Complete Summary

GUIDELINE TITLE

Practice guideline for the treatment of patients with schizophrenia. Second edition.

BIBLIOGRAPHIC SOURCE(S)

American Psychiatric Association. Practice guideline for the treatment of patients with schizophrenia. 2nd ed. Arlington (VA): American Psychiatric Association; 2004 Feb. 114 p. [1391 references]

GUIDELINE STATUS

This is the current release of the guideline.

This guideline updates a previous version:

American Psychiatric Association (APA). Practice guideline for the treatment of patients with schizophrenia. Washington (DC): American Psychiatric Press, Inc; 1997. 146 p.

Practice guideline for the treatment of patients with schizophrenia. American Psychiatric Association (APA). Am J Psychiatry 1997 Apr;154(4 Suppl):1-63.

**** REGULATORY ALERT ****

FDA WARNING/REGULATORY ALERT

Note from the National Guideline Clearinghouse: This guideline references a drug(s) for which important revised regulatory and/or warning information has been released.

- June 17, 2008, Antipsychotics (conventional and atypical]): The U.S. Food and Drug Administration (FDA) notified healthcare professionals that both conventional and atypical antipsychotics are associated with an increased risk of mortality in elderly patients treated for dementia-related psychosis. The prescribing information for all antipsychotic drugs will now include information about the increased risk of death in the BOXED WARNING and WARNING sections.
- December 12, 2007, Carbamazepine: The U.S. Food and Drug Administration (FDA) has provided recommendations for screening that should be performed on specific patient populations before starting treatment with carbamazepine.
- September 17, 2007, Haloperidol (Haldol): Johnson and Johnson and the U.S. Food and Drug Administration (FDA) informed healthcare professionals that

the WARNINGS section of the prescribing information for haloperidol has been revised to include a new Cardiovascular subsection.

COMPLETE SUMMARY CONTENT

SCOPE

DISEASE/CONDITION(S)

Schizophrenia

GUIDELINE CATEGORY

Evaluation
Management
Treatment

CLINICAL SPECIALTY

Psychiatry

INTENDED USERS

Physicians

GUIDELINE OBJECTIVE(S)

To assist psychiatrists in assessing and treating adult patients with schizophrenia

TARGET POPULATION

Patients 18 years of age and older with schizophrenia, according to the criteria defined in the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* (DSM-IV).

INTERVENTIONS AND PRACTICES CONSIDERED

Evaluation

1. Initial evaluation including complete psychiatric and general medical histories, assessment for substance use and physical and mental status examinations
2. Assessment of suicide potential and/or likelihood of dangerous or aggressive behavior
3. Laboratory, electrophysiological, and radiological assessments
    - Pregnancy test in women of childbearing potential
4. More detailed studies as indicated (e.g., screening for heavy metal toxins, electroencephalogram (EEG), magnetic resonance imaging [MRI] scan, or computed tomography [CT] scan)

Treatment/Management

1. Patient/family education including discussion of risks and benefits of treatment
2. Psychosocial interventions
    - Family interventions
    - Supported employment
    - Assertive community treatment
    - Social skills training
    - Cognitive behaviorally oriented psychotherapy
3. Antipsychotic medications
    - First generation agents:
        - Phenothiazines: Fluphenazine, trifluoperazine, perphenazine, mesoridazine, chlorpromazine, thioridazine
        - Butyrophenone: Haloperidol
        - Others: Thiothixene, molindone, loxapine
    - Second generation agents: Aripiprazole, clozapine, risperidone, olanzapine, ziprasidone, and quetiapine
4. Adjunctive medications
    - Benzodiazepines
    - Antidepressants
    - Mood stabilizers
    - Beta-blockers
5. Other somatic therapies
    - Electroconvulsive therapy (ECT)
    - Repetitive transcranial magnetic stimulation (rTMS)
6. Treatment settings and housing options, including hospitalization and day treatment programs

MAJOR OUTCOMES CONSIDERED

- Morbidity and mortality associated with schizophrenia
- Frequency and severity of schizophrenic episodes
- Improvement (or diminution or reduction) in symptoms of schizophrenia
- Improvement in role functioning

METHODOLOGY

METHODS USED TO COLLECT/SELECT EVIDENCE

Searches of Electronic Databases

DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

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 American Psychiatric Association (APA) staff and individual members of the work group on schizophrenia.

NUMBER OF SOURCE DOCUMENTS

Not stated

METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Weighting According to a Rating Scheme (Scheme Given)

RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

[A] *Randomized, double-blind 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; and 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. 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*. Opinion-like essays, case reports, and other reports not categorized above

METHODS USED TO ANALYZE THE EVIDENCE

Review of Published Meta-Analyses
Systematic Review with Evidence Tables

DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

Following the literature review, relevant articles from the search are obtained, in abstract or in entirety. The work group reviews these articles, codes them for study design, and constructs evidence tables for each treatment.

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Expert Consensus

DESCRIPTION OF METHODS USED TO FORMULATE THE RECOMMENDATIONS

The work group constructs evidence tables to illustrate the data regarding risks and benefits for each treatment and to evaluate the quality of the data. These tables facilitate group discussion of the evidence and agreement on treatment recommendations before guideline text is written.

RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

[I] Recommended with substantial clinical confidence.

[II] Recommended with moderate clinical confidence.

[III] May be recommended on the basis of individual circumstances.

COST ANALYSIS

Published cost analyses were reviewed.

METHOD OF GUIDELINE VALIDATION

External Peer Review
Internal Peer Review

DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

Each practice guideline is extensively reviewed at multiple draft stages. Draft 1 is reviewed by the Steering Committee. Draft 2 is reviewed by approximately 50 reviewers with expertise in the topic, representatives of allied organizations, the American Psychiatric Association (APA) Assembly, District Branches, the Joint Reference Committee, the Board of Trustees, the Council on Quality Care, other components related to the subject area, and any APA member by request. Draft 3 is reviewed and approved for publication by the Assembly and the Board of Trustees.

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

Each recommendation is coded according to the degree of clinical confidence with which the recommendations are made. Definitions of the recommendation coding system are provided below.

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 complete blood complete (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 human immunodeficiency virus (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, electroencephalogram [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 recommended **[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 "extrapyramidal symptom 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 body mass index 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 is 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 (including 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 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 population: 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]**.

CLINICAL ALGORITHM(S)

An algorithm is provided in the original guideline document for somatic treatment of schizophrenia.

EVIDENCE SUPPORTING THE RECOMMENDATIONS

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

The evidence base for practice guidelines is derived from two sources: research studies and clinical consensus. Where gaps exist in the research data, evidence is derived from clinical consensus, obtained through extensive review of multiple drafts of each guideline.

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

POTENTIAL BENEFITS

Improved assessment and treatment of adult patients with schizophrenia

POTENTIAL HARMS

Antipsychotic Medications

- *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.

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

Anticonvulsants

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.

Antidepressants

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.

Benzodiazepines

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 problematic 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 dependence on these agents.

Lithium

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.

Electroconvulsive Therapy (ECT)

Effects of ECT on the cardiovascular system are seen in virtually all patients but are typically benign and self-limited. Cognitive side effects may also be observed

with ECT, although there is much individual variation in the extent and severity of such effects. 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.

CONTRAINDICATIONS

CONTRAINDICATIONS

- 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.
- Clozapine is contraindicated in patients with narrow-angle glaucoma and in patients with agranulocytosis or severe granulocytopenia with prior trials of clozapine.
- Although there are no absolute contraindications to electroconvulsive therapy (ECT), recent myocardial infarction, some cardiac arrhythmias, and some intracranial-space occupying lesions may increase risk and are indications for caution and consultation.

QUALIFYING STATEMENTS

QUALIFYING STATEMENTS

This guideline is 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 patterns evolve. These parameters of practice should be considered guidelines only. Adherence to them will not ensure a successful outcome for every patient, nor should they be construed 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.

IMPLEMENTATION OF THE GUIDELINE

DESCRIPTION OF IMPLEMENTATION STRATEGY

After final approval by the Assembly and Board of Trustees, each practice guideline is widely disseminated. Practice guidelines are made available to all psychiatrists in a variety of ways, including publication in *The American Journal of Psychiatry*.

IMPLEMENTATION TOOLS

Clinical Algorithm
Staff Training/Competency Material

For information about availability, see the "Availability of Companion Documents" and "Patient Resources" fields below.

INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

IOM CARE NEED

Getting Better
Living with Illness

IOM DOMAIN

Effectiveness
Patient-centeredness

IDENTIFYING INFORMATION AND AVAILABILITY

BIBLIOGRAPHIC SOURCE(S)

American Psychiatric Association. Practice guideline for the treatment of patients with schizophrenia. 2nd ed. Arlington (VA): American Psychiatric Association; 2004 Feb. 114 p. [1391 references]

ADAPTATION

Not applicable: The guideline was not adapted from another source.

DATE RELEASED

1997 (revised 2004 Feb)

GUIDELINE DEVELOPER(S)

American Psychiatric Association - Medical Specialty Society

SOURCE(S) OF FUNDING

American Psychiatric Association (APA)

GUIDELINE COMMITTEE

Work Group on Schizophrenia
Steering Committee on Practice Guidelines

COMPOSITION OF GROUP THAT AUTHORED THE GUIDELINE

Work Group Members: Anthony F. Lehman, MD, MSPH (Chair); Jeffrey A. Lieberman, MD (Vice-Chair); Lisa B. Dixon, MD, MPH; Thomas H. McGlashan, MD;

Alexander L. Miller, MD; Diana O. Perkins, MD, MPH; Julie Kreyenbuhl, PharmD, PhD, Consultant

Steering Committee on Practice Guidelines Members: John S. McIntyre, MD (Chair); Sara C. Charles, MD (Vice-Chair); Kenneth Altshuler, MD; Ian Cook, MD; C. Deborah Cross, MD; Lisa Mellman, MD; Louis Alan Moench, MD; Grayson Norquist, MD; Stuart W. Twemlow, MD; Sherwyn Woods, MD, PhD; Joel Yager, MD

Consultants and Liaisons: Sheila Hafter Gray, MD (Liaison); Kathleen Askland, MD (Liaison); Rupang Pandya, MD (Liaison); Konasale Prasad, MD (Liaison); Robert Johnston, MD (Area I); James Nininger, MD (Area II); Roger Peele, MD (Area III); Daniel J. Anzia, MD (Area IV); R. Scott Benson, MD (Area V); Lawrence Lurie, MD (Area VI); R. Dale Walker, MD (Area VII)

Staff: Robert Kunkle, MA, Senior Program Manager; Althea Simpson, MBA, Project Coordinator; Laura J. Fochtmann, MD, Medical Editor; Claudia Hart, Director, Department of Quality Improvement and Psychiatric Services; Darrel Regier, MD, MPH, Director, Division of Research

FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

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 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. The guideline has been extensively reviewed by members of the American Psychiatric Association (APA) as well as by representatives from related fields. Contributors and reviewers have all been asked to base their recommendations on an objective evaluation of the available evidence. Any contributor or reviewer who has a potential conflict of interest that may bias (or appear to bias) his or her work has been asked to notify the APA Department of Quality Improvement and Psychiatric Services. This potential bias is then discussed with the work group chair and the chair of the Steering Committee on Practice Guidelines. Further action depends on the assessment of the potential bias.

GUIDELINE STATUS

This is the current release of the guideline.

This guideline updates a previous version:

American Psychiatric Association (APA). Practice guideline for the treatment of patients with schizophrenia. Washington (DC): American Psychiatric Press, Inc; 1997. 146 p.

Practice guideline for the treatment of patients with schizophrenia. American Psychiatric Association (APA). Am J Psychiatry 1997 Apr;154(4 Suppl):1-63.

GUIDELINE AVAILABILITY

Electronic copies: Available in Portable Document Format (PDF) from the American Psychiatric Association (APA) Web site.

Print copies: Available from the American Psychiatric Press, Inc (APPI), 1400 K Street NW, Washington, DC 20005; (202) 682-6262; (800) 368-5777; fax (202) 789-2648.

AVAILABILITY OF COMPANION DOCUMENTS

The following is available:

- American Psychiatric Association practice guideline development process. Washington, DC: APA, 2004.

Electronic copies: Available in Portable Document Format (PDF) from the American Psychiatric Association (APA) Web site.

Print copies: Available from the American Psychiatric Press, Inc (APPI), 1400 K Street NW, Washington, DC 20005; (202) 682-6262; (800) 368-5777; fax (202) 789-2648.

Additionally, a continuing medical education (CME) course is available online at the American Psychiatric Association Web site.

PATIENT RESOURCES

None available

NGC STATUS

This summary was completed by ECRI on December 1, 1998. The information was verified by the guideline developer on February 3, 1999. This NGC summary was updated on July 8, 2004. The information was verified by the guideline developer on August 2, 2004. This summary was updated by ECRI on August 15, 2005, following the U.S. Food and Drug Administration advisory on antidepressant medications. This summary was updated by ECRI on January 18, 2006, following the U.S. Food and Drug Administration advisory on Clozaril (clozapine). This summary was updated by ECRI Institute on October 2, 2007, following the U.S. Food and Drug Administration (FDA) advisory on Haloperidol. This summary was updated by ECRI Institute on November 6, 2007, following the U.S. Food and Drug Administration advisory on Antidepressant drugs. This summary was updated by ECRI Institute on January 10, 2008, following the U.S. Food and Drug Administration advisory on Carbamazepine. This summary was updated by ECRI Institute on July 25, 2008, following the U.S. Food and Drug Administration advisory on Antipsychotics.

COPYRIGHT STATEMENT

This NGC summary is based on the original guideline, which is subject to the guideline developer's copyright restrictions.

DISCLAIMER

NGC DISCLAIMER

The National Guideline Clearinghouse™ (NGC) does not develop, produce, approve, or endorse the guidelines represented on this site.

All guidelines summarized by NGC and hosted on our site are produced under the auspices of medical specialty societies, relevant professional associations, public or private organizations, other government agencies, health care organizations or plans, and similar entities.

Guidelines represented on the NGC Web site are submitted by guideline developers, and are screened solely to determine that they meet the NGC Inclusion Criteria which may be found at http://www.guideline.gov/about/inclusion.aspx .

NGC, AHRQ, and its contractor ECRI Institute make no warranties concerning the content or clinical efficacy or effectiveness of the clinical practice guidelines and related materials represented on this site. Moreover, the views and opinions of developers or authors of guidelines represented on this site do not necessarily state or reflect those of NGC, AHRQ, or its contractor ECRI Institute, and inclusion or hosting of guidelines in NGC may not be used for advertising or commercial endorsement purposes.

Readers with questions regarding guideline content are directed to contact the guideline developer.

Date Modified: 9/29/2008