal dose of clozapine for schizophrenia. Since there have been no trials in which patients were randomly assigned to different doses of clozapine, the only available data are based on studies in which psychiatrists used what they considered the most effective dose. Fleischhacker et al. (874) reviewed 16 controlled trials from Europe and the United States. The mean dose from the European trials was 283.7 mg/day, and the U.S. mean was 444 mg/day. Plasma levels may help guide dosing, with studies suggesting that maximal clinical efficacy may be achieved when plasma levels of clozapine are between 200 and 400 ng/ml (typically associated with a dose of 300–400 mg/day) (875–878).

Although most patients whose symptoms respond to clozapine demonstrate maximal clinical improvement during the first 6–12 weeks of treatment, clinical benefits may continue to develop after 6–12 months (87, 879, 880). Twelve-week empirical trials of clozapine appear to be adequate to determine whether a patient is likely to respond to this medication (881, 882).

The elimination half-life of clozapine is approximately 12 hours, indicating that patients are likely to reach a steady-state plasma concentration after 2–3 days (883). Clozapine is metabolized primarily by the CYP1A2 enzyme. Other liver enzymes also contribute to clozapine metabolism, including CYP2C19, CYP2D6, and CYP3A4. Coadministration of drugs that inhibit cytochrome P450 enzymes (e.g., cimetidine, caffeine, erythromycin, fluvoxamine, fluoxetine, paroxetine, sertraline) may lead to a significant increase in clozapine plasma levels;

inducers of CYP1A2 (e.g., phenytoin, nicotine, rifampin) can significantly reduce clozapine levels. In particular, changes in smoking status may affect clozapine levels (500, 884). The concomitant use of medications such as carbamazepine can lower the WBC count and increase the potential danger of agranulocytosis; such medications should therefore be avoided. Some cases of respiratory or cardiac arrest have occurred among patients receiving benzodiazepines or other psychoactive medications concomitantly with clozapine. While no specific interaction between clozapine and benzodiazepines has been established, judicious use is advised when benzodiazepines or other psychotropic medications are administered with clozapine (885).

Risperidone

Risperidone is a second-generation antipsychotic with antagonist activity at dopamine (D_1 , D_2 , D_3 , D_4), serotonin ($5-HT_{1A}$, $5-HT_{2A}$, $5-HT_{2C}$), α_1 - and α_2 -adrenergic, and histamine (H_1) receptors (816, 817).

Efficacy of risperidone

There are numerous published clinical trials comparing the acute efficacy of risperidone with placebo, first-generation antipsychotics (haloperidol or perphenazine), and other second-generation antipsychotics in patients with schizophrenia, schizoaffective disorder, and schizophreniform disorder. Placebo-controlled studies consistently demonstrate that for acutely relapsed patients, risperidone is efficacious in the treatment of global psychopathology and the positive symptoms of schizophrenia (886–888), as well as in increasing the likelihood of clinical response (e.g., $\geq 20\%$ improvement on rating scales of global psychopathology). There is less consistent evidence that negative symptoms improve with risperidone treatment, as significant improvement compared with placebo was not found at all doses of risperidone (886, 887, 889). It is likely that the improvements in negative symptoms are due to the decreased likelihood of secondary negative symptoms (e.g., related to parkinsonism or to psychosis). Active-comparator-controlled studies demonstrate comparable or occasionally greater likelihood of clinical response and improvement of global psychopathology and positive symptoms with risperidone, compared with haloperidol (886, 887, 890–894) and perphenazine (895). Meta-analyses of these studies suggest that risperidone may have modestly better efficacy, compared with haloperidol and perphenazine, in decreasing positive symptoms (889, 896, 897) and global psychopathology and increasing the likelihood of response (82, 86, 88, 89, 889, 898–900). These studies also show less consistent evidence that negative symptoms improve with risperidone treatment, with any improvements possibly due to the decreased likelihood of secondary negative symptoms or resulting from comparison with high doses of first-generation antipsychotic agents. One study (271) found risperidone to have similar efficacy to haloperidol in the acute treatment of first-episode schizophrenia, as measured by greater response rates, improvement in global psychopathology, and improvement in positive symptoms.

Several studies have examined the efficacy of risperidone in the treatment of neurocognitive deficits of schizophrenia. Generally, these studies find that global measures of neurocognitive function improved with risperidone, although the magnitude of improvement was similar to that observed with haloperidol in two studies (901, 902). However, in one 14-week trial that included 101 patients, treatment with risperidone resulted in statistically significantly greater improvement in global neurocognition, compared with haloperidol (838). The clinical significance of this effect, however, is unclear. Thus, further investigation is required to determine the magnitude and clinical significance of risperidone effects on neurocognition.

Several studies have examined the efficacy of risperidone in patients with treatment-resistant schizophrenia. In an 8-week double-blind study, risperidone (mean dose=7.5 mg/day, N=34) and haloperidol (mean dose=19.4 mg/day, N=33) demonstrated similar efficacy in the treatment of global psychopathology (903). In a 14-week double-blind trial, treatment with risperidone (mean dose=11.6 mg/day, N=41) resulted in significant improvement in global psychopathology scores

but not in positive and negative symptom subscale scores, for which the effects of risperidone were comparable to those of haloperidol (mean dose=25.7 mg/day, N=37) (820). In a 12-week double-blind study, 6 mg/day of risperidone (N=39) was superior to 20 mg/day of haloperidol (N=39) in the treatment of global psychopathology and negative symptoms (904).

Studies comparing risperidone to other second-generation antipsychotics in the treatment of acute episodes have generally found similar efficacy for treatment of psychopathology both in patients with treatment-responsive illness and in those with treatment-resistant illness (848, 902, 905–907).

Compared with haloperidol, risperidone has demonstrated superior efficacy in the prevention of relapse in the maintenance phase of treatment. In a study of 397 stable patients with DSM-IV schizophrenia or schizoaffective disorder, haloperidol-treated patients (mean dose=11.7 mg/day) were 1.93 times more likely to relapse than risperidone-treated patients (mean dose=4.9 mg/day) during the 1-year follow-up period (382). In this study, the risperidone-treated patients also had significantly greater improvement in global psychopathology, compared to the haloperidol-treated patients.

Shared side effects of risperidone

Risperidone is associated with a low risk of sedation, a low to moderate risk of extrapyramidal side effects, a moderate risk of orthostatic hypotension and tachycardia, a low risk of anticholinergic effects, a moderate risk of weight gain and metabolic abnormalities, and a high risk of prolactin elevation and sexual side effects. Risperidone slightly alters cardiac conduction but not to a clinically meaningful extent. Neuroleptic malignant syndrome occurs rarely with risperidone. Details on the nature and management of each of these side effects are provided in Section V.A.1.c, “Shared Side Effects of Antipsychotic Medications.”

Other side effects of risperidone

Clinical trial data suggest a small increase in the risk of stroke in patients with dementia treated with risperidone, compared with placebo-treated patients. Thus, dementia patients treated with risperidone should be carefully monitored for signs and symptoms of stroke (908). Similar increases in risk of stroke have not been reported in elderly risperidone-treated patients with schizophrenia who do not have dementia.

Implementation of treatment with risperidone

While the original efficacy studies comparing different doses of risperidone indicated optimal effectiveness at doses of around 6 mg/day, clinical investigations and subsequent studies indicate that for most adult patients optimal doses are between 2 and 6 mg/day, with a minority of patients requiring higher doses. Higher doses often lead to extrapyramidal side effects without greater effectiveness. Patients who develop parkinsonian symptoms are probably receiving too high a dose, and dose reduction is required for these patients.

During the titration and early treatment phase, risperidone-treated patients should be monitored for extrapyramidal side effects, orthostatic hypotension and reflex tachycardia, side effects associated with prolactin elevation, and sedation. In addition, patients should be monitored for weight gain, glucose abnormalities, and hyperlipidemias that may occur during treatment with risperidone. Table 1 outlines suggested strategies for monitoring and clinical management of such adverse effects. Elderly patients, particularly those with dementia, should be monitored for signs and symptoms of stroke.

Risperidone's effectiveness appears to be related to actions of both the parent compound and a major metabolite, 9-hydroxyrisperidone (909). They are therapeutically equipotent, have similar types of pharmacological activity, and, therefore, probably produce similar therapeutic effects. Although risperidone itself has an elimination half-life of only 3 hours, its metabolite has an elimination half-life of about 24 hours. As a result, most patients can be managed with

a once-daily dose of risperidone. However, since risperidone can cause orthostatic hypotension, twice-daily dosing may be useful during the titration phase and for patients who may be vulnerable to orthostatic changes, such as elderly patients.

Risperidone is primarily metabolized by the hepatic CYP2D6 enzyme into the 9-hydroxyrisperidone metabolite (910). 9-Hydroxyrisperidone may also be metabolized by the CYP3A4 liver enzyme (500, 911). As a result, inducers of CYP3A4 may decrease risperidone blood levels and thus reduce therapeutic efficacy (912). In contrast, inhibitors of CYP2D6 and CYP3A4 may raise blood levels of risperidone and its active metabolite 9-hydroxyrisperidone and thus produce increased side effects, such as extrapyramidal side effects (913). In 5%–8% of Caucasians and 2%–5% of African Americans and Asians, the activity of the CYP2D6 enzyme is very low or absent. In poor metabolizers, the half-life is 17 hours for risperidone and 30 hours for 9-hydroxyrisperidone, compared to half-lives in extensive metabolizers of 3 hours for risperidone and 21 hours for 9-hydroxyrisperidone. Thus, the relative proportion of risperidone to 9-hydroxyrisperidone will be higher in patients who are slow metabolizers. In addition, drugs that inhibit the CYP2D6 enzyme (e.g., quinidine) will effectively turn extensive metabolizers into poor metabolizers. In terms of CYP liver enzymes other than CYP3A4 and CYP2D6, risperidone does not tend to produce significant inhibition or induction.

Olanzapine

Olanzapine is a second-generation antipsychotic with antagonist activity at dopamine (D_1 , D_2 , D_3 , D_4), serotonin ($5-HT_{2A}$, $5-HT_{2C}$), muscarinic (M_1 , M_2 , M_3 , M_5), α_1 -adrenergic, and histamine (H_1) receptors (818, 914).

Efficacy of olanzapine

There are several published clinical trials comparing the acute efficacy of olanzapine with placebo, first-generation antipsychotics (haloperidol or chlorpromazine), and other second-generation antipsychotics in patients with schizophrenia, schizoaffective disorder, and schizophreniform disorder. Placebo-controlled studies consistently demonstrate that in acutely relapsed patients olanzapine is efficacious in treating global psychopathology and the positive symptoms of schizophrenia, as well as in increasing the likelihood of clinical response (e.g., $\geq 20\%$ improvement on rating scales of global psychopathology) (915–917). The evidence that negative symptoms improve with olanzapine treatment, compared with placebo, is less consistently found across doses of the drug (915–917). It is likely that any improvements in negative symptoms in these studies are due to decreased likelihood of secondary negative symptoms (e.g., related to parkinsonism or to psychosis) rather than to direct effects on primary negative symptoms (323). Active-comparator-controlled studies demonstrate similar or occasionally greater likelihood of clinical response and greater improvement of global psychopathology and positive and negative symptoms with olanzapine, compared to haloperidol (279, 319, 916–920). Meta-analyses of these studies suggest that olanzapine may have modestly better efficacy, compared with haloperidol, in the treatment of global psychopathology and positive and negative symptoms (921) and in increasing the likelihood of response (82, 86, 88). Effects on hostility are mixed, with one study (921) showing greater improvement in hostility with olanzapine than with haloperidol, and another study finding no difference in hostility response (440). In patients with a first episode of schizophrenia, one study (a subanalysis of a Lilly olanzapine database) found significantly greater improvement in global psychopathology, positive and negative symptoms, and response rate after a 6-week trial of olanzapine, compared to haloperidol (272). A second study found that a significantly larger proportion of olanzapine-treated patients, compared with haloperidol-treated patients, remained in the trial and completed the first 12 weeks of treatment (279). In addition, the study found that the olanzapine-treated patients had slight but significant improvements in global psychopathology and negative symptoms and were more likely to meet the response criteria, although this difference only approached significance ($p=0.06$).

Four studies have examined the efficacy of olanzapine in the treatment of neurocognitive deficits of schizophrenia. Two of these studies found significant improvement in neurocognition as measured by a global index in olanzapine-treated patients, compared to haloperidol-treated patients (838, 902). One 12-week analysis of treatment effects in first-episode patients found significant improvement with olanzapine, compared to haloperidol, in global neurocognition assessed with a measure derived from a principal-component analysis, but the difference only approached significance when an empirically derived a priori measure of global neurocognition was used (922). The fourth study did not find differences between haloperidol and olanzapine in effects on global neurocognition (923). Olanzapine significantly improved motor function (838, 902), verbal fluency, nonverbal fluency and construction, immediate recall (902), general executive function (838, 923), and perceptual function and attention (838). Although a relatively consistent finding is that olanzapine has beneficial effects on neurocognition in schizophrenia, findings for the specific domains affected and the clinical significance of these effects are less clear. Further study is needed to determine the magnitude and clinical significance of the effects of olanzapine on neurocognition.

Several studies have examined the efficacy of olanzapine in patients with treatment-resistant illness (i.e., patients who have shown little or no response to adequate trials of other antipsychotics). In an 8-week double-blind study, 25 mg/day of olanzapine (N=42) and 1200 mg/day of chlorpromazine (N=39) demonstrated similar efficacy in the treatment of global psychopathology (924). In a 14-week double-blind trial, treatment with a mean dose of 30.4 mg/day of olanzapine (N=39) resulted in significantly greater improvement in global psychopathology and negative symptoms, compared with a mean dose of 25.7 mg/day of haloperidol (N=37) (820). A third study that used a Lilly clinical trial database to retrospectively identify patients without response to first-generation antipsychotics found that olanzapine-treated patients, compared to haloperidol-treated patients, had significantly greater improvements in global psychopathology and positive, negative, and mood symptoms; higher response rates; and higher completion rates (925). Although higher doses of olanzapine (doses up to 60 mg/day) are being used clinically for patients with treatment-resistant illness, current evidence of improved efficacy at higher doses is inconclusive (820, 926, 927).

Studies comparing olanzapine to other second-generation antipsychotics in the treatment of acute episodes have generally found similar efficacy for treatment of psychopathology both in patients with treatment-responsive symptoms and in those with treatment-resistant symptoms (381, 820, 905, 906), with some exceptions in which olanzapine was found to be superior (820, 902).

In terms of treatment during the stabilization and stable phases, analysis of data from the double-blind extension phase of 6-week acute treatment trials suggests that olanzapine may reduce the risk of relapse, compared to haloperidol. Pooling data across three studies, the investigators found that 19.7% of olanzapine-treated patients relapsed during the 1-year follow-up period, compared to 28% of haloperidol-treated patients ($p<0.04$) (928).

Shared side effects of olanzapine

Olanzapine is associated with a low risk of extrapyramidal side effects, a low risk of sedation, a low risk of orthostatic hypotension and tachycardia, a low risk of cardiac conduction abnormalities, a moderate risk of anticholinergic effects, a high risk of weight gain and metabolic abnormalities, and a low risk of prolactin elevation and sexual side effects. Neuroleptic malignant syndrome occurs rarely with olanzapine. Details on the nature and management of each of these side effects are provided in Section V.A.1.c, “Shared Side Effects of Antipsychotic Medications.”

Implementation of treatment with olanzapine

Olanzapine is an effective antipsychotic when administered in doses of 10–20 mg/day in the acute phase of schizophrenia, although higher doses, up to 60 mg/day, have been reported to be used for patients with treatment-resistant schizophrenia (820, 926, 927). With the possible exception of akathisia, parkinsonian symptoms are infrequent at any dose of olanzapine.

During the titration and early treatment phase olanzapine-treated patients should be monitored for extrapyramidal side effects, orthostatic hypotension and reflex tachycardia, and sedation. Orthostatic hypotension may be more likely if benzodiazepines are coadministered (929). Evening administration may improve tolerance of the sedation that is common early in treatment. In addition, patients should be monitored for weight gain, glucose abnormalities, and hyperlipidemias that may occur during treatment with olanzapine. Table 1 outlines suggested monitoring and clinical management of such adverse effects.

Patients are typically managed with a single daily dose of olanzapine since the elimination half-life of olanzapine is 33 hours (ranging from 21 to 54 hours) (929). Olanzapine is primarily metabolized by the hepatic CYP1A2 enzyme, with a minor metabolic pathway involving the CYP2D6 enzyme. Inducers of the CYP1A2 enzyme (such as tobacco use) may reduce olanzapine plasma levels, and so changes in smoking status may affect efficacy and side effects at a given dose (500). There is some evidence to suggest differential metabolism of olanzapine by gender, with women exhibiting higher plasma concentrations than men at equivalent doses (509).

Quetiapine

Quetiapine is a second-generation antipsychotic with antagonist activity at dopamine (D₁, D₂), serotonin (5-HT_{1A}, 5-HT_{2A}, 5-HT_{2C}), α_1 -adrenergic, and histamine (H₁) receptors (818, 930).

Efficacy of quetiapine

There are several published clinical trials comparing the acute efficacy of quetiapine with that of placebo, first-generation antipsychotics (haloperidol or chlorpromazine), and other second-generation antipsychotics in patients with schizophrenia, schizoaffective disorder, and schizophreniform disorder. Placebo-controlled studies consistently demonstrate that in acutely relapsed patients quetiapine is efficacious in the treatment of global psychopathology, in improving the likelihood of clinical response (e.g., $\geq 20\%$ improvement on rating scales of global psychopathology), and in improving the positive symptoms of schizophrenia (318, 931, 932). The evidence that negative symptoms improve with quetiapine treatment is less clear, as significant improvement with quetiapine, compared with placebo, is less consistently found across different doses of the drug and different studies (318, 931, 932). It is likely that the improvements in negative symptoms in these studies are due to decreased likelihood of secondary negative symptoms (e.g., related to parkinsonism or to psychosis) rather than to direct effects on primary negative symptoms. Active-comparator-controlled studies demonstrate comparable or occasionally greater improvement of global psychopathology and positive and negative symptoms, as well as an increased likelihood of clinical response with quetiapine, compared to haloperidol or chlorpromazine (933–935). Meta-analyses of these studies suggest that the efficacy of quetiapine is similar to that of first-generation antipsychotics (82, 86, 88).

In terms of relapse prevention, one 4-month randomized, open-label study compared the efficacy of quetiapine (mean dose=254 mg/day, N=553) to that of risperidone (mean dose=4.4 mg/day, N=175) (907). This study found both antipsychotics to have similar effects on global psychopathology and positive symptoms and negative symptoms, with marginally significant greater improvement in depressive symptoms in the quetiapine-treated patients. While this study lends preliminary evidence for the efficacy of quetiapine in preventing relapse, further studies using blinded methods are needed before definitive conclusions can be made.

One study compared the efficacy of 600 mg/day of quetiapine (N=143) to that of 20 mg/day of haloperidol (N=145) in patients with treatment-resistant illness and found that a significantly greater proportion of the quetiapine-treated patients met the response criteria (52%, compared to 38% of the haloperidol-treated patients) (936). However, the mean changes in global psychopathology, positive symptoms, and negative symptoms were similar for both groups.

Two studies found beneficial effects on neurocognition for quetiapine, compared to first-generation antipsychotics. In a 6-month randomized, double-blind study, significant improvement in global cognition, verbal reasoning and fluency, and immediate recall was found for subjects treated with 300–600 mg/day of quetiapine (N=13) but not for subjects treated with 10–20 mg/day of haloperidol (N=12) (937). Similarly, in a 24-week double-blind, randomized study, significantly greater improvement in global cognition, executive function, attention, and verbal memory was found for subjects treated with 600 mg/day of quetiapine, compared to subjects treated with 12 mg/day of haloperidol (938).

Shared side effects of quetiapine

Quetiapine is associated with a very low risk of extrapyramidal side effects, a high risk of sedation, a moderate risk of orthostatic hypotension and tachycardia, a low risk of cardiac conduction abnormalities, a low risk of anticholinergic effects, a moderate risk of weight gain and metabolic abnormalities, and a low risk of prolactin elevation and sexual side effects. Neuroleptic malignant syndrome occurs rarely with quetiapine. Details on the nature and management of each of these side effects are provided in Section V.A.1.c, “Shared Side Effects of Antipsychotic Medications.”

Other side effects of quetiapine

Preclinical studies in beagles found associations between quetiapine and increased risk of cataracts, prompting the FDA to suggest routine screening ophthalmological examinations before and every 6 months during quetiapine treatment. This risk has not been confirmed in humans, and there is no indication from postmarketing reporting of an association between increased cataract risk and quetiapine use (939).

Implementation of treatment with quetiapine

Quetiapine is an effective antipsychotic when administered in doses of 300–800 mg/day in the acute phase of schizophrenia. Evidence suggests that the higher doses in this range (and perhaps doses greater than 800 mg/day) may be more efficacious (318). Even at doses above 800 mg/day, there are virtually no extrapyramidal side effects, with the possible exception of akathisia. During the titration and early treatment phase, quetiapine-treated patients should be monitored for orthostatic hypotension, reflex tachycardia, and sedation. Patients are typically managed with twice-daily dosing of quetiapine, since the elimination half-life is 6 hours (940). However, uneven dosing with the larger dose given at bedtime may improve tolerance of the sedation that is common early in treatment. In addition, patients should be monitored for weight gain, glucose abnormalities, and hyperlipidemias, which may occur during treatment with quetiapine. Table 1 outlines suggested strategies for the monitoring and clinical management of such adverse effects. Quetiapine is primarily metabolized by the hepatic cytochrome P450 CYP3A4 enzyme. Metabolism of the drug is minimally altered in patients with renal disease, but it may be significantly altered in patients with liver disease. Smoking does not affect the metabolism of quetiapine (500, 940). However, coadministration of phenytoin with quetiapine has been demonstrated to increase the clearance of quetiapine up to fivefold (941). Similarly potent inducers of CYP3A4 are likely to produce similar decreases in quetiapine levels, which may lead to loss of therapeutic efficacy.

Ziprasidone

Ziprasidone is a second-generation antipsychotic with antagonist activity at dopamine (D₂), serotonin (5-HT_{2A}, 5-HT_{2C}, and 5-HT_{1B/1D}), α_1 -adrenergic, and histamine (H₁) receptors. In addition, ziprasidone has partial agonist activity at serotonin 5-HT_{1A} receptors and inhibits neuronal reuptake of serotonin and norepinephrine (942).

Efficacy of ziprasidone

There are several published clinical trials comparing the efficacy of ziprasidone with placebo and with first-generation antipsychotics in the acute treatment of patients with schizophrenia, schizoaffective disorder, and schizophreniform disorder. Placebo-controlled studies consistently demonstrate that in acutely relapsed patients ziprasidone is efficacious in the treatment of global psychopathology and the positive symptoms of schizophrenia, as well as in increasing the likelihood of clinical response (e.g., $\geq 20\%$ improvement on rating scales of global psychopathology) (943, 944). The evidence that negative symptoms improve with ziprasidone treatment is less clear, as significant improvement with ziprasidone, compared with placebo, is less consistently found across doses of drug and across studies (943–945). Active-comparator-controlled studies of ziprasidone compared with haloperidol demonstrate comparable improvement in positive and negative symptoms and in global psychopathology, as well as comparable likelihood of clinical response (945, 946). It is likely that the improvements in negative symptoms in these studies are due to a decreased likelihood of secondary negative symptoms (e.g., related to parkinsonism or to psychosis) rather than to direct effects on primary negative symptoms. However, in an additional placebo-controlled study of stable, residually symptomatic patients, the time course of improvement in negative symptoms was consistent with a therapeutic effect on primary negative symptoms (947). Nonetheless, this study was conducted with environmentally deprived persons who received more attention than usual by participating in the study, which may explain (in part) the observed improvements in negative symptoms.

One 52-week study demonstrated that ziprasidone is effective in reducing risk of relapse, compared with placebo, during the maintenance phase of treatment (947). Relapse risk was 43%, 35%, and 36% for patients receiving 40 mg/day, 80 mg/day, and 160 mg/day of ziprasidone, respectively, compared to 77% for placebo-treated patients.

Several studies have demonstrated the efficacy of intramuscular administration of ziprasidone for the treatment of acute agitation in relapsed patients with schizophrenia or schizoaffective disorder (76, 948, 949).

Shared side effects of ziprasidone

Ziprasidone is associated with a low risk of extrapyramidal side effects, a low risk of sedation, a low risk of orthostatic hypotension and tachycardia, a moderate risk of cardiac conduction abnormalities, a low risk of anticholinergic effects, a low risk of weight gain and metabolic abnormalities, and a low risk of prolactin elevation and sexual side effects. Neuroleptic malignant syndrome occurs rarely with ziprasidone. Details on the nature and management of each of these side effects are provided in Section V.A.1.c, “Shared Side Effects of Antipsychotic Medications.”

Other side effects of ziprasidone

While short-term clinical trials do not report insomnia as an adverse event with ziprasidone, there is some evidence from a longer-term outpatient study to suggest that stable outpatients whose medication is switched to ziprasidone may experience insomnia (945). This insomnia appears early in treatment, is typically transient, and most often responds to usual sedative-hypnotics (e.g., zolpidem, trazodone).

Implementation of treatment with ziprasidone

Ziprasidone is an effective antipsychotic when administered in doses of 80–200 mg/day in the acute phase of schizophrenia. There is emerging evidence that doses up to 320 mg/day may be safe, although there are no published data suggesting improved efficacy at high doses. Stable patients whose medication is switched to ziprasidone may report insomnia, which usually is transient and responsive to sedative-hypnotics.

Before treatment with ziprasidone is initiated in patients with preexisting cardiovascular disease and those who are at risk for electrolyte disturbances (e.g., patients taking diuretics and those with chronic diarrhea), the safety of using the medication should be evaluated. This evaluation should include laboratory assessment of electrolytes and an ECG. Preexisting prolonged QT syndrome, persistent findings of QTc interval >500 msec, history of arrhythmia, recent acute myocardial infarction, or uncompensated heart failure are contraindications to use of ziprasidone. The value of a screening ECG in apparently healthy persons to reliably detect congenital prolonged QT syndrome is not established and is of questionable utility, given the normal variability of the QT interval. During the maintenance phase of treatment, regular monitoring of electrolytes should be done for patients who are also treated with diuretics or who may be at risk for electrolyte disturbances. Patients should be monitored regularly for symptoms of possible arrhythmia, including dizziness, syncopal episodes, and palpitations. Patients with such symptoms should be referred for cardiovascular evaluation. Patients should also be warned about concomitant treatment with other drugs that also may affect the QT interval.

Patients are typically treated with twice-daily dosing of ziprasidone, since the elimination half-life is 7 hours, and steady state is reached after 1–3 days. Food increases the absorption of ziprasidone; under fasting conditions only 60% of ziprasidone will be absorbed. Two-thirds of ziprasidone is metabolized by aldehyde oxidase, and one-third by the cytochrome P450 system, primarily by the liver CYP3A4 enzyme, and to a lesser extent by CYP1A2 (950). Sex, age, smoking, and the presence of renal failure have not been found to affect the metabolism of ziprasidone, but liver disease potentially affects metabolism of the drug (951, 952). Ziprasidone has little effect on other liver enzyme systems and has not been found to affect the metabolism of other drugs.

Aripiprazole

Aripiprazole is pharmacologically distinct from other second-generation antipsychotic medications. It has partial agonist activity at dopamine (D₂) and serotonin (5-HT_{1A}) receptors and antagonist activity at dopamine (D₃), serotonin (5-HT_{2A}, 5-HT_{2C}, 5-HT₇), α_1 -adrenergic, and histamine (H₁) receptors. In addition, aripiprazole inhibits neuronal reuptake of serotonin to a modest extent (953, 954).

Efficacy of aripiprazole

There are several published clinical trials comparing the acute efficacy of aripiprazole with placebo and first-generation antipsychotics in patients with schizophrenia, schizoaffective disorder, and schizophreniform disorder. Placebo-controlled studies consistently demonstrate that in acutely relapsed patients, aripiprazole is efficacious in the treatment of global psychopathology, in improving the likelihood of clinical response (e.g., $\geq 20\%$ improvement on rating scales of global psychopathology), and in improving the positive symptoms of schizophrenia (955). The evidence that negative symptoms improve with aripiprazole treatment is less clear, as significant improvement with aripiprazole, compared with placebo, is less consistently found across doses of drug and studies (955). It is possible that the improvements in negative symptoms in these studies are due to decreased likelihood of secondary negative symptoms (e.g., related to parkinsonism or to psychosis) rather than to direct effects on primary negative symptoms. Active-comparator-controlled studies demonstrate comparable or occasionally greater improvement of global psychopathology and positive and negative symptoms, as well as an increased likelihood of clinical response, with aripiprazole, compared to haloperidol or chlorpromazine (955, 956).

Two studies have found aripiprazole effective in reducing risk of relapse. In a 26-week randomized, double-blind trial that included stable patients with schizophrenia or schizoaffective disorder, the time to relapse was significantly longer for patients treated with aripiprazole

(15 mg/day) than for those who received placebo, and a greater proportion of patients who received placebo (57%) than of aripiprazole-treated patients (34%) met the relapse criteria (957). In a 52-week randomized, double-blind trial that included patients with acute exacerbation of schizophrenia or schizoaffective disorder, the response rate and time to discontinuation for any reason were significantly greater for patients treated with aripiprazole (30 mg/day, N=647) than for those treated with haloperidol (10 mg/day, N=647) (unpublished 2003 manuscript of R.D. McQuade et al.). A greater proportion of aripiprazole-treated patients (43%) than of the haloperidol-treated patients (30%) completed the 52-week trial.

Shared side effects of aripiprazole

Aripiprazole is associated with a low risk of extrapyramidal side effects, a moderate risk of sedation, a low risk of orthostatic hypotension and tachycardia, a low risk of cardiac conduction abnormalities, a low risk of anticholinergic effects, a low risk of weight gain and metabolic abnormalities, and a low risk of prolactin elevation and sexual side effects. There have been no reports to date of neuroleptic malignant syndrome with aripiprazole. Details on the nature and management of each of these side effects are provided below in Section V.A.1.c, “Shared Side Effects of Antipsychotic Medications.”

Other side effects of aripiprazole

Aripiprazole received FDA approval for use in the treatment of schizophrenia in late 2002, and thus experience with the drug in clinical settings and knowledge of rare side effects are limited. Insomnia was not reported as an adverse event in treatment trials involving patients with acutely exacerbated symptoms (955, 956). Trials that included stable patients found transient insomnia and acute agitation early in treatment, but these side effects typically resolved after several weeks (955, 956). While there are no systematic studies, it is reasonable to treat aripiprazole-associated insomnia with sedative-hypnotics (e.g., zolpidem, trazodone, antihistamines) and agitation with benzodiazepines.

Implementation of treatment with aripiprazole

Aripiprazole is an effective antipsychotic when administered in doses of 10–30 mg/day in the acute phase of schizophrenia. With the possible exception of akathisia, parkinsonian symptoms rarely occur within the usual dose range.

Stable patients whose medication was switched to aripiprazole may report insomnia that usually is transient and responsive to sedative-hypnotics.

Patients are typically treated with once-daily dosing of aripiprazole since the elimination half-life is 75 hours (94 hours for the active metabolite dehydro-aripiprazole), and steady state is reached after 14 days. Aripiprazole is metabolized by the cytochrome P450 system, primarily by the liver enzymes CYP2D6 and CYP3A4 (958). Sex, age, smoking, and the presence of renal or hepatic failure have not been found to significantly affect the metabolism of aripiprazole (958). Aripiprazole has little effect on other liver enzyme systems and has not been found to affect the metabolism of other drugs.

c) Shared side effects of antipsychotic medications

This section provides information on the side effects that are shared among multiple antipsychotic medications.

(1) Neurological side effects

Neurological side effects of antipsychotic medications include acute extrapyramidal side effects such as medication-induced parkinsonism, dystonia, and akathisia; chronic extrapyramidal side effects such as tardive dyskinesia and tardive dystonia; and neuroleptic malignant syndrome.

(2) Extrapyramidal side effects

Extrapyramidal side effects are especially common in patients treated with the first-generation antipsychotics and occur to varying extents with several of the second-generation agents, especially higher doses of risperidone. Of the spectrum of adverse effects of first-generation antipsychotic medications, the neurological side effects are the most common and the most troublesome (959, 960). Extrapyramidal side effects can broadly be divided into acute and chronic categories. Acute extrapyramidal side effects are signs and symptoms that occur in the first days and weeks of antipsychotic medication administration, are dose dependent, and are reversible with medication dose reduction or discontinuation. The three types of acute extrapyramidal side effects are parkinsonism, dystonia, and akathisia (961–964). Chronic extrapyramidal side effects are signs and symptoms that occur after months and years of antipsychotic medication administration, are not clearly dose dependent, and may persist after medication discontinuation. Chronic extrapyramidal side effects include tardive dyskinesia and tardive dystonia. Detailed descriptions and differential diagnoses of the extrapyramidal side effect syndromes are provided in the “Medication-Induced Movement Disorders” section of DSM-IV-TR. More than 60% of patients who receive acute treatment with first-generation antipsychotic medications develop clinically significant extrapyramidal side effects in one form or another (959, 960, 965). Some patients may develop more than one form at the same time. Second-generation drugs as a group cause fewer or no extrapyramidal side effects, relative to first-generation drugs. Studies using multiple doses of risperidone (886, 887, 890) have shown that risperidone causes a dose-related increase in extrapyramidal side effects, with risk highest in doses greater than 6 mg/day (82, 899). In any individual patient, it is likely that the maximally clinically effective dose of risperidone is lower than the dose that will cause extrapyramidal side effects. Thus, first-line intervention for extrapyramidal side effects due to risperidone should be to gradually lower the dose until symptoms resolve. The other second-generation drugs cause few or no extrapyramidal side effects, with the possible exception of akathisia. However, younger patients (children, adolescents, and young adults) may be more prone to extrapyramidal side effects from second-generation medications (unpublished 2003 manuscript of L. Sikich et al.).

Medication-induced parkinsonism is characterized by the symptoms of idiopathic Parkinson's disease (rigidity, tremor, akinesia, and bradykinesia) and is the most common form of extrapyramidal side effect caused by first-generation antipsychotics (787, 964). These symptoms arise in the first days and weeks of antipsychotic medication administration and are dose dependent. Medication-induced parkinsonism generally resolves after discontinuation of antipsychotic medication, although some cases of persisting symptoms have been reported (966, 967).

Akinesia or bradykinesia is a feature of medication-induced parkinsonism that affects both motor and cognitive function. A patient with this condition appears to be slow moving, less responsive to the environment, apathetic, emotionally constricted, and cognitively slowed. This effect has been noted alone or with other extrapyramidal side effects in almost one-half of patients treated with first-generation antipsychotics. In very severe cases, it may mimic catatonia. Akinesia is subjectively unpleasant and may be associated with poor medication adherence (968, 969). Depressive symptoms can also be present in patients with akinesia, in which case the syndrome is termed “akinetic depression” (970, 971). Symptoms of medication-induced parkinsonism, in particular the cognitive and emotional features, need to be carefully distinguished from the negative symptoms of schizophrenia. Furthermore, it is noteworthy that patients may experience these emotional and cognitive symptoms of parkinsonism in the absence of detectable motor symptoms.

The first approach to treatment of parkinsonism associated with first-generation antipsychotics should be to lower the antipsychotic dose to the EPS threshold (dose where minimal rigidity is detectable in a physical examination), since studies indicate that doses above the EPS threshold are unlikely to yield further clinical benefits (94). If dose reduction does not sufficiently improve symptoms, then a switch to a second-generation antipsychotic should be

considered. Medications with anticholinergic (e.g., benztropine) or dopamine agonist (e.g., amantadine) activity often reduce the severity of parkinsonian symptoms. However, dopamine agonists carry a potential risk of exacerbating psychosis, and anticholinergic drugs can cause anticholinergic side effects. Thus, excessive doses and chronic use of these agents should be avoided or minimized (972, 973).

Acute dystonia is characterized by the spastic contraction of discrete muscle groups. Dystonic reactions occur in up to 10% of patients beginning therapy with high-potency first-generation antipsychotic agents. Although precise estimates of the incidence of dystonic reactions are not available, they appear to be less common with treatment with low-potency first-generation antipsychotic agents and relatively rare with second-generation antipsychotics. In addition to the use of high-potency medications, other risk factors for dystonic reactions include young age, male gender, high doses, and intramuscular administration. Dystonic reactions frequently arise after the first few doses of medication (90% occur within the first 3 days) (974). They can occur in various body regions but most commonly affect the muscles of the neck, larynx, eyes, and torso (963). The specific name of the reaction is derived from the specific anatomic region that is affected. Hence, the terms “torticollis,” “laryngospasm,” “oculogyric crisis,” and “opisthotonos” are used to describe dystonic reactions in specific body regions (975). These reactions are sudden in onset, are dramatic in appearance, and can cause patients great distress. For some patients, these conditions, e.g., laryngospasm, can be dangerous and even life-threatening.

Acute dystonic reactions respond dramatically to the administration of anticholinergic or antihistaminic medication. Parenteral administration will have a more rapid onset of action than oral administration. Short-term maintenance treatment with an oral regimen of anticholinergic antiparkinsonian medication prevents the recurrence of acute dystonic reactions.

Akathisia is characterized by somatic restlessness that is manifest subjectively and objectively in up to 30% of patients treated with first-generation antipsychotics (961, 970). Although precise estimates of the incidence of akathisia are not available, it appears to be less common with low-potency first-generation antipsychotics and even more infrequent with second-generation antipsychotic agents. Patients characteristically complain of an inner sensation of restlessness and an irresistible urge to move various parts of their bodies. Objectively, this appears as increased motor activity. With mild akathisia, the patient may control body movements; in more severe forms, the patient may rock from foot to foot while standing, pace, and have difficulty sitting still. Even in mild forms in which the patient is able to control most movements, this side effect is often extremely distressing to patients, is a frequent cause of nonadherence with antipsychotic treatment, and, if allowed to persist, can produce dysphoria. Case reports suggest that akathisia may also be a possible contributor to aggressive or suicidal behavior (409). Intervention includes dose reduction or switching to a second-generation antipsychotic with less risk of akathisia. In this regard, however, it is important to note that risperidone may cause akathisia at the higher end of the dose range (887).

Effective treatments for akathisia include centrally acting beta-blockers such as a low dose of propranolol (30–90 mg/day) (972, 976). When these medications are administered, blood pressure and pulse rate should be monitored with dose changes. Benzodiazepines such as lorazepam and clonazepam are also effective in decreasing symptoms of akathisia (977). In contrast, anticholinergic antiparkinsonian medications have limited efficacy in treating akathisia (972). While there has been little systematic study, akathisia induced by risperidone or other second-generation antipsychotics is treated similarly to akathisia associated with first-generation antipsychotic treatment.

A common problem that arises in assessing patients with akathisia is distinguishing this side effect from psychomotor agitation associated with the psychosis. Mistaking akathisia for psychotic agitation and raising the dose of antipsychotic medication usually leads to a worsening of the akathisia and thus the agitation. When the etiology of agitation is unclear, the nonspe-

cific effects of benzodiazepines on akathisia and agitation can be useful, although the dose necessary for therapeutic effects on psychotic agitation usually is higher than that required for akathisia (978).

Given the high rate of acute extrapyramidal side effects among patients receiving first-generation antipsychotic medications, and to a lesser extent risperidone, the prophylactic use of antiparkinsonian medications may be considered. The benefit of this approach has been demonstrated in several studies. For example, Hanlon et al. (979) found that only 10% of patients taking perphenazine with an antiparkinsonian medication developed an extrapyramidal side effect, in contrast to 27% of patients taking perphenazine without an antiparkinsonian medication. The risk is that some patients may be treated unnecessarily with these medications, risking anticholinergic side effects (978). However, schizophrenia is a long-term illness, and the development of a therapeutic alliance is of paramount importance. The minimization of uncomfortable, painful, and unnecessary side effects can contribute significantly to establishing such an alliance. Thus, prophylactic antiparkinsonian medication may be considered for all patients with a prior history of susceptibility to extrapyramidal side effects and for patients for whom antipsychotic agents known to induce these effects (e.g., first-generation agents, high doses of risperidone) are prescribed.

The various medications used to treat acute extrapyramidal side effects are listed in Table 5. The major differences among the anticholinergic medications are in their potencies and durations of action. Patients who are very sensitive to anticholinergic side effects (e.g., dry mouth, blurred vision, constipation) may require lower doses or less potent preparations (e.g., trihexyphenidyl, procyclidine hydrochloride). The need for anticholinergic medications should be reevaluated after the acute phase of treatment is over and whenever the dose of antipsychotic medication is changed. If the dose of antipsychotic medication is lowered, anticholinergic medication may no longer be necessary or may be given at a lower dose.

Tardive dyskinesia is a hyperkinetic abnormal involuntary movement disorder caused by sustained exposure to antipsychotic medication; tardive dyskinesia can affect neuromuscular function in any body region but is most commonly seen in the oral-facial region (980, 981). (For a description of tardive dyskinesia and its differential diagnosis, see DSM-IV-TR.) Evaluation of the risk of tardive dyskinesia is complicated by the fact that spontaneous dyskinesias are clinically indistinguishable from tardive dyskinesia and have been described in up to 20% of never-medicated patients with chronic schizophrenia, as well as in elderly patients (982, 983). Thus dyskinetic movements are part of the natural history of schizophrenia. Tardive dyskinesia occurs at a rate of approximately 4%–8% per year in adult patients treated with first-generation antipsychotics (980, 984). Various factors are associated with greater vulnerability to tardive dyskinesia, including older age, antipsychotic-induced parkinsonian symptoms, female gender combined with postmenopausal status, diagnosis of affective disorder (particularly major depressive disorder), concurrent general medical disease such as diabetes, and use of high doses of antipsychotic medications (982, 985–987). Studies comparing intermittent, targeted first-generation antipsychotic drug treatment with maintenance antipsychotic treatment have found increased risk of tardive dyskinesia with targeted treatment strategies (988).

Tardive dyskinesia has been reported after exposure to any of the available antipsychotic medications, although the risk appears to be substantially less (approximately 10-fold) with the second-generation antipsychotics, compared to first-generation antipsychotics (83, 319, 382, 989–992). One study summarizing available longitudinal clinical trial data with risperidone reports an annual risk of 0.3%, which is substantially less than the expected risk with first-generation antipsychotics of approximately 5% per year (989, 992, 993). In a 9-month study of older patients (mean age=66 years), substantially more patients treated with haloperidol (32%), compared with risperidone-treated patients (5%), developed tardive dyskinesia (535, 990). In these studies the mean dose of both antipsychotics was low, and the rates of tardive dyskinesia in the haloperidol-treated subjects were similar to those reported for older patients in other studies

(987). For olanzapine, analyses of longitudinal double-blind data from multiple studies find a 12-fold lower risk of tardive dyskinesia with olanzapine treatment, compared to haloperidol treatment (0.05% and 7.45%, respectively) (319, 992). There are few systematic data concerning quetiapine and risk of tardive dyskinesia. In a 52-week open-label study of quetiapine that included 184 patients age >65 years, there was no change in the severity of dyskinetic movements, as evaluated by rating scales (994). In addition, emerging results from studies of other second-generation antipsychotics suggest that low risk of tardive dyskinesia may be found with drugs such as quetiapine that have a low risk of extrapyramidal effects.

With clozapine, although long-term prospective incidence studies are lacking, controlled short- and long-term trials generally find that the severity of dyskinetic movements improves with clozapine treatment, compared to treatment with first-generation antipsychotics (769, 995).

Although the majority of patients who develop tardive dyskinesia have mild symptoms, a proportion (approximately 10%) develop symptoms of moderate or severe degrees. An often severe variant of tardive dyskinesia is tardive dystonia, which is characterized by spastic muscle contractions in contrast to choreoathetoid movements (996). Tardive dystonia is often associated with great distress and physical discomfort. Patients receiving antipsychotic medication treatment on a sustained basis (for more than 4 weeks) should be evaluated at a minimum of every 3 months for signs of dyskinetic movements. The occurrence of dyskinetic movements warrants a neurological evaluation (980).

Treatment options for tardive dyskinesia occurring in the context of treatment with first-generation antipsychotic agents include switching to a second-generation antipsychotic or reducing the dose of the first-generation antipsychotic. An initial increase in dyskinetic symptoms may occur after conversion to a second-generation drug or antipsychotic dose reduction (withdrawal-emergent dyskinesia). With sustained first-generation antipsychotic exposure without dose reduction after the development of tardive dyskinesia, the likelihood of reversibility diminishes but is not lost. In some patients dyskinetic movements can persist despite long periods of time without medication. Despite the fact that continued treatment with antipsychotic medication increases the chances for the persistence of tardive dyskinesia symptoms, in many patients the severity of tardive dyskinesia does not increase over time at steady, moderate doses. The documentation in the clinical record should reflect that, despite mild tardive dyskinesia, a risk-benefit analysis favored continued maintenance of antipsychotic treatment to prevent the likelihood of relapse.

A large number of agents have been evaluated as possible treatment for tardive dyskinesia with few positive results. Although not consistent, there is some evidence that vitamin E may reduce the risk of development of tardive dyskinesia (225, 226). Given the low risk of side effects associated with vitamin E, patients may be advised to take 400–800 I.U. daily as prophylaxis. Small clinical trials have investigated the potential benefits of benzodiazepines, anticholinergic agents, calcium channel blockers (997), γ -aminobutyric acid agonists (998), essential fatty acids, estrogen, and insulin, with no studies yet producing convincing data to suggest any of these agents may be effective treatments for tardive dyskinesia (225, 999–1002).

(3) Neuroleptic malignant syndrome

Neuroleptic malignant syndrome is characterized by the triad of rigidity, hyperthermia, and autonomic instability, including hypertension and tachycardia (962). In addition, neuroleptic malignant syndrome is often associated with an elevated level of serum creatine kinase. In patients treated with second-generation antipsychotic medications, this classic triad of symptoms is generally although not invariably present (1003, 1004). The prevalence of neuroleptic malignant syndrome is uncertain, but this effect probably occurs in less than 1% of patients treated with first-generation antipsychotic medications (1005–1007) and is even more rare among patients treated with second-generation antipsychotic medications (1003, 1004, 1008–1012).

Neuroleptic malignant syndrome is frequently misdiagnosed and can be fatal in 5%–20% of patients if untreated (1013). It can be sudden and unpredictable in its onset and usually occurs early in the course of treatment, often within the first week after treatment is begun or the dose is increased. Risk factors for neuroleptic malignant syndrome include acute agitation, young age, male gender, preexisting neurological disability, physical illness, dehydration, rapid escalation of antipsychotic dose, use of high-potency medications, and use of intramuscular preparations (1014, 1015). Other diagnostic considerations in patients presenting with rigidity, hyperthermia, autonomic instability, or elevated levels of serum creatine kinase include neuroleptic-induced heat stroke, lethal catatonia, serotonin syndrome (in patients also taking serotonergic drugs such as SSRIs), anticholinergic syndrome, “benign” elevations in the level of serum creatine kinase, and fever in association with clozapine treatment (855, 1015–1018).

Since neuroleptic malignant syndrome is rare, most evidence regarding treatment comes from single case reports or case series. Antipsychotic medications should always be discontinued, and supportive treatment to maintain hydration and to treat the fever and cardiovascular, renal, or other symptoms should be provided. Some case series suggest that, compared with supportive treatment alone, treatment with dopamine agonists such as bromocriptine and amantadine or with dantrolene, which directly reduces skeletal muscle rigidity, may improve the symptoms of neuroleptic malignant syndrome (1019). Based on the overlap in symptoms between catatonia and neuroleptic malignant syndrome (1020), treatment with benzodiazepines, such as lorazepam, may also be helpful (1021, 1022). In patients with severe and treatment-resistant neuroleptic malignant syndrome, ECT is reported to improve symptoms (107, 1016, 1023). After several weeks of recovery, patients may be retreated with antipsychotic medication cautiously (1024). Generally, when treatment is resumed, doses are increased gradually, and a medication other than the precipitating agent is used (usually a second-generation antipsychotic or a first-generation antipsychotic medication of lower potency).

(4) Sedation

Sedation is a very common side effect of first-generation antipsychotic medications, as well as several of the second-generation agents, including clozapine, risperidone, olanzapine, and quetiapine. This effect may be related to antagonist effects of those drugs on histamine, adrenergic, and dopamine receptors (777, 1025, 1026). Most patients experience some sedation, particularly with the low-potency first-generation agents such as chlorpromazine, but it occurs to some extent with virtually all antipsychotic medications. With clozapine, sedation is very common, and in many patients it may be persistent and severe. Quetiapine has a high risk of sedation that may be maximal at the low end of the dose range (e.g., maximal by 100–200 mg/day). Olanzapine has a moderate dose-related risk of sedation. Risperidone produces dose-related sedation (890); within the usual dose range (<6 mg/day) the risk of sedation is relatively low, compared to the risk with other first-generation and second-generation (e.g., olanzapine, clozapine, quetiapine) antipsychotics.

Sedation is most pronounced in the initial phases of treatment, since most patients develop some tolerance to the sedating effects with continued administration. For agitated patients, the sedating effects of these medications in the initial phase of treatment can have therapeutic benefits. However, persistent sedation, including daytime drowsiness and increased sleep time, can interfere with social, recreational, and vocational function. Lowering of the daily dose, consolidation of divided doses into one evening dose, or changing to a less sedating antipsychotic medication may be effective in reducing the severity of sedation.

There are no systematic data on specific pharmacological interventions for sedation, but caffeine is a relatively safe option (1027). Some forms of psychostimulants (e.g., modafinil) have also been used to treat daytime drowsiness (1028). However, there have been case reports of clozapine toxicity associated with modafinil and other stimulant treatments of sedation, and thus this drug combination should be carefully considered and used with caution (1029, 1030).

(5) Cardiovascular effects

Cardiovascular effects include orthostatic hypotension, tachycardia, and QTc prolongation.

Orthostatic hypotension and tachycardia

Hypotension is related to the antiadrenergic effects of antipsychotic medications. With clozapine treatment initiation and dose escalation, there is a high risk of orthostatic hypotension and compensatory tachycardia, with rare (one of 3,000 patients treated) reports of cardiovascular collapse (854). These side effects typically limit the rate of titration, and orthostatic vital signs should be regularly monitored with dose escalation. When orthostatic hypotension is severe, it can cause dizziness and syncopal episodes. Patients who experience severe postural hypotension must be cautioned against getting up quickly and without assistance. Elderly patients are particularly prone to this adverse effect, and syncopal episodes may contribute to an increased risk of falls and related hip fractures in elderly patients. Risperidone has high affinity and quetiapine has moderate affinity for α -adrenergic receptors and thus can produce orthostatic hypotension and reflex tachycardia. Clozapine has the highest affinity and greatest propensity to cause hypotension. Gradual dose titration starting with a low dose minimizes risk. Management strategies for orthostatic hypotension include decreasing or dividing doses of antipsychotic or switching to an antipsychotic without antiadrenergic effects. Supportive measures include the use of support stockings, increased dietary salt, and, as a last resort, administration of the salt/fluid-retaining corticosteroid fludrocortisone to increase intravascular volume.

Tachycardia can result from the anticholinergic effects of antipsychotic medications but may also occur as a result of postural hypotension. While healthy patients may be able to tolerate some increase in resting pulse rate, this may not be the case for patients with preexisting heart disease. Tachycardia unrelated to orthostatic blood pressure changes that result from anticholinergic effects may occur in up to 25% of patients treated with clozapine. Because of the cardiovascular side effects of clozapine, extreme care should be taken in initiating a clozapine trial in patients with heart disease. Tachycardia due to anticholinergic effects without hypotension can be managed with low doses of a peripherally acting beta-blocker (e.g., atenolol) (1031, 1032).

QTc prolongation

The length of time required for the heart ventricles to repolarize is measured by the QT interval on the electrocardiogram. The QT interval varies with heart rate; thus, a QT interval corrected for heart rate (the “QTc”) is routinely used clinically. Prolongation of the QTc interval above 500 msec is associated with increased risk for a ventricular tachyarrhythmia, “torsades de pointes.” Torsades de pointes is associated with syncopal episodes and may lead to life-threatening consequences (e.g., ventricular fibrillation, sudden death).

Among the first-generation antipsychotic agents, thioridazine, mesoridazine, pimozide, and high-dose intravenous haloperidol have been associated with risk of QTc prolongation (1033). Because of the clinically significant risk of torsades de pointes–type arrhythmias and the potential for related sudden death (1033), the FDA recommends that thioridazine should be used only when patients have not had a clinically acceptable response to other available antipsychotics (885). This safety warning is available online at <http://www.fda.gov/medwatch/safety/2000/mellar.htm> and at www.medsafe.govt.nz/Profs/PUarticles/thioridazine.htm.

Ziprasidone is associated with an average increase of 20 msec in the QTc interval; however, the clinical effects of this magnitude of QT prolongation are uncertain (1034). Unlike drugs that prolong the QTc interval to a greater extent (e.g., thioridazine) (1035), ziprasidone has not been reported to be associated with arrhythmias or sudden death (1034). Patients treated with ziprasidone should be monitored for other risk factors for torsades de pointes, including congenital prolonged QT syndrome, bradycardia, hypokalemia, hypomagnesemia, heart failure, and factors that might increase levels of a drug associated with QTc prolongation (e.g., hepatic or renal failure, overdose of ziprasidone or other drugs known to prolong the QTc

interval). Concomitant treatment with other drugs known to significantly prolong the QTc interval at normal clinical doses should be avoided. A list of such drugs is available at <http://www.torsades.org>. Given the normal variability of the QT interval (about 100 msec), an ECG is of questionable value in screening for congenital prolonged QT syndrome or in evaluating the effects of ziprasidone on the QTc interval in individual patients. Glassman and Bigger (1036) have reviewed the literature on prolonged QTc interval, torsades de pointes, and sudden death with antipsychotic drugs, including ziprasidone.

Anticholinergic and antiadrenergic effects

The anticholinergic effects of first-generation antipsychotic medications (along with the anticholinergic effects of antiparkinsonian medications, if concurrently administered) can produce a variety of peripheral side effects, including dry mouth, blurred vision, constipation, tachycardia, urinary retention, and thermoregulatory effects. Anticholinergic side effects may occur in 10%–50% of treated patients (980, 1037). These effects are also common with the second-generation agent clozapine. Although most anticholinergic side effects are mild and tolerable, these side effects can be particularly troublesome for older patients (e.g., older men with benign prostatic hypertrophy) (1037). In rare instances, serious consequences of anticholinergic effects can occur. For example, death can result from ileus of the bowel if it is undetected. In addition, some patients can develop hyperthermia, particularly in warm weather.

Central anticholinergic effects include impaired learning and memory and slowed cognition. Symptoms of anticholinergic toxicity include confusion, delirium, somnolence, and hallucinations (1038, 1039). Such symptoms are more likely to occur with medications that have more potent anticholinergic effects (e.g., chlorpromazine, thioridazine) or from administration of anticholinergic antiparkinsonian medications and in elderly or medically debilitated patients. Clozapine is frequently associated with anticholinergic side effects, including constipation and urinary retention (1040, 1041). Rarely, these effects have been severe, resulting in fecal obstruction and paralytic ileus and enduring impairment of bladder function (1042). Because of these anticholinergic effects, patients with preexisting prostate hypertrophy require careful monitoring of urinary function, and clozapine is contraindicated in patients with narrow-angle glaucoma (1031, 1032). Olanzapine has moderate affinity for muscarinic receptors and acts as an antagonist at the M₁, M₂, M₃, and M₅ receptors; however, anticholinergic effects are infrequent. The rarity of these effects is believed to be due to a difference between the drug's in vitro binding affinities and its actions in vivo. Constipation is occasionally associated with olanzapine treatment, but generally there is a low risk of anticholinergic side effects with olanzapine. Quetiapine has moderate affinity for muscarinic receptors. Constipation and dry mouth are occasionally associated with quetiapine treatment, and elderly and medically debilitated patients may be more sensitive to its anticholinergic side effects.

Anticholinergic side effects are often dose-related and thus may improve with lowering of the dose or administration of the anticholinergic antiparkinsonian drug in divided doses. In cases of anticholinergic delirium, parenteral physostigmine (0.5–2.0 mg i.m. or i.v.) has been used to reverse the symptoms, although this treatment should be provided only under close medical monitoring.

(6) Weight gain and metabolic abnormalities

Weight gain occurs with most antipsychotic agents. Up to 40% of patients treated with first-generation agents gain weight, with the greatest risk associated with the low-potency antipsychotics (797). The most notable exception is molindone, which may not cause significant weight gain (1043). The risk of weight gain with clozapine is thought to be the highest of all antipsychotics (1043), with studies reporting that between 10% and 50% of clozapine-treated patients are obese (1044, 1045). Typically, weight gain is progressive over the first 6 months of treatment, although some patients continue to gain weight indefinitely. In a meta-analysis of

available studies, the mean weight gain after 10 weeks of treatment with clozapine was estimated at 4.45 kg (1043). Weight gain also is common in patients treated with risperidone and olanzapine. With risperidone, mean weight gain is estimated at 2.1 kg over the first 10 weeks of treatment (1043) and 2.3 kg after 1 year (382). With olanzapine, mean weight gain is estimated at 4.2 kg after 10 weeks of treatment (1043), and one study observed a mean weight gain of 12.2 kg after 1 year of treatment with olanzapine (918). No appreciable weight gain was observed with ziprasidone after 10 weeks (1043) or 1 year (947). Few studies have characterized the extent of weight gain with quetiapine or aripiprazole.

While studies have not systematically examined the health consequences of antipsychotic-related weight gain, the risk of cardiovascular disease, hypertension, cancers, diabetes, osteoarthritis, and sleep apnea is likely similar to that in idiopathic obesity. The association of high cholesterol and triglycerides with weight gain further increases the risk of cardiovascular disease (1046–1052). Adolescents may be particularly vulnerable to these side effects (1053).

Prevention of weight gain should be a high priority, since weight loss is difficult for many patients. Efforts should be made to intervene proactively, since obese persons rarely lose more than 10% of body weight with weight loss regimens. When weight gain occurs, clinicians should suggest or refer patients to diet and exercise interventions (1054). If the patient has not had substantial clinical benefits of the antipsychotic medication that outweigh the health risks of weight gain, a trial of an antipsychotic with lower weight-gain liability should be considered. Few systematic studies have been done to evaluate the effectiveness of specific interventions to prevent antipsychotic-induced weight gain or to promote weight loss, although potential strategies include diet and exercise programs (1055, 1056). No pharmacological interventions have proven efficacy in treating weight gain associated with second-generation antipsychotics, although uncontrolled studies have reported possible benefit from amantadine (1057, 1058), topiramate (1059–1063), the H₂ histamine antagonist nizatidine (1064, 1065), and noradrenergic reuptake inhibitor antidepressants (1066).

Uncontrolled studies and case series suggest that clozapine and olanzapine are associated with increased risk of hyperglycemia and diabetes (1050–1052, 1067–1073). While controlled studies are lacking, one prospective study found that 30 of 82 (36%) clozapine-treated outpatients developed diabetes during the 5-year follow-up period (1050). Complicating the evaluation of antipsychotic-related risk of diabetes is that schizophrenia is associated also with increased diabetes risk (1074). In some patients obesity may contribute to diabetes risk. Other mechanisms may also be involved. For example, insulin resistance may develop early in treatment with olanzapine and contribute to abnormal regulation of glucose and subsequent diabetes (1075, 1076).

Further, some of the second-generation antipsychotic agents, olanzapine and clozapine in particular, have been associated with diabetic ketoacidosis and nonketotic hyperosmolar coma, relatively rare complications of diabetes that are extremely dangerous if untreated (1077–1081). Numerous case reports have described scenarios in which diabetic ketoacidosis appears acutely in the absence of a known diagnosis of diabetes (1082). Diabetic ketoacidosis can present with mental status changes that can be attributed to schizophrenia. The treating psychiatrist must be aware of the possibility of diabetic ketoacidosis, given its potential lethality and its often confusing presentation. The overall prevalence and mechanism of diabetic ketoacidosis associated with antipsychotics and the differential risk of specific antipsychotic agents to cause this side effect are at present unknown.

Given the rare occurrence of extreme hyperglycemia, ketoacidosis, hyperosmolar coma, or death and the suggestion from epidemiological studies of an increased risk of treatment-emergent adverse events with second-generation antipsychotics, the FDA has requested all manufacturers of second-generation antipsychotic medications to include a warning in their product labeling regarding hyperglycemia and diabetes mellitus.

There is also suggestive evidence that certain antipsychotic medications, particularly clozapine and olanzapine, may increase the risk for hyperlipidemias. Most of the evidence is derived from case reports and other uncontrolled studies (1048–1050, 1067, 1070, 1083–1087). Pharmacological treatment with lipid-lowering drugs should be considered in patients with hyperlipidemia.

Table 1 lists suggested strategies for monitoring and clinical management associated with weight gain, glucose abnormalities, and hyperlipidemias in patients with schizophrenia.

(7) Effects on sexual function

Disturbances in sexual function can occur with a number of antipsychotic agents, including first- and second-generation agents (1088). Several mechanisms contribute to the genesis of sexual side effects with these medications. Prolactin elevation is very common in patients treated with first-generation antipsychotics as well as risperidone (1089). Female patients appear to be more sensitive to prolactin elevation than male patients (1090). All first-generation antipsychotic medications increase prolactin secretion by blocking the inhibitory actions of dopamine on lactotrophic cells in the anterior pituitary. This prolactin elevation may be even greater with risperidone than with first-generation antipsychotics. The reason for the propensity of risperidone to elevate prolactin may be due to risperidone's relative difficulty in crossing the blood-brain barrier, with the pituitary, which is outside the blood-brain barrier, exposed to higher peripheral levels of risperidone (1091).

Effects of hyperprolactinemia may include breast tenderness, breast enlargement, and lactation. Since prolactin also regulates gonadal function, hyperprolactinemia can lead to decreased production of gonadal hormones, including estrogen and testosterone. In women decreased gonadal hormone production may disrupt or even eliminate menstrual cycles. In both men and women prolactin-related disruption of the hypothalamic-pituitary-gonadal axis can lead to decreased sexual interest and impaired sexual function (1088).

The long-term clinical consequences of chronic elevation of prolactin are poorly understood. There is some epidemiological evidence, however, that postmenopausal women may have an increased risk of breast cancer if exposed to medications that potentially elevate levels of prolactin (1092). Chronic hypogonadal states may increase risk of osteopenia and osteoporosis (1093–1097), but increased risk of these disorders has not been directly linked to antipsychotic-induced hyperprolactinemia.

If a patient is experiencing clinical symptoms of prolactin elevation, the dose of antipsychotic may be reduced or the medication regimen may be switched to an antipsychotic with less effect on prolactin (e.g., any of the second-generation antipsychotics with the exception of risperidone). When the antipsychotic must be maintained, dopamine agonists such as bromocriptine (2–10 mg/day) or amantadine may reduce prolactin levels and thus the symptoms of hyperprolactinemia (1058).

The association between the other second-generation antipsychotic medications (clozapine, olanzapine, quetiapine, ziprasidone, and aripiprazole) and sexual dysfunction is less clear. Sexual interest and function may be reduced in both men and women receiving clozapine, but generally to a lesser extent than with first-generation antipsychotics (1098, 1099). Sexual dysfunction may also occur in patients treated with olanzapine and quetiapine (1100, 1101), but there is no prospective study that might indicate whether a causal relationship exists.

Erectile dysfunction occurs in 23%–54% of men treated with first-generation medications (812). Other effects can include ejaculatory disturbances in men and loss of libido or anorgasmia in women and men. In addition, with specific antipsychotic medications, including thioridazine and risperidone, retrograde ejaculation has been reported, most likely because of antiadrenergic and antiserotonergic effects (886). Dose reduction or discontinuation usually results in improvement or elimination of symptoms. A 25–50-mg dose of imipramine at bedtime may be helpful for treating retrograde ejaculation induced by thioridazine (1102). If dose

reduction or a switch to an alternative medication is not feasible, yohimbine (an α_2 -antagonist) or cyproheptadine (a 5-HT₂ antagonist) can be used (797). Because retrograde ejaculation is annoying rather than dangerous, psychoeducation may also help the patient tolerate this side effect. Priapism is very rarely associated with clozapine (1103, 1104), risperidone (1104), olanzapine (1105, 1106), quetiapine (1107), and ziprasidone (1108, 1109). There have been no reports to date of priapism associated with aripiprazole.

2. Adjunctive medications

A wide variety of medications, including additional antipsychotics, have been added to antipsychotic medications, either to enhance their efficacy for the treatment of symptoms of schizophrenia or to treat other symptoms often associated with the illness. Targets of these added medications have included residual positive symptoms, negative symptoms, cognitive deficits, depression, agitation and aggression, obsessions and compulsions, and anxiety. Some medications (e.g., antidepressants) have been used for more than one symptom cluster (e.g., depression, obsessions and compulsions).

a) Anticonvulsants

A number of studies of the efficacy of carbamazepine and valproate in schizophrenia have been done. Excluding findings suggesting their use in treating patients whose illness has strong affective components, the evidence is quite convincing that neither agent, used alone, is of significant value in the long-term treatment of schizophrenia. Recent studies have tended to concentrate on use of anticonvulsants in combination with antipsychotics.

With carbamazepine, studies examining the effects of the drug in combination with first-generation antipsychotics have had negative findings (236, 1110). For valproate, on the other hand, both negative and positive results have been noted (102, 235–237, 1111). Most studies have included relatively few patients, but the study by Casey et al. (237) included 242 subjects with acutely exacerbated symptoms who were randomly assigned to receive risperidone or olanzapine, each combined with placebo or divalproex. Compared with the placebo group, the divalproex group improved significantly more rapidly over the first 2 weeks of treatment. Both groups were equally improved by the end of the study at 4 weeks. This intriguing result warrants further study and replication to establish whether divalproex augmentation shortens the time to discharge and to determine the value of longer-term divalproex augmentation.

(1) Side effects

There are generally no additional side effects from the combination of anticonvulsant and antipsychotic medications beyond those of the individual medications themselves. Carbamazepine is not recommended for use with clozapine, because of the potential of both medications to cause agranulocytosis.

(2) Implementation

For patients with schizophrenia, these medications are generally used in the same therapeutic dose ranges and blood levels that are used for the treatment of seizure disorders and bipolar disorder. Studies to determine dosing in schizophrenia have not been reported. A complicating factor is the fact that carbamazepine can decrease the blood levels of antipsychotic medications by induction of hepatic enzymes (1112–1114).

b) Antidepressants

Studies of antidepressants in schizophrenia broadly subdivide into those that have examined these agents as treatment for depression and those that have tested their efficacy for other symptoms, such as negative symptoms. These areas will be reviewed separately.

Good clinical practice dictates that clinicians be alert to the occurrence of depression in a broad spectrum of psychiatric and medical disorders and treat it when it is diagnosed. Earlier work (1115) indicated the effectiveness of a tricyclic antidepressant for symptoms of depression in schizophrenia, and 12-month follow-up showed the advantage of maintenance treatment (1116). One study found the effects of an SSRI (sertraline) to be equal to those of imipramine for treatment of postpsychotic depression (1117) and another noted positive effects of citalopram (540), but the only placebo-controlled study of an SSRI for treatment of depressed patients with schizophrenia showed a large placebo effect and no difference between groups (1118). Although the evidence is most strong for patients who meet the syndromal criteria for depression, two reviews have noted the paucity of evidence for the efficacy of antidepressants in schizophrenia (222, 1119). For clinicians, a further question, not addressed in the literature, is whether failure of an antidepressant to improve depression in a person with schizophrenia is an indication for changing antidepressants or changing antipsychotics.

A number of studies have tested the efficacy of antidepressants in treating the negative symptoms of schizophrenia. The overlap between depressive and negative symptoms has complicated study design and interpretation. In five placebo-controlled studies of SSRIs for negative symptoms, one reported a modest advantage of fluoxetine added to long-acting injectable antipsychotic medication (1120), while four found no advantage for SSRIs, compared with placebo, in patients receiving clozapine (1121) or first-generation antipsychotics (1122–1124). Several studies of adjunctive fluvoxamine have demonstrated positive results (1125–1127). An open-label study of selegiline found beneficial effects on negative symptoms (1128), but in a placebo-controlled trial both the selegiline and placebo groups improved, and there was no difference between them (1129). Overall, the evidence for efficacy of antidepressants for negative symptoms of schizophrenia is very modest. Since most of the studies have been done in combination with first-generation antipsychotics, it is possible that the findings might be different with second-generation antipsychotics, although this possibility seems unlikely.

In terms of treating other symptoms that are sometimes observed in patients with schizophrenia, two small studies found efficacy of clomipramine and fluvoxamine in treating obsessive-compulsive symptoms in schizophrenia (221, 223). In a small crossover study in which citalopram or placebo was added to first-generation antipsychotics, patients with a history of aggression had significantly fewer incidents while taking citalopram (1130).

(1) Side effects

Although the side effects of antidepressants are no different when administered to patients with schizophrenia than to patients with other disorders, combinations of antipsychotics and antidepressants have the potential for adverse, even dangerous, pharmacokinetic and pharmacodynamic interactions. In addition to prior history of response to antidepressant treatment, potential drug-drug interactions should be taken into account in selecting an antidepressant agent. Of particular concern with regard to drug toxicity are the inhibitory effects of some antidepressants on clozapine metabolism, leading to increased serum levels and risk of seizures. Fluvoxamine can cause large increases in clozapine serum levels, and the combination of the two drugs should be avoided. Some other SSRIs and nefazodone may also cause clinically significant increases in clozapine serum levels and should be used carefully in clozapine-treated patients. Clozapine serum levels should be monitored after adding one of the antidepressants discussed earlier to the medication regimen of patients treated with clozapine. Because bupropion itself is associated with a risk of seizures, a pharmacodynamic interaction with clozapine exists. Therefore, the combination of clozapine and bupropion should be avoided. There are many sources of information about drug-drug interactions. A useful, frequently updated web site maintained by D. Flockhart at Indiana University is available at <http://medicine.iupui.edu/flockhart>. Another useful drug interaction computer program maintained by J. Oesterheld and D. Osser is available at <http://www.mhc.com/Cytochromes>.

(2) Implementation

Use of antidepressants in schizophrenia generally has been studied by using the doses and titration schedules that are usually used when the agents are administered by themselves. There is no reason to think that dosing should be modified on the basis of coexisting schizophrenia. As noted earlier, however, the potential for drug-drug interactions suggests that close monitoring of side effects is warranted. Monitoring of the blood levels of the antipsychotic at baseline and after several weeks of antidepressant treatment may be helpful, particularly for clozapine, where there is evidence that high blood levels are associated with increased risk of seizures and low levels may be ineffective. The same considerations apply when an antidepressant is being discontinued.

c) Antipsychotics

Most reports on the combination of antipsychotics describe the effects of combinations with clozapine. The only randomized, controlled trial used sulpiride, a dopamine receptor antagonist similar to first-generation antipsychotics that is available in Europe but not in North America. Shiloh et al. (1131) added placebo or sulpiride, titrated up to a dose of 600 mg/day, to clozapine for 10 weeks in the treatment of 28 partially responsive patients who were taking stable doses of clozapine and who had BPRS scores >42. The sulpiride group had significantly greater decreases in BPRS (15%), Scale for the Assessment of Negative Symptoms (10%), and Scale for the Assessment of Positive Symptoms (12%) scores.

Case series show improvements in residual positive symptoms with the addition of a number of other antipsychotics to clozapine. These agents include loxapine (233), pimozide (234), and risperidone (232).

Although the quality of the evidence for augmentation of clozapine with another antipsychotic is modest, this strategy seems reasonable in treating patients whose response to clozapine is fair at best. Before taking this step, however, the clinician should be sure that the clozapine treatment has been of sufficient duration and that the patient's blood level of clozapine indicates a sufficient dose. The other alternatives—switching to monotherapy with a different antipsychotic not already tried or combining two other antipsychotics—have even less evidence to support them than does augmentation of clozapine.

Combinations of two or more antipsychotics, neither of which is clozapine, are also used frequently for treatment of schizophrenia (1132). Some of this use reflects periods of cross-titration in the transition from one antipsychotic to another, but much of it represents long-term treatment. Evidence for (or against) this practice is minimal, as there are no controlled studies in the literature. The largest case series includes six persons with inadequate responses to 20–40 mg/day of olanzapine, who had average decreases in BPRS and PANSS scores of 35% after addition of 60–600 mg/day of sulpiride for at least 10 weeks (1133). Without a control group, such results are difficult to evaluate. Moreover, sulpiride is not available in the United States, and there is no way to know if similar results might be found with other antipsychotics.

The absence of evidence for combinations of antipsychotics does not mean that there are no patients who are best treated with such a combination. However, their use should be justified by strong documentation that the patient is not equally benefited by monotherapy with either component of the combination. Practitioners should be aware of the problems inherent in combination therapies, including increased side effects and drug interactions as well as increased costs and decreased adherence (1132).

d) Benzodiazepines

Benzodiazepines have been evaluated as monotherapy for schizophrenia and as adjuncts to antipsychotic medications. Wolkowitz and Pickar (224) reviewed double-blind studies of benzodiazepines as monotherapy and found that positive effects (reductions in anxiety, agitation, global impairment, or psychotic symptoms) were reported in nine of 14 studies. Six of 10 studies that specifically examined psychotic symptoms showed greater efficacy for benzodiazepines

than placebo. In a study comparing diazepam, fluphenazine, and placebo as treatments for impending psychotic relapse in patients who were taking no antipsychotic medications, the effects of diazepam and fluphenazine were equal, and both were superior to placebo (1134).

Double-blind studies evaluating benzodiazepines as adjuncts to antipsychotic medications were also reviewed by Wolkowitz and Pickar (224). Seven of 16 studies showed some positive effect on anxiety, agitation, psychosis, or global impairment; five of 13 showed efficacy in treating psychotic symptoms specifically. The reviewers concluded that benzodiazepines may improve the response to antipsychotic medications.

Some studies indicate that the effectiveness of benzodiazepines as adjuncts to antipsychotic medications is limited to the acute phase and may not be sustained. Altamura et al. (1135) found that clonazepam plus haloperidol, but not haloperidol alone or placebo, produced significant lowering of total BPRS scores after 1 week. This reduction, which was primarily due to decreases in anxiety and tension, disappeared by the end of the 4-week study. Csernansky et al. (1136) also found that when alprazolam was added to antipsychotic medication, there was a significant reduction in the BPRS withdrawal/retardation subfactor score after the first week, but this reduction disappeared by study end at week 5.

Benzodiazepines are commonly used alone or in combination with an antipsychotic for acutely agitated patients in emergency department settings. One study compared the effects of lorazepam with those of haloperidol over the first 4 hours of treatment (1137). The compounds were equal in efficacy, and the authors suggested that lorazepam may be preferable, in that delayed extrapyramidal symptoms can occur with haloperidol. Another study compared lorazepam and haloperidol alone with the combination of both over 12 hours (75). Combination treatment was modestly more effective during the first 3 hours, and there were no significant differences between groups at later times. The haloperidol alone group needed more injections and had more extrapyramidal symptoms.

Benzodiazepines are effective for treatment of acute catatonic reactions, whether associated with schizophrenia or other disorders (137, 140, 142, 1138–1141). Although most studies have used lorazepam (1–2 mg i.v. or i.m. or 2–4 mg p.o., repeated as needed over 48–72 hours), beneficial effects have also been found with clonazepam and oxazepam. One report has questioned the value of benzodiazepines in treating chronic catatonia, although patients were maintained on antipsychotic treatment during the study, and the contribution of tardive dystonia to the observed behaviors was uncertain (1142).

(1) Side effects

Benzodiazepines have some limitations in schizophrenia. Their common side effects include sedation, ataxia, cognitive impairment, and a tendency to cause behavioral disinhibition in some patients. This last side effect can be a serious problem in patients who are being treated for agitation. Reactions to withdrawal from benzodiazepines can include psychosis and seizures. In addition, patients with schizophrenia are vulnerable to both abuse of and addiction to these agents.

(2) Implementation

Evidence relating to the choice of a specific benzodiazepine is limited, since few studies have compared the effectiveness of more than one. Important considerations in selection include abuse potential and severity of withdrawal symptoms if treatment is prolonged. In general, longer-acting agents have lower abuse potential. Withdrawal of alprazolam seems more likely to be associated with seizures, compared to withdrawal of other benzodiazepines.

e) Beta-blockers

Beta-blocking agents are often used for treatment of drug-induced akathisia, discussed in Section V.A.1.c, “Shared Side Effects of Antipsychotic Medications.” There are also a few controlled studies of the combination of beta-blockers with antipsychotics to treat aggression.

Pindolol in a dose of 5 mg t.i.d. reduced aggression scores significantly more than placebo in a double-blind crossover study that included 30 male patients with schizophrenia in a maximum-security facility (100). In a psychiatric intensive care setting, 80–120 mg/day of nadolol had initial beneficial effects on psychosis scores and extrapyramidal symptoms, compared with placebo (101). The difference in extrapyramidal symptoms persisted over the 3 weeks of the study. In both of these studies, most patients were taking first-generation agents. Replication of the findings with aggressive patients taking second-generation agents would be helpful. As noted earlier, clozapine is indicated as a treatment for persistently aggressive, psychotic patients.

f) Cognition enhancers

Cognitive deficits are characteristic of schizophrenia, and several studies have examined the efficacy of adding acetylcholinesterase inhibitors developed for use in dementia to treat patients with schizophrenia. One case report found substantial cognitive benefits from donepezil, compared with placebo (247), and an uncontrolled study observed positive results with donepezil on a variety of cognitive measures (249). However, a randomized, placebo-controlled trial of donepezil in 34 patients with chronic schizophrenia reported no group differences (248). As such, there is currently insufficient evidence to support the usefulness of these agents in improving cognitive performance in schizophrenia.

g) Glutamatergic agents

Because phencyclidine, which blocks ion channels associated with NMDA-type glutamate receptors, can produce a clinical state with psychotic and negative symptoms resembling schizophrenia, agents with glutamatergic properties have been tested in schizophrenia (1143). The agents that have been tested are glycine, D-cycloserine, and D-serine. Of these, only D-cycloserine is available for medicinal human use in the United States, as an antituberculosis treatment.

Five randomized, controlled trials have examined the effects of glycine in doses ranging from 0.4 to 0.8 g/kg. Most have reported beneficial effects of glycine on negative symptoms, with decreases of 15%–40% in negative symptom measures (239, 240, 242, 1144). Little effect on positive symptoms has been found in most studies. In a group of 30 patients who were taking clozapine, glycine did not produce any significant symptom changes, compared with placebo (241), confirming the result of an earlier case series report (1145). Javitt et al. (242) did, however, report robust negative symptom improvements in four patients who received clozapine plus glycine.

Results with D-cycloserine are more variable. The usual dose is 50 mg/day. Modest, but significant, decreases in negative symptoms were found by some investigators (244–246) but not others (1146, 1147). In a study of D-cycloserine added to clozapine, there was no benefit of the combination (243), which may be related to its dose-response curve.

A report by Tsai et al. (238) on adjunctive D-serine noted significant decreases in positive and negative symptoms in patients stabilized with a first-generation antipsychotic or risperidone. The same group later reported no benefit from adding D-serine to clozapine (1148).

Overall, the evidence for glutamatergic agents is encouraging, except as additions to clozapine. Most studies have used first-generation antipsychotics, risperidone, or clozapine. It remains to be seen if combinations of glutamatergic agents with other second-generation antipsychotics are helpful. Although the data seem most positive for glycine, studies directly comparing these agents are needed to determine if their effects actually differ.

h) Lithium

Lithium as a sole treatment has limited effectiveness in schizophrenia and is inferior to treatment with antipsychotic medications (1149–1152).

Earlier reports indicated that when added to antipsychotic medications, lithium augmented the antipsychotic response, in general, and improved negative symptoms specifically (1153,

1154). Other evidence indicated benefits of lithium for patients with schizophrenia with affective symptoms and for patients with schizoaffective disorder (1155–1159).

More recent literature, however, has not reported robust effects (1160). Relatively low doses of lithium over an 8-week period improved anxiety symptoms more than did placebo, but effects in other areas of psychopathology were not found (1161). Patients who had not responded to 6 months of treatment with fluphenazine decanoate showed no more improvement than the placebo group after 8 weeks of lithium augmentation at therapeutic levels (1162). There have been no reported controlled trials of lithium combined with second-generation antipsychotics. Since at least some of these agents have evidence for effects on depression, anxiety, and mood stabilization, the potential value of combining lithium with them may be limited.

(1) Side effects

The side effects of lithium include tremor, gastrointestinal distress, sedation or lethargy, impaired coordination, weight gain, cognitive problems, nephrogenic diabetes insipidus with associated polyuria and polydipsia, renal insufficiency, hair loss, benign leukocytosis, acne, and edema. These have been reviewed in detail in APA's *Practice Guideline for the Treatment of Patients With Bipolar Disorder* (1163). The combination of an antipsychotic medication and lithium may increase the possibility of the development of neuroleptic malignant syndrome. However, the evidence for this association comes mainly from some debated reports of cases or series of cases, rather than from quantitative data. Most reported cases of neuroleptic malignant syndrome in patients treated with lithium plus antipsychotic medication have occurred in cases of high lithium blood levels associated with dehydration.

(2) Implementation

Generally, lithium is added to the antipsychotic medication that the patient is already receiving, after the patient has had an adequate trial of the antipsychotic medication but has reached a plateau in the level of response and has persisting residual symptoms. The dose of lithium is that required to obtain a blood level in the range of 0.8–1.2 meq/liter. Response to treatment usually appears promptly; a trial of 3–4 weeks is adequate for determining whether there is a therapeutic response, although some investigators have noted that improvements may emerge only after 12 weeks or more (1160). Patients should be monitored for adverse effects that are commonly associated with lithium (e.g., polyuria, tremor) and with its interaction with an antipsychotic medication (e.g., extrapyramidal side effects, confusion, disorientation, other signs of neuroleptic malignant syndrome) (266), particularly during the initial period of combined treatment. Given the toxicity of lithium in overdose, prescription of conservative quantities should be considered for patients at increased risk for suicidal behaviors.

i) Monoaminergic agents

Some studies have examined the efficacy of adjunctive dopaminergic and noradrenergic agents in schizophrenia. High doses of oral tyrosine added to molindone produced no clinical effects different from placebo in a crossover study of 11 patients, even though there was physiological evidence that the tyrosine had CNS effects (1164). Clonidine added to 20 mg/day of haloperidol reduced psychotic symptoms more than placebo in a small study of 12 patients (1165). The lack of an effect of clonidine on chronic polydipsia in schizophrenia has recently been reported (459).

j) Polyunsaturated fatty acids

Based on hypotheses concerning membrane stability and second messenger dysfunction in schizophrenia, several investigators have tested the efficacy of polyunsaturated fatty acids in the illness. The bulk of the evidence comes from studies of eicosapentaenoic acid (EPA). One study also examined docosahexaenoic acid and found it had no effects (1166).

In separate studies, Peet et al. (1166) found that EPA added to a stable dose of antipsychotic improved total and positive symptoms more than placebo and that EPA alone was more effective as sole treatment for unmedicated schizophrenia patients than placebo alone. By contrast, Fenton et al. (1167) found no benefit of EPA, compared with placebo, in a study of more than 80 patients. Emsley et al. (1168), in a South African cohort, noted greater decreases in PANSS and dyskinesia scores with EPA added to stable antipsychotic dose. The two phenomena were correlated; those with dyskinesia improvements were most likely to also have symptom improvements. Patients taking clozapine did not benefit from EPA treatment.

The EPA data are intriguing but far from definitive. Most data come from studies of combination therapy with first-generation antipsychotics. The compound appears to be free of side effects other than initial mild gastrointestinal upset in some patients.

► B. OTHER SOMATIC THERAPIES

1. ECT

a) Efficacy

The efficacy of acute treatment with ECT in patients with schizophrenia has been described in multiple case series and uncontrolled studies as well as a number of controlled trials; detailed reviews have been provided by Fink and Sackeim (106), an APA task force (107), and Tharyan and Adams (108). Although early research used small patient samples that were not well characterized and probably included some patients with mood disorder, antipsychotic treatment alone generally produced better short-term outcomes than ECT alone. There also appeared to be no advantage to ECT, compared to sham treatment. On the other hand, combined treatment with ECT and first-generation antipsychotic medications was more effective than either treatment by itself in most (109–118) but not all (1169, 1170) studies. In patients with treatment-resistant illness, case series also suggest that ECT may augment response to first-generation antipsychotics (119–125, 229). More recent reports suggest that increased therapeutic benefit may be seen with combined use of ECT and second-generation antipsychotic medications (127–135). Thus, ECT in combination with antipsychotic medications may be considered for patients with schizophrenia or schizoaffective disorder who have severe psychotic symptoms that have not responded to treatment with antipsychotic agents.

In terms of factors that may predict a greater likelihood of response to ECT, little rigorous evidence exists. While many psychiatrists believe that mood symptoms or a diagnosis of schizoaffective disorder suggest a better response to ECT, the evidence supporting this view is inconsistent (1171–1176). However, some reports suggest that greater benefits are observed in patients with positive symptoms (1177), shorter illness and episode durations (125, 1178–1180), or fewer paranoid or schizoid premorbid personality traits (1173).

Patients with catatonic features constitute another group who have been clinically felt to derive particular benefit from treatment with ECT. Evidence in the more recent literature is limited by the inclusion of patients with mood disorder diagnoses and consists primarily of case series (139, 141, 142) and open prospective trials (136–138, 140, 143, 1141). Nonetheless, findings from these studies confirm the clinical impression that ECT is beneficial in patients with schizophrenia who have prominent catatonic features that have not responded to a trial of lorazepam.

The efficacy of ECT as a continuation/maintenance therapy has been evaluated in only one randomized, single-blind clinical trial, which assessed patients with treatment-resistant schizophrenia (229). Patients who had responded to an acute course of treatment with concomitant bilateral ECT and the first-generation antipsychotic flupenthixol (N=45) were randomly as-

signed to receive continuation therapy with ECT alone, flupenthixol alone, or combination treatment. Relapse rates at 6 months in those receiving combined treatment were less than half those in the other treatment groups (40% versus 93%). These findings supplement clinical observations of the benefits of maintenance ECT for some patients (227, 228) and support the use of ECT for those responding to an acute course of ECT in whom pharmacological prophylaxis alone has been ineffective or cannot be tolerated.

b) Side effects

Effects of ECT on the cardiovascular system are seen in virtually all patients but are typically benign and self-limited. With administration of the ECT stimulus, parasympathetic activation produces an initial bradycardia, and, in some instances, a brief sinus pause may be noted. The subsequent sympathetic activation that occurs with induction of a generalized seizure produces a transient rise in heart rate and blood pressure and resulting increases in cardiac workload, intracranial pressure, and blood-brain barrier permeability (107, 1181). Typically, these effects normalize spontaneously; however, when they are prolonged or occur in patients with preexisting cardiac or vascular disease, medications may be needed to minimize these physiological responses (1182, 1183). Less commonly, ECT may be associated with more serious cardiac arrhythmias, ischemia, and infarction, although the type, severity, and likelihood of cardiac complications are generally related to the type and severity of preexisting cardiac disease (1184, 1185).

Cognitive side effects may also be observed with ECT, although there is much individual variation in the extent and severity of such effects (107). In addition, the cognitive effects of ECT in persons with schizophrenia are unclear, since most studies of cognition after ECT have involved patients treated for depression. For many patients, however, the ECT treatment and its associated anesthesia are associated with a transient postictal confusional state, at times accompanied by postictal agitation (1186). Patients may also experience some difficulties with rapid forgetting of newly learned information and in recalling information, particularly for events occurring near the time of the treatment (1187–1189). This retrograde memory impairment typically resolves in a few weeks to months after cessation of treatment (1190, 1191), but, rarely, patients report more pervasive or persistent cognitive disruption that involves more distant memories (1192). On the other hand, for many patients, improvements in concentration and attention with ECT are associated with improvement rather than worsening of objective memory function (1193, 1194).

Other side effects that are commonly noted after ECT include headache, generalized muscle aches, and nausea and/or vomiting. These effects usually resolve spontaneously or with analgesic or antiemetic medications.

c) Implementation

Before initiating a course of ECT, a pre-ECT evaluation is conducted to determine the potential benefits of ECT for the patient, the potential risks of ECT based on the patient's medical and psychiatric status, and the potential modifications that could be made in medications or in the ECT or anesthetic technique to minimize those risks (107). Although there are no absolute contraindications to ECT, recent myocardial infarction, some cardiac arrhythmias, and some intracranial-space-occupying lesions may increase risk and are indications for caution and consultation. Morbidity and mortality with ECT are also increased in the presence of severe preexisting pulmonary disease and with higher levels of anesthetic risk (i.e., status 4 or 5 in the American Society of Anesthesiologists physical status classification [<http://www.asahq.org/clinical/physicalstatus.htm>]).

During the informed consent process, these and other potential risks of ECT will be considered along with the potential benefits of ECT and the corresponding risks and benefits of other therapeutic approaches. The informed consent process will also include a discussion of the ECT procedure, including a description of the anesthesia used for the treatment, the elec-

trode placement being used to administer the treatment, and the likely number of ECT sessions that will be required.

In terms of electrode placement, no recent studies have assessed the effects of differing electrode placements in patients with schizophrenia or schizoaffective disorder who receive ECT. The two studies that did compare bitemporal to unilateral nondominant hemisphere electrode placements in patients with schizophrenia used a sine wave stimulus, did not measure the extent to which stimulus intensities were suprathreshold, and had high rates of patient dropout, making their findings of limited utility to present ECT practice (1195, 1196). Although findings in patients with depression suggest that unilateral (1187–1189) and perhaps bifrontal (1197, 1198) electrode placement may be associated with fewer cognitive effects and that efficacy with unilateral electrode placement may depend on the extent to which the stimulus intensity exceeds the seizure threshold, the applicability of these observations to patients with schizophrenia is uncertain. A single randomized, double-blind study assessed three different stimulus intensities in 66 patients treated with bitemporal ECT and found that rates of remission and effects on cognition were comparable (1199). However, among patients who remitted, those receiving stimulus intensities just above the seizure threshold required more treatments and had a longer time to remission than patients treated with stimulus intensities that were two to four times the seizure threshold. Thus, in making decisions about stimulus intensity and electrode placement for ECT, psychiatrists may wish to consider factors such as past responses to treatment including ECT, existing cognitive impairment, the need for a more rapid response to treatment, and medical problems or concomitant medications that may increase the seizure threshold and/or may increase the risk associated with each ECT treatment. In addition, individualization of the stimulus intensity to the patient by using either stimulus titration or a formula-based dosing strategy is advisable.

The likely number of ECT treatments required should also be reviewed with the patient. Again evidence is limited, although clinical case series primarily from the older literature suggest that achieving full clinical benefit for patients with schizophrenia may require a longer course of acute treatment than for patients with mood disorders (229, 1179, 1200). In general, ECT is given two to three times per week, although some practitioners will taper the frequency of treatments near the end of the treatment course (1201). Additional details on ECT administration can be found in the 2001 APA ECT Task Force Report (107).

2. rTMS

Repetitive transcranial magnetic stimulation (rTMS) has recently been studied as another somatic technique for ameliorating psychotic symptoms. Whereas the electrical stimulation associated with ECT produces a generalized seizure and global central nervous system excitation, rTMS permits targeted stimulation of specific brain regions that may be involved in the genesis of psychosis (144, 145). These unique features suggest that rTMS may be able to produce therapeutic effects without some of the associated side effects and the need for anesthesia with ECT. Data from one small (N=24) randomized, double-blind, sham-controlled trial (146) and two small (N=8 and N=12) randomized, double-blind, crossover trials (147, 148) suggest that improvements in auditory hallucinations occur when rTMS of the left temporal-parietal cortex is used to augment antipsychotic treatment. However, data from another small (N=25) randomized, controlled trial (1202), which stimulated the right dorsolateral prefrontal cortex, showed no such effect of rTMS on psychotic symptoms. In these studies, the effect of rTMS on more global measures of psychopathology was also variable, although no significant changes were noted in mood, anxiety, or cognition. Although these findings of potential benefits of rTMS in schizophrenia and other psychotic disorders are interesting and worthy of future research, rTMS has not been approved for use in patients with schizophrenia, and there is insufficient evidence to recommend its use in clinical practice.

► C. SPECIFIC PSYCHOSOCIAL INTERVENTIONS

As part of a comprehensive treatment approach, psychosocial interventions can improve the course of schizophrenia when integrated with psychopharmacological treatments (1203, 1204). These interventions can provide additional benefits for patients in such areas as relapse prevention, improved coping skills, better social and vocational functioning, and ability to function more independently. While pharmacotherapy focuses on symptom diminution, psychosocial interventions may provide emotional support and address particular deficits associated with schizophrenia. Psychosocial treatments are interpersonal and call on various roles of the clinician: a manager to coordinate the services available within a treatment system, a teacher to provide education about the patient's disorder and how to cope with it, a friendly other to provide support and encouragement, a trained therapist to provide strategies for interpersonal enrichment, and a physician to provide biological treatments. These roles and therapeutic opportunities come in many forms and settings, e.g., individual, group, family. The choice of psychosocial approaches and particular interventions depends on the particular needs of the patient at various phases of his or her life and illness.

The goals and tasks of these treatments vary widely, depending on the individual patient, disorder, and life situation. The central components of psychosocial treatment are described in the earlier section on psychiatric management (see Section II.D.2, "Psychosocial Treatments in the Stable Phase"). The overall goals are to minimize vulnerability and stress and to maximize adaptive capacities and functioning while enhancing social supports.

The evidence supporting psychosocial treatments is quite variable and generally does not correspond well with actual patterns of practice. In order to foster a more evidence-based approach to the selection and application of psychosocial interventions, this section is organized such that the interventions with the best evidence are discussed first for emphasis, followed by discussions of treatments that may be widely used but for which scientific evidence of effectiveness is minimal or lacking.

1. Psychosocial treatments with substantial evidence bases

a) Program for Assertive Community Treatment (PACT)

PACT includes both case management and active treatment interventions by one team using a highly integrated approach. This program is designed specifically for the marginally adjusted and poorly functioning person with schizophrenia to help prevent relapse and maximize social and vocational functioning. It uses an individually tailored treatment program in the community that is based on an assessment of each person's deficits in coping skills, assets, and requirements for community living (181, 1205). Treatment takes place through teams working 24 hours a day, 7 days a week, and most treatment is delivered in patients' homes, neighborhoods, and places of work. Staff members assist patients in daily living tasks, such as clothes laundering, shopping, cooking, grooming, budgeting, and using transportation. In addition, patients are given sustained and intensive assistance in finding a job, schooling, or a sheltered workshop placement; staff members maintain their contact with the patient after these placements to resolve crises and conflicts and to help prevent relapse. Staff members also guide patients in constructive use of leisure time and in social skills.

The key elements in PACT are emphasizing the patients' strengths in adapting to community life (rather than focusing on psychopathology); providing support and consultation to patients' natural support networks (e.g., family members, employers, friends and peers, and community agencies); and providing assertive outreach to ensure that patients remain in the treatment program. Medication adherence is emphasized, as well as ready access to a psychiatrist. Persons with schizophrenia who are marginally functioning and/or poorly adherent to treatment may benefit from such a comprehensive approach. Others who are more able to function in the community and who are adherent to treatment do not need such extensive services.

Controlled studies have shown the efficacy of PACT in improving symptom severity (1206), reducing the length of hospitalizations, and improving living conditions (163–166, 181, 1207–1211). There have been replications of these results in several U.S. locales and in other countries (1212, 1213).

Although it is not clear which particular elements in the PACT program are most essential for positive outcomes, evidence is strongest for programs that closely follow the original PACT model, including maintenance of a patient-staff ratio of approximately 10:1 (1214). Other public mental health systems have attempted to apply PACT principles, but unfortunately, many do not have adequate resources to carry out such a program. Nonetheless, creative reallocation of resources within a system can strengthen PACT programs (1215, 1216). An evidence-based practices project sponsored by SAMHSA is developing a resource kit on assertive community treatment (draft version available at http://www.mentalhealthpractices.org/pdf_files/act_c.pdf).

b) Family interventions

A guiding principle is that the patient's family members should be involved and engaged in a collaborative treatment process to the greatest extent possible. Family members generally contribute to the patient's care and require education, guidance, and support, as well as training to help them optimize their caretaking role and to improve their own well-being. Clinicians must understand that families often experience considerable stress and burdens in providing such caretaking. For these purposes, "family" should be defined broadly and extend beyond blood relatives to include other patient- and self-defined caretakers.

All evidence-based approaches emphasize the value of family participation in treatment and stress the importance of working together in a collaborative endeavor. The main goal of family interventions, referred to as "psychoeducation," is to decrease the risk of the patient's relapse. More recent research has emphasized other goals, such as improving patient functioning, decreasing family burden, and improving family functioning. All effective family interventions include education about the illness and its course, training in coping and problem-solving skills within the family, improved communication, and stress reduction. These interventions use practical educative and behavioral methods to elicit family participation and collaboration in treatment planning, goal setting, and service delivery. All effective family interventions include somatic treatments, such as medication, for the patient and are intended to optimize their use.

The research variants of family psychoeducation are highly structured programs that last 9 months to 2–3 years and embed the psychiatrist's care within a multidisciplinary team approach to the patient and family. While the variations in research studies on family interventions and their control conditions make it difficult to distill the results of the more than 20 controlled studies, family programs have typically halved relapse rates (173, 174, 176, 189, 1207, 1217–1231). Meta-analyses pooling data across studies have consistently shown reductions in relapse rates (157, 158, 1232) and also reduced family burden (1233). The control treatments have included individual supportive therapy, intensive case management, and medication alone.

More recent studies have compared different family interventions. The one consistent finding is that brief interventions lasting less than 9 months have little effect and are therefore inferior to programs lasting 9 months or longer (157). In a multisite study (Treatment Strategies for Schizophrenia, sponsored by the National Institute of Mental Health) that used a less intensive, once-monthly variant of family management as a control condition for a more intensive family management approach, significant differences in relapse rates between the conditions were not found (1234). Families may be seen individually (173, 174) or in multiple-family groups (1223, 1235). McFarlane (1235) found slightly better protection against relapse from the multiple-family groups in a controlled study. However, on the whole, the critical elements of family interventions have not been precisely defined.

The acute phase or times of crisis may be the best time to engage the family in psychoeducational family meetings. When the patient is most ill, family members tend to be most motivated to reach out and make contact, ask questions, and seek information to reassure and guide them.

The practicing psychiatrist should remain flexible when considering the type of family intervention to offer, with the patient's and the family's preferences playing a large role. Structured family psychoeducation approaches may be challenging to implement at mental health agencies, and considerable organizational barriers to their implementation have been identified (1236). If a highly structured clinical program is not possible, a collaborative and supportive approach to families remains beneficial. Also helpful are referrals to family support organizations and peer-based non-clinical programs, such as the National Alliance for the Mentally Ill's widely available Family-to-Family Education Program (1237, 1238). An evidence-based practices project sponsored by SAMHSA is developing a resource kit on family interventions (draft version available at http://www.mentalhealthpractices.org/pdf_files/fpe_pcs.pdf).

c) Supported employment

Supported employment is an approach to improve vocational functioning among persons with various types of disabilities, including schizophrenia (192). A crucial influence on the conceptualization of supported employment for persons with schizophrenia and other severe mental illnesses has been the work of Becker and Drake in the development of the Individual Placement and Support (IPS) model (1239). Among the key principles defining IPS are 1) services focused on competitive employment, 2) eligibility based on the consumer's choice, 3) rapid job search, 4) integration of rehabilitation and mental health, 5) attention to consumers' preferences, and 6) time-unlimited and individualized support (1240). An evidence-based practices project sponsored by SAMHSA is developing a resource kit on supported employment (draft version available at http://www.mentalhealthpractices.org/pdf_files/se_mhpl.pdf).

Several reviewers of the supported employment literature have reached similar conclusions (193, 194, 1241, 1242). The major sources of evidence for supported employment include day treatment conversion studies and randomized, controlled studies.

Four studies have examined the effectiveness of converting day treatment services to supported employment (1243–1247). During follow-up periods ranging from 3 to 18 months, 43% of the patients in the converted supported employment sites were working competitively, compared to only 17% of the patients in the comparison sites that did not convert.

Nine randomized, controlled trials have compared supported employment to a variety of traditional vocational services for people with severe mental illnesses (160, 162, 1248–1253). These nine studies were conducted by seven independent research teams in various geographic locations, representing both urban and rural communities. The studies compared newly or relatively newly established supported employment programs to established vocational services and used a variety of measures to assess employment outcomes, including the percentage of patients who achieve competitive employment, total wages earned, and number of weeks worked. In general, most objective indicators of employment outcomes converged toward similar conclusions. The average competitive employment rate was 56% for patients in supported employment, compared to 19% for those in comparison conditions, yielding a large mean effect size of 0.85.

A continuing challenge even for supported employment is promoting job retention; studies have found that persons with schizophrenia experience considerable difficulties retaining jobs achieved through supported employment (162, 194). This problem appears to be related to neurocognitive impairments (195), among other factors.

Further, there is no evidence that engagement in supported employment leads to stress, increased symptoms, or other negative outcome (159). Evidence is inconsistent about the relationship between clinical and demographic variables and successful vocational performance; therefore, it is recommended that any person with schizophrenia who expresses an interest in work should be offered supported employment.

d) Cognitive behavior therapy

Cognitive behavior therapy was originally crafted for the treatment of depression and anxiety disorders (1254, 1255), but it has been modified for the treatment of schizophrenia in the past decade, largely by clinical investigators in the United Kingdom. The assumptions of cognitive behavior therapy are that normal psychological processes can both maintain and weaken the fixity and severity of psychotic symptoms, especially delusions and hallucinations. Cognitive behavior therapy is usually conducted in a one-to-one therapeutic relationship. Supportive elements precede and always accompany the cognitive work. An empathic and nonthreatening relationship is built during which the patient elaborates his or her experiences with schizophrenia. Specific symptoms are identified as problematic by the patient and/or therapist and become targeted for special attention in cognitive behavior therapy. The therapist does not challenge these symptoms as irrational but helps the patient through guided questions to focus on his or her own beliefs about the symptoms and the natural coping mechanisms the patient has elaborated to deal with the symptoms. Some of cognitive behavior therapy involves endorsing and strengthening natural coping mechanisms; the rest involves supportively guiding the patient to a more rational cognitive perspective about his or her symptom(s). This work may include belief modification, focusing/retribution, and normalizing the psychotic experience, among other strategies (170).

In belief modification, evidence for a delusional belief is gently challenged in reverse order to the strength to which the delusion is held. Focusing/retribution especially targets chronic auditory hallucinations. The therapist encourages the patient to elaborate his or her experience with the hallucination in exhaustive detail, in the process highlighting how the symptom relates to the patient's daily life and ultimately helping the patient reattribute the hallucination to an internal source. In normalizing the patient's psychotic experience, the therapist helps the patient see that his or her symptoms are embedded within the stressful vicissitudes of daily life, thus making them appear more normal and less "crazy."

Several randomized, controlled trials examining the effects of cognitive behavior therapy in schizophrenia have been conducted (356, 1256–1272). This research has been reviewed extensively (158, 168, 170, 188, 1273–1276). Overall, the data support the efficacy of cognitive behavior therapy for reducing the frequency and severity of positive symptoms and the distress associated with these symptoms. Furthermore, these gains appear to continue over time. The benefits do not appear to extend to relapse, rehospitalization, or social functioning. Further, it should be noted that treatment refusal and dropout rates are high for cognitive behavior therapy, perhaps because weekly one-to-one meetings amount to therapeutic overload for many chronic patients with high levels of negative symptoms. Persons with schizophrenia or delusional disorder who appear to benefit from cognitive behavior therapy are largely chronic outpatients with treatment-resistant (and often distressing) delusions and/or hallucinations. The intervention ranges in duration from weeks to years; usually several months are required. Cognitive behavior therapy manuals are available, but application typically requires supervised training.

e) Social skills training

Social skills training is defined by the use of behavioral techniques or learning activities that enable patients to acquire instrumental and affiliative skills in domains required to meet the interpersonal, self-care, and coping demands of community life (1277). The goal of social skills training is to remedy specific deficits in patients' role functioning. Thus, training is targeted rather than broad, and it is a highly structured approach that involves systematically teaching patients specific behaviors that are critical for success in social interactions. Social skills training can also include teaching patients how to manage antipsychotic medications, identify side effects, identify warning signs of relapse, negotiate medical and psychiatric care, express their needs to community agencies, and interview for a job. Social skills training can also be effective in increasing the use of specific social behaviors such as gaze and voice volume. Skills are taught

through a combination of the therapist's modeling (demonstration); the patient's role playing, usually to try out a particular skill in a simulated interaction; positive and corrective feedback to the patient; and homework assignments, by which the patient can practice a skill outside the training session. Social skills training can be provided individually, but it is almost always conducted in small groups of six to eight patients, for cost reasons and so that patients can learn from one another. Large groups (more than 10 patients) are not advised, as patients do not have adequate opportunity to rehearse.

Clinical trials have supported the efficacy of social skills training (149, 150, 173, 542, 1217, 1277–1292). With the exception of a recent meta-analysis (168), reviews have also endorsed social skills training (167, 169, 1293, 1294).

It is evident that patients with schizophrenia can learn a wide variety of social and independent living skills. Follow-up evaluations lasting up to 1 year showed good retention of the skills that were taught earlier (149, 150, 1278, 1282). When patients attempted to document the use of skills learned in the clinic in their natural environments, the results suggested generalization, but much more research is needed (1278, 1286).

While social skills training may have a positive effect on social role functioning (1283, 1295), it is not effective for reducing symptoms or preventing relapse (169). There are several reports of controlled studies in which social skills training significantly reduced relapse rates and symptom levels (1285, 1286), but more research is needed to document the extent to which social skills training actually protects patients from relapse. In fact, a study by Hogarty et al. (173) showed a loss in prophylactic effect at 2-year follow-up.

Skills training can be implemented in individual and group settings with patients, their families, or both. Patients selected for training should have moderate to severe deficits in social functioning; better-functioning patients require other approaches. There are a number of useful tools and guides for learning how to implement social skills training, including several teaching modules with a trainer's manual, a participant's workbook, and demonstration videos (169, 1296).

f) Programs of early intervention to delay or prevent relapse

The use of early intervention with the appearance of prodromal symptoms to relapse is one part of psychiatric management that can be effective in preventing rehospitalization. Studies have shown that relapse is usually preceded by the appearance of prodromal symptoms, which may last a few days, several weeks, or longer. The prodromal phase of relapse usually consists of moderate to severe dysphoric symptoms, such as tension and nervousness, eating less, difficulty concentrating and remembering, trouble sleeping, and depression, and it may also include mild psychotic symptoms and idiosyncratic behaviors (19, 375, 377, 806, 1297–1304). Such changes preceding relapse indicate either the emergence of new symptoms or increases in symptoms that were already present at baseline. In addition to changes in symptoms, changes in observable behaviors are noted by some patients and families. Examples include social withdrawal, wearing makeup in excessive or bizarre ways, and loss of concern about one's appearance. Controlled studies have demonstrated that specific programs to educate patients and families about prodromal symptoms and early intervention when symptoms occur can be helpful in reducing relapse rates (19, 220, 682, 807, 1305–1307).

2. Psychosocial treatments with very limited evidence bases

a) Personal therapy

As developed by Hogarty and colleagues (185–187), personal therapy is an individualized long-term psychosocial intervention provided to patients with schizophrenia with a weekly to bimonthly frequency within the larger framework of a treatment program that provides pharmacotherapy, family work (when a family exists), and multiple levels of both material and psy-

chological support. The primary objective of personal therapy is to achieve and maintain clinical stability in patients who are at risk for future relapses and functional disabilities. The approach is carefully tailored to the patient's phase of recovery from an acute episode and the patient's residual level of symptom severity, disability, and vulnerability to relapse. Personal therapy is delivered in three distinct phases that match the patient's level of clinical recovery and social/instrumental reintegration. Patients graduate to the next phase only if and when they have managed and stabilized at the prior phase. The therapy is therefore flexible, phase relevant, and sensitive to the dangers of environmental overload (including overload within the therapeutic environment). Another operational principle is that recovery requires time and disorder-appropriate treatment. As such, personal therapy is a long-term endeavor, with each phase lasting several months to 1–2 years. Although the initial results of Hogarty's seminal work on personal therapy are very promising, there have been no replications of this study.

b) Group therapies

The group therapies include a range of modalities, such as psychoeducation groups, social skills training groups, group counseling, and group psychotherapy, with some groups providing a blend of these modalities. The goals of group therapy are enhancements of problem solving, goal planning, social interactions, and medication and side effect management (1308). Kanas (1309, 1310) suggests that groups should focus on “here-and-now” issues and can be effective in increasing patients' coping skills, including the ability to cope with psychotic symptoms. In addition, group approaches may aid in teaching persons with schizophrenia interpersonal and coping skills and in providing a supportive social network for patients who tend to be socially isolated. Group meetings on a weekly basis are also a time-efficient way of monitoring patients for the onset of prodromal symptoms (19).

The evidence for the efficacy of group therapy in schizophrenia is not strong (163, 1308, 1311–1317). Most studies of outpatient and inpatient group therapy were conducted in the 1970s; there have been few recent studies. A number of well-controlled studies involving stable outpatients indicate that there is very modest evidence that group therapy can be effective in improving social adjustment (1318–1321) and coping skills (1316). For hospitalized patients in the acute phase of illness, there is no evidence for the effectiveness of insight-oriented group psychotherapy and some evidence that it may be harmful (1322). However, supportive groups may be useful in helping patients learn to cope with their symptoms, practice relating to others in a controlled environment, and develop a therapeutic alliance with the treatment team (1310, 1323, 1324).

The criteria for selection of patients for groups are derived from clinical experience; patients must have sufficient stability and enough reality testing that they can meaningfully participate (the exception may be previous group members who may benefit from group support while being stabilized after an acute episode). Exclusion criteria include constant preoccupation with hallucinations or delusions (especially paranoid), severe thought disorganization, and very poor impulse control. Higher functioning outpatients may benefit from interaction-oriented group therapy, while poorly functioning patients who may be overstimulated may benefit more from group approaches that attempt to reprogram cognitive and behavioral deficits (1325). There should be flexible use of adjunctive individual sessions, especially in times of crisis, for patients whose primary treatment mode is group therapy. It is generally recommended that a group should consist of six to eight patients (1321). A larger number of patients can be assigned to a group if some members do not attend sessions regularly (1326).

c) Programs of early detection and intervention to treat schizophrenia at or before onset

The early course of schizophrenia includes a premorbid stage, a prodromal stage, and a first-episode stage of illness. The premorbid phase refers to an asymptomatic period that may, in a minority of patients, include subtle and stable “neurodevelopmental” deficits in motor, social,

and/or intellectual functioning. While deficits usually mark a vulnerability to developing psychosis, they possess little if any ability to predict later development of psychosis (unpublished 1997 manuscript by P. Jones and J. van Os).

Developmental changes usually associated with adolescence may accelerate neurobiological processes (e.g., cortical-cortical synaptic pruning) that can become expressed symptomatically as neurodegeneration leading to the prodromal phase of disorder. The first signs of disorder are usually functional, not symptomatic, and consist of deficits in social and intellectual functioning and organizational abilities. Prodromal “symptoms” ultimately emerge alongside functional decline between 1 and 24 months before onset of an initial episode of illness. Nonspecific and negative symptoms usually develop first, followed by attenuated positive symptoms. In the year before onset, especially the last 4–6 months, symptoms accelerate in number and intensity. Their characteristic schizophrenic-like phenomenology (e.g., ideas of reference, paranoid ideation, unusual or alien thoughts, unexplained sounds) becomes more apparent, and ultimately psychosis ensues (675, 676, 718, 1327–1330). Criteria that are diagnostic of a prodromal syndrome have been articulated (1331–1333). These criteria predict conversion to psychosis within a year with high frequency, e.g., between 36% and 54% of such samples (1334, 1335).

Early intervention has two aims: 1) to treat active psychotic or prodromal symptoms and 2) to prevent future deterioration and further course progression toward chronicity. Postonset, early intervention targets the duration of untreated psychosis in hopes of reducing future severity and chronicity and preventing the extensive collateral damage that results from active disorder, such as discrimination, social shunning, and poor treatment alliance and adherence (tertiary prevention). Preonset or prodromal phase intervention targets all of the previously mentioned aims plus delaying onset (secondary prevention, reducing prevalence) or preventing onset (primary prevention, reducing incidence).

Because active psychosis is sometimes lethal and often socially destructive, the rationale for treating the symptoms of psychosis as close to onset as possible is compelling (251). Evidence also suggests that existing treatments might affect the natural course of psychosis beyond controlling symptoms. Numerous studies demonstrate significant correlations of earlier intervention (medication and/or psychosocial) after onset with more rapid treatment response and better longer-term outcome (reviewed by McGlashan [254, 1336, 1337]). Not all studies find this correlation, however, and a causal relationship between postonset early intervention and better prognosis has yet to be demonstrated using controlled designs (1338, 1339).

More compelling evidence of the benefit of early intervention comes from recent studies in the prodromal phase. McGorry et al. (262) randomly assigned operationally defined, prodromally symptomatic, high-risk patients to receive one of two open-label treatments. The enriched treatment group received second-generation antipsychotics, cognitive behavior therapy emphasizing stress management, and basic support. The control group received basic support without medication. At 6 months, significantly more patients in the control group had converted to psychosis. McGlashan et al. (263) randomly assigned a similarly defined symptomatic prodromal population (1340) to receive second-generation antipsychotics or placebo in a double-blind design. The study found a significant drug effect on prodromal symptoms at 8 weeks (264) and beyond, up to 1 year (1341).

Overall, the evidence to date indicates that early intervention in psychosis has tertiary preventive benefit and suggests that it also has secondary preventive benefit. Several more studies are necessary before treatment recommendations are appropriate; however, two strategies are clear: 1) first-episode psychosis should be treated as soon as possible and 2) persons who meet the criteria for being prodromally symptomatic and at risk for psychosis in the near future should be assessed carefully and monitored frequently until their symptoms either remit spontaneously, evolve into schizophrenia, or evolve into another diagnosable and treatable mental disorder.

d) Patient education

While patient education must clearly be a part of standard medical practice and is required medicolegally as part of the informed consent process, it has not been clear just how best to provide this education and whether the provision of education actually improves patients' knowledge and changes patients' behavior (30). Over the last few years different types of patient education have been subjected to empirical study (11, 1270, 1342–1346). These so-called educational approaches employed a variety of cognitive, behavioral, and psychological strategies as well. Studies conducted to date provide modest evidence that group approaches improve social functioning (1343) and that interventions focused on medication adherence achieve their intended effect (11, 1270, 1346). However, at this point no specific educational approach can be recommended.

e) Case management

A common observation has been that patients often “fall through the cracks” between different community agencies or program elements and do not receive needed care. To remedy this situation, a case management function has been developed. Either several members of a team or one staff member can be assigned to be the case manager, ensuring that patients receive coordinated, continuous, and comprehensive services. For example, the case manager may accompany a patient to a welfare agency, visit the home if a clinical appointment is missed, or convene a meeting of workers from different agencies serving the patient to formulate an overall treatment plan in conjunction with the psychiatrist.

Results of controlled studies of the effects of case management have yielded inconsistent findings, probably because of methodological problems in design, including 1) lack of specification of the case management intervention, 2) poor characterization of the patient population, 3) inadequacy of outcome measures, 4) inadequate length of the program, and 5) lack of specification of community context (1347). A major problem that has arisen in community mental health planning is that some public programs have developed case management services without having adequate treatment resources for optimal patient care. Problems in implementation also occur when case managers function independently and are not well integrated into the treatment team.

Recent research has focused on the effectiveness of specific models of case management. One approach has been to develop “enhanced” case management programs, either by lowering the caseloads of staff members (1348–1350), emphasizing a team model (1348, 1351–1353), or augmenting the usual services of case managers with those of additional clinician experts (1354–1356). These enhancements have been found to improve outcomes in some studies.

f) Cognitive remediation and therapy

The cognitive deficits associated with schizophrenia have assumed an increasingly central role in explaining the disability associated with the disorder. Distractibility, memory problems, lack of vigilance, attentional deficits, and limitations in planning and decision making characterize these cognitive impairments. Cognitive remediation strategies have attempted to address these problems using restorative, compensatory, and environmental approaches to treatment. The restorative model emphasizes direct elimination of impairments by correction of underlying cognitive deficits. Compensatory strategies attempt to help patients “work around” their deficits, while environmental approaches manipulate the environment to decrease cognitive demands on patients (1357). An underlying premise of these cognitive approaches is that they not only will have direct benefit but will increase the ability of patients to profit from other therapeutic approaches and improve social and other aspects of functioning.

Numerous experimental trials have demonstrated that relatively brief, frequently computer-assisted training programs can improve patients' performance on neuropsychological tests (1207, 1358–1371). However, these studies, while promising, failed to demonstrate durability

and generalizability, failed to control for medication use, and have involved a relatively small number of subjects overall (1207). In one study with encouraging findings, cognitive remediation was paired with work therapy and treatment was sustained over 6 months (1372). Compared with work therapy alone, cognitive remediation yielded significantly greater improvements as measured by neuropsychological tests of executive function and working memory. Working memory effects endured 6 months after the conclusion of treatment (1373). Nevertheless, cognitive remediation must still be regarded as experimental and cannot yet be recommended as part of routine practice. The few studies that focus on compensatory and environmental strategies bear similarities to psychosocial interventions that provide case management. Velligan and colleagues developed cognitive adaptation training (1374, 1375). This compensatory approach improved symptoms, motivation, and functioning, but these findings need to be replicated before such an approach can be recommended.

3. Self-help groups

Patients and their families are taking an increasingly active role in the treatment process. Their goals include increasing their influence on treatment planning and implementation, becoming less dependent on professionals, decreasing the discrimination associated with mental illness, and working to achieve adequate support for treatment and research in mental illness. Consumer organizations fall into three major categories (consumer-run or -operated services, consumer partnership services, and consumers as employees), each with its own membership, purpose, and philosophy (1376). Patients and families should be informed about the existence of these organizations.

a) Patient and self-help treatment organizations

Peer support is social, emotional, and sometimes instrumental support that is mutually offered or provided by persons having a mental health condition (e.g., consumers of mental health services) to others sharing a similar mental health condition to bring about a desired social or personal change (196). Peer support may be either financially compensated or voluntary. A consumer in this context is an individual with severe mental illness who is or was a user or recipient of mental health services and who identifies him- or herself as such (203).

The oldest and most pervasive of peer support types is self-help groups. Although there are groups that cover most mental health-related problems, the most noted ones that are relevant to schizophrenia are GROW, Recovery, Inc., Schizophrenics Anonymous, National Depressive and Manic Depressive Association groups, double-trouble groups (for those with both substance use disorders and other mental disorders), and Emotions Anonymous. Until very recently these groups were required to be face-to-face (196). However, Internet online support groups, with no face-to-face interaction, have come into existence (1377).

Based largely on uncontrolled studies of self-help groups for persons with severe mental illness, Davidson et al. (197) concluded that self-help groups seem to improve symptoms and increase participants' social networks and quality of life. Specifically, Galanter (1378) evaluated Recovery, Inc.; Kennedy evaluated GROW (unpublished 1989 manuscript of M. Kennedy); and Kurtz (1379) evaluated the National Depressive and Manic Depressive Association with regard to hospitalizations. All found reductions in hospitalizations and, in one instance, shorter hospitalization when consumers were hospitalized (unpublished 1989 manuscript of M. Kennedy). In addition, these studies, along with Raiff's (198) study of Recovery, Inc., determined that members had improved coping, greater acceptance of illness, improved medication adherence, lower levels of worry, and higher satisfaction with their health. Further, in a study by Powell et al. (200), self-help participation resulted in improved daily functioning and improved illness management. Furthermore, longer term participants have better outcomes (198, 199, and outcomes are better when participants are involved in operating the group rather than just attending the group (200).

Within the realm of consumer-provided or -delivered services are consumer-run or -operated services, consumer partnership services, and consumers as employees. Consumer-run or -operated services are services that are planned, operated, administered, and evaluated by consumers (201, 202). Examples of consumer-operated services include drop-in centers, club houses, crisis services, vocational and employment services, consumer compeer services, psychosocial educational services, and peer support programs, such as Friends Connection in Philadelphia (207), where consumers with dual diagnoses are matched with recovering consumers. Those service programs that are not freestanding legal entities but share the control of the operation of the program with nonconsumers are categorized as consumer partnerships. Consumer employees are individuals who fill positions designated for consumers as well as consumers who are hired into traditional mental health positions. When consumers are hired into existing mainstream positions, to be considered a consumer employee, the individual must fulfill the definition of a consumer, which includes publicly identifying him- or herself as a consumer. Frequently, these designated consumer positions are adjuncts to traditional mental health services, such as a case manager aid position. Examples of specially designated consumer positions are peer companion, peer advocate, consumer case manager, peer specialist, and peer counselor. The term “prosumer” has also come into use. It refers to a person who is both a consumer and a professional, such as a trained psychologist who identifies him- or herself as a consumer (1380).

Reviews of peer support/consumer-provided services specifically for persons with severe mental illness have generated positive but somewhat tentative results, given the infancy of the research area (197, 203, 204). Consumer-provided services have been found to be as effective as or more effective than services provided by nonconsumers (1381, 1382). Two studies using experimental or quasi-experimental designs found reduced use of hospitalization and/or crisis services associated with peer support (207, 208). In the study by Klein et al., recipients of the consumer-delivered services also had improved social functioning, reduced substance use, and improved quality of life. In a randomized study, consumers assigned to a condition in which a consumer assisted in postdischarge network services had fewer and shorter hospitalizations, relative to comparison subjects, and functioned in the community without utilizing mental health services (205). The addition of a peer specialist to an intensive case management team, compared to addition of a nonconsumer specialist to the team, was associated with gains in some aspects of quality of life, fewer significant life problems, and improved self-esteem and social support among consumers (1383). Other less rigorously designed studies also found fewer hospitalizations for those served by consumers (206, 209). A consumer employment program resulted in higher rates of employment, higher earnings, and a tendency toward better vocational rehabilitation outcomes for program participants, compared with consumers who did not receive peer-supported vocational services (1384). Similarly, recipients of a consumer-operated employment program obtained employment at higher rates than found in usual employment services (1385).

b) Relative organizations

Family associations have taken on very important roles in supporting research, providing education, and supporting the families of the mentally ill (1386–1388).

The myriad services provided by family associations include (but are not limited to):

- Education about mental illness—for the public, as well as for professionals who do not specialize in psychiatric disorders.
- Support for research on family services—not only by raising money directly but also by advocating for government funds (1237). The National Alliance for Research on Schizophrenia and Affective Disorders, NAMI in the United States, and other associations in Europe have helped to fund and support research projects.

- In-depth education for families. This education includes not only help lines and literature for patients and families who call with questions about medication, physicians, or community services but also information about the long-term treatment of the major psychiatric disorders. NAMI's Family-to-Family Education Program is a specific example of an organized educational program offered free to families. This program has been shown to reduce families' subjective burden of illness and improve their well-being (1238).
- Advocacy for the rights of the mentally ill by means of legal action.
- Crisis lines and web sites (1389).
- Centers where consumers can meet, find support, and share their feelings with other families without (what they perceive as) "interference" from mental health professionals. Specific support groups are available for siblings and for families of children or adolescents with schizophrenia.

Studies have suggested that helping families educate and empower themselves and helping them to become more involved in service delivery results in better outcomes for the mentally ill family members (1390, 1391).

PART C:

FUTURE RESEARCH DIRECTIONS

The ultimate goal of treatment is to minimize the effects of illness and to enable patients to live full, productive, and rewarding lives. This goal remains elusive for many persons with schizophrenia. Not only do most persons not receive the full range of evidence-based treatments, but even the best treatments currently available do not enable most patients the opportunity for full and productive lives that they might have experienced without the illness. Available treatments focus primarily on the psychotic symptoms of schizophrenia and are reasonably effective at controlling these symptoms in the majority of patients. Most patients experience symptom reduction with pharmacotherapy, and relapse rates are reduced by more than half with maintenance treatment. Certain family intervention approaches further reduce relapse rates, and selected psychosocial treatments appear beneficial for occupational and social functioning. Despite efficacious treatment, most patients remain symptomatic and vulnerable to relapse. Persistent impairments are common, and long-term outcomes, while heterogeneous, still represent significant morbidity for most patients. Outcomes in other domains, especially the deficit symptoms and impaired functional status, remain unsatisfactory. This situation underscores the need for several research priorities.

Basic research is essential to provide a better understanding of the etiologies and mechanisms of these impairments and to develop treatment technologies derived from new knowledge. It is likely that the schizophrenia syndrome is heterogeneous, and hence future treatment development must be informed through a better understanding of the various components of the syndrome. In particular, attention must be directed toward understanding the deficit syndrome and neurocognitive impairments that account for many of the disabling effects of the illness. Major breakthroughs in prevention or treatment will likely depend on advances in basic knowledge about brain function.

Intervention research must be informed by advances in basic neuroscience so that new treatments more directly affect these aspects of the syndrome that remain largely resistant to current treatments. Priority must be given to pharmacological and psychosocial interventions that address

functional impairments and especially to combined treatment approaches that optimize brain function as well as opportunities for patients to take advantage of improved capacity. Intervention research is needed to examine the relative efficacy of available treatments, especially options that represent substantial cost differentials. Research should continue on psychosocial interventions that show promise when added to antipsychotic medications. These interventions include family interventions, disease-specific forms of psychological treatments, skills training, cognitive therapy, supported employment, and personally tailored combinations of these modalities. Given the crucial importance of adequate housing, research is needed to examine the effectiveness of various approaches to promoting stable, high-quality housing, including the matching of patients to housing resources on the basis of clinical and social characteristics.

Research into early detection and treatment of schizophrenia is also important to determine whether applying existing pharmacological and psychosocial interventions earlier in the course of the disorder provides added efficacy or has the potential for secondary or tertiary prevention.

Clinical research should also attend to a fuller range of outcomes, beyond symptom relief, including functional status and quality of life. These outcomes represent the range of priorities by various “stakeholders”: researchers, practitioners, patients, families, and payers. A more comprehensive approach to outcomes assessment will ensure that studies are viewed as relevant and informative to these various stakeholders, who function as effective advocates at various levels. Furthermore, we must ask for whom outcomes are improved. Clinical research on treatment-relevant subgroups will aid in better treatment matching and more judicious allocation of resources. Genetics research also has the potential for providing data to match patients with optimal treatments. In short, we need to know which treatments enhance which outcomes for which patients.

Clinical services research should address the translation of efficacious interventions into practice. Several questions must be addressed: To what degree are efficacious treatments used in practice? Who receives them, and what are the patient-related and provider-related determinants of these practice patterns? What is the cost-effectiveness in practice of interventions with known efficacy? What are the barriers to the adoption of efficacious treatments in practice, and how can these be overcome? What strategies for changing practices are most effective? Service systems research must tackle these questions at the system level and, in addition, address the question of which organizational and financing strategies promote services that incorporate the most effective treatments. Finally, services research needs to address the current failure of treatment systems to ensure that evidence-based treatments are properly implemented and offered to those who can benefit from them. In addition, services research needs to examine the relationships between patterns of service use and illness characteristics, especially the effect of cognitive deficits on patients’ capacity to gain access to and use services. Such research should also evaluate the effects of interventions in improving patients’ capacity to use services appropriately.

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 American Academy of Geriatric Psychiatry
 American Music Therapy Association
 American Nurses Association

REFERENCES

The following coding system is used to indicate the nature of the supporting evidence in the summary recommendations and references:

- [A] *Double-blind, randomized clinical trial.* A study of an intervention in which subjects are prospectively followed over time; there are treatment and control groups; subjects are randomly assigned to the two groups; both the subjects and the investigators are blind to the assignments.
- [A–] *Randomized clinical trial.* Same as above but not double-blind.
- [B] *Clinical trial.* A prospective study in which an intervention is made and the results of that intervention are tracked longitudinally; study does not meet standards for a randomized clinical trial.
- [C] *Cohort or longitudinal study.* A study in which subjects are prospectively followed over time without any specific intervention.
- [D] *Case-control study.* A study in which a group of patients is identified in the present and information about them is pursued retrospectively or backward in time.

- [E] *Review with secondary data analysis.* A structured analytic review of existing data, e.g., a meta-analysis or a decision analysis.
- [F] *Review.* A qualitative review and discussion of previously published literature without a quantitative synthesis of the data.
- [G] *Other.* Textbooks, expert opinion, case reports, and other reports not included above.

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