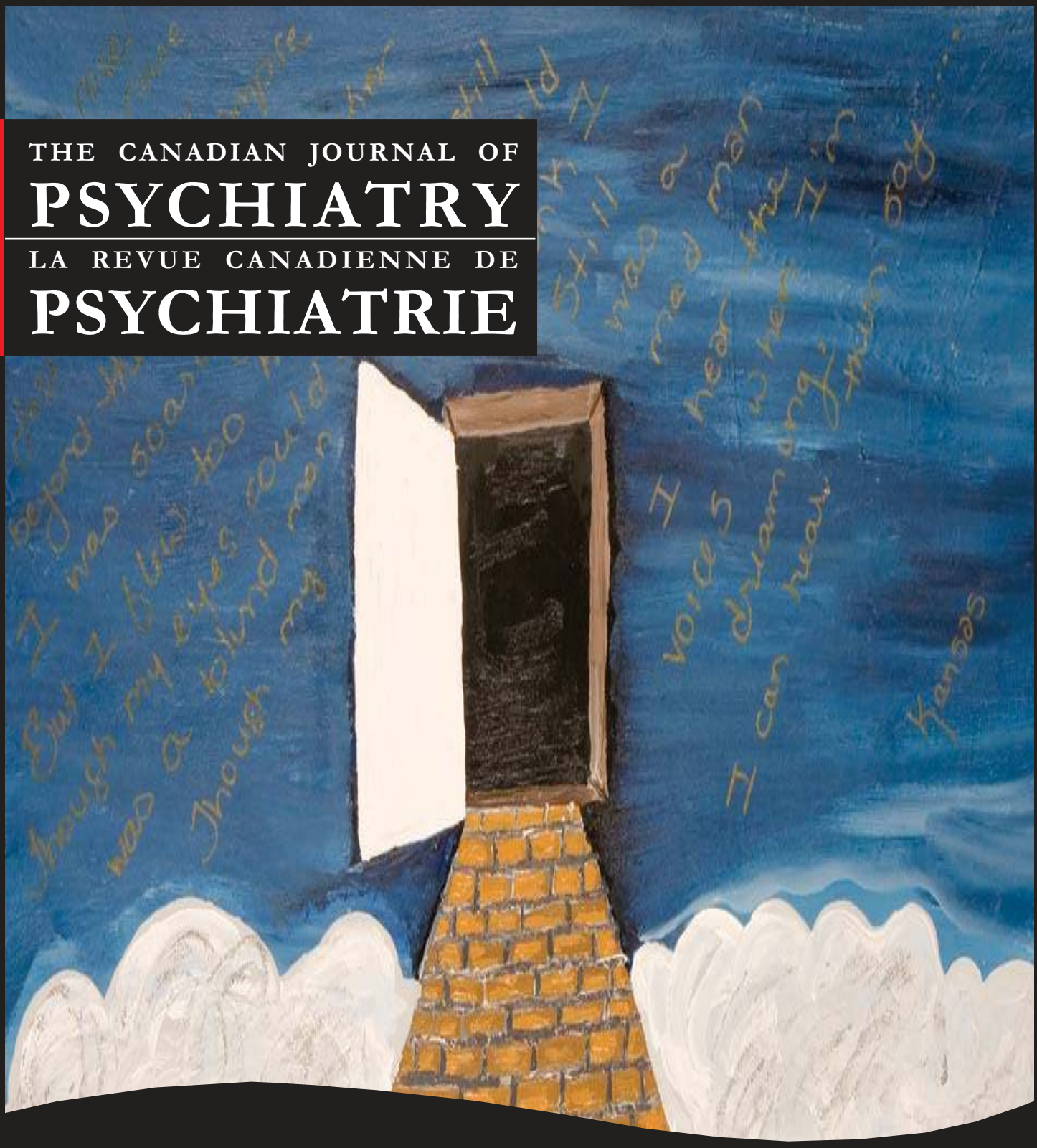
Vol 50, No 13, Supplement 1 November 2005 novembre



THE CANADIAN JOURNAL OF PSYCHIATRY
LA REVUE CANADIENNE DE PSYCHIATRIE

Canadian Psychiatric Association

Association des psychiatres du Canada

CLINICAL PRACTICAL GUIDELINES
Treatment of Schizophrenia

The *Canadian Journal of Psychiatry* (CJP) is published 14 times a year by the Canadian Psychiatric Association. Printed at Tri-graphic Printing Limited, Ottawa, Ontario. Publications Mail Agreement 40012324. Return undeliverable Canadian addresses and all correspondence to: Editor, The *Canadian Journal of Psychiatry*, Editorial Office, 141 Laurier Avenue West, Suite 701, Ottawa, ON K1P 5J3. Tel: (613) 234-2815; Fax: (613) 234-9857. E-mail: cjp@cpa-apc.org. **2005 print subscription prices in Canada:** $160.00 (includes tax); NF, NB, NS: $171.97. **2005 print subscription prices in the US and other countries:** $200 (CDN). Subscription to the print and online versions of the *Canadian Journal of Psychiatry* for members of the CPA is included in the CPA membership fee. For more information, contact subscriptions@cpa-apc.org. **Refunds and back issues:** No refunds will be issued; some back issues available. Claims for missed issues will be honoured up to 6 months after the missed issue within Canada and up to 1 year for foreign claims. Statements made by contributors or advertisers do not necessarily reflect the opinions of the CPA. Acceptance of an advertisement by the Journal does not imply endorsement. Information for Contributors is published periodically and is available from the Editorial Office or on the CPA Website: www.cpa-apc.org. **Advertising:** Smita Hamzeh, CJP, 141 Laurier Avenue West, Suite 701, Ottawa, ON K1P 5J3 Tel: (613) 234-2815.

L'Association des psychiatres du Canada publie 14 numéros par année de La Revue canadienne de psychiatrie (RCP). Elle est imprimée par Tri-graphic Printing Limited, Ottawa (Ontario). Société canadienne des postes — envois de publications canadiennes — contrat de vente no 40012324. Renvoyez toutes les adresses non distribuables au Canada et toute la correspondance à la Revue : Rédacteur, La Revue canadienne de psychiatrie, Bureau de la rédaction, 141, avenue Laurier Ouest, bureau 701, Ottawa (Ontario) K1P 5J3. Tél. : (613) 234-2815, Téléc. : (613) 234-9857. Courriel : cjp@cpa-apc.org. **Tarifs d'abonnement de 2005 au Canada :** 160 $ (taxes comprises –TVH ou TPS); T.-N., N.-B., N-É. : 171.97 $. **Prix de l'abonnement aux imprimés en 2005 aux États-Unis et dans tous les autres pays :** 200 $ (CDN). L'abonnement aux versions imprimée et électronique de la RCP pour les membres de l'APC est inclus dans les frais d'adhésion annuels. Pour de plus amples détails, veuillez communiquer à l'adresse suivante : subscriptions@cpa-apc.org. **Remboursements et numéros précédents :** Aucun remboursement; certains numéros précédents sont disponibles. Nous ferons honneur aux réclamations en provenance du Canada qui sont reçues dans les 6 mois suivant le numéro manquant et dans les 12 mois pour les réclamations en provenance de l'étranger. Les avis exprimés dans les articles et annonces publicitaires ne reflètent pas nécessairement ceux de l'APC. La publication d'une annonce dans la Revue n'implique pas l'approbation de l'association. Information à l'intention des auteurs est publiée périodiquement. On peut en obtenir des copies en communiquant avec le bureau de la rédaction ou sur le site web de l'APC : www.cpa-apc.org. **Annonces :** Smita Hamzeh, RCP, 141, avenue Laurier Ouest, bureau 701, Ottawa (Ontario) K1P 5J3 Tél. : (613) 234-2815.

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The Canadian Journal of Psychiatry
La Revue canadienne de psychiatrie

The Official Journal of the Canadian Psychiatric Association
La Revue officielle de l'Association des psychiatres du Canada

November 2005 (Vol 50, Supplement 1)

CLINICAL PRACTICE GUIDELINES
Treatment of Schizophrenia

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These guidelines will be available in French.
Ces lignes directrices seront disponibles en français.

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ISSN 0706-7437
Vol 50, Supplement 1, 2005
The Canadian Journal of Psychiatry
La Revue canadienne de psychiatrie

CLINICAL PRACTICE GUIDELINES
Treatment of Schizophrenia

Contents

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The Canadian Journal of Psychiatry

Volume 50 | Ottawa, Canada, November 2005 | Supplement 1

CLINICAL PRACTICE GUIDELINES

Treatment of Schizophrenia

I. Introduction

Clinical practice guidelines (CPGs) have been defined as "systematically developed statements of recommendation for patient management to assist practitioner and patient decisions about appropriate health care for specific situations" (1).

The aim of these guidelines is to improve the assessment and treatment of patients with schizophrenia at all stages of the illness. These guidelines are written primarily for physicians; however they may be of value to other clinicians involved in the treatment of patients (aged 16 years or over) who have schizophrenia. The guidelines may also be useful as a guide to provider organizations developing services, to senior students in allied health disciplines, and to those accrediting services.

The guidelines specify 4 main topics, each of which a physician must consider when seeing a patient: assessment, pharmacotherapy, psychosocial interventions, and delivery of services. Within each of the first 3 topics, 3 phases of the illness are distinguished:

- the "acute" phase, wherein signs and symptoms worsen, usually bringing the patient to medical attention
- the "stabilization" phase, wherein the illness is subsiding after an acute episode
- the "stable" or chronic phase, wherein acute symptoms may have subsided but functioning is often persistently impaired

The guidelines highlight for particular attention the treatment possibilities for 2 groups of patients: 1) those in the demographic majority, who have been ill for many years and may have a poor level of functioning and poor quality of life and who deserve a review that takes new information into account; and 2) first-episode patients, in whom the chance to improve long-term outcome may be greatest. The guidelines also address special issues such as the prodromal phase, substance use or abuse, coexisting medical illnesses, pregnancy, coexisting depression, and aging patients.

Rationale

Schizophrenia is a serious but treatable mental illness with significant morbidity and mortality, affecting approximately 0.6% of the general population at some point in their lives (2). Illness onset is most common in young adults, relapses of acute episodes can occur throughout the lifespan, and functioning is often significantly affected. The direct health care and non–health care costs in Canada were estimated to be $1.12 billion in 1996 (3). Patients with schizophrenia are at significantly increased risk for suicide, violence, substance use or abuse, homelessness, unemployment, medical illnesses, and victimization. Life expectancy for persons with schizophrenia is also significantly reduced (4).

The guidelines assert that symptoms and functioning are improved and the risks for suicide and social dysfunction reduced when patients with schizophrenia are given continuous treatment, long-term care from qualified service providers, and access to appropriate housing and services. New treatments and service delivery options reinforce this therapeutic optimism. Guidelines based on this new information should enable physicians to help patients achieve an improved level of functioning while minimizing the potentially harmful effects of the illness or the treatments. The guidelines describe practical clinical assessment and management strategies tailored to the individual. Further, the guidelines emphasize the

Table 1 Criteria for rating quality of published evidence in individual articles reviewed

Ratings	Criteria
I	Evidence from at least one properly randomized controlled trial (RCT)
II-1	Evidence from well-designed controlled trials without randomization (pretest–posttest control group design)
II-2	Evidence from well-designed cohort or case–control analytic studies, preferably from more than one centre or research group
II-3	Evidence from repeated measures studies with no control group (one group pretest–posttest design)
III	Evidence from hypothesis-generating or exploratory studies (modelling, path-analytic or factor-analytic studies) or studies involving subanalyses
IV	Evidence from descriptive, observational, or qualitative studies (case reports, correlational studies, or secondary analyses); opinions of respected authorities, based on clinical experience; reports of expert committees
V-1	Evidence from a metaanalysis, with all studies included in the metaanalysis classified as RCTs
V-2	Evidence from "formal" review (reviews with detailed description of search strategies, such as Cochrane reviews)
V-3	Evidence from "informal" reviews that summarize others' research, or publication that does not provide review details

benefits of combining physical or medical treatments with behavioural or lifestyle interventions. They reflect a biopsychosocial approach that includes both types of intervention as important aspects of a full treatment plan. The guidelines focus on interventions that are most likely to lead to the greatest benefit and least disruption for the individual patient and his or her caregivers. The medications mentioned include only those available in Canada at the time of writing. The guidelines do not address forensic issues such as criminal responsibility and provincial mental health acts that pertain in a general way to all mental disorders.

Guideline Development Process

The development of these guidelines was sponsored by the Canadian Psychiatric Association (CPA). The Association has a Special Committee on Clinical Practice Guidelines that oversees the development of clinical practice guidelines. The Committee has written guidelines for CPG development that specify the process and standards that must be followed. The Committee reviews all CPGs before they are given final approval by the CPA Board. The Committee establishes working groups that produce the guidelines. The CPA raises and administers funds for guideline development. There is no contact between the funders and the working group that develops the guidelines. The working group circulates the guidelines to a wide range of stakeholders for review and comment before sending a final version to the Committee. A draft of these guidelines was also circulated to industry for review and comment regarding errors of fact. All sponsorship is acknowledged when the guidelines are published, and any conflicts of interests of the individual working group members are indicated in the usual *Canadian Journal of Psychiatry* format.

For these guidelines, 2 evidence-based literature reviews were conducted, and their results were combined. One was related to specific treatments, and one was related to models of service delivery. These are described below in more detail. Recommendations were rated on levels of evidence according to an algorithm, also listed below. We also reviewed other schizophrenia clinical practice guidelines, using the AGREE instrument (5), which is designed to provide a framework for assessing the quality of CPGs. This framework and the results of a needs assessment survey were used to develop the outline of the current guidelines.

A systematic needs assessment was conducted with the target audience of psychiatrists. Two processes were used: a focus group at the annual CPA meeting and an on-line survey based on the AGREE framework. The on-line survey was sent to a random sample of 50% of the CPA members, and the response rate was 12%. Ninety percent of respondents were aware of the 1998 CPGs (6). The most frequently referenced section of this guideline was the section on management of refractory symptoms. The top 3 most frequent suggestions were to provide up-to-date information, clear recommendations, and a comprehensive biopsychosocial approach. Finally, the draft

Table 2 Evidence level summary for rating evidence

Evidence level	Description
A	Strong research-based evidence, for example, for interventions, consistent evidence from well-designed randomized controlled trials (RCTs); or a metaanalysis, with all the studies included in the statistical pooling classified as RCTs; or consistent evidence from well-designed cohort and case studies (categories I, V-1, II-2 from Table 1); for evidence relating to prevalence, consistent findings from appropriately designed studies
B	Moderate research-based evidence, for example, from well-designed controlled trials without randomization, cohort studies, case–control analytic studies, comparative studies with historical control, and repeated–measures studies with no control group; this rating is also used when there are well-designed RCTs favouring effectiveness, but the evidence from such trials is not consistent (II-1, II-2, II-3)
C	Weak or reasonable evidence from descriptive, observational, or qualitative studies (case reports, correlational studies, or secondary analyses); formal reviews; expert opinions or consensus in the field; hypothesis-generating or exploratory studies, such as modelling, path-analytic or factor-analytic studies, or subanalyses (III, IV, V-2)
D	No evidence of benefit or harm of treatment

guidelines were sent to a national advisory group for review and comment.

Literature Search

The search strategy covered publications issued between January 1992 and April 2004. In Medline, PubMed, Psycinfo, and CINAHL the following key words were used:

- conventional antipsychotic medications and tranquilizing agents, neuroleptic drugs, effective drug therapy, tranquilizing agents, adjunctive treatments, clozapine and efficacy and side effect profile, ECT, individual psychotherapy, group psychotherapy, family interventions, vocational rehabilitation, psychosocial skills, schizophrenia and social skills training, assertive community treatment, training in community living, family psychoeducation, behavioural family therapy, behavioural family management, cognitive therapy, cognitive-behavioural therapy, token economy
- schizophrenia treatment and group therapy, group homes, psychiatric department hospitals, day care, ambulatory care, outpatients
- cost–utility or cost–benefit analysis, cost effectiveness, health resources, quality of life, case management, outcome assessment, process assessment, patient satisfaction, performance monitoring, performance measures, performance indicators, access to treatment or health services, accessibility, quality indicators, quality measures, health care costs or cost of treatment, mental health delivery system, mental health services, models of care, community care, community mental health services, hospital care, patient retention or physician–patient relations, patient engagement

In the Cochrane database and Cochrane DARE (Database of Abstracts of Reviews of Effectiveness) the search terms used were Cochrane Schizophrenia Group, as well as the key words schizophrenia and treatment.

Screening Process

Several steps were taken in the review process. First as mentioned, we conducted computerized searches of relevant literature. These searches were limited to English-language publications with study subjects aged 18 to 65 years. Second, we undertook a preliminary screening of the title and abstract for each reference to determine eligibility for inclusion in the database. Third, the appropriate references were imported into a Reference Manager, Version 10 database (7) specific to the CPG systematic review. As a result of these searches and the initial review of abstracts, 7707 references were imported into the database. A detailed assessment of each abstract and (or) article resulted in the removal of 5009 references. Reasons for exclusion were that the reference was an inappropriate publication type (that is, dissertation or letter) and the subject matter was irrelevant to the CPG update. During the CPG writing, members of the working group identified additional references. Some were papers of historical interest, whereas others were papers published before the dates encompassed in the evidence-based review. We ranked these in the same way as the references in the evidence-based

review and added them to the database. The final database contains 2864 references, with quality ratings assigned.

Quality-Rating Process

Each reference was given a quality rating by the research coordinator or research assistant, based on the guidelines provided in Table 1. Interrater reliability was established at the start, with at least 85% agreement on a random selection of 40 references. Each case of disagreement was reviewed with the working group chair, and consensus was reached. These guidelines were originally adapted from the Canadian Task Force Methodology (www.ctfphc.org/methods.htm), with further development based on study design detail obtained in *Foundations of Clinical Research: Applications to Practice* (8). Raters blinded to the author name and journal gave clinical trials a second ranking system according to the Jadad Scale (see Appendix 1).

The final CPG recommendations were also ranked according to the strength of evidence supporting them. These rankings were determined by a consensus process involving the members of the Clinical Practice Guideline Working Group. Table 2 outlines the system for ranking the recommendations.

All the citations will be posted on-line with the CPGs. The score for each article will also be included. Rather than cite all possible references in the GPG, we cited references to be illustrative rather than comprehensive. Several systematic reviews are cited, particularly those that summarize the current balance of opinions.

II. Assessments

General Principles

1. Symptoms (mental and physical), signs, activities of daily living (ADLs), level of functioning, and side effects are key areas to assess at all phases of the illness.
2. Collateral information (for example, from family members, caregivers, and health care professionals) is usually essential for a more complete understanding of symptoms, signs, and functioning.
3. Longitudinal follow-up by the same clinician(s) to monitor improvements or worsening is optimal.
4. Patients will often not spontaneously bring complaints and information to clinicians, and therefore, active, specific questioning and informed examination and investigation are usually necessary.
5. The patient's competency to accept or refuse treatment must be periodically assessed and recorded.

Acute Phase

The physician's goals are to make an initial diagnosis and to plan and initiate treatment. Investigation of the symptoms of psychosis begins with a history, a physical examination, and other appropriate investigations. The clinical history should include all aspects of a general psychiatric evaluation as well as a focus on specific issues related to schizophrenia. The primary goal of the assessments described in this section is to provide a guide for clinicians caring for patients with schizophrenia, not for all forms of psychosis. Although not described in detail here, the differential diagnosis of schizophrenia from schizoaffective disorder, bipolar disorder, depression with psychosis, and other forms of psychotic illness has implications for outcome (9–11). Collateral information should be sought, with the knowledge and consent of the patient, from others who knew the patient before the acute episode. Semistructured interviews may increase the reliability of application of diagnostic criteria and may elicit features that might be otherwise overlooked. Clinical rating scales can help quantify symptom severity and permit longitudinal assessment. Most of these instruments require training to ensure reliable administration. Most important, taking time to build rapport with patients and caregivers will help maximize understanding of the longitudinal course and phenomenology of the illness.

The initial assessment should include inquiries specifically directed to the following (Table 3):

- positive symptoms such as hallucinations and delusions
- negative symptoms such as flat or blunted affect, poverty of thought or thought content, and avolition
- disorganization such as thought disorder, inappropriate affect, and disorganized behaviour
- affective symptoms such as anxiety or depression, particularly in relation to the psychotic symptoms
- suicidal or aggressive thinking and behaviour, impulsivity, because any risk for suicide or violence has implications for where the patient should be assessed and treated
- the time of onset or exacerbation of symptoms and the context and possible precipitating factors
- substance use and abuse in relation to the onset and persistence of psychotic and associated symptoms
- the current living situation, including housing, finances, social supports, ADLs, social activity, school, and work
- a mental status examination, including office or bedside assessment of cognitive function, based on data from all sources of information, in which positive and negative findings should be documented, since they may change over time
- a physical examination, including neurologic examination, and laboratory tests, including screening toxicology
- a general medical history and review of symptoms

Repeated relapses necessitate special attention to assessment of the patient's insight (including patient's and family's

Table 3 Assessments for patients with schizophrenia

	Areas	First episode	Acute phase	Stable
Psychopathology	Positive Negative Disorganization Mood Suicide, aggression, or impulsivity	Baseline assessment	Baseline and at least weekly thereafter, more frequently depending on clinical context	At least every 3 months for medication adherent, more frequent for medication nonadherent
Level of function	Social Living situation Occupational or vocational	Baseline assessment	Baseline assessment	Every 3 months
Substance use or abuse	Inquiry Toxicology screen	Baseline assessment	Baseline assessment	As indicated clinically
Cognitive function	Neuropsychological testing	Baseline assessment	As indicated clinically	As indicated clinically
Genetic	Family history of psychosis	Baseline assessment		
	Clinical screening for chromosome 22q11 deletion syndrome (with testing as indicated clinically)	Baseline assessment	As indicated clinically	As indicated clinically
Structural brain abnormalities	CT or MRI	Baseline assessment	As indicated clinically	As indicated clinically
Hematology	CBC	Baseline assessment	Baseline assessment	As indicated clinically
Blood chemistries	Electrolytes Renal function tests Liver function tests Thyroid function tests	Baseline assessment	Baseline assessment	As indicated clinically
Infectious diseases	Syphilis test Hepatitis or HIV tests if indicated	Baseline assessment	As indicated clinically	As indicated clinically
Cataracts	Inquiry Ocular exam	Baseline assessment	Baseline assessment	Every 2 years up to age 40 Yearly for age 40 and older
Cardiovascular	Vital signs	Baseline assessment	As clinically indicated with changes in medications	As indicated clinically
	ECG		QTc indicated when affected by multiple medications	

continued

Table 3 continued

	Areas	First episode	Acute phase	Stable
Extrapyramidal symptoms and signs	Parkinsonism (bradykinesia, rigidity, tremor), Dystonia, Dyskinesia, Akathisia	Baseline assessment	Before initiating a new antipsychotic or when dosage is changed, then weekly for 2 to 4 weeks	Every 6 months, or more often for patients at higher risk
Body mass	BMI Waist circumference	Baseline assessment	Before initiating a new antipsychotic, then monthly for 6 months	Every 3 months on a stable antipsychotic dosage
Blood sugar	Fasting plasma glucose	Baseline assessment	Baseline assessment, 4 months after initiating a new antipsychotic	Yearly, or more frequently if symptomatic or gaining weight
Hyperlipidemia	Lipid panel (total cholesterol, low- and high-density lipoprotein, cholesterol, triglycerides)	Baseline assessment	Baseline assessment	At least every 2 years, or every 6 months if LDL levels above the normal range
Endocrine and sexual function	Functional inquiry: Women: menstruation, libido, galactorrhea Men: libido, erectile and ejaculatory function Where clinically indicated: prolactin level	Baseline assessment	Baseline assessment Monthly for 3 months after initiating a new antipsychotic	Yearly
	Risk behaviours for STDs and HIV	Baseline assessment	As indicated clinically	As indicated clinically

attribution of the patient's behaviour), awareness of the significance of illness, attitude toward treatment and restoring health, medication adherence, substance use or abuse, treatment response, and side effects, as well as attention to the availability and use of psychosocial interventions designed to reduce symptom recurrence. The setting selected for treatment will depend primarily on safety issues and on the ability of the patient to care for him- or herself and adhere to treatment.

Stabilization Phase

The aim of assessment in the stabilization phase is to monitor for symptomatic and functional recovery after an acute episode. Treatment may not completely eliminate symptoms, but it is important to document changes, including diminished frequency or intensity of symptoms or behavioural responses to treatment (12). The extent to which positive and negative symptoms and cognitive impairment persist following optimal treatment of an index episode may be predictive of more severe residual symptoms and a poorer functional recovery (13–16).

Stable Phase

Assessments in the stable phase of the illness support the treatment goals of this phase. These goals are to optimize functional recovery, to promote insight and understanding, to learn to detect early signs of relapse, and to monitor for side effects and comorbid conditions. Patients in the stable phase who have good functional recovery and are in a stable living situation should be assessed by a physician at least every 3 months. More frequent assessments are often required by patients who, for example, have poor functional recovery or associated conditions such as substance use or abuse, have limited social support, are changing medications, are initiating a new psychosocial intervention, or are experiencing stressful life events. Persistent symptoms (positive, negative, and comorbid) are not always associated with overt patient distress but often limit functional recovery (17).

Table 4 Recommendations

Recommendation	Evidence	Evidence level
Symptoms and signs of illness and functional impairment should be carefully evaluated and differential diagnosis made.	Among illnesses with psychosis as a clinical feature, the diagnosis of schizophrenia has significant implications for prognosis.	A
Suicidal and aggressive thinking and behaviour should be regularly assessed.	Patients with schizophrenia have increased risk of suicide and aggression.	A
Regular assessment of substance use and abuse is necessary.	Substance abuse is common in patients with schizophrenia.	A
Neuropsychological testing is suggested in patients with first-episode psychosis and those with poor response to treatment.	Schizophrenia is associated with mild but significant cognitive impairment, which is associated with poor functional recovery.	B
Symptoms, level of function, and factors associated with poor treatment adherence and relapse should be regularly assessed.	Schizophrenia is frequently characterized by exacerbations of symptoms and periods of acute relapse.	A
Clinical features suggestive of chromosome 22q11 syndrome should be evaluated in patients with schizophrenia and laboratory testing obtained when indicated.	Chromosome 22q11 deletion is associated with schizophrenia.	B
Computed tomography or magnetic resonance imaging at illness onset and in patients with refractory illness should be done.	Patients with schizophrenia have an increased prevalence of structural brain abnormalities.	B
Regular clinical and laboratory monitoring for movement disorders, obesity, diabetes, hyperlipidemia and sexual dysfunction indicated in patients with schizophrenia. (see Table 3)	Patients with schizophrenia have reduced life expectancy; the combination of illness and the effects of antipsychotic treatment place patients at risk of movement disorders, obesity, diabetes, hyperlipidemia, and sexual dysfunction.	A

Assessments of functional recovery focus on the severity of persisting or residual symptoms, on the ability to perform basic self-care functions and ADLs, on the extent of social relationships, on the ability to learn and work, and on the frequency of hospitalization due to relapses. Thorough assessment may be particularly important to inform decisions concerning level of care and housing support needed in the community. Collateral information from caregivers and (or) a home visit may be very helpful in this assessment. Poor recovery of ADLs and social function is often related to persisting cognitive dysfunction. In addition to objectively assessing functional recovery, seek the patient's own account of satisfaction or quality of life. Setting realistic goals and expectations for functional recovery requires knowledge of the patient's longitudinal history, including his or her best level of functioning, educational history, culture, interests, and supports.

Relapse and Adherence to Treatment

The course of schizophrenia is often characterized by relapses of acute psychosis (18). Signs and symptoms associated with relapse are often observed by relatives or caregivers and usually appear more than 1 week prior to relapse. Initial signs and symptoms are likely to be nonpsychotic (such as anxiety, tension, depression, decreased insight, trouble sleeping, and social withdrawal). A relapse may also coincide with sensitivity to minor stresses or "hassles" at home or work. Relapse prevention is closely related to effective antipsychotic medication and to adherence to treatment. Adherence to treatment is promoted by a good relationship with the clinician, by patient and family knowledge about the illness, by understanding the risk of nonadherence to medication (up to 90% chance of relapse within 1 year), and by low medication side effects. Nonadherence is associated with denial of illness, distressing side effects, complicated dosage schedules,

substance abuse, problems with access to treatment, financial obstacles to receiving medication, and stigma.

Specific Clinical Situations and Assessments

First Episode

The assessment for a first episode of psychosis is similar to an acute phase assessment. Particular attention should be paid to the longitudinal assessment of the onset of changes in behaviour and to the timing and course of onset of the first symptoms of psychosis. Developmental history, including social and academic functioning in childhood and adolescence, may help indicate the onset of decline in function and may be of prognostic value regarding degree of symptomatic and functional recovery. The duration of untreated psychosis (DUP) may have similar prognostic value (19–21).

For individuals referred with a suspicion of psychosis, variables that may be associated with increased risk of conversion to psychosis include poor level of functioning (particularly with recent decline), long duration of symptoms, depression, impaired attention, family history of psychosis, and recent subclinical symptoms of psychosis (22).

Neuropsychological Assessment

A consensus on cognitive testing for clinical trials in schizophrenia is developing through a US National Institute of Mental Health initiative (23). Preliminary reports from this group and additional studies suggest that cognitive testing in first-episode illness may be of prognostic value for functional recovery. As well, cognitive decline to frank dementia can occur over the course of illness in schizophrenia, although it is uncommon (24). Baseline assessments are particularly valuable should reassessment be indicated clinically later in the illness course. Cognitive testing should include an estimate of premorbid IQ, current IQ, and specific tests related to working memory, attention, verbal learning and memory, visual learning and memory, reasoning and problem solving, speed of processing, and social cognition. Adequate assessment of these domains of function is more important than the specific tests administered.

Cognitive testing in the stable phase of illness may also be of significant value in addressing different issues related to the heterogeneity of schizophrenia and variability in functional recovery. Strengths and weaknesses in specific domains of cognitive function may help guide the design of individual strategies for rehabilitation. Documentation of capacity to learn may be particularly important.

The timing of neuropsychological assessment also needs to be individualized. Psychometrists and psychologists experienced in testing patients with psychosis can obtain valid information in the presence of positive symptoms; however, testing in the stable rather than the acute phase of illness is generally preferred. For patients experiencing a first episode of illness, testing within the first 3 months at a time where symptoms do not directly disrupt the assessment process is suggested. Finally, for any specialized assessment (neuropsychological or the following genetic and imaging studies), sufficient information should be provided to the consulting clinician to help inform the tests to be carried out. Requesting information on the previously described domains of cognitive function is preferable to a referral question such as "rule out organicity."

Genetic Assessment

Schizophrenia is a "complex disorder" with significant interactive components of genes and environment as etiologic factors. There are no screening genetic tests available that provide useful information in regard to most patients. However, genetic assessment is indicated in patients who have dysmorphic or other features suggesting the presence of chromosomal syndromes. Chromosome 22q11 deletion syndrome is associated with significantly increased risk for psychosis, predominantly schizophrenia (25). This syndrome is present in approximately 1/4000 births and increases the risk for schizophrenia approximately 25-fold. Chromosome 22q11 deletion syndrome is also known as velocardiofacial syndrome, DiGeorge syndrome, and Shprintzen syndrome. Testing samples of patients with schizophrenia for 22q11 deletion yields widely variable prevalence estimates, likely influenced significantly by the ascertainment criteria used. Overall, 1% to 2% of individuals with schizophrenia have 22q11 deletion syndrome (26). This is medically significant, as a range of associated conditions exists, including cardiac defects, immune system dysfunction, platelet abnormalities, and hypocalcemia. Clinical features of 22q11 deletion syndrome in individuals with schizophrenia or first-episode psychosis include the following:

- childhood learning difficulties, such as special education, developmental delay, or articulation disorder
- palatal features, such as hypernasal speech, high arched palate, or history of cleft palate
- cardiac features, that is, a history of congenital cardiac abnormalities
- craniofacial abnormalities, such as dysmorphic facies (typically, long, narrow face, flat cheeks, prominent nose with bulbous tip, minor ear anomalies, may also include narrow or slanted palpebral fissures and retrognathia)
- other physical congenital abnormalities, including slender or tapered fingers, high arches or talipes, and scoliosis
- a history of recurrent ear infections or hearing loss may also be relevant. Clinical screening of patients for the presence of features from 2 or more of the above areas may indicate the need for fluorescent in situ hybridization

(the FISH test) testing for diagnosis and (or) referral to a medical geneticist (27,28). Presence of 22q11 deletion syndrome is also an indication for genetic counselling.

Neuroimaging

Other brain diseases can mimic the presentation of schizophrenia. Rarely, patients with first-episode psychosis and no neurologic findings will have an unsuspected brain disease revealed by brain imaging with computed tomography (CT) or magnetic resonance imaging (MRI). The most common finding with CT imaging in first-episode psychosis is nonspecific ventricular and cortical sulcal enlargement, which may be present in 30% to 40% of patients (29). More severe atrophy is related to poorer outcome. Focal findings, usually developmental anomalies that do not influence treatment, will occur in 2% to 6% of patients imaged with CT. Over 20% of MRI scans at the onset of psychosis may be read as abnormal by radiologists; this increases to as high as 50% in chronic illness (30). Excluding patients with head injury, neurologic disease, seizures, or substance abuse, 7.9% of MRI scans obtained in first-episode patients were of "clinical importance, affecting prognosis, diagnosis, or management" (30, p 334) and led to referral for additional evaluation. The comparable frequency in patients with chronic illness was 20%. In this study and in other studies of volunteers, incidental findings led to referral in 3% to 5% (30,31). Imaging data may help patients and families to accept that neurologic causes of illness have been excluded.

Poorly Responsive or "Refractory" Illness

Diagnostic reassessment is a first step in developing a treatment plan for individuals with incomplete treatment response. Very few patients with apparently treatment-resistant schizophrenia actually have schizoaffective disorder, a mood disorder with psychosis, or undetected physical conditions that may have different treatment implications (32,33). Diagnostic criteria must be applied systematically. Factors that contribute to misdiagnosis in severely ill patients include failure to consider lifetime history of illness; an assumption that all severe, chronic psychosis with functional impairment is schizophrenia; failure to appreciate irritability, which may indicate mania; and confusion between negative symptoms and depression. Access to collateral sources of information for assessment is particularly important in this group of patients.

Comorbid Conditions

Comorbid conditions include suicidal behaviour, anxiety and depressive symptoms, and substance abuse. Completed suicide and suicide attempts are distressingly common in schizophrenia patients (34). The following specific factors further increase the risk for suicide in those with schizophrenia: depression, being within 6 years of first hospitalization, young age, high IQ, high premorbid achievement and aspirations, and awareness of loss of functioning. As well, command auditory hallucinations, recent discharge from hospital, treatment nonadherence, and akathisia may be related to suicide risk.

Depressive symptoms are common in schizophrenia and must be differentiated from negative symptoms such as blunting of emotional expression, decreased spontaneous speech, and lack of motivation (35). Depressive symptoms may precede or be coincident with psychotic symptoms, particularly in the early course of illness, or may be more prominent following resolution of psychotic symptoms.

Anxiety symptoms may be comorbid in schizophrenia, part of a relapse, or secondary to caffeine, other drugs, or alcohol abuse. Agitation and (or) violence may accompany an exacerbation of symptoms but must be distinguished from akathisia or delirium (such as may occur secondary to substance abuse or excessive water drinking).

Substance abuse is common in schizophrenia, with up to an 80% lifetime prevalence and 25% cross-sectional prevalence (36). Multiple substances are often abused, and this is associated with poor functional recovery. Substance use or abuse may represent self-treatment of residual symptoms or distressing side effects. Common substances include tobacco, alcohol, cannabis, and amphetamines. Nonprescription antihistamines and analgesics may also be used. Knowledge of the patient's substance use history will aid inquiries about the use of specific substances. Collateral information and specific urine drug screens may help assess the extent of substance use or abuse. Up to 80% of patients with schizophrenia smoke; as for any patient, smoking cessation strategies should be pursued (37).

Polydipsia and resulting hyponatremia may manifest as late afternoon restlessness, irritability, nausea, diarrhea, salivation, ataxia, and eventually stupor. The clinician should specifically enquire whether fluid intake exceeds about 3 L of fluid (any) daily. Weight gain of more than 2 kg during the day, excessive bathroom use, or daytime wetting may also indicate compulsive water drinking.

Physical Health Monitoring

Patients with schizophrenia are at high risk for underrecognition and undertreatment of physical illnesses. Specific questioning to uncover physical illnesses is more necessary than with other patients. As well as having a high suicide rate, patients with schizophrenia have a higher mortality rate from other causes, compared with the general population (38,39). Additional risks may be present that are related to antipsychotic medications, high prevalence of smoking, caffeine ingestion, comorbid alcohol or other substance abuse, and self-neglect. Common comorbid illnesses include cardiovascular disease, obesity, type II (adult onset) diabetes

mellitus, hyperlipidemia, and sexual dysfunction. Table 2 indicates a suggested approach to screening for these illnesses and pathophysiological states.

Monitoring for obesity can be carried out with assessment of body mass index (BMI) and waist circumference. Information concerning these measures can be found on-line at Health Canada (www.hc-sc.gc.ca/hpfb-dgpsa/onpp-bppn/weight_book_tc_e.html). A BMI of 25.0 to 29.9 indicates overweight and an increased risk related to morbidity and possible mortality, and a BMI of 30.0 or greater is classified as obesity and is associated with a sharp rise in risk. Waist circumference of 102 cm (40 inches) or greater in men, and 88 cm (35 inches) or greater in women is associated with increased risks to health. In addition to these absolute values, an increase of 1 BMI unit during treatment should lead to considering an intervention (40) such as prescribing a weight-loss program, as would a 10% increase in total body weight.

Canadian Diabetes Association CPGs identify schizophrenia as a risk factor for type II diabetes (41). An algorithm for screening is available on-line (www.diabetes.ca/cpg2003/chapters.aspx). Health care providers, patients, and family members should be able to recognize the signs and symptoms of diabetes, including weight loss, polyuria, polydipsia and diabetic ketoacidosis, nausea, vomiting, dehydration, rapid respiration, and clouding of the sensorium.

Particular attention should be paid to patients who meet criteria for the metabolic syndrome, characterized by abdominal obesity, dyslipidemia, hypertension, dysglycemia, and insulin resistance. Although complete consensus on the definition of this syndrome is lacking, a working definition is as follows: the presence of 3 or more of fasting plasma glucose = 6.1 mmol/L, blood pressure = 130/85 mm Hg, triglycerides = 1.7 mmol/L, HDL-C < 1.0 mmol/L (men) or < 1.3 mmol/L (women), and abdominal obesity indicated by waist circumference >102 cm (men) or 88 cm (women) (35).

Assessment of sexual functioning should be part of a systematic review of side effects in patients receiving antipsychotics. In women, menstrual calendars may be helpful. Questioning masturbatory activities and, in men, the presence of spontaneous morning erections may help differentiate deleterious pharmacologic impacts of medication from relational difficulties related to schizophrenia itself. Prolactin levels should be routinely assessed in the presence of menstrual changes in women and sexual dysfunctions or galacthorrea in both sexes. If isolated hyperprolactinemia is detected without clinical symptoms, treatment providers should remember that hormonal perturbations and consequences are still possible during the long-term course of treatment.

Dual Diagnosis (Mental Retardation)

Patients with mental retardation, especially those who are nonverbal, may be more challenging to assess; collateral information from caregivers is important. Cognitive and functional testing to delineate the patient's developmental level and relative strengths and weaknesses are also essential. Consultation with a medical geneticist is recommended if there are any dysmorphic features or congenital anomalies. Chromosomal studies using modern techniques may reveal detectable anomalies of diagnostic significance.

III. Pharmacotherapy

Medications

These guidelines only refer to medications available in Canada at the time of writing. They refer to clozapine, olanzapine, quetiapine, and risperidone as second-generation antipsychotics (SGAs) or atypical antipsychotics; all other antipsychotic medications are referred to as first-generation antipsychotics (FGAs).

General Principles

1. Pharmacotherapy with antipsychotic medications is an essential component of a treatment plan for most patients with schizophrenia.
2. Psychosocial interventions work synergistically with medication to optimize treatment adherence and successful community living.
3. Medications must be individualized because the individual response is highly variable. Consideration should be given to the immediate presenting problem and the patient's prior response to pharmacotherapy, including efficacy and side effects. Patients with a first episode of psychosis usually require a lower dosage, as do the elderly.
4. Patients must be involved in decisions and choices for pharmacotherapy. This includes being provided with information on the risks and benefits of both taking and not taking medications. However, because a high level of benefit is achieved with medication, it should be recommended assertively, and patients' agreement in taking mediation should be sought actively.
5. Side effect profiles vary according to the duration of drug exposure, the evolution of the disorder, and the patient's general health.
6. Simple medication regimens, such as once-daily dosing, promote adherence to treatment.
7. Dosages should be maintained within the recommended range, and reasons for going outside the range should be clearly documented and justified.
8. Using more than one antipsychotic simultaneously is not supported by available evidence.
9. Regular and ongoing evaluations are equally necessary when patients respond to medications, when they fail to respond, and when they develop side effects. Standardized scales are useful tools for baseline and later assessments.

Second-Generation Antipsychotics

SGAs are increasingly replacing FGAs as first-line treatments. Reviews have not found clear and consistent differences between FGAs and SGAs in regard to treatment response for positive symptoms, with the notable exception of clozapine for treatment-resistant patients (42). Second-generation drugs have a broader spectrum of therapeutic effects, with a small but significant effect size superiority in the treatment of negative symptoms and cognitive impairment (43,44). It has also been suggested that they are more effective in the treatment of depressive symptoms (45).

The management of the metabolic side effects of SGAs is discussed under assessment issues and, later in this section, under side effects. For clinicians, the challenge in managing these side effects is that they must shift their thinking from the earlier focus on managing extrapyramidal side effects (EPSEs). The focus on managing weight, glucose, and lipids brings psychiatrists back into the realm of general medicine and away from purely pharmacologic considerations. Strategies for dealing with EPSEs, such as dosage adjustment, medication switches, or the addition of adjunctive medications, are not strategies that have an immediate impact on metabolic parameters. Psychiatrists should not hesitate to consult with their internal medicine colleagues on these issues. Shared care with family physicians is also helpful. Difficulty in accessing such resources should not lead to postponing primary interventions.

There are significant differences in side effect profiles among first- and second-generation drugs. In general, SGAs induce fewer neurologic side effects (that is, EPSEs or tardive

dyskinesia [TD]) (46) and may have a greater propensity for metabolic side effects (that is, weight gain, diabetes mellitus, dyslipidemia, or metabolic syndrome), although the evidence is mainly based on clinical experience and nonrandomized published reports (40,47). Depot preparations were limited to first-generation drugs, with the exception of risperidone, which is now available in an intramuscular (IM), long-acting formulation (48). Other new formulations, such as rapid-dissolving tablets (olanzapine and risperidone) (49), concentrate liquid (risperidone), and parenteral short-acting form (olanzapine), offer advantages in several situations where drug administration can become an issue (for example, emergency or geriatrics).

Pharmacologic Strategies for Phase-Specific Treatment

Schizophrenia is a chronic disease that can be arbitrarily divided into 3 phases: the acute, the stabilizing, and the stable phase of the disorder. In the acute phase, the patient experiences an escalating level of positive psychotic symptoms associated with varying degrees of distress and disorganization that often lead to treatment seeking. The earlier in this phase of escalation that treatment can be initiated, the less the disruption to the patients and their environments. If intervention does not occur earlier in the escalation, emergency intervention is required, with several different emergency treatment options being available. In the recovering stage of the illness, the levels of symptoms and disorganization are usually declining as a result of treatment, and the patient needs less care. In the stable phase, symptoms and disorganization have been reduced as much as possible, and longer-term psychosocial and rehabilitation strategies can be implemented.

Acute Phase

The general principles are as follows:

1. The assessment in the acute phase should be as comprehensive as possible under the circumstances.
2. Particular attention needs to be paid to the potential for danger to self or others.
3. Engagement with the patient in the acute phase is facilitated by acknowledging his or her experiences, providing clear simple communication, and including family and supports where possible. Explaining the patient's rights and any legal process is essential.
4. Pharmacologic treatment should be initiated as soon as possible, and the risks and benefits of pharmacotherapy should always be explained.
5. All these principles apply in emergency situations, but emergency medication strategies are available to contain the patient and maintain staff safety.

Emergency Treatment. Emergencies are defined as situations or conditions having a high probability of disabling or immediately life-threatening consequences or requiring first aid or other immediate interventions (Medical Subject Headings). Individuals with schizophrenia frequently present to emergency rooms, requiring immediate treatment. The Canadian Emergency Department Triage and Acuity Scale (50) classifies acute psychosis as either a Level 2 or Level 3 emergency according to the degree of agitation. Where the patient is aggressive or agitated and uncooperative, several pharmacologic interventions are available, often in combination with psychosocial interventions.

Verbally engaging an agitated patient should always be tried in the setting of an appropriately safe emergency room environment with available security personnel. Oral medications should be offered and, if accepted, can be as effective as IM medications (51). The rapid-dissolving forms of SGAs may have benefits for treatment in emergency situations because it is easier to confirm compliance. However, there are no studies comparing similar medications in different oral preparations in emergency situations. When necessary to preserve patient and staff safety, restraint measures should be taken by a trained team following an approved protocol.

Historically, IM haloperidol has been the most widely used treatment for agitated patients with psychosis. The combination of haloperidol 5 mg IM with lorazepam 2 mg IM has been shown to be more effective than haloperidol alone (52). Treatment of schizophrenia is not an approved indication for lorazepam in the current *Compendium of Pharmaceuticals and Specialties* (53) product monograph. Olanzapine is the first SGA in Canada to become available in an IM form for acute treatment. IM olanzapine 2.5 mg to 10 mg has been demonstrated to be as effective as haloperidol alone (54,55) while showing fewer EPSEs. In practice, 10 mg is the most frequently prescribed single dosage, except in special populations. Combining parenteral olanzapine with benzodiazepine should be avoided because cardiac and respiratory difficulties, including fatalities, have been associated with this combination in postmarketing reports. Several studies have reported that oral solution or rapid-dissolving tablets of either risperidone or olanzapine are as effective as haloperidol IM (56). In Canada, zuclopenthixol acetate has been available for the treatment of acute agitation. Following injection, it reaches a peak serum level in 24 to 48 hours and declines to one-third of peak concentrations at 72 hours. These pharmacokinetic properties support a potential reduction in the number of injections required to stabilize agitation and aggression, but the agent should be avoided in drug-naive

Table 5 Second-generation antipsychotic dosages and titration

Agent	Introduction dosage range, mg[a]	Incremental dosage range, mg	Usual target dosage, mg	Monograph maximal dosage, mg (CPS)[b]
Risperidone	0.5 to 1.0	↑ 0.5 to 1.0 every 3 to 4 days, up to ↑ 1.0 daily	2.0 to 6.0	8.0
Risperidone long-acting injectable	25.0 IM every 2 weeks (oral supplementation required for the first 3 weeks)	↑ 12.5 every 4 to 8 weeks	25.0 to 37.5 IM every 2 weeks	50.0 IM every 2 weeks
Olanzapine	5.0 to 10.0	↑ 2.5 to 5.0 every 3 to 4 days, up to ↑ 5.0 daily	10.0 to 20.0	20.0
Quetiapine	100.0	↑ 100.0 daily	600.0	800.0
Clozapine	12.5 to 25.0	↑ 12.5 to 25.0 on the second day, ↑ up to 25.0 to 50.0 daily	300.0 to 600.0	900.0

[a]Adult recommendations, not adapted for elderly
[b]*Compendium of Pharmaceuticals and Specialties* (53)

patients. A recent Cochrane review (57) found that zuclopenthixol was as effective as control treatments in controlling psychotic symptoms and agitation but had no consistent advantages. It had a side effect profile similar to other FGAs.

Nonemergency Treatment. An acute relapse or a first presentation of psychosis may not present as an emergency but may present in the clinic as an urgent problem that may or may not require admission. The decision to admit will depend on the acuity of the problem, the capacity of the patient and caregivers to manage in a nonhospital environment, and the resources available to support the patient and caregivers in the community.

The pharmacologic approach to treatment has to be adapted to the treatment setting. When appropriate, the patient and caregivers need to be engaged in the treatment process and provided with information and options. It may be possible to engage the patient in treatment from the perspective of his or her concerns for secondary symptoms such as depression, anxiety, or insomnia, rather than from the perspective of the primary symptoms of psychosis.

First Episode of Illness, No Previous Antipsychotic Treatment. In recent years, there has been a burgeoning interest in first-episode psychosis (FEP) and the early phase of schizophrenia (54,55). Following an appropriate assessment, antipsychotic pharmacotherapy should be started as soon as possible. There are 2 reasons for initiating treatment urgently. First, delay in treatment is associated with distress and increasing risk (58). Second, a longer DUP, which is the time from the onset of the psychotic disorder to the onset of treatment, appears to be related to a less favourable outcome (59). Many patients experiencing a first episode of psychosis can be treated at home if safety and support issues are addressed. SGA medications are indicated in the treatment of a first episode of psychosis because previously unmedicated patients are especially sensitive to the acute extrapyramidal and sedative side effects caused by antipsychotic medications (60). Benzodiazepines may be adequate to control agitation while initiating a low dosage with slow titration of an SGA. Low initial dosages of the medication should be used and titrated at not less than weekly intervals if the clinical situation is not emergent (61). Avoidance of side effects early in treatment is important for later adherence to treatment. Dosages beyond the recommended range should be restricted to exceptional circumstances only.

Multiple-Episode Patient. A first step in deciding on the selection of an antipsychotic is to obtain a medication history with a view to evaluating drug response and adverse events. It is important to consider the patient's preferences about drugs and route of administration. The SGA medications have

become the treatments of choice for the reasons mentioned above. Although they do differ in terms of their side effect profiles, there is no clear evidence that, apart from clozapine, there are consistent group differences in efficacy among the SGAs (62). The general principle is to titrate up to an initial target dosage (in 1 to 2 weeks in most cases) and monitor for side effects while awaiting an initial response. An adequate trial of 4 to 8 weeks' duration on the maximum tolerated dosage within the recommended range is generally accepted (63). Akathisia can be misinterpreted as psychotic agitation; if the patient is not responding to acute treatment with an antipsychotic, rule out akathisia before administering more antipsychotic medication.

Dosing and Titration. Different approaches are possible when a new medication is introduced. A first approach is the prescription of a targeted dosage started on Day 1 and maintained at that level. Olanzapine can often be prescribed according to this approach but can also be introduced according to a gradual titration over a few weeks to minimize early side effects and ease medication acceptance. A second approach is to titrate the medication according to the patient's response and tolerance. A third approach is fast titration over a few days to promote a rapid development of tolerance to side effects. With quetiapine, this is particularly useful to diminish the duration of sedation and hypotension frequently observed at the beginning of treatment. When medications are being started or changed, follow-up visits for outpatients need to be frequent (weekly intervals), but they may be much less frequent when the medication is established in terms of dosage, response, and side effects and when the patient is stable. SGAs can be taken once or twice daily. A single daily dosage has advantages for patient treatment adherence (64). Rapid-dissolving tablets or liquid formulation may promote adherence to treatment.

Stabilization Phase

The general principles are as follows:

1. The goals of pharmacotherapy in this phase are to reduce the intensity and duration of active psychotic symptoms as fully as possible, to minimize side effects, and to promote adherence.

2. Medications selected for short-term control of agitated behaviour during the acute psychotic phase may not be optimal for efficacy and tolerability.

3. Adjust the dosage to the individual within the given range for each medication. Seek the patient's medication cooperation to enhance compliance.

4. Significant and sustained reduction in acute psychotic symptoms often takes 4 to 8 weeks. Improvements in other symptoms and functioning may take much longer. Improvement may continue over 1 year or more of uninterrupted treatment.

5. Premature discontinuation or reduction of antipsychotic medication during this phase places the patient at high risk for relapse.

First Episode of Psychosis, No Previous Antipsychotic Treatment. In recent years, there has been an increasing interest in the clinical care of the patient with a first episode of psychosis (65,66). Many of the challenges for the treatment of the patient with a first episode of psychosis arise in the stabilization phase of a first episode. The initial treatment response tends to be better in first-episode than in multiple-episode schizophrenia (66,67), but adherence tends to be poor (68). It is important to maintain an active treatment relationship with frequent contact and easy access. In the face of nonadherence to pharmacologic recommendations, other components of treatment, including family education, become even more important. A supportive educational approach is recommended.

Depression is a more common problem in the stabilization phase of the first episode (69). Whereas depression tends to abate with the remission of psychosis in the multiple-episode patient, it tends to increase for the first 3 months following the first episode (70). The specific management of depression is covered below. The diagnosis of first-episode psychosis needs to be kept under review, and pharmacotherapy may need to be adjusted should the criteria change.

Multiple-Episode Patient. Medication management in the stabilization phase should focus on continuity of care and fine tuning the medication to adjust to developing side effects or changes in the patient's living situation. The stabilization phase provides the opportunity to review the causes of relapse. These may include poor treatment adherence. The use of long-acting injectable formulations is an evidence-based pharmacologic recommendation for reducing nonadherence (71). The strength of the evidence is limited by the methodological difficulties of enrolling nonadherent patients in randomized controlled studies. More recently, the first long-acting atypical antipsychotic has become available. The evidence suggests that long-acting risperidone should have the same benefits as the first-generation depot medications from an adherence perspective, but with fewer EPSEs (72).

Stable Phase

The general principles are as follows:

1. Relapse prevention is an important but not exclusive goal of pharmacotherapy in the stable phase.

2. Over the longer term, other goals include minimizing negative and comorbid symptoms and promoting maximal functional ability.
3. There is a high level of individual variability in the antipsychotic dosage required to achieve functional recovery with minimal side effects.
4. To maintain treatment adherence in this phase, it is crucial to have the patient participate in pharmacotherapy and to address individual barriers and resistance to ongoing therapy.
5. Assessments should take place at least every 3 months to achieve optimal dosages and choice of antipsychotic medications and to monitor for drug-induced side effects.
6. There are no predictive factors indicating which patients can safely and permanently discontinue antipsychotic medication.

First Episode of Psychosis. An important issue that arises for the patient with a first episode of psychosis is the duration of prophylaxis for relapse prevention. The difficulties of conducting randomized controlled studies of medication withdrawal make it difficult to provide precise, evidence-based recommendations. In one of the larger early randomized placebo-controlled studies of maintenance antipsychotics, 62% of those on placebo relapsed over 2 years, compared with 46% of those on maintenance pharmacotherapy (73). However, a review of longitudinal cohort studies of patients in natural treatment settings showed relapse rates of 60% at 2 years (74). A pragmatic recommendation to patients and their families is that patients who have made a functional recovery and have been in remission on medication for at least 1 to 2 years may be considered candidates for a trial of no medication. Withdrawal of antipsychotic medication should be done slowly over 6 to 12 months. The patient's symptoms, functioning, insight, and attitude toward adhering to the treatment plan must be monitored closely. Patients who were ill for an extended period before initial treatment, who met criteria for the diagnosis of schizophrenia at first contact, and (or) who have a history of violent or suicidal behaviour may require more extended antipsychotic medication treatment. Eighty percent of patients with first-episode psychosis are at risk for a second episode within the first 3 to 5 years, and recovery from a second episode is slower and often less complete.

Multiple-Episode Patient. There are no guidelines for identifying those patients who may remain relapse-free. A minimum of 5 years of stability, without relapse and with adequate functioning, should be observed before a slow withdrawal of antipsychotic medication over 6 to 24 months is considered. Being medication-free is an unrealistic objective for many patients, especially those with a history of suicidality, violence, family history of schizophrenia, or the inability to care for themselves.

Strategies for Inadequate Response. If response is inadequate, the diagnosis must be reviewed, adherence must be explored, and substance use or abuse must be ruled out. The 4 main pharmacologic strategies for initial nonresponders include optimization, substitution, augmentation, and combination. If there is a partial response, the best strategy is optimization. In optimization, the trial of the original antipsychotic is continued with the dosage increased or decreased as appropriate. In the case of no response, substitution can be tried. The antipsychotic is gradually stopped, and another one is introduced with a short period where the 2 antipsychotics overlap. Although there are other medication-switching strategies, this method may be the safest way to switch from one agent to another (75). The second trial is also likely to be an SGA. The same rules apply to the second drug trial, with optimization and substitution being instituted as needed.

Persistent Positive Symptoms. Research definitions of treatment resistance have tended to focus on persistent positive symptoms (76). Despite adequate pharmacotherapy, at least 20% of multiple-episode patients have no positive-symptom response to antipsychotics. A further 30% respond only partially. Failed trials of 2 antipsychotics are accepted as evidence of treatment refractoriness. There is no consensus on how many or in which order the SGAs should be tried prior to classifying the patient as treatment-resistant. If poor treatment adherence is a factor, an IM long-acting medication can be considered. Given the options now available, physicians should actively evaluate treatment responsiveness and determine whether patients who have a poor functional recovery should be offered trials of clozapine. Clozapine remains the treatment of choice for partial (77) or total nonresponse to treatment (76,78). Clozapine should be considered as soon as treatment nonresponse has been demonstrated, even in the first or second year of the disorder. The duration of an adequate trial with clozapine is considered to be 4 to 6 months.

If a trial of clozapine is not effective, the next steps are augmentation, followed by combination strategies. A useful general principle is "monotherapy before polytherapy" (79). The commonly used augmentation strategies include addition of lithium, anticonvulsants (that is, valproate, carbamazepine, topiramate, and lamotrigine), antidepressants, benzodiazepines, and electroconvulsive therapy (ECT) (80). These combination strategies have been proposed essentially on the basis of case reports (79), but a randomized controlled trial (RCT) has yielded some evidence for the efficacy of lamotrigine (81). The last strategy is a combination treatment with a second antipsychotic. The efficacy of combined antipsychotic treatment has not been adequately tested, but

there is ample evidence of the likelihood of additional side effects. There is a lack of research evidence to support this strategy. The clinician should document the reasons for employing this, closely monitor side effects and response, and stop the combination in case of no clear benefit.

ECT continues to be a strategy to consider for treatment-resistant schizophrenia. A recent Cochrane review identified 24 trials and concluded that there was limited evidence to support its use as adjunctive treatment with antipsychotics for those who show limited response to medication alone (82).

Persistent Negative Symptoms. Negative symptoms have been defined as the reduction or absence of several normal capacities, such as the ability to experience pleasure (anhedonia), the free flow of thoughts (alogia) and the normal expression of emotions (affective flattening). However, this definition is problematic in that several factors can cause these reductions. This has led to the concept of primary and secondary negative symptoms or deficit syndrome (83). This concept can be applied in clinical practice; clinicians should first assess and treat any causes of secondary negative symptoms such as residual paranoid delusions, anxiety, oversedation, depression, or EPSEs. When the secondary negative symptoms have been dealt with, those remaining symptoms can be considered primary negative symptoms. This distinction can be useful for the clinician at the level of the single patient. It makes it more difficult, however, to address the issue of whether SGAs are more effective against negative symptoms, compared with first-generation compounds. Most studies are based on general measures of negative symptoms, which do not make the distinction. It could be argued that the distinction is not important from the patient's perspective, whereas it is important to the clinical scientist. A recent and comprehensive metaanalysis comparing SGAs and FGAs supports the superior efficacy of several of the SGAs, compared with FGAs (62). It reaches this conclusion primarily by analyzing the global outcome of positive, negative, and general symptoms. Smaller analyses of risperidone and olanzapine undertaken by the same authors support the conclusion that both were slightly superior to FGAs on positive symptoms but moderately superior on negative and general symptoms (84,85).

Depression. In a longitudinal cohort study of 3 clinical groups, the presence of a major depressive episode (MDE) was as frequent in the schizophrenia sample as it was in the schizoaffective group and the depression group (86). Depression in schizophrenia is associated with reduced subjective quality of life and with both attempted and completed suicide and, as a result, should be an important focus of clinical attention.

In the acute stage, symptoms of depression remit along with the positive symptoms. There is some evidence that SGAs are more effective than FGAs in the treatment of these depressive symptoms (62). There is no evidence to support the addition of an antidepressant at this stage of the disorder.

In the stabilization phase, individuals with a first episode of schizophrenia are more likely to experience a depression than are those with multiple-episode schizophrenia (70). The DSM-IV recognized postpsychotic depressive disorder of schizophrenia as a criteria set for further study (87). A review of several clinical trials that have evaluated the treatment of an MDE with antidepressant medications in the stabilization or stable phase of the disorder provided cautious support (87). Psychosocial interventions such as cognitive-behavioural therapy (CBT)can also be useful (see Psychosocial Interventions below for more information).

Suicide and Attempted Suicide. Suicide and attempted suicide are common problems in schizophrenia, with a lifetime expectancy of about 10% and 30%, respectively (89). The critical nature of suicide sets it apart as an issue of concern. Attention to all facets of the care of the patient is seen as critical to the prevention of attempted and completed suicide (90). In particular, attention should be paid to the assessment of suicidality at moments of risk, such as during transitions from hospital to the community. The critical nature of suicide also argues for the routine assessment of suicidality. From the pharmacologic perspective, 3 related symptom clusters may be the focus of attention: psychosis, depression, and suicidality. Optimal pharmacotherapy for these target symptoms requires optimal dosing, duration of treatment, and adherence. There is some evidence, discussed above, that SGAs are more effective than FGAs in the treatment of these symptoms. In the face of persisting suicidal ideation, clozapine has been shown to be more effective than other antipsychotics (91).

Violence. Most patients with schizophrenia are not violent; however, violence is a problem in a subgroup of the population. As in dealing with other clinical issues, pharmacologic interventions for violence need to be integrated with other interventions, particularly with interventions for substance abuse. The care of acutely agitated patients is discussed above.

In the stabilization and stable phases, persistent aggression can be associated with residual psychotic features, which should be one focus of clinical attention. In general, more effective treatment will generally the lower the association between a specific disorder such as schizophrenia and the probability of violence (92). There is some anecdotal evidence that clozapine may have some specific benefit in the situation of persistent aggression (93).

Sex Differences. Sex differences are recognized in multiple aspects of schizophrenia such as pathophysiology, symptoms, response to treatment, and side effects (94,95). Women experience later age of onset, more comorbid problems, and polypharmacy. They show higher plasma concentration at equivalent dosage and more side effects (94). Although it has been reported that women usually respond to lower antipsychotic dosages before menopause (95), this has not translated into evidence-based recommendations regarding different dosage ranges for men and women.

Physiological changes that occur during pregnancy modify antipsychotic elimination (that is, increased plasma volume, increased glomerular filtration rate, and increased hepatic enzyme activity). All psychotropic drugs pass though the placenta, as do the fat-soluble drugs in the breast milk. Sparse data are available on the use of antipsychotics during pregnancy. It is of primary importance to discuss fertility issues and contraception with antipsychotic-exposed women. Although empirical data preclude strong recommendations, experts generally agree that the safest option is to avoid the use of antipsychotics during the first trimester. In many situations, minimal time of antipsychotic exposure at the lowest effective dosage may be inevitable (94,96).

Management of Side Effects

Weight Gain and Abdominal Obesity

All antipsychotics may increase body weight, but a differential liability is well known among agents. Clozapine and olanzapine have been associated with significant weight gain; risperidone and quetiapine have been associated with moderate weight gain (40,47,97). Detailed mechanisms underlying body fat, particularly visceral fat, accumulation are unknown. Lean persons as well as young patients seem to be particularly vulnerable to dramatic weight gain, but no clinical tool is yet available to predict such an effect (98,99). Combinations with some psychotropic drugs such as lithium, valproate, and some antidepressants may significantly worsen the weight-gain profile (100).

Preventive lifestyle strategies should be encouraged, even if it is well known that such strategies are difficult to implement, not only in patients with schizophrenia but also in the general population. Benefits of physical activities and good nutrition habits should be emphasized both to the patient and to his or her family (101). If prevention is insufficient to limit weight gain, a change to an antipsychotic with a lower weight-gain liability could be considered (102,103). In such cases, modification of lifestyle habits should still be a goal. (The Canadian Task Force on Preventive Health Care recommendations on the detection, prevention, and treatment of obesity are available on-line at www.ctfphc.org/Tables/Obesity_tab.htm.)

Impairment in Glucose Regulation and Diabetes

Many glucose abnormalities have been reported with atypical antipsychotic treatment: insulin resistance, hyperglycaemia, exacerbation of type 1 diabetes, new onset of type 2 diabetes mellitus, and diabetic ketoacidosis (104,105). Additional studies are required to determine the differential liability of glucose impairment among agents and the differences in liability possibly owing to genetic factors. It is possible that there are differential responses between atypical agents; however, this is a subject of active debate (104,105). In Canada, all SGAs carry a warning for potential glucose abnormalities (53).

If diabetes is diagnosed, the Canadian Diabetes Association Guidelines should be followed. (Clinical guidelines on diabetes are available on line at www.diabetes.ca/cpg2003/default.aspx.) A switch of antipsychotic could be considered in some cases, although few studies have directly assessed the impact of a switch on metabolic parameters.

Dyslipidemia

Second-generation antipsychotics may elevate lipids. Clinical experience and published reports indicate that clozapine and olanzapine can be associated with hyperlipidemia. A few cases have also been reported with the use of quetiapine, while risperidone appears to be more neutral (40,104,106,107).

The 2003 update of Canadian recommendations for the management of dyslipidemia should be followed when lipids abnormalities are detected. A switch of antipsychotic could be considered in some cases, but advantages still need to be confirmed. (Clinical guidelines on dyslipidemia are available on-line at www.cmaj.ca/cgi/data/169/9/921/DC1/1 and www.nhlbi.nih.gov/guidelines/cholesterol/index.htm.) Psychiatrists should participate in the implementation and follow-up of both nonpharmacologic and pharmacologic treatment in such cases (103,107).

QT Prolongation

Prolongation of the QT interval is an ECG abnormality that can lead to torsades de pointes, arrhythmia, syncope, ventricular fibrillation, and sudden death. Risk seems to be greater with QTc values over 500 ms (108). Thioridazine has for some time not been permitted as a first-line antipsychotic, owing to concerns about QT prolongation (53), and is now off the market. FGAs such as mesoridazine and pimozide should be avoided in patients with heart disease, familial history of death at an early age (aged 40 years and under), and congenital long QT syndrome (40,108).

Endocrine and Sexual Side Effects

In women, changes in libido, delayed or absent orgasm, menstrual changes, or galactorrhea and, in men, changes in libido, erectile or ejaculatory troubles, or galactorrhea are among frequently experienced side effects (109), especially with FGAs.

Hyperprolactinemia may lead to decreased production of gonadal hormones in both men and women and may in part explain sexual side effects, along with modulation of neurotransmitters (110). Prolonged hyperprolactinemia and decreased hormonal levels may increase risk of osteopenia, osteoporosis (111), and impaired reproductive function in women (102).

SGAs show a lesser degree of elevation of prolactin levels, with the exception of risperidone, which is frequently associated with marked and sustained hyperprolactinemia, particularly if higher dosages are used (112). Transient prolactin elevation is possible with olanzapine. Quetiapine and clozapine are considered prolactin-sparing agents (113). Still, sexual dysfunctions may be seen with all available antipsychotics, regardless of their propensity to induce prolactin elevation (114).

In the presence of signs and symptoms of endocrine disturbance or impaired sexual functioning, a dosage reduction of the antipsychotic may be attempted. If unsuccessful, a switch to a prolactin-sparing agent should be tried (112). If adjunctive medication, particularly a selective serotonin reuptake inhibitor, is also being prescribed, the need for these medications should be reassessed. Careful attention should be paid to issues of birth control for women changing from an FGA or risperidone to a prolactin-sparing agent, since fertility level may be unexpectedly restored (102,115).

Cognitive Side Effects and Sedation

FGAs induce sedation, and many patients complain of a subjective dulling effect. Cognitive testing has shown no benefit in cognitive functioning with FGAs. SGAs appear to show statistically significant improvements in cognitive performance (43,116). Significant sedation may still occur, at least transiently, mainly with clozapine but also to a lesser extent with olanzapine and quetiapine. It is worse during the titration phase and may remit over time, but in some patients, increased sleep time and excessive diurnal sedation persist. Risperidone may be associated with both mild sedation or insomnia in some cases (117). High risperidone dosages (and to a lesser extent, high olanzapine dosages) increase EPSEs, which in turn may impair cognitive performance (114). Concomitant agents such as anticholinergics or anticonvulsants may increase cognitive problems (78,118). The therapeutic goal should be to at least prevent any cognitive harm and, ideally, to promote cognitive performance. In case of persistent cognitive dulling or sedation, dosage reduction should be tried. If insufficient, a switch to another agent should be considered (117).

Extrapyramidal Side Effects

EPSEs are particularly associated with FGA medications. Acute reactions occurring in the first days or weeks of treatment include dystonia, parkinsonism (akinesia or bradykinesia, tremor, and rigidity), and akathisia. Chronic side effects, some irreversible and appearing months or years after treatment, include TD and tardive dystonia. Neurologic side effects are the major burden of FGAs and a limitation to their use (44,79,114). When used in the recommended dosage range, risks of neurologic side effects from SGAs are minimal, but subtle signs of tremor, rigidity, and akathisia still can be detected and could be easily mistaken for anxiety, agitation, or negative symptoms. Higher dosages of risperidone (and to a lesser extent olanzapine) are associated with a higher risk of EPSEs (44,79,114).

If neurologic symptoms are detected, a dosage reduction of the antipsychotic should be tried, or switch to another SGA. A benzodiazepine or beta blocker can be prescribed for akathisia if a dosage reduction is insufficient. Anticholinergic medication is usually not recommended with the use of SGAs (79,114).

The annual risk of TD with FGAs is about 4% to 5%, with a cumulative risk of up to 50%, even when low dosages are used. SGAs are possibly associated with a reduced risk, where clozapine exhibits the lowest risk and may improve existing TD. Symptoms are not alleviated by antiparkinsonian medication and may worsen. A switch to an SGA is recommended, and a clozapine trial should be considered in the presence of persistent symptoms of TD (119). There is no evidence-based treatment formally indicated for TD, so prevention is the preferred strategy.

Neuroleptic Dysphoria

Neuroleptic dysphoria includes various subtle, unpleasant, subjective changes in arousal, mood, thinking, and motivation. It is associated with noncompliance, substance abuse, poor clinical outcome, increased suicidality, and compromised quality of life. SGAs are less likely to induce such dysphoric responses (120).

Neuroleptic Malignant Syndrome

Neuroleptic malignant syndrome (NMS) is a rare and severe condition with symptoms of rigidity, tachycardia, hyperthermia, elevated levels of serum creatine kinase, autonomic dysfunctions, and altered consciousness. It can occur with any antipsychotic agent, at any dosage, and any time. NMS constitutes a medical emergency with a high mortality rate. Risk factors include young age, male sex, neurologic disabilities, dehydration, exhaustion, agitation, and rapid or parenteral administration of antipsychotic. This side effect is potentially fatal if not managed promptly. Antipsychotic medication should be stopped and supportive therapy instituted. Agonists such as dantrolene, bromocriptine, or amantadine may improve symptoms (121).

Table 6 Recommendations

Recommendation	Evidence	Evidence level
Antipsychotic medications are indicated for nearly all patients experiencing an acute relapse; the choice of medication should be guided by individual patient factors.	Multiple randomized controlled studies and metaanalyses show that antipsychotics are effective for treatment of acute relapse.	A
Dosing in the acute phase should be in the range of 300 to 1000 mg CPZ equivalents for FGAs and within the approved dosage ranges for the SGA medications.	Review studies do not show evidence of increased efficacy with higher dosages above the recommended treatment range.	A
In first-episode psychosis, dosages should be started in the lower half of the treatment range; SGAs are indicated owing to the lower risk of short- and long-term extrapyramidal side effects.	RCTs in first-episode cases and dosage finding have not usually been the focus of the studies.	B
Maintenance pharmacotherapy is indicated for relapse prevention in the stabilization and the stable phase; maintenance dosages should be in the range of 300 mg to 600 mg CPZ equivalent for FGAs and within the recommended treatment range for the SGA.	Dosage-finding studies support the recommended dosage range for FGAs; RCTs of relapse prevention have been done with SGA medications but not studies comparing different dosing strategies.	A
Antipsychotic medication for the treatment of a first-episode psychosis should be continued for a minimum of 2 years following first recovery of symptoms.	There is evidence to suggest that the risk of relapse is greatest in the first 5 years.	B
Long-acting injectable antipsychotic medication should be considered for those patients who show poor medication adherence.	The nature of nonadherence makes it hard to conduct RCTs in this population.	B
Treatment nonresponse to adequate trials of antipsychotics from 2 different classes is an indication for a trial of clozapine.	RCTs and metaanalyses support the superiority of clozapine over other antipsychotics for treatment nonresponse.	A
Persistent aggressivity may be helped by a trial of clozapine.	Case series support the benefit of clozapine for persistent aggressivity.	C
Persistent suicidal thoughts or behaviours are an indication that clozapine should be considered.	One randomized open-label study has shown significant reduction in suicidality, compared with active control treatment.	B
A major depressive episode in the stable phase of schizophrenia is an indication for a trial of an antidepressant.	Results of some RCTs comparing antidepressants with placebo have been positive.	B

Clozapine Side Effect Profile

Clozapine is associated with several serious and potentially fatal side effects, including agranulocytosis (0.5% to 2.0%), seizures (2% to 3%) (122), and rare occurrences of myocarditis and cardiomyopathy. It is also associated with significant weight gain and glucose and lipid disturbances. Among other side effects, clozapine may also induce sialorrhea, significant sedation, hypotension, tachycardia, and significant anticholinergic side effects such as constipation, dry mouth, blurred vision, gastroparesis, and enuresis. It does not elevate prolactin levels or induce EPSEs (122).

Risk of agranulocytosis is higher in the first 6 months of treatment, requiring a weekly assessment to ensure that white blood count (WBC) and absolute neutrophils counts remain over $3000/mm^3$ and $1500/mm^3$, respectively. Thereafter, blood monitoring of complete blood count (CBC) and differential is reduced to every 2 weeks. A monitoring program has been shown to reduce agranulocytosis risk to less than 0.5%. Certain medications such as carbamazepine may increase the risk of clozapine-induced agranulocytosis and should be avoided (122).

Clozapine may induce seizures at a higher dosage (≥ 500 mg). Lower dosages and slower titration may reduce risk of seizure. Adjunctive anticonvulsants can be considered to manage seizures. Smoking cessation has been associated with seizures, since it may significantly reduce metabolism (via CYP1A2) and increase clozapine levels. Preventive dosage reduction (up to 50%) in case of smoking cessation would be judicious (122).

Patients taking clozapine should be advised to contact their physician if signs of infections occur (that is, fever, chills, and sore throat). Signs of myocarditis (such as fever, chest pain, peripheral oedema, tachycardia, and respiratory distress) should also be known by patients and their family (122).

Drug–Drug Interactions

Pharmacodynamic interactions between SGAs and frequently used adjunctive agents may lead to excessive sedation (for example, association with benzodiazepines), cognitive impairment (for example, association with valproate or lithium), and weight gain and metabolic perturbations (for example, association with lithium or valproic acid or some antidepressants). Important pharmacokinetic drug–drug interactions with antipsychotics should also be considered. Any drug or so-called natural product that may interfere with hepatic metabolism either as a substrate, an inducer, or an inhibitor of hepatic metabolic enzymes–cytochrome P450 system is likely to interfere with antipsychotics. Risk for such significant interactions with clozapine is greater (118).

IV. Psychosocial Interventions

General Principles

1. Optimal management requires the integration of medical and psychosocial interventions. Such interventions should not be seen as competing approaches but, in most cases, as necessary complementary interventions to improve clinical symptoms, functional outcome, and quality of life.
2. Effective psychosocial interventions may improve medication adherence, reduce risk of relapse and the need for readmission to hospital, reduce distress resulting from symptoms, improve functioning and quality of life, and provide support for patients, their families, and caregivers.
3. Common comorbid conditions such as substance abuse, anxiety disorders, and depression need to be recognized and addressed with psychosocial interventions.
4. Psychosocial interventions can be best implemented when acute symptomatology has been reduced and the patient can be successfully engaged in treatment.
5. Psychosocial interventions should be adjusted to the stage of the illness and needs of the patients and their families.
6. Listening and attending to the patient's concerns develops empathy, rapport, and a good therapeutic relationship. As well, it can improve engagement and adherence to treatment.
7. Patients, their families, and caregivers should be educated about the course and treatment of the disorder, as well as about ways to reduce risk of relapse. It is also important to provide a realistically hopeful attitude for the future. The physician is an extremely important contributor to this process.
8. The clinical team, the patient, and family members should develop shared, realistic goals for treatment and recovery. Progress toward these goals should be carefully monitored and evaluated.
9. Treatment providers should share plans for early recognition of relapse and crisis response with patient, family, and caregivers.
10. All patients should have access to evidence-based programs that develop skills for ADLs, meeting vocational and educational goals, managing finances, developing and maintaining social relationships, and coping with the impact of symptoms. (A useful Web-based reference is www.mentalhealthpractices.org.)
11. Staff providing psychosocial interventions should be appropriately trained.

Medication Adherence and Psychoeducation

Despite the effectiveness of psychopharmocological interventions in producing improved outcomes in schizophrenia, medication nonadherence occurs frequently (in up to 50% or more of cases) and for various reasons (123). A recent comprehensive review identified that the lack of awareness of illness was a key factor in medication nonadherence (124). Such lack of insight has been hypothesized by some to be a cognitive impairment associated with schizophrenia itself (125,126). Other issues contributing to nonadherence include concurrent alcohol or drug abuse, problems with the therapeutic alliance (127), medication side effects (128) and complicated dosage schedules, problems with access to treatment, and financial obstacles to obtaining medication (129). The impact of nonadherence is costly, not only for the person and his or her family but also more generally for the health care system (130).

Psychoeducational interventions that are aimed at increasing knowledge about the illness have shown some effectiveness in conveying facts, according to metaanalysis and systematic reviews (131,132), but have not been found to show increased adherence (123) unless also accompanied by motivational enhancement and the use of specific "behavioural tailoring" strategies such as reminders, prompting, and self-monitoring cues (133). Case reports highlight the importance of introducing concrete coping aids and behavioural compensation

methods, such as keeping medication regimens as simple as possible, "pillbox" dosette use, establishing a regular medication routine and monitoring it regularly, and including home visits as needed (134). Motivational strategies emphasize the links between medication adherence and benefits in the individual's life circumstances as well as the heightened risk of relapse when medication is not taken.

Vocational Interventions

Employment rates among individuals with schizophrenia and related disorders are substantially lower than in the general population (135–137). Employment status appears likely to have substantial impact on the economic circumstances of many patients and influences many aspects of quality of life. In the past, there was considerable emphasis on providing extensive preparation for employment before an individual was placed in a job setting; more recently, the emphasis appears to have been on placing individuals in competitive employment sooner and offering considerable after-placement job-support services. The latter approach, usually referred to as supported employment, includes the following elements: developing job opportunities appropriate for the individual, rapid placement that emphasizes competitive employment, providing ongoing support after job placement, and integrating vocational and mental health services. There have now been several studies contrasting supported employment with more traditional approaches (138–142). Recent metaanalyses of research findings concluded that the supported employment approach generally leads to better employment rates (135,143), although long-term job-retention rates may be less positive (144,145). There is no evidence that employment obtained with these methods leads to increased stress or exacerbation of symptoms (136,141,146); there is some, but not entirely consistent, evidence that such beneficial effects on employment status may have positive impacts on self-esteem, on aspects of psychiatric symptoms, and on the likelihood of relapse (144,147–149).

Skills Training

Individuals with schizophrenia frequently have difficulties related to social interaction and coping with aspects of independent living. Such difficulties may result from several factors, including early illness onset, which interferes with development of social and living skills; the impact of some aspects of impaired cognitive functioning; and the impact of the illness and its associated stigma. Interventions used to address these issues include social skills and life skills training. Social skills training uses methods based on learning theory and attempts to improve interpersonal skills related to conversational skills, making friends, and social interaction. Methods include instruction about the significance of various verbal and nonverbal aspects of social behaviour, modelling, role playing, behavioural rehearsal, corrective but supportive feedback, and behavioural homework and practice to increase generalization to the individual's daily environment. Life skills training focuses on skills related to practical aspects of living, such as managing money and domestic skills, and personal self-care, such as grooming and hygiene.

Although there have been many reports interpreted as supporting the value of these interventions (for example, 149–151), the results of recent metaanalyses of true RCTs have indicated caution regarding their impact. Pilling and others examined the outcomes of 9 RCTs that could be analyzed on an intention-to-treat basis and concluded that there was no clear evidence that patients who received social skills training had better outcomes, compared with other active treatment conditions, on any of various measures, including relapse rates, global adjustment, social functioning, or quality of life (153). When Robertson and others examined the literature on life skills training, they found only 2 studies that met criteria for an unbiased RCT, and the results of the metaanalysis (based on only 38 patients) did not demonstrate clear effects (154). Individual reports (for example, 152,155–157) suggest the potential of these interventions (particularly social skills training) to improve outcomes, and it would be contentious to suggest that results of metaanalyses of rigorously selected RCTs should be the only evidence examined with reference to their effectiveness (for example, 152,158). In particular, the effectiveness of the interventions used in social skills training may be best assessed with very situationally specific behavioural measures rather than with the standardized measures favoured by formal metaanalyses (151,152). Nevertheless, the metaanalysis results certainly suggest a need for further, well-designed evaluations of these interventions.

Cognitive-Behavioural Interventions

There is evidence for the effectiveness of cognitive-behavioural techniques in the treatment of several forms of psychopathology, including anxiety and affective disorders. In recent years there has been considerable interest in using cognitive-behavioural techniques in the treatment of psychotic disorders. When applied to schizophrenia and related disorders, the most frequently used cognitive-behavioural interventions include

- development of a collaborative understanding of the nature of the illness, which encourages the patient's active involvement in treatment
- identification of factors exacerbating symptoms
- learning and strengthening skills for coping with and reducing symptoms and stress
- reducing physiological arousal

- testing of key beliefs that may be supporting delusional thinking
- development of problem-solving strategies to reduce relapse

There have been significant variations in the treatments used in controlled trials of CBT, and so it is difficult to assess the effectiveness of each specific intervention. Both individual and group formats have been used, although most research on impact has involved evaluation of individualized treatment approaches. There has been considerable variation in the frequency and duration of treatment formats (varying between 6 and 50 sessions). It appears that weekly or biweekly sessions over a period of 4 to 9 months are typical of the trials.

There have been several reviews of the evidence concerning the effectiveness of such interventions (159–162), the most recent being a Cochrane Review metaanalysis (163). The evidence available at this point suggests that, as well as reducing psychiatric symptoms, adding cognitive-behavioural interventions to standard care (including medication) can have an impact on time to discharge from hospital and on general psychological functioning. Although Cormac and others (163) concluded that there is little evidence that CBT has an impact on likelihood of relapse, one recent trial using cognitive-behavioural interventions focused on dealing with early signs of relapse has reported promising results in this respect (164). Several studies in this field have focused on demonstrating symptom reduction in patients who are otherwise considered to be treatment-resistant.

Reviewers have come to different conclusions regarding whether there are high rates of attrition from treatment with cognitive-behavioural interventions (159,161,163). Carrying out controlled trials of these interventions is challenging. While some researchers have used outcomes assessed by raters blind as to condition, more such studies are needed, and a wider variety of medium- and long-term outcomes should be assessed.

The extent to which cognitive-behavioural interventions lead to better outcomes regarding symptoms and mental state, compared with less specific supportive psychotherapy, is unclear. Many reviewers have reached different conclusions. Bechdolf and others recently reported a controlled trial comparing group-administered CBT with a simpler psychoeducation intervention (165). They found that, while the CBT condition had fewer postintervention hospitalizations, the 2 groups did not differ significantly on indices of clinical relapse, symptoms, or adherence to medication. There is general agreement on the need for more studies comparing the effectiveness of CBT and simpler, less resource-intensive, psychosocial interventions (159,162,163).

The opinion of authoritative commentators suggests that cognitive-behavioural treatment of schizophrenia and related disorders requires substantial training and experience and has to occur within the context of a good therapeutic relationship characterized by trust and respect, but empirical research relevant to these issues is sparse. One controlled trial suggests that community psychiatric nurses who received 10 days' training in CBT were able to provide interventions that reduced overall symptoms (as assessed by the Comprehensive Psychopathology Rating Scale), reduced depression, and improved insight but did not have an impact on symptoms specific to schizophrenia. Only the change in insight was sufficient to be considered clinically significant by the authors (166). There can be little doubt that resources for providing cognitive-behavioural interventions for psychotic disorders are often limited, and therefore, it is important that we know more about identifying those patients most likely to benefit from such interventions and when they are likely to be cost-effective (167).

Family Interventions

Current approaches to family interventions recognize that families are often the primary caregivers and that they can consequently experience a burden from those demands (168). Regardless of whether the patient with schizophrenia is actually living with his or her family in the community, most families provide support and assistance to their ill relative. Families are often left in the position of assuming the role of caregiver, for which they are neither trained nor psychologically prepared (169). As well, professionals do not always accurately understand what factors caregivers find burdensome when coping with an ill relative (170). The degree and nature of burden has been found to vary with the phases of the disorder. In the early phase, families are faced with feelings of uncertainty and emotional shock. In later phases, families face dealing with the everyday impact of negative symptoms, such as lack of interests and loss of initiative (171).

Treatment efficacy can be enhanced and relapses can be prevented when family members participate in a structured program of family psychoeducation (172), which has been shown to relieve caregiver distress (173). There are core curriculum components to psychoeducational family treatment, an approach that offers empathy, knowledge sharing, and problem-solving skills training. Home visits are a part of some programs.

Family psychoeducational interventions should be introduced during the early phases of treatment when a patient is experiencing a first episode (174). There is some evidence that multiple-family groups may have more enduring benefit than individual approaches during the first episode (175). However, many families will not attend groups and need

individualized treatment and outreach. Educational interventions may subsequently need to be supplemented, depending on individual circumstances such as the needs of siblings and needs related to the illness phase. In working with family members, sensitivity to confidentiality issues is required, including the use of appropriate information-release forms, to maintain a trusting relationship with the patient. However, family members should not be underused: they provide a valuable consultation resource for mental health professionals, and they are allies in patient recovery efforts (176). Working with families should include listening to family members' concerns, exploring family expectations about treatment and their understanding of the patients' illness, making adjustments that acknowledge and respect family culture and values, assessing family members' capacity to cope with and support their ill relative, and developing a crisis plan. Mental health practitioners can also assist in linking family members to other ongoing supports as needed, including family organizations such as the Schizophrenia Society of Canada (www.schizophrenia.ca) or the Canadian Mental Health Association (CMHA, www.cmha.ca).

Cognitive Remediation

Individuals with schizophrenia and related disorders not only have disturbing and pathological thought content related to delusions and hallucinations, they can also have anomalies in thought form or information processing, such as difficulties with attention, learning, memory, executive functioning, and planning. When they occur, such cognitive deficits are often related to negative symptoms, appear to have substantial implications for an individual's daily functioning, and may compromise the individual's ability to benefit from psychosocial interventions (177,178). Recently, there has been increased interest in the possibility of developing interventions to help patients reduce such cognitive difficulties and (or) their impact, and these efforts are referred to by varying terms, the most common of which are cognitive remediation, cognitive training, and cognitive rehabilitation.

Such efforts usually involve one or more of 3 strategies: restorative approaches, in which efforts are made to reduce the underlying cognitive deficits; compensatory strategies, which aim to help patients work around or compensate for cognitive deficits; and environmental approaches, which try to provide situational supports, such as external reminders, to decrease the impact of cognitive deficits.

Several studies have examined the impact of cognitive remediation training strategies on standardized neuropsychological tests (179,180), but of greater clinical significance would be studies assessing the impact of such strategies on daily functioning. Although there are some encouraging initial reports that aspects of cognitive remediation or compensatory strategies have beneficial real-life impact (181,182), several recent literature reviews conclude that there is a need for further research on the impact of cognitive remediation techniques on patients' functioning outside laboratory or other controlled settings. There is currently no clear and consistent evidence that such interventions have a significant effect in such domains (153,177,183–185). Hopefully, future research will provide more definitive evidence regarding these issues, but currently, there is not sufficient research to justify recommending cognitive retraining as part of routine clinical care.

Peer Support, Self-Help, and Recovery

Over the past decade, the concept of recovery has been used increasingly to refer to both the process and outcome of efforts by individuals with schizophrenia to succeed in overcoming illness barriers (186). The "recovery vision" focuses on "consumer" involvement (empowerment) in setting rehabilitation goals leading to improved community functioning (not just stability of symptoms) and on the development of a "recovery-oriented system" that advocates for supports beyond standard health care (187). Key components of system-level change have been the introduction of self-help programs (188), including peer-run services (189), and the use of peer-support workers or peer providers as staff members of multidisciplinary teams (190) and alternative mental health delivery services.

Critical ingredients of peer-provider services hold promise for benefits beyond typical practices (191). These include their use of experiential knowledge ("street smarts") to enhance pragmatic support efforts and the positive impact of social role modelling. For example, peer-assistant workers, including graduates of previous training groups, have been incorporated into skills training groups to deliver some of the training, such as social skills role-play instruction or training as worker-assistants in collective kitchens. The effectiveness of peer providers in case-worker roles has not been well examined in controlled clinical research (192,193) and may be limited by their own state of recovery (191). There are modest findings from less rigorous studies (189) of some benefits, including improvements in self-esteem and increased social networks. Peer services and, more generally, recovery-oriented practitioner perspectives work toward maintaining and inspiring a sense of hope, levels of which have been consistently found to be unrelated to the actual severity of the psychotic symptoms (194). There have been some suggestions from a CMHA survey (195) that peer supports provide patients with increased satisfaction regarding their community adjustment and with increased feelings of self-worth.

Stigma

Stigma and discrimination against people who suffer from severe mental illness, especially against those with schizophrenia, have been considered crucial barriers to recovery and successful community adjustment (196), indicated by obtaining desirable jobs and housing ("not in my neighbourhood"). Research findings confirm that most people with mental illness report such stigma-related experiences as stereotyped societal misconceptions about their propensity to violence or being blamed for not taking more responsibility in getting over their mental and emotional problems (197). A coping manual has been developed for dealing with dilemmas such as "to disclose or not disclose" illness with landlords or employers (198). Public education talks that actually include contact with a person with mental illness who tells his or her story have been shown to be most effective in changing societal attitudes (199).

Associated Features and Special Situations

Treatment of Comorbid Symptoms

Individuals with schizophrenia have relatively high rates of symptoms of stress, anxiety, and depression (200–202). There is evidence that stress, anxiety, and depression show covariation with positive symptoms of schizophrenia and may be precursors of relapse (203,204). Such symptoms of dysphoria may have a substantial independent impact on patients' quality of life (205). While there is strong evidence that stress, anxiety, and depression in other populations can respond to psychosocial interventions, particularly forms of CBT, there is little research evaluating the impact of such interventions specifically among those with schizophrenia and related disorders. Many of the interventions described under CBT for the defining symptoms of schizophrenia (above) may have their effects on or be mediated through reductions in stress, anxiety, or depression, although only a few studies provide relevant data (166,206,207). A few recent studies have examined the effectiveness of transferring methods used with other clinical populations in reducing stress and dysphoria in schizophrenia patients; these have shown some promising results (208,209), but more research in this area is needed.

Substance Use

Addressing the special needs of schizophrenia patients who have cooccurring substance use or abuse (termed concurrent disorders) presents several challenges for practitioners. First-episode psychosis has been found to be precipitated at an earlier age when associated with substance use (210), including higher rates of smoking found among adolescents later diagnosed with schizophrenia (211). Cannabis use has been associated with a doubled the risk of psychosis onset, according to a comprehensive review (212). For the long-term stable phase of the illness, specialized interview methods (213) should be considered to identify concurrent substance abuse.

In terms of psychosocial treatments, difficulties in even engaging the patient in therapy pose the first and seemingly biggest obstacle to recovery (214). Mental health workers familiar with the stages of change model (215) recognize that many individuals who abuse substances are not even considering making a change in their substance use lifestyle, a phase termed precontemplation. Motivational interviewing (216) is a technique that has been shown to be effective in moving patients toward considering making changes (contemplation phase) and eventually taking action such as entering treatment. The most effective outpatient treatment for substance abuse disorders involves a comprehensive, integrated approach (217). The historical dual-treatment team approach not only lacks cohesiveness but has in the past provided discrepant messages on issues such as the role of medications in recovery and the failure to accommodate the addiction therapy to the cognitive learning deficits associated with schizophrenia. Integrated residential treatment, especially over a period of up to 1 year, has also proven to be successful, especially for those who do not respond to outpatient intervention (217). The prevalence of "legal" drug use, including nicotine, caffeine, and alcohol, has been found to be higher among individuals with schizophrenia (218). Significant associated health hazards exist, including complications with psychopharmacologic intervention. Specialized behaviour-based interventions for smoking cessation have been tailored successfully for schizophrenia patients (37).There are suggestions that patients treated with clozapine (219), and possibly other atypical antipsychotics, may smoke less after being switched from a first-generation treatment.

Prenatal Planning

Although the image of a schizophrenia patient may be of someone who is single and living alone, there are estimates that up to one-half of people diagnosed with schizophrenia are married or living with an intimate partner (220). Where one or both of the partners have schizophrenia, clinicians are sometimes faced with tough questions from couples asking advice about the decision to have children. Several issues can be discussed with the couple. These include medication during the prenatal period (including the potential need to stop the medication and the ensuing risk for relapse), genetic risks that the child will develop schizophrenia (thought to be about 1 in 10 where one partner has schizophrenia and 4 in 10 where both partners have schizophrenia), risk for postpartum conditions, the responsibilities associated with parenting and handling caregiver demands, the availability of parenting supports (such as grandparents or, in some cases, the Children's Aid Society), and more general emotional issues such as desires to

experience parenthood and both worries and wishes about having someone depend on them (221).

Psychosocial Interventions Across Illness Phases

Acute Phase

It is generally accepted that psychosocial interventions are difficult to implement and probably less effective during the acute phase of psychotic illness, when the ill person's thoughts and behaviours are often highly disrupted. However, there are 2 important caveats to this observation. The first is that, while it may not be optimal to provide structured and often subtle psychosocial interventions to an individual when he or she is acutely ill, those factors that facilitate the ill person's trust in clinicians and engagement in treatment during the acute phase are likely to also have beneficial effects for facilitating engagement in subsequent psychosocial interventions. Second, the acute phase of illness may be a critical period with respect to engaging families in psychosocial interventions. The response to families and the provision of basic education and support to them during the acute phase may critically influence their interest and willingness to later engage in ongoing family psychoeducation and support interventions. Although there has been little empirical research relevant to this point, many clinicians are convinced that the acute phase of illness can be a critical period for family engagement.

Stabilization Phase

The stabilization phase provides an opportunity to assess the extent to which pharmacologic interventions are successful in bringing about remission of positive symptoms and the likely extent of ongoing negative symptoms and cognitive difficulties. As noted earlier, there is some evidence that cognitive-behavioural intervention can be of value in reducing serious and disruptive psychosis symptoms (207). If the resources are available, this phase could offer an opportunity to introduce the individual to interventions that address positive symptoms that may otherwise become treatment-resistant. This also appears to be an opportunity to introduce interventions designed to address substance use or abuse as well as comorbid syndromes, such as anxiety, that may be making a major contribution to patient distress. Programs of structured activity and peer support may also be important in reducing a slide into social withdrawal and behavioural apathy. If possible, it is important in the stabilization phase to introduce families to the issues of ongoing treatment, monitoring of recovery, and support, rather than let them assume that resolution of an acute crisis is sufficient.

Stable Phase

With the focus changing to functional recovery and preventing relapse, many psychosocial interventions become relevant. They include interventions that may have already been introduced to the patient in regard to substance use and reduction in residual and comorbid symptoms. In addition, interventions related to employment, education, and social activity (such as supported employment, social and ADL skills training, and compensatory interventions for cognitive dysfunctions) may be very relevant. For patients, educational and cognitive-behavioural intervention related to reducing stress and preventing relapse can be beneficial; parallel issues can also be addressed with family members. As noted in the section on assessment, it is important to tailor psychosocial interventions to the carefully assessed goals, needs, abilities, and circumstances of individuals, rather than assuming a "one size fits all" approach.

Table 7 Recommendations

Recommendations	Evidence	Evidence level
Psychoeducation		
Psychoeducation is an important intervention that needs to be accompanied by training in practical illness management strategies to achieve medication treatment adherence and to prevent relapse.	Psychoeducation can improve knowledge about illness, but there are equivocal findings that it increases treatment adherence unless there are also motivational enhancement and behavioural strategies for taking medication as prescribed.	B
Vocational interventions		
A wide range of possibilities should be considered for patients who are able to work, including volunteer work, supported, or transitional employment.	Individuals who suffer from schizophrenia have historically had low rates of employment; meaningful vocational activity, including paid employment, can be positive for individuals' psychological health and quality of life.	B
For many patients it is important to formulate goals for competitive paid employment and, in general, supported employment programs appear to offer the best approach to meeting such goals.	Supported employment approaches result in greater success in obtaining competitive paid employment.	A
Skills training		
Social skills training should be available for patients who are having difficulty and (or) experiencing stress and anxiety related to social interaction.	Social skills training leads to better outcomes with reference to symptoms, social functioning, and quality of life, compared with other standard care and (or) other interventions such as supportive psychosocial intervention and occupational therapy.	B
Life skills training in an evidence-based format should be available for patients who are having difficulty with tasks of everyday living.	Life skills training leads to better outcomes with reference to social functioning and quality of life, compared with standard care.	B
Cognitive-behavioural interventions		
Cognitive therapy should be offered to treatment-resistant patients.	Randomized controlled studies have shown benefits of CBT for patients with treatment-resistant schizophrenia.	B
Family interventions		
Family interventions should be part of the routine care for patients with schizophrenia.	Patients with schizophrenia whose families receive psychoeducation demonstrate reduced rates of hospitalization and show delayed or reduced symptomatic relapse.	A
Family psychoeducation programs should last more than 9 months and include features of engagement, support, and skills-building, not simply information- or knowledge-sharing.		B

continued

Table 7 Recommendations *continued*

Recommendations	Evidence	Evidence level
Peer support, self-help, and recovery		B
Local antistigma campaigns should include contact with people with schizophrenia.	Strategies to combat societal stigma and discrimination against the mentally ill are most effective when the public education includes contact with people who have schizophrenia telling their story.	C
Peer provider services should be included in the continuum of care; such services include consumer roles in group-based skills training, peer support, and public education programs.	Peer provider services contribute beneficial role-modelling and experiential knowledge but have not been adequately studied in controlled research designs.	
Treatment of comorbid symptoms		
Cognitive-behavioural interventions should be considered in the treatment of stress, anxiety, and depression in patients with schizophrenia; some adaptation of the techniques used in other populations may be necessary.	Symptoms of distress, anxiety, and depression occur in a substantial proportion of patients with schizophrenia.	B
	Psychosocial interventions, particularly cognitive-behavioural interventions used in other populations may be useful in reducing symptoms of stress, anxiety, and depression in patients with schizophrenia.	B
Substance use		
Integrated programs for concurrent substance use disorders should be available for people with schizophrenia	The optimal intervention is integrated treatment of both psychosis and substance use in a single program.	B

V. Service Delivery

Service Delivery and the Treatment System

General Principles

1. All patients should have access to a comprehensive continuum of services that provides continuity of care, including physical care.
2. All patients in longer-term programs should have a written care plan that should be available to family members, with patients' permission, when possible.
3. The continuum of care should include 24-hour crisis services, acute inpatient care in a medical setting, nonmedical crisis stabilization, acute day hospital treatment, community-based rehabilitation, integrated addiction services, comprehensive services for early psychosis, assertive community treatment programs, consumer-driven services such as club houses, and supported employment programs.
4. All patients should have access to a continuum of housing support, including long-term hospital care, supportive housing in the community, independent housing with supports, or affordable general housing.
5. Services should be accessible in the patients' own language and in their own area.

This section addresses the broader role of mental health services in the provision of care for people with schizophrenia. Whereas the 3 earlier sections focused on assessing and treating individuals with schizophrenia, this section deals with the range of mental health services needed for these individuals. This is a relatively new area for a clinical practice guideline; however, its inclusion within an evidence-based guideline is justified by the increasing body of knowledge in this area. The knowledge comes from the expanding discipline of health services research, which has been defined as follows. "Health Services Research is usually concerned with the relationships between need, demand, supply, use and outcome of health services. The aim of the research is evaluation particularly in terms of structure, process, output and outcome" (222).

Despite the robust evidence for the efficacy of many pharmacologic (223–225) and psychosocial interventions, a relatively limited proportion of schizophrenia patients receive optimum care, particularly for psychosocial treatment (226). The potential benefits of psychosocial intervention are minimized by lack of access to, and availability of, such treatments. Hence, the systemic context within which treatment is delivered acquires prime importance.

The very nature of the needs associated with service delivery and the variations seen in the extent to which aspects of service delivery are available in different jurisdictions means that the standard RCT levels of evidence may be either unavailable or not applicable for practical and ethical reasons. The limitations of the RCT for evaluating what have been called socially complex services have been outlined (227). Socially complex services are characterized by complex, diverse, and nonstandardized staffing arrangements; ambiguous protocols; hard-to-define study samples and unevenly motivated subjects; and dependence on broader social environments. There are difficulties in ensuring precise protocols, equivalent groups (tied to a meaningful target population) and neutral and equivalent trial environments under real-world conditions.

Several service delivery attributes are key to the success of services designed for a whole population. These attributes include, but are not limited to, access, availability, and continuity of care. Chronic disease management systems provide a population-based approach to organizing such services. Five components have been described: the use of evidence-based, planned care; reorganization of practice systems and provider roles; improved patient self-management support; increased access to expertise; and greater availability of clinical information. The challenge is to organize these components into an integrated system of chronic illness care (228).

Access

Access to adequate treatment is especially important at the time of the first episode of the illness. Such treatment is often

delayed for an average of 1 to 2 years (229). Such delay is not only encountered in the process of seeking help; it is more importantly associated with further delays within the health care system (both primary and mental health care) (230–232).

Availability

Most jurisdictions not only have waiting periods for access to treatment, they also lack available effective treatments. This is related to lack of resources, poor allocation of resources, and lack of adequately trained staff to deliver interventions, especially psychosocial treatments. In a Canadian survey of adherence to schizophrenia practice guidelines, most psychiatrists reported that less than one-half of their schizophrenia patients received appropriate psychosocial therapies (233). For many patients, these services did not exist.

Coordination and Continuity of Care

While most patients spend most of their time in the community, some require periodic hospitalizations. Therefore, it is important that hospital care and community care be well coordinated. Attention to patients' physical or medical needs also needs to be coordinated with primary health care. Hence, every patient should have a designated family physician whom he or she visits regularly, and any change in treatment of the primary psychiatric disorders or of other medical disorders should be communicated to all involved professionals.

Patients must not be allowed to fall between various components of the treatment system. The separation of addiction services from other mental health services was formerly frequent in Canada, although this is changing. The available evidence supports the integration of mental health treatment and addictions treatment in the same program. Patients who attend outpatient clinics and do not have ongoing needs for case management should be monitored regularly. Patients treated in outpatient clinics should be reminded of their upcoming appointments, preferably through a written or oral prompt (234). Those whose needs require them to engage in a case-management program should retain contact with the same treatment team, even if the individual case manager moves.

Service Delivery Components

Treatment for schizophrenia is delivered in multiple settings across the continuum of care. This continuum includes both long- and short-stay inpatient units, day clinics or hospitals, outpatient and ambulatory clinics, outreach programs such as assertive community treatment programs, and nonclinical community services. There is considerable variation among and also within regions in the components of each service. A brief description of each component's role and its importance in providing adequate services follows.

Early Psychosis Treatment Services

In some jurisdictions, there are specialized treatment programs available for patients presenting with a first episode of psychosis (235–237). Early-intervention services are being established on the basis of 3 main premises. First, there is a critical, albeit narrow, window of opportunity for influencing the course of psychotic disorders following their onset. Second, adequate, phase-specific treatment delivered within a comprehensive model of care is more likely to improve outcome by reducing the negative consequences of the illness (238,239). Third, delay in treating psychosis is related negatively to outcome (240). Emerging evidence suggests that increasing patient retention in treatment as a result of improved engagement is an important benefit of comprehensive early psychosis treatment services (241). The evidence for the impact of early psychosis treatment services on reducing the delays encountered in treatment is also being investigated and shows modest success (242,243). The evidence for the impact on treatment outcomes is only just emerging but appears to be promising, although still limited (65,241,244) and perhaps even equivocal (245).

Acute Inpatient Care

Despite some alternatives such as home treatment, crisis houses, and acute day hospitals, all jurisdictions still require several acute care beds for treatment of acute episodes of the illness that cannot be managed in other settings. The extent to which such beds will be used, and the number required, will depend on available alternatives and on local social and cultural characteristics (246). Patients will still require admission to hospital in an acute care bed, even if such alternatives are available. The indications for admission include the need to manage high levels of risk for suicide or assaultive behaviour and the need for urgent medical assessment if the patient suffers from severe and comorbid medical conditions.

Episodes of illness requiring treatment in an acute care setting almost invariably occur in the context of crises and therefore are likely to provoke fear and anxiety in the patient and his or her family. Consequently, provision of acute inpatient care requires the most humane and least institutionalized approach, and one that is also culturally sensitive. Such an approach requires taking into consideration patients' and families' needs and acceptance (247,248).

Day Hospitals

Day hospitals have been developed for 3 main purposes: as alternatives to acute inpatient care, as alternatives to outpatient care, and as sources of vocational rehabilitation. Two published, systematic reviews have examined these 3 forms of "day care" (249,250). As alternatives to inpatient care, acute day hospitals were found to be suitable for between one-quarter and one-third of inpatients. For patients who managed

to attend day hospital, symptoms improved more quickly than for those who were admitted as inpatients. In addition, the costs were lower. Day hospital patients used fewer inpatient days than the inpatient group who had not been previously admitted to a day hospital; there were no differences in readmission between the 2 groups. This form of acute day hospital care was seen as a useful service in health systems with limited access to acute inpatient services.

In comparison with outpatient care, day hospital treatment programs offered greater symptom improvement than outpatient clinic care but no additional benefit in clinical or social outcome. When rehabilitation was the goal of day programs, they were found to be less effective than supportive employment programs in getting people back to work.

Home-Based Acute Care

Home-based acute care has been recommended as a preferred treatment where feasible from a risk perspective. The evidence suggests that there are some modest advantages in favour of home-based care that tend to be lost with time. However, patients and relatives report greater satisfaction with home-based care, even after 3 to 4 years (251–254).

Mobile Crisis Service

Mobile crisis services usually comprise a mobile, specialized, multidisciplinary team that provides assessment, crisis intervention, and appropriate referral to ongoing care. The team does not typically initiate and provide ongoing home treatment. Such services appear to be effective in providing services in the least restrictive environment and in avoiding hospitalization (255).

Outpatient and Community Mental Health Services

It is generally agreed that most services should be provided in outpatient settings while the patients are living in the community. However, there is little evidence about what should be the key components of outpatient care. It is generally agreed that active follow-up by a case manager and monitoring of treatment adherence and patient outcomes should be included in what is provided (256). Community mental health teams are regarded as basic building blocks of a community-based mental health service (246). Generic, community-based, multidisciplinary teams have the advantages of improving engagement with services, increasing user satisfaction, increasing met needs, and improving treatment adherence (257–259).

Case Management

Case management is designed to ensure that patients receive individual and tailored treatment programs that meet their needs. Case management has been advocated because patients with schizophrenia may have cognitive, emotional, and organizational deficits, along with poor adherence to treatment and rehabilitation. The goal of case management is to assist patients to live more independently in the least restrictive setting, according to their needs and capacities.

A comprehensive review has reported 6 models of case management with overlapping characteristics: clinical (260), brokerage, assertive community treatment (ACT), intensive case management (ICM), strengths (261), and rehabilitation models (262,263). In everyday practice, the type of case management is not clear-cut, because most case managers use a blend of brokerage and clinical case management (263).

Assertive Community Treatment. ACT combines a team-based and outreach approach to case management. ACT teams have a high staff-to-patient ratio (that is, 1:10) and some teams are on call 24 hours, 7 days weekly. Staff members operate in both clinical settings and patients' community environments. They provide a specialized approach to treatment of patients with psychotic disorders who are more clearly disabled (264). ACT programs are now available in most jurisdictions and have been shown to be effective in reducing hospital readmission rates and improving housing and occupational functioning, as well as quality of life and service satisfaction (265). These programs do not lead to any differential improvement in clinical state and do not change the overall costs of care (266,267).

A criticism of the ACT approach is that it may reduce self-determination by supporting "treatment guardianship." Reducing or withdrawing from ACT programs is an important and controversial issue. This area of ACT interventions requires further research to identify the patient characteristics that predict a favourable outcome following withdrawal, as well as the critical components that need to be in place for transfers to be successful.

Intensive Case Management. The ICM model was designed to meet the needs of high service users who were not being adequately engaged by brokerage and clinical case management practices (268). Similar to the ACT model, ICM employs a low patient-to-staff ratio, provides assertive outreach in the community, and assists with daily living skills. One difference between ICM and ACT models is that caseloads are not shared between clinicians in ICM. However, researchers refer quite often in the literature to ICM models as having shared caseloads. Mueser and others prefer to include ICM studies with studies of ACT programs (263).

Case Management Outcome Results. Research results on case management outcomes are mixed. One Cochrane review (269) found that, in comparison with standard care, case management increased hospital admissions and length of stay, which resulted in increased costs. However, case management increased the number of patients in contact with service and, hence, with medication. The general practice is to

use case management for patients who have complex service needs. ACT and ICM are more often used for hard-to-engage or treatment-resistant patients. In a recent study assessing the satisfaction with standard or intensive case management, patients were equally satisfied by both approaches (270).

Residential Care

A continuum of housing support is required for persons with schizophrenia. An appropriate continuum will not only provide the most choice for individuals with schizophrenia, it will also support early discharge from hospital. Estimates exist of residential needs for all patients with severe and persistent mental illness when they are not acutely ill, based on an overall prevalence of 171 patients per 100 000 population. The estimated residential care needs (including hospitalization) are as follows: 20/100 000 for long-stay hospital units, 20/100 000 for nursing homes, 40/100 000 for group homes, 40/100 000 for private hostels or foster families, and 51/100 000 for supervised apartments (271). There is evidence that individuals with schizophrenia have an increasing desire to manage living situations that are as independent as possible (272) and to choose options that avoid the more institutional feel of shared accommodation. Evidence from one RCT found that an integrated housing program (with on-site support staff) was found to be superior to mobile team supports in providing housing stability for those patients who are at risk for homelessness (273). Family members may voice preferences that their relative live in housing with more supervision (274). However, the best housing outcome occurs when there is a match between patients' perspectives and those of their families.

Patients with long-standing illness who have severe and long-term disabilities fare better when treated in community-based residential care facilities (for example, group homes), compared with those treated in large institutions (275–277). Patients with less severe disabilities but who are unable to live independently should be housed in community-based housing with graded supervision depending on their needs.

Table 8 Recommendations

Recommendations	Evidence	Evidence Level
Admission to acute care inpatient beds		
Acute inpatient care is indicated for patients at high risk for suicide or assaultive behaviour and for those with complex psychiatric and medical comorbidities.	Randomized controlled studies of alternatives to inpatient care consistently demonstrate a need for inpatient care.	B
Services for patients presenting with a first episode of psychosis should be available on an urgent basis.	Naturalistic studies demonstrate negative clinical outcomes prior to treatment; studies show correlations between duration of untreated psychosis and poor longer-term outcomes.	B
Continuous care should be available in a comprehensive treatment program for up to 3 years following the first episode.	Consistent application of evidenced-based care including pharmacotherapy, family therapy, and patient education yields superior outcomes.	A
Specialized treatment services should be available for patients with a first episode of psychosis.	Preliminary randomized controlled studies have provided some evidence of superior outcomes for specialized services, in addition to evidence from uncontrolled studies.	B to C
ACT programs should be available to selected patients who have a history of repeated admissions, are hard to engage in usual clinical settings or are homeless.	Numerous RCTs have demonstrated some benefits from ACTs.	A
Case management		
Case management service should be available for those patients who have difficulty accessing the full range of services in the community.	Case management and ACTs can reduce the symptoms and the number and length of psychiatric hospitalizations.	B
Day hospitals		
Acute day hospital care is an alternative to full-time hospitalization for acute crises and as a step-up service for those who are doing poorly in outpatient care.	Day hospital admissions result in improved symptoms and treatment satisfaction; day hospitals cost less than inpatient care.	B

VI. Special Issues

The Prodromal Phase of Schizophrenia

The prodromal phase of the illness is defined as the period of nonspecific behavioural changes and symptoms that occur before the onset of clearly identifiable psychotic symptoms. The prodromal phase is usually preceded by a premorbid phase during which there may be general deficits in social and academic functioning. However, not all behaviours and symptoms regarded as prodromal lead to psychosis, and hence the utility of this concept is limited. Nonpsychotic prodromal symptoms such as depression, anxiety, and social withdrawal are relatively common phenomena seen in different psychiatric disorders and in the general population, especially among adolescents. Hence, such symptoms have limited specificity for predicting future psychosis. However, in patients with established illness, these symptoms may be useful as monitoring warning signs for an impending relapse (238,278–280).

Recently, there has been a significant improvement in more reliably defining the period immediately preceding the full onset of psychosis. This has been termed the "ultra high-risk mental state" and is defined by either onset of attenuated psychotic symptoms not reaching threshold for psychosis or brief intermittent psychotic symptoms lasting less than 7 days or a combination of a trait (positive family history of psychosis in first-degree relatives) and a significant decline in global functioning in the previous year. According to these criteria, the ultra high-risk group has shown transition to psychosis at the rate of around 30% to 40% in the first year (22,281,282).

While no definitive treatment can be recommended at this time for individuals meeting criteria for ultra high risk prior to the full onset of psychosis, there is preliminary evidence that low-dosage risperidone (283) and medium-dosage olanzapine (284–286) may reduce the risk of conversion to psychosis, reduce symptoms, and improve functioning. Similar reduced conversion to psychosis has been reported recently with the use of CBT (287). However, well-designed investigations of nonpharmacologic therapies and pharmacologic interventions other than antipsychotic drugs have not yet been carried out.

Table 9 Recommendations

Recommendations	Evidence	Evidence level
Patients who meet criteria for "ultra high-risk mental state" for psychosis should be offered monitoring for at least 1 to 2 years; if clinically indicated, they may be offered supportive therapy and symptomatic treatment for emerging psychotic symptoms, depression, or anxiety.	Patients who meet criteria for ultra high-risk mental state for risk of psychosis show a 30% to 40% rate of conversion to psychosis within 1 year of observation.	B
If they convert to psychosis, treatment for psychosis should begin immediately; this will avoid any delay in treatment and may portend better engagement and improved outcome.	Delay in treatment of psychosis is related to poor outcome.	B

List of Abbreviations

ACT	assertive community treatment
ADLs	activities of daily living
BMI	body mass index
CBC	complete blood count
CBT	cognitive-behavioural therapy
CMHA	Canadian Mental Health Association
CPA	Canadian Psychiatric Association
CPGs	clinical practice guidelines
CPZ	chlorpromazine
CT	computed tomography
DARE	Cochrane Database of Abstracts of Reviews of Effectiveness
DUP	duration of untreated psychosis
ECT	electroconvulsive therapy
EPSEs	extrapyramidal side effects
FEP	first-episode psychosis
FGAs	first-generation antipsychotics
FISH	fluorescent in situ hybridization
HDL-C	high-density lipoprotein cholesterol
ICM	intensive case management
IM	intramuscular
IV	intravenous
LDL	low-denisty lipoprotein
MDE	major depressive episode
MRI	magnetic resonance imaging
NIMH	National Institute of Mental Health
NMS	neuroleptic malignant syndrome
RCT	randomized controlled trial
SGAs	second-generation antipsychotics
STDs	sexually transmitted diseases
TD	tardive dyskinesia
WBC	white blood count

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Appendices

Appendix I
Jadad Scale for Rating Clinical Trials (288)

This scale was adapted to use for rating the clinical trials in the CPG database. Each clinical trial in the database was assigned a Jadad rating as part of its quality rating.

Instructions

This is not the same as being asked to review a paper. It should not take more than 10 minutes to score a report, and there are no right or wrong answers. Please read the article and try to answer the following questions (see attached instructions):

1. Was the study described as randomized (this includes the use of words such as randomly, random, and randomization)?
2. Was the study described as double blind?
3. Was there a description of withdrawals and dropouts?

Scoring the items

Either give a score of 1 point for each "yes" or 0 points for each "no". There are no in-between marks.

Give one additional point if:	For question 1, the method to generate the sequence of randomization was described, and it was appropriate (for example, table of random numbers or computer generated)
and (or):	If for question 2, the method of double blinding was described, and it was appropriate (for example, identical placebo, active placebo, dummy)
Deduct 1 point if:	For question 1, the method to generate the sequence of randomization was described, and it was inappropriate (for example, patients were allocated alternately, according to date of birth, or hospital number)
and (or);	For question 2, the study was described as double blind, but the method of blinding was inappropriate (for example, comparison of tablet vs injection with no double dummy)

Guidelines for assessment

1. Randomization

   A method to generate the sequence of randomization will be regarded as appropriate if it allowed each study participant to have the same chance of receiving each intervention and the investigators could not predict which treatment was next. Methods of allocation using date of birth, date of admission, hospital numbers, or alternation should not be regarded as appropriate.

2. Double blinding

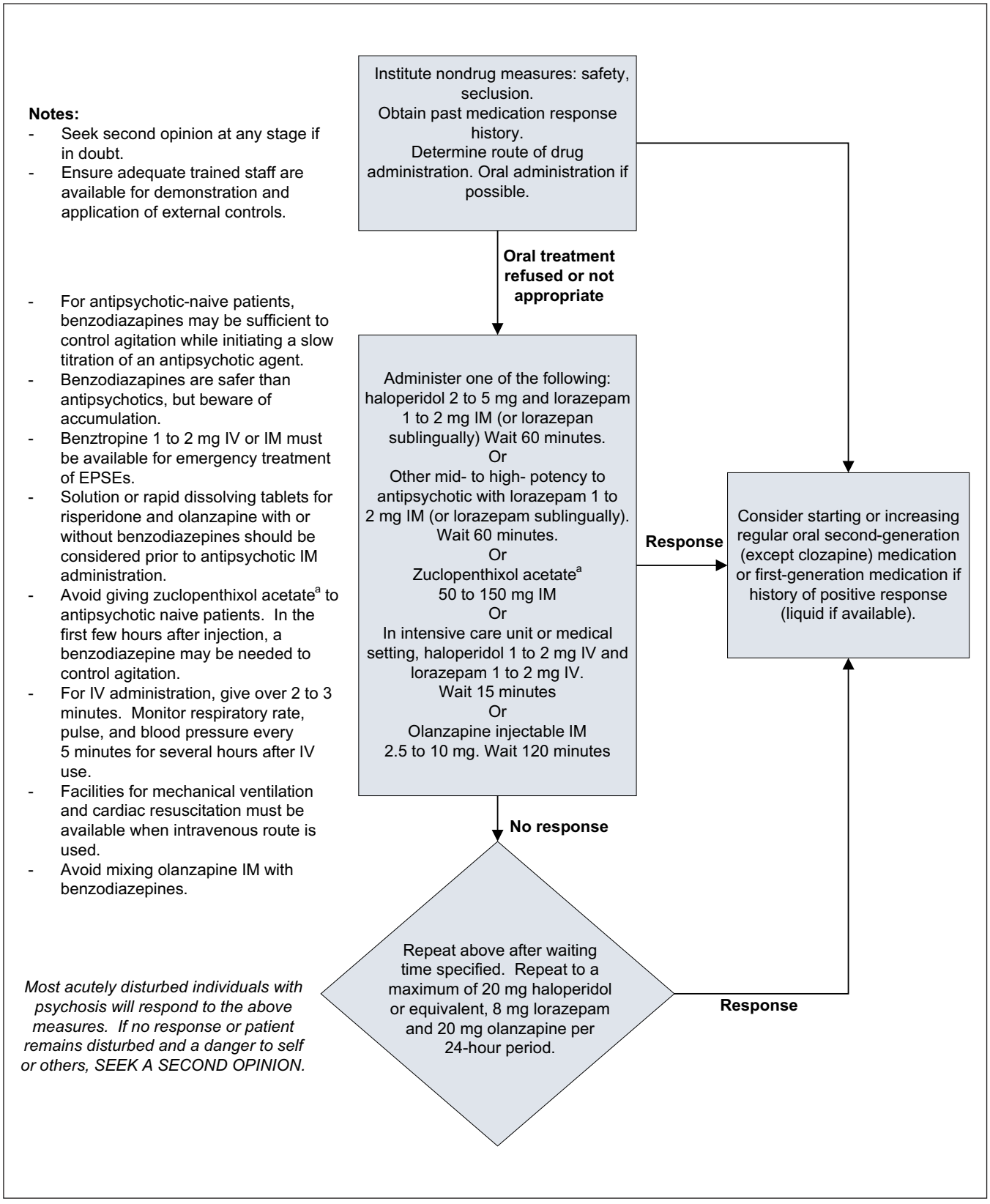
   A study must be regarded as double blind if the word "double blind" is used. The method will be regarded as appropriate if it is stated that neither the person doing the assessments nor the study participant could identify the intervention being assessed, or if in the absence of such a statement the use of active placebos, identical placebos, or dummies is mentioned.

3. Withdrawals and dropouts

   Participants who were included in the study but did not complete the observation period or who were not included in the analysis must be described. The number and the reasons for withdrawal in each group must be stated. If there were no withdrawals, it should be stated in the article. If there is no statement on withdrawals, this item must be given no points.

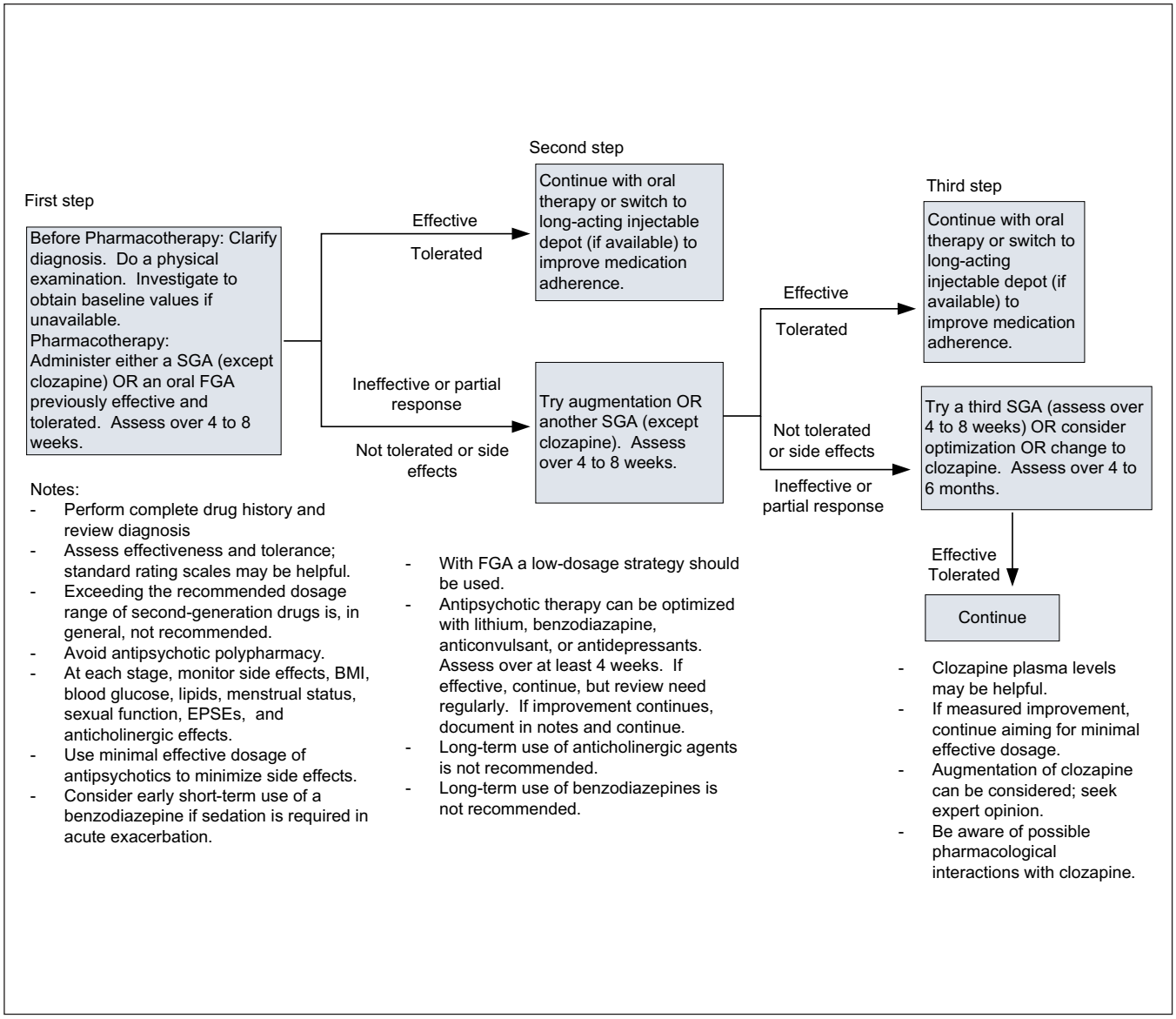
Appendix II

Algorithm A. Pharmacotherapy. Acute emergent phase: the severely aggressive and (or) agitated patient.



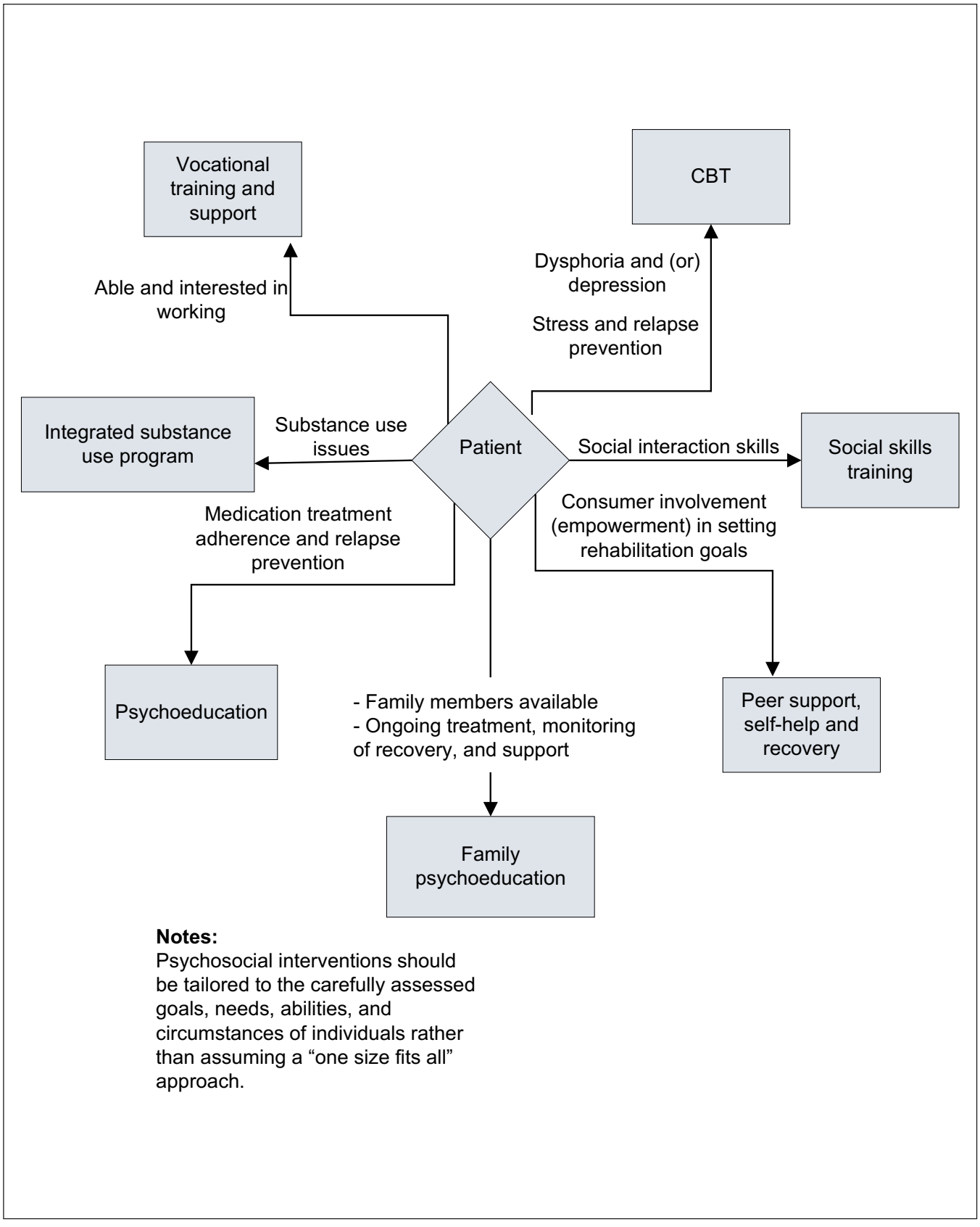
[a] Zuclopenthixol acetate peaks at 24-36 hours, effective for up to 72 hours. See comments in notes above.

Appendix III
Algorithm B. Pharmacotherapy: Stabilization and Stable Phase



Note: Tailor all treatment approaches to the individual patient. Consider assessment, pharmacotherapy, and psychosocial interventions AT ALL stages of treatment. BMI (weight/height squared [kg/m^2])

Appendix IV
Schema of Psychosocial Interventions: Stabilization/ Stable Phase



Acknowledgements

The authors thank Marie-France Demers and Julie Villeneuve for their contributions to the Pharmacotherapy section. We also thank Emily Mckenzie, who coordinated the literature review and the rating of individual articles.

We also thank the many external international and Canadian reviewers who took the time to provide valuable comments on a draft of this guideline.

The development, printing, and distribution of these guidelines was made possible through the CPA CPG Fund, to which each of the following companies made equal, arm's-length, unrestricted grants:

AstraZeneca Canada Inc.
Eli Lilly Canada Inc.
Janssen-Ortho Inc.
Pfizer Canada Inc.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