Newer Oral Atypical Antipsychotic Agents: A Review

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Educational Objectives

After completing this program, readers should be able to:
- Describe the newer oral antipsychotic agents and indicate the differences between them.
- Compare and contrast the newer oral antipsychotic agents with the older atypical antipsychotic medications.
- Review the appropriate use of these agents, including dosing, contraindications, side-effect profiles, and interactions.

Introduction

Antipsychotic drugs are commonly prescribed for a variety of psychiatric conditions. In addition to individuals with schizophrenia, the original target patient population, several antipsychotic medications are widely used for bipolar disorder, depression, anxiety, delirium, insomnia, agitation, and aggression in various patient types. Despite their important role in the treatment of psychotic and other illnesses, these medications have some shortcomings. Some patients with psychosis fail to respond to treatment, or they may respond incompletely. Some patients experience neurological events such as extrapyramidal side effects or, more rarely, tardive dyskinesia. Neuroleptic malignant syndrome is another rare but potentially life-threatening complication of treatment with antipsychotic drugs.

Recently, the antipsychotic medications (particularly the atypical, “second-generation” antipsychotics) have come under scrutiny because of an increased risk of weight gain and metabolic adverse effects (AEs), such as glucose intolerance and lipid abnormalities. These AEs have the potential to increase the risk of type-2 diabetes mellitus and cardiovascular disease as well as morbidity and mortality rates related to these conditions.1 Antipsychotic drugs are often prescribed “off-label” for the management of agitation and psychosis in patients with dementia without an approved FDA indication. The use of these medications in elderly dementia patients has become controversial and has been reported by the FDA to increase the risk of cerebrovascular events as well as the all-cause death rate among these patients, leading to the advent of “black-box” warnings for all antipsychotic drugs.2

Antipsychotic agents may be classified in several ways. Commonly, they can be designated as older drugs (often called conventional or “typical” antipsychotics) and newer “atypicals.” The term atypical refers to the perceived lower likelihood of extrapyramidal symptoms, a sequela that had been deemed characteristic of the first generation of antipsychotic drugs. The atypicals are widely prescribed based on the perception that they are more effective and produce fewer side effects than the typicals, even though some atypicals are much more expensive.

CATIE (Clinical Antipsychotic Trials in Intervention Effectiveness), a large study published in 2005, cast doubt on the relative overall effectiveness of the atypicals, which seemed to perform no better than perphenazine (formerly Trilafon, Schering-Plough), an older, less expensive typical antipsychotic medication.3 Some observers have suggested a return to the use of the less expensive typical medications. In this setting, the field is in need of better agents to bring about improved antipsychotic effects, a lower rate of refractory illness, and reduced both metabolic and neurological side effects.

The atypical antipsychotics include risperidone (Risperdal, Janssen), olanzapine (Zyprexa, Eli Lilly), quetiapine (Seroquel, AstraZeneca), ziprasidone (Geodon, Pfizer), and aripiprazole (Abilify, Bristol-Myers Squibb/Otsuka). Clozapine (Clozaril, Novartis) is usually included in this list as the prototypical agent, although its potential for bone marrow suppression sets it apart.

Since the introduction of aripiprazole in 2002, there has been a relative hiatus in the development of new atypical antipsychotic drugs. In this article, we review four oral atypical antipsychotic agents introduced since 2007: paliperidone (Invega, Ortho-McNeil-Janssen), iloperidone (Fanapt, Vanda), asenapine (Saphris, Organon), and lurasidone (Latuda, Sunovion). We discuss their classification, indications, mechanism of action, clinical trials, efficacy, adverse effects, comparisons with other antipsychotics, new indications being sought, dosing and administration, absorption, distribution, metabolism, excretion, contraindications, FDA warnings, and drug–drug interactions. We excluded antipsychotic agents that are currently under investigation and those that have not yet been approved by the FDA.

We conducted a Medline search for the terms paliperidone, iloperidone, asenapine, and lurasidone to identify efficacy and tolerability trials for each drug. Product information and results from unpublished studies were obtained from the manufacturers.
The Four New Atypicals

**Paliperidone (Invega)**

Paliperidone belongs to the benzisoxazole derivative class of atypical antipsychotic agents. It was approved by the FDA in December 2006 for the treatment of schizophrenia and for the maintenance treatment of schizophrenia in April 2007. In July 2009, it received an indication for the acute treatment of schizoaffective disorder, both as monotherapy and as an adjunct to mood stabilizers or antidepressants.

Paliperidone is the major active metabolite of risperidone (9-hydroxy risperidone). It is an antagonist at D2-dopaminergic receptors, alpha1-adrenergic and alpha2-adrenergic receptors, and H1-histaminergic receptors. Paliperidone demonstrates serotonin (5-HT2A) agonist activity and displays no affinity for muscarinic cholinergic or beta-adrenergic receptors.

Compared with risperidone, paliperidone exhibits easier dissociation from the D2 receptors; this is thought to make it less likely to induce extrapyramidal symptoms when compared with the parent compound.

In three six-week, double-blind, placebo-controlled studies, paliperidone was effective as monotherapy for the acute exacerbations of schizophrenia; it also demonstrated efficacy as a maintenance therapy in 14-week and 52-week clinical trials. In two six-week clinical trials, paliperidone demonstrated efficacy either as monotherapy or as an adjunct to mood stabilizers or antidepressants in patients with schizoaffective disorder. In another 6-week study, paliperidone showed greater efficacy than a comparable dose of quetiapine for symptom control in patients with acute exacerbations of schizophrenia who required hospitalization.

Patients with schizophrenia who were suboptimally responsive to risperidone reported improved satisfaction with paliperidone after 4 to 6 weeks of treatment. Although paliperidone is not currently indicated for the treatment of bipolar disorder, two studies of 6 and 9 weeks in duration found it effective as monotherapy in reducing acute manic or mixed symptoms in patients with bipolar disorder. However, in another 6-week trial, paliperidone did not show greater efficacy as an adjunct to lithium or valproate (e.g., Depakene, Abbott) when it was compared with mood-stabilizer monotherapy in patients with acute mania.

In a pooled analysis of three six-week trials, the most serious AE associated with paliperidone was worsening psychosis or schizophrenia. The most common treatment-emergent AEs were headache, akathisia, insomnia, somnolence, and orthostatic hypotension. In the treatment group, weight gain was less than 2 kg, and there was a minimal, clinically insignificant change (less than 0.1 mmol/L) in the lipid profile. No information was available to determine whether additional treatment indications are currently being sought for paliperidone.

Paliperidone is sold in 1.5-mg, 3-mg, 6-mg, and 9-mg extended-release (ER) formulation tablets as well as in a long-acting injection formulation known as Invega Sustena. It is administered whole, with liquid, and without regard to food intake. For patients with schizophrenia and schizoaffective disorder, the recommended dosage is 6 mg once daily in the morning. The maximum recommended dosage is 12 mg/day. Because of its extended-release delivery system, the tablets should not be chewed, divided, or crushed.

Following ingestion, paliperidone absorption occurs through an osmotic, controlled-release mechanism that delivers paliperidone at a controlled rate. In the aqueous environment of the gastrointestinal (GI) tract, the tablet overcoat erodes quickly and water enters the tablet core at a controlled rate through a semipermeable membrane. Hydrophilic polymers in the core hydrate and swell to create a paliperidone-containing gel that is then pushed out through laser-drilled orifices on the dome of the tablet. Biologically inert components of the tablet remain intact during transit through the GI tract and are eliminated in the stool as a tablet shell. Patients should be informed that it is normal to occasionally find the tablet shell eliminated in feces.

The absolute oral bioavailability of paliperidone following administration is 28%, and steady-state concentrations are attained within 4 or 5 days of administration in most subjects. As a result of the extended delivery system, the elimination half-life of paliperidone is approximately 23 hours.

Paliperidone undergoes primarily renal metabolism. Although four hepatic metabolic pathways have been identified in vivo, none of these could be shown to account for more than 10% of the metabolized dose. Similarly, in vitro studies showed that paliperidone does not substantially inhibit the metabolism of drugs by cytochrome P450 (CYP) isozymes. Therefore, paliperidone is not expected to cause clinically important pharmacokinetic interactions with drugs that are metabolized by CYP isozymes, and no dosage adjustment is required in patients with mild-to-moderate hepatic impairment.

For patients with mild renal impairment (a creatinine clearance [CrCl] of 50 to 80 mL/minute), the recommended initial dosage of paliperidone is 3 mg once daily. The dosage may then be increased to a maximum of 6 mg once daily according to the patient’s clinical response and tolerance. For patients with moderate-to-severe renal impairment (CrCl, 10–50 mL/minute), the recommended initial dosage of paliperidone is 1.5 mg once daily, which may be increased to a maximum of 3 mg once daily after clinical reassessment.

Paliperidone is not recommended in patients with a CrCl below 10 mL/minute, and it is contraindicated in patients with hypersensitivity to this drug or to risperidone. Paliperidone may antagonize the effect of levodopa and other dopamine agonists.

Because of its potential to induce orthostatic hypotension, paliperidone may have an additive effect if it is given with antihypertensive agents. Coadministration of 6 mg of paliperidone daily with carbamazepine (Carbatrol, Shire) 200 mg twice daily caused a decrease of approximately 37% in the mean steady-state concentration of paliperidone, largely as a result of increased renal clearance (35%) of paliperidone. Conversely, administration of paliperidone with divalproex sodium extended-release tablets (Depakote, Abbott) resulted in an increase of approximately 50% in the peak concentration (Cmax) of paliperidone.

A reduced dosage of paliperidone should be considered if it is administered with valproate. The renal metabolism of paliperidone and lithium is through separate mechanisms, which allows for coadministration without the risk of adverse drug interactions. Like other antipsychotic agents, paliperi-
done carries an FDA boxed warning that mentions increased mortality rates in elderly patients with dementia-related psychosis.

### Iloperidone (Fanapt)

Iloperidone belongs to the piperidinyl-benzisoxazole derivative class of antipsychotic drugs. Introduced in May 2009, iloperidone was approved by the FDA for the treatment of schizophrenia. Its mechanism of action involves high-affinity antagonism of serotoninergic (5-HT1A, alpha1- and alpha2-adrenergic, and D2- and D3-dopaminergic receptors.23 The Positive and Negative Syndrome Scale (PANSS) and the Brief Psychiatric Rating Scale (BPRS) were used to evaluate iloperidone in two randomized, placebo-controlled, double-blind trials (one lasting 4 weeks and one lasting 6 weeks).24,25 The drug was found to reduce symptoms in individuals experiencing acute exacerbations of schizophrenia or schizoaffective disorder. In a 52-week trial, a pooled analysis of the active-treatment group showed the efficacy of iloperidone as maintenance therapy in reducing positive and negative symptoms of schizophrenia.26

The safety of iloperidone in individuals with schizophrenia or schizoaffective disorder has also been demonstrated. In 1,044 patients who were randomly assigned to receive iloperidone during three 6-week clinical trials, the most common AEs were dizziness, dry mouth, dyspepsia, and somnolence. Extrapyramidal Symptom Rating Scale (ESRS) scores improved with all iloperidone doses. Akathisia scores were reduced significantly from baseline in groups receiving iloperidone at a dosage of either 10 to 16 mg/day or 20 to 24 mg/day. The incidence of akathisia in treated patients was comparable to that in patients receiving placebo, according to the Barnes Akathisia Scale.

Statistically significant changes in vital signs, particularly hypotension, orthostatic hypotension, and tachycardia, were noted in all iloperidone-treated groups.27 Such changes occurred most frequently with iloperidone therapy, but they were generally short-lived and occurred in the first week of treatment. Although the corrected QT interval (QTc, Fridericia) increased in all treatment groups, no deaths or arrhythmias attributable to iloperidone were reported in clinical trials. The mean elimination half-life of iloperidone is 18 to 31 hours, depending on whether the patient is a normal, poor, or extensive metabolizer. Steady-state concentrations are attained within 3 to 4 days after administration. The bulk of iloperidone metabolites are recovered in urine.

The drug was metabolized hepatically through carbonyl reductase, hydroxylation (mediated by CYP2D6), and O-demethylation (mediated by CYP3A4).22 Inhibitors of either isozyme, such as ketoconazole (Nizoral, Janssen), paroxetine (Paxil, GlaxoSmithKline), and fluoxetine (Prozac, Eli Lilly), demonstrated a serum increase in iloperidone. Inhibitors or inducers of other CYP isozymes are unlikely to affect the metabolism of iloperidone. Iloperidone has not been shown to significantly affect metabolism and bioavailability of other drugs. The renal clearance of iloperidone is 47 to 102 L/hour, with a volume of distribution of 1,340 to 2,800 L.

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Iloperidone is available in tablet strengths of 1 mg, 2 mg, 4 mg, 6 mg, 8 mg, 10 mg, and 12 mg, and an injectable depot formulation is under development.22,28 The medication is administered without regard to food intake, with twice-daily dosing starting at 1 mg. The dosage may be titrated to efficacy (6–24 mg/day total) over 1 to 2 weeks. The maximum dosage is 24 mg/day.22

To prevent hypotension, iloperidone is initiated at a dosage of 1 mg twice daily and is then increased to 2 mg, 4 mg, 6 mg, 8 mg, 10 mg, and 12 mg twice daily on each subsequent day to reach the target dosage of 12 to 24 mg/day.22 Iloperidone is not recommended for patients with hepatic impairment.22 In addition to an FDA boxed warning regarding increased mortality rates in elderly patients with dementia-related psychosis, iloperidone is contraindicated in patients with hypersensitivity to iloperidone or to its formulation components. Iloperidone should not be used with other drugs that prolong the QT interval.22 The dose should be reduced in patients who are receiving a strong CYP2D6 or CYP3A4 inhibitor.

### Asenapine (Saphris)

Asenapine belongs to the dibenzo-oxepino pyrrole class of atypical antipsychotic agents. It was approved by the FDA in August 2009 for the treatment of schizophrenia in adults and as acute therapy (either as monotherapy or adjunctive therapy) for manic or mixed episodes associated with bipolar I disorder.29 Asenapine is a high-affinity antagonist at 5-HT1A, 5-HT2A, 5-HT2B, 5-HT2C, and 5-HT7 serotonergic receptors; at D1- and D2-dopaminergic receptors; at alpha1- and alpha2-adrenergic receptors; and at H1-histaminergic receptors. It demonstrates moderate antagonist affinity for histamine H2 receptors and no appreciable affinity for muscarinic cholinergic receptors.29

In 6-week and 1-year clinical trials, asenapine reduced both positive and negative symptoms in acute exacerbations of schizophrenia, and it was effective as a maintenance therapy. In acute (6-week) and maintenance (12- and 40-week) trials, asenapine reduced symptoms of acute manic or mixed states as monotherapy or in combination with valproate or lithium in individuals with bipolar disorder type I. In clinical trials, the most common AEs were sedation, dizziness, somnolence, fatigue, oral hypoesthesia, dry mouth, and increased weight. Extrapyramidal symptoms occurred in fewer than 5% of patients; the most common AEs were dystonia,
akathisia, parkinsonism, and dyskinesia.

No published studies have compared the efficacy of asenapine with that of other atypicals, and no information is available regarding possible future indications.

Asenapine is available in 5- and 10-mg unflavored and black cherry–flavored tablets for sublingual administration.29 The drug is rapidly absorbed, and the C_{max} occurs within 30 to 90 minutes.29 To ensure optimal absorption, patients should be instructed not to crush, chew, or swallow the tablets. The tablets should be placed under the tongue and should be allowed to dissolve completely. Patients should also be instructed not to eat or drink for 10 minutes after taking asenapine; in efficacy studies, water intake to 5 minutes after administration resulted in decreased asenapine exposure.

The mean terminal half-life of asenapine is approximately 24 hours, and the absolute bioavailability of a 5-mg tablet is 35%; however, bioavailability is only 2% if the tablet is swallowed instead of being dissolved.29 With multiple-dose twice-daily dosing, steady state is attained within 3 days.29 About 90% of the dose is eliminated; approximately 50% was recovered in urine and 40% was recovered in feces.29

Asenapine is cleared primarily through glucuronidation by UDP-glucuronosyltransferase (UGT) 1A4 and through oxidative metabolism by CYP isoenzymes (predominantly CYP1A2 and, to a lesser extent, CYP3A4 and CYP2D6).29 Asenapine is a weak inhibitor of CYP2D6 and does not cause induction of CYP1A2 or CYP3A4 activities.29 Inhibitors and inducers of other CYP pathways—paroxetine, imipramine (Tofranil, Mallinckrodt), cimetidine (Tagamet, GlaxoSmithKline), carbamazepine, and valproic acid—have not been found to significantly affect the C_{max} of asenapine and do not warrant dosage adjustments for asenapine.

A population analysis indicated that the concomitant administration of lithium had no effect on the pharmacokinetics of asenapine.29 Coadministration of fluvoxamine (Luvox, Solvay/Jazz/Abbott), a CYP1A2 inhibitor, at a dosage of 25 mg twice daily for 8 days and one dose of asenapine 5 mg increased the C_{max} of asenapine by 13%; therefore, the manufacturer recommends coadministration with caution.29 As a result of alpha_{adrenergic} antagonism, asenapine may enhance the effects of some antihypertensive agents.

Asenapine is not recommended for patients with severe hepatic impairment; however, no dosage adjustments are required based on the degree of renal impairment.29 Although no contraindications are listed in the prescribing information, a boxed warning mentions an increased mortality rate in older patients with dementia-related psychosis.

In adults with acute schizophrenia, the recommended starting and target dosage of asenapine is 5 mg twice daily. In a maintenance trial in patients with schizophrenia, the starting dosage was 5 mg twice daily, with an increase to 10 mg twice daily after one week, based on the patient’s tolerance. As an acute therapy for manic or mixed episodes, the recommended starting dosage of asenapine is 10 mg twice daily. This dosage can be decreased to 5 mg twice daily if warranted by adverse effects or individual tolerance.29

When administered as an adjunctive therapy with lithium or valproate, the recommended starting dosage of asenapine is 5 mg twice daily; this dosage can be increased to 10 mg twice daily, depending on the clinical response and patient tolerance. There is no recommendation for the duration or dose of maintenance therapy with asenapine in patients with schizophrenia or bipolar disorder.

**Lurasidone (Latuda)**

Lurasidone belongs to the benzisothiazol class of atypical antipsychotic drugs and was approved for the treatment of schizophrenia in October 2010. It acts as an antagonist at dopamine (D_{2}) and serotonin (5-HT_{2A} and 5-HT_{7}) receptors, as a partial agonist at 5-HT_{1A} receptors, as a moderate agonist at alpha_{1C} receptors, and as a minimal agonist at alpha_{1D}–noradrenergic receptors.25

In a 6-week, double-blind, placebo-controlled studies that evaluated the safety and efficacy of lurasidone in reducing psychotic symptoms in individuals with schizophrenia, lurasidone was found to be as efficacious as haloperidol and olanzapine.36,39 Although lurasidone did not demonstrate efficacy in a fifth clinical trial, the data were included in a pooled safety analysis.29

In the pooled analysis, 78.9% of individuals receiving lurasidone experienced at least one treatment-emergent AE.35 Those AEs leading to discontinuation of lurasidone were worsening of schizophrenia, akathisia, psychotic disorders, dystonia, and agitation. Other AEs included nausea, vomiting, dyspepsia, salivary hypersecretion, fatigue, somnolence, dizziness, insomnia, agitation, anxiety, and restlessness.

No information was available about future indications being sought for lurasidone, although studies of patients with bipolar disorder are under way.41,42 A boxed warning mentions increased mortality rates in older patients with dementia-related psychosis.

Lurasidone is available in tablet strengths of 40 and 80 mg. The tablets should be administered orally with food (an intake of at least 350 calories), because food affects the drug’s bioavailability.25 The initial dosage, 40 mg once daily, can be increased to 80 mg once daily if indicated.25 Following ingestion, lurasidone is rapidly absorbed and reaches the C_{max} within 1 to 3 hours. Approximately 9% to 19% of the administered dose is absorbed. The mean half-life varies from 29 to 37 hours, but it may last nearly 40 hours in patients with schizophrenia when given at a dosage of 120 to 160 mg/day.35

The volume of distribution is approximately 6,173 L, and the apparent CrCl is 3,902 mL/minute.35 Lurasidone undergoes hepatic metabolism, primarily by the CYP3A4 isozyme. It undergoes biotransformation pathways through N-dealkylation, hydroxylation, and S-oxidation, which in turn produces pharmacologically active metabolites.35 Lurasidone is eliminated primarily in feces, with the remainder excreted in the urine.35

When lurasidone was administered with ketoconazole (a potent CYP3A4 inhibitor), there was a seven-fold increase in the serum concentration of lurasidone; administration with diltiazem (Cardizem, Biovail/Valenta/Abbott), a moderate CYP3A4 inhibitor, nearly doubled the serum concentration of lurasidone.35 With coadministration of rifampin, a potent CYP3A4 inducer, serum lurasidone concentrations were decreased by more than 80%. Therefore, lurasidone is contraindicated in patients receiving CYP3A4 inducers or inhibitors...
and in patients with a hypersensitivity to the drug or its formulation components.35

Although lurasidone demonstrates some CYP3A4 inhibition, no decrease in the dosage was required when the drug was coadministered with midazolam (Versed, Roche), a CYP3A4 substrate. No clinically significant metabolic interactions were noted when lurasidone was given with lithium.35

Discussion

Paliperidone, iloperidone, asenapine, and lurasidone are the newest oral atypical antipsychotic medications to be introduced since the approval of aripiprazole in 2002. Important characteristics of these drugs are summarized in Table 1.

Except for paliperidone, all of these medications undergo hepatic metabolism and can be altered by CYP450 inducers or inhibitors. Mechanisms of action (a combination of dopamine blockade and various serotonin effects) are similar to those of other atypical antipsychotic drugs. Clinical trials suggest that the antipsychotic effects of these agents are generally similar to those of other atypicals, although direct comparisons are difficult, given the dearth of head-to-head trials.

In comparison to the typical (older) and atypical antipsychotic agents, the newer atypicals have the potential advantages of a favorable metabolic profile; an apparently lower risk of extrapyramidal AEs; and, in the case of asenapine, sublingual administration, which may be useful for patients with dysphagia or a history of noncompliance by “cheeking” medications.

Disadvantages of the newer oral atypicals include the class effects of possible orthostatic hypotension, prolongation of the QTc interval, sedation, and weight gain. Despite claims of minimal weight gain and metabolic abnormalities with the newest atypicals, many patients in clinical trials were probably not treatment-naïve. Patients may have experienced the greatest changes in weight or metabolic profile when they received a previous antipsychotic medication; this makes it difficult to determine causality when a subsequent switch to a newer atypical antipsychotic drug seems to lead to relative improvement in the metabolic profile or in weight.

In addition, 6-week trial durations might have been insufficient to observe significant changes in the metabolic profile or emerging extrapyramidal symptoms. Given the short duration of published trials and the relatively brief period that these drugs have been on the market, it is difficult to state the possible risks of tardive dyskinesia or neuroleptic malignant syndrome.

Paliperidone’s close relationship with the parent compound, risperidone, is worthy of consideration. Financial constraints may make it difficult to justify prescribing paliperidone in place of its less expensive, and apparently equally efficacious, mother compound. However, the cost of prescribing paliperidone may be considered reasonable for three groups of patients: those with hepatic impairment who previously responded to risperidone, those with limited compliance who previously responded to risperidone but declined depot risperidone, and those who responded to risperidone but could not tolerate the drug’s extrapyramidal effects.43

The need for a slow titration to efficacy may limit the usefulness of iloperidone in an acute setting. Studies of iloperidone have included the comparators haloperidol, ziprasidone, and risperidone for assay sensitivity, and they were not designed or powered to be viewed as head-to-head trials of comparative effectiveness. Nevertheless, the apparent trend toward lower efficacy for iloperidone is not reassuring.

The sublingual formulation of asenapine can pose a potential disadvantage for some patients, because no alternative administration option exists for those who experience unpleasant taste or tongue sensations. Twice-a-day dosing, as recommended in the package insert despite asenapine’s relatively long half-life, may have a negative impact on adherence, especially for those who find the drug’s taste unpleasant. Patients who swallow the tablet, instead of allowing it to dissolve in the mouth, may experience poor absorption.
**Conclusion**

With daily or twice-daily administration and generally favorable metabolic profiles, paliperidone, iloperidone, asenapine, and lurasidone offer new treatment options for schizophrenia, schizoaffective disorder, bipolar disorder, or antidepressant augmentation. Given the number of patients who fail to respond or to tolerate existing antipsychotic medications, it is likely that some patients will find one of more of these newer oral drugs useful. However, at present they appear to represent an evolution of existing therapeutic approaches rather than a paradigm shift in the effectiveness and safety of antipsychotic medications.

The brief (6-week) duration of most clinical trials, as well as the relatively short time on the market for these drugs, limits an overall analysis of their value relative to that of pre-existing drugs. If any or all of these products prove to offer improved efficacy or a reduced risk of neurological and metabolic side effects over a period of time, the additional costs incurred in prescribing them might be a good value.

**References**

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Multiple Choice

Select the one correct answer.

1. The main finding of the CATIE trial was that the atypical class of antipsychotics was observed to be:
   a. as effective as chlorpromazine.
   b. as effective as haloperidol.
   c. less effective than haloperidol.
   d. less effective than perphenazine.

2. Paliperidone is the major active metabolite of:
   a. quetiapine.
   b. aripiprazole.
   c. olanzapine.
   d. risperidone.

3. All of the following are mechanisms of action of paliperidone except:
   a. antagonist at D2 receptors.
   b. antagonist of alpha1 and alpha2 receptors.
   c. antagonist of 5-HT2A receptors.
   d. antagonist of H1 receptors.

4. According to the article, the most serious adverse effect of paliperidone is:
   a. worsening psychosis.
   b. akathisia.
   c. tardive dyskinesia.
   d. prolongation of the QT interval.

5. All of the following statements about the administration of iloperidone are true except:
   a. Patients should be instructed to not eat or drink for 10 minutes after taking iloperidone.
   b. Dosing should be titrated over 1 to 2 weeks to avoid hypotension.
   c. The starting dose of iloperidone is 1 mg twice daily.
   d. Iloperidone is not recommended for patients with hepatic impairment.

6. Which of the following atypical antipsychotics is available in a sublingual form, which may prevent “cheeking” in some patients?
   a. paliperidone
   b. iloperidone
   c. asenapine
   d. lurasidone

7. Which of the following does not interact with lurasidone via the CYP3A4 pathway?
   a. ketoconazole
   b. diltiazem
   c. rifampin
   d. midazolam

8. Common side effects seen among the atypical antipsychotics include the following except:
   a. tardive dyskinesia.
   b. somnolence.
   c. orthostatic hypotension.
   d. akathisia.

9. Which of the following antipsychotic medications must be taken with at least 350 calories because of bioavailability?
   a. paliperidone
   b. iloperidone
   c. asenapine
   d. lurasidone

10. Which of the following is an advantage that the newer atypical antipsychotics may have over older atypicals?
    a. a decreased risk of extrapyramidal side effects
    b. a favorable metabolic profile
    c. less expense
    d. no need to titrate the dose
    e. both a and b.
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Registration

Name: ____________________________________________________________ Degree: ____________________________
Street address: ___________________________________________________ Last 4 Digits of Social Security No. (Web ID): __________
City: ______________________________________ State: _________ Zip:__________ Telephone: _____________________________
E-mail address: ________________________________________________ Check one: □ Physician □ Pharmacist □ Other

Time needed to complete this CE activity in hours: □ 0.5 hr □ 1 hr □ 1.5 hr □ 2 hr □ Other __________

NABP ID # (required for pharmacists only): ________________ Date of birth (MM/DD): __________

Certification: I attest to having completed this CE activity. ________________________________________________________

Answer Sheet

Please fill in the box next to the letter corresponding to the correct answer

1. a □ b □ c □ d □ 5.   a □ b □ c □ d □
2. a □ b □ c □ d □ 6. a □ b □ c □ d □
3. a □ b □ c □ d □ 7. a □ b □ c □ d □
4. a □ b □ c □ d □ 8. a □ b □ c □ d □
5. a □ b □ c □ d □ 9. a □ b □ c □ d □
10. a □ b □ c □ d □ e □

Evaluation

Rate the extent to which: Very High High Moderate Low Very Low

1. Objectives of this activity were met □ □ □ □ □
2. You were satisfied with the overall quality of this activity □ □ □ □ □
3. Content was relevant to your practice needs □ □ □ □ □
4. Participation in this activity changed your knowledge/attitudes □ □ □ □ □
5. You will make a change in your practice as a result of participation in this activity. Specify the changes you plan to make. _________________________________________________________________________________________
6. This activity presented scientifically rigorous, unbiased, and balanced information □ □ □ □ □
7. Individual presentations were free of commercial bias □ □ □ □ □
8. Adequate time was available for Q&A □ □ □ □ □
9. Which ONE of the following best describes the impact of this activity on your performance:
   □ This program will not change my behavior because my current practice is consistent with what was taught.
   □ This activity will not change my behavior because I do not agree with the information presented.
   □ I need more information before I can change my practice behavior.
   □ I will immediately implement the information into my practice.

10. Will you take any of the following actions as a result of participating in this educational activity (check all that apply)
    □ Discuss new information with other professionals
    □ Consult the literature
    □ Participate in another educational activity
    □ Discuss with industry representative(s)
    □ None

Send the completed form and $15 payment (make checks payable to P&T) to: The Jefferson School of Population Health, Attn: Continuing Education Credit, 1015 Walnut Street, Suite 115, Philadelphia, PA 19107.

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