Asenapine, Blonanserin, Iloperidone, Lurasidone, and Sertindole: Distinctive Clinical Characteristics of 5 Novel Atypical Antipsychotics

Sheng-Min Wang, MD, Changsu Han, MD, PhD,† Soo-Jung Lee, MD, PhD,* Ashwin A. Patkar, MD,‡ Prakash S. Masand, MD,§ and Chi-Un Pae, MD, PhD*‡*

Abstract: Schizophrenia is a serious, chronic, and devastating mental illness with a substantial impact on psychological, physical, social, and economical areas of an individual and society. To treat such critical mental illness, a number of first-generation (typical) and second-generation (atypical) antipsychotics are currently available in the market. Despite such treatment options, most of patients with schizophrenia have a poor treatment outcome and become treatment resistant, causing continual deterioration on positive, negative, and cognitive symptoms, resulting in impairment of socio-occupational functioning. Hence, additional novel antipsychotics with better efficacy, safety, and tolerability profiles are needed to enable clinicians to diversify treatment options to improve treatment of schizophrenia. Recently, the 3 antipsychotics, including iloperidone (2009), asenapine (2009), and lurasidone (2010), have been approved by the US Food and Drug Administration. Two other atypical antipsychotics, including sertindole and blonanserin, are approved and used outside the United States for treatment of schizophrenia. Sertindole, after it has been voluntarily suspended by the manufacturer in 1998 due to its potential risk in causing cardiovascular-related death, was relaunched to the European market in 2005. More recently, blonanserin was approved in Japan (2008) and in Korea (2009) for the management of schizophrenia. Individual antipsychotic may have differential pros and cons compared with other antipsychotic in terms of efficacy, safety, tolerability, restoration of functional capacity, and economic aspect reflecting relapse prevention. The purpose of this review was to provide distinctive clinical characteristics and up-to-date of clinical trial data of the 5 novel atypical antipsychotics for the management of schizophrenia, which may deliver clinicians better understanding in the use of such atypical antipsychotics for the treatment of schizophrenia in clinical practice.

Key Words: asenapine, blonanserin, iloperidone, lurasidone, sertindole, clinical characteristics

(*Clin Neuropharm* 2013;36: 223–238)

Schizophrenia, which affects approximately 1% of the population, is a devastating illness with a chronic impact on psychological, physical, social, and economical areas of an individual.[1,2] Symptoms of schizophrenia are categorized as positive (eg, hallucinations), negative (eg, flat affect), and cognitive (eg, impaired attention).[3,4] After serendipitous discovery of chlorpromazine in 1953, antipsychotics have long been the mainstay of treatment for schizophrenia. Antipsychotics are generally classified as first-generation (typical) and second-generation (atypical) medications.

Typical antipsychotics work by dopamine D_2 receptor antagonism activity, whereas both dopamine D_2 and serotonin 5-HT_{2A} receptor antagonism play an important role in the action of atypical antipsychotics. Both typical and atypical antipsychotics are known to be effective for reducing symptoms and preventing relapse in adults with schizophrenia.[5,6] Initially, atypical antipsychotics were speculated to have better treatment effect in improving negative symptoms and cognitive functioning than typical antipsychotics. However, recent studies failed to prove this speculation.[7,8] More importantly, a study suggests that only 10% to 20% of patients with schizophrenia show a good outcome and recover to their preillness levels of functioning.[9] Another 15% to 20% of patients show a poor outcome and become treatment resistant, causing continual deterioration on positive, negative, and cognitive symptoms, resulting in impairment of socio-occupational functioning. Therefore, additional novel antipsychotic drugs with better efficacy, safety, and tolerability profiles are needed to enable clinicians to diversify treatment options to improve treatment of schizophrenia.[10]

Currently, 10 atypical antipsychotics are approved by the US Food and Drug Administration (FDA) for the treatment of schizophrenia. The 3 most recently approved antipsychotics include iloperidone (2009), asenapine (2009), and lurasidone (2010). Two other atypical antipsychotics, having no FDA indication, are approved and used outside the United States for treatment of schizophrenia. Sertindole, after it has been voluntarily suspended by the manufacturer in 1998 due to its potential risk in causing cardiovascular-related death, was relaunched to the European market in 2005. More recently, blonanserin was approved in Japan (2008) and in Korea (2009) for the management of schizophrenia.[11]

The purpose of this review was to provide distinctive clinical characteristics of the 5 novel atypical antipsychotics. We have reviewed available clinical data of each drug, focusing on their approved indications. The 5 drugs are presented in an alphabetical order. A search of the studies used the key terms "names of five each antipsychotics" from the databases (PubMed and MEDLINE) and web resources such as the FDA. The studies searched were verified for publication in peer-reviewed journals. We also used reference lists from identified articles and reviews to find additional studies. No date or language constraints were used. Proceedings of the scientific meetings were also searched for paper and poster presentations. Literature search and verification were handled first by one of the authors (S.M.W.) and then independently reassessed by (C.H. and C.U.P.). The style of this paper is a narrative review and

*Department of Psychiatry, The Catholic University of Korea, College of Medicine; †Department of Psychiatry, Korea University College of Medicine, Seoul, Republic of Korea; ‡Department of Psychiatry and Behavioural Sciences, Duke University Medical Center, Durham, NC; and §Global Medical Education, New York, NY.

Conflicts of Interest and Source of Funding: The authors have no conflicts of interest to declare.

Address correspondence and reprint requests to Chi-Un Pae, MD, PhD, Department of Psychiatry, Bucheon St Mary's Hospital, The Catholic University of Korea, College of Medicine, 2 Sosa-Dong, Wonmi-Gu, Bucheon 420-717, Kyeonggi-Do, Republic of Korea; E-mail: pae@catholic.ac.kr

DOI: 10.1097/WNF.0b013e3182aa38c4

thereby all relevant studies meeting a scope of the present review purpose were selected based on the consensus among the authors.

INDICATION AND DOSAGE

Asenapine

Asenapine is FDA approved for both schizophrenia and bipolar disorder.[12] It is available as a sublingual tablet. Thus, asenapine must be placed under the tongue and allow it to dissolve completely to ensure optimal absorption. Eating and drinking should be avoided for 10 minutes after tablet administration. For schizophrenia, the recommended initial and target dose of asenapine is 5 mg twice a day (bid), which could be incremented up to 10 mg bid after 1 week of dosage titration.[12,13] In patients with bipolar disorder, 10 mg bid could be administered without dosage titration.

Blonanserin

Blonanserin has no FDA approval. However, it is approved for treatment of schizophrenia in Japan,[14] available as both tablet and 2% powder formulation, and in South Korea,[15] available only as tablet formulation. The recommended starting dose of blonanserin is 4 mg bid, taken after a meal. A gradual dose increment is recommended, and maximum daily dose should not exceed 24 mg.

Iloperidone

Iloperidone is FDA approved for acute treatment of schizophrenia.[16] The drug is available as 1, 2, 4, 6, 8, 10, and 12 mg in tablet formulations. The recommended initial dose of iloperidone is 1 mg bid with effective dose ranging 12 to 24 mg/d. Gradual dosage increment, with doubling the dosage each day, is needed to reduce risk of developing orthostatic hypotension.[16,17] Iloperidone can be given with or without food.

Lurasidone

Lurasidone is FDA approved for acute treatment of schizophrenia.[18] The drug is available as 20, 40, 80, and 120 mg in tablet formulations. The recommended starting dose of lurasidone is 40 mg/d, taken after a meal containing at least 350 calories.[18,19] It has been shown to be effective in dose range of 40 to 160 mg/d. Thus, no initial dose titration is required and maximal daily dose should not exceed 160 mg.

Sertindole

Sertindole was initially approved for the treatment of schizophrenia within the European Union in 1996. However, it was voluntarily suspended by the manufacturer in 1998 because of higher cardiovascular mortality associated with sertindole was suggested when compared with other atypical antipsychotics.[20] Data from subsequent extensive postmarket and epidemiological studies regarding safety of sertindole failed to show a direct association of the development of fatal arrhythmias and prolonged QTc interval with sertindole use in treatment of schizophrenia.[21] Therefore, it was relaunched to the European market in 2005 under the agreement that close electrocardiographic (ECG) monitoring would be conducted.[22] The recommended initial dose of sertindole is 4 mg/d with effective dose ranging 12 to 20 mg/d. A gradual dose increment over a week is recommended to minimize risk of orthostatic hypotension, and maximum daily dose should not exceed 24 mg.

PHARMACODYNAMICS

The summary of pharmacodynamic characteristics of the 5 atypical antipsychotics is provided in Table 1.

Asenapine

Asenapine targets the widest ranges of receptor. Specifically, asenapine has a high affinity and antagonistic properties for the following 5-HT 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; dopamine receptors: D_1, D_2, D_3, D_4; and α-adrenergic receptors: α_1, α_{2A}, α_{2B}, and α_{2C}.[12] Its affinity for 5-HT_{2A} is the highest

TABLE 1. Binding Affinities (*Ki* Values in nM)* of Asenapine, Blonanserin, Iloperidone, Lurasidone, and Sertindole

Receptors	Asenapine[12,27]	Blonanserin[14,29]	Iloperidone[16,32,33]	Lurasidone[18,34]	Sertindole[42,43]
D_1	1.4^{+++}	1070	216^{+}	262^{+}	
D_2	1.3^{+++}	0.14^{++++}	$6.3–21.4^{+++}$	0.994^{++++}	0.45^{++++}
D_3	0.42^{++++}	0.49^{++++}	7.1^{+++}		
D_4	1.1^{+++}		25^{++}		
5-HT_{1A}	2.5^{+++}		168^{+}	6.75^{+++}	
5-HT_{2A}	0.06^{++++}	0.81^{++++}	5.6^{+++}	0.47^{++++}	0.2^{++++}
5-HT_{2C}	0.034^{++++}	26.4^{++}	42.8^{++}	415^{+}	0.51^{++++}
5-HT_6	0.25^{++++}	41.9^{++}	63.1^{++}		0.74^{++++}
5-HT_7	0.13^{++++}		112^{+}	0.495^{++++}	
α_1	1.2^{+++}	26.7^{++}	$<5^{+++}$	48^{++}	1.4^{+++}
α_2	$0.33–1.2^{++++}$		16^{++}	$10.8–40.7^{++}$	
H_1	1^{+++}	—	437^{+}	$>1000^{-}$	—
M_1	8128^{-}	—	$>10{,}000^{-}$	$>1000^{-}$	—

**Ki*: 1001–10,000, minimal to none (−); 101–1000, low affinity (+); 10–100, moderate affinity (++); <10, high affinity (+++); <1, very high affinity (++++).

5-HT_{1A}, serotonin$_{1A}$ receptor; 5-HT_{2A}, serotonin$_{2A}$ receptor; 5-HT_{2C}, serotonin$_{2C}$ receptor; 5-HT_6, serotonin$_6$ receptor; 5-HT_7, serotonin$_7$ receptor; D_1, dopamine D_1 receptor; D_2, dopamine D_2 receptor; D_3, dopamine D_3 receptor; D_4, dopamine D_4 receptor; H_1, histamine$_1$ receptor; M_1, muscarine$_1$ receptor; α_1, α_1-adrenoreceptor; α_2, α_2-adrenoreceptor.

among the 5 atypical antipsychotics. Among currently available antipsychotics, asenapine has the highest affinity for 5-HT_{2C} receptors. Thus, asenapine may have an advantage over other antipsychotics in terms of improving schizophrenia's negative symptoms.[23,24] Because asenapine has high affinity for 5-HT_6, 5-HT_7, and α-adrenergic receptors with no appreciable affinity for muscarinic cholinergic M_1 receptors, it may potentially improve cognitive functions. A study in rat brain showed that asenapine might have a reduction in inotropic glutamate *N*-methyl-D-aspartate receptor binding and increased α-amino-3-hydroxyl-5-methyl-4-isoxazole-propionate receptor binding activity.[25] This unique activity of asenapine may play an important role in the treatment of schizophrenia and bipolar disorder.[26] Asenapine is also known to have an up-regulating effect on D_1-like receptors.[27] Thus, asenapine might potentially have a decreased likelihood of causing extrapyramidal symptom (EPS)–related adverse events (AEs).[28]

Blonanserin

Blonanserin has a very high affinity for D_2, D_3, and 5-HT_{2A} receptors.[29] It displays a unique pharmacodynamic property, with having the highest D_2 receptor occupancy among the 5 atypical antipsychotics. More importantly, in contrast with most other atypical antipsychotics, its receptor occupancy was several-fold higher for D_2 receptors than for 5-HT_{2A} receptors. Striatal D_2 receptor occupancy rates 2 and 12 hours after blonanserin 15 mg/d were 95% and 76%, respectively.[14] Thus, its higher D_2 receptor occupancy and potent antagonism at such receptors may contribute to a higher risk of EPS than other atypical antipsychotics.[30] A study has confirmed this speculation by reporting that higher incidence of EPS was observed with blonanserin than with risperidone in patients with schizophrenia (CLINICAL EFFICACY section, Blonanserin).[29] The functional significance of D_3 receptors is still not known. Except for iloperidone, blonanserin's adrenergic α_1 receptor blocking activity is the lowest among the 5 atypical antipsychotics. Thus, blonanserin might have less risk of causing dizziness and hypotension.[31] It is almost completely devoid of histamine H_1 and muscarinic M_1 antagonist activity, so its risk of causing sedation is minimal.[14]

Iloperidone

Along with asenapine, iloperidone targets the widest ranges of receptor with varying affinities. Iloperidone demonstrates high binding affinity for α_1-adrenergic receptors, 5-HT_{2A}, and D_2 and D_3 receptors.[16] However, receptor affinity for 5-HT_{2A}, and D_2 of iloperidone are the lowest among the 5 atypical antipsychotics. Iloperidone's affinity for H_1 receptors is minimal, so it is expected to have a very low risk of sedation or weight gain.[32] Its high affinity for noradrenergic α_1 and moderate affinity for α_2 receptors predict a higher risk of dizziness, syncope, and orthostatic hypotension.[30,32] Iloperidone's affinities for 5-HT_{2C}, 5-HT_6, 5-HT_{1A}, and D_1 receptors are moderate to low.[33] Functionally, iloperidone is an antagonist at the D_2, D_3, 5-HT_{1A}, and norepinephrine α_1 and α_{2C} receptors.

Lurasidone

Lurasidone is a potent antagonist of the D_2 and $5HT_{2A}$ receptors, with a stronger affinity for the $5HT_{2A}$ receptor.[18] A study showed that occupation of D2 receptor at lurasidone dosages of 10, 20, 40, 60, and 80 mg ranged from 41.3% to 43.3%, 51% to 54.8%, 63.1% to 67.5%, 77.4% to 84.3%, and 72.9% to 78.9%, respectively.[34] Because 60% to 80% receptor occupancy of D_2 is required to exhibit an antipsychotic response, its antipsychotic effect is expected from 40 mg/d.[35] Lurasidone also has a very strong affinity for 5-HT_7 receptor, which might provide a potential benefit on cognition.[36] Lurasidone has a partial agonistic activity at 5-HT_{1A} receptor, which may be linked with antidepressant- or anxiolytic-like effects.[36,37] Lurasidone has a low weak affinity for $5HT_{2C}$ receptors, and minimal affinity for H_1 or M_1 receptors.[18,36] Thus, lurasidone theoretically would have less risk of weight gain, sedative effect, and anticholinergic effect.

Sertindole

Sertindole has a very strong affinity for α_1-adrenergic, 5-HT_{2A}, 5-HT_{2C}, and 5-HT_6 receptors, whereas its effect on M_1 and H_1 receptors is minimal.[38] Sertindole's 5-HT_6 receptor antagonistic activity in the absence of anticholinergic and antihistaminic actions might provide a potential benefit on improving cognitive functions while having lower risk of sedation.[39] Such a potential benefit has been indeed shown in several animal studies.[39–41] The fact that sertindole binds more selectively to dopamine receptors in mesolimbic pathways, while having very little effect on nigrostriatal pathways,[42] might contribute to causing less EPS compared with other antipsychotics.[43,44]

PHARMACOKINETICS

Table 2 summarizes pharmacokinetic properties of 5 atypical antipsychotics.

Asenapine

Asenapine is the only drug requiring sublingual administration because its bioavailability in sublingual form is 35%, but its bioavailability decreases to less than 2% when it is swallowed in tablet form.[12] Intake of water can also decrease its bioavailability by 6%. Thus, patients taking asenapine should avoid eating and drinking for at least 10 minutes after taking the medication. Asenapine has the shortest time to peak plasma concentrations (t_{max}) among the 5 atypical antipsychotics (0.5–1.5 hours). Primary clearance route of asenapine is hepatic. Direct glucuronidation by UTG1A4 and oxidative metabolism by cytochrome P450 (CYP) isoenzymes (predominantly 1A2) are the major routes of elimination.[12,45] Therefore, caution is needed when asenapine is coadministered with fluvoxamine, a potent CYP1A2 inhibitor. Asenapine was well tolerated in patients with mild to moderate hepatic impairment, but asenapine exposures were 7 times higher in patients with severe hepatic impairment than in patients with normal hepatic function.[12,46] Thus, dose adjustment is not required in patients with mild-moderate hepatic impairment, but its use in severe hepatic impairment patients is not recommended. The exposure of asenapine was comparable with subjects in normal renal functions and in mild to moderate renal impairment. However, the use of asenapine in patients receiving dialysis has not been studied.

Blonanserin

Blonanserin's oral bioavailability is 84%, which is relatively higher than other 4 atypical antipsychotics except for iloperidone. The protein binding of blonanserin is greater than 99.7%, which is one of the highest among the 5 atypical antipsychotics.[14] Blonanserin is recommended taken after a meal because its C_{max} was 2.68 times higher in the fed state than in the fasting state. Steady state was reached about 5 days after receiving 4 mg/d in 10 healthy volunteers.[31] Blonanserin is mainly eliminated through urine (59%) and feces (30%).

TABLE 2. Pharmacokinetics of Asenapine, Blonanserin, Iloperidone, Lurasidone, and Sertindole*

Pharmacokinetic Parameter	Asenapine[12,45]	Blonanserin[14,31]	Iloperidone[16,47]	Lurasidone[18,19]	Sertindole[49–51]
Bioavailability, %	35	84	96	9–19	75
C_{max}, ng/mL	4	0.14	2.2–5.2		2.0–9.1
t_{max}, h	0.5–1.5	1.5	2–4	1–3	10
Time to steady state concentration, d	3 (twice daily dosing)	5	3–4	7	14–21
Protein bound, %	95	≥99.7%	93	99.8	99.5
$t_{1/2}$, h	24	10.7	13.5–14	18	53
Clearance rate, L/h	52	0.15 (2 mg/d)	47–102	3.9	10–15
CYP metabolism	1A2	3A4	3A4, 2D6	3A4	3A4, 2D6
Main excretion route	Hepatic	Urination and defecation	Urination and defecation	Defecation	Defecation

*All data are from single daily dose unless otherwise specified: asenapine, single dose of 5 mg in sublingual form; blonanserin, single dose of 4 mg in tablet form; iloperidone, single dose of 3 to 5 mg; lurasidone, single dose of 40 mg.

C_{max}, maximum plasma concentration; CYP, cytochrome P450; ER, extended release; $t_{½}$, terminal elimination half-life; t_{max}, time to C_{max}.

It is also extensively metabolized via CYP3A4. Thus, blonanserin is contraindicated in patients taking CYP3A4 inhibitors (ie, ketoconazole). Use of blonanserin in patients with renal or hepatic impairment has not been studied.[14] However, because plasma concentrations of blonanserin may be increased, careful administration is recommended in patients with hepatic impairment.

Iloperidone

Iloperidone's oral bioavailability is 96%, which is the highest among the 5 atypical antipsychotics.[16] A study showed that t_{max} is increased after food intake (2.2 hours in fasting state vs 4.3 hours in fed state).[47] However, it can be administered regardless of meals.[16] Most of iloperidone is recovered in feces, which indicates that the drug undergoes biliary excretion. Iloperidone is extensively metabolized by CYP3A4 and 2D6.[16] Thus, 50% dose reduction of iloperidone is recommended when coadministered with potent inhibitors of CYP3A4 or 2D6. No dose adjustment of iloperidone is required in patients with renal or hepatic impairment. However, half-life was significantly prolonged in patients with renal impairment compared to healthy controls (33.7 vs 15 hours, $P < 0.05$).[48] In addition, patients with hepatic impairment showed significantly greater C_{max} of P88-8991, which is one of 2 metabolites of iloperidone.

Lurasidone

Lurasidone has the lowest oral bioavailability (9%–19%) and the highest protein biding abilities (99.8%) among the 5 atypical antipsychotics.[18] Food intake resulted in 2-fold and 3-fold increase of C_{max} and area under the curve, respectively, over fasting condition. Thus, lurasidone should be taken with a meal. Lurasidone is chiefly eliminated through feces (80%) and only 9% of the orally administered drug is recovered in urine.[18] Lurasidone, like blonanserin, is also extensively metabolized by CYP3A4. Therefore, lurasidone dosage should not exceed 40 mg/d when coadministered with a moderate CYP3A4 inhibitor (diltiazem), and it should not be coadministered with drug having strong CYP3A4 inhibiting properties (ie, ketoconazole).[19] Lurasidone concentration was increased by 1.5, 1.7, and 3 times in patients with mild, moderate, and severe hepatic impairment, respectively, and 1.5 to 2 times in patients with moderate or severe renal impairment.[18] Thus, maximum daily dose of lurasidone in patients with moderate to severe hepatic or renal impairment should not exceed 40 mg.

Sertindole

The protein binding of sertindole is relatively high (99.5%), which is comparable to that of blonanserin and lurasidone. Sertindole has the longest terminal elimination half-life (>53 hours) among the 5 atypical antipsychotics.[49,50] Accordingly, time to steady-state concentration of sertindole (2–3 weeks) is also the longest. Sertindole is primarily eliminated through defecation. Like iloperidone, it is extensively metabolized by CYP3A4 and 2D6. No dose adjustment of sertindole is needed in patients with mild to severe renal impairment.[51] However, dose reduction is required in patients with mild to moderate hepatic impairment because clearance of sertindole is decreased in patients with such a condition. Sertindole is contraindicated in patients with severe hepatic impairment.[22] More importantly, sertindole is contraindicated in patients receiving drugs with potential of increasing QT intervals.[22,38] These drugs include class Ia and III antiarrhythmic (amiodarone and quinidine), some macrolides (erythromycin) and quinolone antibiotics, some antihistamines (terfenadine and astemizole) and lithium.[21,52]

CLINICAL EFFICACY

This section summarizes data regarding clinical efficacy of the 5 antipsychotics by focusing on pivotal randomized clinical trials (RCTs) forming the basis of these drugs' FDA approval (Table 3). Studies investigating long-term efficacy of each drug were also reviewed although they are not included in the table. Because blonanserin and sertindole are not yet FDA approved, all the available double-blind RCTs were included in this section.

Asenapine

Schizophrenia

Three pivotal 6-week, randomized, double-blind, placebo- and active-controlled trials investigated efficacy of asenapine for treatment of acute schizophrenia, and 2 of them formed the basis of FDA approval (Table 3).[53–55] Improvement from baseline of positive and negative syndrome scale (PANSS) total score was the primary outcome measure for all 3 studies. In

TABLE 3. Summary of Pivotal RCTs for Each of 5 Atypical Antipsychotics

	Study	Patient	Duration, wk	Dose, mg*	Comparator, mg*	n†	Primary Outcome	Results
ASN	Potkin et al[54]	SPR	6	10 dv	PBO; RPR 6 dv	174	PANSS	ASN > PBO¶; RPR = PBO
	Kane et al[53]	SPR	6	10, 20 dv	PBO; HPD 4 fd	448	PANSS	ASN 10 & HPD 4 > PBO§; ASN 10 = PBO
	Szegedi et al[55]	SPR	6	10, 20 dv	PBO; OZP 15	386	PANSS	ASN 10, 20 = PBO; OZP 15 > PBO§
	McIntyre et al (1)[58]	BPD	3	10–20 dv	PBO; OZP 5–20 fd	470	YMRS	ASN & OZP > PBO¶
	McIntyre et al (2)[59]	BPD	3	10–20 dv	PBO; OZP 5–20 fd	480	YMRS	ASN > PBO‖; OZP > PBO‖; AZP < OZP‖
	Szegedi et al[97]	BPD	12	10–20 dv + VPR or Li	PBO + VPR or PBO + Li	316	YMRS	(ASN + VPR or Li) > (PBO + VPR or Li)§
BLO	Murasaki[63]	SPR	8	8–24 fd	HPD 4–12 fd	225	PANSS	BLO & HPD vs baseline¶ BLO = HPD
	Miura et al[61]	SPR	8	8–24 fd	RPR 2–6 fd	301	PANSS	BLO & RPR vs baseline¶; BLO = RPR
	Garcia et al[62]	SPR	6	2.5, 5, 10	HPD 10; PBO	307	PANSS	PANSS: BLO 2.5, 5, 10 & HPD 10 > PBO¶; PANSS–n: BLO 5, 10 > HPD§
	Yang et al[60]	SPR	8	8–24 fd	RPR 2–6 fd	206	PANSS	BLO = RPR
ILO	Potkin et al (study 1)[66]	SPR	6	4, 8, 12 dv	PBO; HPD 15	573	PANSS	ILO 12§ & HPD 15‖ > PBO; BPRS: ILO 12§, HPD 15¶ > PBO
	Potkin et al (study 2)[66]	SPR, SAD	6	4–8, 10–16	PBO; RPR 4–8	590	PANSS	ILO 4–8§, ILO 10–16‖ & RPR 4–8‖ > PBO; BPRS: ILO 4–8§, ILO 10–16‖ & RPR 4–8¶ > PBO
	Potkin et al (study 3)[66]	SPR	6	12–16, 20–24 dv	PBO; RPR 6–8 dv	671	PANSS	ILO 20–24‖ & RPR 6–8¶ > PBO; BPRS: ILO 20–24§ & RPR 6–8¶ > PBO
	Cutler et al[67]	SPR	4	24 dv	PBO; ZIP 160 dv	567	PANSS	ILO > PBO‖, ZIP > PBO§
LUR	Ogasa et al[73]	SPR	6	40, 120	PBO	145	BPRSd	LUR 40 > PBO§, LUR 120 > PBO‖
	Nakamura et al[72]	SPR	6	80	PBO	180	BPRSd	LUR 80 > PBO§
	Nasrallah et al[74]	SPR	6	40, 80, 120	PBO	489	PANSS	LUR 80 > PBO§; LUR 40, 120 = PBO
	Meltzer et al[75]	SPR	6	40, 120	PBO; OZP 15	471	PANSS	LUR 40 & OZP 15 > PBO¶, LUR 120 > PBO§
	Loebel et al[76]	SPR	6	80, 160	PBO; QXR 600	482	PANSS	LUR 40, 120 & QXR 600 > PBO¶
SER‡	van Kammen et al[80]	SPR	6	8, 12, 20	PBO	205	PANSS, BPRS, CGI	SER 20 > PBO in PANSS§, BPRS§, CGI§; SER 8, 12 = PBO in PANSS, BPRS, CGI
	Daniel et al[81]	SPR	52	24	HPD 10	242	Time to treatment failure	SER = HPD; PANSS change from baseline: SER§ & HPD§
	Zimbroff et al[44]	SPR	8	12, 20, 24	PBO; HPD 4, 8, 16	497	PANSS, BPRS, CGI	All SER > PBO in PANSS‖, BPRS‖, CGI‖; SER = HPD in all doses; SER 20 > PBO in SANS§

Continued next page

TABLE 3. *(Continued)*

Study	Patient	Duration, wk	Dose, mg*	Comparator, mg*	n†	Primary Outcome	Results
Hale et al[82]	SPR	8	16, 20, 24	HPD 10; SER 8 (sub–therapeutic, pseudo–PBO)	595	PANSS, CGI	SER 16–24 > SER 8 (pseudo–PBO) in PANSS§; SER +16–24 = HPD 10 in PANSS; SER 16 > HPD 10 in PANSS–n§
Kane et al[84]	SPR	12	12–24 fd	RPR 6–12 fd	317	PANSS	SER = RPR
Azorin et al[83]	SPR	12	12–24 fd	RPR 4–10 fd	172	PANSS	SER = RPR; PANSS–n: SER > RPR§
Kwon et al[85]	SPR	12	12–20 fd	OZP 10–20 fd	389	PANSS	SER failed to prove non–inferiority to OZP

* Dosages are in mg once per day in fixed dose, unless otherwise specified.
† Number of total intent–to–treat patients.
‡ No FDA approval.
§ $P < 0.05$.
‖ $P < 0.01$.
¶ $P < 0.001$.
ASN, asenapine; BLO, blonanserin; BPRS, Brief Psychiatric Rating Scale; BPRSd, Brief Psychiatric Rating Scale derived; dv, divided into twice per day; ER, extended release; fd, flexible dosage; HAM–D–21, Hamilton depression rating scale 21–item version; HPD, haloperidol; ILO, iloperidone; LUR, lurasidone; OZP, olanzapine; PANSS, positive and negative syndrome scale total score; PANSS–n, positive and negative syndrome scale negative subscale; PANSS–p, positive and negative syndrome scale positive subscale; PBO, placebo; QXR, quetiapine XR; RPR, risperidone; SAD, schizoaffective disorder; SANS, scale for the assessment of negative symptoms; SER, sertindole; SPR, schizophrenia; ZIP, ziprasidone.

the first study, asenapine showed superior improvement on PANSS total score ($P < 0.005$) and on the positive ($P = 0.01$), negative ($P = 0.01$), and general psychopathology ($P < 0.005$) than placebo. Risperidone did not separate from placebo on the primary outcome measure.[54] The second study compared asenapine 5 and 10 mg bid with placebo and haloperidol 4 mg bid.[53] Although asenapine 5 mg bid separated from placebo on PANSS total score, asenapine 10 mg failed to show superior outcome over placebo. In the third study, both 5 and 10 mg bid of asenapine did not separate from placebo, whereas an active comparator (olanzapine 15 mg/d) showed superior outcome over placebo.[55] For asenapine, this study was considered a negative trial.

The long-term efficacy of asenapine in schizophrenia was assessed in 2 studies.[56,57] The first study included 700 stable schizophrenic patients who were cross-titrated from previous asenapine and remained stable during 26 weeks of open-label treatment.[52] Time to relapse was the primary outcome measure; 386 entered (asenapine, number of intention to treat analysis (ITT) = 194; placebo, ITT = 192) the double-blind phase. The results showed that time to relapse and time to discontinuation were significantly longer with asenapine than with placebo (both, $P < 0.0001$). The second study compared efficacy of flexible dose of asenapine (5 or 10 mg bid) and olanzapine (10 or 20 mg/d) in a 52-week, randomized, double-blind, multicenter study in patients with schizophrenia.[57] Mean PANSS total score changes of both groups were comparable (−37.0 vs −35.3, $P > 0.05$) at week 52. However, when last-observation carried-forward (LOCF) method was used, the changes in PANSS total scores of asenapine at week 52 were significantly inferior to that of olanzapine (asenapine, −21.0, vs olanzapine, 27.5; $P < 0.0001$).

Bipolar Disorder

Two pivotal 3-week, randomized, double-blind, placebo- and active-controlled trials enrolling adult bipolar I disorder patients with Young Mania Rating Scale (YMRS) scores greater than or equal to 20 formed the basis of the efficacy evaluation of asenapine for treatment of bipolar disorder (Table 3).[58,59] Both studies started with a 7-day placebo washout period, after which patients were randomized to receive asenapine 5 or 10 mg bid, olanzapine 5 to 20 mg/d, or placebo. Primary outcome measure, YMRS total score change from baseline to day 21, was assessed using analysis of covariance with LOCF method for both studies. The results illustrated that both asenapine and olanzapine showed greater improvement in YMRS than placebo.[58,59] A 12-week randomized, placebo-controlled study formed basis of efficacy of asenapine as an adjunctive therapy with either lithium or valproate for the treatment of bipolar disorder (Table 3). In this study, patients with bipolar I disorder experiencing manic or mixed episodes despite pretreatment with lithium or valproate monotherapy were treated with flexible-dose, twice-daily asenapine 5 or 10 mg (ITT, 154) or placebo (ITT, 162). The results showed that adjunctive asenapine significantly improved mania versus adjunctive placebo at week 3 (primary end point) and weeks 2 to 12. There are no long-term or maintenance studies of asenapine for the treatment of bipolar disorder. Thus, the long-term efficacy of asenapine in bipolar disorder is not yet established.

Blonanserin

As stated earlier, blonanserin is not yet FDA approved. Thus, all available double-blind RCTs investigating efficacy of blonanserin for the treatment of schizophrenia were reviewed

in this section. In total, 4 double-blind RCTs involving 1039 ITT patients with schizophrenia were identified (Table 3). Two studies used risperidone as a comparator.[60,61] A study by Garcia et al[62] used both placebo and haloperidol as comparators, whereas a study by Murasaki[63] used only haloperidol as a comparator. Overall, the efficacy of blonanserin seems to be superior than placebo[62] and comparable to haloperidol[63] and risperidone.[60,61]

In addition, although there was no significant difference between blonanserin and haloperidol treatment groups in terms of mean improvements from baseline in PANSS total scores, 1 study showed that blonanserin group had significantly greater improvements from baseline in PANSS negative subscores than haloperidol group.[62] Such a potential befit of blonanserin in negative subscores of PANSS was also shown in a meta-analysis. In this meta-analysis, which included 4 previously mentioned RCTs, blonanserin showed greater efficacy in the PANSS negative subscale scores than haloperidol (weighted mean difference, −1.29; confidence interval [CI], −2.29 to −0.30; $P = 0.01$).[29] In line with results from the 4 RCTs, the meta-analysis revealed no significant differences in PANSS total ($P = 0.75$), PANSS positive ($P = 0.41$), negative ($P = 0.09$), and general psychopathology subscale scores ($P = 0.96$), or response rate ($P = 0.72$) when comparing blonanserin with other pooled antipsychotics.

There are no RCTs investigating long-term or maintenance treatment of blonanserin for patients with schizophrenia. However, 2 multicenter, open studies demonstrated long-term efficacy of blonanserin for schizophrenia. In both studies, patients received blonanserin (8–24 mg/d) for up to 56 weeks. The primary efficacy measures included changes from baseline in Brief Psychiatric Rating Scale (BPRS) and PANSS scores and final global improvement.[64,65] The results showed that significant improvement from baseline in PANSS and BPRS scores at week 56. Overall improvement rate after 28 weeks was 51.9% and at 52 to 56 weeks was 55.5%.

Iloperidone

The efficacy of iloperidone was evaluated in 4 double-blind, placebo- and active-controlled short-term (4- and 6-week) controlled trials (Table 3).[66,67] Potkin et al[66] report efficacy results from three 6-week, randomized, double-blind, placebo- and active comparator-controlled trials in patients with schizophrenia or schizoaffective disorder. The primary and secondary efficacy outcome measure was change in PANSS total and BPRS scores from baseline, respectively. In the first trial, a significant improvement in PANSS total score was observed in patients treated with iloperidone 12 mg/d, but iloperidone 4 and 8 mg/d did not significantly reduce PANSS total scores compared with placebo ($P = 0.097$ and 0.227, respectively). Similar trend was observed for BPRS scores, which showed that iloperidone 12 mg/d was significantly more effective than placebo at end point in improving BPRS scores (−6.8 vs −3.6, $P < 0.05$). However, a trend-level difference was noted with iloperidone 4 (−6.4, $P = 0.07$) and 8 mg/d (−6.2, $P = 0.095$). The second trial involved patients with acute schizophrenia or schizoaffective disorder, which showed that iloperidone 4 to 8 and 10 to 16 mg/d and risperidone 4 to 8 mg/d showed significantly superior outcome over placebo in both PANSS and BPRS. In the third trial, iloperidone 20 to 24 mg/d (higher dose) and risperidone 6 to 8 mg/d showed significantly greater improvement than placebo in PANSS total scores. However, iloperidone 12 to 16 mg/d failed to show superior efficacy over placebo. In terms of BPRS, both iloperidone 20 to 24 mg/d and risperidone 6 to 8 mg/d again demonstrated significantly greater improvement than placebo, whereas a trend-level difference was noted with iloperidone 12 to 16 mg/d ($P = 0.09$). All 3 studies used dosage-escalation schemes in their protocols and allowed haloperidol and risperidone to reach steady-state levels faster than iloperidone. This might have contributed to greater overall improvements observed in PANSS total and BPRS scores in the active-comparator group (haloperidol or risperidone) than the iloperidone-treated group.[68,69] The fourth trial conducted by Cutler et al[67] involved a 4-week, placebo-controlled trial comparing iloperidone 24 mg/d, placebo, and an active comparator ziprasidone 160 mg/d. The study, similar to the three 6-week studies, also used dosage-escalation methods. The results showed that iloperidone 24 mg/d and ziprasidone 160 mg/d were superior to placebo in the PANSS total score (Table 3).

Kane et al[70] conducted a study to investigate the long-term efficacy of iloperidone. The analysis of data was pooled from the 3 prospective multicenter studies, each with 6-week stabilization followed by 46-week, double-blind maintenance phases to compare iloperidone with those of haloperidol. Patients who completed the initial 6-week phase with at least 20% reduction in PANSS total score at weeks 4 and 6 were included in this study. These patients were randomized to iloperidone 4 to 16 mg/d (n = 359) or haloperidol 5 to 20 mg/d (n = 114). The primary outcome measure was time to relapse, and secondary outcome measures included changes in PANSS total and BPRS scores from baseline. Relapse was defined as 25% or more increase in PANSS total score. The study showed that iloperidone was equivalent to haloperidol in preventing relapse (relapse rate: iloperidone, 43.5%, vs haloperidol, 41.2%; $P = 0.84$). Both iloperidone and haloperidol treatment groups also showed similar improvements in PANSS total (−16.1 vs −17.4, $P = 0.338$) and BPRS scores (−9.0 vs −9.6, $P = 0.390$), indicating improvement in both treatment groups.

A study reported that 6 single nucleotide polymorphisms can predict a patient's response to iloperidone. Seventy-five percent of iloperidone-treated patients in the group with at least 1 genetic single nucleotide polymorphism showed a 20% or greater improvement in PANSS total score, compared with 37% of iloperidone-treated patients with other genotypes.[71] Moreover, this relationship between treatment efficacy and genotype was not observed in ziprasidone-treated group. This study suggests that iloperidone might have potential benefit in individualized treatments for schizophrenia, but further researches are required regarding these findings.

Lurasidone

Five pivotal 6-week, randomized, double-blind, placebo-controlled trials (of which 2 used an active comparator) established the efficacy of lurasidone for the treatment of acute schizophrenia (Table 3). Two placebo-controlled studies used mean change of Brief Psychiatric Rating Scale derived (BPRSd) as their primary efficacy measures.[72,73] The results of these 2 studies showed that mean change in BPRSd was significantly greater in patients receiving lurasidone 40, 80, and 120 mg/d than in patients receiving placebo. Another placebo-controlled study used mean change of PANSS as a primary efficacy measure.[74] In this study, patients were randomized to 6 weeks of double-blind treatment with lurasidone 40, 80, and 120 mg/d, or placebo. Lurasidone 80 mg/d resulted in significantly greater improvement in PANSS total score than placebo (−23.4 vs −17.0, $P < 0.05$), but lurasidone 40 mg/d (−19.2) and lurasidone 120 mg/d (−20.5) failed to separate from the placebo. The fourth study used olanzapine as an active

comparator.[75] All treatment groups including lurasidone 40 and 120 mg/d, and olanzapine 15 mg/d were associated with significantly greater improvement on PANSS total score than placebo. In addition, there was no statistically significant difference in mean PANSS total scores for the lurasidone groups compared with the olanzapine group. A study conducted by Loebel et al[76] used quetiapine XR as an active comparator. In this study, patients were randomized to receive lurasidone 80 mg, lurasidone 160 mg, quetiapine XR 600 mg/d, or placebo. Again, mean PANSS total score was used as a primary efficacy measure. The results showed that both doses of lurasidone and QXR 600 mg was associated with significantly greater improvement on PANSS total score compared with placebo. A 6-week, randomized, double-blind, placebo-controlled trial involving 353 patients with acute schizophrenia investigated efficacy of lurasidone (20, 40, and 80 mg/d) using haloperidol 10 mg as an active comparator.[77] However, this was a failed study because not only lurasidone but also the positive control haloperidol failed to separate from placebo in BPRSd (primary outcome measure).

In a 3-week randomized, double-blind trial cognitive effect of lurasidone was evaluated in comparison with ziprasidone.[78] A performance-based cognitive assessment battery based on tests from the MATRICS Consensus Cognitive Battery (MCCB) and an interviewer-rated measure of cognitive functioning, the Schizophrenia Cognition Rating Scale (SCoRS) were used for outcome measure. The 2 groups did not differ in performance on the MCCB or the SCoRS ratings. However, lurasidone group demonstrated significance within-group improvement from baseline on the MCCB composite score ($P = 0.026$) and on the SCoRS ($P < 0.001$), whereas no within-group improvement was noted for ziprasidone group on both ziprasidone MCCB composite ($P = 0.25$) and SCoRS ($P = 0.19$). Although this study suggests lurasidone has a potential effect on improving cognition, the study has important limitations such as short duration of the study, using only high dose of lurasidone, and use of an incomplete battery of tests.

The long-term effectiveness of lurasidone in patients with schizophrenia was investigated in a 52-week randomized, double-blind study.[79] Although the study aimed to evaluate the long-term safety and tolerability of lurasidone, it also assessed clinical efficacy of lurasidone. A total of 639 clinically stable outpatients with schizophrenia were randomized in a 2:1 ratio to 12 months of double-blind treatment with lurasidone (40–120 mg/d; mean, 84.7 mg/d) or risperidone (2–6 mg/d; mean, 4.3 mg/d). Two groups did not significantly differ in rate of relapse (lurasidone, 20%, vs risperidone, 16%; HR, 1.31; 95% CI, 0.87–1.97). Relapse was defined as an increase from baseline in PANSS total score by greater than 30%. PANSS total scores showed significant improvement from baseline to 12 months in both treatment groups (lurasidone, −4.7; risperidone, −6.5) with no significant differences observed between the 2 groups.

Sertindole

Sertindole, after voluntarily suspended from the market by the manufacturer in 1998, was relaunched to the European market in 2005, but its use is still not approved by the FDA. Thus, all the randomized, double-blind, studies investigating efficacy of sertindole were included in the present review. The efficacy of sertindole has been assessed in 7 randomized, double-blind, clinical trials (Table 3). One study have compared sertindole with placebo only,[80] 3 studies have compared sertindole with haloperidol,[44,81,82] 2 studies have compared sertindole with risperidone,[83,84] and a recent study compared sertindole with olanzapine.[85] Overall, the clinically effective dose range of sertindole was 12 to 20 mg/d. However, the greatest improvement in positive and negative symptoms occurred at the higher doses (20–24 mg/d) of sertindole.[80,82] The efficacy of sertindole seemed to be superior compared with placebo,[44,80] comparable to haloperidol[44,82] and risperidone.[37,70] A recent study failed to show noninferiority of sertindole to olanzapine in terms of reduction in PANSS total score with the LOCF analysis.[85] However, both olanzapine and sertindole significantly improved PANSS total score when compared to the baseline. The authors of the study speculated that the higher withdrawal rate in the sertindole group during the titration period could have affected the results to the disadvantage of sertindole.[85] In another study, sertindole failed to show superiority with regard to negative symptoms when compared with risperidone,[84] whereas a statistically significant difference between the 2 drugs was found in a previous study, favoring sertindole.[83] Only 1 of the 7 trials investigated the long-term outcome.[81] The primary end point of this study assessed the time to treatment failure, which showed no significant difference between patients receiving sertindole compared with patients receiving haloperidol. Both patient groups showed improvement in PANSS total score from baseline to day 365.

Sertindole has a clear effect on 5-HT_6 receptors, whereas its affinity for M_1 and H_1 receptors is rather low.[39] Hence, sertindole seems to have a potential benefit on cognitive impairment, which has been shown in several animal studies.[39–41] Two studies conducted in human also support potential beneficial effects of sertindole on cognition.[86,87] A study by Buchsbaum et al[87] demonstrated that, in patients with schizophrenia, sertindole group have higher metabolic rates in the dorsolateral prefrontal cortex when compared with haloperidol group. In addition, patients who were not taking medication showed normalization of the dorsolateral prefrontal, medial prefrontal, and cingulate cortex after receiving sertindole. Potential beneficial effects on cognition are also supported by reported findings of Gallhofer et al.[86] This study compared the Reaction Time Decomposition and the Wisconsin Card Sorting Test between schizophrenic patients receiving sertindole (10–24 mg/d) and haloperidol (5–15 mg/d) at baseline, week 4, and week 12. Results of the study illustrated that patients on sertindole showed significant improvement on the Reaction Time Decomposition task after 4 and 12 weeks of treatment, whereas patients receiving haloperidol showed marked impairment at week 4 and only a partial recovery at week 12. However, small sample size of the study (n = 34) and the fact that the study included patients receiving benztropine and benzodiazepines are the 2 important limitations. Thus, more controlled studies are needed to prove sertindole's potential beneficial effects on schizophrenia-related cognitive disturbances.

SAFETY AND TOLERABILITY

This section summarizes data regarding safety and tolerability of the 5 atypical antipsychotics by focusing on pooled analysis of pivotal trials for each of these 5 atypical antipsychotics. For blonanserin, a meta-analysis was included because no pooled analysis has been conducted. Sertindole's potential risk of developing sudden cardiac death has been a concern for a long period. Thus, in addition to the pooled analysis provided by the manufacturer, the 5 important studies including clinical trials and large epidemiological studies were also included in this section to review sertindole's safety and tolerability (Table 4).

TABLE 4. Safety and Tolerability of the 5 Antipsychotics

	Study	Subject	Study Type	Drug, mg*	n†	Results
ASN	Merck & CO[12]	SPR	Pooled data from three 6–wk RCTs	ASN 10–20 PBO	572 378	TAE ≥ 5% and at least twice of PBO (ASN vs PBO): Akathisia (6% vs 3%), oral hypoesthesia (5% vs 1%), somnolence (14% vs 7%).
		BPD	Pooled data from two 3–wk RCTs (for BPD monotherapy)	ASN 10–20 PBO	379 203	TAE ≥ 5% and at least twice of PBO (ASN vs PBO): EPS other than akathisia (7% vs 2%), dizziness (11% vs 3%), somnolence (24% vs 6%), weight gain (5% vs <1%)
BLO	Kishi et al[29]	SPR	MTA of 4 RCTs with varying durations	BLO 8–24 RPR 2–6 HAL 4–12	563 248 177	Relative risk of TAE: BLO¶ < RPR & HPD for hyperprolactinemia; BLO > RPR‖, BLO < HPD§ for akathisia; BLO < HPD§ for dizziness
ILO	Weiden et al[89]	SPR	Pooled data from three 6–wk RCTs	ILO 4–24 HAL 15 RPR 4–8 PBO	1162 118 306 440	Improvement of akathisia: ILO 10–16 & ILO 20–24 > PBO§, HPD < PBO§; Weight gain: ILO (all dose) & RPR > PBO§; Glucose change: ILO (all dose) & HAL > PBO§; Improvement of cholesterol: ILO 4–8 < PBO§; Improvement of TG: ILO 4–8, HAL > PBO§; Prolactin change: ILO 4–8 & ILO 1–16 = PBO, HAL & RPR > PBO§; QTc prolongation: ILO (all dose) & HAL > PBO§
LUR	Sunovion Inc[18]	SPR	Pooled data from 5 pivotal RCTs	LUR 40–160 PBO	1508 708	TAE ≥ 5% and at least twice of PBO (LUR vs PBO): Nausea (10% vs 5%), somnolence (17% vs 7%), akathisia (13% vs 3%), parkinsonism (10% vs 5%)
SER	Product monograph[22]	SPR	Pooled data from RCTs‡	SER PBO	704 290	SER > PBO: Postural hypotension§, QT prolongation§, dizziness§, paresthesia§, dry mouth§, peripheral edema§, weight gain§, dyspnea§, rhinitis§, abnormal ejaculation§
	Wilton et al[91] (PEM)	All with SER	Prescription event monitoring	SER RPR OZP	462 7684 8858	All–cause mortality rates: SER (1.51%, 7/462) = RPR & OZP (2.41%, 397/16542).
	Peuskens et al[92] (ESES)	All with SER	A nested case–control study	SER all dose	8608	Patients died: 35 (8=suicide, 11=cardiac death); Cardiac or unexplained death risk: higher in patients with history of hypertension, cardiovascular disorders, diabetes or metabolic disorder
	Lancon et al[93] (SSS)	All with SER	Retrospective analysis	SER all dose	1432	SAE: 97 (10 = fatal death); All–cause mortality rate: 0.51/100 PYE (95% CI, 0.23–0.97); QTc prolongation: 15 patients (1.05%).
	Kasper et al[94] (EPOS)	SPR	Cohort study	SER 4–20 Non–SER	1064 1257	Crude mortality: SER = non–SER; cardiac death: SER = non–SER
	Thomas et al.[95] (SCoP)	SPR	Randomized, open–label, parallel–group study	SER 12–24 RPR 4–6	4905 4904	All cause mortality: SER = RPR; Cardiac mortality: SER > RPR‖ Suicide mortality: SER = RPR; suicide attempt: SER < RPR§

*Dosages are in mg, once per day fixed dose.

†Number of total intent–to–treat patients for randomized controlled trials.

‡Does not specify which RCTs were included.

§$P < 0.05$.

‖$P < 0.01$.

¶$P < 0.001$.

ASN, asenapine; BLO, blonanserin; EPOS, European Post–marketing Observational Sertindole study; ESES, Sertindole European Safety and Exposure Survey; HPD, haloperidol; ILO, iloperidone; LUR, lurasidone; MTA, meta–analysis; OLS, open–label study; OZP, olanzapine; PAL: PBO, placebo; PEM, prescription event monitoring; PYE, person–years of exposure; QTc, corrected interval of QT; QXR, quetiapine XR; RCT, randomized–controlled trial; RPR, risperidone; SAD, schizoaffective disorder; SCoP, Sertindole Cohort Prospective study; SER, sertindole; SPR, schizophrenia; SSS, Sertindole Safety Survey; TG, triglycerides; ZIP, ziprasidone.

Asenapine

An analysis of pooled data from the 3 RCTs[53–55] investigated the short-term safety and tolerability of asenapine in patients with schizophrenia (Table 4).[12] Discontinuation rates due to treatment-related AEs (TAEs) of asenapine (9%) were comparable to that of placebo (10%). Treatment-related AEs with greater than 5% and at least twice of placebo were akathisia (6% vs 3%), oral hypoesthesia (5% vs 1%), and somnolence (14% vs 7%). No dose-response relationship was evident for somnolence and oral hypoesthesia, but there was a clear dose-response relationship for akathisia. The analysis of pooled data from the 2 RCTs[58,59] investigating short-term safety and tolerability of asenapine in patients with bipolar disorder also showed similar results.[12] Treatment-related AEs with greater than 5% and at least twice of placebo included EPS other than akathisia (7% vs 2%), dizziness (11% vs 3%), somnolence (24% vs 6%), and weight gain (5% vs <1%).

Given asenapine's high affinity for H_1 and 5-HT_{2c} receptors, it potentially has a high risk of causing weight gain.[30] In short-term clinical trials, 4.9% of asenapine-treated group showed an increase in body weight of 7% or more (mean weight gain, 1.1 kg) compared with 2% of placebo-treated group (mean weight gain, 0.1 kg). In a long-term trial, the incidence of clinically significant weight gain (≥7% increase from double-blind baseline) was 3.7% with asenapine and 0.5% with placebo.[56] However, when compared with olanzapine, mean weight increase was significantly less with asenapine (4.2 [7.5] vs 0.9 [4.8] kg, $P < 0.05$).[57] These studies suggest that asenapine may cause weight gain, and when it does, the degree is modest and occurs relatively early in treatment and is not progressive.[13] Although asenapine has a high affinity for α_1-adrenergic receptors, evidence does not suggest its association with orthostatic hypotension or syncope.[12] Furthermore, asenapine did not show clinically significant differences in fasting glucose, triglycerides, lipoproteins or total cholesterol levels, prolactin change, and QTc interval change compared with placebo.[12,88] Hypersensitivity reactions including anaphylaxis, angioedema, hypotension, tachycardia, swollen tongue, dyspnea, wheezing, and rash have been observed in patients treated with asenapine.[12] Thus, the FDA has warned health care professionals and patients that serious allergic reactions could occur with asenapine, even after the first dose.

Blonanserin

A meta-analysis including the 4 RCTs[60–63] (total ITT, 1039) showed there is no difference in the discontinuation due to any cause ($P = 0.29$), or due to inefficacy ($P = 0.32$), AEs ($P = 0.56$), and death ($P = 0.33$) between blonanserin and other pooled antipsychotics (Table 4).[29] Blonanserin had a 0.31 lower risk of hyperprolactinemia than haloperidol and risperidone. Incidence of dizziness (RR, 0.47; CI, 0.23–0.93) and akathisia (RR, 0.54; CI, 0.32–0.90) were significantly lower with blonanserin than with haloperidol. However, the risk of akathisia was 1.62 times higher in blonanserin than in risperidone (CI, 1.18-2.22). According to the package information of blonanserin, 75.5% (673/891) of patients receiving blonanserin experienced TAEs in the clinical trials conducted before its approval.[14] The most frequent TAEs were Parkinson syndrome (35%), akathisia (24%), insomnia (22.4%), increased blood prolactin levels (19.6%), dyskinesia (14%), somnolence (11.8%), and anxiety or irritability (11.2%).

According to 2 noncomparative studies of up to 56-week duration, the longer-term treatment with blonanserin in patients with schizophrenia was generally well tolerated.[14,64] The TAE incidence did not increase during long-term blonanserin therapy (68.5%–72.1%), and serious adverse reactions were observed in 5.9% to 9.8% of patients.[31] The most common TAEs (except for the EPS) that occurred greater than 10% during long-term blonanserin treatment were impaired urination (34.4%), insomnia (18.0%), somnolence (12.8%–16.4%), thirst (14.8%), constipation (12.8), and dizziness (11.5%).[14,64] The incidence of hyperprolactinemia was also high in the long-term study (20.9%–34.4%).[14,64] However, a short-term study showed that hyperprolactinemia was reported significantly lower in patients receiving blonanserin than in patients receiving risperidone.[61]

Iloperidone

A study assessed the short-term safety of iloperidone using a pooled analysis of three 6-week RCTs[66] (Table 4).[89] The most common TAEs of iloperidone were dizziness, headache, dry mouth, nausea, and insomnia. Discontinuation rate due to TAEs of iloperidone were comparable to that of placebo (for both, 4.8%) and were lower than risperidone (6.2%) and haloperidol (7.6%). Iloperidone-treated group showed significantly superior in improvement of akathisia from the baseline than placebo group. Weight gain was significantly greater in iloperidone (+1.5 to 2.1 kg) and risperidone (+1.5 kg) than those on placebo (−0.3 kg). Serum glucose elevation was significantly higher in iloperidone (+7.2 to 16.2 mg/dL) and haloperidol (+10.8 mg/dL) than in placebo (−3.6 mg/dL). Iloperidone was not associated with increase in total cholesterol, but placebo-treated group showed greater decrease in total cholesterol than those on iloperidone 4 to 8 mg/d. Slight decrease in triglycerides level was noted in all doses of iloperidone, but this decrement was significantly lower in those on iloperidone 4 to 8 mg/d than those on placebo. Prolactin level decreased with iloperidone (−23–38 μg/L) and increased significantly with risperidone (+214.5 μg/L) and haloperidol (+116 μg/L). The QT interval corrected by Fridericia formula (QTcF) showed significantly greater increase in iloperidone- and haloperidol-treated group than in placebo-treated group. Thus, iloperidone was associated with higher risk of weight gain, glucose elevation, and QTcF interval prolongation than placebo.

A more recent study conducted by Cutler et al[90] supports the long-term safety and tolerability of iloperidone for the treatment of schizophrenia. This study involved results from the 25-week open-label extension of a 4-week placebo- and ziprasidone-controlled clinical trial of iloperidone.[67] The results showed that most common TAEs included headache (13.9%), weight gain (9.2%), dizziness (6.9%), nausea (6.4%), sedation (6.4%), and insomnia (5.2%). Among them, weight gain and headache were only notable dose-related TAEs. Iloperidone was not associated with increase in serum glucose level. In accordance with the pooled analysis, rate of akathisia and EPS and serum level of lipids, and prolactin improved or were unchanged and during treatment with iloperidone.

Lurasidone

The short-term tolerability and safety of lurasidone was reported in a pooled safety data from the 5 pivotal RCTs[72–76] (Table 4).[18] The study included 1508 patients receiving lurasidone (40–160 mg/d) and 708 patients receiving placebo. The most common TAEs with greater than 5% and at least twice that of placebo included nausea (10% vs 5%), somnolence (17% vs 7%), akathisia (13% vs 3%), and parkinsonism (10% vs 5%); 4.8% of lurasidone-treated and 3.3% of placebo-treated patients showed significant weight gain, which was defined as a greater than 7% increase in body weight from baseline. Rate of akathisia increased with

lurasidone dose, showing a dose-dependent relationship. The rate of akathisia increased from 5.6% for 20 mg/d to 10.7% for 40 mg/d, 12.3% for 80 mg/d, and 22.0% for 120 mg/d.

The long-term safety and tolerability of lurasidone in schizophrenia was investigated in a 52-week randomized, double-blind study. The study randomized 629 clinically stable outpatients with schizophrenia in a 2:1 ratio to 12 months of double-blind treatment with lurasidone 40 to 120 mg/d or risperidone 2 to 6 mg/d. Discontinuation from the TAEs was higher in the lurasidone group than risperidone group (21.5% vs 14.4%, NNH, 14 [95% CI, 8–113]). The most common TAEs in the lurasidone (vs risperidone) were nausea (16.7% vs 10.9%, $P < 0.05$), insomnia (15.8% vs 13.4%, P = not significant), sedation (14.6% vs 13.9%, P = not significant), and akathisia (14.3% vs 7.9%, $P < 0.05$). In addition, occurrence rate of vomiting was significantly higher in lurasidone group than in risperidone group (10% and 3.5%, respectively; $P < 0.05$). A lower proportion of patients in the lurasidone group reported constipation (lurasidone, 1.9%, vs risperidone, 6.9%; $P < 0.05$) and weight gain (lurasidone, 9.3%, vs risperidone, 19.8%; $P < 0.05$). The median end point change in prolactin was also significantly higher for risperidone (lurasidone, +5.16 [34.89] ng/mL vs risperidone, +33.90 [53.31] ng/mL; $P < 0.001$). Baseline to end point changes in total cholesterol, triglycerides, glucose, and ECGs were minimal in both groups.

Sertindole

The analysis of pooled data from placebo-controlled studies, which investigated safety and tolerability of sertindole, was provided in its product monograph.[22] However, the product monograph does not specify which RCTs were included in the analysis. The most common TAEs of sertindole were headache (37%), insomnia (31.4%), and rhinitis (26.7%). Significantly higher proportion of patients in the sertindole group reported postural hypotension (sertindole, 4.8%, vs placebo, 1.4%; $P < 0.05$), QT prolongation (sertindole, 1.6%, vs placebo, 0%; $P < 0.05$), dizziness (sertindole, 12.1%, vs placebo, 7.6%; $P < 0.05$), paresthesia (sertindole, 2.7%, vs placebo, 0.3%; $P < 0.05$), dry mouth (sertindole, 9.5%, vs placebo, 4.5%; $P < 0.05$), peripheral edema (sertindole, 3.0%, vs placebo, 0.3%; $P < 0.05$), weight gain (sertindole, 3.6%, vs placebo, 1.0%; $P < 0.05$), dyspnea (sertindole, 2.8%, vs placebo, 0.7%; $P < 0.05$), rhinitis (sertindole, 25.7%, vs placebo, 11.0%; $P < 0.05$), abnormal ejaculation (sertindole, 12.9%, vs placebo, 2.5%; $P < 0.05$) compared to the patients in placebo group. After sertindole was voluntarily suspended by the manufacturer because of its association with higher cardiovascular mortality, several clinical trials and large epidemiological (involved in postmarketing surveillance) studies were conducted to closely investigate its safety and tolerability. These include prescription event monitoring (PEM),[91] Sertindole European Safety and Exposure Survey (ESES),[92] Sertindole Safety Survey (SSS),[93] European Post-marketing Observational Sertindole study (EPOS),[94] and Sertindole Cohort Prospective study (SCoP).[95]

The PEM investigated mortality rates of patients receiving sertindole in the United Kingdom.[91] The all-cause mortality rates of sertindole recipients were comparable with that of risperidone- and olanzapine- recipients. Moreover, among patients who received antipsychotics from a general practitioner, the all-cause mortality of sertindole was 2.34 deaths/100 person-years exposure (PYE), whereas risperidone and olanzapine patients were 4.97 deaths/100 PYE and 3.34 deaths/100 PYE, respectively. Thus, this study showed that mortality rates between sertindole and comparator cohort were comparable. However, the sertindole cohort was too small so it was not possible to rule out an association between sertindole use and cardiovascular deaths. In the ESES, patients who were treated with sertindole in Germany, Austria, Belgium, Hungary, the Netherlands, and the United Kingdom were included.[92] The follow-up study included a total of 8608 for 3819 PYE. Total number of death was 35 (all-cause mortality rate was 0.92/100 PYE). Eight of them died because of suicide, and cardiac-related deaths occurred in 11 patients. More importantly, the study showed that those who died from cardiac disorders were older. The nested case-control study demonstrated that patients receiving sertindole who had hypertension or other cardiovascular disorders associated with diabetes or metabolic disorder were associated with a higher risk of premature cardiac or unexplained death. A retrospective survey under a named patient use program in Europe (NPU), Sertindole Safety Survey (SSS), was conducted to prescribe sertindole to patients who did not show response to or did not tolerate alternative treatments.[93] The study prospectively followed an exhaustive cohort of NPU patients to evaluate sertindole's modalities of prescription, document any serious AEs (SAEs), and assess the mortality rate. A total of 1432 patients in 11 countries were included in the study. The mean dose of sertindole was 13.4 mg/d. The rate for all-cause mortality and QTc prolongation were 0.5/100 PYE (95% CI, 0.23-0.97) and 0.85/100 PYE (95% CI, 0.48–1.41), respectively. Total SAEs reported were 97, and 10 have died among them. EPOS compared the safety of treatment with sertindole with that of usual treatment in patients with schizophrenia.[94] The study was a multicenter, multinational, referenced, cohort conducted in normal European clinical practice. The study planned to include 12,000 patients, but only 2321 patients were included because it was prematurely terminated in 1998 as a result of sertindole's temporary suspension from the market. The results demonstrated similar mortality rates for the sertindole group (1.45 death/100 PYE; 95% CI, 0.53–3.16) and the non–sertindole group (1.5 death/100 PYE; 95% CI, 0.72–2.76). More importantly, sertindole group did not have more cardiac deaths than non–sertindole group had. Thus, the study did not suggest evidence against the use of sertindole under normal conditions. SCoP conducted a multinational randomized, open-label, parallel-group, partly blinded, postmarketing surveillance with blinded classification of outcomes.[95] The study included a total of 9858 patients with schizophrenia, and aimed to investigate whether sertindole (ITT, 4905) is associated with increase in all-cause mortality or cardiac events requiring hospitalization, compared with risperidone (ITT, 4904). After 14147 person-years, 2 groups did not differ in terms of overall mortality (sertindole, 64, vs risperidone, 61; HR, 1.12) or cardiac events requiring hospitalization (sertindole, 10, vs risperidone, 6; HR, 1.73). However, cardiac mortality was significantly higher in sertindole group than in risperidone group (sertindole, 31, vs risperidone, 12; HR, 2.84). In terms of suicide, 2 groups did not differ in completed suicide, but fewer sertindole recipients attempted suicide than risperidone recipients (sertindole, 68, vs risperidone, 78; HR, 0.67) (Table 4).

Recently, a randomized, double-blind, parallel-group, flexible-dose study investigated the efficacy, safety, and tolerability of sertindole in comparison with olanzapine.[85] A total of 389 patients, 16 with sertindole and 193 with olanzapine, with chronic schizophrenia who did not respond successfully to their previous treatments were included in the study. Although sertindole group had higher incidence of asymptomatic QT prolongation than olanzapine group (sertindole, 26.5%, vs olanzapine, 5.5%; $P < 0.05$), 2 groups did not differ in other

safety profiles. Thus, the authors concluded that both drugs are comparable in terms of safety profile.

DIRECT COMPARISON OF SAFETY AND TOLERABILITY OF ASENAPINE, ILOPERIDONE, AND LURASIDONE

Clinical trials directly comparing different antipsychotics were scarcely available and briefly described in the previous antipsychotic section. However, studies directly comparing the safety and tolerability of the 5 atypical antipsychotics are not yet conducted. A systematic review and meta-analysis compared effects of asenapine, iloperidone, lurasidone, and paliperidone ER on body weight and other metabolic parameters (cholesterol, triglycerides, and glucose) by investigating short-term, randomized, placebo-controlled or head-to-head trials of patients with acute schizophrenia or bipolar disorder.[96] Most of the trials (64.3%) were of less than or equal to 12-week duration, and longer-term studies were available only for asenapine and paliperidone ER. In the short-term studies, rate of significant weight gain, defined by a greater than or equal to 7% weight increase from baseline, relative to placebo was highest for asenapine (total n = 1360 in 5 trials; RR, 4.09; 95% CI, 2.25–7.43; NNH, 17) followed by iloperidone (total n = 1931 in 4 trials; RR, 3.13; 95% CI, 2.08–4.70; NNH, 11) and paliperidone ER (total n = 4087 in 12 trials; RR, 2.17; 95% CI, 1.64–2.86; NNH, 20). Lurasidone did not show statistically significant weight change (total n = 1793 in 6 trials; RR, 1.42; 95% CI, 0.87–2.29). In analysis of longer-term studies, asenapine (total n = 311 in 3 trials; +1.30 kg; 95% CI, 0.62–1.98) and paliperidone ER (total n = 1174 in 6 trials; +0.50 kg; 95% CI, 0.22–0.78) showed significantly (for both, $P < 0.001$) greater weight gain than placebo. Iloperidone significantly increased total-cholesterol (total n = 300 in 1 trial; +11.60 mg/dL; 95% CI, 4.98–18.22; $P < 0.001$), HDL cholesterol (total n = 300 in 1 trial; + 3.6 mg/dL; 95% CI, 1.58–5.62; $P < 0.001$), and LDL-cholesterol compared to placebo (total n = 300 in 1 trial; +10.30 mg/dL; 95% CI, 4.94–15.66; $P < 0.001$). In longer-term studies, lurasidone was associated with significant increase in high-density cholesterol (total n = 1004 in 5 trials; +1.50 mg/dL; 95% CI, 0.56–2.44; $P < 0.01$), whereas asenapine was associated with significant increase in total cholesterol (total n = 194 in 1 trial; +6.53 mg/dL; 95% CI, 1.17–11.89; $P < 0.05$). In terms of triglycerides and glucose level, none of the 4 drugs showed with clinically significant changes.

DISCUSSION

In this article, we reviewed currently available data focusing on clinical characteristics of 5 novel antipsychotics including asenapine, blonanserin, iloperidone, lurasidone, and sertindole. This section summarizes distinctive clinical characteristics of each of these 5 atypical antipsychotics (Table 5).

Asenapine is efficacious in the treatment of both schizophrenia and bipolar I disorder (manic or mixed episode). Among the 5 atypical antipsychotics reviewed, it is the only drug requiring sublingual administration and restriction of food or water after taking medication. It targets the widest ranges of receptors, with relatively higher affinity for 5-HT_{2A} and 5-HT_{2C} receptors than other antipsychotics. It is absorbed through the oral mucosa with the shortest t_{max} (approximately 1 hour) among the 5 atypical antipsychotics. Although it is primary metabolized in liver, CYP1A2 having the major role, no dose adjustment is required in patients with mild to moderate hepatic impairment. However, its use in patients with severe hepatic impairment is not recommended. Dose adjustment is also not required for patients with mild to moderate renal impairment, but its use in patients receiving dialysis has not been studied. The recommended initial dose of asenapine is 5 mg bid for patients with schizophrenia, which could be incremented up to 10 mg bid after 1 week of dosage titration; 10 mg bid could be administered without dosage titration in patients with bipolar disorder. Asenapine has a favorable profile in terms of prolactin change and QTc prolongation, but it can cause serious allergic reactions and risk of weight gain might be higher than other 4 atypical antipsychotics. Theoretically, asenapine have decreased likelihood of causing EPS because of its up-regulating effect on D_1-like receptors. However, studies suggest that it is associated with high risk of EPS, including akathisia. Dizziness, somnolence, and oral hypoesthesia are important risks of asenapine.

Blonanserin is not FDA indicated, but it is approved for treatment of schizophrenia in Japan and Korea. It is available as both tablet and 2% powder formulation. The recommended starting dose of blonanserin is 4 mg bid, and it should be taken after a meal. A gradual dose increment is recommended to reduce the risk of akathisia and EPS, and maximum daily dose should not exceed 24 mg. Blonanserin is mainly eliminated through urine (59%) and feces (30%). CYP3A4 plays an important role in its metabolism, so it should not be administered in patients taking CYP3A4 inhibitors. Its use in patients with renal or hepatic impairment has not been documented. Blonanserin has high binding affinity for D_2, D_3, and 5-HT_{2A} receptors. It has a low affinity for other neurotransmitter receptors, including H_1, α_1-adrenergic, and M_1 receptors, but its D_2 receptor occupancy is the highest among the 5 atypical antipsychotics. Unlike other atypical antipsychotics, its receptor occupancy for D_2 receptors is higher than that for 5-HT_{2A} receptors. Accordingly, studies indicate that it might have a favorable profile in terms of hyperprolactinemia, sedation, dizziness, and weight gain, but it is associated with high risk of akathisia and EPS. More importantly, studies investigating safety and tolerability of blonanserin are very limited. Thus, more well-controlled trials are required to shed light on these safety issues.

Iloperidone is FDA approved for the treatment of acute schizophrenia. Along with asenapine, iloperidone targets the widest ranges of receptor, and it is a pure antagonist at these receptors. It is the first antipsychotic to have pharmacogenomic studies indicating predictive response based on 6 identified polymorphisms. Thus, it might open door to tailored therapy for patients with schizophrenia. Oral bioavailability of iloperidone is the highest among the 5 atypical antipsychotics (96%), and it could be administered regardless of meals. The effective dose range is 12 to 24 mg/d, and dosage must be slowly increased from 1 mg bid, with doubling the dosage each day, to avoid orthostatic hypotension. Theoretically, iloperidone might have a lower risk of sedation and weight gain due to its very low affinity for H_1. Studies did not suggest its advantage in terms of weight gain, but metabolic adverse effects other than weight gain were reported to be low. Although risk of sedation was not high, insomnia along with dizziness, headache, dry mouth, and nausea were the most common TAEs. Iloperidone also significantly increased the risk of QTc prolongation, similar to that seen with ziprasidone.

Lurasidone is the most recent atypical antipsychotic to receive FDA approval for the treatment of schizophrenia (2010). Among the 5 atypical antipsychotics, it has the lowest oral bioavailability and the highest protein biding abilities. The recommended starting dose of lurasidone is 40 mg/d, and it should be taken after a meal. The effective dose range is 40 to 160 mg/d, and no initial dose titration is needed. Lurasidone is chiefly

TABLE 5. General Comparative Profiles of Asenapine, Blonanserin, Iloperidone, Lurasidone, and Sertindole

	Asenapine	Blonanserin	Iloperidone	Lurasidone	Sertindole
FDA-approved indications	1. Acute and maintenance treatment of SPR	1. No FDA approval	Acute treatment of SPR	Acute treatment of SPR	1. No FDA approval
	2. Acute treatment for BPD, manic, or mixed (monotherapy or adjunctive therapy with either lithium or valproate)	2. Approved only in Korea and Japan for the treatment of SPR			2. Approved in Europe and Australia for SPR (withdrawn due to QT prolongation and serious dysrhythmia in 1998. Relaunched in Europe market since 2005)
Optimal dose, mg/d	10–20	8–24	12–24	40–160	12–20 (maximum, 24)
	Once a day	Two divided doses	Two divided doses	Once a day	Once a day
Optimal form	Sublingual	Tablet or 2% powder	Oral	Tablet	Tablet
Distinctive properties	1. Eating and drinking avoided for 10 min after its administration	1. Should be taken after a meal	1. Administered regardless of meals	1. Should be taken after a meal	1. Need ECG monitoring
	2. Highest affinity for 5-HT_{2C} among currently available antipsychotics	2. Highest D_2 occupancy among the 6 antipsychotics	2. Slow dose increment to reduce orthostatic hypotension	2. 5-HT_{1A} partial agonistic activity	2. Titration needed to minimize risk of orthostatic hypotension
	3. No dose adjustment needed for mild to moderate hepatic and renal impairment	3. Receptor affinity is higher for D_2 than for 5-HT_{2A}	3. Six identified polymorphisms might predict responsiveness to iloperidone	3. In moderate to severe hepatic or renal impairment, maximum dose need to be decreased to 40 mg/d	3. Highly selective to dopamine receptors in mesolimbic pathways
Safety profiles	1. Favorable in prolactin change and QTc prolongation	1. Might be favorable in prolactin change, sedation, dizziness, and weight gain	1. Favorable in sedations, akathisia, EPS, and prolactin change.	1. Favorable in prolactin change, QTc prolongation, weight gain, and metabolic effects	1. Favorable in EPS and prolactin change
	2. High risk of weight gain, akathisia, EPS dizziness, somnolence, and oral hypoesthesia	2. High risk of akathisia and EPS	2. High risk of insomnia, QTc prolongation, dizziness, and orthostatic hypotension	2. High risk of nausea, vomiting, akathisia (dose-dependent), EPS	2. Higher risk of QTc prolongation and cardiac mortality (must not be coadministered with drugs causing QTc prolongation)

5-HT_{1A}, serotonin$_{1A}$ receptor; 5-HT_{2A}, serotonin$_{2A}$ receptor; 5-HT_{2C}, serotonin$_{2C}$ receptor; BPD, bipolar disorder; D_2, dopamine D_2 receptor; OROS, Osmotic Controlled-Release Oral Delivery System; QTc, corrected QT interval; SAD, schizoaffective disorder; SPR, schizophrenia.

eliminated through feces (80%), whereas only 9% is recovered in urine. It is extensively metabolized by CYP3A4, so it should not be used in patients taking a drug having a strong CYP3A4 inhibiting activity. In addition, the maximum daily dose of lurasidone in patients with moderate to severe hepatic or renal impairment should not exceed 40 mg/d. A study suggests that its 5-HT_{1A} partial agonistic activity may be linked with antidepressant- or anxiolytic-like effects, whereas its high affinity for 5-HT_7 receptors might provide a potential benefit on cognition. It also has a low affinity for $5HT_{2C}$ receptors, and minimal affinity for H_1 or M_1 receptors. Accordingly, lurasidone have low risk of weight gain and metabolic disturbances. Moreover, it also seemed to have less risk of hyperprolactinemia and QTc prolongation, but its risk of nausea, vomiting, akathisia, and EPS seemed to be high.

Sertindole, having no FDA approval, was initially introduced within European Union in 1996 for the treatment of schizophrenia. It was suspended by the manufacturer in 1998 because of risk for cardiovascular mortality, but was relaunched in Europe in 2005. Among the 5 atypical antipsychotics, it has the longest terminal elimination half-life (>53 hours). Fecal excretion is the major route for its elimination, so dose adjustment is not needed for patients with renal impairment. However, dose adjustment is needed in patients with mild to moderate hepatic impairment, and it is not indicated in patients with severe hepatic impairment. The initial dose of sertindole is 4 mg/d, with effective dose ranging 12 to 20 mg/d, and maximum dose is 24 mg/d. A gradual dose increment over a week is recommended to minimize risk of orthostatic hypotension. Its strong 5-HT_6 receptor antagonistic activity in the absence of anticholinergic and antihistaminic actions might potentially improve cognitive functions. It also binds more selectively to dopamine receptors in mesolimbic pathways, whereas its effect on nigrostriatal pathways is very low. Accordingly, it has a favorable profile in terms of EPS and prolactin changes. The most common TAEs included headache, insomnia, and rhinitis. In terms of QT prolongation, 5 important studies (ie, PEM, ESES, SSS, EPOS, and SCoP) conducted after it was suspended showed that sertindole was not associated with higher risk in overall mortality. However, the SCoP study showed that it was associated with higher risk of cardiac mortality than risperidone. The ESES showed that among patients receiving sertindole, cardiac or unexplained death risk were higher in patients with history of hypertension, cardiovascular disorders, diabetes, or metabolic disorder. Thus, ECG monitoring for QT prolongation is mandatory in patients taking sertindole, and it is still contraindicated in patients receiving drugs with a potential of increasing QT intervals.

CONCLUSIONS

Individual antipsychotic may have differential advantages and disadvantages in terms of efficacy, adverse effect, restoration of function, and economic aspect reflected by relapse prevention. However, limited evidence comparing these antipsychotics exists, and all the pivotal RCTs included in this review were sponsored by the industry. This is due to the recent introduction of these compounds and the origin of the trial data, which is an important limitation of not only our review but also of the 5 atypical antipsychotics. Thus, further well-controlled, adequately powered, head-to-head clinical trials not sponsored by the industry are strongly required in the nearest future. In final, the choice of an individual antipsychotic is influenced by several factors mentioned earlier, but until sufficient comparative data on differential efficacy are available, the choice of using a particular drug among the reviewed antipsychotics might still be relied on their adverse effect profiles.

REFERENCES

1. Rice DP. The economic impact of schizophrenia. *J Clin Psychiatry* 1999;60(Suppl 1):4–6; discussion 28–30.
2. Buoli M, Caldiroli A, Panza G, et al. Prominent clinical dimension, duration of illness and treatment response in schizophrenia: a naturalistic study. *Psychiatry Investig* 2012;9(4):354–360.
3. Association AP. *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition—Text Revision*. Washington, DC: American Psychiatric Association; 2000.
4. Lee JG, Lee SW, Lee BJ, et al. Adjunctive memantine therapy for cognitive impairment in chronic schizophrenia: a placebo-controlled pilot study. *Psychiatry Investig* 2012;9(2):166–173.
5. Leucht S, Corves C, Arbter D, et al. Second-generation versus first-generation antipsychotic drugs for schizophrenia: a meta-analysis. *Lancet* 2009;373(9657):31–41.
6. Leucht S, Tardy M, Komossa K, et al. Antipsychotic drugs versus placebo for relapse prevention in schizophrenia: a systematic review and meta-analysis. *Lancet* 2012;379(9831):2063–2071.
7. van Os J, Kapur S. Schizophrenia. *Lancet* 2009;374(9690):635–645.
8. Kane JM, Correll CU. Past and present progress in the pharmacologic treatment of schizophrenia. *J Clin Psychiatry* 2010;71(9):1115–1124.
9. Tamminga CA, Holcomb HH. Phenotype of schizophrenia: a review and formulation. *Mol Psychiatry* 2005;10(1):27–39.
10. Song YY, Kim KR, Park JY, et al. Associated factors of quality of life in first-episode schizophrenia patients. *Psychiatry Investig* 2011; 8(3):201–206.
11. Lopez-Munoz F, Shen WW, Pae CU, et al. Trends in scientific literature on atypical antipsychotics in South Korea: a bibliometric study. *Psychiatry Investig* 2013;10(1):8–16.
12. Hibbeln JR, Nieminen LR, Blasbalg TL, et al. Healthy intakes of n-3 and n-6 fatty acids: estimations considering worldwide diversity. *Am J Clin Nutr* 2006;83(Suppl 6):1483S–1493S.
13. Potkin SG. Asenapine: a clinical overview. *J Clin Psychiatry* 2011; 72(Suppl 1):14–18.
14. Lonansen (Blonanserin): prescribing information. Osaka: Dainippon Sumitomo Pharma Co. Ltd M.
15. Administration KFaD. Ronasenjeong.
16. Fanapt (Iloperidone): Highlights of prescribing information [online]. Available at: http://www.pharma.us.novartis.com/product/pi/pdf/fanapt.pdf. Accessed March 1, 2013.
17. Crabtree BL, Montgomery J. Iloperidone for the management of adults with schizophrenia. *Clin Ther* 2011;33(3):330–345.
18. Latuda (Lurasidone): Highlights of prescribing information [online]. Available at http://latuda.com/LatudaPrescribingInformation.pdf. Accessed March 1, 2013.
19. Sanford M. Lurasidone: in the treatment of schizophrenia. *CNS Drugs* 2013;27(1):67–80.
20. Moore N. Higher cardiovascular mortality with sertindole in ADROIT: a signal not confirmed. *Int J Psychiatry Clin Pract* 2002; 6(Suppl 1):S3–S9.
21. Glassman AH. Schizophrenia, antipsychotic drugs, and cardiovascular disease. *J Clin Psychiatry* 2005;66(Suppl 6):5–10.
22. Lundbeck H. *Serdolect (sertindole) monograph*. Copenhagen: H. Lundbeck; 2005.
23. Shahid M, Walker GB, Zorn SH, et al. Asenapine: a novel psychopharmacologic agent with a unique human receptor signature. *J Psychopharmacol* 2009;23(1):65–73.

24. Bishara D, Taylor D. Upcoming agents for the treatment of schizophrenia: mechanism of action, efficacy and tolerability. *Drugs* 2008;68(16):2269–2292.
25. Tarazi FI, Choi YK, Gardner M, et al. Asenapine exerts distinctive regional effects on ionotropic glutamate receptor subtypes in rat brain. *Synapse* 2009;63(5):413–420.
26. Stoner SC, Pace HA. Asenapine: a clinical review of a second-generation antipsychotic. *Clin Ther* 2012;34(5):1023–1040.
27. Tarazi FI, Moran-Gates T, Wong EH, et al. Differential regional and dose-related effects of asenapine on dopamine receptor subtypes. *Psychopharmacology (Berl)* 2008;198(1):103–111.
28. Den Boer J, Korf J. Dopamine receptor subtypes and schizophrenia: a clinical perspective. In: Cools AR, ed. *Atypical Antipsychotics*. Basel, Switzerland: Birkhäuser Verlag, Ellenbroek BA; 2000:163–190.
29. Kishi T, Matsuda Y, Nakamura H, et al. Blonanserin for schizophrenia: systematic review and meta-analysis of double-blind, randomized, controlled trials. *J Psychiatr Res* 2013;47(2):149–154.
30. Richelson E. Receptor pharmacology of neuroleptics: relation to clinical effects. *J Clin Psychiatry* 1999;60(Suppl 10):5–14.
31. Deeks ED, Keating GM. Blonanserin: a review of its use in the management of schizophrenia. *CNS Drugs* 2010;24(1):65–84.
32. Kalkman HO, Subramanian N, Hoyer D. Extended radioligand binding profile of iloperidone: a broad spectrum dopamine/serotonin/norepinephrine receptor antagonist for the management of psychotic disorders. *Neuropsychopharmacology* 2001;25(6):904–914.
33. Kongsamut S, Roehr JE, Cai J, et al. Iloperidone binding to human and rat dopamine and 5-HT receptors. *Eur J Pharmacol* 1996; 317(2–3):417–423.
34. Meyer JM, Loebel AD, Schweizer E. Lurasidone: a new drug in development for schizophrenia. *Expert Opin Investig Drugs* 2009;18 (11):1715–1726.
35. Citrome L. Lurasidone for schizophrenia: a review of the efficacy and safety profile for this newly approved second-generation antipsychotic. *Int J Clin Pract* 2011;65(2):189–210.
36. Ishibashi T, Horisawa T, Tokuda K, et al. Pharmacological profile of lurasidone, a novel antipsychotic agent with potent 5-hydroxytryptamine 7 (5-HT7) and 5-HT1A receptor activity. *J Pharmacol Exp Ther* 2010;334(1):171–181.
37. Newman-Tancredi A. The importance of 5-HT1A receptor agonism in antipsychotic drug action: rationale and perspectives. *Curr Opin Investig Drugs* 2010;11(7):802–812.
38. Karamatskos E, Lambert M, Mulert C, et al. Drug safety and efficacy evaluation of sertindole for schizophrenia. *Expert Opin Drug Saf* 2012;11(6):1047–1062.
39. Rodefer JS, Nguyen TN, Karlsson JJ, et al. Reversal of subchronic PCP-induced deficits in attentional set shifting in rats by sertindole and a 5-HT6 receptor antagonist: comparison among antipsychotics. *Neuropsychopharmacology* 2008;33(11):2657–2666.
40. Didriksen M, Kreilgaard M, Arnt J. Sertindole, in contrast to clozapine and olanzapine, does not disrupt water maze performance after acute or chronic treatment. *Eur J Pharmacol* 2006;542(1–3):108–115.
41. Didriksen M, Skarsfeldt T, Arnt J. Reversal of PCP-induced learning and memory deficits in the Morris' water maze by sertindole and other antipsychotics. *Psychopharmacology (Berl)* 2007;193(2):225–233.
42. Hyttel J, Nielsen JB, Nowak G. The acute effect of sertindole on brain 5-HT2, D2 and alpha 1 receptors (ex vivo radioreceptor binding studies). *J Neural Transm Gen Sect* 1992;89(1–2):61–69.
43. Hietala J, Kuonnamaki M, Palvimaki EP, et al. Sertindole is a serotonin 5-HT2c inverse agonist and decreases agonist but not antagonist binding to 5-HT2c receptors after chronic treatment. *Psychopharmacology (Berl)* 2001;157(2):180–187.
44. Zimbroff DL, Kane JM, Tamminga CA, et al. Controlled, dose-response study of sertindole and haloperidol in the treatment of schizophrenia. Sertindole Study Group. *Am J Psychiatry* 1997;154 (6):782–791.
45. van de Wetering-Krebbers SF, Jacobs PL, Kemperman GJ, et al. Metabolism and excretion of asenapine in healthy male subjects. *Drug Metab Dispos* 2011;39(4):580–590.
46. Peeters P, Bockbrader H, Spaans E, et al. Asenapine pharmacokinetics in hepatic and renal impairment. *Clin Pharmacokinet* 2011; 50(7):471–481.
47. Sainati SM, Hubbard JW, Chi E, et al. Safety, tolerability, and effect of food on the pharmacokinetics of iloperidone (HP 873), a potential atypical antipsychotic. *J Clin Pharmacol* 1995;35(7):713–720.
48. Sedek G, Wolfgang C. Iloperidone is well tolerated by subjects with renal or hepatic impairment in single-dose clinical pharmacokinetic studies. Presented at: American Psychiatric Association Annual Meeting, San Diego, CA, May 27, 2007.
49. Wong SL, Cao G, Mack RJ, et al. Pharmacokinetics of sertindole in healthy young and elderly male and female subjects. *Clin Pharmacol Ther* 1997;62(2):157–164.
50. Wong SL, Linnen P, Mack R, et al. Effects of food, antacid, and dosage form on the pharmacokinetics and relative bioavailability of sertindole in healthy volunteers. *Biopharm Drug Dispos* 1997;18(6):533–541.
51. Wong SL, Menacherry S, Mulford D, et al. Pharmacokinetics of sertindole and dehydrosertindole in volunteers with normal or impaired renal function. *Eur J Clin Pharmacol* 1997;52(3):223–227.
52. Glassman AH, Bigger JT Jr. Antipsychotic drugs: prolonged QTc interval, torsade de pointes, and sudden death. *Am J Psychiatry* 2001;158(11):1774–1782.
53. Kane JM, Cohen M, Zhao J, et al. Efficacy and safety of asenapine in a placebo- and haloperidol-controlled trial in patients with acute exacerbation of schizophrenia. *J Clin Psychopharmacol* 2010; 30(2):106–115.
54. Potkin SG, Cohen M, Panagides J. Efficacy and tolerability of asenapine in acute schizophrenia: a placebo- and risperidone-controlled trial. *J Clin Psychiatry* 2007;68(10):1492–1500.
55. Szegedi A, Verweij P, van Duijnhoven W, et al. Meta-analyses of the efficacy of asenapine for acute schizophrenia: comparisons with placebo and other antipsychotics. *J Clin Psychiatry* 2012;73(12):1533–1540.
56. Kane JM, Mackle M, Snow-Adami L, et al. A randomized placebo-controlled trial of asenapine for the prevention of relapse of schizophrenia after long-term treatment. *J Clin Psychiatry* 2011;72 (3):349–355.
57. Schoemaker J, Stet L, Vrijland P, et al. Long-term efficacy and safety of asenapine or olanzapine in patients with schizophrenia or schizoaffective disorder: an extension study. *Pharmacopsychiatry* 2012;45(5):196–203.
58. McIntyre RS, Cohen M, Zhao J, et al. A 3-week, randomized, placebo-controlled trial of asenapine in the treatment of acute mania in bipolar mania and mixed states. *Bipolar Disord* 2009; 11(7):673–686.
59. McIntyre RS, Cohen M, Zhao J, et al. Asenapine in the treatment of acute mania in bipolar I disorder: a randomized, double-blind, placebo-controlled trial. *J Affect Disord* 2010;122(1–2):27–38.
60. Yang J, Bahk WM, Cho HS, et al. Efficacy and tolerability of Blonanserin in the patients with schizophrenia: a randomized, double-blind, risperidone-compared trial. *Clin Neuropharmacol* 2010;33(4):169–175.
61. Miura S. Clinical evaluation of blonanserin for schizophrenia: a randomized study comparing blonanserin with risperidone (in Japanese). *Jpn J Clin Psychopharmacol* 2008;11:297–314.
62. Garcia E, Robert M, Peris F, et al. The efficacy and safety of blonanserin compared with haloperidol in acute-phase schizophrenia:

a randomized, double-blind, placebo-controlled, multicentre study. *CNS Drugs* 2009;23(7):615–625.

63. Murasaki M. Clinical evaluation of blonanserin for schizophrenia: a double-blind trial comparing blonanserin with haloperidol. *Jpn J Clin Psychopharmacol* 2007;10:2059–2079.
64. Murasaki M. Long-term clinical study of blonanserin for schizophrenia: a multicenter open study to determine safety and effectiveness in schizophrenic patients (Kanagawa Region Clinical Psychopharmacology Study Group) [English abstract]. *Jpn J Clin Psychopharmacol* 2007;10:2241–2257.
65. Kinoshita T. Long-term clinical study of blonanserin for schizophrenia: a multicenter open study to determine safety and effectiveness in schizophrenic patients (Japanese) [English abstract]. *Jpn J Clin Psychopharmacol* 2008;11:135–153.
66. Potkin SG, Litman RE, Torres R, et al. Efficacy of iloperidone in the treatment of schizophrenia: initial phase 3 studies. *J Clin Psychopharmacol* 2008;28(2 Suppl 1):S4–S11.
67. Cutler AJ, Kalali AH, Weiden PJ, et al. Four-week, double-blind, placebo- and ziprasidone-controlled trial of iloperidone in patients with acute exacerbations of schizophrenia. *J Clin Psychopharmacol* 2008; 28(2 Suppl 1):S20–S28.
68. Arif SA, Mitchell MM. Iloperidone: a new drug for the treatment of schizophrenia. *Am J Health Syst Pharm* 2011;68(4):301–308.
69. Sacristan JA, Gomez JC, Montejo AL, et al. Doses of olanzapine, risperidone, and haloperidol used in clinical practice: results of a prospective pharmacoepidemiologic study. EFESO Study Group. Estudio Farmacoepidemiologico en la Esquizofrenia con Olanzapina. *Clin Ther* 2000;22(5):583–599.
70. Kane JM, Lauriello J, Laska E, et al. Long-term efficacy and safety of iloperidone: results from 3 clinical trials for the treatment of schizophrenia. *J Clin Psychopharmacol* 2008;28(2 Suppl 1):S29–S35.
71. Volpi S, Potkin SG, Malhotra AK, et al. Applicability of a genetic signature for enhanced iloperidone efficacy in the treatment of schizophrenia. *J Clin Psychiatry* 2009;70(6):801–809.
72. Nakamura M, Ogasa M, Guarino J, et al. Lurasidone in the treatment of acute schizophrenia: a double-blind, placebo-controlled trial. *J Clin Psychiatry* 2009;70(6):829–836.
73. Ogasa M, Kimura T, Nakamura M, et al. Lurasidone in the treatment of schizophrenia: a 6-week, placebo-controlled study. *Psychopharmacology (Berl)* 2013;225(3):519–530.
74. Nasrallah HA, Silva R, Phillips D, et al. Lurasidone for the treatment of acutely psychotic patients with schizophrenia: a 6-week, randomized, placebo-controlled study. *J Psychiatr Res* 2013;47(5):670–7.
75. Meltzer HY, Cucchiaro J, Silva R, et al. Lurasidone in the treatment of schizophrenia: a randomized, double-blind, placebo- and olanzapine-controlled study. *Am J Psychiatry* 2011;168(9):957–967.
76. Loebel A, Cucchiaro J, Sarma K, et al. Efficacy and safety of lurasidone 80 mg/day and 160 mg/day in the treatment of schizophrenia: a randomized, double-blind, placebo- and active-controlled trial. *Schizophr Res* 2013;145(1–3):101–9.
77. Samalin L, Garnier M, Llorca PM. Clinical potential of lurasidone in the management of schizophrenia. *Ther Clin Risk Manag* 2011;7:239–250.
78. Harvey PD, Ogasa M, Cucchiaro J, et al. Performance and interview-based assessments of cognitive change in a randomized, double-blind comparison of lurasidone vs. ziprasidone. *Schizophr Res* 2011;127(1–3):188–194.
79. Citrome L, Cucchiaro J, Sarma K, et al. Long-term safety and tolerability of lurasidone in schizophrenia: a 12-month, double-blind, active-controlled study. *Int Clin Psychopharmacol* 2012;27(3):165–176.
80. van Kammen DP, McEvoy JP, Targum SD, et al. A randomized, controlled, dose-ranging trial of sertindole in patients with schizophrenia. *Psychopharmacology (Berl)* 1996;124(1–2):168–175.
81. Daniel DG, Wozniak P, Mack RJ, et al. Long-term efficacy and safety comparison of sertindole and haloperidol in the treatment of schizophrenia. The Sertindole Study Group. *Psychopharmacol Bull* 1998;34(1):61–69.
82. Hale A, Azorin MA, Kasper S, et al. Sertindole improves both the positive and negative symptoms of schizophrenia: results of a phase III trial. *Int J Psychiatry Clin Pract* 2000;4:55–62.
83. Azorin JM, Strub N, Loft H. A double-blind, controlled study of sertindole versus risperidone in the treatment of moderate-to-severe schizophrenia. *Int Clin Psychopharmacol* 2006;21(1):49–56.
84. Kane JM, Potkin SG, Daniel DG, et al. A double-blind, randomized study comparing the efficacy and safety of sertindole and risperidone in patients with treatment-resistant schizophrenia. *J Clin Psychiatry* 2011;72(2):194–204.
85. Kwon JS, Mittoux A, Hwang JY, et al. The efficacy and safety of 12 weeks of treatment with sertindole or olanzapine in patients with chronic schizophrenia who did not respond successfully to their previous treatments: a randomized, double-blind, parallel-group, flexible-dose study. *Int Clin Psychopharmacol* 2012;27(6):326–335.
86. Gallhofer B, Jaanson P, Mittoux A, et al. Course of recovery of cognitive impairment in patients with schizophrenia: a randomised double-blind study comparing sertindole and haloperidol. *Pharmacopsychiatry* 2007;40(6):275–286.
87. Buchsbaum MS, Haznedar M, Newmark RE, et al. FDG-PET and MRI imaging of the effects of sertindole and haloperidol in the prefrontal lobe in schizophrenia. *Schizophr Res* 2009;114(1–3): 161–171.
88. Bobo WV. Asenapine, iloperidone and lurasidone: critical appraisal of the most recently approved pharmacotherapies for schizophrenia in adults. *Expert Rev Clin Pharmacol* 2013;6(1):61–91.
89. Weiden PJ, Cutler AJ, Polymeropoulos MH, et al. Safety profile of iloperidone: a pooled analysis of 6-week acute-phase pivotal trials. *J Clin Psychopharmacol* 2008;28(2 Suppl 1):S12–S19.
90. Cutler AJ, Kalali AH, Mattingly GW, et al. Long-term safety and tolerability of iloperidone: results from a 25-week, open-label extension trial. *CNS Spectr* 2013;18(1):43–54.
91. Wilton LV, Heeley EL, Pickering RM, et al. Comparative study of mortality rates and cardiac dysrhythmias in post-marketing surveillance studies of sertindole and two other atypical antipsychotic drugs, risperidone and olanzapine. *J Psychopharmacol* 2001;15(2):120–126.
92. Peuskens J, Moore N, Azorin JM, et al. The European sertindole safety and exposure survey: a follow-up study of 8600 patients. *Pharmacoepidemiol Drug Saf* 2007;16(7):804–811.
93. Lancon C, Toumi M, Sapin C, et al. The Sertindole Safety Survey: a retrospective analysis under a named patient use programme in Europe. *BMC Psychiatry* 2008;8:57.
94. Kasper S, Moller HJ, Hale A. The European post-marketing observational sertindole study: an investigation of the safety of antipsychotic drug treatment. *Eur Arch Psychiatry Clin Neurosci* 2010;260(1):59–68.
95. Thomas SH, Drici MD, Hall GC, et al. Safety of sertindole versus risperidone in schizophrenia: principal results of the sertindole cohort prospective study (SCoP). *Acta Psychiatr Scand* 2010;122(5):345–355.
96. De Hert M, Yu W, Detraux J, et al. Body weight and metabolic adverse effects of asenapine, iloperidone, lurasidone and paliperidone in the treatment of schizophrenia and bipolar disorder: a systematic review and exploratory meta-analysis. *CNS Drugs* 2012;26(9):733–759.
97. Szegedi A, Calabrese JR, Stet L, et al. Asenapine as adjunctive treatment for acute mania associated with bipolar disorder: results of a 12-week core study and 40-week extension. *J Clin Psychopharmacol* 2012;32:46–55.