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Survey Review

Safety and effectiveness of oral blonanserin for schizophrenia: A review of Japanese post-marketing surveillances

Yoshifumi Inoue [a], Kimiko Tsuchimori [b], Hiroshi Nakamura [a, *]

[a] Medical Affairs, Sumitomo Dainippon Pharma Co., Ltd., Tokyo, Japan
[b] Corporate Governance Material Review Group, Sumitomo Dainippon Pharma Co., Ltd., Osaka, Japan

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ABSTRACT

Schizophrenia significantly limits social functioning with positive and negative symptoms and cognitive dysfunction. Blonanserin (LONASEN®), a novel second-generation antipsychotic approved for treating schizophrenia in Japan in 2008, reportedly shows beneficial effects on cognitive function as well as positive and negative symptoms, with potential for improving social functioning. To understand the safety and effectiveness of blonanserin in the real clinical practice, five Japanese post-marketing surveillances have been conducted and published to date. In this article, we reviewed all the Japanese post-marketing surveillances and discussed the clinical usefulness of blonanserin in patients with schizophrenia having diverse clinical characteristics. Adverse drug reactions, such as akathisia and extrapyramidal symptoms, were common in all surveillances. However, those specific to second-generation antipsychotics, such as weight gain and abnormalities in glycometabolism or lipid metabolism, were rarely observed. In addition, no adverse drug reactions apart from clinical trial results were found. Brief Psychiatric Rating Scale total scores in all surveillances significantly lowered at the last evaluation than at baseline. These results were consistent through 1-year of treatment, suggesting that effectiveness is maintained even after long-term use. In conclusion, blonanserin is considered a beneficial drug in real clinical practice for patients with schizophrenia having diverse characteristics.

1. Introduction

The clinical trial data of a new drug for approval has various limitations when compared with real clinical practice data. Clinical trial data packages for drug approval generally include small sample sizes, short usage periods, and limited patient demographics such as concomitant medications, complications, and age. In other words, drug use cannot be considered to have been evaluated under diverse conditions as those observed in actual practice. Especially in terms of safety evaluation, there have been cases where the drug marketing approvals have been revoked due to unexpected serious adverse events or new risks found in "real clinical setting." The "Law for Ensuring the Quality, Efficacy, and Safety of Drugs and Medical Devices" in Japan mandates manufacturers to conduct post-marketing surveillance (PMS) (usually during 8 years after the release of new drugs) to check for differences in the drug profile obtained through clinical trials and that observed in "real clinical setting." As approved drugs are administered to a broader range of patients in actual practice, physicians are bound to encounter the following clinical questions: "Is the drug as effective as shown in clinical trials?," "Have there been any occurrences of unknown adverse drug reactions (ADRs) or remarkable changes in the incidences of known ADRs?," and "Are there any considerable changes in the effectiveness of the drug or the severity of ADRs due to dose, dosing period, complications, concomitant medication, etc.?" It is important to establish evidence for answering these clinical questions for more proper usage of drugs. A thorough analysis of the information collected through PMS should contribute to the development of such evidences.

Blonanserin (BNS; LONASEN®) is a second-generation antipsychotic (SGA) that was approved in Japan in 2008 for treating schizophrenia. Since then, it has also been launched in South Korea and China. Clinical trial data have shown that apart from

* Corresponding author. Sumitomo Dainippon Pharma Co., Ltd., Medical Affairs, Kyobashi Chuo-ku, Tokyo, 104-8356, Japan.
E-mail addresses: yoshifumi-inoue@ds-pharma.co.jp (Y. Inoue), kimiko-tsuchimori@ds-pharma.co.jp (K. Tsuchimori), hiroshi-nakamura@ds-pharma.co.jp (H. Nakamura).

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improvements in positive and negative schizophrenia symptoms, BNS demonstrated low risks of weight gain, abnormal glucose tolerance, and hyperprolactinemia, which are associated with some SGAs.[1–3] However, a meta-analysis of randomized controlled trials has shown that BNS poses a higher risk for akathisia, agitation/excitement, and extrapyramidal symptoms (EPS) when compared with a combination of risperidone and paliperidone.[4]

The efficacy of BNS for schizophrenia is comparable with that of other SGAs, as shown in the same meta-analysis comparing BNS with other antipsychotics.[4] Of the SGAs other than BNS, however, only aripiprazole and olanzapine have data showing a significantly higher efficacy than haloperidol, which is the first generation antipsychotic (FGA), against negative symptoms in Japanese patients with schizophrenia.[5,6] BNS improves verbal fluency and executive function (cognitive function) as well as daily living and work skills (social function) in patients with acute-phase schizophrenia.[7] In addition, switching to BNS from a relatively high dose of other antipsychotics (773.4 ± 442.7 mg/day chlorpromazine equivalent dose) resulted in improvements in both social and occupational function and subjective well-being in patients with schizophrenia.[8] Furthermore, add-on treatment with BNS improves psychotic symptoms and reduces the total amount of antipsychotic drugs, leading to BNS monotherapy by itself for patients with dopamine-supersensitivity psychosis, which contributes to the development of antipsychotic treatment-resistant schizophrenia.[9]

Currently, a total of five types of PMSs for BNS, as described in the methods section, have already been conducted in Japan, and published. The approved dose and administration of BNS should be 4 mg once orally twice daily after meal, and the dose should be increased gradually. The maximum daily dose is 24 mg. The maintenance dose is 8–16 mg daily given orally in 2 divided doses after meals.[10] This review summarizes the safety and effectiveness of BNS in "real clinical setting," including dosing information, based on the results of all PMSs and discusses the roles of BNS in real clinical practice.

2. Pharmacological profile of blonanserin

BNS has high affinity for the dopamine D_{2L} receptor (Ki; 0.284 nM), dopamine D_3 receptor (Ki; 0.277 nM) and serotonin2A (5-HT_{2A}) receptor (Ki; 0.640 nM)[11,12] and it completely blocks dopamine D_2 and D_3 receptors as well as serotonin 5-HT_{2A} receptors, but has low or negligible affinity for adrenergic α_1, serotonin 5-HT_{2C}, histamine H_1, and muscarinic M_1 and M_3 receptors. Unlike most other SGAs known as serotonin-dopamine antagonists, BNS showed two times higher affinity for dopamine D_2 receptors than that for 5-HT_{2A} receptors in *in vitro* studies,[12] making it pharmacologically classified as a "dopamine-serotonin antagonist." Despite this, BNS exhibits efficacy profile that aligns with SGAs. It is known that prolonged exposure to antipsychotic medications leads to cognitive deficits in both schizophrenia patients and animal models.[13–15] Ibi D and his colleagues have shown that chronic treatment with the SGAs, but not with the FGA haloperidol, increases *Hdac2* transcription, via 5-HT_{2A}-receptor-dependent upregulation of NF-κB activity, which leads to synaptic and cognitive side effects.[16] From the viewpoint of cognition, considering the negative effects of 5-HT_{2A} blocking activity, BNS may be favorable compared to other SGAs.

BNS acts as a full antagonist of D_3 receptor, showing the binding affinity for human D_3 receptors higher than risperidone, olanzapine, and aripiprazole, and comparable to cariprazine (dopamine D_2/D_3 receptor partial agonist) in vitro, and high D_3 receptor occupancy in vivo in rats.[11,17] Positron emission tomography (PET) study using [^{11}C]-(+)-PHNO as a tracer revealed that at a clinical dose BNS occupied dopamine D_3 receptor as much as D_2 receptors in healthy subjects.[18] The dopamine D_3 receptor predominantly localizes in the ventral striatum, a region that plays a role in reward and motivation, and is known to modulate dopamine release.[19] Animal studies suggest that D_3 receptor antagonism might have beneficial effects on functions of the frontal cortex, such as the negative symptoms and cognitive deficits associated with schizophrenia, and might act on the reward system to enhance motivation.[19,20] Improvement of negative symptoms relates to improvement of social function, which is associated with intrinsic motivation enhancement or activation of the reward system.[21] BNS, with its selective antagonism of dopamine D_3 receptors, is expected to contribute to the improvement of social functioning by enhancing motivation and by reducing negative symptoms, ultimately leading to a personal recovery in patients with schizophrenia.

On the other hand, blockade of dopamine D_3 receptors has been reported to prevent the development of supersensitivity to dopamine-like drug.[22] Moreover, dopamine D_3 receptor knockout mice showed no supersensitivity to dopamine-like drugs and no elevation in the proportion of D_2^{High} receptors.[23] In addition, PG-01037, an antagonist of D_3 receptor, prevent the development of dopamine supersensitivity induced by continuous administration with haloperidol[24] In the animal study, it is reported that repetitive administration of BNS did not induce supersensitivity to dopamine, whereas repetitive administration of haloperidol induced supersensitivity to dopamine.[24]

3. Target surveillances and data evaluation

The safety and effectiveness of BNS in real clinical practice were confirmed from all PMSs on BNS conducted in Japan (a total of five surveillances described below). Eligibility criteria of each surveillance are presented in Table 1.

1. 12-week surveillance: A surveillance conducted for 12 weeks in patients with schizophrenia to evaluate the safety and effectiveness of BNS in real clinical practice[25]
2. Long-term surveillance: A follow-up surveillance conducted in patients with schizophrenia who were enrolled in the 12-week surveillance to evaluate the safety and effectiveness of long-term BNS use in real clinical practice[26]
3. Surveillance in treatment-naïve patients with first-episode schizophrenia: A surveillance conducted in newly diagnosed patients with schizophrenia who have never received antipsychotics, to evaluate the safety and effectiveness of BNS in real clinical practice[27]
4. Surveillance in patients with comorbid diabetes: A surveillance conducted in patients with schizophrenia who have comorbid diabetes, to primarily evaluate the impact of BNS on glucose intolerance in real clinical practice[28]
5. Surveillance in patients with an acute exacerbation of schizophrenia: A surveillance conducted in patients who experience an acute exacerbation of schizophrenia to evaluate BNS dosing information, safety, and the effectiveness in real clinical practice[29]

This review focused on evaluating endpoints common to all the surveillances in order to address the clinical questions mentioned above. The "safety analysis population" was used to evaluate safety endpoints, such as ADRs, along with the dosing information. ADRs were evaluated for events with high incidence and those that were most common in all the surveillances. The "effectiveness analysis population [patients who had Brief Psychiatry Rating Scale (BPRS) data at baseline and after BNS administration]" was used for the evaluation of effectiveness endpoints. Data were not combined for

Table 1
Eligibility criteria of five Japanese post-marketing surveillances for blonanserin.

Surveillance	Duration	Eligibility criteria
1. 12-week surveillance	12 weeks	Diagnosed with schizophrenia and has never been administered BNS before
2. Long-term surveillance	1 year	Patient enrolled in the 12-week surveillance and started BNS therapy between October 2008 and March 2010
3. Surveillance in treatment-naïve patients with first-episode schizophrenia	12 weeks	New schizophrenic patient, age at onset between 15 and 45 years, first antipsychotic treatment was BNS monotherapy
4. Surveillance in patients with comorbid diabetes	1 year	Patients with schizophrenia and diabetes, receiving BNS for the first time, meeting the following criteria: - Information concerning the disease condition of diabetes is available from 3 months before the start of BNS therapy - Information concerning treatments that have been given (medications, diet, and physical treatment) is available from 3 months before the start of BNS therapy - Laboratory tests have been performed regularly for glycometabolism (i.e., blood glucose, HbA1c, etc.) - HbA1c at the start of BNS administration (4 weeks before administration to 2 weeks after the start of administration) is <8.0% in JDS value and <8.4% in NGSP value - Fasting blood glucose at the start of BNS administration (4 weeks before administration to 2 weeks after the start of administration) is <160 mg/dL or non-fasting blood glucose is <220 mg/dL
5. Surveillance in patients with an acute exacerbation of schizophrenia	12 weeks	Patients with schizophrenia, receiving BNS for the first time, meeting the following criteria: - Patient is in the acute exacerbation phase (psychotic symptoms have become worse within the 3 months before the start of administration) - Experiencing a recurrent episode of schizophrenia - Evaluation using Brief Psychiatric Rating Scale (BPRS) has been performed at the start of BNS therapy - Evaluation using Drug Induced Extrapyramidal Symptoms Scale (DIEPSS) has been performed at the start of BNS therapy

Abbreviations: JDS, Japan Diabetes Society; NGSP, National Glycohemoglobin Standardization Program.

analysis given the differences in target patients and observation period between the surveillances.

4. Evidence and findings from real clinical practice

The disposition of patients in each surveillance is presented in Table 2. The primary reasons for being excluded from the safety analysis population were “Did not come to the hospital after first administration” and “Did not meet the enrollment criteria,” while the primary reason for being excluded from the effectiveness analysis population was “No evaluation of the effectiveness endpoint.” Overview of patient characteristics in each surveillance is presented in Table 3. The proportion of males was approximately the same among the surveillances. Relatively more old patients aged ≥60 years (44.3%) were included in the surveillance on patients with comorbid diabetes, while relatively more young patients aged ≤29 years (49.3%) were included in surveillance on treatment-naïve patients with first-episode schizophrenia. The proportion of outpatients (67.8%) was highest in the surveillance on treatment-naïve patients with first-episode schizophrenia and lowest (34.3%) in the surveillance on patients with acute exacerbation. In the surveillance on treatment-naïve patients with first-episode schizophrenia, 59.9% of the patients had illness duration of <1 year. In all other surveillances, proportions of patients with an illness duration of ≥20 years were the highest.

Dosing information in each surveillance is presented in Table 4. The maximum daily BNS dose was >16 mg in 21.1%–32.7% of the patients, while it was ≤8 mg in 34.0%–46.0% of the patients.

The main safety and effectiveness results for each surveillance are presented in Table 5. Accordingly, the highest incidence of ADR was 45.4%, which was found in treatment-naïve patients with first-episode schizophrenia with an observation period of 12 weeks; whereas, the lowest incidence of ADR was 19.8%, which was found in patients with comorbid diabetes, despite relatively long observation period of 1 year. The most commonly reported ADRs are listed in Table 6 and include akathisia, EPS, somnolence, tremors, and salivary hypersecretion, with akathisia having the highest incidence in each surveillance. The BPRS total score in all surveillances was significantly lower at the last evaluation than at the baseline.

Patients with distinctive characteristics, such as treatment naivety, diabetes, or acute exacerbation, were evaluated in the surveillances. Considering all of the surveillance data together, it is apparent that this review covers diverse background of interest

Table 2
Disposition of patients.

	12-week surveillance	Long-term surveillance	Surveillance in treatment-naïve patients with first-episode schizophrenia	Surveillance in patients with comorbid diabetes	Surveillance in patients with an acute exacerbation of schizophrenia
Enrolled[a]	3229 (362)	1357 (224)	173 (47)	250 (62)	1174 (196)
Case report forms collected	3182	1329	172	244	1174
Safety analysis population	3130	1311	152	237	1144
Reasons for exclusion from the safety analysis population					
Not administered blonanserin	1	1	0	0	1
Did not come to the hospital after first administration	43	13	8	1	9
Did not meet the enrollment criteria	8	4	11	6	20
Off-label use	0	0	1	0	0
Effectiveness analysis population	3017	1256	144	222	1128
Reasons for exclusion from the effectiveness analysis population					
No evaluation of the effectiveness endpoint	113	51	8	15	16
Off-label use	0	4[b]	0	0	0

[a] The number in brackets indicates the number of sites.
[b] Patients who received more than the approved maximum daily dose of 24 mg in the long-term surveillance were excluded from the effectiveness analysis.

Table 3
Baseline patient characteristics.

Parameter	Category	12-week surveillance N = 3130 n (%)	Long-term surveillance N = 1311 n (%)	Surveillance in treatment-naïve patients with first-episode schizophrenia N = 152 n (%)	Surveillance in patients with comorbid diabetes N = 237 n (%)	Surveillance in patients with an acute exacerbation N = 1144 n (%)
Sex	Male	1385 (44.3)	566 (43.2)	72 (47.4)	116 (48.9)	504 (44.1)
Age (years)	10–19	108 (3.5)	44 (3.4)	25 (16.4)	0 (0.0)	10 (0.9)
	20–29	431 (13.77)	180 (13.73)	50 (32.9)	9 (3.8)	117 (10.2)
	30–39	725 (23.16)	306 (23.34)	49 (32.2)	20 (8.4)	217 (19.0)
	40–49	627 (20.03)	272 (20.75)	21 (13.8)	39 (16.5)	279 (24.4)
	50–59	552 (17.64)	243 (18.54)	2 (1.3)	64 (27.0)	215 (18.8)
	60–69	435 (13.90)	177 (13.50)	3 (2.0)	69 (29.1)	187 (16.3)
	70–79	212 (6.77)	78 (5.95)	1 (0.7)	32 (13.5)	98 (8.6)
	80–89	39 (1.25)	10 (0.76)	1 (0.7)	4 (1.7)	20 (1.7)
	90–99	1 (0.03)	1 (0.08)	0 (0.0)	0 (0.0)	1 (0.1)
Outpatient/inpatient	Outpatient	1576 (50.4)	593 (45.2)	103 (67.8)	138 (58.2)	392 (34.3)
Duration of illness (years)	<1	320 (10.2)	133 (10.1)	91 (59.9)	12 (5.1)	61 (5.3)
	≥1, <5	438 (14.0)	186 (14.2)	33 (21.7)	28 (11.8)	141 (12.3)
	≥5, <10	453 (14.5)	199 (15.2)	14 (9.2)	22 (9.3)	181 (15.8)
	≥10, <20	682 (21.8)	309 (23.6)	14 (9.2)	38 (16.0)	275 (24.0)
	≥20	1083 (34.6)	447 (34.1)	0 (0.0)	133 (56.1)	486 (42.5)
	Unknown	154 (4.9)	37 (2.8)	0 (0.0)	4 (1.7)	0 (0.0)

Table 4
Dosing information.

Parameter	Category	12-week surveillance N = 3130 n (%)	Long-term surveillance N = 1311 n (%)	Surveillance in treatment-naïve patients with first-episode schizophrenia N = 152 n (%)	Surveillance in patients with comorbid diabetes N = 237 n (%)	Surveillance in patients with an acute exacerbation of schizophrenia N = 1144 n (%)
Dose on the first day of administration (mg)	≤4	724 (23.1)	273 (20.8)	54 (35.5)	77 (32.5)	238 (20.8)
	>4, ≤8	1481 (47.3)	641 (48.9)	82 (53.9)	114 (48.1)	593 (51.8)
	>8, ≤12	352 (11.3)	168 (12.8)	12 (7.9)	28 (11.8)	95 (8.3)
	>12, ≤16	343 (11.0)	135 (10.3)	3 (2.0)	13 (5.5)	156 (13.6)
	>16, ≤20	29 (0.9)	15 (1.1)	0 (0.0)	0 (0.0)	1 (0.1)
	>20, ≤24	201 (6.4)	79 (6.0)	1 (0.7)	5 (2.1)	61(5.3)
	>24	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Maximum daily dose (mg)	≤4	422 (13.5)	143 (10.9)	7 (4.6)	46 (19.4)	111 (9.7)
	>4, ≤8	814 (26.0)	303 (23.1)	45 (29.6)	63 (26.6)	329 (28.8)
	>8, ≤12	396 (12.7)	168 (12.8)	30 (19.7)	33 (13.9)	130 (11.4)
	>12, ≤16	645 (20.6)	268 (20.4)	38 (25.0)	43 (18.1)	273 (23.9)
	>16, ≤20	108 (3.5)	62 (4.7)	7 (4.6)	5 (2.1)	34 (3.0)
	>20, ≤24	738 (23.6)	363 (27.7)	25 (16.4)	47 (19.8)	267 (23.3)
	>24	7 (0.2)	4 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)
Daily dose at the last evaluation (mg)	≤4	510 (16.3)	211 (16.1)	24 (15.8)	60 (25.3)	154 (13.5)
	>4, ≤8	908 (29.0)	381 (29.1)	52 (34.2)	66 (27.8)	363 (31.7)
	>8, ≤12	417 (13.3)	185 (14.1)	31 (20.4)	33 (13.9)	129 (11.3)
	>12, ≤16	595 (19.0)	230 (17.5)	27 (17.8)	38 (16.0)	256 (22.4)
	>16, ≤20	96 (3.1)	44 (3.4)	4 (2.6)	6 (2.5)	31 (2.7)
	>20, ≤24	600 (19.2)	257 (19.6)	14 (9.2)	34 (14.3)	211 (18.4)
	>24	4 (0.1)	3 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)

of patients with schizophrenia receiving BNS in real clinical practice.

Details of the results obtained in each surveillance are presented in the following sections.

4.1. Safety and effectiveness of blonanserin administered to patients with schizophrenia for 12 weeks in real clinical practice[25]

Among the 3130 patients in the safety analysis population, 73.7% were able to continue administration up to 12 weeks. A total of 822 patients discontinued administration, with the most common reason being (multiple reasons could be selected) “lack of effectiveness” in 329 patients. Among the 329 patients, 113 received a maximum daily dose of ≤8 mg. The mean daily BNS dose was 9.4 ± 5.4 mg at the start of administration and 12.8 ± 7.0 mg at the last evaluation, with a mean maximum daily dose of 13.8 ± 7.1 mg (Table 4). The dose used at the start of administration was almost similar to that in the surveillance on patients with acute exacerbation, but tended to be higher than that in the surveillance on treatment-naïve patients with first episode or the surveillance on patients with comorbid diabetes.

Among the 3130 patients in the safety analysis population, 730 (23.3%) experienced ADRs (Table 5), with akathisia having the highest incidence (4.3%), followed by hyperprolactinemia (2.8%) and EPS (2.4%) (Table 6). No correlation was found between the maximum daily BNS dose and the incidence of akathisia. Through appropriate treatment, such as dose reduction, BNS discontinuation, or the administration of antiparkinsonian drugs, 95.6% of all akathisia were resolved or relieved. ADR incidences according to illness duration were 37.8% (<1 year), 29.2% (≥1 year but <5 years),

Table 5
Summary of outcomes.

Surveillance	Analysis population	Safety outcome (Incidence of adverse drug reactions)	Effectiveness outcome (BPRS total score)
12-week surveillance	Safety: 3130 Effectiveness: 3017	23.3% (730 of 3130 patients)	54.9 ± 16.8 (baseline) vs. 44.7 ± 15.9 (last evaluation) [$P < 0.001$]
Long-term surveillance	Safety: 1311 Effectiveness: 1256	32.1% (421 of 1311 patients)	54.8 ± 16.6 (baseline) vs. 43.1 ± 16.2 (last evaluation) [$P < 0.001$]
Surveillance in treatment-naïve patients with first-episode schizophrenia	Safety: 152 Effectiveness: 144	45.4% (69 of 152 patients)	58.6 ± 15.9 (baseline) vs 38.3 ± 15.1 (last evaluation) [$P < 0.001$]
Surveillance in patients with comorbid diabetes	Safety: 237 Effectiveness: 222	19.8% (47 of 237 patients)	53.9 ± 15.4 (baseline) vs. 44.7 ± 14.1 (last evaluation) [$P < 0.001$]
Surveillance in patients with an acute exacerbation of schizophrenia	Safety: 1144 Effectiveness: 1128	20.5% (234 of 1144 patients)	59.8 ± 16.8 (baseline) vs. 43.5 ± 16.6 (last evaluation) [$P < 0.001$]

Note: The BPRS total score at the last evaluation was compared with that at baseline using the Wilcoxon signed-rank test, at a significance level of 0.05.

Table 6
Most common adverse drug reactions.

Preferred term	12-week surveillance N = 3130 n (%)	Long-term surveillance N = 1311 n (%)	Surveillance in treatment-naïve patients with first-episode schizophrenia N = 152 n (%)	Surveillance in patients with comorbid diabetes N = 237 n (%)	Surveillance in patients with an acute exacerbation of schizophrenia N = 1144 n (%)
Akathisia	136 (4.3)	69 (5.3)	36 (23.7)	6 (2.5)	52 (4.5)
Extrapyramidal symptoms	75 (2.4)	54 (4.1)	2 (1.3)	3 (1.3)	27 (2.4)
Somnolence	46 (1.5)	26 (2.0)	7 (4.6)	2 (0.8)	12 (1.0)
Tremor	37 (1.2)	27 (2.1)	12 (7.9)	1 (0.4)	28 (2.4)
Salivary hypersecretion	32 (1.0)	20 (1.5)	10 (6.6)	2 (0.8)	24 (2.1)
Insomnia	39 (1.2)	26 (2.0)	0 (0.0)	3 (1.3)	8 (0.7)
Hyperprolactinaemia	89 (2.8)	60 (4.6)	0 (0.0)	0 (0.0)	18 (1.6)

21.6% (≥5 years but <10 years), 25.4% (≥10 years but <20 years), and 17.2% (≥20 years), which tended to be higher for shorter illness durations. A total of 936 patients received BNS monotherapy, among whom 21.4% developed ADRs. The most common ADRs included akathisia (6.4%), hyperprolactinemia (2.6%), and EPS (2.4%). These incidences did not differ greatly from those found in the overall safety analysis population. Among the 3106 patients for whom EPS severity (classified as no, mild, moderate, or severe symptoms) was evaluated, 311 (10.0%) experienced symptom aggravation throughout treatment period, 217 of whom had only a one-level increase in their symptom severity. No changes in severity were found during treatment in 2488 (80.1%) patients. Meanwhile, improvements in symptom severity were seen after treatment in 307 (9.9%) patients. The number of patients with moderate or severe symptoms was reduced by treatment (moderate symptoms: from 372 to 351 patients, severe symptoms: from 109 to 73 patients). The mean weight was significantly lower at the last evaluation (60.4 ± 13.8 kg) compared to baseline (60.8 ± 14.3 kg). No clinically meaningful changes in body mass index (BMI) or laboratory values such as fasting blood glucose, HbA1c (NGSP), total cholesterol, and high-density lipoprotein (HDL) cholesterol were found during BNS treatment.

In the effectiveness analysis population (3017 patients), a significant reduction was found in the mean BPRS total score at the last evaluation compared to baseline (Table 5). The mean change from baseline in the BPRS total score to the last evaluation was −10.2 ± 13.2, while that among the 903 patients who received BNS monotherapy was −13.8 ± 14.8 (baseline: 54.7 ± 17.4, last evaluation: 40.9 ± 15.8).

In this surveillance, the BPRS total score demonstrated the effectiveness of BNS in real clinical practice in patients with schizophrenia.

4.2. Long-term safety and effectiveness of blonanserin for 1 year in real clinical practice[26]

In total, 1357 patients who were enrolled at the early stage of the 12-week surveillance were continuously enrolled in the long-term surveillance. The relationship of enrollment between 12-week surveillance and long-term surveillance is shown in Fig. 1. Among the 1311 patients in the safety analysis population, 50.0% were able to continue administration up to 1 year. A total of 632 patients discontinued administration. The most common reasons for discontinuation (multiple reasons could be selected) included “lack of effectiveness,” “adverse events,” and “transferred to another hospital” in 263, 151, and 112 patients, respectively. Similar to the 12-week surveillance, the long-term surveillance identified “lack of effectiveness” as the most common reason for treatment discontinuation. Among the 599 patients who continued administration up to a year, the mean daily dose of BNS was 9.4 ± 5.0, 13.4 ± 6.6, 13.7 ± 6.7, and 14.0 ± 7.0 mg at baseline, 12 weeks, 6 months, and 1 year (last evaluation), respectively (Table 4). The mean first dose was similar to that in the 12-week surveillance and the surveillance on patients with acute exacerbation, but higher than that in the surveillance on treatment-naïve patients with first-episode or the surveillance on patients with comorbid diabetes. The mean daily dose of BNS in patients who received BNS monotherapy (145 patients) was 10.1 ± 5.4, 11.4 ± 6.0, 11.6 ± 6.0, and 11.9 ± 6.5 mg at baseline, 12 weeks, 6 months, and 1 year (last evaluation), respectively.

Among the 1311 patients in the safety analysis population, 421 (32.1%) experienced ADRs, with akathisia having the highest incidence (5.3%), followed by hyperprolactinemia (4.6%) and EPS (4.1%).

An analysis of the proportion of patients who experienced ADRs by 3-month time period showed that ADRs occurred most

frequently within 12 weeks from starting BNS (26.5%), followed by 12 weeks to 6 months (10.4%), 6 months–9 months (3.4%), and 9 months to 1 year (2.8%). Approximately 75% of all ADRs occurred within 12 weeks after starting BNS. Serious tardive dyskinesia or dystonia was not found through this surveillance period. There was no remarkable increase in the incidences of ADRs even after long-term treatment with BNS. No clinically meaningful changes in weight or laboratory values, such as lipid, glycometabolism, and prolactin, were observed after long-term BNS treatment.

In the effectiveness analysis population (1256 patients), a significant reduction was found in the mean BPRS total score at the last evaluation (at 1 year) compared to baseline (Table 5). The mean change from baseline in the BPRS total score at the last evaluation was −11.7 ± 15.2, while that among the 306 patients who received BNS monotherapy was −14.7 ± 17.1 (baseline: 52.9 ± 17.6, last evaluation: 38.2 ± 15.4).

This surveillance found no remarkable increase in ADR incidence after long-term use (1 year), as well as no newly occurring ADR specific to long-term use. Moreover, the BPRS total score demonstrated the effectiveness of BNS in patients with schizophrenia after a year of treatment in real clinical practice.

4.3. Safety and effectiveness of blonanserin for 12 weeks in antipsychotic-naïve patients with first-episode schizophrenia[27]

Among the 152 patients in the safety analysis population, 57.9% were able to continue administration up to 12 weeks. A total of 64 patients discontinued administration during the observation period. The most common reasons for discontinuation (multiple reasons could be selected) included “did not visit the hospital,” “adverse events,” and “transferred to another hospital” in 17, 16, and 15 patients, respectively. This surveillance differed from the other surveillances in that “did not visit the hospital” was the most common reason for discontinuation. Among the 152 patients included in the safety analysis population, the mean daily dose of BNS was 7.1 ± 3.1 mg at baseline and 11.3 ± 5.8 mg at the last evaluation, with a mean maximum daily dose of 13.7 ± 6.0 mg (Table 4). The mean daily dose at baseline for this surveillance was the lowest among all surveillances. Among the 152 patients in the safety analysis population, 69 (45.4%) developed 133 ADRs, the most common being akathisia (23.7%, 36 cases), bradykinesia (9.2%, 14 cases), and tremors (7.9%, 12 cases); 103 cases were EPS. The incidence of akathisia in this surveillance was the highest among all surveillances. No serious EPS were found to have occurred during the observation period, and symptoms were generally resolved or relieved through appropriate treatment, such as dose reduction, BNS discontinuation, or the administration of antiparkinsonian drugs.

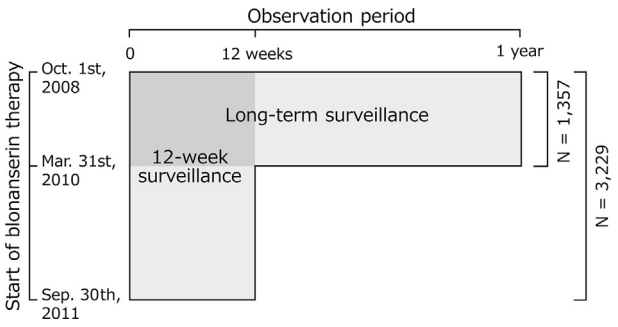

Fig. 1. The relationship of enrollment between 12-week surveillance and long-term surveillance. Patients enrolled in the 12-week surveillance who started BNS therapy by March 2010 were continuously enrolled in the Long-term surveillance.

In the effectiveness analysis population (144 patients), a significant reduction was found in the mean BPRS total score at the last evaluation compared to baseline. The mean change from baseline in the BPRS total score at the last evaluation was −20.2 ± 15.5 (Table 5), which was greater than that in the 12-week surveillance.

This surveillance had higher ADR incidences compared to the 12-week surveillance and the most common ADRs were EPS. Moreover, the BPRS total score demonstrated the effectiveness of BNS for antipsychotic-naïve patients with first-episode schizophrenia in real clinical practice.

4.4. Safety and effectiveness of blonanserin for 1 year in patients with schizophrenia and comorbid diabetes[28]

Among the 237 patients in the safety analysis population, 69.2% were able to continue administration up to 1 year. A total of 73 patients discontinued administration; the most common reason for discontinuation (multiple reasons could be selected) was “adverse events” in 26 patients, which was unlike other surveillances. Among these patients, 21 experienced ADRs, while approximately half of these patients (11 patients) experienced EPS, such as parkinsonism. None of the patients discontinued administration due to glucose intolerance. The next most common reason for discontinuation was “lack of effectiveness” in 22 patients, of whom the maximum daily dose was ≤8 mg in 12 patients. Among the 237 patients included in the safety analysis population, the mean daily dose of BNS was 7.8 ± 4.1 mg at baseline and 11.2 ± 6.9 mg at the last evaluation, with a mean maximum daily dose of 12.5 ± 7.1 mg (Table 4). The mean daily dose at the last evaluation and the mean maximum daily dose in this surveillance was the lowest among all surveillances. The 67 elderly patients (65 years old or older) received a mean daily dose of 7.9 ± 4.6 mg at baseline and 10.4 ± 7.1 mg at the last evaluation, with a mean maximum daily dose of 11.6 ± 7.0 mg.

Among the 237 patients in the safety analysis population, 47 (19.8%) experienced 76 ADRs, with akathisia (2.5%) and blood glucose increased (2.5%) having the highest incidences. The incidence of blood glucose increased was higher in this surveillance compared to that in long-term surveillance. ADRs related to glucose intolerance were found in six patients, while those related to glucose intolerance (1 case of diabetes mellitus, 2 cases of blood insulin increased, 6 cases of blood glucose increased, and three cases of glucosuria) occurred in nine patients (12 cases). During the observation period, 22 patients (9.3%) underwent adding, switching, or dose increasing of their antidiabetic drugs. Incidence of the first-onset ADRs was highest during the first 12 weeks after starting BNS (12.7%), followed by 12 weeks to 6 months (5.4%), 6 months–9 months (2.5%), and 9 months–12 months (2.4%). Mean weight was significantly lower at the last evaluation (61.7 ± 14.8 kg) compared to baseline (63.1 ± 14.7 kg). No clinically meaningful changes in BMI, HbA1c, fasting blood glucose, non-fasting blood glucose, insulin, total cholesterol, low-density lipoprotein cholesterol, HDL cholesterol, remnant-like particle cholesterol, and triglycerides, were found throughout BNS treatment period in the overall safety analysis population, non-elderly patients subpopulation, or even in the elderly patients subpopulation (≥65 years).

In the effectiveness analysis population (222 patients), a significant reduction was found in the mean BPRS total score at the last evaluation compared with baseline (Table 5).

Although ADRs related to glucose intolerance were found in this surveillance, none of the patients had to discontinue BNS

administration as a result thereof. Changes in mean laboratory values throughout BNS administration period did not suggest worsening of glucose tolerance. The same results were obtained in the analyses performed on elderly patient subpopulation. Moreover, the evaluation of BPRS total score demonstrated the effectiveness of BNS for patients with schizophrenia with comorbid diabetes in real clinical practice.

4.5. Safety and effectiveness of blonanserin for 12 weeks in patients with acute exacerbation of schizophrenia[29]

Among the 1144 patients in the safety analysis population, 69.9% were able to continue administration. A total of 353 patients discontinued administration; the most common reason for discontinuation (multiple reasons could be selected) was "lack of effectiveness" in 120 patients. Among these 120 patients, 24 received a daily dose of 24 mg, while 60 received ≤8 mg even at the last evaluation. The mean daily dose of BNS was 9.4 ± 5.1 mg at baseline and 12.9 ± 6.8 mg at the last evaluation, with a mean maximum daily dose of 14.0 ± 6.8 mg (Table 4). These results were similar to those observed in the 12-week surveillance.

Among the 1144 patients in the safety analysis population, 234 (20.5%) experienced ADRs (Table 5), with akathisia (4.5%) having the highest incidence, followed by EPS (2.4%) and tremors (2.4%). The types of ADRs that found in this surveillance were similar to those found in the 12-week surveillance. Eight cases of serious EPS-related ADRs were reported in five patients, which included two cases of akathisia and one case each of dystonia, EPS, gait disturbance, bradykinesia, salivary hypersecretion, and muscle rigidity. All symptoms were resolved or relieved by discontinuing BNS or by administering antiparkinsonian drugs. The total score for the Drug-Induced Extrapyramidal Symptoms Scale (DIEPSS) was significantly lower at the last evaluation (2.2 ± 3.6) than at baseline (2.6 ± 3.9). On the other hand, a significant reduction was found in the mean weight at the last evaluation (60.4 ± 15.1 kg) compared to baseline (61.0 ± 15.9 kg). Similarly, BMI reduced significantly. In the laboratory test, no significant changes in fasting blood glucose, non-fasting blood glucose, HbA1c, total cholesterol, and serum prolactin were observed throughout BNS treatment period. Although mean triglyceride levels increased significantly over time in the safety analysis population, change like this was not observed in the BNS monotherapy subpopulation.

Incidences of ADRs in this surveillance were similar to those observed in the 12-week surveillance. Although EPS-related ADRs occurred in this surveillance, the total DIEPSS score was found to be lower at the last evaluation than at the baseline. In the effectiveness analysis population (1128 patients), the mean BPRS total score decreased significantly from the first week after BNS initiation compared to baseline. The evaluation of the BPRS total score demonstrated the effectiveness of BNS in real clinical practice in patients with acute exacerbation of schizophrenia.

5. Discussion

5.1. Safety of blonanserin

In the clinical trials conducted leading up to the approval, ADRs and laboratory test abnormalities were found in 673 out of 891 patients (75.5%) who received BNS, the most common of which (incidence of ≥10%) included EPS (35.0%), akathisia (24.1%), insomnia (22.4%), prolactin levels increased (19.6%), dyskinesia (14.0%), somnolence (11.8%), anxiety/feeling irritated/irritability (11.2%), and constipation (10.1%).[30] The incidences of ADRs in each PMS were lower (ranging from 19.8% to 45.4%) than those found in the clinical trials for approval and no ADRs apart from those reported in the results of clinical trials were found.

Accordingly, differences in the methods of collecting safety information, targeted patient populations and sample sizes, and the non-mandatory laboratory tests in PMS may account for the lower incidence of ADRs in PMS compared to clinical trials, with similar results being obtained with other drugs.[31–33]

The difference in ADR incidence between treatment-naïve patients with first-episode schizophrenia (45.4%) and patients with comorbid diabetes (19.8%) may be the result of illness duration; as mentioned previously 59.9% of the treatment-naïve patients with first-episode schizophrenia had an illness duration of <1 year; whereas, 56.1% of the patients with comorbid diabetes had an illness duration of ≥20 years. A similar trend was shown in several studies, where the illness duration was predictive of treatment response in schizophrenia and patients with a shorter illness duration seemed to be more responsive.[34–36] It is also known that treatment-naïve patients are generally more responsive to treatment and sensitive to ADRs, as mentioned in the practice guideline by American Psychiatric Association,[37] supported by various papers.[38–40]

Patients with schizophrenia have a shorter life expectancy that is 20% less or 12–15 years less compared with the life expectancy of the general population.[41] The mortality rate from cardiovascular disease is reported to be 2.3 times higher in male patients and 2.1 times higher in female patients with schizophrenia.[42] Risk factors for cardiovascular disease include metabolic disorders, such as diabetes and obesity. It has been reported that patients with schizophrenia receiving antipsychotic treatment have a higher prevalence of metabolic syndrome than the general population.[43,44] According to a survey conducted in Japan, the prevalence of metabolic syndrome in outpatients was 2–3 times higher than that of inpatients.[45,46] Furthermore, it has been reported that the obesity rate of patients with schizophrenia is 40%–60%, which is higher than the obesity rate of 30% in the general population.[47]

Surveillances have shown that ADR incidences related to glucose tolerance, weight gain, and metabolic abnormalities, such as lipids disorders, were generally higher in SGAs than FGAs.[48,49] With BNS, however, no serious adverse events related to glucose tolerance, such as diabetic coma or diabetic ketoacidosis, as well as no clinically meaningful changes in blood glucose, HbA1c, insulin, lipids, or weight, were reported during the clinical development stage.[3]

The following paragraphs will discuss notable ADRs and long-term safety based on the adverse event incidences in the five PMSs.

5.1.1. Glucose tolerance abnormalities and dyslipidemia

Although outpatients accounted for 58.2% in this survey, ADRs related to glucose intolerance occurred in nine patients (12 cases) in the BNS surveillance on patients with schizophrenia and comorbid diabetes, and this incidence was lower than those in PMSs involving other antipsychotic drugs[31,50] conducted in Japan on patients with concurrent schizophrenia and diabetes. Moreover, none of the patients were discontinued due to hyperglycemia, and no occurrences of serious acute metabolic disorders, such as diabetic ketoacidosis, were found. None of the changes in laboratory values related to glucose tolerance were found to be statistically significant and clinically meaningful in any of the BNS surveillances. In addition, statistically significant changes in laboratory values suggesting abnormal lipid metabolism were not found in any of the BNS surveillances except for that on patients suffering from acute exacerbation of schizophrenia. In the surveillance on patients with acute exacerbation, a significant increase in triglycerides was found in the antipsychotic combination subpopulation as well as in the overall population. However, considering

that no significant change in triglycerides was found in the BNS monotherapy subpopulation, the impact of concomitant medications may have accounted for the hypertriglyceridemia.

5.1.2. Weight gain

Weight gain in patients with schizophrenia has been attributed to decreased activity due to the underlying illness, as well as the antagonistic actions of serotonin 5-HT_{2c}, histamine H_1, and muscarinic M_3 receptors of SGAs. Weight gain has also been considered one of the main reasons for poor medication adherence.[51,52] One study involving olanzapine treatment showed that patient weight increased gradually after drug administration, with patients having a mean weight gain of approximately 3.5 kg after approximately 6 months.[32] Meanwhile, PMS data of olanzapine tablet in Japan showed that 4.7% (59/1250) of patients gained more than 7% of weight in the first 4 weeks of treatment, and the weight gain thereafter was very slow.[53] Other studies showed that adverse weight gain was seen in 3.0% of patients treated with risperidone long-acting injection for 1 year,[54] and in 3.5% of patients treated with paliperidone for 1 year.[55] Despite these observations seen in SGAs, a significant weight gain was not found in any of the PMS during BNS administration. This may be due to the negligible affinity of BNS toward 5-HT_{2c}, H_1 and M_3 receptors. A significant decrease in weight was observed instead in the 12-week surveillance and the surveillances on patients with comorbid diabetes and on patients with acute exacerbation. Therefore, consistent with clinical trial results for approval, the possibility of BNS causing weight gain, which is a general concern among SGAs, was lower in real clinical practice. Considering that weight gain not only causes poor adherence to treatment but also affects quality of life and self-view of patients,[56] BNS can be expected to have excellent value as an antipsychotic drug.

5.1.3. Akathisia and extrapyramidal symptoms

The incidence of akathisia with BNS in the 12-week surveillance, long-term surveillance, and 12-week surveillance in patients with acute exacerbation of schizophrenia was 4.3%, 5.3%, and 4.5%, respectively, the highest among all ADRs found in each surveillance. Although a simple comparison cannot be performed due to differences in surveillance designs, the PMSs of other SGAs targeting patients with schizophrenia have shown akathisia incidences ranging from 2.3% to 5.4% for 1 year surveillance[31–33] and from 2.5% to 5.0% for 8-week surveillance in patients with acute exacerbation of schizophrenia,[57,58] suggesting that the incidence of akathisia found in these surveillances for BNS was not especially high. In the 12-week surveillance, no correlation was found between the maximum daily dose and the incidence of akathisia. Moreover, 95.6% of akathisia were resolved or relieved through appropriate treatment, such as dose reduction, BNS discontinuation, or the administration of antiparkinsonian drugs, and therefore was considered manageable. Furthermore, decreased incidences of severe EPS were found by evaluating the severity of EPS over time. In addition, none of the PMSs found refractory tardive motor disorders, such as tardive dyskinesia or dystonia, after long-term use. The aforementioned results suggest a low possibility for worsening EPS severity or the occurrence of tardive disorders. The PMS on treatment-naïve patients with first-episode schizophrenia found 36 cases (23.7%) of akathisia, 14 cases (9.2%) of bradykinesia, and 12 cases (7.9%) of tremor, all of which were at higher incidence than those found in other surveillances. Thus, close attention needs to be paid to EPS-related ADRs at the beginning of treatment among treatment-naïve patients with first-episode schizophrenia.

5.1.4. Long-term use

PMSs of olanzapine[32] and aripiprazole[31] having a 1-year observation period revealed an ADR incidence of 38.5% and 28.0%, respectively. Meanwhile, long-term PMSs for BNS having a 1-year observation period (i.e., the long-term surveillance and the surveillance of patients with comorbid diabetes) showed an ADR incidence of 32.1% and 19.8%, respectively. The low incidence of ADRs in the surveillance on patients with comorbid diabetes may be attributed to the high proportion of patients with long illness duration. Both surveillances found no remarkable increase in ADR incidences after long-term administration, as well as no ADR specific to long-term use. Similarly, clinical studies for approval of BNS showed that safety was maintained during long-term use.[59,60]

5.2. Effectiveness of blonanserin

In the active-controlled, non-inferiority studies of BNS conducted in Japan, efficacy of BNS assessed by the Positive and Negative Syndrome Scale (PANSS) total score was non-inferior to that of risperidone or haloperidol, with significantly greater improvement of negative symptoms for BNS than that for haloperidol.[2,3] Efficacy of BNS was also demonstrated to be maintained after long-term use in the long-term studies conducted in Japan.[59,60]

In the PMSs, effectiveness was evaluated using the BPRS total score, which has been demonstrated to be correlated with PANSS total score.[61] The BPRS total score at the last observation was lower than that at the baseline in all the surveillances. Similar results were obtained for 1-year treatment, confirming the long-term effects of BNS on patients with psychotic symptoms as reported in Japanese clinical studies. In addition, a significant reduction in the BPRS total score compared with baseline was found from the first week after starting BNS in the surveillance on patients with acute exacerbation, suggesting that effectiveness of BNS can be exerted early after the initiation of its administration. Effectiveness of BNS was also shown through the fact that 26.8% (307/1144) of patients with acute exacerbation were able to continue monotherapy with BNS throughout the observation period; at the last observation, 38.5% (441/1144) of the patients were prescribed BNS alone, among all antipsychotics.[62] These results demonstrate that BNS may be a beneficial option to treat psychotic symptoms of schizophrenia and can be used for long-term therapy in real clinical practice.

5.3. Administration status

According to the “Guideline for Pharmacological Therapy of Schizophrenia issued by the Japanese Society of Neuropsychopharmacology,”[63] the dose of antipsychotic should be increased to the maximum dose within the tolerable range and within the approved dose range, and responses should be evaluated 2–4 weeks after the dose increase. On the other hand, the same guidelines also recommend starting treatment at a low dose as a pharmacotherapy for patients with first-episode schizophrenia. Concerning the dosing information in each surveillance, the percentage of patients receiving a daily BNS dose of $\leq$8 mg at the last evaluation was highest in the surveillance on patients with comorbid diabetes (53.1%) and lowest in the surveillance on patients with acute exacerbation (45.2%). Furthermore, the surveillance on treatment-naïve patients with first-episode schizophrenia showed that 89.4% of the patients initially received a daily dose of $\leq$8 mg. By the last evaluation, however, the surveillance on treatment-naïve patients with first-episode schizophrenia, when compared to the other surveillances, showed the highest percentage of patients receiving a daily dose of “>8 mg but $\leq$12 mg” and the lowest

percentage of those receiving a daily dose of ">20 mg but ≤24 mg" Moreover, among the patients who discontinued BNS administration due to lack of effectiveness, 34.35% had a maximum daily dose of ≤8 mg. The surveillance on patients with acute exacerbation revealed that half (60 patients) of the 120 patients who discontinued BNS administration due to lack of effectiveness, had received a daily dose of ≤8 mg at the last evaluation. In the same surveillance of patients with acute exacerbation, it was also shown that the change from baseline in the BPRS score was greater in patients who received higher initial doses of BNS.[29] These observations suggest that a daily dose of ≤8 mg is insufficient for BNS effectiveness and that it is important to administer sufficient dosing at the initiation of treatment.

Maximum dose of BNS approved is 24 mg per day[10] and further clinical study conducted using PET suggested that a BNS dose of ≥12.9 mg/day was necessary to allow a striatal dopamine D_2 receptor occupancy of ≥70%, an amount considered necessary for an antipsychotic drug to show efficacy.[64] The dosing information obtained from all five PMSs showed that the BNS dose was not sufficiently increased even when it was determined to lack effectiveness. Especially in treatment-naïve patients with first-episode schizophrenia, who were particularly responsive to treatment and more susceptible to ADRs, the administration of high doses seemed to have been avoided.[38,65,66]

Thus, the lack of effectiveness at a low dose should not prompt the immediate discontinuation of BNS. Instead, the dose should be increased as appropriate for each patient while paying careful attention to ADRs. This method of evaluating responses could potentially allow BNS to become a valuable drug therapy.

The aforementioned findings show that although careful attention should be provided to both akathisia and EPS, BNS treatment offers the advantages of less negative effects on glucose tolerance and lipid metabolism, which are usual concerns with SGAs, decreased occurrence of ADRs, such as weight gain, that can lead to medication non-adherence, and sustained effectiveness even after long-term use without an increase in ADRs. Considering the results from the surveillance of patients with acute exacerbation, BNS can also be used without regard to the stage of schizophrenia. By administering appropriate dose of BNS for an adequate period of time in accordance with the clinical condition of each individual patient, BNS can become a valuable treatment option in the drug therapy of schizophrenia.

5.4. Limitation

Despite the prospective nature of the PMS, the following limitations inherent in observational surveillances need to be considered. First, the surveys lacked a control group and were non-interventional. Second, no detailed inclusion and exclusion criteria were established for target patients, allowing diverse patient demographics. Third, no limitations on concomitant drugs, including antipsychotics, were set. Fourth, given that laboratory data were not mandatory, only the obtained data were analyzed. Lastly, multiplicity was not considered during statistical analyses.

6. Conclusion

Overall, despite several methodological limitations, the results from the PMSs showed that BNS is a beneficial drug that can be used in "real clinical setting" for the treatment of patients with schizophrenia having diverse demographics. Given its favorable safety profile even after long-term use, BNS can be considered a beneficial therapeutic agent for patients with schizophrenia.

Declaration of competing interest

All the authors are employees of Sumitomo Dainippon Pharma Co, Ltd. The authors report no other conflicts of interest related to this work.

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