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Comparison of long-term efficacy and safety of blonanserin treatment in individuals with first-episode and relapsed schizophrenia: a 3-year retrospective study

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ABSTRACT

Purpose: The objective of this retrospective chart review study was to evaluate the long-term efficacy and tolerability of blonanserin treatment in individuals with schizophrenia.

Patients and methods: We collected data from 28 (56%) antipsychotic-naïve subjects with first-episode (FE) schizophrenia and 22 subjects with relapsed schizophrenia treated with blonanserin. We investigated psychiatric hospitalization and medication discontinuation rates, Positive and Negative Syndrome Scale (PANSS) scores, Clinical Global Impression–Severity (CGI-S) scale scores, body mass index (BMI) at baseline to endpoint and laboratory tests including serum prolactin, total cholesterol (TC), low-density lipoproteins (LDL), high-density lipoproteins (HDL), triglycerides (TG), and glucose. Additionally, we measured the differences between the two groups and overall changes in levels.

Results: Thirty-one subjects received blonanserin for 3 years. Significant improvements in psychiatric symptoms from baseline to endpoint were observed in individuals with schizophrenia who received blonanserin treatment. There were remarkable changes in PANSS and CGI-S scores between baseline and those measured after 3 years ($p < .01$) in both groups; the FE schizophrenia group demonstrated better improvement as reflected by clinical changes assessments. Compared to baseline values, the endpoint measurements showed no statistical differences in terms of serum prolactin, glucose, or LDL and HDL cholesterol ($p > .05$) in both groups. After 3 years of treatment, there was a statistically significant increase in TC and TG with only a minimal increase in BMI ($p < .05$). However, there were no statistical differences between the two groups.

Conclusion: Blonanserin is useful for the maintenance treatment of schizophrenia due to its therapeutic efficacy; moreover, it does not induce hyperprolactinaemia, significant weight gain, or cause problematic endocrine effects. Its strength might be attributed to its unique pharmacological properties.

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Introduction

The goal for treating schizophrenia is to preserve the progress made during acute treatment, prevent symptom exacerbation, enhance psychosocial functioning and improve quality of life [1]. Relapse prevention is one of the most important targets for acquiring these goals [2,3]. A large portion of individuals with schizophrenia fail to achieve remission or recovery: approximately, 80% of individuals treated after their first-episode (FE) relapse within 5 years [4,5]. Maintenance treatment using antipsychotics is the most important method in preventing relapse in schizophrenia [4,6]. There are several guidelines for the treatment of FE schizophrenia and most recommend using second-generation antipsychotics (SGAs) to rapidly stabilize psychosis, achieve full symptomatic remission and prevent relapse with fewer side effects of antipsychotics

[7–10]. Although taking medication regularly is essential for effective maintenance treatment, non-adherence to oral antipsychotics is a major problem in a significant proportion of patients [11] non-adherence to antipsychotic medication is associated with an increased risk of relapse, more frequent hospitalizations, and a poorer quality of life [12–14].

A comprehensive review of the literature has shown that at least half of the patients prescribed antipsychotic medications failed to take them [15]. The most common and important factors influencing non-adherence are lack of support from family, perception and stigma of mental illness, relationship with the health care provider, lack of insight, concurrent alcohol and drug use and, side effects of medication, including extrapyramidal symptoms (EPS) and endocrine effects such as increasing serum prolactin levels and body weight [16–23]. Paradoxically, the typically rapid resolution

of symptoms following treatment for FE schizophrenia also can lead patients to believe that therapy is no longer necessary [4,24,25]. Additionally, it is well established that complete discontinuation of antipsychotic treatment delays the time to remission and increases the risk of relapse after remission [3,4,6]. Moreover, in a recent 10-year follow-up study, it was recommended that patients continue the medication for at least 3 years after starting treatment to decrease the risk of relapse and poor long-term clinical outcomes [26].

It is important for clinicians to understand not only the clinical stages of patients but also the characteristics of antipsychotics. It could help in promoting adherence to prescribed antipsychotic medication, as short breaks in this treatment can delay remission and increase the risk of relapse [24].

In general, first-generation antipsychotics (FGAs) have a different side-effect profile than SGAs, as they are associated with a higher risk of movement disorders, such as EPS and tardive dyskinesia; however, SGAs have been linked to weight gain and increased metabolic risk [27,28]. Compared to FGAs, SGAs have been widely believed to represent an advancement in the long-term management of schizophrenia, however, in pragmatic trials, SGAs were not found to be more effective than FGAs [29].

Blonanserin was approved in Japan in January 2008, in South Korea in August 2009 and in China in February 2017 for the management of schizophrenia [30]. It acts by a blocking activity of the dopamine (D₂, 3) and serotonin (5-HT_{2A}) receptors. Moreover, it provides weak D₁ receptor-blocking activity and adrenergic alpha (α₁) receptor-blocking activity. However, there is very little histamine (H₁) and muscarinic (M₁) receptor-blocking activity [30,31]. Previous reports have described its unique effects, which include a lower increase in serum prolactin levels than other dopamine receptor-blocking antipsychotics. Furthermore, it is associated with fewer side effects, such as weight gain, elevated cholesterol levels, and drowsiness, when compared to other atypical antipsychotics [30,32].

Considering these features, we hypothesized that blonanserin may be useful in the long-term treatment of schizophrenia, especially in individuals with FE schizophrenia. Nonetheless, there is a lack of research showing the long-term outcome of blonanserin treatment in schizophrenia patients [30]. Therefore, in this study, we investigated whether blonanserin treatment could be a candidate for long-term use in the treatment of FE schizophrenia based on its (a) relapse-free survival rate; (b) therapeutic efficacy; and (c) metabolic effect profile, including increasing prolactin levels and weight gain. We thereby aimed to better characterize the features of blonanserin treatment of individuals with FE schizophrenia who need to maintain long-term antipsychotics treatment.

Materials and methods

Study design and subjects

This retrospective chart review, single-centre study was conducted at the Department of Psychiatry, Inje University Haeundae Paik Hospital. The study sample included the charts of 50 subjects diagnosed with schizophrenia who had been started on or switched to blonanserin treatment during the period of August 2012 to December 2015. The sample included 28 subjects with FE schizophrenia patients and 22 with multiple episodes of schizophrenia (one more relapse experience after remission of the FE of the psychotic disorder). These patients were aged 18–65 years. All patients were hospitalized at Inje University Haeundae Paik Hospital, attended follow-ups after discharge, received a clinical diagnosis of schizophrenia according to the DSM-IV-TR criteria [33], and underwent a clinical assessment to obtain data on the variables examined in our study. Documentation of continuous treatment defined as regular visits with the treating clinicians and no more than two missed visits during the 36-month observation period was required. The exclusion criteria were as follows: (a) treatment with blonanserin before entering the study; (b) any comorbid disorder of the central nervous system confirmed from medical records; (c) meeting the DSM-IV-TR criteria for current and/or past alcohol or other substance dependence or abuse; (d) meeting the DSM-IV-TR criteria for mental retardation determined through psychological assessments; (e) taking tricyclic antidepressants; (f) meeting the operational criteria (minimum requirement) of treatment-resistant schizophrenia [34] and (g) treatment with electroconvulsive therapy within the 12 weeks preceding the study.

This study was approved by the Medical Research Ethics Committee and the Institutional Review Board of the Inje University Haeundae Paik Hospital (2019-03-013).

Outcome measures

Primary outcome

Psychiatric hospitalization was defined as a hospitalization due to a definite reemergence of psychotic symptoms associated with a significant disturbance in social and occupational functioning as a result of worsening symptoms, which was based on at least 25% [35,36] worsening (or a 25% increase from baseline) of the Positive and Negative Syndrome Scale (PANSS) [37] score and substantial clinical deterioration, as indicated by a score of 6 or 7 on the Clinical Global Impression–Severity (CGI-S) scale [38]. Treatment discontinuation was defined as ceasing to take medication without the clinician's assent or more than two missed visits to the outpatient department.

Secondary outcome

Changes in psychiatric symptoms from baseline to endpoint during blonanserin treatment and safety and tolerability assessments were determined from data collected from clinical records and laboratory tests, such as serum prolactin, total cholesterol (TC), low-density lipoproteins (LDL), high-density lipoproteins (HDL), triglycerides (TG), glucose, and body mass index (BMI).

Clinical assessments

The following measurements were collected as they were available in the clinical records. PANSS is an internationally validated assessment tool based on 30 items that measures positive and negative psychotic symptoms and general psychopathology symptoms. Each item is rated base on seven categories of severity, resulting in a total score that ranges from 30 to 210 [37]. The CGI-S scale is a tool that measures global impression of illness severity, and it is scored on a 7-point scale: 1 = normal, not at all ill; 2 = borderline mentally ill; 3 = mildly ill; 4 moderately ill; 5 markedly ill; 6 = severely ill; and 7 = among the most severely ill patients [38]. Clinical improvements were defined as a 30% [36,39] decrease in the mean PANSS total score from baseline to endpoint or an improvement in the CGI-S score of at least 2 points from baseline to endpoint.

Statistical analysis

Variables were summarized by frequency and percentage for categorical data and mean \pm standard deviation for numerical data. Group differences were analysed using chi-squared test or Fisher's exact test for categorical data and independent *t*-test or Mann-Whitney's *U* test for numerical data. A two-tailed hypothesis was used for statistical analysis. All statistical analyses were performed using IBM SPSS Statistics version 24.0 (IBM Corp., Armonk, NY, USA), and *p*-values less than .05 were considered statistically significant.

Results

Demographic and clinical characteristics

Of 50 participants, 19 discontinued treatment, and 31 [seven men and 24 females; mean age 34.8 ± 11.5 years; mean education level, 13 ± 2.4 years; mean duration of untreated psychosis (DUP), 3.13 ± 3.14 years; 2.16 ± 1.65 years for FE schizophrenia patients and 5.15 ± 4.48 years for non-FE schizophrenia patients] participated in this study: 21 patients (67.7%) had FE schizophrenia, and the majority of subjects (90%) had no family history of schizophrenia (Table 1). Subjects discontinued treatment (7 FE

Table 1. Demographic features of patients at baseline (*n* = 50).

Variable	Schizophrenia			<i>p</i> -Value
	Overall	First-episode	Relapsed	
All patients (%)	31 (100.0)	21 (67.7)	10 (32.3)	
Sex				
Male	7 (22.6)	5 (23.8)	2 (20.0)	.631 ^a
Female	24 (77.4)	16 (76.2)	8 (80.0)	
Age	34.86 ± 11.54	31.11 ± 9.88	39.64 ± 11.93	.008 ^c
Education (years)	13.34 ± 2.44	13.36 ± 1.89	13.32 ± 3.05	.567 ^c
Family history				
Yes	3 (9.7)	2 (9.5)	1 (10.0)	.643 ^b
No	28 (90.3)	19 (90.5)	9 (90.0)	
DUP (years)	3.13 ± 3.14	2.16 ± 1.65	5.15 ± 4.48	.545 ^c

Note: DUP: duration of untreated psychosis.

^a*p*-Values were derived from χ^2 test.

^b*p*-Values were derived from Fisher's exact test.

^c*p*-Values were derived from Mann-Whitney's *U* test.

subjects and 12 non-FE subjects) on account of having moved to another city (*n* = 1) or having transferred to another hospital (*n* = 2); the motivation for discontinuation among the remaining patients (*n* = 13) remains unknown. The mean durations of blonanserin treatment were 37.9 and 11.9 months for those who maintained and discontinued treatment, respectively. Of the 28 patients with FEP, 21 (75%) continued to maintain the treatment. Only 10 (45.4%) out of the 22 non-FEP subjects continued treatment (*p* = .03).

Dose of blonanserin and concomitant drugs

The mean daily dose of blonanserin at the endpoint was 9.7 ± 6.5 mg: 8.6 ± 6.5 and 10.7 ± 5.5 for patients with FE and non-FE schizophrenia, respectively. None of the patients had taken any anticholinergics, hypnotics, antidepressants, or mood stabilizers at baseline; however, nine patients had taken daytime benzodiazepines (FE = 4, non-FE = 5). At the endpoint, 23 (74.2%) subjects had taken anticholinergics for drug-induced Parkinsonism (FE = 15, non-FE = 8); 12, daytime β -adrenergic antagonists for akathisia (FE = 7, non-FE = 5); and four, hypnotics for insomnia (FE = 1, non-FE = 3).

Psychiatric hospitalization and blonanserin treatment discontinuation rates

The psychiatric hospitalization and discontinuation rate for individuals with schizophrenia undergoing blonanserin treatment was 3.2% (*n* = 1) and 38% (*n* = 12) after the first year of treatment, respectively. And treatment discontinuation rates of two groups showed statistical differences (*p* = .0434) (Figure 1). Compared with relapsed subjects, the hazard ratio for treatment discontinuation in FE subjects was 0.39 (95% confidence interval, 0.15–0.97). After 3 years of blonanserin treatment, 38% of the patients discontinued treatment.

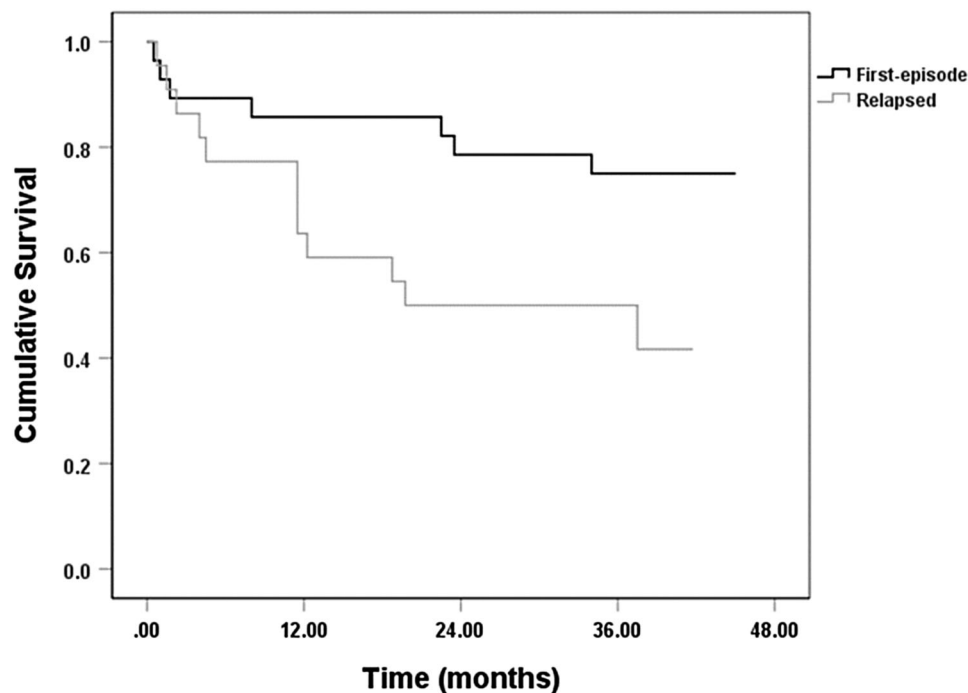


Figure 1. Kaplan–Meier survival curves for time to treatment discontinuation between groups.

Effect of blonanserin on clinical assessments

No clinically significant treatment-emergent changes were observed in the physical examination findings. All patients had a PANSS and a CGI-S assessment performed at or around the study baseline and endpoint periods. The results from these clinical assessments are shown in Table 2. Overall significant improvements from baseline to endpoint were observed in both the FE and non-FE group. Mean changes in the PANSS score of the FE group were 109.62 ± 11.7 (at baseline) and 68.19 ± 13.7 (at the endpoint), showing a 37% improvement. The mean PANSS scores of the non-FE group were 109.44 ± 9.6 (at baseline) and 75.56 ± 6.6 (at the endpoint), showing approximately 30% improvement. Mean changes in the CGI-S score of the FE group were 5.81 ± 0.8 (at baseline) and 3.14 ± 0.8 (at the endpoint), showing approximately 2.67 points of improvement. The mean CGI-S score of the non-FE group were 5.78 ± 0.4 (at baseline) and 3.44

± 0.7 (at the endpoint), showing approximately 2.33 points of improvement. A total of 21 (68%) patients in the FE group showed a 30% improvement in the PANSS total score and a decrease of 2 points in the CGI-S score; however, only 13 (56%) patients in the non-FE group showed these respective changes. Both the FE and non-FE groups evinced statistically significant clinical improvement.

Effect of blonanserin on endocrine and laboratory parameters

Most of the subjects ($n = 28$, 56%) who participated in this study were antipsychotic-naïve at baseline; thus, the present results may reflect the actual long-term effects of blonanserin on BMI, serum prolactin, fasting glucose, TC, TG, LDL, and HDL. Compared to baseline values, the endpoint measurements following blonanserin treatment showed no numerical differences in

Table 2. Comparison of PANSS and CGI scores between groups.

Variable	Schizophrenia			p-Value
	Overall	First-episode	Relapsed	
Baseline				
PANSS* (score)	109.57 ± 10.98	109.62 ± 11.75	109.44 ± 9.62	.910 ^b
CGI** (score)	5.80 ± 0.71	5.81 ± 0.81	5.78 ± 0.44	.899 ^b
At 3 years				
PANSS	70.40 ± 12.41	68.19 ± 13.72	75.56 ± 6.65	.139 ^a
CGI	3.23 ± 0.82	3.14 ± 0.85	3.44 ± 0.73	.300 ^b
Change at 3 years compared to baseline				
PANSS (%)	35.25 ± 12.46	37.47 ± 12.19	30.07 ± 12.17	.139 ^a
CGI (score)	2.57 ± 1.04	2.67 ± 1.06	2.33 ± 1.00	.492 ^b

Note: PANSS: Positive and Negative Syndrome Scale; CGI-S: Clinical Global Impression–Severity scale. Shapiro–Wilk’s test was employed for test of normality assumption.

The per cent change from baseline in PANSS scores were calculated by $\frac{\text{Value at baseline} - \text{value at 3 years}}{\text{Value at baseline}} \times 100 (\%)$.

^ap-Values were derived from independent t-test.

^bp-Values were derived from Mann–Whitney’s U test.

Table 3. Comparison of blood test results and BMI at baseline and at 3 years.

Variable	Baseline	At 3 years	Change	<i>p</i> -Value
PRL (ng/dl)	48.34 ± 33.53	67.03 ± 46.98	18.69 ± 54.72	.267 ^b
TC (mg/dl)	161.50 ± 29.91	181.04 ± 38.60	19.54 ± 41.46	.024 ^a
LDL (mg/dl)	95.18 ± 29.64	101.61 ± 45.25	6.43 ± 41.52	.532 ^a
HDL (mg/dl)	49.33 ± 11.47	49.06 ± 15.72	−0.28 ± 13.77	.933 ^a
TG (mg/dl)	87.27 ± 46.02	154.47 ± 101.55	67.20 ± 112.60	.036 ^b
Glucose (mg/dl)	91.23 ± 24.07	96.35 ± 22.22	5.12 ± 21.31	.198 ^b
BMI (kg/m ²)	24.17 ± 4.39	25.46 ± 4.77	1.30 ± 2.11	.006 ^b

Note: PRL: prolactin; TC: total cholesterol; LDL: low-density lipoproteins; HDL: high-density lipoproteins; TG: triglycerides; BMI: body mass index. Shapiro–Wilk's test was employed for test of normality assumption.

^a*p*-Values were derived from paired *t*-test.

^b*p*-Values were derived from Wilcoxon's signed rank test.

terms of serum prolactin ($p = .267$), fasting glucose ($p = .198$), LDL ($p = .532$), or HDL ($p = .933$) levels. However, after 3 years of treatment, there were statistical changes reflecting an increase in TC, TG, and BMI measurements ($p < .05$) (Table 3). Comparison of the subgroup assessments between the FE and non-FE groups showed no statistically significant differences in terms of the laboratory parameters or body weight changes.

Discussion

With a pragmatic, retrospective approach, our study explored the efficacy and tolerability of blonanserin in individuals with schizophrenia who received long-term treatment over 3 years. This retrospective and non-interventional design enabled the evaluation of individuals who had been diagnosed with schizophrenia including drug-naïve subjects without study-related influences in routine clinical practice.

The characteristics of the subjects in the present study reflect the natural clinical settings in that baseline scores of clinical symptom severity meet acute florid psychotic state of schizophrenia. The mean dose of blonanserin was 13.7 mg, which is half of the maximum suggested dose of blonanserin. The mean dose in the FE group was 11.07 ± 5.03 mg and 17 ± 4.81 mg in the non-FE group ($p < .001$). Most of the subjects in the FE group received a dose decrease of blonanserin; however, each patient's highest dose was maintained in the non-FE group. This finding suggests that FE individuals require normal or lower doses of blonanserin [40].

The findings concerning the treatment discontinuation rate at 3 years (38%) are consistent with or even favourable relative to the results of a naturalistic study performed in Hong Kong (relapse rate of 40–48.1%) [3,41]. Even though the blonanserin treatment discontinuation rates were high, the percentage of those who maintained treatment for 1 year was approximately 98%, and the mean duration of maintaining treatment in discontinued subjects was about 12 months. The rates of maintaining treatment in the FE group were better during the first 3 years than those of the non-FE group; additionally, the rates in

both groups during first the 3 years were better than those measured in other studies [3,42]. These better outcomes may be attributed to psychoeducation guidelines, which provide recommendations on maintenance treatment for relapse prevention. Previously, there were no definite treatment guidelines regarding the duration of maintenance treatment in individuals with schizophrenia. According to the psychoeducation programme, at least 3 years of maintenance treatment has been recommended to individuals with FE schizophrenia for relapse prevention and functional improvement and for long-term treatment in individuals with relapse schizophrenia [47].

There was an improvement from baseline clinical symptoms to endpoint clinical symptoms based on a statistically significant decrease in the PANSS and CGI-S scores ($p < .01$). We assessed symptom reduction based on the total PANSS score of approximately over 35 points and a decrease of over 2 points in the CGI-S score, which was comparable with that in the EUFEST study (PANSS around 35 points) [43].

Overall, blonanserin was well tolerated. No serious adverse events occurred, and no patients discontinued the medication due to treatment-related adverse events induced by the long-term treatment course. The incidence of EPS and the use of antiparkinsonian medications were high (74.2%). This result was inconsistent with previous studies [42,48]. However, the dosage of anticholinergics was very low. Only one patient was hospitalized due to lack of efficacy in the non-FE group. Even in the long-term blonanserin treatment period, no significant changes in serum prolactin levels from baseline to endpoint were observed; small increases, such as 18.7 ng/ml, were not statistically significance ($p = .267$). Even though the prolactin levels at the endpoint were higher than normal levels, there was no complaint of amenorrhoea; however, two patients complained of irregular menstruation. Hyperprolactinaemia is often prevalent in individuals with schizophrenia who are treated with dopamine receptor-blocking antipsychotics. The potential effects of untreated hyperprolactinaemia include short-term effects such as sexual dysfunction, amenorrhoea, and infertility and long-term consequences including bone fractures and breast cancer [44,45]. During the

treatment period, no clinically significant changes occurred in other laboratory parameters, such as fasting glucose ($p = .198$), LDL ($p = .532$), or HDL cholesterol ($p = .933$). There was only a slight increase in BMI (average 1.30, $p = .006$), and BMI ranges were still within the same category as the over-weight group, indicating that blonanserin has minimal effects on the metabolic system and weight gain. Our study showed that blonanserin could be used as an effective treatment strategy for schizophrenia patients with subjective distress over weight gain. Based on the promising results of this long-term treatment period, it appears that blonanserin may be an effective maintenance treatment option for schizophrenia due to its therapeutic efficacy and tolerability. The use of blonanserin seems to be especially effective in the treatment of individuals with FE schizophrenia who require long-term antipsychotics therapy at the early stage of disease to prevent relapse and functional decline.

We suspect that the strength of blonanserin is attributed to its unique pharmacological properties. Many atypical antipsychotics, such as risperidone and olanzapine, have a higher binding affinity to 5-HT_{2A} receptors than to dopamine D₂ receptor, which categorizes them as serotonin-dopamine antagonists (SDA). However, blonanserin has a relatively higher binding affinity to D₂ receptors ($K_i = 0.142$ nM) than to 5-HT_{2A} receptors ($K_i = 0.812$ nM), and it is recognized as a dopamine-serotonin antagonist (DSA) [46,47]; additionally, it has a low or very low affinity for other neurotransmitter receptors including D₁, 5-HT_{2C}, histamine H₁, muscarinic M₁, and α_1 adrenergic receptors [30,48]. The pituitary gland, which secretes hormones including prolactin, exists outside the blood-brain barrier (BBB). With blonanserin treatment, the brain/pituitary (B/P) ratio, calculated from the D₂ receptor occupancy in the temporal lobe and the pituitary gland, showed that the percentage of drug crossing the BBB was greater than that of other antipsychotics [49]. This feature of blonanserin suggests that it may have considerable ability to distribute to the brain with a therapeutic efficacy that does not cause hyperprolactinaemia and problematic endocrine effects. Body weight is regulated by an intricate system of central and peripheral factors that determine energy intake and energy expenditure. One factor that plays a role in body weight regulation is histamine, a neurotransmitter released by the posterior hypothalamus. Intravascular administration of histamine reduces food intake in animal studies, while histamine antagonism stimulates food intake [50,51]. This may help explain why blonanserin, which has a low affinity to histamine receptors, is favourable in terms of body weight.

The present study did have limitations. This was a retrospective, chart review study designed to inspect treatment outcomes from blonanserin treatment in

individuals with schizophrenia over a long-term period. Due to the characteristics of this study, there was low power to support the efficacy and tolerability of blonanserin, but it also has real-world treatment characteristics of FE and non-FE schizophrenia patients. Furthermore, the sample size was small, and this study had sample selection bias. The subjects were neither randomized nor consecutive patients. Also, we did not include subjects who did not complete a 30-month treatment period. Many of them who dropped out during the course of treatment might have exhibited the negative aspects of treatment with blonanserin. Thus, it is unclear whether the results of the present study are potentially generalizable to individuals with schizophrenia in a real-world setting. Even though the study did not comprise all FE schizophrenia patients, 56% of the subjects who were antipsychotic-naïve at baseline may reflect the actual long-term effects of blonanserin. Moreover, blonanserin has been favourable for long-term treatment in individuals in the non-FE group. Therefore, we believe it could provide meaningful results in actual clinical practice, and we hope larger, randomized, blinded, and controlled prospective studies will make explore the differences between the two groups and confirm favourable findings in all subjects.

In conclusion, blonanserin is effective in improving symptoms and preventing relapse of schizophrenia. Moreover, during the 3-year study period, there were no statistically significant differences in prolactin, LDL, HDL, and glucose levels, and there was a minimal increase in weight. Additionally, based on the length of this study period, the results suggest that blonanserin is highly effective in boosting medication adherence in long-term treatment.

The present study aimed to address the efficacy and tolerability of blonanserin in the treatment of individuals with schizophrenia using naturalistic data. Our data did not show any difference between the FE and non-FE group; however, it did show favourable treatment outcomes, which is appropriate for long-term maintenance treatment in individuals with schizophrenia.

Disclosure statement

No potential conflict of interest was reported by the authors.

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