New Options for the Treatment of Schizophrenia: A Clinical Review of the Three Most Recent Antipsychotic Drugs

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Abstract: This clinical review summarizes the pharmacological characteristics, efficacy, and tolerability of asenapine, iloperidone, and lurasidone, the most recently approved antipsychotics in the treatment of schizophrenia. Newer agents have the task of distinguishing themselves for clinical use based on patient-relevant characteristics; some provide specialized features. The agents reviewed here are similar in overall clinical efficacy and tolerability, as well as being in a low risk for weight gain and metabolic syndrome, but are different in terms of formulation, schedule of administration, and particular side effects. Based on these distinguishing characteristics, we offer recommendations for the optimal clinical use of each drug.

Clinical context

Schizophrenia is arguably the most serious of mental illnesses and has been with us throughout civilization. Its most defining symptom set is psychotic symptoms, although cognitive, affective, and negative symptoms are present and remain treatment-resistant. Until the mid-20th century, no pharmacological treatments had yet been demonstrated for improving psychosis. In the 1950s, the discovery that chlorpromazine has antipsychotic properties revolutionized the treatment of schizophrenia (1). It was the subsequent discovery that the mechanism of action of chlorpromazine was monoamine (predominantly dopamine) receptor blockade (2) that filled our treatment coffers with many antidopaminergic antipsychotic drugs (APDs). In the early 1990s, the new wave of "second generation" APDs provided the added benefit of motor side effect relief, but these came with the additional side effect burden of exaggerated metabolic side effects. Now, however, the most recent APDs have tried to capture the best antipsychotic action with the lowest motor and metabolic (and other) side effects. The goal has been to reduce psychotic symptoms optimally, improve negative and cognitive symptoms (although all agree that this may involve additional neural pathways and novel agents), and increase patient satisfaction and compliance. In this paper we review the three newest antipsychotic drugs according to these treatment goals and provide data to support their specific actions and their best application. This discussion comes in the context of there being no firmly identified molecular targets for schizophrenia pathophysiology. Nonetheless, even though the discovery of these drugs was serendipitous and not rational, they do afford considerable relief for individuals with psychotic illness and physicians should be able to personally

Author Information and CME Disclosure

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optimize treatment plans for their patients with the many medications at hand.

Asenapine was approved by the Food and Drug Administration (FDA) in 2009 and is marketed under the brand name of *Saphris*. Structurally, its molecule belongs to the dibenzo-oxepino-pyrrole class and it resembles the tetracyclic antidepressant, mirtazapine (3).

Iloperidone obtained FDA approval in 2009 under the brand name *Fanapt* (4). The drug is structurally a piperidinyl-benzisoxazole derivative, similar to risperidone. During development, it was selected from a larger series of chemically related compounds because it showed higher potency in a test for limbic activity than in a test for nigrostriatal activity (5), thus being expected to show a favorable antipsychotic activity to extrapyramidal symptom ratio (5, 6).

Lurasidone gained FDA approval in 2010 for the treatment of schizophrenia. It is marketed as *Latuda*. Structurally, it is a benzisothizol derivative (7), similar to ziprasidone (8).

This review will summarize the pharmacological characteristics of the drugs, as well as their clinical development data as a way to inform their best use in patients with psychotic illnesses.

Pharmacodynamics

Drug receptor profiles indicate the propensity and potency of a specific compound for antipsychotic drug action (evidenced primarily by D_2 and 5-HT_{2A} affinity), as well as their potential side effect profile of motor, metabolic, and other actions.

Asenapine

In summary, asenapine has binding properties similar to quetiapine, olanzapine, and clozapine (9). Among the three newest antipsychotics, it has the broadest receptor binding profile. It has very high affinity for the dopamine receptors D_1, D_2, D_3, D_4, serotoninergic receptors 5-HT_{1A}, 5-HT_{1B}, 5-HT_{2A}, 5-HT_{2B}, 5-HT_{2C}, 5-HT_5, 5-HT_6, and 5-HT_7, alpha-adrenergic receptors α_{1A}, α_{2A}, and α_{2C}, and histaminic H_1 and H_2 receptors. It has negligible affinity for muscarinic receptors (10, 11) (Table 1).

Iloperidone

In summary, iloperidone has binding properties similar to risperidone, paliperidone, and ziprasidone (5, 9). Similar to asenapine, iloperidone displays a wide receptor binding profile. It has a very high binding affinity for dopamine D_3 receptors, the α_1 adrenergic and the serotoninergic 5-HT_{2A} receptors, and a high binding affinity for the dopamine D_2 and D_4 receptors, alpha-adrenergic α_{2C} receptors, and serotoninergic 5-HT_{1A}, 5-HT_6, and 5-HT_7 receptors. It has very low or negligible activity at the muscarinic receptors (11–14). Interestingly, at clinically relevant doses, iloperidone is a potent blocker of the hERG voltage gated, delayed, inwardly directed K^+ rectifying channel (15) (Table 1), and therefore may be associated with QT_c prolongation and cardiac arrhythmias.

Lurasidone

In summary, lurasidone has binding properties similar to risperidone, paliperidone, iloperidone, and ziprasidone. Lurasidone has a high binding affinity for the dopamine D_2, serotoninergic 5-HT_{2A}, 5-HT_7, 5-HT_{1A}, and alpha-adrenergic α_{2C} receptors. It has weak binding affinity for the adrenergic α_1, α_{2A}, and 5-HT_{2C} receptors, and has virtually no affinity for histamine H_1 and muscarinic acetylcholine receptors (16)(Table 1).

Pharmacokinetics, formulation, and metabolism

Asenapine is available as 5 mg and 10 mg rapidly dissolving tablets intended for sublingual administration. The recommended dosage is 5–10 mg twice daily. Food or liquid intake within 10 minutes of tablet administration considerably reduces its bioavailability. Moreover, swallowing the tablets reduces the bioavailability to less than 2%. Peak plasma concentrations are reached within 0.5–1.5 hours and steady state is attained 3 days after twice daily administration. Asenapine is metabolized mainly by glucuronidation by UGT1A4 and oxidation by CYP1A2 isoenzyme. In spite of smoking being a CYP1A2 inducer, it does not affect asenapine clearance. Caution is required when coadministering with fluvoxamine, a strong CYP1A2 inhibitor. Asenapine is contraindicated in severe hepatic impairment; no dose adjustment is necessary in renal impairment (17).

Iloperidone is formulated as 1, 2, 4, 6, 8, 10, and 12 mg tablets for oral administration. The recommended dosage of iloperidone is 12–24 mg divided in two daily doses. Because of the risk of orthostatic hypotension, the target dose requires titration, starting at 1 mg twice daily and escalating in increments not to exceed a total increase of 4 mg daily. Meals have no effect on iloperidone bioavailability. Peak plasma concentrations are reached within 2–4 hours and steady-state concentrations are attained after 3–4 days. Iloperidone undergoes hepatic metabolism, mainly by the CYP2D6 and CYP3A4 isoenzymes. Poor metabolizers of CYP2D6 substrates should have their

Table 1. Comparative Receptor Binding Affinities of Asenapine, Iloperidone, Lurasidone, Haloperidol, Clozapine, and Olanzapine

Receptor	Asenapine	Iloperidone	Lurasidone	Haloperidol	Risperidone	Clozapine	Olanzapine
Dopamine							
D_1	++++	++		+++	++	++	+++
D_2	++++	+++	++++	++++	++++	++	+++
D_3	++++	++++		++++	++++	++	+++
D_4	++++	+++		++++	+++	+++	+++
D_5		++		++	++	++	+++
Serotonergic							
5-HT_{1A}	+++/++++	+++	++++	+	++	+/++	- /+
5-HT_{1B}	++++	+++					
5-HT_{1D}	+++	+++			++++	++	++
5-HT_{2A}	++++	++++	++++	+++	++++	++++	+++/++++
5-HT_{2C}	++++	+++		+	+++	+++/++++	++++
5-HT_6	++++	+++		+	+	++++	+++
5-HT_7	++++	++/+++	++++	+/++	++++	+++	++
Alpha-adrenergic							
α_1	++++	++++	+++	+++	++++	+++/++++	+++
α_2	++++	+++	+++	+	+++	+++	
Histaminic							
H_1	++++	++	+	++	++++	++++	++++
Muscarinic							
M	-/+	-/+		-/+	-/+	++++	+++/++++
	(10, 11)	(11–14)	(16)	(11, 14, 16)	(11, 14, 16)	(11, 14, 16)	(11, 14, 16)

Empty cells correspond to receptor binding affinities that have not been studied for a particular drug.
Legend:
++++ = Very high affinity (<10 nM);
+++ = High affinity (equilibrium dissociation constant K_i = 10–100 nM);
++ = Moderate affinity (equilibrium dissociation constant K_i = 100–1,000 nM);
+ = Low affinity (equilibrium dissociation constant K_i = 1,000–10,000 nM); and
- = Negligible affinity (equilibrium dissociation constant K_i > 10,000 nM).

doses reduced by half. Likewise, coadministration of iloperidone with strong inhibitors of CYP2D6 requires halving the dose. Because of its propensity to prolong the QTc interval, administering iloperidone with other drugs prolonging the QTc interval should be avoided. Dose adjustments are not necessary in renal impairment. As iloperidone has not been studied in patients with hepatic impairment, its use is not recommended in this population (18).

Lurasidone is available in 20, 40, 80, and 120 mg formulations. The recommended dosing range is 40–160 mg administered once daily. To ensure maximum absorption, lurasidone should be taken with a meal containing at least 350 calories (19). Peak plasma concentrations are attained 1–3 hours after oral administration and steady state is reached after 7 days. It is metabolized in the liver mainly by the CYP3A4 isoenzyme, therefore coadministration with moderate CYP3A4 inhibitors require cutting the doses in half, whereas coadministration with moderate CYP3A4 inducers might require increased doses. Coadministration with strong CYP3A4 inhibitors or inducers is contraindicated. Dose adjustments are necessary in moderate and severe hepatic and renal impairment (20).

Antipsychotic efficacy

Asenapine

Short-Term Efficacy. The short-term efficacy of asenapine was assessed in two 6-week, double-blind trials, where patients with acute exacerbations of schizophrenia were randomized to receive fixed doses of asenapine, placebo, and an active comparator (21, 22). In both studies the primary efficacy measure was the improvement from baseline in the Positive and Negative Syndrome Scale (PANSS) total score. All

Table 2. Short-Term Efficacy of Asenapine

Study	Asenapine Dose	Active Comparator	Primary Outcome	Results
Kane et al. (21)	Asenapine 5 mg b.i.d. Asenapine 10 mg b.i.d	Haloperidol 4 mg BID	PANSS	With last observations carried forward (LOCF), mean PANSS total score reductions from baseline to endpoint were significantly greater with asenapine at 5 mg b.i.d (–16.2) and haloperidol (–15.4) than placebo (–10.7; both $p<0.05$); using mixed model for repeated measures (MMRM), changes at week 6 were significantly greater with asenapine 5 and 10 mg b.i.d (–21.3 and –19.4, respectively) and haloperidol (–20.0) than placebo (–14.6; all $p<0.05$).
Potkin et al. (22)	Asenapine 5 mg b.i.d	Risperidone 3 mg p.o. b.i.d	PANSS	Mean improvements on PANSS total were all significantly greater with asenapine than with placebo ($p<0.005$).

PANSS = Positive and Negative Syndrome Scale. BPRSd = Brief Psychiatric Rating Scale derived from PANSS.

studied doses of asenapine proved superior to placebo in decreasing the PANSS total score (Table 2).

Long-Term Efficacy. The long-term efficacy of asenapine in preventing relapses in schizophrenia was evaluated in stable participants with schizophrenia who were cross-titrated from their previous medications and underwent a 26-week course on open-label asenapine dosed as clinically indicated. The patients who remained stable entered a 26-week double-blind randomization phase, where they received either asenapine or placebo. The primary outcome was time to relapse/impending relapse based on the predetermined criteria. Times to relapse/impending relapse were significantly longer with asenapine than with placebo (both $p<0.0001$), with the incidence of relapse/impending relapse lower with asenapine than placebo (12.1% versus 47.4%, $p<0.0001$) (23).

Schoemaker et al. conducted a 52-week double-blind trial in which participants with schizophrenia treated in an inpatient or outpatient setting were randomized to receive asenapine 5–10 mg b.i.d or olanzapine 10–20 mg daily dosed as clinically indicated (24). Trial completion rates were 38% with asenapine and 57% with olanzapine; with the last observation forward, at the end of the trial, mean reductions in PANSS total scores were significantly higher for olanzapine (asenapine -21.0 ± 22.8; olanzapine -27.5 ± 22.0; $p<0.0001$, however, there was no significant difference between asenapine and olanzapine with observed case analysis (asenapine -35.9 ± 16.3; olanzapine -35.4 ± 16.2; $p=0.88$) (24). Patients who completed the 52-week trial and benefitted from treatment were eligible to continue until the study blind was broken (311.0±146.1 days for asenapine and 327.4±139.6 days for olanzapine). An additional PANSS total score improvement of -1.6 for asenapine and -0.8 for olanzapine was noted at the end of the extension study (25).

ILOPERIDONE

Short-Term Efficacy. Four randomized, placebo-controlled studies evaluated the short-term efficacy of iloperidone (26, 27), with three studies published within the same report and identified as study 1, study 2, and study 3, respectively (Table 3) (27). Multiple doses of iloperidone, ranging from 4 mg to 24 mg daily, were used. All studies included active comparators. The study duration was either 4 weeks (26) or 6 weeks (27). The primary efficacy measure was the change from baseline to endpoint in the PANSS total score (26, 27) or the BPRSd (Brief Psychiatric Rating Scale extracted from PANSS) score (27). Only selective doses of iloperidone led to statistically significant differences from placebo in the primary efficacy outcomes: iloperidone 24 mg daily ($p<0.01$) (26); study 1, iloperidone 12 mg/day ($p=0.047$); study 2, iloperidone 4–8 mg/day ($p=0.012$), and iloperidone 10–16 mg/day ($p=0.001$); and study 3, iloperidone 20–24 mg/day ($p=0.010$) (27) (Table 3). The data from these four studies was reexamined in a pooled analysis (28) that showed that only treatment with iloperidone 10–16 mg/day, iloperidone 20–24 mg/day, and the active comparators were associated with significantly improved BPRSd, PANSS total, PANSS positive, and PANSS negative scores versus treatment with placebo (all $p<0.05$).

Long-Term Efficacy. The long-term efficacy of iloperidone was evaluated in a 52-week double-blind study, where patients were randomized to

Table 3. Short-Term Efficacy of Iloperidone

Study	Iloperidone Dose	Active Comparator	Primary Outcome	Results
Potkin et al. (27)	Iloperidone 4 mg p.o. daily Iloperidone 8 mg p.o. daily Iloperidone 12 mg p.o. daily	Haldol 15 mg p.o. daily	PANSS total score	PANSS total scores significantly improved from baseline with iloperidone 12 mg/day ($p=0.047$) and with haloperidol ($p<0.001$).
Potkin et al. (27)	Iloperidone 4–8 mg p.o. daily Iloperidone 10–16 mg p.o. daily	Risperidone 4–8 mg p.o. daily	BPRSd	BPRSd scores significantly improved from baseline with iloperidone 4 to 8 mg/day ($p=0.012$), iloperidone 10 to 16 mg/day ($p=0.001$), and risperidone 4–8 mg p.o.daily ($p<0.001$).
Potkin et al. (27)	Iloperidone 12–16 mg p.o. daily Iloperidone 20–24 mg p.o.daily	Risperidone 6–8 mg p.o. daily	BPRSd	BPRSd scores significantly improved from baseline with iloperidone 20 to 24 mg/day ($p=0.010$) and risperidone 6–8 mg p.o. daily ($p<0.001$).
Cutler et al. (26)	Iloperidone 24 mg p.o. daily	Ziprasidone 160 mg p.o.daily	PANSS total score	PANSS total scores significantly improved from baseline with iloperidone 24 mg/day ($p<0.01$) and with ziprasidone ($p<0.05$).

a iloperidone 4–16 mg/day or haloperidol 5–20 mg/day. Patients who met the predetermined criteria for stabilization at 6 weeks were further continued in a 46-week extension study, where the primary efficacy variable was time to relapse. The reasons for relapse and the rates of relapse were similar for the iloperidone (43.5%) and haloperidol (41.2%) groups. The mean time to relapse was 89.8 days with iloperidone (median, 50.0 days) and 101.8 days with haloperidol (median, 78.0 days), however, the difference between the groups was not statistically significant (29).

LURASIDONE

Short-Term Efficacy. The short-term efficacy of lurasidone was evaluated in five 6-week, double-blind, placebo-controlled studies conducted in patients with exacerbations of schizophrenia (30–34). All studies used different fixed doses of lurasidone in the range of 40 to 120 mg daily, which was sometimes compared with a well-established antipsychotic to control for assay sensitivity (30, 31). In all but two studies (32, 34), the primary efficacy measure was the change from baseline to week 6 in the PANSS total score. In the two remaining studies (32, 34), the change from baseline on the BPRSd (Brief Psychiatric Rating Scale extracted from PANSS) was used as the primary outcome measure. With one exception (33), all studied doses of lurasidone proved superior to placebo at 6 weeks. In the study by Nasrallah et al. (33), while all three doses of lurasidone (40 mg, 80 mg, 120 mg) lead to meaningful clinical improvements in the PANSS total, only treatment with lurasidone 80 mg/day resulted in a statistically significantly improvement in the PANSS total score compared with placebo (Table 4).

Long-Term Efficacy. Two of the 6-week placebo-controlled studies (30, 31) continued as open-label extension studies assessing the long-term efficacy of flexibly dosed lurasidone in schizophrenia.

In the Loebel et al. study (35), participants who achieved predefined response criteria were continued on their initial medications (lurasidone or quetiapine XR) for 12 months, and participants initially treated with placebo were started on lurasidone. Both medications were flexibly dosed: lurasidone 40–160 mg p.o. daily and quetiapine XR 200–800 mg p.o. daily. The primary outcome measure was the time to relapse. The Kaplan-Meier estimate of the probability of relapse over 12 months was 23.7% for subjects receiving lurasidone versus 33.6% for quetiapine XR; additionally, the probability of hospitalization at 12 months was lower for the lurasidone group compared with the quetiapine XR group (9.8% versus 23.1%; log-rank $p=0.049$).

In the study by Stahl et al. (36), participants who completed the 6-week, double-blind, placebo-controlled study evaluating the efficacy of fixed doses of lurasidone 40 mg, lurasidone 120 mg, or olanzapine 15 mg (31) were eligible to continue flexibly dosed lurasidone 40–120 mg daily for a duration of 6 months. Overall, participants demonstrated continued improvement in the PANSS total score, with the mean change of −8.7 from the open-label baseline to the end of the study.

Table 4. Short–Term Efficacy of Lurasidone

Study	Lurasidone Dose	Active Comparator	Primary Outcome	Results
Nasrallah at el. (33)	40 mg/day 80 mg/day 120 mg/day	No	PANSS total score	All three dose of lurasidone resulted in PANSS total score decreases, however only treatment with lurasidone 80 mg/day separated from placebo (–23.4 versus –17.0; $p<0.05$).
Loebel et al. (30)	80 mg/day 160 mg/day	Quetiapine XR 600 mg/day	PANSS total score	All three active treatment arms achieved significant improvements in PANSS total score. Responder rates (≥20% improvement in PANSS total score) were significantly higher in the groups receiving active treatments: lurasidone 80 mg (65%; $p<0.001$), lurasidone 160 mg (79%; $p<0.001$), and quetiapine XR 600 mg (79%; $p<0.001$) compared with placebo (41%).
Ogasa et al. (34)	40 mg/day 120 mg/day	No	BPRSd	Both doses of lurasidone significantly separated from placebo in the primary outcome measure (mean change from baseline –9.4 versus –3.8, p=0.0018 for lurasidone 40 mg versus placebo; –11.0 versus –3.8, p=0.004 for lurasidone 120 mg versus placebo).
Meltzer et al. (31)	40 mg/day 120 mg/day	Olanzapine 15 mg/day	PANSS total score	All three active treatment groups experienced greater symptomatic improvement as compared with placebo on all PANSS total score [lurasidone 40 mg (–25.7; adjusted p=0.002); lurasidone 120 mg (–23.6; adjusted p=0.022); olanzapine group (–28.7, $p<0.001$); placebo (–16.0)].
Nakamura et al. (32)	80 mg/day	No	BPRSd	Lurasidone 80 mg achieved proved superior to placebo on BPRSd (least squares mean +/− SE=–8.9 +/–1.3 versus –4.2 +/–1.4; p=0.012).

Safety and tolerability

Asenapine

The *short-term* safety and tolerability data for asenapine were derived (17) from a pooled analysis of three 6-week fixed-dose trials and one 6-week flexible-dose trial conducted in participants with acute exacerbations of schizophrenia. The most common side effects (frequency >5% and twice the rate of placebo) were somnolence (13%), akathisia (6%), and oral hypoesthesia (5%). A total of 9% of participants in the asenapine group and 10% in the placebo group discontinued the study because of treatment-related side effects.

The *long-term* safety and tolerability of asenapine was investigated by Schoemaker et al. (24) in the previously mentioned 52-week double-blind trial in which participants with schizophrenia were randomized to receive asenapine 5–10 mg b.i.d or olanzapine 10–20 mg daily dosed as clinically indicated. The most frequently noted adverse effects were for weight gain (12% in the asenapine group; 29% in the olanzapine group), insomnia (7% in the asenapine group; 5% in the olanzapine group), sedation (8% in the asenapine group; 10% in the olanzapine group), somnolence (9% in the asenapine group; 10% in the olanzapine group), gastro-intestinal symptoms (9% in the asenapine group; 7% in the olanzapine group), and akathisia (8% in the asenapine group; 4% in the olanzapine group). Weight gain at week 52 was 1.6±5.7 kg for asenapine and 5.6±8.4 kg for olanzapine.

ILOPERIDONE

The *short-term* safety and tolerability of iloperidone was evaluated (37) in a pooled analysis of the three previously described 6-week phase 3 trials (27). Most commonly, patients treated with iloperidone experienced dizziness, headache, dry mouth, nausea, and insomnia. Discontinuation rates due to adverse effects were similar for iloperidone and placebo (4.8%), and lower than those for haloperidol (7.6%) and risperidone (6.2%). Extrapyramidal symptoms and akathisia significantly improved from baseline with iloperidone, remained unchanged with risperidone, and worsened with haloperidol. The QTc interval significantly increased with iloperidone (9.1 ms) and haloperidol (5.0 ms) and remained unchanged with placebo. Significant weight changes from baseline were observed with iloperidone (1.5−2.1 kg, dependent on the dose) and risperidone (1.5 mg kg), but not with haloperidol (−0.1 kg). Prolactin levels generally decreased with iloperidone treatment, and significantly increased with risperidone and haloperidol. Blood glucose, cholesterol, and triglyceride levels underwent negligible and similar changes across all treatment groups (37).

The *long-term* safety data were derived from the pooled analysis of three 52-week prospective multicenter studies, each with 6-week stabilization followed by 46-week double-blind maintenance phases, whereby iloperidone was compared with haloperidol (29). The most common adverse events observed with iloperidone were insomnia (18.1%), anxiety (10.8%), and acute relapses (8.9%). Similar to the observation in the acute tolerability studies, extrapyramidal symptoms improved with iloperidone and worsened with haloperidol. The QTc interval increased in both groups (10.3 msec with iloperidone and 9.4 msec with haloperidol). A more recent 25-week study (38) investigated the safety and tolerability of iloperidone 12–24 mg daily dosed as clinically indicated in comparison with ziprasidone. The most common side effects reported with iloperidone were headache, weight gain, nausea and vomiting, dry mouth, and stomach discomfort. Glucose, lipids, and prolactin did not increase over the study period.

LURASIDONE

The *short-term* safety data for lurasidone were derived from the pooled analysis (20) of the five 6-week randomized clinical trials (30–34), totaling N=1,508 participants treated with lurasidone 20–160 mg daily. The most common side effects with lurasidone (occurring at incidence >5% and at a rate twice that of placebo) included somnolence (17%), akathisia (13%), extrapyramidal symptoms (14%), and nausea (10%).

The *long-term* safety and tolerability of lurasidone were investigated in a clinically stable population of participants with schizophrenia, who received either lurasidone 40–120 mg p.o. daily or risperidone 2–6 mg daily for a period of 12 months (39). The most common side effects occurring in the lurasidone group were nausea (16.7% in the lurasidone group; 10.9% in the risperidone group), insomnia (15.8% in the lurasidone group; 13.4% in the risperidone group), and sedation (14.6% in the lurasidone group; 13.9% in the risperidone group). The most common side effects in the risperidone group were weight gain (19.8% in the risperidone group; 9.3% in the lurasidone group), somnolence (17.8% in the risperidone group; 13.6% in the lurasidone group), and headache (14.9% in the risperidone group; 10.0% in the lurasidone group) (14.9 versus 10.0%). The median baseline to endpoint increase in prolactin was significantly higher for risperidone ($p<0.001$). Overall, a higher proportion of patients discontinued the study because of an adverse effect in the lurasidone group (21.5%) than in the risperidone group (14.4%).

COST OF TREATMENT

Information about the cost of therapy for each drug, in comparison with the pricing information for the generic risperidone and olanzapine tablets, was extracted from www.uptodate.com and is presented in Table 5.

RECOMMENDATIONS FROM THE AUTHORS

Asenapine is the only medication among the three newest antipsychotics with a sublingual administration, making it an ideal choice when treatment compliance needs to be monitored. Additionally, as glucuronidation is one of the major metabolism pathways, asenapine has the lowest risk of important drug–drug interactions. Furthermore, it represents a safe choice in patients with renal impairment, where no dose adjustments are necessary. However, the drug sedative properties may be bothersome, especially following morning administration.

The advantages of iloperidone are a favorable extrapyramidal symptom profile, with a low risk of akathisia, a relatively low propensity to cause metabolic syndrome, including weight gain and impairment of glucose and lipid metabolism, modest prolactin elevation, and the safe administration in renal impairment. However, because of the propensity to produce orthostatic hypotension, it requires a slow titration that may delay the therapeutic effect. Its propensity to prolong the QTc interval requires careful

Table 5. Comparative Pricing Information for 10 Tablets of Asenapine, Iloperidone, Lurasidone, Generic Risperidone, and Generic Olanzapine (40)

Drug	Cost
Asenapine	5 mg tablets: $ 137.94 10 mg tablets: $137.94
Iloperidone	1, 2, 4, 6, 8, 10, 12 mg tablets: $153.17
Lurasidone	20, 40, 60, 80 mg tablets: $267 120 mg tablets: $398.52
Risperidone	0.25 mg tablets: $39 0.5 mg tablets: $42.81 1 mg tablets: $45.51 2 mg tablets: $76.06 3 mg tablets: $89.33 4 mg tablets: $120
Olanzapine	2.5 mg tablets: $111.85 5 mg tablets: $132 7.5 mg tablets: $160.65 10mg tablets: $198.93 15 mg tablets: $298.4 20 mg tablets: $397.66

ECG monitoring and makes it an undesirable choice in clinical situations where risks of arrhythmias are high.

Lurasidone is a medication with a favorable tolerability and safety profile. Among the three newest antipsychotics, it is the only one that can be dosed once daily; additionally, it does not require titration to reach a therapeutic dose. Importantly, it is not associated with significant risk of weight gain or metabolic syndrome, making it a rational choice when the consideration of metabolic risks weighs heavily in the medical decision-making. The most commonly observed side effects are sedation and extrapyramidal symptoms, which are present especially at the beginning of the treatment.

Finally, these three drugs do not differ in their therapeutic actions on psychosis, but may provide considerable individual optimal treatment based on their side effect profiles. Characteristics of their individual pharmacology are also distinguishing and provide treatment rationales. Individual preference around side effect profile may influence treatment compliance and ultimate treatment efficacy.

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