Second-Generation Antipsychotics in the Treatment of Schizophrenia

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Lesson description

Schizophrenia is a chronic condition that has a dramatic effect on both the health and the quality of life of the individuals affected. People with schizophrenia are at higher risk of substance abuse, suicide, diabetes, cardiovascular disease, and premature death. Pharmacists can make a tremendous difference for these individuals by showing empathy and utilizing proper patient counselling tips and tools. This continuing education lesson will help provide the reader with the tools required to deliver the best possible patient care to individuals with schizophrenia.

Learning objectives

Upon successful completion of this home study lesson, you should be able to:

- discuss current concepts of the prevalence and underlying pathophysiology of schizophrenia
- distinguish between positive and negative symptoms of schizophrenia
- provide guidance on how to interact with and counsel patients with schizophrenia
- compare and contrast the pharmacological and adverse effect profiles of clozapine, risperidone, olanzapine, quetiapine, paliperidone, and ziprasidone
- describe reasons for and methods of switching antipsychotic agents
- describe metabolic syndrome and identify differences among the antipsychotics with respect to the syndrome
- devise a treatment plan for a person with schizophrenia, given their medication and medical history
- identify clinically significant drug interactions with second-generation antipsychotics
- identify treatment options for patients who have not responded adequately to any of the second-generation antipsychotics, including clozapine

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Contents

1. Schizophrenia

1.1 Prevalence and cost to society

The lifetime prevalence of schizophrenia is about 0.7%; the peak age of onset is between 15 and 25 years for men and between 25 and 35 years for women.[1] Although the clinical presentation can differ significantly between male and female patients, there is no difference in the prevalence in between sexes.[2] Schizophrenia has been described in all cultures and socioeconomic classes and its incidence has been stable.

Schizophrenia can have a significant affect on morbidity and mortality. It is estimated that people with schizophrenia have 2.5 times risk of dying compared to the general population.[3] Patients with this condition are at higher risk of substance dependence, cardiovascular disease, diabetes, poverty, and homelessness.[1] People with schizophrenia commonly make poor lifestyle choices (e.g., smoking, unhealthy diets, lack of exercise, substance abuse). Also, many are less likely to seek health care services due to social instability, homelessness, poor motivation, and cognitive dysfunction. Suicide is a major problem in patients with schizophrenia. Up to 30% of patients attempt suicide, and 4–10% die by it.[1]

Patients with schizophrenia account for 1 of every 12 Canadian hospital beds and nearly half of all repeat admissions for mental illness. The direct cost of schizophrenia to the Canadian health care system was estimated to be $2 billion dollars a year in 2004.[4] The loss of productivity due to high unemployment rates and high morbidity and mortality was estimated to be $4.83 billion dollars.[4]

The vast majority of people with schizophrenia are unemployed. Since the onset of the illness is relatively early, they often lose contact with colleagues at school or work and become socially isolated and unable to financially support themselves. The only means of survival for many is through public assistance and family support, and many live in conditions of poverty.

1.2 Pathophysiology of schizophrenia

The pathophysiology of schizophrenia is very complex and not clearly understood. Some of the theories of the biological cause of schizophrenia have been derived from clinical observations of patients receiving psychotropic medication. The "dopamine hypothesis" arose from the observation that all of the agents that decreased or eliminated some of the symptoms of schizophrenia blocked the effects of the neurotransmitter dopamine. This led to the belief that schizophrenia was due to an excess of dopamine in the brain. It became apparent, however, that this theory was inadequate because it did not explain why all of the symptoms did not resolve when dopamine was blocked. Also, the advent of clozapine, a very weak dopamine antagonist and most effective antipsychotic, forced researchers to take a closer look at the role of other neurotransmitters, such as serotonin.

Despite further advancement in knowledge regarding the role of other neurotransmitters, it is evident that schizophrenia is not solely due to neurotransmitter abnormalities. There are morphological differences in the brains of patients with schizophrenia. Numerous theories regarding the cause for these changes have been suggested, but none have been proven to be correct. It is, however, clear that schizophrenia has a genetic basis and an environmental basis. If one monozygotic twin (twins who share the same genetic information) has schizophrenia, the risk of the condition in the other is 40–50%.[5] Environmental risk factors are believed to have a role in the development of schizophrenia.[5] These environmental risk factors include lower socioeconomic classes, maternal infection in the first or second trimester, substance abuse, recent immigration, and urban living.[5]

1.3 Neurotransmitter abnormalities in schizophrenia

Besides differences in the morphological development of the brain of an individual with schizophrenia, alterations in neurotransmitter transmission have also been identified. As was previously discussed, the neurotransmitter dopamine has been associated with schizophrenia for several decades and, more recently, serotonin and glutamate have also been implicated. These different neurotransmitter pathways are responsible for both the positive and negative symptoms in people with schizophrenia. These symptoms will be discussed in greater detail in the next section. Currently, almost all of the methods of treatment for schizophrenia involve modulating the functioning of neurotransmitters by medications.

1.3.1 Dopaminergic mechanisms

The belief that there is excess in dopamine functioning in schizophrenia has been held since the 1960s. This theory arose because all effective agents in schizophrenia block dopamine receptors with varying degrees of affinity. It wasn't until the arrival of clozapine, which has very weak affinity for dopamine receptors, that further elaboration of the "excess dopamine" theory became necessary. We now know that increased dopaminergic transmission in parts of the brain is still at the core of the some of the symptoms of schizophrenia, but decreased dopaminergic transmission occurs in

other parts of the brain and this results in another set of symptoms.

Dopamine receptor subtypes

There are five dopamine receptor subtypes, grouped into two pharmacologically distinct categories. One category exhibits affinities that are D1-like (D1 and D5) and the other are more D2-like (D2, D3, and D4 receptors).[6,7] The affinity of conventional antipsychotics for the D2 receptor has been linked to their effects in improving psychosis, in particular the positive symptoms. Positron emission tomography (PET) studies of people with schizophrenia have shown that the therapeutic efficacy of conventional antipsychotics is associated with a 60% or greater occupancy of D2 receptors.

Dopamine pathways

The dopaminergic system arises from groups of cells in the midbrain and projects into the forebrain.[8] In schizophrenia, both under- and overfunctioning of the dopaminergic system can exist in different parts of the brain, resulting in positive and negative symptoms. There are four dopamine pathways in the brain:

Mesolimbic dopamine pathway

The positive symptoms of schizophrenia may be the result of excessive dopaminergic transmission in the mesolimbic projections. Antipsychotics reduce positive symptoms by blocking dopamine D2 receptors in this region.[9]

Mesocortical dopamine pathway

The mesocortical area is involved with cognition, modulation of motivation, and reward-seeking behaviours.[8] Dopamine release in this pathway is thought to be involved in emotional learning and long-term memory.[8] Evidence from studies in the central nervous system has indicated that dopaminergic activity is reduced here in schizophrenia, which may result in negative symptoms. Blocking dopamine receptors with antipsychotics in this region further reduces cognition and worsens negative symptoms. This can occur in clinical practice, especially when using excessive doses of conventional antipsychotics.

Nigrostriatal dopamine pathway

The nigrostriatal pathway is associated with motor behaviour coordination. Blocking dopamine receptors here results in extrapyramidal adverse effects.[9] Evidence has shown that dopamine stimulation in this region is responsible for motor learning and habit formation.[8]

Tuberoinfundibular dopamine pathway

Dopamine prevents the release of prolactin in the tuberoinfundibular tract. When dopamine receptors in this area are antagonized, hyperprolactinemia (high blood prolactin levels), breast enlargement (in men and women), and galactorrhea can occur. Amenorrhea (absence of a menstrual period in a woman of reproductive age), weight gain, and sexual dysfunction are also common.

1.3.2 Serotonergic mechanism

Serotonergic projections innervate virtually all regions of the brain. Although 14 serotonin receptor subtypes have been identified to date, the 5-HT_2 receptor is the one that most consistently plays a role in schizophrenia.[10,11] The second-generation antipsychotics (SGAs) clozapine, risperidone, olanzapine, paliperidone, quetiapine, and ziprasidone are potent 5-HT_2 receptor blockers, and have higher affinity for serotonin receptors than for dopamine receptors.

Interaction between dopamine and serotonin

Serotonergic projections inhibit the release of dopamine in the prefrontal cortex, and a lack of dopaminergic activity is believed to contribute to negative symptoms. SGAs are all potent serotonin antagonists and may improve negative symptoms by increasing dopamine levels indirectly through their effects on serotonin in the cortex.[12]

Serotonergic projections also directly inhibit prefrontal neurons. Therefore, some effects of serotonin antagonists on negative symptoms may reflect a direct rather than a dopamine-mediated effect on prefrontal neurons.

In the striatum, serotonin also inhibits dopamine release. Thus, serotonin antagonists would be expected to increase concentrations of dopamine in the nigrostriatal pathway, diminishing the extrapyramidal symptoms caused by dopamine antagonists.

1.3.3 Excitatory amino acid mechanism

There is also evidence for abnormalities in the levels of glutamate, an excitatory amino acid, in schizophrenia.[13] Research into the cerebrospinal fluid of glutamate in patients with schizophrenia found the quantity of glutamate to be about half the normal value.

Investigations into the possible role of glutamate began because of the disturbing side effects that patients experienced after receiving phencyclidine (PCP).[14] PCP has been used as an analgesic in conscious subjects. Some reported hallucinations,

cognitive disturbances, agitation, and a confusional psychosis. This "confusional psychosis" involved paranoia, confusion, depression, anxiety, and depersonalization. It was suggested that PCP intoxication be used as a model for psychosis because it resembled schizophrenia.

2. Second-generation antipsychotics in the treatment of schizophrenia

2.1 Introduction

The first of the second-generation antipsychotics (SGAs), clozapine, became available in Canada in 1991. Clozapine use is restricted to those patients who have not responded to other agents, as is it associated with an increased risk of agranulocytosis (an acute condition involving a severe and dangerous leukopenia (reduction in the number of white blood cells) in the body). Risperidone became available in 1993, followed by olanzapine and quetiapine. Ziprasidone and paliperidone are the newest agents marketed in 2008. SGAs have gained acceptance as first-line treatment because they are much less likely to cause movement disorders and it was suggested that SGAs were better than first-generation agents (FGAs) in improving negative symptoms of schizophrenia. The recent CATIE 1 and CATIE 2 studies have found few differences between the SGAs and the FGA perphenazine in the treatment of positive and negative symptoms.[15–17] Differences were found in their adverse effect profiles and time to discontinuation of treatment. Although SGAs do not cause patients to suffer from movement disorders, some of them are associated with metabolic syndrome, which is associated with significant health risks. This continuing education lesson reviews pharmacological treatment options for schizophrenia based on currently available literature.

2.2 Definition

Is there any literature that compares FGAs to SGAs with respect to efficacy data?

The most recent and comprehensive studies that address differences between an FGA and SGAs have been the CATIE Phase 1 and CATIE Phase 2 studies.[15–17] CATIE refers to Clinical Antipsychotic Trials for Intervention Effectiveness. The trials were designed to examine several issues regarding SGAs, namely their relative effectiveness and their effectiveness compared to an FGA, perphenazine. The primary outcome measure was time to discontinuation of treatment. Only 26% of subjects completed the 18-month trial on the medicine to which they were initially randomized. Subjects receiving olanzapine experienced a longer time to discontinuation than did those receiving the other agents. The time to discontinuation was 9.2 months, 4.6 months, 4.8 months, 5.6 months, and 3.5 months for olanzapine, quetiapine, risperidone, perphenazine, and zisprasidone respectively. Thus, based only on the single criterion of time to discontinuation, olanzapine showed greater effectiveness than the other agents. However, olanzapine was associated with significant metabolic problems, especially with weight gain. Perphenazine showed comparable effectiveness and produced no more extrapyramidal side (EPS) effects than the other agents. The lack of an increase in EPS in the perphenazine group has been the source of controversy. Patients with pre-existing EPS were not randomized into the perphenazine group and the study time frame of 18 months has been cited as too short a period to measure for EPS symptoms.[18,19] Risperidone was best tolerated even though it showed significant elevations in prolactin levels. Ziprasidone was associated with weight loss and a positive impact on lipids and blood glucose.[16]

In CATIE phase 2, clozapine demonstrated better effectiveness compared to other SGAs for those who discontinued their Phase 1 medication because of efficacy. The time to discontinuation was longer with clozapine than with the other agents: 10.5 months, 3.3 months, 2.8 months, and 2.7 months for clozapine, quetiapine, risperidone, and olanzapine respectively. Olanzapine and risperidone were tolerated better.[20] Improvements in cognition and psychosocial function (interpersonal relations, community living skills) were modest among all the agents in use in Phase 1, and perphenazine was no less effective than the SGAs.[15,16]

In the recently published CATIE phase 3, participating patients were placed in an open-label trial of aripiprazole, clozapine, olanzapine, perphenazine, quetiapine, risperidone, ziprasidone, long-acting fluphenazine decanoate, or combination therapy of any two treatments.[21] Even though all these agents have been shown to be effective, patients and their clinicians selected treatment options based on patient clinical factors. Patients with resistant symptoms selected clozapine or combination therapies. Patients with high body mass index (BMI) readings typically chose aripiprazole or ziprasidone. Although the side effects reported varied considerably amongst the treatment groups, discontinuation due to intolerability was rare. Of interesting note, only a very small percentage of patients and clinicians chose perphenazine and long-acting fluphenazine decanoate injection.[21]

A recently published meta-analysis evaluated the differences between first- and second-generation antipsychotics.[22] The authors evaluated 150 studies with 21,533 participants and found that most SGAs are not more effective that FGAs, even for negative symptoms.[22] Although SGAs induce fewer EPS than haloperidol, only a few SGAs induce fewer EPS than low-potency FGAs.[22] With the data from this meta-analysis and the CATIE trials, the current classification system for antipsychotics is being called into question, as there are overlapping pharmacological properties with individual drugs.

2.3.Case 1: Mr. Jones

Mr. Jones hands you a prescription for risperidone 1 mg po twice a day for 3 days and then increase to 2 mg twice a day for 30 days. When he gives you the prescription, you find his hand is shaking and his fingers are stained from nicotine. He is in his mid-30s and somewhat disheveled in his clothing and grooming.

You examine his profile and see the following:

- *loxapine 40 mg bid*
- *benztropine 2 mg bid*
- *60 tablets of each last filled 24 days ago and first filled 7 months ago*

When you ask Mr. Jones if he is being switched from loxapine to risperidone he says that he thinks so. While talking with him you are aware that he does not make eye contact with you and appears very uncomfortable with your question. You ask him if his doctor told him to finish the loxapine and then start the risperidone or is he to start the risperidone right away. He says he should start today and does not elaborate. You would like to ask him a few more questions but he walks away and stands with his back to the wall and watches another client walking up to the prescription counter.

With Mr. Jones not being sure about what to do with his loxapine dosing you decide to call his physician to clarify. His physician provides you with an exact tapering schedule for the loxapine and benztropine and the titration schedule for the risperidone.

What symptoms are risperidone supposed to help alleviate, and is it possible that Mr. Jones is exhibiting some of those symptoms?

Schizophrenia is a mixture of positive, negative, and cognitive symptoms.[2] Positive symptoms commonly involve bizarre, different, or inappropriate behaviours, as well as hallucinations and delusions.[23] Delusions are firmly held erroneous beliefs due to distortions or exaggerations of reasoning and/or misinterpretations of perceptions or experiences.[24] Examples of delusions include the belief that the person is being followed or watched and that comments on radio or TV programs are sending special messages directly to them.[24] Hallucinations are distortions or exaggerations in any of the senses. Patients will feel, hear, see, or smell things that don't really exist. Auditory hallucinations are the most common, with patients hearing voices distinct from their thought.[24] Visual hallucinations are also common.

Negative symptoms commonly present as blunted personalities, socialization, and emotional expressions. Affective flattening is a common negative symptom and involves the reduction in the range and intensity of emotional expressions, including voice, eye contact, body language, and facial expressions.[24] Alogia is the poverty of speech. Many patients with this negative symptom have lessened speech fluency and productivity.[24] Alogia commonly manifests as empty replies to questions. Avolition is another common negative symptom of schizophrenia. It is the reduction, difficulty, or inability to initiate and persist in goal-directed behaviors.[24]

There is a significant range of cognitive impairment in patients with schizophrenia. There is generalized intellectual impairment in this patient population.[2] Many of these patients have difficulty with executive function, memory, psychomotor speed, attention, and cognition.[2]

The symptoms of schizophrenia will vary in severity among patients and throughout the course of the illness.[2] Table 1 lists some of the common symptoms of schizophrenia.

Mr. Jones makes little or no eye contact and gives very short answers to your questions. He

Table 1. Positive, negative, and cognitive symptoms of schizophrenia[25,26]

Positive symptoms	Negative symptoms	Cognitive symptoms
• hostility	• emotional withdrawal	• disorganized thinking
• excitement	• uncooperativeness	• slow thinking
• hallucinations	• lack of emotion	• difficulty understanding
• delusions	• low energy	• poor concentration
• suspiciousness	• affective flattening	• poor memory
• grandiosity	• poverty of thought	• difficulty expressing thoughts
• disorganization	• social withdrawal	• impaired verbal fluency
	• lack of spontaneity	
	• poor abstract thinking	

also is poorly groomed and uncomfortable around people. The fact that he prefers to stand off and observe others may imply that he is mistrustful and perhaps paranoid. Mr. Jones is displaying some positive and negative symptoms of schizophrenia. His negative symptoms include poor eye contact, decrease in speech, and perhaps social withdrawal. If he is afraid that someone might hurt him and he needs to watch people, he is likely experiencing the positive symptom of paranoia.

Risperidone (and the other SGAs) can decrease or eliminate positive symptoms such as hallucinations and delusions and may improve Mr. Jones' negative symptoms. There is some evidence that both FGAs and SGAs can also improve negative symptoms to some degree. This improvement is not consistent with all doses of SGAs.[1] One of the key advantages of SGAs is their improvement on cognitive impairment. SGAs are more effective than FGAs at reducing verbal dysfunction, attention, declarative memory, and fine motor performance.[27] In one trial of oral and long-acting risperidone it was found to improve processing speed, attention, verbal and visual learning, memory, and problem solving.[28] This improvement in cognitive impairment may help improve social skills and increase the potential for employment.[27]

Are there any potential problems associated with switching Mr. Jones from 80 mg/day of loxapine to risperidone? What should he do with his benztropine therapy?

Switching antipsychotic therapy can be challenging and can place the patient at risk of adverse effects and exacerbations in their symptoms.[29] The main reasons for switching therapy include lack of efficacy and the presence of adverse effects. Lack of efficacy may be due to inadequate dosages, development of tolerance to the medication, and patient variability in responses.[29] Non-adherence is also a common cause of lack of efficacy. Switching due to adverse effects can also be challenging, as each patient has a unique response to individual agents, so switching may not lead to the desired effect. Table 2 lists indications for antipsychotic switching.

There are several contraindications to switching antipsychotic therapy. These include recent recovery from a psychotic episode and taking a medication that is successfully controlling recovery from a psychotic episode, unless they are stable for 3–6 months.[29] Clinicians are cautioned on switching patients who are refusing to change, have current alcohol or drug abuse, are at risk of danger to themselves or others, or are at a major time of change in the patient's life, as they are at particular risk of problems if their symptoms increase.[30]

There are three main methods of switching antipsychotics:[29]

- abrupt switching – abrupt discontinuation of one drug with abrupt introduction of the new one at the expected therapeutic dose
- gradual switching – slow downward adjustment of the dosage of the current medication, with slow upward adjustment of the dosage of the new medication
- overlapping switching – abrupt introduction of the new medication overlapping with the current medication followed by the downward adjustment of the dosage of the current medication

Table 2. Indications for switching antipsychotic medications[30]

- cannot tolerate current regimen
- only partial remission achieved
- refractory to treatment
- relapse
- request from patient
- comorbid psychiatric conditions
- comorbid physical conditions

Table 3. Advantages and disadvantages of different antipsychotic switching methods[29]

Method	Advantages	Disadvantages
abrupt switching	• less likelihood of errors • rapid • appropriate for depot formulations	• greater chance of flare-ups and withdrawal symptoms • supervision may be required • not recommended for patients receiving clozapine (increased seizure risk)
gradual switching	• may provide relief of EPS	• possibility of a sub-therapeutic dosage if tapering is too rapid
overlapping switching	• most effective strategy in preventing relapse • appropriate for recently stabilized patients	• increased possibility of continued poly-pharmacy • higher risk of medication adverse effects

There is no single correct method of switching antipsychotics, but there are some specific recommendations that may predispose clinicians to prefer one method or another. Abrupt discontinuation is less likely to cause errors but is associated with an increased risk of a flare in psychosis symptoms.[29] Also, patients who abruptly discontinue an FGA are at increased risk of cholinergic rebound (nausea, restlessness, insomnia, anxiety, confusion, cold sweats, muscle pain, and diaphoresis).[30] Cross-tapering may be preferred for outpatients and may be associated with higher risk of adverse effects.[29] Table 3 lists the advantages and disadvantages of each switching method.

It is better to taper the loxapine and introduce risperidone at the same time as the taper because loxapine has anticholinergic properties and risperidone does not.[31] Stopping anticholinergic agents without tapering them can lead to cholinergic rebound. Although the withdrawal symptoms are not dangerous, they can be very unpleasant and can be easily avoided by decreasing the dose of loxapine by about 25% every 3–4 days. It would also be preferable to continue benztropine until the switch to risperidone has taken place, because loxapine has a fairly long half-life and the patient may require the benztropine for residual extrapyramidal side effects (EPS) from loxapine. Benztropine can then be decreased to 1 mg bid for 4 days and then discontinued.

How would you counsel Mr. Jones about potential adverse effects he may encounter with risperidone?

Since the patient does not appear very interactive in communicating, it is best to supply him with written information to support what you are going to tell him.

The most common side effects that patients experience with risperidone are insomnia, agitation, anxiety, and headache.[32] He may experience orthostatic hypotension when he first starts taking risperidone, and he should be told that if he gets dizzy he should rise slowly when seated or lying down. It is important that he be told that normally the dizziness goes away but that he is to inform his doctor if it doesn't.

Extrapyramidal side effects such as rigidity, akinesia, bradykinesia, tremor, and dystonia are uncommon and occur at a similar rate to placebo at low doses.[33] The risk of EPS increases when the dosage is greater than 4 mg/day.[1] Geriatric patients are much more sensitive to EPS. This lower incidence of EPS is directly related to SGAs' lower affinity for the dopamine receptor. In clinical practice risperidone is the SGA associated with the highest frequency of EPS.

Another potential problem with risperidone is sexual dysfunction and increased prolactin levels in both genders.[1] Increased prolactin levels can result in amenorrhea, breast engorgement, and galactorrhea in women and breast enlargement and retrograde ejaculation (ejaculation into the bladder) in males when risperidone is used chronically.[1] These effects are due to dopamine antagonism in the tuberoinfundibular tract; dopamine inhibits the release of prolactin from the pituitary.

How does paliperidone compare to risperidone?

Paliperidone is one of the newest SGAs available in the Canadian market. Paliperidone is a derivative and the principle active metabolite of risperidone.[34] The pharmacodynamic action of paliperidone is nearly identical to that of risperidone, as they have a similar receptor antagonist profile and much of the risperidone dosage is converted to paliperidone (i.e., most of the pharmacological effect of risperidone occurs in the body after it is converted to paliperidone).[34] Paliperidone is similar in efficacy to other SGAs and has adverse effects of increasing prolactin levels and sexual dysfunction similar to those of risperidone.[35]

What other information may be important for the client?

Non-adherence with antipsychotic therapy is very common in patients with schizophrenia. Non-adherence estimates range from 20% to 89% with an average of approximately 50%.[36] The risk of relapse is 3.7 times as high in non-adherent patients as in patients who are completely adherent to their regimen.[36] The cost of non-adherence is significant, with a direct relationship between adherence and economic cost of schizophrenia.[37] Patients who are non-adherent are at an increased risk of all-cause and psychosis-related hospitalization.[38]

The causes of non-adherence are multifaceted and it is crucial pharmacists reinforce to patients the need to continue to take their medications. Many patients do not believe that they actually have a mental illness and do not notice an improvement in their symptoms even though it may be evident to caregivers and family members. Sometimes they notice that their symptoms have resolved and think that they no longer need medication. Other risk factors for non-adherence include:[39,40,36]

- adverse effects
- influence by peers or family members
- the stigma attached to mental illness
- co-morbid substance abuse
- poor patient/clinician relationship
- disease severity and higher levels of agitation

- recent hospital discharge
- younger patients

Many SGAs are available in dosage forms such as dissolving tablets (olanzapine, risperidone) or extended-release formats (quetiapine). This selection of dosage forms may help to improve adherence by simplifying the administration process, by helping for swallowing issues, or through once-daily administration.

The pharmacist may be able to help by asking the client what they think of the medication and then provide insight based on the feedback. If the patient believes the medication helps them and they have reservations about the adverse effects, the pharmacist can explain that adjustments in dose can be made and some adverse effects may stop with longer treatment. Sometimes explaining that mental illness is no different than a medical illness except that the problem is in the brain rather than another organ, such as the heart, helps the client accept medication more readily. Obviously, such a conversation requires that the client place his/her trust in the pharmacist and feel comfortable discussing these issues. It may take time to develop rapport with the client, which will require genuine concern and effort by the pharmacist.

When looking at Mr. Jones's case, you remember there is an injection form of risperidone. Who are the best candidates for this injection?

Long-acting depot formulations are an option for patients who are non-adherent with their antipsychotic regimen. Long-acting FGAs depots have been available for some time, but long-acting risperidone is the first SGA in Canada with a depot format.

Long-acting risperidone (LAR) depot injection contains microspheres that slowly break down over time, releasing risperidone at a constant rate.[41] LAR is administered intramuscularly once every 2 weeks.[40] There is a latent period of 2–3 weeks before risperidone builds up to a therapeutic level, with a peak concentration achieved at 5–6 weeks.[41] For this reason, patients will need an oral SGA for the first 3 weeks and dosage adjustments should not be made at intervals of less than 4 weeks.[40]

The safety of this product is established, and patients switched to LAR from other oral or long-acting antipsychotics do not appear to have an increase in the risk of adverse effects compared to placebo.[43] LAR gives the clinician and patient a tool to help improve adherence, as some patients may find one injection every 2 weeks much easier than taking oral medication daily.[41] In select patients, LAR should help to reduce hospitalization and cost of care in a manner similar to that demonstrated by both FGA depots and SGAs.[44]

Mr. Jones returns to the pharmacy with a new prescription after having received risperidone for about 5 months. His prescription is for olanzapine 10 mg at bedtime for 2 weeks. He tells you that he is no longer taking risperidone and his psychiatrist wants him to try olanzapine. This time he makes eye contact and appears more willing to speak with you. What information would you want give Mr. Jones when he receives his new prescription?

When switching antipsychotic medications it is important to inform patients of the differences between the two treatments. Olanzapine, like risperidone, rarely causes EPS but, unlike risperidone, it is unlikely to have any effect on prolactin levels and on sexual function.[1] Olanzapine has a moderate risk of anticholinergic adverse effects and he should know that he might experience some constipation, dry mouth, and possibly blurred vision and urinary retention.[1] He may experience some sedation at the onset of treatment, but this will decrease over time. He should also be informed that his appetite may increase and he may start eating more than usual; this could result in weight gain, and he should be encouraged to engage in regular exercise if he is not already doing so. Increased appetite is likely related to olanzapine's antihistaminic and antiserotonergic properties. You should tell him that not everyone gets these side effects but some individuals are more sensitive than others.

Over the next 5 months you notice that Mr. Jones has been steadily gaining weight. He tells you that his appetite has increased dramatically and that he has gained 6 kg since olanzapine was started. He lets you know that the doctor is planning on putting him on a pill to decrease his sugar levels. What are the long-term implications of weight gain and increased glucose levels, and are they common to all SGAs?

Certain SGAs have been reported to produce substantial weight gain and an increased risk for dyslipidemia and type 2 diabetes mellitus (T2DM).[45] The constellation of the diseases of obesity, diabetes (insulin resistance), hyperlipidemia, and hypertension is termed metabolic syndrome. Metabolic syndrome puts a patient at higher risk of cardiovascular disease.

The first year of treatment with certain SGAs has been associated with significant weight gain. Long-term data indicate that olanzapine is associated with some of the greatest weight gain over 1 year of treatment.[46] Weight gain with olanzapine at the commonly used dose of 15 mg/day may exceed 10 kg in the first year of treatment.[46] Risperidone, paliperidone, and quetiapine are associated

with a smaller weight gain of approximately 2–3 kg in the first year.[46] Ziprasidone is associated with approximately 1 kg of weight gain in the first year of treatment.[46]

Although SGAs have been associated with weight gain in patients with schizophrenia, there also seem to be other mechanisms at work in this patient population. Early reports of obesity in the pre-antipsychotic era and higher–than-normal prevalence of obesity in unmedicated schizophrenia patients suggest that factors other than antipsychotics may have a role.[47] Also, patients with schizophrenia tend to make unhealthy diet choices and tend to have more sedentary lifestyles than the standard population.[47]

Several reports on hyperglycemia, including metabolic acidosis or ketoacidosis and subsequent death in some cases, have been filed with the FDA MedWatch Drug Surveillance System on clozapine and olanzapine.[48,49] Similar reports have also been filed for risperidone and quetiapine; however, the incidence of hyperglycemia and obesity is lower with risperidone and quetiapine than with clozapine and olanzapine.[50,51]

The long-term risks of having hyperglycemia and T2DM include microvascular disease (retinopathy, nephropathy, and diabetic neuropathy) and macrovascular disease (coronary heart disease, cerebrovascular disease, and peripheral vascular disease).

An American Diabetes Association consensus development report noted that, among SGAs, clozapine and olanzapine are associated with the greatest potential weight gain with an increased risk of T2DM and dyslipidemia.[52] (See Table 4 for comparative risks among SGAs for metabolic abnormalities)

What guidelines are there to monitor metabolic abnormalities with SGAs?

The American Diabetes Association consensus report recommends that a change in SGA should be considered when a patient gains ≥5% of their initial weight at any time during therapy.[52] Table 5 lists their recommendations for monitoring and follow-up.[52] They include baseline and monitoring for weight, waist circumference, blood pressure (BP), fasting blood glucose (BG), and fasting lipids. A history of the patient's pattern of weight changes (if any) should also be recorded.

Is there an alternate SGA that could be used, given his increased weight and blood glucose?

Switching to ziprasidone from olanzapine or risperidone has been found to result in statistically significant reductions in body weight over period of 6 weeks.[53] Furthermore, a 58-week study examined the effects on weight and fasting lipids of switching from olanzapine, risperidone, or first-generation antipsychotics to ziprasidone.[54] Clinically significant, sustained improvements in weight, BMI, and plasma lipids were observed among patients switched from risperidone or olanzapine to ziprasidone. Similar results with weight loss occurred after switching to ziprasidone during the CATIE 1 study.[16]

Ziprasidone is generally well tolerated, with

Table 4. SGAs and metabolic abnormalities[52]

Drug	Weight gain	Risk for diabetes	Worsening of lipid profile
clozapine	+++	+	+
olanzapine	+++	+	+
risperidone	++	D	D
quetiapine	++	D	D
ziprasidone	–	–	–

+ = increased; D = discrepant results; – = little or no effect

Table 5. Metabolic monitoring protocol for patients on SGAs[52]

Parameter	Baseline	4 weeks	8 weeks	12 weeks	Quarterly	Annually	Q5yrs
personal & family history	X						
weight (BMI)	X	X	X	X	X		
waist circumference	X					X	
fasting BG	X			X		X	
fasting lipids	X			X			X
BP	X			X		X	

The recommended timings of these tests are only suggestions and the clinician may consider more frequent monitoring if there is any change in the status of the patient (e.g., diabetes, weight gain)

Table 6. Positive and negative effects of receptor profiles[58]

Receptor	Effects	Side effects	Interactions
D_2 blockade	Antipsychotic effect (from dopamine receptor blockade in mesolimbic area)	• EPS (from dopamine receptor blockade in nigrostriatal tract) • Endocrine changes (dopamine receptor blockade in tuberoinfundibular tract increases prolactin release) • Sexual dysfunction	
5-HT_2 blockade	• Antipsychotic effect (may improve negative symptoms) • Modulates effects of D_2 blockade (decreases extrapyramidal side effects – EPS)	• Weight gain • Somnolence • Changes in libido	
Muscarinic (M_1)	Antiparkinsonian effect	Anticholinergic (e.g. dry mouth, blurred vision, sinus tachycardia, ejaculatory incompetence and at higher doses in adults and at normal doses in elderly memory dysfunction)	Potentiation of effects of drugs with anticholinergic properties
H_1 blockade	Anti-emetic effect	• Sedation, drowsiness • Weight gain	Potentiation of effects of other CNS drugs
α_1 blockade	May help improve negative symptoms	• Postural hypotension, dizziness • Reflex tachycardia • Sedation	Potentiation of antihypertensive drugs acting through α_1 blockade (e.g. prazosin)
α_2 blockade	May help improve negative symptoms	Sexual dysfunction	Antagonism of antihypertensives acting as α_2 stimulants (e.g. clonidine, methyldopa)

Table 7. Relative neurotransmitter receptor affinity for SGAs at therapeutic doses[57,34]

Receptor	Clozapine	Risperidone	Paliperidone	Olanzapine	Quetiapine	Ziprasidone
D_1	+	+	+	++	–	+
D_2	+	+++	+++	++	+	+++
$5HT_{1A}$	–	–	–	–	–	+++
$5HT_{2A}$	+++	++++	++++	+++	++	++++
α_2	+	++	++	+	–	–
H_1	+++	–	–	+++	++	–
M_1	++++	–	–	+++	++	–

Note : – = weak; + = moderate; ++ = good; +++ = strong; ++++ = strong shown by meta-analysis

the most common adverse effects reported include somnolence, nausea, and respiratory infection.[55] Although EPS is reported in patients, the overall incidence in all schizophrenia trials was <5%.[55] Case reports of prolongation of QT interval have been reported. The QT interval is the length of time for the heart to repolarize. The FGAs pimozide and thioridazine both prolong the QT interval and there have been reports of sudden death.[26] Although ziprasidone may prolong the QT interval, there have been no reports of arrhythmias or sudden death.[1]

If Mr. Jones had been put on quetiapine, would the information you gave to Mr. Jones have been different than with olanzapine? How is quetiapine dosed?

Quetiapine's maximum dose is between 800 mg and 1000 mg a day and is usually started at 50 mg twice daily. Doses should be increased based on the patient's tolerance for its side effects, especially the sedation, tachycardia and orthostatic hypotension.[56] Generally, dose increases of 25–50 mg bid at intervals of not less than 2 days are recommended to the target dose of 300 mg/day.[56] Quetiapine is associated with a low risk of EPS, anticholinergic effects, and increase in prolactin levels.[1] Quetiapine is also less likely to cause as much weight gain as olanzapine.[52]

Receptor profiles of different SGAS

Although all SGAs have been shown to be effective, the differences in the products are related to their receptor profile. Most of the adverse effects of these medications can be directly related to the receptors they interact with. Tables 6 and 7 discuss the affinities of the Canadian SGAs and the positive and negative effects of this affinity.

2.4 Case 2: Ms. Gibbon

Your pharmacy supplies medication to a boarding home for patients suffering from psychiatric illnesses and you visit the home once a month. During this monthly visit you speak with the new psychiatrist, Dr. Ferguson. He tells you that one of the patients, Ms. Gibbon, has recently had a flare in her psychosis despite receiving risperidone in doses of 6 mg a day. He tells you that she is experiencing an increase in the voices she was hearing, which are telling her that a device was implanted in her brain and she is being controlled by aliens. She has become very fearful and is refusing to eat any food because she thinks it may be poisoned. He asks you about her medication history because he will likely change her medication and wants to make sure he doesn't restart anything she had been on before.

Your records show that she is 33 years old and that she was on olanzapine 20 mg per day for about 2 years. She was switched to risperidone 8 months ago. She has also had numerous trials of conventional antipsychotics, including haloperidol, perphenazine, and flupenthixol. You know from previous visits to the home that she has been sensitive to EPS and has had dystonic reactions to haloperidol.

Based on the history that you give Dr. Ferguson, he decides to start her on clozapine.

How is the decision made as to which antipsychotic to try?

The patient's medication history is important when it comes to deciding which agent is to be tried next. Any SGA is effective at helping for positive symptoms, and the primary differences are the adverse effect profiles. Clozapine has been shown to be effective for treatment-resistant symptoms. Patient and clinician preference also comes into play. There are several algorithms for the treatment of schizophrenia; the Texas Medication Algorithm project is displayed in Figure 1.[59–61] The recommended dosages for the SGAs available in Canada are listed in Table 8.

How would you initiate clozapine treatment, and what information should Dr. Ferguson have before starting clozapine?

Clozapine is restricted for use in patients who have failed to respond to at least 2 other antipsychotics or who cannot tolerate other antipsychotics. In CATIE phase 2, treatment with clozapine was shown to be more effective for patients who failed to respond to other anti-psychotic treatment.[20]

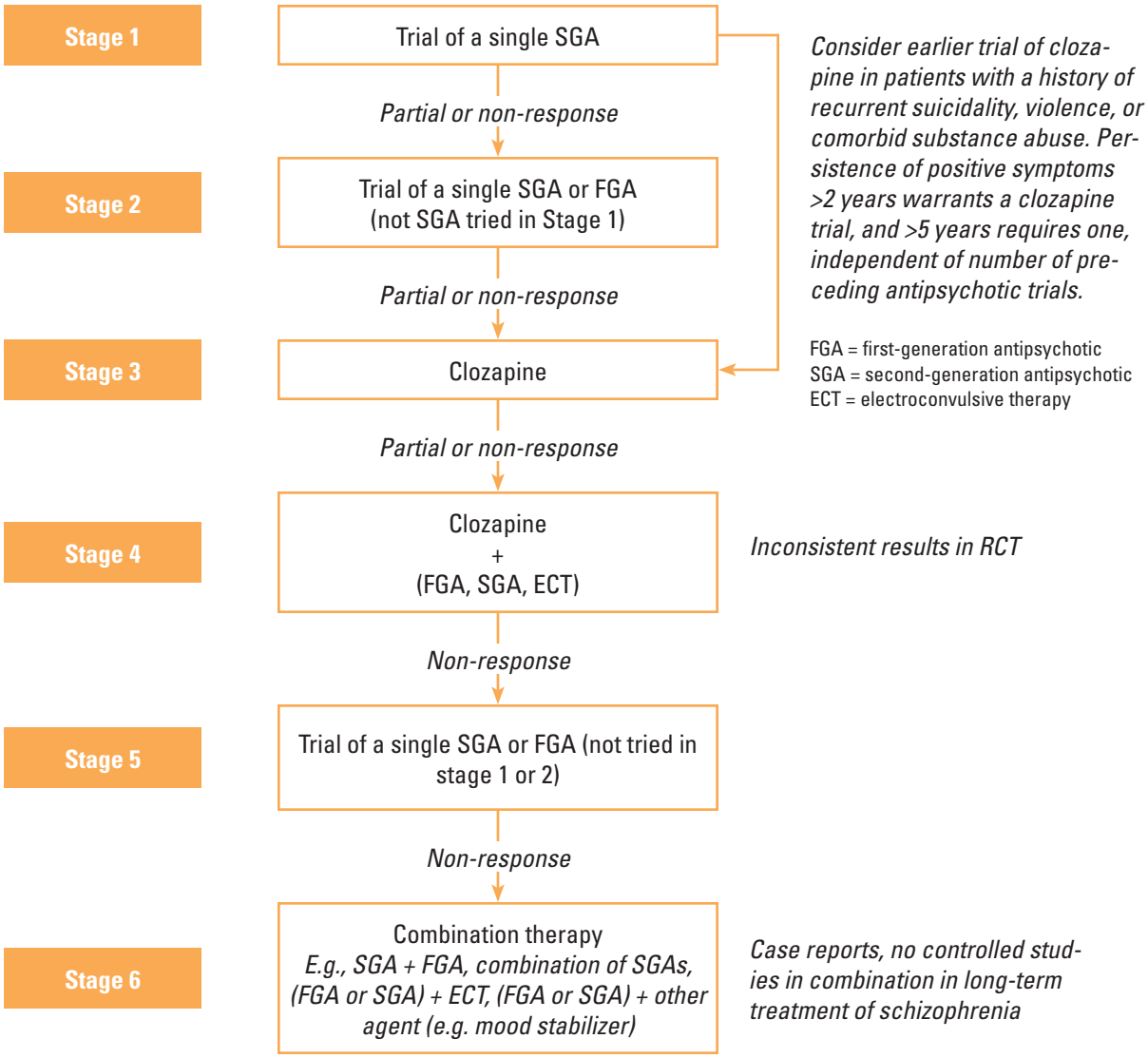
All patients taking clozapine must be registered in a national database to ensure that patients who have developed agranulocytosis on clozapine in the past are not re-challenged with it. In Canada, clozapine distribution is only available through the CSAN distribution system. Clozapine causes agranulocytosis in about 0.5–1% of individuals.[1] The risk is highest in the first 6 months and requires weekly blood tests for WBC and neutrophil monitoring.[1] After 6 months, blood tests should be done every 2 weeks.[1] Clozapine also increases the risk of seizures. Seizures occur in approximately 2% of patients on clozapine and the effect is dose-related, with high-dose clozapine causing seizures more frequently.[1]

How should the patient be monitored as the dose of clozapine is increased?

Clozapine carries a high risk of sedation, anticholinergic adverse effects, orthostatic hypotension, and tachycardia.[1] Ms. Gibbon should be checked for sedation and dizziness as the dose increases. If she complains of dizziness when she gets out of bed or stands up from a sitting pos-

Figure 1. Schizophrenia treatment algorithm[61]

Choice of antipsychotic (AP) should be guided by considering the clinical characteristics of the patient and the efficacy and side effect profiles of the medication. Any stage(s) can be skipped, depending on clinical picture or history of antipsychotic failure, and returning to an earlier stage may be justified by history of past response.



Notes:
If patient is inadequately adherent at any stage, the clinician should assess and consider a long-acting antipsychotic preparation, such as risperidone microspheres, haloperidol decanoate, or fluphenazine decanoate.
A treatment refractory evaluation should be performed to re-examine diagnosis, substance abuse, medication adherence, and psychosocial stressors. Cognitive behavioural therapy (CBT) or psychosocial augmentation should be considered.

Table 8. Dosages for second-generation antipsychotics[34,62]

Medication	Dose				
	Initial	Titration	Usual	Max	Dosed
clozapine	12.5–25 mg/day	Increase by 12.5–25 mg on second day, then by 25–50 mg daily depending on tolerance. When restarting patients who have had even a brief interval off clozapine, i.e., 2 days or more since the last dose, it is recommended that treatment be re-initiated with 12.5 mg once or twice on the first day.	300–600 mg/day	900 mg day	Divided in 1–3 daily doses
olanzapine	5–10 mg/day	Increase by 2.5–5 mg every 3 to 4 days.	10–20 mg/day	20 mg/day (monograph); doses of up to 40 mg/day are occasionally used in clinical practice.	Once daily. High doses may be given bid.
risperidone	0.5–1 mg/day	0.5–1 mg every 3 to 4 days	2–6 mg/day	8 mg/day	Once daily, preferably at bedtime
risperidone long-acting intramuscular injection	25 mg IM every 2 weeks (supplementation with current antipsychotic for first 3 weeks)	Depending on response, increase by 12.5–25 mg every 4–8 weeks.	25–37.5 mg IM every 2 weeks	50 mg IM every 2 weeks	
paliperidone	6 mg/day (some patients will only require 3 mg/day)	May not be required, as target is 6 mg for most patients. Clinicians can titrate in increments of 3 mg/day at intervals of >5 days if they feel it is warranted.	6 mg/day	12 mg/day	Once daily, preferably in the morning
quetiapine regular-release tablets	25 mg twice daily	Increase by 25–50 mg twice daily per day until at the target range of 300 mg/day.	300 mg/day		Doses up to 1200 mg/day are used in clinical practice. Divided in 1–3 daily doses per day Time-released format given once daily in the evening.
quetiapine extended release	300 mg/day	600 mg day 2. After day 2, up to 800 mg/day.	600 mg/day	800 mg/day (monograph)	
ziprasidone	40 mg twice daily	Dosage adjustments every 2 days up to 80 mg twice daily	80–200 mg/day	200 mg/day	Twice daily with food to increase absorption

ition, her blood pressure should be monitored. She should be monitored for anticholinergic symptoms such as blurred vision, constipation, and urinary retention.

Clozapine can increase significant increases in blood glucose, triglycerides, cholesterol, and weight. Clinicians are encouraged to follow the American Diabetes Associations monitoring guidelines presented in Table 5.

Would it be useful to find out what her clozapine plasma concentration is?

Although serum levels should not be done routinely, it could be done for two reasons: to check to see if she is compliant with clozapine, and because there is a threshold concentration at about 1000 nmol/L (350 ng/ml).[63] A larger percentage of patients respond when they are above this concentration of clozapine. If she has not reached this level, then the physician should increase the dose in an effort to exceed the desired plasma concentration. This may result in further clinical improvement, and augmentation with other agents may not be necessary. Some patients experience intolerable side effects or seizures at lower levels than others, and monitoring levels for toxicity is not very reliable.

What is considered an adequate time period for a trial of clozapine and what is the dose range?

Clozapine should be tried for at least 3 months; improvement in symptoms can continue for up to one year. The average dose for most patients is 350–450 mg per day, with the maximum dose being 900 mg a day. The incidence of seizures increases significantly when doses exceed 600 mg a day.

Six months later you receive a prescription for Ms. Gibbon from Dr. Ferguson for fluvoxamine 50 mg HS for five days then increase to 100 mg HS thereafter. Dr. Ferguson is concerned that she is depressed. Her medication record shows that she is now receiving clozapine 100 mg AM and 350 mg HS. What concerns would you have with this combination?

Clozapine undergoes metabolism of drugs goes through the cytochrome P450 (CYP 450) enzyme system.[64] Drugs can be metabolized by more than one pathway, resulting in different active and inactive metabolites. Each pathway is catalyzed by different isoenzymes. Isoenzymes CYP 1A2, CYP 2C19, CYP 2D6, and CYP 3A4 are the most important in psychotropic drug metabolism.

Clozapine is mainly metabolized by CYP 1A2, and fluvoxamine is a potent inhibitor of this enzyme. Adding fluvoxamine to Ms. Gibbon's clozapine will result in a significant increase in her clozapine plasma concentration, which may subsequently increase her side effects. Of particular concern is the increased risk of seizures.

The pharmacist should call Dr. Ferguson about the interaction and suggest an alternative that does not increase clozapine levels (such as citalopram) if he wishes to treat the patient with another selective serotonin reuptake inhibitor (SSRI).[64]

Besides pharmacokinetic drug interactions, are there pharmacodynamic interactions with SGAs?

Pharmacodynamic interactions occur when the pharmacological effects of one agent are affected by another co-administered agent. For example, when alcohol is used in combination with clozapine, increased sedation and orthostatic hypotension can occur. Tables 9, 10, 11, and 12 provide some pharmacokinetic data on the SGAs as well as potential drug interactions with these medications. The SGAs affected in Tables 10, 11, and 12 are listed in parentheses.

Table 9. Main pharmacokinetic parameters of SGAs[34,64]

Medication	Half life (hours)	Time to steady state (days)	P450 isoenzymes*	Active metabolites
clozapine	6–33	4–8	**CYP 1A2**, CYP 2C19 (CYP 3A4, CYP 2D6)	norclozapine
risperidone	3–24	4–6	**CYP 2D6, CYP 3A4**	9-hydroxyrisperidone
olanzapine	20–70	5–7	**CYP 1A2**, CYP 2D6	
quetiapine	5–8	2–3	**CYP 3A4**	
paliperidone	23	4–5	**CYP 2D6**	
ziprasidone	4–10	2–3	CYP 3A4	

* Isoenzymes in bold are the most likely to have clinical relevance

Table 10. Medications that increase plasma concentrations of SGAs[64]

Drug/class	Examples	SGA affected and mechanism*	Clinical significance
antibiotics	erythromycin clarithromycin	Inhibits 3A4 (seizures reported with clozapine; increased quetiapine levels)	high moderate
	ciprofloxacin	Inhibits 1A2 (increase in clozapine level)	moderate
antidepressants	fluvoxamine	Inhibits 1A2 (clozapine concentration increased 3–4-fold; moderate increase in olanzapine level).	high
	fluoxetine	Inhibits 2D6, 2C9, 3A4 (increased clozapine level – seizure risk increased, increased risperidone level)	high
	paroxetine	Inhibits 2D6 (increase in clozapine and risperidone)	moderate
	tricyclic antidepressants	Inhibits 2D6 (clozapine, olanzapine)	moderate
Ca channel blockers	diltiazem, verapamil	Inhibit 3A4 (quetiapine)	moderate
caffeine		Inhibits 1A2 (clozapine)	moderate
cimetidine		Inhibits multiple isoenzymes (clozapine)	moderate
ketoconazole, fluconazole		Inhibits 3A4 (quetiapine levels increased)	high moderate
ritonavir		Inhibits 3A4 (risperidone)	high
valproate		Inhibits 2C9 not normally involved in SGA metabolism (case reports of increased quetiapine levels)	moderate

* The SGAs affected are listed in parenthesis

Table 11. Medications that decrease plasma concentrations of SGAs[64]

Drug/class	SGA affected and mechanism*	Clinical significance
phenobarbital	Induces 1A2, 3A4 (clozapine)	moderate
carbamazepine	Induces 1A2, 3A4 (decrease in clozapine, risperidone, paliperidone, olanzapine, quetiapine, ziprasidone)	high-moderate
cigarette smoking	Induces 1A2 (decrease in clozapine, olanzapine)	moderate
phenytoin	Induces 3A4 (quetiapine)	moderate

* The SGA's affected are listed in parenthesis

Table 12. Pharmacodynamic interactions with SGAs[58]

Drug/class	Examples	SGA affected and mechanism*	Clinical significance
anticholinergics	benztropine, antihistamines	Additive atropine-like effects: dry mouth, blurred vision, constipation (clozapine, olanzapine)	moderate
tricyclic antidepressants	amitriptyline, nortriptyline	Additive hypotension, sedation anticholinergic effects (clozapine, olanzapine)	moderate
antihypertensives	clonidine, methyldopa, doxazosin, terazosin, prazosin	Additive hypotension (clozapine)	moderate
anxiolytics	lorazepam, clonazepam	Increased sedation (clozapine, olanzapine, quetiapine)	moderate
bone marrow suppressants	carbamazepine, captopril, sulfonamides, procainamide, propylthiouracil, sulfasalazine	May increase the risk or severity of agranulocytosis with clozapine	high
CNS depressants	alcohol	Increased sedation (clozapine, olanzapine, quetiapine)	moderate

* The SGAs affected are listed in parenthesis

If Ms. Gibbon does not respond sufficiently to clozapine, are there any other options for treatment?

There is limited evidence to guide clinicians when it comes to deciding what strategy to follow if the patient has not responded to clozapine. Several adjunctive medication and combination strategies have been tried, but only a few double-blind studies have been published. Adjunctive medication in schizophrenia refers to the addition of a non-antipsychotic drug to an antipsychotic. Combination strategies refer to the combination of two antipsychotics. The following is a brief synopsis of the results of the double-blind studies with clozapine using adjunctive medication and combination methods. Other combinations besides those involving clozapine exist, but they are beyond the scope of this study program.

Adjunctive medication with clozapine:

- **lithium:** 4-week double-blind (DB) crossover study; lithium was added to clozapine in patients with schizophrenia and schizoaffective disorder; the dose of lithium was titrated to achieve levels of 0.5 nmol/L. No improvement was noted in patients with schizophrenia.[65] Another small trial evaluated the addition of lithium and divalproex to clozapine treatment versus clozapine alone.[66] Although all treatment groups improved in 6 months, the patients using divalproex and lithium had greater improvement in the first month. There was also a greater trend for more weight gain and higher blood glucose in the patients treated with the combination of lithium and clozapine.[66]
- **lamotrigine:** Although early work showed promise for lamotrigine as an addition to clozapine in treatment resistant schizophrenia,[67] a Cochrane Collaboration review of the topic and a more recent clinical trial question the effects of earlier trials and both authors concluded there is little data to recommend adjunctive lamotrigine.[68,69] The combination of lamotrigine and clozapine should be used with caution, as both agents may cause bone marrow suppression.
- **fluoxetine:** 8-week DB parallel group trial of clozapine and fluoxetine; mean dose of fluoxetine was 48.9 mg/d. No difference in efficacy was seen between the 2 groups.[70]
- **mirtazapine:** 8-week DBPC trial of clozapine and mirtazapine; mirtazapine dose was 30 mg/d. Clozapine/mirtazapine group had significantly greater reductions in total Brief Psychiatric Rating Scale (BPRS) and Schedule for Assessment of Negative Symptoms (SANS).[71]
- **combination antipsychotics:** Many clinicians are trying a combination of antipsychotics for treatment-resistant schizophrenia. Some physicians will use a combination of an FGA with an SGA or two SGAs. Although these combinations are being used more frequently, there are very few controlled studies evaluating the efficacy, and a potential exists for increased drug interactions and adverse effects. Clozapine has been used with the SGAs zisprasidone, risperidone, and quetiapine. There is a review of the com-

bination of clozapine and risperidone therapy.[72] The authors found 15 clinical trials that used this combination. The mean clozapine dose for these trials was 474.2 mg/day and the mean risperidone dosage 4.7 mg/day. Significant improvement was seen in 43% of patients. The authors concluded there is encouraging evidence for the combination of risperidone with clozapine in treatment resistant patients.[72]

- **essential fatty acids:** Essential fatty acids are polyunsaturated fatty acids that cannot be synthesized by the body and are only available from diet. There is some conflicting evidence that the intake of a certain omega 3 fatty acids (ethyleicosapentanoate or E-EPA) may help to reduce symptoms in patients with schizophrenia.[73] Although the results with E-EPA look positive, a Cochrane Collaboration review suggests the positive effects are inconclusive due to a limited number of studies.[73]

2.5 Role of the pharmacist in treating patients with schizophrenia

Schizophrenia is a complex condition that significantly impairs the lives of the people it affects. Not only are these patients commonly stigmatized due to their condition, but people with schizophrenia are at increased risk of premature death.

Pharmacists are in an optimal role to help these patients achieve their best possible outcomes. By working in the health care team they can work to limit adverse effects, improve adherence, and optimize the efficacy of a patient's antipsychotic therapy. Pharmacists can work with the patient and their caregivers to provide current information regarding the condition and correct any misconceptions about the therapy and schizophrenia.

Through listening and working as a patient advocate, pharmacists can help to improve the quality of life of this often-forgotten patient population.

References

1. Lehman AF, Lieberman JA, Dixon LB, et al. Practice guideline for the treatment of patients with schizophrenia, second edition. Am J Psychiatry. 2004;161(2 Suppl):1–56.
2. Tandon R, Keshavan MS, Nasrallah HA. Schizophrenia, "Just the Facts": What we know in 2008: Part 1: Overview. Schizophrenia Research. 2008;100(1–3):4–19.
3. Saha S, Chant D, McGrath J. A systematic review of mortality in schizophrenia: is the differential mortality gap worsening over time? Arch Gen Psychiatry. 2007;64(10):1123–1131.
4. Goeree R, Farahati F, Burke N, et al. The economic burden of schizophrenia in Canada in 2004. Curr Med Res Opin. 2005;21(12):2017–2028.
5. Tandon R, Keshavan MS, Nasrallah HA. Schizophrenia, "Just the Facts" What we know in 2008. 2. Epidemiology and etiology. Schizophrenia Research. 2008;102(1–3):1–18.
6. Meader-Woodruff J. Update on Dopamine Receptors. Annals of Clinical Psychiatry. 1994;6(2):79–89.
7. Reynolds GP. Dopamine receptors and schizophrenia. Biochem Soc Trans. 1996;24(1):202–205.
8. Goto Y, Grace AA. The Dopamine System and the Pathophysiology of Schizophrenia: A Basic Science Perspective. In: Integrating the Neurobiology of Schizophrenia.Vol Volume 78. Academic Press; 2007:41–68. www.sciencedirect.com.myaccess.library.utoronto.ca/science/article/B7CV0–4N6Y5T2–2/2/17561f7966d2a8f023d88b2eac7a34ef, accessed January 11, 2009.
9. Reynolds GP. Receptor Mechanisms in the treatment of Schizophrenia. J Psychopharmacol. 2004;18(3):340–345.
10. Abi-Dargham A, Laruelle M, Aghajanian GK, Charney D, Krystal J. The role of serotonin in the pathophysiology and treatment of schizophrenia. J Neuropsychiatry Clin Neurosci. 1997;9(1):1–17.
11. Schmidt CJ, Kehne JH, Carr AA, et al. Contribution of serotonin neurotoxins to understanding psychiatric disorders: the role of 5-HT_2 receptors in schizophrenia and antipsychotic activity. Int Clin Psychopharmacol. 1993;8 Suppl 2:25–32.
12. Kapur S, Remington G. Serotonin-dopamine interaction and its relevance to schizophrenia. Am J Psychiatry. 1996;153(4):466–476.
13. Halberstadt AL. The phencyclidine-glutamate model of schizophrenia. Clin Neuropharmacol. 1995;18(3):237–249.
14. Goff DC, Wine L. Glutamate in schizophrenia: clinical and research implications. Schizophrenia Research. 1997;27(2–3):157–168.
15. Swartz MS, Perkins DO, Stroup TS, et al. Effects of Antipsychotic Medications on Psychosocial Func-

tioning in Patients With Chronic Schizophrenia: Findings From the NIMH CATIE Study. Am J Psychiatry. 2007;164(3):428–436.
16. Lieberman JA, Stroup TS, McEvoy JP, et al. Effectiveness of Antipsychotic Drugs in Patients with Chronic Schizophrenia. N Engl J Med. 2005;353(12):1209–1223.
17. Stroup TS, Lieberman JA, McEvoy JP, et al. Effectiveness of Olanzapine, Quetiapine, and Risperidone in Patients With Chronic Schizophrenia After Discontinuing Perphenazine: A CATIE Study. Am J Psychiatry. 2007;164(3):415–427.
18. Manschreck TC, Boshes RA. The CATIE - Schizophrenia Trial: Results, Impact, Controversy. Harvard Review of Psychiatry. 2007;15(5):245.
19. Swartz MS, Stroup TS, McEvoy JP, et al. What CATIE Found: Results From the Schizophrenia Trial. Psychiatr Serv. 2008;59(5):500–506.
20. McEvoy JP, Lieberman JA, Stroup TS, et al. Effectiveness of Clozapine Versus Olanzapine, Quetiapine, and Risperidone in Patients With Chronic Schizophrenia Who Did Not Respond to Prior Atypical Antipsychotic Treatment. Am J Psychiatry. 2006;163(4):600–610.
21. Stroup TS, Lieberman JA, McEvoy JP, et al. Results of phase 3 of the CATIE schizophrenia trial. Schizophrenia Research. 2009;107(1):1–12.
22. Leucht S, Corves C, Arbter D, et al. Second-generation versus first-generation antipsychotic drugs for schizophrenia: a meta-analysis. The Lancet. 373(9657):31–41.
23. Clinical practice guidelines. Treatment of schizophrenia. Can J Psychiatry. 2005;50(13 Suppl 1):7S-57S.
24. Mental Health: A Report of the Surgeon General - Chapter 4. www.surgeongeneral.gov/library/mentalhealth/chapter4/sec4.html#table4_7, accessed January 23, 2009.
25. Schizophrenia Symptoms. www.schizophrenia.com/diag.php#common, accessed January 23, 2009.
26. Noel JM. ASHP therapeutic position statement on the use of second-generation antipsychotic medications in the treatment of adults with psychotic disorders. Am J Health Syst Pharm. 2007;64(8):863–876.
27. Meltzer HY. What's atypical about atypical antipsychotic drugs? Current Opinion in Pharmacology. 2004;4(1):53–57.
28. Houthoofd SA, Morrens M, Sabbe BG. Cognitive and psychomotor effects of risperidone in schizophrenia and schizoaffective disorder. Clinical Therapeutics. 2008;30(9):1565–1589.
29. Ganguli R. Rationale and strategies for switching antipsychotics. Am J Health Syst Pharm. 2002;59(22 Suppl 8):S22-S26.
30. Burns T, Chabannes JP, Demyttenaere K. Switching antipsychotic medications: general recommendations and switching to amisulpride. Curr Med Res Opin. 2002;18(4):201–208.
31. Ereshefsky L, Lacombe S. Pharmacological profile of risperidone. Can J Psychiatry. 1993;38 Suppl 3:S80-S88.
32. Green B. Focus on Risperidone. Current Medical Research and Opinion. 2000;16:57–65.
33. Simpson GM, Lindenmayer JP. Extrapyramidal symptoms in patients treated with risperidone. J Clin Psychopharmacol. 1997;17(3):194–201.
34. Dolder C, Nelson M, Deyo Z. Paliperidone for schizophrenia. Am J Health Syst Pharm. 2008;65(5):403–413.
35. Nussbaum A, Stroup T. Paliperidone for the treatment of adults with schizophrenia. Cochrane Database of Systematic Reviews. 1912;2008(2).
36. Singh AC, Massey AJ, Thompson MD, Rappa LR, Honeywell MS. Addressing Nonadherence in the Schizophrenic Population. Journal of Pharmacy Practice. 2006;19(6):361–368.
37. Thieda P, Beard S, Richter A, Kane J. An Economic Review of Compliance With Medication Therapy in the Treatment of Schizophrenia. Psychiatr Serv. 2003;54(4):508–516.
38. Ward A, Ishak K, Proskorovsky I, Caro J. Compliance with refilling prescriptions for atypical antipsychotic agents and its association with the risks for hospitalization, suicide, and death in patients with Schizophrenia in Quebec and Saskatchewan: A retrospective database study. Clinical Therapeutics. 2006;28(11):1912–1921.
39. Gilmer TP, Dolder CR, Lacro JP, et al. Adherence to Treatment With Antipsychotic Medication and Health Care Costs Among Medicaid Beneficiaries With Schizophrenia. Am J Psychiatry. 2004;161(4):692–699.
40. Pfeiffer PN, Ganoczy D, Valenstein M. Dosing Frequency and Adherence to Antipsychotic Medications. Psychiatr Serv. 2008;59(10):1207–1210.
41. Möller H. Long-acting injectable risperidone for the treatment of schizophrenia: clinical perspectives. Drugs. 2007;67(11):1541–1566.
42. Canadian Pharmacists Association. e-Therapeutics+ : e-CPS : Drug Monographs : Risperdal Consta. www.e-therapeutics.ca, accessed January 24, 2009.
43. Möller H. Long-acting risperidone: Focus on safety. Clinical Therapeutics. 2006;28(5):633–651.
44. Love RC. Strategies for increasing treatment compliance: the role of long-acting antipsychotics. Am J Health Syst Pharm. 2002;59(22 Suppl 8):S10-S15.
45. Newcomer JW. Second-generation (atypical) antipsychotics and metabolic effects: a comprehensive literature review. CNS Drugs. 2005;19 Suppl 1:1–93.
46. Haupt DW. Differential metabolic effects of antipsychotic treatments. European Neuropsychopharmacology. 2006;16(Supplement 3):S149-S155.
47. Bushe C, Haddad P, Peveler R, Pendlebury J. The role of lifestyle interventions and weight management in schizophrenia. J Psychopharmacol.

2005;19(6_suppl):28–35.
48. Koller E, Schneider B, Bennett K, Dubitsky G. Clozapine-associated diabetes. Am J Med. 2001;111(9):716–723.
49. Koller EA, Doraiswamy PM. Olanzapine-associated diabetes mellitus. Pharmacotherapy. 2002;22(7):841–852.
50. Koller EA, Cross JT, Doraiswamy PM, Schneider BS. Risperidone-associated diabetes mellitus: a pharmacovigilance study. Pharmacotherapy. 2003;23(6):735–744.
51. Koller EA, Weber J, Doraiswamy PM, Schneider BS. A survey of reports of quetiapine-associated hyperglycemia and diabetes mellitus. J Clin Psychiatry. 2004;65(6):857–863.
52. American Diabetes Association. Consensus Development Conference on Antipsychotic Drugs and Obesity and Diabetes. Diabetes Care. 2004;27:596–601.
53. Weiden PJ, Daniel DG, Simpson G, Romano SJ. Improvement in indices of health status in outpatients with schizophrenia switched to ziprasidone. J Clin Psychopharmacol. 2003;23(6):595–600.
54. Weiden PJ, Loebel A, Yang R. Course of weight and metabolic benefits one year after switching to ziprasidone. In: the Annual Meeting of the American Psychiatric Association. New York; 2004.
55. Canadian Pharmacists Association. e-Therapeutics+ : e-CPS : Drug Monographs: Zeldox. www.e-therapeutics.ca, accessed January 24, 2009.
56. Canadian Pharmacists Association. e-Therapeutics+ : e-CPS : Drug Monographs: Seroquel. www.e-therapeutics.ca, accessed January 24, 2009.
57. Hales RE, Yudofsky SC, Gabbard GO, eds. The American Psychiatric Publishing Textbook of Psychiatry. 5th ed. American Psychiatric Publishing; 2008:1786.
58. Bezchlibnyk-Butler K, Jeffries J, Virani A. Clinical Handbook of Psychotropic Drugs. 17th ed. Hogrefe; 2007.
59. Mental Health Prescribing Group. Algorithm for antipsychotic treatment of schizophrenia. www.nhstaysideadtc.scot.nhs.uk/approved/policy/algorant.pdf, accessed January 23, 2009.
60. International Psycopharmacology Algorithm Project. IPAP Schizophrenia Algoritm. www.ipap.org/pdf/schiz/IPAP_Schiz_flowchart20060327.pdf, accessed January 25, 2009.
61. Texas Medication Algorithm Project Procedural Manual. Schizophrenia Treatment Algorithms. www.dshs.state.tx.us/mhprograms/pdf/Schizophrenia-Manual_060608.pdf, accessed January 25, 2009.
62. Milliken H. e-Therapeutics+ – Psychoses. www.e-therapeutics.ca, accessed October 18, 2008.
63. Schulte PF. What is an Adequate Trial with Clozapine? Therapeutic Drug Monitoring and Time to Response in Treatment-Refractory Schizophrenia. Clinical Pharmacokinetics. 2003;42:607–618.
64. Spina E, de Leon J. Metabolic drug interactions with newer antipsychotics: a comparative review. Basic Clin Pharmacol Toxicol. 2007;100(1):4–22.
65. Small JG, Klapper MH, Malloy FW, Steadman TM. Tolerability and efficacy of clozapine combined with lithium in schizophrenia and schizoaffective disorder. J Clin Psychopharmacol. 2003;23(3):223–228.
66. Kelly DL, Conley RR, Feldman S, et al. Adjunct divalproex or lithium to clozapine in treatment-resistant schizophrenia. Psychiatr Q. 2006;77(1):81–95.
67. Tiihonen J, Hallikainen T, Ryynänen O, et al. Lamotrigine in treatment-resistant schizophrenia: a randomized placebo-controlled crossover trial. Biol Psychiatry. 2003;54(11):1241–1248.
68. Premkumar TS, Pick J. Lamotrigine for schizophrenia. Cochrane Database Syst Rev. 2006;(4):CD005962.
69. Goff DC, Keefe R, Citrome L, et al. Lamotrigine as add-on therapy in schizophrenia: results of 2 placebo-controlled trials. J Clin Psychopharmacol. 2007;27(6):582–589.
70. Buchanan RW, Kirkpatrick B, Bryant N, Ball P, Breier A. Fluoxetine augmentation of clozapine treatment in patients with schizophrenia. Am J Psychiatry. 1996;153(12):1625–1627.
71. Zoccali R, Muscatello MR, Cedro C, et al. The effect of mirtazapine augmentation of clozapine in the treatment of negative symptoms of schizophrenia: a double-blind, placebo-controlled study. Int Clin Psychopharmacol. 2004;19(2):71–76.
72. Kontaxakis V, Ferentinos P, Havaki-Kontaxaki B, et al. Risperidone augmentation of clozapine. European Archives of Psychiatry and Clinical Neuroscience. 2006;256(6):350–355.
73. Joy CB, Mumby-Croft R, Joy LA. Polyunsaturated fatty acid supplementation for schizophrenia. Cochrane Database Syst Rev. 2006;3:CD001257.

Questions

You are working at your busy pharmacy with your pharmacy intern, Allan, when your regular patient Roger comes in with a prescription for citalopram 20 mg daily. You have developed a relationship with Roger over the last several years and you know that he was diagnosed with schizophrenia about 5 years ago. He has told you on previous interactions that before he was diagnosed he started to hear whispers that nobody else could hear. He also became more suspicious of everything and everyone, as he felt that everyone was talking about him. For this reason he became more comfortable spending more time in his parents' basement sleeping and watching television.

When you approach him you notice that he doesn't really say much and hands you the prescription and heads to your waiting area. You pull up his profile and see the following:

- *Roger S.*
- *30 years old*
- *Current medications: olanzapine 20 mg HS for the last 3 years*

Allan is starting to look a bit worried, as he has not counselled a patient with schizophrenia and was wondering if you could provide him some information on schizophrenia so he has a better understanding of the condition.

1. Allan remembers from school the about the dopamine hypothesis and the pathophysiology of the condition. When discussing the pathophysiology of schizophrenia with Allan, which of the following statements is appropriate to use?
   a. The positive and negative symptoms of schizophrenia are due to dopamine excess.
   b. Affinity to the D2 receptor has been linked to improvements in the positive symptoms.
   c. Blocking the dopamine in the mesocortical dopamine pathway is responsible for extrapyramidal adverse effects.
   d. Blocking dopamine receptors in the nigrostriatal pathway can lead to amenorrhea.

2. Allan wants to know more about the condition before talking to Roger. When discussing risk factors with Roger, which of the following statements is **true**?
   a. If one monozygotic (identical) twin has schizophrenia, the risk of schizophrenia in the second is close to 100%.
   b. Schizophrenia is strictly a neurotransmitter abnormality and if corrected the patient would be cured.
   c. Environmental risk factors for this condition include lower socioeconomic status and living in a city.
   d. Schizophrenia is more common in men than women.

3. Allan asks if you know anything about the Canadian incidence of the condition. Which of the following statements would be appropriate to tell Allan?
   a. Schizophrenia accounts for 1 in 12 Canadian hospital beds.
   b. The lifetime prevalence is 1.3%.
   c. The estimated cost of schizophrenia in Canada exceeds 5 billion dollars.
   d. Schizophrenia is responsible for a quarter of all repeat admissions for mental illness.

4. Allan remembers seeing some information regarding the CATIE trials at school. Which of the following was found from the CATIE Phase 1 trial?
   a. Approximately 26% of the patients completed the trial on their initially randomized medication.
   b. Perphenazine had significantly higher EPS than the second-generation antipsychotics.
   c. Zisprasidone was the best-tolerated medication in the trial.
   d. Risperidone showed the greatest efficacy based on time to discontinuation.

5. Phase 2 of the CATIE trial showed that:
   a. perphenazine was less effective than SGAs
   b. clozapine was better tolerated than olanzapine and risperidone
   c. clozapine demonstrated better effectiveness compared to other SGAs
   d. improvements in cognition were significant with perphenazine and all SGAs

6. After your overview of the condition, you start to evaluate Roger and his new prescription. Which of Roger's following symptoms are positive symptoms?

a. hearing whispers that nobody else hears
b. spending most of the time in his parents' basement
c. lack of conversation
d. all of the above are positive symptoms of schizophrenia

7. Allan remembers that olanzapine has been associated with significant weight gain. How often should Roger have his fasting blood glucose checked?

a. every 4 weeks
b. every 8 weeks
c. quarterly
d. annually

8. When looking at Roger's prescription for citalopram, which of the following is an appropriate course of action?

a. Fill the prescription as usual.
b. Fill the prescription but warn Roger that it can increase his olanzapine levels and lead to more adverse effects.
c. Call his physician to change the prescription to another class of antidepressants.
d. Talk to Roger, as he does not need citalopram, as he is likely non-adherent with his antipsychotic.

You bring Roger into your semi-private counselling area (an area he is comfortable with). He opens up a bit about the reason for the citalopram prescription. He has been feeling down, as he has gained about 20 kg since starting on the olanzapine. He was told today that he has prediabetes. He wants to implement some lifestyle changes to help improve his health.

9. He currently smokes about a pack of cigarettes per day and is thinking of quitting. Which of the following would be appropriate to recommend to Roger?

a. Smoking cessation is very difficult for people with his condition and he should not even attempt it.
b. He should talk to his doctor first, as he may need to change the olanzapine to clozapine.
c. He should talk to his doctor first, has he may need to decrease his olanzapine dose.

10. Roger also drinks approximately 10 cups of coffee a day and is looking at cutting back. Which of following is a good recommendation for Roger?

a. He should see his doctor, as this may increase his olanzapine level.
b. He should see his doctor, as this may decrease his olanzapine level.
c. He shouldn't worry, as this will not likely have any effect on his olanzapine therapy.

11. Roger says that the last time he was in the hospital he heard there was a treatment that is less likely to cause weight gain. Which of the following therapies is least likely to cause weight gain?

a. quetiapine
b. risperidone
c. clozapine
d. ziprasidone

Cameron enters the pharmacy and hands you a prescription for clarithromycin 250 mg bid for 10 days. He says the doctor at the walk-in clinic wanted to double-check if it was OK with his other medication. When you look up his file you see the following:

- *Cameron J.*
- *28 years old*
- *Risperidone 3 mg bid (30-day supply) last filled 45 days ago*

He mentioned that he is using the clarithromycin for a chest infection. You notice from his profile that he has been non-adherent to his risperidone therapy.

12. What is the appropriate course of action for the clarithromycin prescription?

a. Fill it as usual.
b. Change to another medication.

13. Which of the following statements regarding non-adherence with antipsychotics is **false**?

a. Patients who are non-adherent are at an increased risk of hospitalization.
b. Substance abuse is a risk factor for non-adherence.
c. The risk of relapse is approximately 7.8 times as high in non-adherent patients.
d. Non-adherence with antipsychotics is approximately 50%.

14. When you talk to Cameron about his therapy, he wonders if he would be a candidate for long-acting risperidone. If we were to start Cameron on risperidone long-acting injection, which of the following would be the most appropriate way to initiate his therapy?

a. Stop oral risperidone and start long-acting risperidone on the same day.
b. Taper oral risperidone until he is off, then start risperidone long-acting injection.
c. Continue on oral risperidone for 3 weeks, start long-acting injection (given q 2 weeks), and quickly increase the dosage until the level is therapeutic.
d. Continue on oral risperidone for 3 weeks, start long-acting injection (given q 2 weeks), and increase the dosage no sooner than every 4 weeks.

15. If Cameron is non-adherent due to sexual dysfunction adverse effects from risperidone, a change to which second-generation antipsychotic is the **least** likely to improve this adverse effect?

a. quetiapine
b. paliperidone
c. olanzapine
d. ziprasidone

16. When discussing non-adherence with Cameron, which of the following strategies would be the **least** appropriate?

a. Explain to Cameron that even though his symptoms may seem better, his condition, like other medical conditions, requires long-term therapy.
b. Check for the reason for non-adherence, and if it is an adverse effect, explain that it is possible it may go away or we can work together to find another treatment option.
c. Tell Cameron he has no choice and he simply has to take the medication or he won't get any better.
d. Empathize with Cameron of the difficulty of his condition, show genuine concern, and work with him to develop a solution to improve adherence.

You notice Charles, one of your regular patients, in your store. You have developed a rapport with him over the last several years and he came to ask you a question regarding his schizophrenia medication. He has been taking quetiapine 300 mg bid to help control his symptoms but he has found some of his symptoms have been coming back. He was on risperidone therapy 2 years ago. His psychiatrist has recommended that he change his regimen to clozapine. He has heard that it has quite a few side effects and because he knows and trusts you he wanted to discuss them with you. He wants to know as much as you can tell him about this drug and its side effects.

17. Clozapine has a:

a. low risk of sedation
b. low risk of blurred vision, urinary retention, and constipation
c. high risk of sexual side effects
d. high risk of an increase in total cholesterol

18. When discussing the possible change to clozapine for Charles, which of the following statements is the most appropriate?

a. This change is appropriate, as Charles is having an increase in his symptoms and clozapine may help for patients who fail on other antipsychotics.
b. This change is appropriate, as most patients with schizophrenia will eventually require clozapine therapy.
c. This change is not appropriate, as a change to any SGA is likely to produce the same effect as clozapine.
d. This change is not appropriate, as the cost of monitoring and risk of adverse effects is too high for most patients with schizophrenia.

19. Charles heard that he has to have a large amount of monitoring for a possible blood problem. When discussing monitoring with Charles, which of the following is appropriate to include?

a. Severe problems occur in about 5% of people on clozapine.
b. All patients on clozapine must be registered in a national database, to prevent people who have had the blood problem from taking clozapine again.
c. The risk of this problem is the highest in the first year of treatment.
d. He will have to have a blood test every 4–6 weeks.

20. Charles decides to take the clozapine therapy. He wants to know if there are any other options if the clozapine doesn't work. Which of the following could be considered to add to his clozapine if it was not effective?

a. lithium
b. risperidone
c. fluoxetine
d. lamotrigine