

Profile of blonanserin for the treatment of schizophrenia

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Abstract: Blonanserin was developed as an antipsychotic drug in Japan and approved for the treatment of schizophrenia. It belongs to a series of 4-phenyl-2-(1-piperazinyl)pyridines and acts as an antagonist at dopamine D_2 , D_3 , and serotonin $5-HT_{2A}$ receptors. Blonanserin has low affinity for $5-HT_{2C}$, adrenergic α_1 , histamine H_1 , and muscarinic M_1 receptors, but displays relatively high affinity for $5-HT_6$ receptors. In several short-term double-blind clinical trials, blonanserin had equal efficacy as haloperidol and risperidone for positive symptoms in patients with chronic schizophrenia and was also superior to haloperidol for improving negative symptoms. Blonanserin is generally well tolerated and has a low propensity to cause metabolic side effects and prolactin elevation. We recently reported that blonanserin can improve some types of cognitive function associated with prefrontal cortical function in patients with first-episode and chronic schizophrenia. Taken together, these results suggest that blonanserin may be a promising candidate for a first-line antipsychotic for acute and maintenance therapy for schizophrenia. Further comparative studies are warranted to clarify the benefit/risk profile of blonanserin and its role in the treatment of schizophrenia.

Keywords: blonanserin, schizophrenia, pharmacology, pharmacokinetics, efficacy, safety

Introduction

Schizophrenia is a heterogeneous devastating psychiatric disorder characterized by positive, negative, affective, and cognitive symptoms. It generally presents in late adolescence or early adulthood and is associated with an increased risk of mortality and social or occupational dysfunction.¹ Most patients with the illness usually need life-long treatment, and antipsychotic drugs are the mainstay of the pharmacologic treatment for schizophrenia.²

The introduction of second-generation antipsychotics (SGAs) or atypical antipsychotics represented an important advance in the pharmacologic treatment of the disorder.^{3,4} Accumulating evidence suggests that SGAs have at least equal or superior efficacy as first-generation antipsychotics (FGAs) and may offer some advantages over FGAs such as fewer extrapyramidal symptoms (EPS).⁵⁻⁸ SGAs excluding clozapine are currently recommended in many guidelines as first-line agents for acute and maintenance therapy for schizophrenia.⁹⁻¹¹ However, increased concern has arisen regarding the safety profile of SGAs, as problems such as weight gain, metabolic abnormalities, and/or hyperprolactinemia have been noted.^{3,4} These side effects are associated with potential long-term health risks for patients as well as decreased adherence to treatment regimens. The need for more effective and safer agents has prompted the development of new antipsychotics.¹²

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Blonanserin was developed as a novel antipsychotic drug in Japan and was approved in Japan in 2008 and Korea in 2009 for the treatment of schizophrenia. It is currently under clinical investigation in a Phase III trial in the People's Republic of China.¹³ This article reviews the available data about the pharmacological profile, clinical efficacy, safety, and tolerability of blonanserin, and discusses its place in the treatment of schizophrenia as well as future perspectives.

Pharmacological profile

Pharmacodynamics

Blonanserin belongs to a series of 4-phenyl-2-(1-piperazinyl) pyridines and acts as an antagonist at dopamine D₂, D₃, and serotonin 5-HT_{2A} receptors (Table 1).¹⁴ Its affinity for D₂ receptors is approximately 6 times greater than that for 5-HT_{2A} receptors. This feature is different from that of most other SGAs. Thus, blonanserin is pharmacologically more similar to FGAs than new generation drugs,⁴ and in Japan, it is often called a “dopamine-serotonin antagonist”.¹⁵ The affinity of blonanserin for D₂ receptors is 20- and 94-fold higher than that of haloperidol and risperidone, respectively.

In contrast, blonanserin has low affinity for 5-HT_{2C}, adrenergic α_1 , histamine H₁, and muscarinic M₁ receptors (Table 1).¹⁴ These receptor binding profiles may minimize its potential to induce certain adverse effects such as orthostatic hypotension, oversedation, weight gain, metabolic abnormalities, and peripheral anticholinergic side effects.^{16,17}

Blonanserin has a relatively high affinity for 5-HT₆ receptors ($K_i = 11.7$ nM) that is likely involved in the improvement of cognitive function.¹⁸ It also shows low inhibitory activity of neuronal re-uptake of dopamine, 5-HT, and norepinephrine.¹⁷ A positron emission tomography (PET) study of healthy volunteers showed that blonanserin occupies approximately 80% of striatal D₂-like receptors with normal clinical doses.¹⁶

A preclinical study demonstrated that systematic administration of blonanserin increases extracellular levels of norepinephrine and dopamine, but not levels of 5-HT, glutamate, or gamma-aminobutyric acid in the prefrontal cortex.¹⁹ It also enhances neuronal activity in the locus coeruleus and ventral tegmental area without affecting activity in the dorsal raphe nucleus or the mediodorsal thalamic nucleus. Another study showed that blonanserin attenuates the enhancement of immobility in the forced swimming test induced by repeated treatment with phencyclidine in mice.¹⁴ Moreover, it improves apomorphine-induced prepulse inhibition disruption in rats. These effects of blonanserin suggest a potential efficacy for treating negative symptoms and cognitive impairment in schizophrenia.

Pharmacokinetics

Blonanserin is rapidly absorbed from the gastrointestinal tract (with the exception of the stomach) after oral administration and reaches a maximum plasma concentration (C_{max}) within 2 hours in healthy volunteers.²⁰ Steady-state levels

Table 1 Receptor binding affinities of blonanserin, risperidone, and haloperidol (K_i values, nM)

| Receptor | Preparation | Ligand | Blonanserin | Risperidone | Haloperidol |
|--------------------|-------------------|----------------------------|-------------|-------------|-------------|
| Dopamine | | | | | |
| D ₁ | Human recombinant | ³ H-SCH23390 | 1,070 | 761 | 2,300 |
| D ₂ | Human recombinant | ³ H-spiperone | 0.142 | 13.2 | 2.73 |
| D ₃ | Human recombinant | ³ H-spiperone | 0.494 | | |
| D ₄ | Human recombinant | ³ H-spiperone | 150 | | |
| D ₅ | Human recombinant | ³ H-SCH23390 | 2,600 | | |
| Serotonin | | | | | |
| 5-HT _{1A} | Human recombinant | ³ H-8-OH-DPAT | 804 | | |
| 5-HT _{2A} | Human recombinant | ³ H-ketanserin | 0.812 | 1.09 | 45.7 |
| 5-HT _{2C} | Human recombinant | ³ H-mesulergine | 26.4 | | |
| 5-HT ₆ | Human recombinant | ¹²⁵ I-LSD | 41.9 | | |
| 5-HT ₇ | Human recombinant | ¹²⁵ I-LSD | 183 | | |
| Adrenergic | | | | | |
| α_1 | Rat brain | ³ H-prazosin | 26.7 | 0.657 | 8.75 |
| α_2 | Rat cortex | ³ H-RX821002 | 530 | | |
| Histamine | | | | | |
| H ₁ | Human recombinant | ³ H-pyramine | 765 | | |
| Muscarinic | | | | | |
| M ₁ | Human recombinant | ³ H-NMS | 100 | | |

Note: Data are mean values. Data reprinted from *Jpn J Clin Psychopharmacol*, Volume 10, Une T, Kurumiya S, Pharmacological profile of blonanserin, pages 1263–1272. Copyright © 2007, with permission from Seiwa Shoten Publishers Tokyo.

Abbreviations: LSD, lysergic acid diethylamide; NMS, N-methyl scopolamine.

of blonanserin are attained within 5 days after repeated administration of blonanserin (4 mg/day) in healthy individuals,²⁰ and the plasma concentration is correlated with the administered dose.²¹ Binding to plasma proteins is almost 100% over the concentration range of 10 ng/mL–2 µg/mL with albumin contributing the most to binding.²⁰ Brain uptake is extensive, and P-glycoprotein, an efflux transporter expressed in the brain, does not actively transport blonanserin as a substrate in humans or mice.²² Results of PET studies, in which D₂ receptor occupancy of several antipsychotics in the pituitary and temporal cortex was calculated, demonstrated that blonanserin has the highest brain/plasma concentration ratio (B/P ratio = 3.88) compared with that of olanzapine (B/P ratio = 2.70), haloperidol (B/P ratio = 2.40), risperidone (B/P ratio = 1.61), and sulpiride (B/P ratio = 0.34).^{23,24} The B/P ratio represents the penetrating capability of antipsychotics across the blood–brain barrier,²³ and thus, blonanserin appears to pass into the brain more easily than these other antipsychotics.

Food significantly affects the bioavailability of blonanserin in healthy individuals. Both C_{max} and area under the plasma concentration–time curve (AUC) from time 0 to 12 hours after a single oral administration of blonanserin are 2.7-fold higher in the fed state compared with the fasting state, and the time to C_{max} (T_{max}) is significantly prolonged under fed conditions.²⁰ Thus, blonanserin should be taken after meal intake. However, Saruwatari et al²⁵ demonstrated that the increase in systemic exposure to blonanserin continues until at least 4 hours after food intake, and thus, the drug can be administered immediately before bedtime.

Blonanserin is mainly metabolized by cytochrome P450 (CYP) 3A4 in the liver, and its major metabolites are M-1 (N-deethylated blonanserin) and M-3 (7- and 8-hydroxylated blonanserin).²⁰ M-1 has the highest binding affinity for D_{2/3} receptors and 5-HT_{2A} receptors, but it shows pharmacological activity several fold lower than that of the parent drug.¹⁶

Elimination of blonanserin is predominantly in the urine and feces.²⁰ The terminal elimination half-life ($t_{1/2}$) of blonanserin was 10.7, 12.0, and 16.2 hours after administration of a single oral dose of 4, 8, and 12 mg, respectively, in healthy volunteers. Thus, the manufacturer's prescribing information recommends twice-daily administration. However, the elimination $t_{1/2}$ was 67.9 hours after repeated administration of blonanserin (4 mg/day) for 10 days in healthy individuals.²⁰ Thus, it can be effectively administered once a day in clinical practice.

Drug interactions

As described previously, blonanserin is predominantly metabolized by CYP3A4. Coadministration of potent CYP3A4 inhibitors such as azole antifungal agents and human immunodeficiency virus protease inhibitors with blonanserin may increase the plasma concentration of blonanserin, and coadministration of these drugs is contraindicated.²⁰ In addition, concomitant administration of blonanserin with adrenaline is contraindicated due to the potential risks of serious reductions in blood pressure.

The package inserts also provide cautions about coadministration of blonanserin with other CYP3A4 inhibitors such as erythromycin, clarithromycin, cyclosporine, diltiazem, and grapefruit juice.²⁰ In contrast, CYP3A4 inducers such as phenytoin, carbamazepine, barbiturate, and rifampicin should be carefully administered with blonanserin, because of the potential for decreased plasma blonanserin concentrations.

The effects of blonanserin may be enhanced after coadministration with central nervous system depressant drugs or alcohol and may be reduced after coadministration with dopamine agonists (eg, levodopa and bromocriptine), and patients should be cautioned to coadminister carefully.²⁰

Therapeutic efficacy

The therapeutic efficacy of blonanserin for the treatment of patients with schizophrenia was evaluated in four comparative short-term trials^{26–29} and three non-comparative long-term studies.^{30–32}

Short-term efficacy

Four randomized, double-blind, placebo- and active comparator-controlled clinical trials evaluated the short-term efficacy of blonanserin (Table 2).^{26–29} In a haloperidol-controlled, 8-week Phase III trial,²⁷ a total of 265 patients were randomized. Patients were randomly assigned to receive twice daily doses of blonanserin (8–24 mg/day) or haloperidol (4–12 mg/day). Results for the primary endpoint, the final global improvement rate (percentage of patients graded “markedly improved” or “moderately improved”), were 61.2% improvement in the blonanserin group and 51.3% improvement in the haloperidol group. Blonanserin was non-inferior to haloperidol ($P = 0.001$). Secondary efficacy measures included scores from the Positive and Negative Syndrome Scale (PANSS) and the Brief Psychiatric Rating Scale (BPRS). No significant differences were found between the treatment groups regarding mean improvements from

Table 2 Published short-term, randomized, double-blind studies of blonanserin in patients with schizophrenia

| Study (year of publication) | Type of study and duration (weeks) | Diagnoses, n and age of randomized patients | Blonanserin regimen (n of patients; % discontinuation) | Active comparator regimen (n of patients; % discontinuation) | Placebo (n of patients; % discontinuation) | Outcome measures | Main efficacy results (primary outcomes) |
|-----------------------------|---|---|--|--|--|--|--|
| Murasaki (2007) | Randomized, double-blind, active controlled, 8 weeks | Schizophrenia 265 patients aged 16–64 years | 8–24 mg/day (n = 129; 24.0%) | Haloperidol 4–24 mg/day (n = 134; 29.1%) | NA | Primary: final global improvement rate Secondary: PANSS, BPRS | Final global improvement rate ^a (% of patients) B = 61.2 H = 51.3 (<i>P</i> = 0.001) ^b |
| Miura (2008) | Randomized, double-blind, active controlled, 8 weeks | Schizophrenia 302 patients aged ≥ 15 years | 8–24 mg/day (n = 156; 29.5%) | Risperidone 2–6 mg/day (n = 145; 25.5%) | NA | Primary: PANSS-T Secondary: PANSS-P, PANSS-N, PANSS-GP, BPRS, final global improvement rate Primary: PANSS-T | PANSS-T score mean change from baseline [baseline] B = -11.05 [87.1] R = -11.51 [86.7] (<i>P</i> < 0.001) ^c |
| Garcia et al (2009) | Randomized, double-blind, placebo- and active controlled, 6 weeks | Schizophrenia (with an acute exacerbation) 307 patients aged 18–65 years | 2.5 mg/day (n = 61; 27.9%) 5 mg/day (n = 58; 20.7%) 10 mg/day (n = 64; 21.9%) | Haloperidol 10 mg/day (n = 60; 18.3%) | Placebo (n = 64; 39.1%) | Primary: PANSS-T Secondary: PANSS-P, PANSS-N, BPRS, CGI-S | PANSS-T score mean change from baseline ^d B 2.5 = -20.60* B 5 = -27.19* B 10 = -30.18* H 10 = -28.16* PI = -12.58 |
| Yang et al (2010) | Randomized, double-blind, active controlled, 8 weeks | Schizophrenia 206 patients aged 18–65 years | 8–24 mg/day (n = 92; 39.8%) | Risperidone 2–6 mg/day (n = 91; 28.2%) | NA | Primary: PANSS-T Secondary: BPRS, CGI-I | PANSS-T score mean change from baseline [baseline] ^e B = -23.48 [86.91] R = -25.40 [86.49] (<i>P</i> = 0.3014) ^f |

Notes: ^aProportion of patients with an improvement rating of “improved” or “markedly improved” at completion of study treatment; ^bthe noninferiority of blonanserin compared with haloperidol for final global improvement was verified using the handicap method (noninferiority margin of -10%); 95% confidence interval (CI) -2.7, +22.4; ^cthe predefined criterion for the noninferiority of blonanserin compared with risperidone for the change from baseline in PANSS total score (lower limit of two-sided 95% CI for the between-group difference of >-7) was met; 95% CI -4.40, +3.48; ^dstatistical analysis used an analysis of covariance model. Treatment effects were estimated by least squares means; ^etreatment effects were estimated by least squares means; ^fWilcoxon rank sum test; *statistically significant vs placebo (*P* < 0.001).

Abbreviations: n, number; B, blonanserin; H, haloperidol; R, risperidone; PI, placebo; PANSS-T (P, N, GP), Positive and Negative Syndrome Scale-Total (Positive, Negative, and General Psychopathology subscales); BPRS, Brief Psychiatric Rating Scale; CGI-S (I), Clinical Global Impression of Severity Scale (Improvement); P, *P*-value; NA, not available.

baseline in PANSS, BPRS total scores, PANSS positive or general psychopathological subscores. However, blonanserin produced significantly greater decreases in the PANSS negative subscale scores ($P = 0.025$) and the “anergia cluster” score of BPRS ($P = 0.022$) compared with haloperidol.

Garcia et al²⁶ conducted a 6-week, placebo- and haloperidol-controlled, international, multicenter study in 307 patients with an acute exacerbation of schizophrenia. Patients were randomized into one of five treatment groups (blonanserin 2.5, 5, or 10 mg, haloperidol 10 mg, or placebo once daily). All active treatments produced significantly greater reductions from baseline in the PANSS total and positive scores at week 6 compared with placebo ($P < 0.001$). Blonanserin (5 and 10 mg/day) was superior to haloperidol for treating the negative symptoms of schizophrenia.

In an 8-week, risperidone-controlled, Phase III trial conducted in Japan,²⁸ 302 patients with chronic schizophrenia were randomly assigned to receive twice daily doses of blonanserin (8–24 mg/day) or risperidone (2–6 mg/day). Blonanserin was as effective as risperidone regarding mean improvements from baseline in the PANSS total score and each of the subscale scores as well as the BPRS total and cluster scores.

Yang et al²⁹ conducted an 8-week, risperidone-controlled trial in 206 Korean patients with chronic schizophrenia. Patients were randomly assigned to take twice daily doses of blonanserin (8–24 mg/day) or risperidone (2–6 mg/day). Blonanserin showed equal efficacy as risperidone regarding mean improvements from baseline in the PANSS total score and the subscale scores as well as the BPRS total and cluster scores.

Kishi et al¹³ recently performed a systematic review and meta-analysis of these four studies and found no significant differences in discontinuation due to any cause ($P = 0.29$) or due to ineffectiveness ($P = 0.32$) between blonanserin and other pooled antipsychotics. Moreover, they did not find significant heterogeneity in the response rate between blonanserin and other antipsychotics.

In summary, blonanserin had equal short-term efficacy as haloperidol and risperidone regarding positive symptoms in patients with chronic schizophrenia. It was also superior to haloperidol for improving negative symptoms.

Long-term efficacy

Three open-label, non-comparative studies were conducted in Japan to evaluate the long-term efficacy of blonanserin.^{30–32}

Data are available from two studies ($n = 61$ ³⁰ and 321 ³¹) that were both conducted for 28 and 52–56 weeks of treatment.

Of the 61 patients eligible for analysis, 48 patients (78.7%) received blonanserin for 28 weeks, and 38 patients (62.3%) were treated for up to 56 weeks.³⁰ Of the 321 patients eligible for analysis, 264 patients (82.2%) received blonanserin for 28 weeks, and 155 patients (48.3%) were treated for more than 52 weeks.³¹ The final global improvement rate was 52%–87% after 28 or 52–56 weeks of treatment.^{30,31} Blonanserin produced significant improvements from baseline in the PANSS total score and the subscale scores as well as the BPRS total score ($P < 0.0001$).

In an extended long-term trial, nine (42.9%) of 21 patients who were enrolled in the study completed over 6 years of treatment with blonanserin.³² The final mean dose was 14.2 mg/day, and the final global improvement rate was 86%. Blonanserin produced significant reductions from baseline in the BPRS total score ($P < 0.001$).

In summary, these data suggest that blonanserin may have long-term efficacy for the treatment of schizophrenia. However, data on direct head-to-head comparison with other antipsychotics are lacking for the maintenance treatment of the illness.

Effect of blonanserin on cognitive function

Cognitive impairment is a core feature of schizophrenia^{33,34} and is present early in the course of the illness.^{35,36} A number of studies have reported a 1–2 standard deviation decline in performance on tests of multiple cognitive domains, including attention, executive function, memory, and processing speed, compared to healthy individuals.^{35,37–39} These cognitive deficits largely determine social and occupational functioning, as well as quality of life (QOL) in patients with schizophrenia.⁴⁰

We previously conducted an 8-week, randomized, double-blind comparison of blonanserin ($n = 10$) and risperidone ($n = 12$) to evaluate the effects of these antipsychotics on cognitive functions in patients with chronic schizophrenia.⁴¹ Both antipsychotics significantly improved some types of verbal memory, whereas greater improvement was seen with blonanserin for attention and processing speed.

We recently conducted an 8-week, open-label study to evaluate the effects of blonanserin on clinical efficacy including cognitive function and subjective QOL in patients with antipsychotic-naïve first-episode schizophrenia.⁴² Cognitive function was assessed with the Brief Assessment of Cognition in Schizophrenia Japanese-language version (BACS-J),⁴³ and subjective QOL was assessed with the Schizophrenia Quality of Life Scale Japanese-language version (SQLS-J).⁴⁴

Twenty-four patients were recruited and tested at baseline. Of these, 20 completed the study. The mean daily doses of blonanserin at the start after baseline assessment and at 8 weeks were 2.9 mg/day and 7.2 mg/day, respectively. Results of paired *t*-tests demonstrated that *z*-scores of the letter fluency score (verbal fluency) and the Tower of London score (executive function) assessed with BACS-J were significantly increased after treatment with blonanserin ($P < 0.05$ each) (Figure 1). The effect sizes for these changes were in the moderate range (0.58 and 0.62, respectively). All items on the PANSS, SCLS-J, and Clinical Global Impression-Severity of Illness Scale significantly improved after 8 weeks of treatment (all $P < 0.01$).⁴² These results suggest that blonanserin improves some types of cognitive function (letter fluency and executive function) that are associated with prefrontal cortical function in patients with first-episode schizophrenia. Moreover, blonanserin may have beneficial effects on psychiatric symptoms and subjective QOL in this population. Further studies with a large sample size and longer duration of treatment are warranted to confirm our findings.

Safety and tolerability

Short-term treatment

In a meta-analysis of four short-term double-blind trials in 1080 patients with schizophrenia, blonanserin had a 0.31 lower risk of hyperprolactinemia than risperidone and haloperidol ($P < 0.00001$, numbers-needed-to-harm (NNH) = not significant).¹³ Blonanserin had lower rates of dizziness (risk ratio (RR) = 0.47, $P = 0.03$, NNH = not significant) and akathisia (RR = 0.54, $P = 0.02$, NNH = 7) than haloperidol.

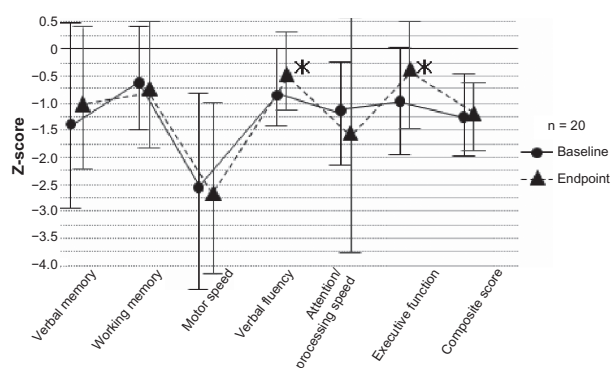


Figure 1 Changes in *z*-score of BACS-J subscales at baseline and endpoint.

Notes: The data are the mean \pm standard deviation. *Z*-score was calculated by using the mean raw scores and standard deviation of each assessment in pooled healthy controls ($n = 340$). A composite score was calculated by averaging all *z*-scores of the six subscale measures. Paired *t*-tests were used to compare changes in *z*-score.

Abbreviation: BACS-J, Brief Assessment of Cognition in Schizophrenia in a Japanese-language version.

However, it demonstrated a 1.62 higher risk of akathisia than risperidone ($P = 0.003$, NNH = 3). No significant differences were found in the rate of other adverse events between blonanserin and other pooled antipsychotics. In addition, no differences were found in discontinuation due to adverse events ($P = 0.56$) or death ($P = 0.33$).

Long-term treatment

The long-term safety and tolerability of blonanserin were evaluated in three open-label, non-comparative studies in Japan.^{30–32} However, the number of patients who completed the longest-term study³² was very small ($n = 9$), and thus, these data are not discussed in this section.

Long-term treatment with blonanserin is generally well tolerated. The overall incidence of adverse drug reactions did not increase during blonanserin therapy for 56 weeks (72.1%³⁰ and 68.5%³¹). Serious adverse reactions were observed in 9.8%³⁰ and 5.9%³¹ of patients. However, only two patients reported serious adverse events, including stupor, anxiety, irritability, and akathisia, which were considered to be related to treatment with blonanserin.³¹

The most frequent adverse reactions with blonanserin were EPS, which were observed in 52.5%³⁰ and 35.8%³¹ of patients. The most commonly (ie, incidence $> 10\%$) reported EPS were akathisia (32.8%³⁰ and 17.1%³¹), tremor (21.3%³⁰ and 15.9%³¹), and hypokinesia (13.1%³⁰ and 10.9%³¹). However, significant mean decreases ($P < 0.01$) from baseline were noted in the Drug-Induced Extrapyramidal Symptoms Scale total score and overall severity score after 28 and 52–56 weeks of treatment with blonanserin.^{30,31} Newly occurring tardive dyskinesia was not found during the studies.^{30,31}

Other frequently reported adverse drug reactions were hyperprolactinemia (34.4%³⁰ and 20.9%³¹), insomnia (18.0%³⁰ and 17.4%³¹), somnolence (16.4%³⁰ and 12.8%³¹), thirst (14.8%³⁰), constipation (12.8%³¹), and dizziness (11.5%³⁰). Of note, at week 52 or 56, mean changes from baseline in serum prolactin levels were -8.4 ng/mL³⁰ and -5.0 ng/mL.³¹ Moreover, the incidence of abnormal menstruation was low (6.6%³⁰ and 1.9%³¹).

Weight gain was reported in 8.2%³⁰ and 5.0%³¹ of patients. However, no significant changes from baseline in body weight were noted at week 52 or 56 (from 60.5 to 61.5 kg³⁰ and 62.3 to 62.5 kg³¹). Results also showed no significant changes in fasting glucose, cholesterol, or triglycerides.^{30,31} The incidence of QTc interval prolongation was very low; only one of 321 (0.3%) blonanserin recipients experienced this adverse event.³¹

The place of blonanserin in therapy and future perspectives

Although a number of antipsychotic drugs are currently available on the market, certain needs in the treatment of schizophrenia have clearly not yet been met.³ Available antipsychotics are considerably effective for positive symptoms of schizophrenia, but they do little to improve negative symptoms and cognitive impairments, which are recognized as core features of schizophrenia and play a greater role in poor functional outcome.¹

Furthermore, many of the available FGAs can cause acute and chronic EPS, and SGAs can cause considerable weight gain and metabolic abnormalities.^{3,4} Accordingly, an antipsychotic drug that can alleviate negative and cognitive symptoms as well as positive symptoms of schizophrenia and that is metabolically neutral and has a low propensity for EPS is absolutely needed. Several SGAs already meet some of these conditions, but an alternative would be helpful.^{12,45}

As described previously, oral blonanserin showed short- and long-term efficacy for treating both positive and negative symptoms of schizophrenia in several randomized and non-comparative studies. Blonanserin was as effective as haloperidol and risperidone for primary endpoints in three 8-week, randomized, double-blind trials,^{27–29} although it appeared to be better than haloperidol in ameliorating negative symptoms.²⁷ Moreover, blonanserin improved some types of cognitive function associated with prefrontal cortical function in patients with first-episode and chronic schizophrenia.^{41,42}

Blonanserin appears to be generally well tolerated and has minimal effects on weight, metabolic parameters, and QTc interval. It may have tolerability benefits regarding prolactin elevation compared with risperidone. Taken together, these data suggest that blonanserin may be a promising candidate for a first-line antipsychotic for patients with first-episode and chronic schizophrenia.

However, one limitation is that individuals who participated in the Phase III trials may be dissimilar to patients routinely encountered in clinical practice in terms of comorbid psychiatric and somatic conditions. No evidence currently exists to demonstrate that blonanserin may be useful as an alternative to clozapine in treatment-resistant schizophrenia. Additional clinical studies with a broader population of patients with schizophrenia will be useful.

Conclusion

Blonanserin appears to be effective for a wide range of symptoms in adult patients with first-episode and multiple episodes of schizophrenia. The data provide initial support for a potential cognitive benefit of blonanserin in schizophrenia.

The drug has a low propensity to cause weight gain, metabolic abnormalities, and prolactin elevation. Further large-scale long-term trials comparing blonanserin with other SGAs, especially regarding relapse prevention, QOL, and functional ability of patients, are warranted to establish its efficacy, safety, and effectiveness for the treatment of schizophrenia.

Disclosure

Dr Tenjin has received speaker's honoraria from Dainippon Sumitomo. Dr Miyamoto is a consultant for Dainippon Sumitomo and has received advisory board honoraria from Chugai Pharmaceutical and speaker's honoraria from Dainippon Sumitomo and Eli Lilly. Dr Miyake has received speaker's honoraria from Dainippon Sumitomo, Eli Lilly, Mitsubishi Tanabe, Otsuka, and Yoshitomi. Drs Tenjin, Miyamoto, and Miyake declare that they have no direct conflict of interest or grant support that is directly related to the content of this article. Dr Yamaguchi has received advisory board and/or speaker's honoraria from Daiichi Sankyo, Eisai, Eli Lilly, Janssen, Otsuka, and Takeda. The other authors have no conflicts of interest to declare.

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