Psychoses

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Introduction

Psychoses are brain disorders that cause a distortion of, or loss of contact with, reality and affect a patient's ability to think, feel, perceive and act. Psychotic symptoms include delusions, hallucinations, disorganized thinking and bizarre or disorganized behaviour. Approximately 3% of people worldwide will experience at least 1 psychotic episode during their lifetime. See Table 1 for a list of differential diagnoses.

The age of onset of schizophrenia spectrum psychotic disorders is usually late adolescence/early adulthood. There is increased emphasis on earlier detection and intervention[1][2][3] because the duration of untreated psychosis correlates to poorer outcomes in both the short- and long-term.[4][5]

Common prodromal psychosis symptoms (in order of decreasing frequency) include:

- Reduced concentration and attention
- Reduced drive and motivation; lack of energy
- Depressed mood
- Sleep disturbance
- Anxiety
- Social withdrawal
- Deterioration in functioning
- Irritability

Increasingly research has focused on the identification and treatment of individuals who are at "clinical high-risk" of developing a psychotic disorder or may be in the prodromal phase.[6][7][8]

Family physicians can play an important role in early detection.[9][10] A number of tools including structured interviews and rating scales have been developed to identify individuals who may meet criteria for being at clinical high-risk of progressing to a psychotic disorder.[11] Examples include the Prevention through Risk Identification, Management, and Education (PRIME) screening test, Structured Interview for Prodromal Syndromes (SIPS) and Scale of Prodromal Syndromes (SOPS). The PRIME screening test can be accessed via www.schizophrenia.com/sztest/primetest.pdf.

The primary goal of treatment for individuals who meet the criteria for a prodromal psychosis syndrome is to prevent the progression to psychosis and to alleviate current and distressing symptoms such as anxiety and depression. While studies have demonstrated the effectiveness of low-dose antipsychotics in preventing progression to psychosis in clinical high-risk individuals, antipsychotics are not recommended due to high rates of false positives of the screening tools and the potential for serious adverse effects with the use of antipsychotic medications.[12]

There are a few studies demonstrating the potential effectiveness of cognitive behavioural therapy (CBT)[13] and long-chain omega-3 fatty acids[8] in preventing progression to psychosis but further research is needed; these options are not recommended for routine clinical care.

If an individual is deemed to be at clinical high-risk of developing a psychotic disorder or may be in the prodromal phase, referral to a specialized early psychosis program (if available), psychiatrist or community mental health team is recommended.

Table 1: Differential Diagnosis of Psychotic Episodes[14]

Disorder	Characteristics
Schizophrenia	Signs of illness for ≥6 months; psychotic symptoms (delusions and/or hallucinations and/or disorganized speech) for ≥1 month; social/occupational dysfunction
Schizophreniform psychosis	Similar to schizophrenia except duration of illness of <6 months
Schizoaffective disorder	Uninterrupted period of illness in which symptoms of schizophrenia and mood disorder occur concurrently; during lifetime duration of illness, ≥2 weeks of delusions or hallucinations in absence of major mood episode; major mood episode is present >50% of total duration of illness
Delusional disorder	Nonbizarre delusions for ≥1 month and does not meet criteria for schizophrenia

Disorder	Characteristics
Brief psychotic disorder	Psychotic symptoms for ≥1 day but <1 month; may or may not be related to marked stressor; eventual full return to premorbid level of functioning
Substance-induced psychotic disorder	Delusions or hallucinations develop during or within 1 month of substance intoxication or withdrawal or are etiologically related to medication use and are not better accounted for by another psychotic disorder
Psychotic disorder associated with another medical condition	Delusions or hallucinations are direct physiological consequence of a medical condition and occur in absence of delirium
Psychotic disorder not elsewhere classified	Psychotic symptoms present but criteria for specific disorder not met or there is insufficient or contradictory information
Major depression with psychotic features	Major depressive episode with concurrent mood-congruent (most common) or mood-incongruent psychotic symptoms
Bipolar disorder	Manic episode with concurrent mood-congruent (most common) or mood-incongruent psychotic symptoms

Goals of Therapy

- Reduce psychotic agitation in acute episodes
- Achieve remission of:
  - positive symptoms such as delusions, hallucinations, disordered thinking and disorganized behaviour
  - negative symptoms such as apathy, anhedonia, social withdrawal
  - mood symptoms such as dysphoria, anxiety, emotional lability
  - cognitive symptoms such as impaired attention, concentration and memory
- Reduce risk of psychiatric comorbidity, particularly suicide and depression
- Reduce risk of substance abuse
- Reduce risk of harm to self and others
- Facilitate recovery of functioning and healthy development
- Reduce risk of social isolation due to alienation from family, friends and social supports
- Reduce risk of physical comorbidity including metabolic syndrome and cardiovascular disease
- Prevent recurrence of psychotic episodes

Investigations

- Family physicians are often the initial contact for a person experiencing a 1st psychotic episode. They should have a high index of suspicion in any young individual who is experiencing persistent changes in behaviour, mood and functioning, especially in the presence of other risk factors such as substance abuse or a family history of mental illness, particularly a history of psychotic disorders.
- In addition to the common prodromal symptoms previously discussed, signs and symptoms of possible first-episode psychosis include:[1]
  - rapid fluctuations in mood (emotional lability) or showing very little emotion or facial expression
  - unreasonable suspiciousness
  - insomnia; restlessness and pacing at night
  - unusual or bizarre behaviour
  - unusual perceptual experiences including hypersensitivity, illusions and/or brief intermittent hallucinations
  - difficulties in thinking such as organizing and/or expressing thoughts
- Substance use (particularly cannabis) is common in first-episode psychosis. Individuals may therefore be misdiagnosed with a substance-induced psychosis and not receive appropriate ongoing treatment. Cannabis use can trigger the onset of a schizophrenia spectrum disorder in genetically vulnerable individuals.[15]
- A high index of suspicion for a functional psychosis is warranted, even in the presence of substance use, if:
  - symptoms precede the onset of substance use
  - symptoms are bizarre or there is marked thought disorder
  - symptoms persist beyond the period of intoxication or withdrawal
- Individuals with suspected first-episode psychosis require urgent services. If available, refer to a psychiatrist, community mental-health clinic or specialized early psychosis program.[16]

- Appropriate investigations, based on both the phase of the psychotic disorder and individual patient characteristics, are listed in Table 2.
- In an acute psychotic episode, assess the nature and extent of psychopathology:
  - thorough history of presenting problems with special attention to onset and course of prodromal symptoms
  - onset, characteristics and severity of psychotic symptoms
  - changes in behaviour and functioning
  - history of any suicidal ideation or behaviour and/or aggressive/violent ideation or behaviour
  - history of substance use/abuse in relation to onset and course of psychotic symptoms
- A thorough mental status examination is essential. Competency to consent to treatment needs to be assessed in all acutely psychotic individuals.
- Obtain information from as many sources as possible since individuals with psychotic disorders are often poor historians. Interview family members whenever possible with the consent of the individual. If a patient is unwilling to give consent to interview family members, a clinician may still accept collateral information provided by a family member (e.g., in a phone call) but cannot divulge any information that would constitute a breach of patient confidentiality. If a patient is judged unable to give informed consent, then legally a substitute decision maker (usually a family member) has to be contacted in order to provide informed consent on behalf of the patient.
- A variety of clinical rating scales can be used at baseline and repeated periodically to monitor for symptomatic and functional recovery following an acute psychotic episode:
  - The Clinical Global Impression Scales for Severity (CGI-S)[17] and for Change (CGI-C)[17] and the Social and Occupational Functioning Assessment Scale (SOFAS)[18] for documenting changes over time are easy to use.
  - Training is required in order to reliably use the Brief Psychiatric Rating Scale (BPRS, available at www.priory.com/psych/bprs.htm) and the Positive and Negative Syndrome Scale (PANSS). Alternatively, the semistructured interview guide SCI-PANSS[19] takes approximately 30–40 minutes to complete and can be helpful in eliciting signs and symptoms of psychopathology.
- Patients with only partial symptomatic and/or functional recovery following an acute psychotic episode require diagnostic reassessment by a psychiatrist.

Table 2: Investigations and Monitoring of Psychoses

Parameter	Phase of Illness, Recommended Monitoring/Frequency[16][20]
Psychopathology Assess via: CGI-S, CGI-C, BPRS, PANSS	**First episode:** baseline then weekly for first 4–8 wk; more often if clinically indicated **Recurrent acute episode:** baseline then weekly for first 4–8 wk; more often if clinically indicated **Stabilization phase:** monthly for first 6 months following first or recurrent acute episode; more often if clinically indicated **Stable phase:** every 3 months for individuals with good symptomatic and functional recovery and medication adherence; more often for individuals with poor medication adherence, residual symptoms, poor functioning; substance abuse
Substance use	**First episode:** baseline **Recurrent acute episode:** baseline **Stabilization phase:** at every patient visit or as clinically indicated **Stable phase:** at every patient visit or as clinically indicated
Level of functioning (activities of daily living; social and occupational functioning); assess via: SOFAS	**First episode:** premorbid level of functioning; baseline assessment of current functioning **Recurrent acute episode:** baseline assessment of current functioning **Stabilization phase:** monthly for first 6 months following first or acute episode **Stable phase:** every 3 months
Past psychiatric history	**First episode:** baseline **Recurrent acute episode:** baseline with focus on past antipsychotic treatment including type of medication, dose, side effects, response, duration of treatment and medication adherence **Stabilization/Stable phases:** N/A
Family psychiatric history	**First episode:** baseline **Recurrent acute episode:** baseline **Stabilization/Stable phases:** N/A
Developmental history	**First episode:** baseline **Recurrent acute episode:** N/A

Parameter	Phase of Illness, Recommended Monitoring/Frequency[16][20]
(mother's obstetrical history including pre- and perinatal complications; developmental milestones; history of learning disabilities)	**Stabilization/Stable phases:** N/A
Medical history (past and current conditions and treatment)	**First episode:** baseline **Recurrent acute episode:** baseline **Stable phase:** yearly
Extrapyramidal signs and symptoms (parkinsonism, dystonia, akathisia, dyskinesia); see Table 4 for EPS rating scales	**First episode:** baseline; when dosage of antipsychotic is changed or new antipsychotic is started, then weekly for 2–4 wk **Recurrent acute episode:** baseline; when dosage of antipsychotic is changed or new antipsychotic is started, then weekly for 2–4 wk **Stabilization phase:** as clinically indicated **Stable phase:** every 6 months or more often for individuals at higher risk
Cognitive functions (estimates of premorbid/current IQ, attention and concentration, working memory, verbal and visual learning and memory, executive functions such as abstract thinking, reasoning, problem solving, judgment)	**First episode:** referral to a psychologist is recommended for neurocognitive testing within 3 months after psychotic symptoms have remitted **Recurrent acute episode:** N/A **Stabilization phase:** N/A **Stable phase:** referral to a psychologist for neurocognitive testing as clinically indicated (clinical evidence of ongoing cognitive impairment that affects functioning)
Functional enquiry and physical examination with focus on current complaints, endocrine and sexual function, vital signs, weight, body mass index (BMI)	**First episode:** baseline and then as clinically indicated; weight and BMI monthly for 6 months; baseline waist circumference; blood pressure at baseline and 12 wk or more often if clinically indicated **Recurrent acute episode:** baseline and then as clinically indicated; weight and BMI monthly for 6 months after initiation of a new antipsychotic; baseline waist circumference; blood pressure at baseline and 12 wk or more often if clinically indicated **Stabilization phase:** as clinically indicated **Stable phase:** as clinically indicated; weight and BMI every 3 months when on stable antipsychotic dosage; waist circumference annually; blood pressure annually or more often if clinically indicated; functional enquiry (including endocrine and sexual function) and physical exam at least yearly
Laboratory investigations (including CBC/differential, electrolytes, kidney/liver function, fasting glucose and lipid profile, TSH, baseline prolactin, routine urinalysis. If clinically indicated: urine drug screen, tests for STIs, HIV and hepatitis)	**First episode:** baseline; fasting glucose at baseline and repeat at 12 wk or more often as clinically indicated; fasting lipid profile at baseline and 12 wk, and repeat as clinically indicated **Recurrent acute episode:** baseline; fasting glucose at baseline and repeat at 12 wk or more often as clinically indicated; fasting lipid profile at baseline and 12 wk and repeat as clinically indicated **Stabilization phase:** as clinically indicated **Stable phase:** fasting glucose annually or more frequently if gaining weight or symptomatic; fasting lipid profile annually or every 6 months if LDL or triglyceride levels above normal range; other tests as clinically indicated
CT brain	**First episode:** recommended if signs & symptoms are suggestive of intracranial pathology or if onset of symptoms is later in life **Recurrent acute episode:** as clinically indicated

Abbreviations: BPRS = Brief Psychiatric Rating Scale; CGI-C = Clinical Global Impression Scales for Change; CGI-S = Clinical Global Impression Scales for Severity; EPS = extrapyramidal side effects; HIV = human immunodeficiency virus; LDL = low-density lipoprotein; N/A = not applicable; PANSS = Positive and Negative Syndrome Scale; SOFAS = Social and Occupational Functioning Assessment Scale; STI = sexually transmitted infection; TSH = thyroid-stimulating hormone

Therapeutic Choices

- Antipsychotic medications are considered the most effective treatment option for patients with schizophrenia and related psychotic disorders[21][22] but antipsychotic agents need to be integrated with psychosocial interventions to optimize outcomes.[16]
- Both pharmacologic and psychosocial interventions should be tailored to the individual, based on phase of illness, severity of symptoms, past history of treatment response (if applicable), degree of insight and acceptance of treatment, presence of comorbid psychiatric/physical disorders and family medical/psychiatric history.

Nonpharmacologic Choices

First Episode/Recurrent Acute Episode

- Determine appropriate treatment setting (least restrictive setting possible), ensure safety and reduce environmental stressors and stimuli.
- Acutely agitated patients and those at imminent risk of harm to self or others will require hospitalization, if necessary on an involuntary basis. Criteria for involuntary psychiatric assessment and/or admission are determined by each province's mental-health legislation.
- See patient frequently (for outpatients at least weekly for first 4–6 weeks) in order to:
  - build rapport
  - provide support, practical advice and psychoeducation
  - promote medication adherence
  - monitor treatment response (both adverse effects and improvement in symptoms)
- Foster a collaborative therapeutic relationship between the patient, family/caregivers and treatment team.

Stabilization/Stable Phases

- In schizophrenia and related psychotic disorders, recovery (stabilization phase) from an acute psychotic episode usually occurs over 6 months but may take longer and may be incomplete. Focus should be on medication adherence, stress management, assessment of signs and symptoms of postpsychotic depression and suicidality, assessment of substance use, and education about early warning signs of relapse.
- Psychosocial interventions such as individual psychoeducation, family psychoeducation, CBT, motivational interviewing, social and vocational skills training, and peer support groups have been shown to improve functional outcome and community reintegration, promote treatment adherence and help prevent relapse.[16] Furthermore, CBT may be effective in treating residual psychotic symptoms as well as symptoms of depression and anxiety.[23]
- Exercise and tai chi may reduce symptoms and improve motor coordination and memory.[24]
- Maintain continuity of care with an individual clinician or multidisciplinary treatment team.
- Individuals with serious ongoing illness and functional disability or comorbid problems such as substance abuse may benefit from referral to an Assertive Community Treatment (ACT) team if available.[16]

Pharmacologic Choices

Choice of Antipsychotics

Two major classes of **antipsychotics** are currently available in Canada:

- First-generation antipsychotics (FGAs), also known as "typical" or "conventional" antipsychotics, can be classified according to their chemical structure (e.g., phenothiazines such as **fluphenazine** or butyrophenones such as **haloperidol**) or potency (low, intermediate, high) as determined by dopamine D_2-receptor binding affinity. When comparing low- and high-potency agents, differences in side effect profiles are observed (see Table 5).
  - low-potency agents (e.g., **chlorpromazine**, **methotrimeprazine**) have greater rates of sedation, cardiovascular effects, anticholinergic effects and weight gain
  - high-potency agents (e.g., **fluphenazine**, **haloperidol**) have greater rates of extrapyramidal side effects (EPS; e.g., parkinsonism, tardive movement disorders such as tardive dyskinesia), neuroleptic malignant syndrome (NMS) and elevated prolactin levels
- Second-generation antipsychotics (SGAs) or "atypical" antipsychotics (**aripiprazole**, **asenapine**, **brexpiprazole**, **clozapine**, **lurasidone**, **olanzapine**, **paliperidone**, **quetiapine**, **risperidone** and **ziprasidone**) have greater 5HT affinity relative to D_2 affinity. The duration of binding to D_2 receptors and differences in binding affinity to other neurotransmitters (serotonergic, muscarinic, histaminic, alpha-adrenergic) may account for clinical differences in dosing requirements and side effect profiles among SGAs (see Table 3, Table 4 and Table 6).[25] Aripiprazole,

asenapine, brexpiprazole, lurasidone and ziprasidone have slightly different binding affinities compared with other SGAs:

- Aripiprazole has partial agonist activity at D_2 and $5HT_{1A}$ receptors and potent antagonism activity at $5HT_{2A}$ receptors (potential efficacy in treating negative and depressive symptoms). It can be given once daily with or without food, and is usually given in the morning because it can be activating and cause insomnia. Changes in dosage should be made no more frequently than every 14 days due to its uniquely long half-life. Aripiprazole is also available in a long-acting injectable formulation that is administered once a month.
- Asenapine is derived from the antidepressant mirtazapine and is a potent multireceptor antagonist with strong affinity for a number of serotonergic and dopaminergic receptors.[26] Asenapine dissolves rapidly after being administered sublingually and is given twice daily due to its short half-life. Oral hypoesthesia and paresthesia may occur directly after administration and usually resolve within 1 hour. Hypersensitivity reactions including anaphylaxis and angioedema have occurred in patients treated with asenapine, often after the 1st dose.[27] Inform patients of the signs and symptoms of a serious allergic reaction and advise them to seek immediate medical attention if they occur. The initial and target dose for the treatment of schizophrenia and related psychotic disorders is 5 mg twice daily. An increase in dose to 10 mg twice daily is recommended only after clinical assessment.
- Brexpiprazole is a novel drug with a unique receptor binding profile. It acts as a partial agonist at the $5HT_{1A}$, dopamine D_2 and D_3 receptors and as an antagonist at the 5-HT_{2A}, 5-HT_{2B}, 5-HT_7, noradrenergic alpha-$_{1A}$, alpha-$_{1B}$, alpha-$_{1D}$ and alpha-$_{2C}$ receptors.[27] This receptor profile leads to a favourable antipsychotic profile for the treatment of positive, negative, mood and cognitive symptoms of schizophrenia with a low risk of akathisia and EPS, weight gain, and metabolic complications.[28] The initial dose is 1 mg daily for 4 days; it can then be increased to 2 mg daily on days 5–7. Based on clinical response and tolerability, increase to 4 mg daily on day 8.
- Lurasidone has high affinity for D_2, 5-HT_{2A} and 5-HT_7 receptors, moderate affinity for alpha-adrenergic receptors and little or none for muscarinic and histaminic receptors. Lurasidone is given once daily with food (minimum of 350 calories, irrespective of fat content) to maximize bioavailability, usually with the supper meal or a bedtime snack. The initial and target dose is 40 mg daily, with most patients responding to 40–80 mg daily. Doses higher than 80 mg daily may be required by some patients who fail to respond after 2 weeks of treatment.[29] Consultation with a psychiatrist is recommended prior to increasing the dose above 80 mg daily. Lurasidone is generally well tolerated with minimal effect on weight, glucose, cholesterol or triglycerides.[30] The most common side effects are nausea, somnolence, akathisia and dose-related EPS.[27] Nausea is related to initiation of therapy and increases in dosage, and can be persistent and distressing to patients. It is often worst 2–3 hours post dose (time of peak plasma levels) and does not appear to be related to the presence or absence of food. Nausea can be managed by lowering or splitting the dose (e.g., 40 mg twice daily rather than 80 mg once daily) or giving the dose at bedtime. Ginger or peppermint remedies may also be helpful.
- Paliperidone is the active metabolite of risperidone. It is not metabolized by the liver and therefore has minimal risk of drug-drug interactions compared with other oral antipsychotics. The oral extended-release formulation is intended for once-daily dosing with or without food. Morning administration is recommended as it can cause insomnia. Paliperidone palmitate is available as a prolonged-release injectable suspension. In contrast to long-acting injectable risperidone, initiation of treatment involves a loading dose strategy with 2 initial injections in the deltoid muscle 7 days apart followed by monthly maintenance injections in either the deltoid or gluteal muscles. Supplementation with oral antipsychotics during the first 3 weeks after initiation of treatment is not required (see Table 6). Once stable on the long-acting paliperidone palmitate (Invega Sustenna) for at least 4 months, patients may be eligible for a new long-acting injectable formulation that is injected every 3 months (Invega Trinza) if they have received the same dose of Invega Sustenna for at least 2 consecutive months. Patient acceptance may be improved with paliperidone palmitate maintenance dose injections every 1 or 3 months compared with risperidone long-acting injections given every 2 weeks.
- Ziprasidone has agonist activity at $5HT_{1A}$ receptors and, unlike other SGAs, has antagonist activity at $5HT_{1D}$ receptors and moderate inhibition of synaptic reuptake of serotonin and norepinephrine. Though once-daily dosing may be appropriate for some patients, ziprasidone usually requires twice-daily administration due to its short half-life (6.6 hours), and must be taken with food (at least 500 calories) to ensure optimal absorption and therapeutic serum concentrations. Bioavailability of ziprasidone is reduced by 50% if taken on an empty stomach. It is important to educate patients and family members/caregivers regarding adequate caloric intake and to monitor the patient's food intake for several weeks following initiation of treatment.

- All FGAs and SGAs, with the exception of clozapine, have similar efficacy in treating the positive (psychotic) symptoms of schizophrenia and related disorders. While some studies have found that SGAs may have advantages in first-episode psychosis[31][32] (improving negative symptoms, mood and cognitive deficits[33][34] and in preventing relapse[35] and rehospitalization), overall the results have been mixed and greater efficacy for SGAs has not been consistently demonstrated.[36] No differences in effect on quality of life have been found between FGAs and SGAs.[37] While there is some evidence that long-term exposure to antipsychotics may increase mortality in schizophrenia, more rigorously designed prospective studies are needed.[38] **Clozapine** is the only antipsychotic with proven efficacy in treatment-resistant schizophrenia[21] in reducing hostility and aggression,[39][40] persistent suicidality[41] and all-cause mortality.[42]
- With the exception of clozapine, SGAs are now considered a first-line treatment choice.[33][34][43]
- Clozapine is reserved for treatment-resistant schizophrenia due to the risk of agranulocytosis and the need for regular blood monitoring. A discussion on the assessment and management of treatment-resistant schizophrenia is beyond the scope of this chapter.

Dosing and Duration of Treatment

Tailor treatment to the specific phase of the disorder, and to the patient's signs and symptoms.[16][43]

Acute Phase

An algorithm in Figure 1 illustrates the management of patients in the acute phase of a psychotic episode.

- **Haloperidol** IM has been the most widely used treatment for psychotic agitation. Haloperidol 5 mg IM combined with **lorazepam** 2 mg IM has been shown to be more effective than haloperidol alone.[44] Furthermore, the combination of haloperidol and **promethazine** is safe and effective in the management of psychosis-induced aggression.[45]
- While only studied in mildly to moderately agitated patients, **olanzapine** 2.5–10 mg IM appears to have efficacy similar to haloperidol and causes less EPS.[46][47] Do not use the parenteral formulations of benzodiazepines and olanzapine in combination as there have been reports of cardiac and respiratory problems including death.
- Rapid-dissolving oral formulations of olanzapine and risperidone are as effective as haloperidol IM[48] if the patient is able and willing to take oral medications.
- **Zuclopenthixol acetate** is an injectable FGA with a pharmacokinetic profile (peak serum level in 24–48 hours, declining to one-third of peak concentration in 72 hours) that may reduce the number of injections required in severe acute agitation and/or aggression. It should not be used in antipsychotic-naïve patients.
- Patients with first-episode psychosis are more responsive to lower doses of antipsychotics,[49][50] have a greater rate of recovery[49] and are more prone to side effects.
    - Starting doses for asenapine (5 mg twice daily) and lurasidone (40 mg daily) are also the target therapeutic doses.
    - When initiating SGAs (with the exception of ziprasidone and extended-release quetiapine), begin with a low dose and titrate gradually over 1–2 weeks up to the usual therapeutic range (see Table 6). Aripiprazole, brexpiprazole, lurasidone, olanzapine, paliperidone, extended-release quetiapine and risperidone are usually administered once daily. Although twice-daily dosing is recommended for immediate-release quetiapine, many patients can be maintained on a single daily dose at bedtime.[51] Twice-daily dosing with meals (of at least 500 calories) is recommended for ziprasidone.
    - Optimal dosing for ziprasidone is 80–160 mg daily for first-episode psychosis and 120–160 mg daily for chronic schizophrenia. Rapid titration to the target dose is required; slow titration is associated with poorer outcomes and the development of restlessness, agitation and insomnia (ziprasidone-induced activation syndrome) that occurs at the lower end of the dose range (20–40 mg BID). Advise patients that they may experience some initial restlessness or agitation that should subside with rapid titration to the target dose.
      The recommended titration schedule for an early psychosis outpatient is:[52]
        - Day 1: 20 mg a.m., 40 mg p.m.
        - Day 2: 40 mg a.m., 60 mg p.m.
        - Day 3: 60 mg a.m., 60 mg p.m.
        - Day 4: Reassess
    - Extended-release quetiapine is usually administered once daily, preferably in the evening. The recommended initial dose is 300 mg daily. Dosage increases can be made rapidly at intervals as short as 1 day and in increments of up to 300 mg/day, to a range of 400–800 mg daily.
    - If a FGA is used, consider an intermediate-potency agent such as **loxapine** or **perphenazine**.
    - Benzodiazepines can be used to treat anxiety and agitation while titrating the dose of antipsychotic.
- With the exception of ziprasidone and extended-release quetiapine (both are quickly titrated to avoid adverse reactions), rapid titration and high doses of antipsychotics do not accelerate or enhance response and are rarely indicated. Even in patients with a chronic course, doses in the range of 2–5 mg of haloperidol are as effective as 10–40 mg and associated with fewer side effects and greater tolerability.[53] Only a very small subgroup of patients appears to benefit from high-dose therapy.[54][55] Doses exceeding the recommended daily maximum (e.g., olanzapine >20 mg/day or quetiapine >800 mg/day) are sometimes required but should be used under the care of a psychiatrist.
- An adequate trial of antipsychotic therapy is 4–8 weeks at a dose within the usual therapeutic range.[16][34][43] Patients who fail to demonstrate even minimal response by that time are unlikely to benefit from a longer trial; consider switching to a different antipsychotic and consulting a psychiatrist.
- There is no good evidence to guide switching from one antipsychotic medication to another. Crossover medication strategies, over 2 weeks to 3 months,[56] are preferred. It is important to complete the crossover; combination therapy with more than 1 antipsychotic medication is not supported by strong evidence and should be used only in exceptional circumstances under the care of a psychiatrist.[57] Patients successfully stabilized on clozapine have not been shown to benefit from switching to any other antipsychotic medication, or from the addition of a 2nd antipsychotic.[16] SwitchRx (www.switchrx.ca) is a Canadian online medication switching tool that provides clinicians with guidance on how to transition patients from one antipsychotic to another.

Stabilization/Stable Phases

- During the stabilization (recovery) phase, patients are vulnerable to relapse. Avoid changes in antipsychotic medication unless there are intolerable side effects or persistent residual symptoms that are distressing and/or disabling to the patient.
- Maintenance therapy is essential to prevent relapse. First-episode psychosis is associated with a 70–90% risk of relapse within 5 years. A significant percentage of patients relapse as early as the 2nd year following discontinuation of antipsychotic therapy for first-episode psychosis.[58]
    - Continue maintenance pharmacotherapy for at least 1–2 years for first-episode patients who achieve symptom remission and functional recovery.[16][43][59] Longer treatment (2–5 years) may be required for individuals with a long duration of untreated psychosis, more severe illness, slower response, substance abuse and history of suicidal or aggressive behaviour.[16][43] For patients with a history of 2 or more episodes, continue maintenance pharmacotherapy until the patient has been stable and relapse-free for at least 5 years.[16]
    - Many patients will require antipsychotic treatment indefinitely.
    - In general, the lowest effective antipsychotic dose used during the acute phase should also be used in maintenance treatment.[16][21] There is little evidence to support the use of more than 1 antipsychotic in acute or maintenance treatment for the majority of patients.[60]
- Poor medication adherence is common in patients with schizophrenia and related psychotic disorders. Adherence rates of <70–80% are associated with a significantly increased risk of relapse and hospitalization.[61][62] Patients who discontinue medications are 5 times more likely to relapse.[22] Recovery from recurrent acute psychotic episodes (relapses) may take longer with each subsequent episode and the degree of recovery may not be as great, resulting in persistent residual symptoms and functional disability.[22]
- Consider long-acting injectable antipsychotics (LAIs) such as aripiprazole, paliperidone palmitate or risperidone in all phases of illness but especially in the first 2–5 years after onset of illness when patients are most vulnerable ("critical period").[63] LAIs are as effective as oral antipsychotics.[64][65] In addition to promoting adherence, LAIs may improve rates of remission and decrease the risk of hospitalization and relapse.[66][67][68]
- LAI usage rates in Canada are low (6.3%) compared with the rest of the world (15–80%).[67] Canadian qualitative studies of physician and patient attitudes toward LAIs indicate that physicians' lack of knowledge and training in the use of LAIs, negative biases toward LAIs (treatment of last resort) and unfounded beliefs regarding patients' rejection of LAIs due to fear of needles may contribute to the low rates of use.[69][70]
- When discontinuing medication, gradually reduce the dose by ≤20% every 2–4 weeks. Reduce over a period of 6–12 months for first-episode patients and 6–24 months if patients have experienced 2 or more episodes.[16][21] Monitor closely and if patients experience early signs of relapse, restabilize them on the previously effective dose of antipsychotic as quickly as possible.

Treatment of Comorbid Conditions

Depression and Suicidality

- Psychiatric comorbidities are common among individuals with schizophrenia with an estimated prevalence of 50% for depression, 29% for post-traumatic stress disorder, 23% for obsessive-compulsive disorder and 15% for panic disorder.[71] The lifetime risk of suicide is approximately 5%.[72]
- Depressive symptoms are common in the prodromal phase preceding the onset of a 1st episode of psychosis. In the acute phase, particularly in multiple-episode patients, depressive symptoms usually remit along with the positive psychotic symptoms.
    - SGAs may be more effective than FGAs in treating depressive symptoms[73] in the acute phase. There is no evidence to support the use of an antidepressant in the acute phase.[16]
- Major depressive episodes occur as often in individuals diagnosed with schizophrenia as in those with either schizoaffective disorder or nonpsychotic major depression.[74]
    - Patients with first-episode psychosis have a greater risk of depression compared with multiple-episode patients, particularly in the stabilization phase (postpsychotic depression),[75] and depressive symptoms tend to increase for the first 3 months following a 1st episode of psychosis.[76]
- It can be difficult to differentiate between depression and ongoing negative symptoms or antipsychotic-induced emotional blunting, and rating scales such as the Hamilton Rating Scale for Depression (HAM-D) and the Beck Depression Inventory have not been validated in individuals with schizophrenia. The Calgary Depression Scale for Schizophrenia (CDSS)[77] can be used to differentiate between negative symptoms and symptoms of major depression. A CDSS score ≥6 is considered clinically significant.[78]
- Antidepressant medication may be useful in the treatment of major depression in the stabilization or stable phases.[76][79] As stated in Nonpharmacologic Choices, CBT may be effective in treating residual psychotic symptoms as well as symptoms of depression and anxiety.[23]

Substance Abuse

- Higher rates of substance abuse/dependence disorders are found in individuals with schizophrenia (lifetime prevalence of 47–50%) compared with the general population. Persistent substance abuse is associated with poor treatment adherence, greater risk of suicidality and aggression, and significantly poorer outcomes.
- **Cannabis** use is a risk factor for psychosis and there appears to be a dose-response relationship between amount of use and risk of psychosis.[80][81][82] The prevalence of cannabis use in individuals with psychotic disorders is higher than in the general population, particularly in early psychosis where rates of use are as high as 86% and rates of cannabis abuse/dependence range from 14–28%.[83] Cannabis use is associated with poor antipsychotic adherence, greater severity and chronicity of symptoms, and 4 times the risk of relapse.[84]
- The rate of smoking in individuals with schizophrenia and related psychotic disorders is extremely high (70% in Canada),[85] compared with a rate of approximately 20% in the general population (www.smoke-free.ca). Patients with psychotic disorders are more likely to be heavy smokers and are 2–3 times more likely than nonsmokers to abuse other substances.[86]
    - It is estimated that patients with schizophrenia have a life expectancy that is 20% lower than the general population. This is mostly attributable to increased rates of cardiovascular disease and metabolic syndrome, for which smoking is a significant risk factor.[87]
    - Smoking induces the metabolism of some antipsychotics (e.g., clozapine and olanzapine); smokers require higher doses of these antipsychotics, leading to increased adverse effects.[88][89]
    - Actively encourage smoking cessation even though success rates are low in patients with psychotic disorders (in patients with psychoses, only 9% are former smokers compared with 14–49% in the general population).[85] Nicotine replacement therapies may be helpful. **Bupropion** and **varenicline** are also effective in smoking cessation; the risks of new or worsening neuropsychiatric symptoms have been shown to be lower than previously reported.[90] However, monitoring for changes in mood and behaviour should still occur, especially in those with a history of suicidal ideation/attempts, depressed mood or agitation/hostility. For more information, see Tobacco Use Disorder: Smoking Cessation.
- In patients (and particularly in those with first-episode psychosis) who appear to have been using substances as a form of self-medication, substance abuse may remit spontaneously with recovery from the acute episode.
- A harm-reduction approach that incorporates motivational interviewing is recommended for individuals with comorbid substance abuse problems. Refer patients with persistent substance abuse to a mental-health program that can provide a comprehensive, integrated approach.[91]

Side Effects of Antipsychotics

Table 3 compares the side effect profile of second-generation antipsychotics. Table 4 provides guidance on the assessment and management of antipsychotic-induced side effects.

- Closely monitor and manage side effects since they are the leading cause of nonadherence to medication.
- Patients taking antipsychotics long-term ranked the most burdensome and function-impairing side effects as follows: sedation/tiredness, weight gain, difficulty thinking/concentrating and restlessness.[99]

Neuroleptic Malignant Syndrome

- Neuroleptic malignant syndrome (NMS) is a medical emergency with a high mortality rate. It is a rare but serious side effect characterized by muscle rigidity, fever, autonomic disturbance, labile blood pressure, fluctuating levels of consciousness, and elevated levels of creatine kinase (CK) and white blood cells (WBC).
- NMS has been reported with all antipsychotics and can occur at any dosage and at any time. Dehydration is a risk factor (see Table 4).

Sedation, Insomnia and Cognitive Side Effects

- Sedation is a very common side effect, especially after starting a new antipsychotic or increasing the dose. It can be very disabling and distressing. Sedation occurs most frequently with low-potency FGAs, clozapine, olanzapine [16] and quetiapine, and to a lesser extent with asenapine[27] and lurasidone.[27] Several antipsychotics (aripiprazole, risperidone [mild], ziprasidone) have the potential to cause sedation or insomnia. Adjust the dose to provide the greatest amount of the total daily dosage at the time of day (morning or evening) that would be most helpful to manage these side effects.[100] Aripiprazole can cause dose-related somnolence but can also be activating and cause insomnia. Paliperidone is associated with insomnia. Both are usually administered in the morning.
- FGAs can cause a subjective cognitive “dulling” effect and do not improve cognitive deficits, whereas SGAs have shown statistically significant improvement on a variety of cognitive measures,[101][102] but clinical significance has not been demonstrated.

- Concomitant medications such as anticholinergics (used to treat EPS) and antiepileptic drugs (used as mood stabilizers) can worsen cognitive deficits[103][104] and may add to the sedative effect.
- Cognitive deficits are correlated with poorer functional outcomes such as social and occupational functioning and activities of daily living.[105]

Extrapyramidal Side Effects

- In general, the major advantage of the SGAs is the significantly reduced risk of EPS (acute dystonia, parkinsonism, akathisia) and tardive dyskinesia (TD) compared with FGAs.[21][33][34][106][107] Asenapine, aripiprazole and lurasidone, however, can cause akathisia at any dose; the risk increases at higher doses. Olanzapine, paliperidone, risperidone and ziprasidone can cause akathisia at high doses. Parkinsonism can occur at high doses of asenapine, lurasidone, paliperidone, risperidone and ziprasidone.
- Parkinsonism can be associated with dysphoria, decreased concentration and slowing of cognition.
- Akathisia (subjective and objective restlessness) is often misidentified as psychotic agitation, which can result in an increase in dose of the offending antipsychotic.
- Tardive dyskinesia consists of repetitive, involuntary choreoathetoid movements usually involving the buccal-oral-lingual musculature, face, trunk, extremities, or respiratory muscles and can be permanent and disabling.
    - The incidence of TD is 5% per year with FGAs and the cumulative risk is up to 50%, even if low doses of FGAs are used.[16] The incidence is significantly less with aripiprazole, asenapine, lurasidone, olanzapine, paliperidone, risperidone and ziprasidone. Quetiapine and clozapine have rates of TD equivalent to placebo. Clozapine may improve existing TD.[16]
    - Inform patients of the risk of TD when initiating treatment with any antipsychotic medication, especially a FGA.

Weight Gain, Diabetes and Dyslipidemia

- Antipsychotic-induced weight gain and metabolic side effects are serious, given that individuals with schizophrenia and bipolar disorder are already at higher risk of metabolic syndrome compared with the general population.
- For FGAs, the risk of weight gain is greatest with low-potency agents.
- For many SGAs, there is a higher risk of weight gain compared with FGAs. Among SGAs, clozapine and olanzapine are associated with the greatest weight gain followed by quetiapine, risperidone, paliperidone and aripiprazole.[108] Asenapine, lurasidone and ziprasidone are associated with minimal or no weight gain. In the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE), ziprasidone was the only agent to show improvement in weight and metabolic parameters following a switch from another SGA.[97]
- In studies of 1 year or longer, weight gain did not correlate to dosage; therefore, dose reductions are unlikely to result in weight loss. In some individuals, weight gain may be rapid. Weight usually plateaus over time, although it can continue to increase for over a year. Weight gain often leads to treatment nonadherence and requests to stop or switch antipsychotic medication.
- Compared with FGAs, SGAs are associated with greater risk of glucose abnormalities including hyperglycemia, insulin resistance, new onset type 2 diabetes, exacerbation of type 1 diabetes and diabetic ketoacidosis.[109] Although rare, antipsychotics (especially olanzapine) have been associated with an increased risk of type 2 diabetes in youth.[110] Type 2 diabetes is 2–4 times more prevalent in individuals with schizophrenia compared with the general population, and abnormal glucose tolerance and insulin resistance are also more common.[111]
- Independent of risks for weight gain, there are different degrees of risk of glucose abnormalities among SGAs. Clozapine and olanzapine have the highest risk. Aripiprazole, asenapine, lurasidone, paliperidone, risperidone and ziprasidone have minimal risk of glucose abnormalities.
- Hyperlipidemia has been associated with clozapine and olanzapine. Increased triglycerides have been reported with quetiapine. Aripiprazole, asenapine, lurasidone, paliperidone, risperidone and ziprasidone have not been associated with dyslipidemia.[112][113] Switching to ziprasidone from other agents such as olanzapine or quetiapine has demonstrated improvements in dyslipidemia.[108]
- In first-episode psychosis, treatment with an SGA with less risk of weight gain and metabolic side effects is recommended.
- Consider switching patients with antipsychotic-induced weight gain and metabolic side effects to an SGA with a lower risk of these side effects (considering risks vs. benefits of switch).
    - Diabetes Canada recommends use of an SGA that is associated with less risk of weight gain, glucose abnormalities and dyslipidemia in individuals with high-risk of weight gain, diabetes, metabolic syndrome and cardiovascular disease.[114]

Cardiovascular Side Effects

- Orthostatic hypotension is the most common antipsychotic-induced cardiovascular side effect, particularly in elderly patients or those with heart disease or diabetes. It is more common with low-potency first-generation

antipsychotics and with clozapine, but can occur with aripiprazole, asenapine, lurasidone, olanzapine, quetiapine or risperidone.

- Prolongation of the QT_c interval is associated with torsades de pointes, and can cause recurrent syncope, ventricular fibrillation and sudden cardiac death. Clinically, a QT_c interval of >450 msec is concerning.[115]
  - QT_c prolongation occurs with chlorpromazine, pimozide (particularly at doses >8 mg/day) and haloperidol, although the incidence is low. The SGAs olanzapine, quetiapine and risperidone cause modest QT_c prolongation (mean <30 msec).[116] Minimal QT_c prolongation has been reported with aripiprazole, asenapine, clozapine and lurasidone.[27][117]
  - Ziprasidone has a greater (though modest) capacity for QT_c prolongation compared with other antipsychotics. It is contraindicated in individuals with a known history of QT_c prolongation, including congenital long QT_c syndrome or individuals with recent acute myocardial infarction or uncompensated heart failure. Baseline ECGs are not required unless clinically indicated. Before initiating therapy in individuals at risk of electrolyte disturbance, particularly hypokalemia and/or hypomagnesemia (e.g., history of kidney disease, diuretic therapy, water intoxication, eating disorders, prolonged vomiting/diarrhea, alcoholism), measure baseline electrolytes and correct abnormalities.
  - To date, there has been no significant increase in morbidity or mortality associated with SGA-induced QT_c prolongation. Nevertheless, all antipsychotics that prolong the QT_c interval should not be combined with any other drug that is known to prolong QT_c.[27][52] Consult the ziprasidone product monograph and other references such as crediblemeds.org for an extensive list of drugs that may prolong the QT_c interval. Advise patients taking ziprasidone to consult their physician and/or pharmacist before taking any concomitant medications.
- Antipsychotic drugs confer a dose-related increase in the risk of sudden cardiac death.[118] This risk is increased when more than 1 antipsychotic is used concurrently.
- Individuals who take antipsychotic drugs may have an increased risk of myocardial infarction compared with non-users.[119]
- Clozapine is associated with an increased risk of myocarditis (especially in, but not limited to, the first month of therapy), pericarditis, pericardial effusion, cardiomyopathy, heart failure, myocardial infarction and mitral insufficiency. If signs and symptoms of any of these disorders appear, seek urgent assessment by a cardiologist.

Dermatologic Side Effects

- Several atypical antipsychotics (olanzapine, ziprasidone, clozapine, quetiapine, risperidone, aripiprazole, paliperidone and lurasidone) are associated with a rare but serious skin condition known as Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS).[120]

  Symptoms of DRESS include rash, fever, swollen lymph nodes and swollen face, and can result in injury to liver, kidneys, lungs, heart and pancreas. Mortality rates of up to 10% have been reported.[121] Management consists of early recognition, stopping the antipsychotic and supportive care(see Drug-Induced Skin Reactions).

Endocrine, Sexual and Urinary Side Effects

- Hyperprolactinemia is a common side effect of FGAs (especially high-potency agents such as haloperidol), risperidone and paliperidone (especially at higher doses). Transient hyperprolactinemia can occur with olanzapine and ziprasidone. No differences in prolactin levels have been found with aripiprazole, asenapine, clozapine, lurasidone or quetiapine compared with placebo.[27][122][123]
  - Hyperprolactinemia often causes no clinically significant effects but can be associated with menstrual irregularities and galactorrhea in women, galactorrhea and gynecomastia in men and sexual dysfunction in both men and women.
  - Reducing the antipsychotic dose is the 1st approach to managing clinically significant side effects associated with hyperprolactinemia.
- Sexual dysfunction, however, is associated with all antipsychotics and is not necessarily related to elevated prolactin levels alone.
- Urinary retention has been associated with antipsychotic use. Risk is greatest with drugs that have significant anticholinergic activity.[124]

Table 3: Comparative Side Effects of Second-Generation Antipsychotics

Medication [27]	Sedation	Insomnia	Extra-pyramidal Side Effects[a]	Weight Gain	Metabolic Abnormalities [b]	Hyperprolactinemia	Cardiovascular Effects[c]
aripiprazole	+/–	++	++	+	+/–	+/–	+
asenapine	+/–	+/–	+	+/–	+/–	+/–	+

Medication [27]	Sedation	Insomnia	Extra-pyramidal Side Effects[a]	Weight Gain	Metabolic Abnormalities [b]	Hyperprolactinemia	Cardiovascular Effects[c]
brexpiprazole	+/–	+/–	–	+	+/–	+/–	+/–
clozapine	++++	–	–	++++	++++	–	++
lurasidone	+	+/–	+	+/–	+/–	+/–	+
olanzapine	+++/++	–	+/–	++++	++++	+/–	+
paliperidone	+/–	++	+++/++	++/+	+/–	+++/++	+
quetiapine	+++	–	–	+++	++	–	+
risperidone	+	+	+++	++	+/–	+++	+
ziprasidone	+	+	+	+/–	+/–	+	++

[a] Includes akathisia.

[b] Includes glucose abnormalities and dyslipidemias.

[c] Includes orthostatic hypotension and/or QT_c prolongation.

Legend: ++++ = high; +++ = moderate; ++ = low; + = very low; +/– = minimal or none; – = equivalent to placebo

Table 4: Antipsychotic-Induced Side Effects: Assessment, Monitoring and Management[16][92][93]

Side Effect	Assessment and Monitoring	Management
Neuroleptic malignant syndrome	**Assessment:** physical exam with focus on level of consciousness; vital signs (fever, tachycardia, fluctuations in BP); look for evidence of muscle rigidity **Monitoring:** rare, but can occur with any antipsychotic at any dose and at any time; risk factors include young age, male gender, neurologic disabilities, dehydration, agitation, exhaustion, and rapid or parenteral administration of antipsychotic	Medical emergency: discontinue antipsychotic and provide supportive care (hydration and cooling) Other measures may include **dantrolene** 2–3 mg/kg TID–QID IV (maximum 10 mg/kg daily) and/or **bromocriptine** 2.5–5 mg TID PO, increasing by 2.5 mg TID Q24H (maximum 60 mg daily)[56]
Sedation and cognitive effects	**Assessment:** ask patient about daytime drowsiness, excessive sleep, cognitive "dulling"; obtain collateral information from caregivers and family **Monitoring:** see outpatients at least	Use SGAs as first-line treatment to reduce risk of cognitive side effects. Use a low initial dose and gradual titration based on degree of sedation, especially with clozapine and first-episode psychosis (exceptions include quetiapine XR and ziprasidone, for which rapid titration is recommended). Give entire daily dose at HS if possible to reduce daytime drowsiness; do not use anticholinergic antiparkinsonian agents prophylactically and avoid prolonged use when treating acute EPS

Side Effect	Assessment and Monitoring	Management
	weekly for first 4–6 wk after initiating new antipsychotic	
Extrapyramidal side effects (EPS; dystonia, parkinsonism, akathisia, tardive dyskinesia, tardive dystonia, tardive akathisia)	**Assessment:** rating scales such as Simpson-Angus Scale, Barnes Akathisia Scale or ESRS[94] are useful to assess EPS and the Abnormal Involuntary Movement Scale or the ESRS is used to assess TD **Monitoring:** baseline assessment in antipsychotic-naïve first-episode patients, in multiple-episode patients when initiating a new antipsychotic, and in first-episode and multiple-episode patients whenever dosage of antipsychotic is changed; assess weekly for 2–4 wk or until EPS resolves; in stable patients, assess for TD every 6 months or more often in patients at higher risk (on FGAs, erratic medication adherence or intermittent treatment, female, age >55, diagnosis of an affective disorder, substance abuse, diabetes)	Prevention is key—use SGAs first-line. If EPS occurs, first reduce dose; consider switch to SGA if on FGA. Prophylactic use of anticholinergics (benztropine, procyclidine, trihexyphenidyl) is not recommended even with FGAs, and should usually be used only on a short-term basis to treat parkinsonism associated with FGAs.[95] Anticholinergics are generally not recommended with SGAs[96] For akathisia: if dose reduction is not effective, beta-blockers (e.g., propranolol 10–120 mg/day) are the treatment of choice with monitoring for hypotension. Benzodiazepines also provide symptom relief. Anticholinergics are ineffective For acute dystonia (acute torticollis, oculogyric crisis): benztropine or diphenhydramine IM, followed by reduction in dose or switch to SGA For tardive dyskinesia: there is no evidence-based treatment—prevention is key. Use SGAs first-line. Antiparkinsonian medications are not effective and may worsen symptoms. If TD occurs, suggest consultation with a psychiatrist. Consider switching to an SGA. For persistent, severe TD, consider clozapine trial
Weight gain	**Assessment:** baseline weight, body mass index (BMI) and waist circumference **Monitoring:** weight and BMI monthly for 6 months with new antipsychotic then every 3 months when on a stable dosage; waist circumference annually	Prevention is critical as weight reduction is especially difficult in individuals with mental illness. Educate about risk of weight gain and provide dietary and exercise counselling If weight increases >7% over baseline, implement behavioural weight reduction program. If unsuccessful, assess risks/benefits of continuing current antipsychotic vs. switching; no consistent evidence of efficacy of adjunctive weight loss pharmacotherapy

Side Effect	Assessment and Monitoring	Management
Glucose abnormalities	**Assessment:** baseline fasting plasma glucose; HbA_{1c} if difficult to obtain fasting plasma glucose; oral glucose tolerance test (OGTT) if evidence of impaired glucose tolerance; obtain family history and medical history **Monitoring:** inquire about signs and symptoms of emergent diabetes; fasting plasma glucose 12 wk after initiating new antipsychotic, then yearly; more frequent monitoring required if significant weight gain or if symptomatic; OGTT if evidence of impaired glucose tolerance	Educate about signs and symptoms of emergent diabetes. If diabetes is diagnosed, follow the Diabetes Canada guidelines for diabetes and mental health (guidelines.diabetes.ca/docs/cpg/Ch18-Diabetes-and-Mental-Health.pdf). Consider switching to another antipsychotic
Dyslipidemias	**Assessment:** baseline fasting lipid profile (total cholesterol, LDL, HDL, triglycerides) **Monitoring:** fasting lipid profile at 12 wk after initiation of a new antipsychotic, then annually; more frequent monitoring if significant weight gain, and every 6 months if LDL and/or triglycerides above the normal range	Educate on change in diet. Consider switching to ziprasidone.[97][98] Consult Canadian Cardiovascular Society guidelines for management of dyslipidemia at www.onlinecjc.ca/article/S0828-282X(12)01510-3/fulltext
Cardiovascular side effects	**Assessment:** baseline vital signs; obtain family history and medical history; ECG in individuals >40 y and as clinically indicated **Monitoring:** vital signs at 12 wk then annually; monitor more frequently as indicated and when initiating	Educate about risks and prevention of orthostatic hypotension. If symptoms persist, decrease dose of antipsychotic if possible or switch to another antipsychotic For clozapine-induced myocarditis: discontinue clozapine immediately and consult cardiology

Side Effect	Assessment and Monitoring	Management
	clozapine until dose is stable; ECG as clinically indicated; monitor QT_c when affected by multiple medications. For clozapine: troponin, CRP and ECG in presence of signs and symptoms of possible myocarditis	
Endocrine, sexual and urinary side effects	**Assessment:** baseline functional inquiry including menstrual history and libido in women, and libido, erectile and ejaculatory function in men; baseline prolactin level in first episode psychosis, before initiating an antipsychotic associated with hyperprolactinemia and when indicated **Monitoring:** monitor monthly for 3 months after initiating a new antipsychotic, then yearly	Determine underlying cause of endocrine or sexual dysfunction and treat accordingly. Consider drugs for erectile dysfunction. For clinically significant hyperprolactinemia, first reduce dose of antipsychotic. If dose reduction is not tolerated (emergence of or increase in psychotic symptoms), consider switching to an antipsychotic not associated with hyperprolactinemia
Abbreviations: BP = blood pressure; CRP = C-reactive protein; EPS = extrapyramidal side effects; FGA = first-generation antipsychotic; HDL = high-density lipoprotein; LDL = low-density lipoprotein; OGTT = oral glucose tolerance test; SGA = second-generation antipsychotic; TD = tardive dyskinesia		

Choices during Pregnancy and Breastfeeding

Prenatal and Perinatal Risk Factors for Schizophrenia

A number of prenatal and perinatal factors have been associated with an increased risk of schizophrenia in the offspring to varying degrees. These include malnutrition, viral illnesses such as influenza, obesity, x-ray radiation, exposure to cats infected with *Toxoplasmosis gondii* protozoa, use of analgesics (ASA), season of birth (lack of sunlight exposure/vitamin D deficiency), maternal-fetal Rh incompatibility, low birth weight and obstetric complications (hypoxia).

Psychosis and Pregnancy

The onset of a 1st episode of psychosis during pregnancy is uncommon but if it occurs, it is considered a psychiatric emergency and requires treatment because of the potential adverse effects of psychosis on both mother and fetus. Women who experience a psychotic episode during pregnancy have twice the rate of adverse outcomes including stillbirth, infant death, prematurity and small for gestational age, even when controlling for other variables including age, education, smoking, marital status, parity and pregnancy-induced hypertension.[125]

Although women with schizophrenia may have lower fertility rates compared with the general population, their relative fertility has increased since deinstitutionalization, possibly due to a change in drug selection. High-potency antipsychotics are

prescribed less often or at lower doses, resulting in less effect on prolactin levels and ovulation inhibition. More recent studies have found similar numbers of pregnancies in women with schizophrenia compared with the general population.[126][127] Women with schizophrenia also have higher rates of unplanned and unwanted pregnancies; less social support; poorer antenatal care; poorer nutrition; greater use of tobacco, alcohol and illicit substances; and the majority experience intermittent loss of custody.[128]

Women with schizophrenia and related psychotic disorders should receive counselling about contraception and pregnancy early in the course of their illness. If a pregnancy is planned, a consultation with a psychiatrist is recommended to evaluate the risks/benefits of maintenance antipsychotics during pregnancy. Pregnancy in a woman being treated for schizophrenia is considered high-risk; referrals to a mental-health clinic and obstetrician are recommended and, if possible, the pregnancy should be managed through a high-risk clinic.

Psychosis and the Postpartum Period

Postpartum psychosis usually occurs within 2–4 weeks after delivery. The rate of postpartum psychosis is 1–2/1000 births. This is a psychiatric emergency because of the rare but serious risk of suicide and infanticide. If hospitalization is required and the mother's condition does not pose a risk to the newborn, the mother and baby should be kept together, ideally in a specialized unit.

In the postpartum period, the risk of relapse of schizophrenia and related psychosis is high (~24%) and is greatest during the first 3 months. Women with schizoaffective disorder are particularly at risk.[129] If a woman has a history of postpartum psychosis, the overall risk of relapse in a subsequent pregnancy is approximately 35%.[130]

Antipsychotics and Pregnancy

There have been no randomized controlled trials of FGAs or SGAs in pregnant patients. Teratogenic effects, including major congenital malformations, have not been demonstrated with the use of antipsychotics during pregnancy.[131] Hypertonia in neonates has been noted following prepartum use of high-potency FGAs. Use of antipsychotics during pregnancy has not been associated with an increased risk of gestational diabetes.[131]

While minimizing exposure to all medications is advisable, especially during the 1st trimester, the risks/benefits of antipsychotic use and the choice of medication must be carefully weighed for each patient, considering factors such as severity of past psychotic episodes, vulnerability to relapse, remission versus ongoing residual symptoms, current substance use, level of functioning, availability of social supports and history of prior response including side effects (EPS, weight gain, diabetes).

For many women with schizophrenia and related psychotic disorders, maintenance antipsychotics during pregnancy at the lowest dose possible to prevent relapse will be recommended, as maintenance therapy may ultimately reduce risks to the fetus associated with an acute psychotic relapse, such as exposure to higher maternal doses of medication.[128]

Antipsychotics and the Postpartum Period

Because of the high-risk of relapse in the postpartum period, re-start antipsychotics immediately after the delivery if they were discontinued during pregnancy. Closely monitor women maintained on low-dose maintenance antipsychotics during pregnancy for early signs of relapse, as an increase of dose may be needed in the postpartum period.

Antipsychotics and Breastfeeding

All antipsychotics pass into breast milk. The American Academy of Pediatrics considers the transfer of less than 10% of a drug into breast milk to be compatible with breastfeeding.[132] Less than 3% of a dose of FGA is transferred into breast milk.[132] Drowsiness and lethargy have been reported, although many studies cite no adverse events.[132] No adverse effects of any SGAs on breastfeeding infants have been reported, but data are very limited and long-term studies are needed.

There is no consensus regarding breastfeeding in women being treated with antipsychotics; some experts recommend against breastfeeding until further data are available.[128] The potential benefits of breastfeeding must be weighed against potential adverse effects, and discussed with each individual patient.

A discussion of general principles on the use of medications in these special populations can be found in Drug Use during Pregnancy and Drug Use during Breastfeeding. Other specialized reference sources are also provided in these appendices.

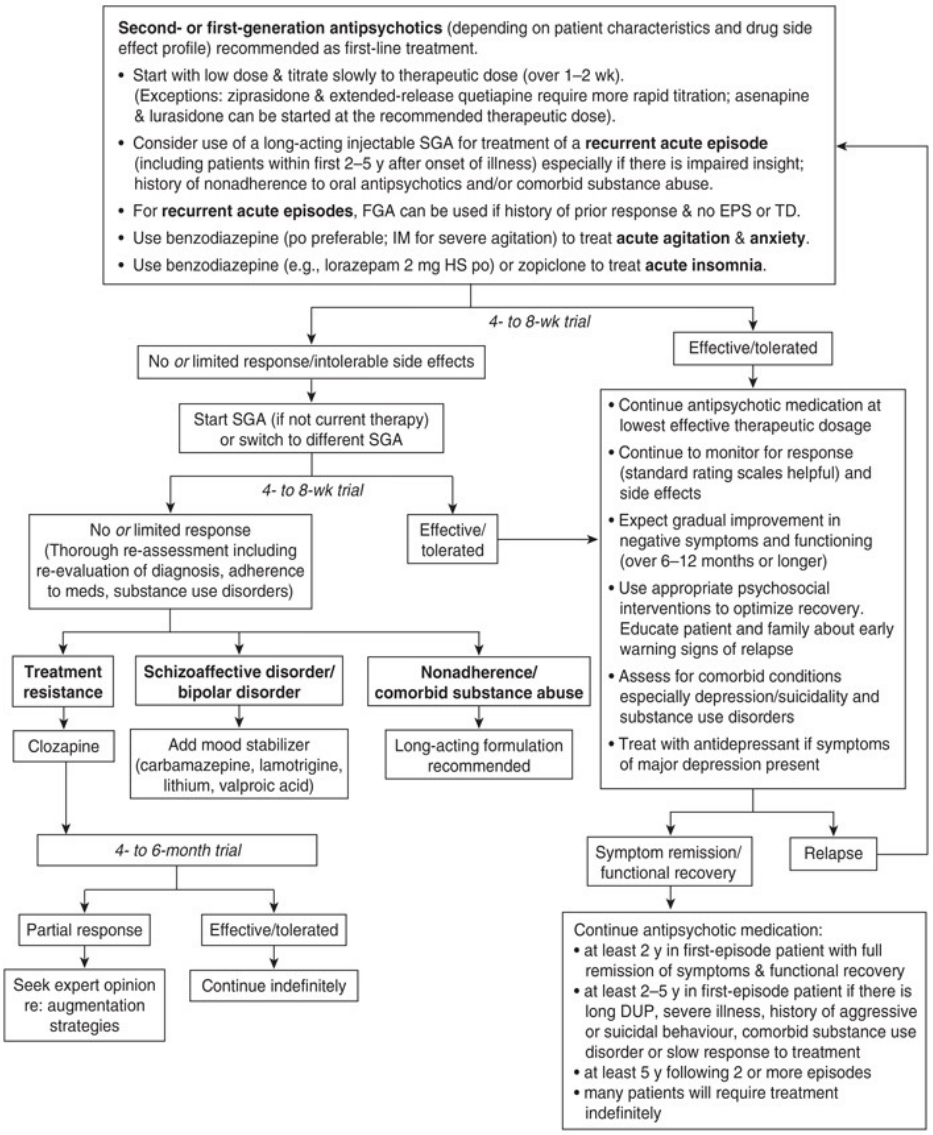
Therapeutic Tips

- Initiate treatment before the development of a crisis such as self-harm, aggression or violence.[16][43]
- Provide treatment in the least restrictive setting, considering safety issues, availability of community resources (including both caregiver and mental-health supports), the patient's insight and competency to consent to treatment, and ability to cooperate with treatment.[16][43]

- Integrate psychosocial interventions such as patient and family psychoeducation, supportive therapy, motivational interviewing and stress management with the use of antipsychotic medications in order to promote adherence to treatment and optimize outcomes.[16][43]
- Conduct baseline and regular ongoing assessments of signs and symptoms, possible comorbid conditions, level of functioning, response to treatment, side effects and medication adherence during all phases of the disorder. A variety of standardized scales and semi-structured interviews facilitate these assessments.[16]
- To ensure continuity of care, longitudinal follow-up by the same clinician or multidisciplinary team is optimal.[16][43]

Algorithms

Figure 1: Management of Acute Psychotic Episodes



Abbreviations: DUP = duration of untreated psychosis; EPS = extrapyramidal symptoms; FGA = first-generation antipsychotic; SGA = second-generation antipsychotic; TD = tardive dyskinesia

Drug Tables

Table 5: Drug Therapy for Psychosis: First-generation Antipsychotics

Drug/Cost[a]	Dosage	Adverse Effects	Drug Interactions	Comments
Drug Class: Antipsychotics, first-generation, low potency				

Drug/Cost[a]	Dosage	Adverse Effects	Drug Interactions	Comments
chlorpromazine generics $$	Initial: 50 –100 mg/dayPO Usual: 200 –400 mg/day PO Maximum: 1000 –2000 mg/day Divided in 1–4 doses/day	More common with low-potency agents: sedation, cardiovascular effects, anticholinergic effects, weight gain, lower seizure threshold, photosensitivity. More common with high-potency agents: increased prolactin, EPS, NMS, tardive movement disorders. Liver function abnormalities.	Additive effects with other CNS depressants, anticholinergics, alpha-adrenergic antagonists; inhibitors of cytochrome P450 enzymes (e.g., TCAs, fluoxetine, fluvoxamine, paroxetine) may increase serum levels; inducers of cytochrome P450 enzymes (e.g., carbamazepine, phenytoin) may decrease serum levels; effects of levodopa may be inhibited.	Advise patients about antipsychotic-associated body temperature dysregulation and prevention of heat stroke, e.g., hydration, sun protection.
methotrimeprazine generics $$	Initial: 25 –75 mg/day PO Usual: 50 –200 mg/day PO Maximum: 1000 mg/day Divided in 1–3 doses/day	More common with low-potency agents: sedation, cardiovascular effects, anticholinergic effects, weight gain, lower seizure threshold, photosensitivity. More common with high-potency agents: increased prolactin, EPS, NMS, tardive movement disorders. Liver function abnormalities.	Additive effects with other CNS depressants, anticholinergics, alpha-adrenergic antagonists; inhibitors of cytochrome P450 enzymes (e.g., TCAs, fluoxetine, fluvoxamine, paroxetine) may increase serum levels; inducers of cytochrome P450 enzymes (e.g., carbamazepine, phenytoin) may decrease serum levels; effects of levodopa may be inhibited.	Advise patients about antipsychotic-associated body temperature dysregulation and prevention of heat stroke, e.g., hydration, sun protection.
Drug Class: Antipsychotics, first-generation, intermediate potency				
loxapine Xylac, generics $$	Initial: 10 –20 mg/day PO Usual: 20 –100 mg/day PO Maximum: 250 mg/day Divided in 2–3 doses/day	More common with low-potency agents: sedation, cardiovascular effects, anticholinergic effects, weight gain, lower seizure threshold, photosensitivity. More common with high-potency agents: increased prolactin, EPS, NMS, tardive movement disorders. Liver function abnormalities.	Additive effects with other CNS depressants, anticholinergics, alpha-adrenergic antagonists; inhibitors of cytochrome P450 enzymes (e.g., TCAs, fluoxetine, fluvoxamine, paroxetine) may increase serum levels; inducers of cytochrome P450 enzymes (e.g., carbamazepine, phenytoin) may decrease serum levels; effects of levodopa may be inhibited.	Advise patients about antipsychotic-associated body temperature dysregulation and prevention of heat stroke, e.g., hydration, sun protection.
perphenazine generics $	Initial: 4 –12 mg/day PO Usual: 12 –48 mg/day PO Maximum: 48 –64 mg/day Divided in 2–3 doses/day	More common with low-potency agents: sedation, cardiovascular effects, anticholinergic effects, weight gain, lower seizure threshold, photosensitivity.	Additive effects with other CNS depressants, anticholinergics, alpha-adrenergic antagonists; inhibitors of cytochrome P450 enzymes (e.g., TCAs, fluoxetine, fluvoxamine, paroxetine) may increase serum levels; inducers of cytochrome P450 enzymes (e.g., carbamazepine,	Advise patients about antipsychotic-associated body temperature dysregulation and prevention of heat stroke, e.g., hydration, sun protection.

Drug/Cost[a]	Dosage	Adverse Effects	Drug Interactions	Comments
		More common with high-potency agents: increased prolactin, EPS, NMS, tardive movement disorders. Liver function abnormalities.	phenytoin) may decrease serum levels; effects of levodopa may be inhibited.	
zuclopenthixol Clopixol $$$	Initial: 10 –20 mg/day PO Usual: 20 –60 mg/day PO Maximum: 100 mg/day Divided in 1–3 doses/day	More common with low-potency agents: sedation, cardiovascular effects, anticholinergic effects, weight gain, lower seizure threshold, photosensitivity. More common with high-potency agents: increased prolactin, EPS, NMS, tardive movement disorders. Liver function abnormalities.	Additive effects with other CNS depressants, anticholinergics, alpha-adrenergic antagonists; inhibitors of cytochrome P450 enzymes (e.g., TCAs, fluoxetine, fluvoxamine, paroxetine) may increase serum levels; inducers of cytochrome P450 enzymes (e.g., carbamazepine, phenytoin) may decrease serum levels; effects of levodopa may be inhibited.	Advise patients about antipsychotic-associated body temperature dysregulation and prevention of heat stroke, e.g., hydration, sun protection.
zuclopenthixol acetate injection Clopixol Acuphase $/50 mg dose	50–150 mg IM Q2–3 days Maximum: cumulative dose of 400 mg or 4 injections	More common with low-potency agents: sedation, cardiovascular effects, anticholinergic effects, weight gain, lower seizure threshold, photosensitivity. More common with high-potency agents: increased prolactin, EPS, NMS, tardive movement disorders. Liver function abnormalities.	Additive effects with other CNS depressants, anticholinergics, alpha-adrenergic antagonists; inhibitors of cytochrome P450 enzymes (e.g., TCAs, fluoxetine, fluvoxamine, paroxetine) may increase serum levels; inducers of cytochrome P450 enzymes (e.g., carbamazepine, phenytoin) may decrease serum levels; effects of levodopa may be inhibited.	Advise patients about antipsychotic-associated body temperature dysregulation and prevention of heat stroke, e.g., hydration, sun protection. Not to be used in antipsychotic-naïve patients with first-episode psychosis. Intended for use in acute psychosis, for up to 2 wk.
zuclopenthixol decanoate long-acting injection Clopixol Depot $$	Range: 100–400 mg IM Q2–4 wk Usual dose: 150–300 mg IM Q2–4 wk	More common with low-potency agents: sedation, cardiovascular effects, anticholinergic effects, weight gain, lower seizure threshold, photosensitivity. More common with high-potency agents: increased prolactin, EPS, NMS, tardive movement disorders. Liver function abnormalities.	Additive effects with other CNS depressants, anticholinergics, alpha-adrenergic antagonists; inhibitors of cytochrome P450 enzymes (e.g., TCAs, fluoxetine, fluvoxamine, paroxetine) may increase serum levels; inducers of cytochrome P450 enzymes (e.g., carbamazepine, phenytoin) may decrease serum levels; effects of levodopa may be inhibited.	Advise patients about antipsychotic-associated body temperature dysregulation and prevention of heat stroke, e.g., hydration, sun protection.
Drug Class: Antipsychotics, first-generation, high potency				
flupentixol Fluanxol	Initial: 3 mg/day PO	More common with low-potency agents:	Additive effects with other CNS depressants,	Advise patients about

Drug/Cost[a]	Dosage	Adverse Effects	Drug Interactions	Comments
$$	Usual: 3 –6 mg/day PO Maximum: 12 mg/day Divided in 3 doses/day	sedation, cardiovascular effects, anticholinergic effects, weight gain, lower seizure threshold, photosensitivity. More common with high-potency agents: increased prolactin, EPS, NMS, tardive movement disorders. Liver function abnormalities.	anticholinergics, alpha-adrenergic antagonists; inhibitors of cytochrome P450 enzymes (e.g., TCAs, fluoxetine, fluvoxamine, paroxetine) may increase serum levels; inducers of cytochrome P450 enzymes (e.g., carbamazepine, phenytoin) may decrease serum levels; effects of levodopa may be inhibited.	antipsychotic-associated body temperature dysregulation and prevention of heat stroke, e.g., hydration, sun protection.
flupentixol decanoate long-acting injection Fluanxol Depot $$	Range: 20–100 mg IM Q2–3 wk Usual dose: 20–40 mg IM Q2–3 wk	More common with low-potency agents: sedation, cardiovascular effects, anticholinergic effects, weight gain, lower seizure threshold, photosensitivity. More common with high-potency agents: increased prolactin, EPS, NMS, tardive movement disorders. Liver function abnormalities.	Additive effects with other CNS depressants, anticholinergics, alpha-adrenergic antagonists; inhibitors of cytochrome P450 enzymes (e.g., TCAs, fluoxetine, fluvoxamine, paroxetine) may increase serum levels; inducers of cytochrome P450 enzymes (e.g., carbamazepine, phenytoin) may decrease serum levels; effects of levodopa may be inhibited.	Advise patients about antipsychotic-associated body temperature dysregulation and prevention of heat stroke, e.g., hydration, sun protection.
fluphenazine generics $	Initial: 2 –5 mg/day PO Usual: 2.5 –10 mg/day PO Maximum: 20 mg/day Divided in 1–2 doses/day	More common with low-potency agents: sedation, cardiovascular effects, anticholinergic effects, weight gain, lower seizure threshold, photosensitivity. More common with high-potency agents: increased prolactin, EPS, NMS, tardive movement disorders. Liver function abnormalities.	Additive effects with other CNS depressants, anticholinergics, alpha-adrenergic antagonists; inhibitors of cytochrome P450 enzymes (e.g., TCAs, fluoxetine, fluvoxamine, paroxetine) may increase serum levels; inducers of cytochrome P450 enzymes (e.g., carbamazepine, phenytoin) may decrease serum levels; effects of levodopa may be inhibited.	Advise patients about antipsychotic-associated body temperature dysregulation and prevention of heat stroke, e.g., hydration, sun protection.
fluphenazine decanoate long-acting injection Modecate $$	Range: 12.5–100 mg IM Q2–3 wk Usual dose: 25–50 mg IM Q2–3 wk	More common with low-potency agents: sedation, cardiovascular effects, anticholinergic effects, weight gain, lower seizure threshold, photosensitivity. More common with high-potency agents: increased prolactin, EPS, NMS, tardive movement disorders.	Additive effects with other CNS depressants, anticholinergics, alpha-adrenergic antagonists; inhibitors of cytochrome P450 enzymes (e.g., TCAs, fluoxetine, fluvoxamine, paroxetine) may increase serum levels; inducers of cytochrome P450 enzymes (e.g., carbamazepine, phenytoin) may decrease serum levels; effects of levodopa may be inhibited.	Advise patients about antipsychotic-associated body temperature dysregulation and prevention of heat stroke, e.g., hydration, sun protection. Preferred route is IM; can be given SC.

Drug/Cost[a]	Dosage	Adverse Effects	Drug Interactions	Comments
		Liver function abnormalities.		
haloperidol generics $	Initial: 1.5 –3 mg/day PO Usual: 4 –12 mg/day PO Maximum: 20 mg/day Divided in 1–3 doses/day	More common with low-potency agents: sedation, cardiovascular effects, anticholinergic effects, weight gain, lower seizure threshold, photosensitivity. More common with high-potency agents: increased prolactin, EPS, NMS, tardive movement disorders. Liver function abnormalities.	Additive effects with other CNS depressants, anticholinergics, alpha-adrenergic antagonists; inhibitors of cytochrome P450 enzymes (e.g., TCAs, fluoxetine, fluvoxamine, paroxetine) may increase serum levels; inducers of cytochrome P450 enzymes (e.g., carbamazepine, phenytoin) may decrease serum levels; effects of levodopa may be inhibited.	Advise patients about antipsychotic-associated body temperature dysregulation and prevention of heat stroke, e.g., hydration, sun protection.
haloperidol decanoate long-acting injection generics $$	Range/usual dose: 50–300 mg IM Q4 wk Maximum: 450 mg/month	More common with low-potency agents: sedation, cardiovascular effects, anticholinergic effects, weight gain, lower seizure threshold, photosensitivity. More common with high-potency agents: increased prolactin, EPS, NMS, tardive movement disorders. Liver function abnormalities.	Additive effects with other CNS depressants, anticholinergics, alpha-adrenergic antagonists; inhibitors of cytochrome P450 enzymes (e.g., TCAs, fluoxetine, fluvoxamine, paroxetine) may increase serum levels; inducers of cytochrome P450 enzymes (e.g., carbamazepine, phenytoin) may decrease serum levels; effects of levodopa may be inhibited.	Advise patients about antipsychotic-associated body temperature dysregulation and prevention of heat stroke, e.g., hydration, sun protection. Dose is approximately 10 –15 × daily oral dose.
pimozide generics $	Initial: 2 –4 mg/day PO Usual: 2 –12 mg/day PO Maximum: 20 mg/day Once daily dosing	More common with low-potency agents: sedation, cardiovascular effects, anticholinergic effects, weight gain, lower seizure threshold, photosensitivity. More common with high-potency agents: increased prolactin, EPS, NMS, tardive movement disorders. Liver function abnormalities. Pimozide: QT_c prolongation with doses >8 mg/day.	Additive effects with other CNS depressants, anticholinergics, alpha-adrenergic antagonists; inhibitors of cytochrome P450 enzymes (e.g., TCAs, fluoxetine, fluvoxamine, paroxetine) may increase serum levels; inducers of cytochrome P450 enzymes (e.g., carbamazepine, phenytoin) may decrease serum levels; effects of levodopa may be inhibited. Pimozide: avoid use with sertraline due to increased risk of QT_c prolongation.	Advise patients about antipsychotic-associated body temperature dysregulation and prevention of heat stroke, e.g., hydration, sun protection.
trifluoperazine generics $	Initial: 2 –10 mg/day PO Usual: 6 –20 mg/day PO Maximum: 40 mg/day	More common with low-potency agents: sedation, cardiovascular effects, anticholinergic effects, weight gain,	Additive effects with other CNS depressants, anticholinergics, alpha-adrenergic antagonists; inhibitors of cytochrome P450 enzymes (e.g., TCAs, fluoxetine, fluvoxamine,	Advise patients about antipsychotic-associated body temperature dysregulation and prevention of heat

Drug/Cost[a]	Dosage	Adverse Effects	Drug Interactions	Comments
	Divided in 1–2 doses/day	lower seizure threshold, photosensitivity. More common with high-potency agents: increased prolactin, EPS, NMS, tardive movement disorders. Liver function abnormalities.	paroxetine) may increase serum levels; inducers of cytochrome P450 enzymes (e.g., carbamazepine, phenytoin) may decrease serum levels; effects of levodopa may be inhibited.	stroke, e.g., hydration, sun protection.

[a] Cost of 30-day supply of mean usual dose unless otherwise specified; includes drug cost only.

Abbreviations: CNS = central nervous system; CV = cardiovascular; EPS = extrapyramidal symptoms; NMS = neuroleptic malignant syndrome; TCA = tricyclic antidepressant

Legend: $ < $25 $$ $25–50 $$$ $50–75

Table 6: Drug Therapy for Psychosis: Second-Generation Antipsychotics

Drug/Cost[a]	Dosage	Adverse Effects	Drug Interactions	Comments
Drug Class: Antipsychotics, second-generation				
aripiprazole Abilify, generics $	Initial: 10–15 mg/day PO. Best taken in the morning due to risk of activating side effects (i.e., insomnia) In first-episode psychosis: 2–5 mg then gradually titrate to 10–15 mg/day Titration: If necessary increase dose after 2 wk Maximum: 30 mg/day	EPS (akathisia, parkinsonism), dizziness, orthostatic hypotension, headache, GI complaints, nasopharyngitis, tremor, sedation, insomnia. Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) is a rare but very serious adverse effect.	Carbamazepine (or other strong inducers of CYP2D6 or CYP3A4 such as phenytoin, rifampin) can decrease aripiprazole levels significantly. Ketoconazole, quinidine, fluoxetine or paroxetine (or other strong inhibitors of CYP2D6 or CYP3A4) can increase levels substantially.	Advise patients about antipsychotic-associated body temperature dysregulation and prevention of heat stroke, e.g., hydration, sun protection.
aripiprazole prolonged release injectable suspension Abilify Maintena $$$	Ensure patient tolerates aripiprazole oral doses before initiating IM dose Initial: 400 mg IM 1 dose; continue aripiprazole 10–20 mg daily PO × 14 days Maintenance: 400 mg monthly IM In first-episode psychosis: 300 mg monthly IM	EPS (akathisia, parkinsonism), dizziness, orthostatic hypotension, headache, GI complaints, nasopharyngitis, tremor, sedation, insomnia. Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) is a rare but very serious adverse effect. Consider dose reduction to 300 mg monthly IM if adverse reactions with higher dose.	Carbamazepine (or other strong inducers of CYP2D6 or CYP3A4 such as phenytoin, rifampin) can decrease aripiprazole levels significantly. Ketoconazole, quinidine, fluoxetine or paroxetine (or other strong inhibitors of CYP2D6 or CYP3A4) can increase levels substantially. Concomitant administration of CYP3A4 inducers for more than 14 days may cause lower aripiprazole levels and reduce efficacy. Increased sedation when combined with alcohol or other CNS drugs.	Advise patients about antipsychotic-associated body temperature dysregulation and prevention of heat stroke, e.g., hydration, sun protection. Dose adjustments recommended when patients are adding or discontinuing concomitant strong inhibitors of CYP3A4 or CYP2D6.
asenapine Saphris $	Initial: 5 mg BID SL Titration: Target therapeutic dose	Hypersensitivity reactions, oral hypoesthesia and paresthesia, orthostatic	May potentiate antihypertensive drug effects.	Advise patients about antipsychotic-associated body

Drug/Cost[a]	Dosage	Adverse Effects	Drug Interactions	Comments
	same as initial dose (5 mg BID SL) Maximum: 10 mg BID SL	hypotension, sedation, insomnia, EPS (akathisia, parkinsonism), constipation. Minimal effect on weight, glucose, lipids.	Strong inhibitors of CYP1A2 (such as fluvoxamine) increase asenapine levels. Other CYP1A2 inducers or inhibitors may affect asenapine levels.	temperature dysregulation and prevention of heat stroke, e.g., hydration, sun protection. Instruct patients to handle the tablet with dry hands, to place it immediately under the tongue, to allow it to dissolve completely (do not chew or swallow) and to not drink or eat for 10 minutes afterward. If asenapine is taken in combination with other oral medications it should be taken last.
brexpiprazole Rexulti $	Initial: 1 mg daily Titration: Day 1–4: 1 mg daily Day 5–7: 2 mg daily Depending on clinical response and tolerability, on Day 8, increase to 4 mg	Headache, insomnia or sedation, nausea, constipation, orthostatic hypotension, EPS (akathisia, parkinsonism). Cases of hyperglycemia, dyslipidemia, weight gain and sleep apnea have been reported.	Ketoconazole, quinidine, fluoxetine or paroxetine (and other strong inhibitors of CYP2D6 or CYP3A4) can increase levels substantially; modify dose as appropriate. Brexpiprazole levels can be reduced by strong CYP3A4 inducers (e.g., carbamazepine, phenobarbital, phenytoin, rifampin). Modify dose as appropriate. Not affected by smoking.	Advise patients about antipsychotic-associated body temperature dysregulation and prevention of heat stroke, e.g., hydration, sun protection. Reduce dose to maximum of 3 mg in patients with moderate-severe hepatic and renal impairment.
clozapine Clozaril, generics $$	Initial: 12.5–25 mg/day PO Titration: increase by 12.5–25 mg on 2nd day and then by 25–50 mg daily PO depending on tolerance Usual: 300–600 mg/day PO Maximum: 900 mg/day Divided in 1–3 doses/day	Agranulocytosis (<1%), seizures (1–5%; dose-related), sedation, orthostatic hypotension, tachycardia, fever, nausea, weight gain, hypersalivation (30–50%), urinary incontinence, constipation; increased risk of diabetes and hyperlipidemia; myocarditis and other cardiac effects (see Pharmacologic Choices). Constipation may evolve into potentially fatal intestinal obstruction. DRESS is a rare but very serious adverse effect.	Additive sedation with CNS depressants; may potentiate antihypertensive drug effects; inhibitors of CYP1A2, such as diltiazem, fluvoxamine or propranolol, or of CYP3A4, such as clarithromycin, erythromycin, grapefruit juice or prednisone, may increase clozapine levels; inducers of CYP1A2 or CYP3A4 such as carbamazepine, phenytoin, rifampin or cigarette smoking may reduce clozapine levels; respiratory depression with higher doses of benzodiazepines; avoid use with bone marrow suppressants and drugs that lower the seizure threshold.	Advise patients about antipsychotic-associated body temperature dysregulation and prevention of heat stroke, e.g., hydration, sun protection.
lurasidone Latuda	Initial: 40 mg daily PO (with food)	Nausea and vomiting, sedation, EPS (including	May potentiate antihypertensive drug	Advise patients about

Drug/Cost[a]	Dosage	Adverse Effects	Drug Interactions	Comments
$	Titration: Target therapeutic dose same as initial dose (40 mg daily PO) Usual: 40–80 mg daily PO Maximum: 160 mg daily PO	akathisia), orthostatic hypotension, insomnia. DRESS is a rare but very serious adverse effect.	effects; do not use in combination with strong inhibitors of CYP3A4 such as ketoconazole; do not exceed doses of 40 mg daily PO in combination with other inhibitors of CYP3A4 such as diltiazem, clarithromycin, erythromycin, prednisone, grapefruit juice (increased lurasidone levels); do not use in combination with strong inducers of CYP3A4 such as carbamazepine, phenytoin (decreased lurasidone levels).	antipsychotic-associated body temperature dysregulation and prevention of heat stroke, e.g., hydration, sun protection. Administer with meals of >350 kcal to maximize absorption and therapeutic effect.
olanzapine (including oral disintegrating tablets) Zyprexa, Zyprexa Zydis, generics $	Initial: 5–10 mg/day PO Titration: increase by 2.5–5 mg every 3–4 days Usual: 10–20 mg/day Maximum: 20 mg/day (product monograph). Doses of up to 40 mg/day are used in clinical practice under care of a psychiatrist Frequency: 1 dose/day; higher doses may be given in 2 divided doses	Weight gain, dizziness, sedation, anticholinergic effects, hepatic aminotransferase elevation, orthostatic hypotension, increased risk of diabetes and dyslipidemia, EPS (especially akathisia). DRESS is a rare but very serious adverse effect.	Sedation with CNS depressants; may potentiate antihypertensive drug effects; inhibitors of CYP1A2 or CYP2D6 such as diltiazem, fluvoxamine, or paroxetine may increase olanzapine levels; inducers of CYP1A2 or CYP3A4 such as barbiturates, carbamazepine, phenytoin, rifampin or cigarette smoking may decrease olanzapine levels.	Advise patients about antipsychotic-associated body temperature dysregulation and prevention of heat stroke, e.g., hydration, sun protection.
olanzapine injection Zyprexa Intramuscular, generics $/10 mg dose	Initial: 5–10 mg IM Usual: 10 mg IM. If necessary 2nd dose of 5–10 mg IM may be given 2 h after 1st injection Maximum: 20 mg/day (oral and IM) with no more than 3 injections in 24 h	Weight gain, dizziness, sedation, anticholinergic effects, hepatic aminotransferase elevation, orthostatic hypotension, increased risk of diabetes and dyslipidemia, EPS (especially akathisia). DRESS is a rare but very serious adverse effect.	Sedation with CNS depressants; may potentiate antihypertensive drug effects; inhibitors of CYP1A2 or CYP2D6 such as diltiazem, fluvoxamine, or paroxetine may increase olanzapine levels; inducers of CYP1A2 or CYP3A4 such as barbiturates, carbamazepine, phenytoin, rifampin or cigarette smoking may decrease olanzapine levels. Should not be administered simultaneously with parenteral benzodiazepines due to reports of cardiac and respiratory problems including deaths.	Advise patients about antipsychotic-associated body temperature dysregulation and prevention of heat stroke, e.g., hydration, sun protection.
paliperidone Invega $$	Initial: 3–6 mg daily PO Titration: If necessary	Insomnia, headaches, weight gain, orthostatic hypotension, rhinitis, anxiety, dose-related	Minimal risk of drug interactions. Carbamazepine may	Advise patients about antipsychotic-associated body

Drug/Cost[a]	Dosage	Adverse Effects	Drug Interactions	Comments
	increase by 3 mg /day at 5-day intervals Maximum: 12 mg daily	hyperprolactinemia and EPS. Risk of intraoperative floppy iris syndrome in patients undergoing cataract surgery who have been exposed to paliperidone. DRESS is a rare but very serious adverse effect.	decrease paliperidone serum concentrations.	temperature dysregulation and prevention of heat stroke, e.g., hydration, sun protection. Less orthostatic hypotension and weight gain and more insomnia compared with risperidone.
paliperidone palmitate long-acting injectable Invega Sustenna $$$	Initial: 150 mg IM (deltoid muscle) and 100 mg IM (deltoid muscle) 7 days later. No oral supplementation required Usual: 100 mg IM monthly in either deltoid or gluteal muscle Range: 25–150 mg IM monthly	Insomnia, headaches, weight gain, orthostatic hypotension, rhinitis, anxiety, dose-related hyperprolactinemia and EPS. Risk of intraoperative floppy iris syndrome in patients undergoing cataract surgery who have been exposed to paliperidone. DRESS is a rare but very serious adverse effect.	Minimal risk of drug interactions. Carbamazepine may decrease paliperidone serum concentrations.	Advise patients about antipsychotic-associated body temperature dysregulation and prevention of heat stroke, e.g., hydration, sun protection. Less orthostatic hypotension and weight gain and more insomnia compared with risperidone.
paliperidone palmitate long-acting injectable Invega Trinza ~$1,500/3 months	Initial/usual: 175 –525 mg Q3 months IM Multiply Invega Sustenna dose by 3.5 to determine appropriate dosage	Insomnia, headaches, weight gain, orthostatic hypotension, rhinitis, anxiety, dose-related hyperprolactinemia and EPS. Risk of intraoperative floppy iris syndrome in patients undergoing cataract surgery who have been exposed to paliperidone. DRESS is a rare but very serious adverse effect.	Minimal risk of drug interactions. Carbamazepine may decrease paliperidone serum concentrations.	Advise patients about antipsychotic-associated body temperature dysregulation and prevention of heat stroke, e.g., hydration, sun protection. Less orthostatic hypotension and weight gain and more insomnia compared with risperidone. Must first establish Invega Sustenna as a tolerable and effective treatment for ≥4 months, with the last 2 doses equivalent in strength, before starting Invega Trinza.
quetiapine immediate-release Seroquel, generics $	Initial: 50–100 mg/day PO Titration: increase by 100 mg/day Usual: 600 mg/day Maximum: 800 mg/day (product monograph)	Sedation, dizziness, weight gain, orthostatic hypotension, hepatic aminotransferase elevation, headache, anticholinergic effects, increased risk of diabetes and dyslipidemia, possible increased risk of cataracts; may reduce thyroid hormone levels.	Additive sedation with CNS depressants; may potentiate antihypertensive drug effects; inhibitors of CYP3A4 (e.g., clarithromycin, erythromycin, grapefruit juice, ketoconazole, prednisone) may increase quetiapine levels; inducers of CYP3A4 (e.g.,	Advise patients about antipsychotic-associated body temperature dysregulation and prevention of heat stroke, e.g., hydration, sun protection.

Drug/Cost[a]	Dosage	Adverse Effects	Drug Interactions	Comments
	Doses of up to 1200 mg/day used in clinical practice under care of a psychiatrist Divided in 1–3 doses/day	DRESS is a rare but very serious adverse effect.	carbamazepine, phenytoin, rifampin) may decrease quetiapine levels.	
quetiapine extended-release Seroquel XR, generics $	Initial: 300 mg QHS PO (200 mg for first-episode psychosis) Titration (rapid): may increase dose in increments of ≤300 mg/day at intervals ≥1 day Usual: 400–800 mg/day Given as a once-daily dose, generally in the evening	Sedation, dizziness, weight gain, orthostatic hypotension, hepatic aminotransferase elevation, headache, anticholinergic effects, increased risk of diabetes and dyslipidemia, possible increased risk of cataracts; may reduce thyroid hormone levels. DRESS is a rare but very serious adverse effect.	Additive sedation with CNS depressants; may potentiate antihypertensive drug effects; inhibitors of CYP3A4 (e.g., clarithromycin, erythromycin, grapefruit juice, ketoconazole, prednisone) may increase quetiapine levels; inducers of CYP3A4 (e.g., carbamazepine, phenytoin, rifampin) may decrease quetiapine levels.	Advise patients about antipsychotic-associated body temperature dysregulation and prevention of heat stroke, e.g., hydration, sun protection.
risperidone (including oral disintegrating tablets) Risperdal, generics $	Initial: 0.5–1 mg/day PO Titration: increase by 0.5–1 mg PO every 3–4 days Usual: 2–6 mg/day PO Maximum: 6 mg/day PO Frequency: 1 dose/day, preferably QHS	Sedation, headaches, weight gain, orthostatic hypotension, rhinitis, anxiety, dose-related hyperprolactinemia and EPS. Risk of intraoperative floppy iris syndrome in patients undergoing cataract surgery who have been exposed to risperidone. DRESS is a rare but very serious adverse effect.	Additive sedation with CNS depressants; may potentiate antihypertensive drug effects; inhibitors of CYP3A4 (e.g., clarithromycin, erythromycin, grapefruit juice, ketoconazole, prednisone) may increase risperidone levels; inducers of CYP3A4 (e.g., carbamazepine, phenytoin, rifampin) may decrease risperidone levels.	Advise patients about antipsychotic-associated body temperature dysregulation and prevention of heat stroke, e.g., hydration, sun protection.
risperidone long-acting injection Risperdal Consta $$$	Initial: 25 mg IM every 2 wk (oral supplementation with current antipsychotic required for first 3 wk) Titration: Depending on response, increase by 12.5 mg every 4–8 wk Usual: 25–37.5 mg IM every 2 wk. Some patients can be maintained on a dose of 12.5 mg every 2 wk Maximum: 50 mg IM every 2 wk	Sedation, headaches, weight gain, orthostatic hypotension, rhinitis, anxiety, dose-related hyperprolactinemia and EPS. Risk of intraoperative floppy iris syndrome in patients undergoing cataract surgery who have been exposed to risperidone. DRESS is a rare but very serious adverse effect. Adverse effects may be less severe compared with oral risperidone due to decreased peak to trough serum fluctuations.	Additive sedation with CNS depressants; may potentiate antihypertensive drug effects; inhibitors of CYP3A4 (e.g., clarithromycin, erythromycin, grapefruit juice, ketoconazole, prednisone) may increase risperidone levels; inducers of CYP3A4 (e.g., carbamazepine, phenytoin, rifampin) may decrease risperidone levels.	Advise patients about antipsychotic-associated body temperature dysregulation and prevention of heat stroke, e.g., hydration, sun protection.
ziprasidone Zeldox, generics $	Start with 40 mg BID PO (20 mg BID for antipsychotic-naïve first-episode	Orthostatic hypotension, EPS, sedation, insomnia. Prolonged QT_c-interval; contraindicated in patients with history of	Contraindicated with any other drug that prolongs the QT_c interval such as: antibiotics (azithromycin, clarithromycin and	Administer with meals of ≥500 kcal to maximize absorption and therapeutic effect.

Drug/Cost[a]	Dosage	Adverse Effects	Drug Interactions	Comments
	patients) and rapidly titrate in the 1st wk up to 120–160 mg/day Administer doses with food (see Comments)	QT_c prolongation, recent MI, uncompensated heart failure or with concomitant use of any other drug that prolongs the QT_c interval. Rapid titration is recommended to avoid ziprasidone-induced "activation" syndrome consisting of anxiety, restlessness, insomnia, increased energy and hypomanic-like symptoms which develop soon after treatment initiation and occur at the lower end of the dosage range (20–40 mg BID PO). DRESS is a rare but very serious adverse effect.	erythromycin); antiarrhythmics (amiodarone, ibutilide, procainamide, quinidine and sotalol); lithium; methadone; venlafaxine. May potentiate antihypertensive drug effects.	Advise patients about antipsychotic-associated body temperature dysregulation and prevention of heat stroke, e.g., hydration, sun protection.

[a] Cost of 30-day supply of mean usual dose unless otherwise specified; includes drug cost only.

◗ Dosage adjustment may be required in renal impairment; see Dosage Adjustment in Renal Impairment.

Abbreviations: CNS = central nervous system; GI = gastrointestinal; EPS = extrapyramidal symptoms

Legend: $ < $150 $$ $150–350 $$$ $350–550

Suggested Readings

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