

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 medication 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-naïve

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

^aAdult recommendations, not adapted for elderly
^bCompendium 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 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 through 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/mm³ and 1500/mm³, 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).