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Atypical Antipsychotics: Overview, Metabolic Abnormalities, and Newer Agents

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Mona T. Thompson has no relevant financial relationships to disclose.

Goal. The goal of this lesson is to provide an overview of atypical antipsychotics that are commonly prescribed for schizophrenia and bipolar disorder; summarizing available comparative data regarding efficacy, tolerability, and adverse events of the most recently approved agents which are iloperidone (Fanapt®), asenapine (Saphris®), and lurasidone (Latuda®).

Objectives. At the completion of this activity, the participant will be able to:

1. compare and contrast the effectiveness and side effects of the first and second generation antipsychotics;
2. demonstrate an understanding of the role that second generation antipsychotics (SGAs), also known as atypical antipsychotics, play in the treatment of schizophrenia and bipolar disorder;
3. demonstrate an understanding of the SGA-induced metabolic abnormalities and their management; and
4. recognize the indications, mechanisms of actions, dosages, common adverse events, warnings (including black box warnings), precautions, and counseling points of three recently approved SGAs.

Background

Antipsychotic medications are indicated for the treatment of schizophrenia, bipolar disorder, and in some cases major depressive disorders. In addition, antipsychotic agents are increasingly being prescribed off-label for various other mental disorders including agitation in dementia, anxiety, obsessive-compulsive disorder, autism, developmental disorders, delirium, aggressive behavior, personality disorders, and post-traumatic stress disorder.

Antipsychotics are divided into two groups: first generation antipsychotics (FGAs) or typical antipsychotics; and second generation antipsychotics (SGAs), commonly referred to as atypical antipsychotics. The first generation antipsychotics were developed in the 1950s and include agents such as haloperidol, chlorpromazine, fluphenazine, thioridazine, thiothixene, and pimozide. These agents are effective in treating the positive symptoms of psychosis such as hallucinations and delusions. However, FGAs do not adequately treat many of the other problematic aspects of psychiatric illness such as negative symptoms, cognitive impairment, and affective symptoms. They are also largely associated with extrapyramidal side effects (EPS) at clinically effective doses, including dystonic reactions (sustained muscle contractions), drug-induced parkinsonism (characterized by tremors, postural instability, and rigidity), akathisia (inability to remain motionless), and tardive dyskinesia (involuntary, repetitive body movements).

Overview of Second Generation Antipsychotics (SGAs)

Second generation antipsychotics were developed in an effort to find more effective agents with fewer and more manageable side effects. The first of these was clozapine, which was clinically introduced in 1989. Since then, nine other oral atypical antipsychotics have been brought to market: risperidone (1993), olanzapine (1996), quetiapine (1997), ziprasidone (2001), aripiprazole (2002), paliperidone (2006), asenapine (2009), iloperidone (2009), and finally lurasidone (2010).

While the pharmacologic properties, therapeutic effects, and adverse events vary between FGAs and SGAs, the most accepted distinction is that the newer, second generation antipsychotics tend to have a decreased risk of extrapyramidal side effects compared to FGAs. This is possibly due to their lower affinity for the dopamine 2, or D_2 receptor. These agents predominantly work on dopamine and serotonin receptors in the central nervous system, as well as cholinergic, adrenergic, and histaminergic receptors. The degree and selectivity of receptor inhibition varies between antipsychotic classes and agents which results in the differing side effect profiles that are observed. SGAs differ from

Table 1
SGA adult dosing* and formulations for schizophrenia and bipolar disorder

SGA	Schizophrenia Dosing** (Max)	Bipolar Disorder Dosing (Max)	Formulations
Aripiprazole	10-15 mg/day (30 mg/day)	15 mg/day (30 mg/day)	tablet, ODT, oral solution, IM§
Asenapine	5-10 mg BID (20 mg/day)	5-10 mg BID (20 mg/day)	SL tablet (regular and cherry)
Clozapine	300-400 mg/day (900 mg/day)	N/A	tablet
Iloperidone	6-12 mg BID (24 mg/day)	N/A	tablet
Lurasidone	40-160 mg/day (160 mg/day)	20-120 mg/day (120 mg/day)	tablet
Olanzapine	5-10 mg/day (10 mg/day)	10-15 mg/day	tablet, ODT, IM§
Paliperidone	3-12 mg/day (12 mg/day)	N/A	ER (extended release) tablet
Paliperidone	117-234 mg/month	N/A	ER-IM
Quetiapine	150-750 mg/day (750 mg/day)	400-800 mg/day (800 mg/day)	tablet
Quetiapine XR	400-800 mg/day (800 mg/day)	400-800 mg/day (800 mg/day)	ER (extended release) tablet
Risperidone	4-16 mg/day	1-6 mg/day	tablet, ODT, oral solution
Risperidone	12.5-50 mg/2 weeks (50 mg)	12.5-50 mg/2 weeks (50 mg)	IM (long-acting injection)
Ziprasidone	20-100 mg BID (200 mg/day)	40-80 mg BID	capsule, IM§

*From patient package inserts; **Acute phase dosing; §Indicated for agitation associated with schizophrenia and bipolar disorder
ODT: oral disintegrating tablet; IM: intramuscular; SL: sublingual tablet; ER-IM: extended-release intramuscular

the first generation agents, as the serotonin 5-HT_2 receptor binding can exceed their affinity for dopamine D_2 receptors. This inhibition of 5-HT_2 may be one justification for the lower risk of EPS.

In general, SGAs are better tolerated and many of them are more effective than the older agents at treating negative, cognitive, and affective symptoms associated with schizophrenia. Unfortunately, their use is associated with weight gain, diabetes, and an atherogenic lipid profile, all of which are risk factors for the development of cardiovascular disease (CVD).

Other noteworthy side effects, warnings, and precautions associated with SGAs include hyperprolactinemia, neuroleptic malignant syndrome, blood dyscrasias (leukopenia, neutropenia, and agranulocytosis). There are black box warnings with all the SGAs for increased risk of mortality when used to treat dementia-related psychosis in elderly patients. Iloperidone, quetiapine, and ziprasidone are associated with the highest risk for QTc prolongation; asenapine, clozapine, olanzapine, paliperidone, and risperidone exhibit this effect to a lesser degree. Aripiprazole and lurasidone have no clinically relevant QTc effect. Additionally, black box warnings for aripiprazole, quetiapine, and lurasidone include increased suicidal thoughts and behaviors in children, adolescents and young adults. Understanding the varying degrees of severity of side effects is critical to selecting appropriate therapies for patients and maximizing adherence.

In addition to oral tablets, several antipsychotic medications are available in other formulations. Rapid-disintegrating tablets and liquid formulations for oral or intramuscular administration can be used in emergency situations, or for patients who have difficulty swallowing. Rapid-disintegrating formulations may be useful in patients suspected of "cheeking" or concealing oral tablets in their mouths to later dispose of them. Long-acting injectable antipsychotic agents may be used in patients with repeated nonadherence to pharmacological treatment.

A summary of various dosing formulations and approved dosing ranges for each of the 10 SGAs is listed in Table 1. The next sections of this lesson will very broadly discuss the role of atypical antipsychotics in the treatment of schizophrenia and bipolar disorder. Individual product information leaflets and up-to-date treatment recommendations should be referred to for more comprehensive guidance.

Atypical Antipsychotic Use in Schizophrenia

Schizophrenia is a complex disorder characterized by delusions, hallucinations, inappropriate affect, and impaired psychosocial functioning. According to the Centers for Disease Control and Prevention (CDC), worldwide prevalence of schizophrenia ranges from 0.5 to 1 percent. This disorder affects men and women at equal rates; however, the first episode usually occurs earlier in men (early twenties) than women (late twenties). Suicide is common in schizophrenic persons; approximately one third of patients with this disorder will attempt suicide, and one in 10 will succeed in taking their own lives.

Symptoms of schizophrenia are divided into three broad categories: positive, negative, and cognitive. Positive symptoms consist of hallucinations, delusions, thought disorders (disorganized thinking), and movement disorders. Negative symptoms refer to disruptions of normal emotions and behaviors, and include flat affect and lack of pleasure in everyday life. Examples of cognitive symptoms include poor executive functioning and trouble focusing or paying attention.

Antipsychotics are first-line treatment for schizophrenia. The selection and use of antipsychotics

must be individualized based on the patient's past medication history, current symptoms and concomitant conditions. Additionally, recognizing the different phases of illness (acute, stabilization, and stable), guides treatment selection and drug dosing. Systematic reviews and meta-analyses have not strongly concluded that any of the antipsychotics are more effective than any other for acute schizophrenia, with the exception of clozapine. Therefore, the side effect and tolerability profile and cost effectiveness are utilized to make therapy selection. The Schizophrenia Patient Outcomes Research Team (PORT) recommended treating initial, acute episodes with antipsychotics other than clozapine or olanzapine, because both are associated with greater weight gain, insulin resistance, and dyslipidemia compared to the others. Additionally, Schizophrenia PORT recommended that first-episode patients receive antipsychotic doses in the lower half of the recommended dose range.

The American Psychiatric Association recommends that second generation agents, with the exception of clozapine, should be considered for initial therapy in patients in the acute phase of schizophrenia. However, the guideline notes that, in some instances, first generation agents may be an appropriate first-line option. Debate over the relative advantages and disadvantages of first and second generation agents continues. As older second generation drugs come off patent and newer drugs (e.g., asenapine, iloperidone, lurasidone, and paliperidone) are marketed, cost effectiveness should be considered.

A patient experiencing partial or no response to the first SGA should be trialed on a different second generation or a first generation antipsychotic. Patients not adequately responding after trials with at least two different SGAs may be initiated on clozapine monotherapy. Clozapine is generally reserved for refractory cases, although it can be considered sooner if the patient has a history of suicidality, violence, or co-morbid substance abuse. Treatment-resistant schizophrenics have been shown to have greater rates of improvement with the use of clozapine compared to many other antipsychotic options. However, clozapine use is reserved due to its black box warnings (i.e., agranulocytosis, orthostatic hypotension, seizure, myocarditis and cardiomyopathy, and increased mortality in elderly patients with dementia-related psychosis). The most common potentially fatal adverse effect of clozapine is agranulocytosis. This occurs in approximately one percent of all patients using the drug. Because of this risk, clozapine is only available through a REMS (Risk and Evaluation Mitigation Strategies) program, in which prescribers, patients and pharmacies must be enrolled. FDA requires baseline monitoring of white blood cell count and absolute neutrophil count, as well as monitoring throughout treatment. If the patient is still refractory after clozapine monotherapy, other medications and adjuncts, such as electroconvulsive therapy (ECT), can be tried based on the physician's experience.

Once the patient has entered the stable or maintenance phase, antipsychotic medication should be continued at the dose that was effective during the acute phase. This has shown to reduce the rate of relapse at one year. It is unknown what the ideal duration of maintenance therapy should be for stable patients, but some experts recommend treatment indefinitely. Patients with schizophrenia may also require treatment for comorbid conditions, such as agitation, depression, anxiety, and substance abuse.

Antipsychotic Use in Bipolar Disorder

Bipolar disorder, also known as manic depressive illness, is a mood disorder that is thought to be genetic, causing unusual shifts in mood, energy, activity levels, and the inability to carry out day-to-day activities. The disease consists of episodes of mania or hypomania, as well as mixed episodes of concurrent major depression and mania or hypomania.

A manic episode is defined as a period of at least one week (or any duration if hospitalization is necessary) of abnormality and persistently elevated, expansive, or irritable mood with functional impairment. Manic symptoms include grandiosity, fast speech, racing thoughts, and distractibility. Hypomania is a less severe form of mania that does not involve functional impairment. Some patients with severe episodes of mania or depression have psychotic symptoms such as hallucinations or delusions.

Among the multiple subtypes of this disease are bipolar I and bipolar II disorder, distinguishable by specific mood episodes. Bipolar I disorder is characterized by a manic episode with or without a major depressed or mixed episode (major depression concurrent with mania). The lifetime prevalence of bipolar I disorder is 0.4 to 1.6 percent, and occurs equally in men and women. Bipolar II disorder is characterized by at least one major depressive episode accompanied by at least one hypomanic episode, and occurs more frequently in women. The average age of the first manic episode is 21 years for both men and women.

Pharmacological therapy is essential for the stabilization and prevention of relapse for each of these types of bipolar disorder. Treatment of bipolar disorder is individualized based on type of bipolar disorder, associated features, and severity and frequency of episodes. For patients with severe manic and mixed episodes, the mainstay of treatment consists of lithium or valproate plus an antipsychotic. This regimen is endorsed by multiple treatment guidelines. Numerous meta-analyses indicate that the combination of antipsychotics and lithium or valproate leads to an increase in rate of response (measured using mania rat-

ing scale) in a significantly shorter time period.

The SGAs most studied in bipolar disorder include aripiprazole, olanzapine, quetiapine, and risperidone. Patients who do not respond to one medication combination should be treated with a second combination. Similar to schizophrenia treatment, the choice of antipsychotic is based on past medication use outcomes, patient preference, side effect profile, comorbid conditions, and cost as head-to-head trials comparing antipsychotics in combination with lithium or valproate are lacking.

In patients with hypomania and mild to moderate manic and mixed episodes, monotherapy with SGAs (e.g., risperidone, olanzapine, aripiprazole, quetiapine, or ziprasidone) is a reasonable option. In addition, a large meta-analysis of 68 randomized trials attempted to rank these agents by efficacy and by frequency of treatment discontinuation for any reason, including adverse effects or lack of efficacy. These rankings indicated that both risperidone and olanzapine were likely the most effective agents with the lowest dropout rate.

The pharmacological treatment of bipolar depression mostly consists of combinations of at least two drugs, including a mood stabilizer, atypical antipsychotic, and antidepressant. Among atypical antipsychotics, quetiapine is recommended by most guidelines as first choice. Benzodiazepines may also be used for adjunct treatment of insomnia, agitation, or anxiety. Long term maintenance therapy is also required for bipolar disorder.

Atypical Antipsychotic Metabolic Effects

SGAs can induce metabolic abnormalities that are associated with an increased risk of type 2 diabetes mellitus, metabolic syndrome, and cardiovascular disease. These metabolic changes include weight gain, hyperglycemia, and dyslipidemia. It is believed that individuals with schizophrenia and affective disorders have approximately a 1.5 to 2 percent times higher prevalence of both obesity and diabetes compared to the general population. Patients with a first episode of schizophrenia who have not previously taken an antipsychotic agent appear to be the most vulnerable to these side effects. Characteristics of schizophrenic lifestyle, including sedentary behavior, may contribute. Because other major risk factors for diabetes were not controlled in past studies, it remains unclear whether the psychiatric condition, independent of other risk factors, accounts for the increased prevalence. Evidence suggests that personal, familial, or genetic factors also influence how much weight is gained. When coupled with high rates of smoking and physical inactivity in this population, the relative risk of CVD mortality is significantly greater in this population.

Table 2
Metabolic risks associated with atypical antipsychotics

Drug	Weight Gain	Diabetes	Lipid Profile
Aripiprazole	–	low	low
Asenapine	+	low*	low*
Clozapine	+++	high	high
Iloperidone	++	mild*	mild*
Lurasidone	–	low*	low*
Olanzapine	+++	high	high
Paliperidone	++	mild	mild
Quetiapine	++	moderate	moderate
Risperidone	++	mild	mild
Ziprasidone	–	low	low

*Limited data
Adapted from *CNS Drugs*. 2012; 26 (9) and *Diabetes Care*. 2004; 27 (2)

Weight Gain. Excessive weight gain during antipsychotic drug treatment was identified as early as 1958, and was mainly associated with low potency phenothiazines. However, this side effect was somewhat ignored during the 1970s and 1980s as it was found to be minimal in the more potent FGAs. Since the introduction of atypical antipsychotics in the 1990s, however, the concern has been renewed. Weight gain has been estimated to affect between 15 to 72 percent of patients with schizophrenia.

The exact mechanism of this process is controversial and not well understood. Yet, evidence suggests that the antipsychotics with the highest tendency to induce significant weight gain are also potent appetite stimulants. This may be due to the drugs' interactions with peptides, steroid hormones, amino acids, and neurotransmitters. Atypical antipsychotic-induced weight gain may also arise from excessive fat deposition, coupled with reduced energy expenditure. Another assessment is that drug-induced weight gain may be a result of gene polymorphism.

Evidence suggests that treatment with SGAs in patients with schizophrenia can cause rapid weight gain in the first few months of therapy, that may or may not stabilize within a year. Variability in weight gain among the agents is summarized in Table 2. A meta-analysis of multiple studies on antipsychotics found that clozapine was associated with the greatest weight gain after 10 weeks of treatment, compared to ziprasidone which was linked to the least weight gain. Other studies have made this same conclusion, showing that clozapine and olanzapine are associated with the most weight gain, and ziprasidone and aripiprazole with the least. Initial data indicate that lurasidone, a newer agent that will be discussed in more detail, is also benign in regards to weight gain. No antipsychotic agent is entirely body weight

neutral, as the proportion of individuals who experience clinically relevant weight gain, traditionally defined as ≥7 percent of pretreatment weight, is greater with any agent versus placebo.

Diabetes. Extensive reporting has documented the onset or exacerbation of diabetes following the initiation of SGAs. Large retrospective cohort studies have been conducted to report the estimated prevalence of diabetes in patients using SGAs. While these studies have limitations, undeviating data indicate that the risk is highest in patients treated with clozapine or olanzapine, compared with those on other antipsychotics. Quetiapine has a moderate risk of hyperglycemia, followed by risperidone. It appears that aripiprazole and ziprasidone do not show an effect. The mechanism of this side effect is thought to be drug-induced insulin resistance, due to weight gain or a direct effect on insulin-sensitive tissues.

Dyslipidemia. Dyslipidemia is also a related consequence of SGA use. Recent evidence suggests that dyslipidemia is not only a consequence of weight gain, but may occur as a separate and direct adverse effect of SGA treatment. Clozapine and olanzapine are associated with the greatest risk of dyslipidemias, followed by quetiapine then risperidone. The dyslipidemic adverse effects of clozapine, olanzapine, and quetiapine manifest as abnormal elevations in serum triglyceride levels, total cholesterol, and low-density lipoprotein (LDL) cholesterol, and as a decrease in high-density lipoprotein (HDL) cholesterol. Aripiprazole and ziprasidone present a low risk.

De Hert *et al.* completed a systematic review to determine the weight gain and metabolic adverse effects associated with asenapine, iloperidone, lurasidone, and paliperidone. The researchers concluded that preliminary data suggest that lurasidone is associated with the lowest weight gain potential. The reviewers stated that insufficient evidence is available to draw firm conclusions about the metabolic effects of the newly approved SGAs. Table 2 summarizes the metabolic adverse events associated with each SGA, including the newest agents, utilizing limited available data.

Management of Metabolic Adverse Effects with SGAs

In 2003, the American Diabetes Association, the American Psychiatric Association, the American Association of Clinical Endocrinologists, and the North American Association for the Study of Obesity held a consensus development conference on the subject of antipsychotic drugs and obesity. At the time, the panel developed baseline and follow-up monitoring recommendations for patients in whom SGAs are prescribed. Baseline monitoring includes personal and family history of obesity, diabetes, dyslipidemia, hypertension, or cardiovascular disease; weight and height (to calculate BMI); waist circumference; blood pressure; fasting plasma glucose; and fasting lipid profile (Table 3). Nutritional counseling, as well as cognitive behavioral counseling, have been found to be effective in reducing antipsychotic induced weight gain. Health care providers, as well as patients, family members and caregivers, should be aware of the signs and symptoms of diabetes, including diabetic ketoacidosis (DKA), which can be life-threatening.

Follow-up monitoring is also recommended which includes routine reassessment of weight and, initially, quarterly plasma glucose, lipid levels, and blood pressure checks. Many drugs have been studied to counteract the weight gain as well, including metformin, amantadine, and topiramate. Metformin has shown the most success, although none of these drugs has enough evidence to recommend for broad clinical use.

Recently Approved Atypical Antipsychotics

Three of the most recently approved atypical antipsychotics, iloperidone, asenapine and lurasidone, have been added to the psychiatric armamentarium. These agents were developed with the hope of maintaining efficacy with improved adverse effect profiles and decreased cardiovascular risk. Collectively, these agents have been subject to fewer clinical studies and less clinical experience.

Iloperidone, marketed as Fanapt, was introduced in 2009 for the treatment of schizophrenia. It

Table 3
Monitoring protocol for patients on SGAs*

	Baseline	4 weeks	8 weeks	12 weeks	quarterly	annually
personal/ family history	X					X
weight (BMI)	X	X	X	X	X	
waist circumference	X					X
blood pressure	X			X		X
fasting plasma glucose	X			X		X
fasting lipid profile	X			X		

*Consensus Development Conference on Antipsychotic Drugs and Obesity and Diabetes. *Diabetes Care*, February 2004, vol. 27, no. 2, 596-601.

is dosed at 12 to 24 mg daily, divided in two doses without regard to meals. Its pharmacodynamic profile differs from other SGAs in that it has a relatively higher affinity for noradrenergic alpha 1 receptors, compared to affinity for serotonin 5-HT_{2A} and dopamine D_2 receptors. This variation in receptor affinity explains why iloperidone has been associated with dizziness and orthostatic hypotension. For this reason, dosing titration is recommended to begin at 1 mg twice daily, and increasing daily until the treatment dose is attained. Other receptor binding characteristics which may be important include a lower affinity to muscarinic receptors and histamine receptors, potentially leading to fewer anticholinergic side effects such as cognitive dysfunction and gastrointestinal disturbances, as well as less weight gain and sedation, respectively. Proof that these characteristics translate to relevancy in clinical practice is yet to be determined through clinical trials.

Iloperidone is considered low risk for causing extrapyramidal symptoms, and low to intermediate for adverse metabolic effects. The slow titration schedule makes it less ideal for a patient with acute exacerbations of schizophrenia, and may lead to longer hospital stays as a delay in symptom control may occur when compared to other antipsychotic agents. Also, the dose titration has the potential for increased medication errors. Comparison studies have indicated that its efficacy is similar to ziprasidone, and is not superior to the other atypical antipsychotics. Lastly, it possesses a risk for QTc interval prolongation.

In a clinical review of iloperidone conducted by Arif and Mitchell, the authors concluded that iloperidone may be a viable and safe option for the treatment of schizophrenia in patients who cannot tolerate the side effects of other agents. However, iloperidone lacks clear superiority over other antipsychotics.

Asenapine, marketed as Saphris, is indicated for the treatment of acute and maintenance phases of schizophrenia in adults. It is also approved as monotherapy or adjunct to lithium or valproate for the treatment of bipolar manic or mixed episodes in adults. It differs from other oral antipsychotics as it is only available as an orally disintegrating tablet administered sublingually for absorption through oral mucosa. Patients should be instructed to place the tablet under the tongue and allow it to dissolve. The patient should not eat or drink for 10 minutes following administration. The tablet should not be swallowed. If it is swallowed, its bioavailability is reduced to <2 percent. Note that this differs from olanzapine, risperidone, and aripiprazole oral disintegrating tablets which must be swallowed to be effective. Asenapine has a higher affinity to serotonin 5-HT_{2C}, 5-HT_{2A}, 5-HT_7, 5-HT_{2B}, 5-HT_6, and dopamine D_2 receptors. It also has a low affinity to muscarinic receptors predicting a possible lower risk for anticholinergic side effects. The indication-specific dosing of 5 to 10 mg twice daily may be reached quickly without titration. Because the elimination half-life is 24 hours, a once daily dosing trial was recently conducted. However, study results were not available at the time this lesson was written.

The single most common side effect experienced in trials was somnolence, which is usually transient and highest in the first week of treatment. Other common side effects include weight gain, dizziness, EPS (akathisia, dose-related), and oral hypoesthesia. Oral hypoesthesia (numbness) or oral dysgeusia (distorted, altered, or unpleasant taste) is a unique side effect to asenapine. This SGA has minimal effect on the QTc interval, which is not expected to be clinically significant.

Stoner and Pace conducted a review of efficacy and safety profiles based on the findings from clinical trials in schizophrenia and bipolar disorder available through November 2011. Their review suggested that asenapine is efficacious in the conditions for which it is indicated. While the safety profile was acceptable, metabolic and EPS-related adverse events were present.

Lurasidone, marketed as Latuda, was introduced in 2010 with FDA-approved indications for schizophrenia, and for depressive episodes associated with bipolar I disorder, as monotherapy and as adjunctive therapy with lithium or valproate. Indication specific dosing recommends a starting dose of 20 to 40 mg daily, with a maximum daily dose of 160 mg. Initial dose titration is not required with lurasidone. Administration with food greatly increases the absorption of lurasidone; therefore, it is recommended to be taken with food (at least 350 calories). Patients should be instructed to read the *Medication Guide* each time the prescription is filled.

Administration with strong CYP3A4 inhibitors (e.g., ketoconazole, clarithromycin, ritonavir, voriconazole) and CYP3A4 inducers (e.g., rifampin, St. John's wort, phenytoin, carbamazepine) is contraindicated. Dosing modifications are required in patients with moderate to severe renal and hepatic impairment.

Similar to other SGAs, lurasidone possesses dopamine D_2 and serotonin 5-HT_{2A} antagonism. It also has potent-5HT_7 antagonism which may provide cognition improvement. However, results from longer term trials are needed to determine the significance. It has low affinity to muscarinic, histamine H_1, and alpha-1-adrenergic receptors. Common side effects include somnolence, akathisia, nausea, and parkinsonism. Less commonly reported adverse effects were acute dystonia, agitation, anxiety, and dizziness.

In a review article conducted by Citrome, the author summarized advantages of lurasidone as minimal weight gain (and possible best in class) with no clinically meaningful alterations in glucose,

lipids, prolactin, or QTc interval.

Risbood *et al.* concluded that, due to pricing and lack of evidence demonstrating a difference in efficacy when compared to other antipsychotics, its place in therapy may be behind available generic antipsychotics.

Conclusion

Antipsychotics are primarily indicated for the treatment of schizophrenia and bipolar disease. Side effect profiles differ across classes and agents, and oftentimes dictate therapy. Pharmacists can help maximize patient outcomes with a thorough understanding of the differences between agents.

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This lesson is a knowledge-based CE activity and is targeted to pharmacists in all practice settings.

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Atypical Antipsychotics: Overview, Metabolic Abnormalities, and Newer Agents

1. Antipsychotics are indicated for treatment of all of the following EXCEPT:
   a. schizophrenia. c. obsessive-complusive disorder.
   b. bipolar disporder. d. depression.

2. Which of the following drugs is a first generation antipsychotic (FGA)?
   a. Ziprasidone c. Paliperidone
   b. Olanzapine d. Haloperidol

3. Which of the following SGAs has no clinically relevant effect on QTc interval?
   a. Quetiapine c. Iloperidone
   b. Aripiprazole d. Asenapine

4. The Schizophrenia PORT recommends treating initial, acute episodes with any of the following EXCEPT:
   a. olanzapine. c. lurasidone.
   b. risperidone. d. quetiapine.

5. At least how many different SGAs should be trialed before clozapine monotherapy may be initiated?
   a. None c. Three
   b. Two d. Four

6. Which of the following SGAs has a black box warning for fatal agranulocytosis?
   a. Quetiapine c. Clozapine
   b. Olanzapine d. Paliperidone

7. Which of the following atypical antipsychotics is recommended by most guidelines as first choice in treatment of bipolar depression?
   a. Quetiapine c. Risperidone
   b. Clozapine d. Aripiprazole

Completely fill in the lettered box corresponding to your answer.

1. [a] [b] [c] [d]	6. [a] [b] [c] [d]	11. [a] [b] [c] [d]
2. [a] [b] [c] [d]	7. [a] [b] [c] [d]	12. [a] [b] [c]
3. [a] [b] [c] [d]	8. [a] [b] [c] [d]	13. [a] [b] [c]
4. [a] [b] [c] [d]	9. [a] [b] [c] [d]	14. [a] [b] [c]
5. [a] [b] [c] [d]	10. [a] [b] [c]	15. [a] [b] [c]

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8. Which of the following SGAs is likely associated with the least effect on weight gain?
   a. Paliperidone c. Asenapine
   b. Iloperidone d. Ziprasidone

9. Which of the following pairs of SGAs is associated with the highest risk of hyperglycemia?
   a. Olanzapine and quetiapine
   b. Quetiapine and risperidone
   c. Risperidone and clozapine
   d. Clozapine and olanzapine

10. Data indicate that which of the following pairs of SGAs is associated with the lowest risk of dyslipidemias?
   a. Aripiprazole and ziprasidone
   b. Olanzapine and quetiapine
   c. Risperidone and paliperidone

11. Recommendations for baseline evaluation of patients initiated on SGA therapy include all of the following EXCEPT:
   a. weight and height. c. serum creatinine.
   b. fasting plasma glucose. d. waist circumference.

12. The product insert for which of the following SGAs recommends a slow daily titration schedule?
   a. Iloperidone c. Lurasidone
   b. Asenapine

13. Patients are instructed not to eat or drink for at least 10 minutes following administration of which of the following?
   a. Iloperidone c. Lurasidone
   b. Asenapine

14. Oral hypoesthesia or dysgeusia is a unique side effect of which of the following SGAs?
   a. Iloperidone c. Lurasidone
   b. Asenapine

15. Food containing at least 350 calories is required with the administration of:
   a. iloperidone. c. lurasidone.
   b. asenapine.

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