Long-term oral blonanserin treatment for schizophrenia: a review of Japanese long-term studies

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Abstract

In general, the course of schizophrenia is chronic accompanied not only by positive and negative symptoms but also by cognitive dysfunction associated with psychosocial disability, and thus treatment combining antipsychotics and psychological therapy is considered promising. This review focused on two prospective, open-label, multicenter, phase 3 long-term studies for approval of oral blonanserin for the treatment of schizophrenia. These two studies included both inpatients and outpatients with variable disease duration or symptom prominence according to the Positive and Negative Syndrome Scale (PANSS). The selected two studies consisted of almost the same study schedule and eligibility criteria but different protocols regarding prior medications and concomitant antipsychotics. The proportion of patients who had a baseline PANSS negative score higher than the positive score was 82.2 and 67.2% in the two studies. In both studies, patients with an illness duration of ≥10 years were the most common. Based on the clinical symptoms at baseline, the physician determined the treatment: blonanserin monotherapy, blonanserin in combination with the existing antipsychotic medication, or therapy simplified to haloperidol together with blonanserin. The 28-week completion rate for long-term blonanserin treatment was high in both studies (82.2 and 78.7%). The types of adverse events in both studies were similar to those in the preceding 8-week randomized, active-controlled studies in Japan, which were included in the application package for the approval of oral blonanserin for patients with schizophrenia. Long-term blonanserin use did not increase the risk of extrapyramidal symptoms but reduced the dose of antiparkinsonian drugs, minimally affecting functioning. In both studies, the PANSS total score, positive score, and negative score were improved at the last observation carried forward compared with those at baseline. In conclusion, blonanserin is useful for long-term treatment of chronic schizophrenic patients when the appropriate management of clinical symptoms and adverse drug reactions are applied. Blonanserin might represent a promising treatment option that partially or completely relieves patients with chronic schizophrenia of polypharmacy. Blonanserin may possibly fit both the current real-world clinical setting and the currently recommended approach to antipsychotic medication.

Keywords: Atypical antipsychotics, Blonanserin, Long-term treatment, Schizophrenia, Dopamine D3 receptor antagonist

Background

The combination of pharmacotherapy using antipsychotics and psychological therapy, such as psychosocial rehabilitation, is considered a promising treatment option for improving cognitive and social functioning as well as the psychiatric symptoms of schizophrenia.
Schizophrenia is a chronic, debilitating psychiatric disorder with positive and negative symptoms as well as cognitive dysfunction and significant impairment in psychosocial functioning [2–4]. Furthermore, negative symptoms represent an unmet need in treating schizophrenia, as they are strongly associated with poor social functions [5]. The functional disability related to schizophrenia is even associated worldwide with stigma and discrimination which seriously interfere with social recovery of the patients. In particular, the genetic explanation of psychosis is frequently associated with stigmatizing attitudes. In a survey of medical students, medical doctors, nurses and psychiatric outpatients, it is worrying that medical students reported the highest level of perceived stigmatizing attitudes, such as assumptions of dangerousness, unpredictability and the desire for social distance regardless of the preferred aetiological model underlying schizophrenia [6]. On the other hand, recent studies using voxel-based morphometry approaches have shown that reductions in the superior temporal gyrus and cerebellum can be interpreted as markers of a first onset of the illness [7]. While certain genetic vulnerability is involved in the pathogenesis of schizophrenia, longitudinal studies are needed to elucidate the interaction between genetic risks and environmental/social effects. Heritability, as an index of genetic influence, may have limited explanatory power unless viewed in the context of interaction with environmental/social effects [8].

To facilitate positive discussion on early medical intervention in patients with early psychosis, further evidence should be accumulated to clarify the relationship between genetic vulnerability and environmental/social effects in the pathogenesis of schizophrenia.

As schizophrenia has a chronic course and requires long-term treatment, antipsychotics that could be prescribed long-term and that could enhance social functioning or daily activities without adverse side effects and without disturbing the effect of psychological therapies are desirable. The Japanese Guideline for Pharmacological Therapy of Schizophrenia strongly recommends the continuous use of antipsychotics, because their discontinuation may lead to the progression or relapse of psychiatric symptoms [9]. A systematic review of clinical trials regarding first-episode psychosis stated the importance of reducing the discontinuation rate to enable the remission of psychiatric symptoms and improvement of functional recovery [10]. Preferably, antipsychotics are selected and used for a long time so as not to induce tardive dyskinesia or treatment resistance associated with dopamine supersensitivity psychosis [11].

Blonanserin is a relatively new second-generation antipsychotic agent (SGA) for schizophrenia that has been approved in Japan, South Korea, and China. Blonanserin exhibits high receptor selectivity, being a potent full antagonist of the dopamine D2, D3, and serotonin 5-HT2A receptors and exhibiting low or negligible affinity for the dopamine D1, serotonin 5-HT2C, adrenaline α1, histamine H1, and muscarinic M1 and M3 receptors [12]. In addition, positron emission tomography study using [11C]-(+)-PHNO as a tracer revealed that, at a clinical dose, blonanserin occupied dopamine D2 receptors to the same degree as D2 receptors in healthy subjects [13]. The superiority of blonanserin over placebo in relation to the primary efficacy endpoint has been demonstrated in a randomized, double-blind, placebo-controlled study in patients with schizophrenia [14]. A systematic review and meta-analysis of randomized controlled studies comparing blonanserin with other antipsychotics demonstrated that the efficacy of blonanserin is comparable to that of other SGAs and even higher regarding the negative symptoms [15]. In another meta-analysis of 10 randomized controlled studies, the overall safety outcome did not differ between blonanserin and other antipsychotics, including risperidone or aripiprazole, with some variations regarding adverse events, e.g., akathisia, extrapyramidal symptoms, prolactin levels, or weight gain [16].

The therapeutic efficacy of blonanserin was confirmed in both short-term and long-term treatments [17]; however, the concomitant use of antipsychotics is generally prohibited in short-term, randomized controlled studies. This current review focused on two prospective, open-label, long-term, phase 3 studies in Japanese patients with schizophrenia who, depending on their clinical symptoms, received blonanserin as monotherapy or combination therapy with other antipsychotics. Compared with randomized active-controlled studies, as the inclusion/exclusion criteria were less stringent, patients with more variable pathological conditions of schizophrenia were included, e.g., inpatients as well as outpatients and patients with different disease durations or symptom prominence according to PANSS, and the limitations regarding the concomitant drugs or eligibility were smaller in these two studies. Moreover, although these two studies were almost similar in the study design, they had difference in the protocols for prior medication and concomitant antipsychotic use, which reflect both conventional antipsychotic polypharmacy and currently recommended monotherapy in the real-world clinical settings. Here, we present the safety and efficacy of long-term blonanserin treatment and discuss the potential therapeutic benefit of blonanserin.
Methods
Overview of the studies
Two prospective, open-label, multicenter, phase 3 studies were conducted to evaluate the long-term safety and efficacy of blonanserin in patients with schizophrenia. Both studies were conducted in accordance with good clinical practice and local regulatory requirements. The BNS01 study was conducted nationwide in Japan between December 1998 and April 2002 [18]. The BNS02 study was conducted in the Kanagawa region of Japan between March 1998 and September 2000 [19]. The same inclusion/exclusion criteria were applied. Patients were eligible if they were aged 16 years or older and met the F20 schizophrenia criteria of the International Classification of Diseases 10, Diagnostic Criteria for Research. Patients were excluded if they had a history or presence of convulsive disease, organic brain disease, malignant syndrome, debilitation by dehydration or malnutrition, or high risk of self-harm or suicide attempt. Nevertheless, the protocols for prior medication and concomitant antipsychotic use differed between the BNS01 and BNS02 studies (Table 1).

Blonanserin treatment
In both studies, eligible patients orally received 8–24 mg/day of blonanserin (Sumitomo Dainippon Pharma Co, Ltd) twice daily for 26–56 weeks. The starting dose was 8 mg/day and thereafter adjusted for each patient within the range of 8–24 mg/day (in increments of 2–8 mg/day). For elderly patients (≥ 65 years of age), precautionary safety measures were taken, i.e., reducing the initial dose to 4 mg/day.

Concomitant drugs
Antipsychotics
The protocol for concomitant antipsychotic use is shown in Table 1. The physician determined the treatment patterns based on the clinical symptoms or prior medication; blonanserin was started as monotherapy or added as combination therapy to the antipsychotics already in use. In the BNS01 study, concomitant SGA use was prohibited. Depending on the symptom severity, the dose of the concomitant antipsychotic drugs was gradually reduced and terminated if possible. In the BNS02 study, the only accepted concomitant antipsychotic was haloperidol. Any other prescribed antipsychotics were switched to haloperidol alone at < 12 mg/day, in consideration of the chlorpromazine equivalent dose. Thereafter, blonanserin monotherapy was initiated. However, if physicians determined that haloperidol could not be discontinued due to uncontrolled symptoms, haloperidol was reduced/discontinued and switched to blonanserin by week 12 only if the symptoms were relieved.

Antiparkinsonian drugs
Concomitant use of antiparkinsonian drugs was permitted according to the rules, as shown in Table 1; however, these drugs were gradually discontinued, if possible. The dose of antiparkinsonian drugs was carefully reduced, because malignant syndrome can occur in patients receiving high doses of antiparkinsonian drugs.

Other psychotropic drugs (hypnotics, anxiolytics, and antidepressants)
Concomitant use of psychotropic drugs was permitted according to the rules, as shown in Table 1. The dosing regimens of these drugs were not changed during the study as far as possible.

Results
Patient characteristics
The patient characteristics are shown in Table 2. In the BNS01 study, one patient (out of 322 patients) withdrew consent before the initiation of the study. Of the patients receiving blonanserin, 82.2% (263/321) exhibited negative symptom dominance, i.e., had a higher negative than positive score according to the Positive and Negative Syndrome Scale (PANSS). Furthermore, 72.0% of patients (231/321) had been hospitalized for a long period of time (i.e., their illness duration was > 10 years). In the BNS02 study, 61 patients were enrolled and received blonanserin. The proportion of patients with negative symptom dominance was 67.2% (41/61). In both studies, patients with an illness duration of ≥ 10 years predominated. Most of the patients were receiving antiparkinsonian drugs and antipsychotics at baseline.

Completed cases and reasons for discontinuation
The completion rate and reasons for discontinuation are shown in Table 3. The completion rates at week 28 were 82.2% (264/321; BNS01) and 78.7% (48/61; BNS02) and at weeks 52–56 were 48.3% (155/321; BNS01) and 62.3% (38/61; BNS02). The mean durations of the study treatments were 268.2 ± 123.2 (SD) days (BNS01) and 301.9 ± 126.5 days (BNS02). The mean final and maximum doses of blonanserin were 13.0 ± 6.7 and 14.8 ± 7.2 mg/day (BNS01), respectively, and 12.8 ± 6.1 and 14.0 ± 6.1 mg/day (BNS02), respectively. Discontinuation due to the patients’ requests was the most common reason in both studies.

Treatment patterns
In the BNS01 study, 89.1% of patients (286/321) concomitantly used antipsychotics, and 93.1% (299/321) used
Table 1 Concomitant drugs

Study protocol for concomitant drugs

| Study          | Concomitant use of antipsychotics                                                                 |
|----------------|-------------------------------------------------------------------------------------------------|
|                | Based on the clinical symptoms, physicians determined the concomitant patterns (1) or (2)      |
|                | Pattern (1)                                                                                     |
|                | No prior antipsychotics, or prior antipsychotics could be switched to BNS monotherapy.          |
|                | BNS monotherapy was started                                                                     |
|                | If symptoms could not be controlled by dose adjustment of BNS, concomitant use of antipsychotics was permitted |
|                | Following antipsychotics were prohibited: risperidone, quetiapine fumarate, perospirone hydrochloride, and olanzapine |
|                | Concomitant antipsychotics were reduced/discontinued if the symptoms were relieved               |
| BNS01 study    | Pattern (2)                                                                                     |
|                | Prior antipsychotics could not be discontinued.                                                 |
|                | BNS was added to the prior antipsychotics                                                       |
|                | Continuous use of prior antipsychotics was permitted, but risperidone, quetiapine fumarate, perospirone hydrochloride and olanzapine were prohibited |
|                | Depending on the symptom severity, concomitant antipsychotics were reduced and discontinued if possible |
|                | If symptoms could not be controlled by dose adjustment of BNS, additional antipsychotic use (including dose increase) was permitted |
| BNS02 study    | Pattern (1)                                                                                     |
|                | No prior antipsychotics, or prior antipsychotics could be switched to BNS monotherapy.          |
|                | BNS monotherapy was started                                                                     |
|                | If symptoms could not be controlled by dose adjustment of BNS, concomitant use of antipsychotics was permitted |
|                | Concomitant antipsychotics were reduced/discontinued when the symptoms were relieved            |
|                | Pattern (2)                                                                                     |
|                | Regimen was simplified to HAL (up to 12 mg/day) while considering chlorpromazine equivalent dosage |
|                | If HAL could not be discontinued at the start of BNS, concomitant use of HAL up to 12 mg/day was permitted |
|                | HAL was discontinued by week 12 while adjusting the dose of BNS                                  |
|                | Concomitant HAL was reduced/discontinued when the symptoms were relieved                         |

Concomitant use of antiparkinsonian drugs

| Study          | If an antiparkinsonian drug was used before the start of BNS, continued use of it was permitted otherwise its use was prohibited. If extrapyramidal symptoms developed or worsened, antiparkinsonian drugs could be used appropriately. In BNS01 study, antiparkinsonian drugs were tapered off and terminated if possible for patients with a score of < 2 for each of the seven Drug Induced Extra-Pyramidal Symptoms Scale (DIEPSS) items |
|----------------|-------------------------------------------------------------------------------------------------|

Concomitant use of other psychotropics

| Study          | If a psychotropic drug was used before the start of BNS, the continuous use of it was permitted. If symptoms such as insomnia developed or worsened, the use of psychotropic drugs was permitted as appropriate. In BNS02 study, concomitant use of vegetamin or levomepromazine was prohibited |
|----------------|-------------------------------------------------------------------------------------------------|

BNS bionanserin, HAL haloperidol
antiparkinsonian drugs. In the BNS02 study, 27.9% (17/61) of patients concomitantly used haloperidol, and 90.2% (55/61) used antiparkinsonian drugs. Of the patients taking antiparkinsonian drugs at baseline, 21.4% (63/294; BNS01) and 39.3% (22/56; BNS02) reduced or discontinued these drugs at the last observation carried forward endpoint.

Safety

Adverse events

The overall adverse event incidence rates were 96.9% (311/321; BNS01) and 96.7% (59/61; BNS02) (Table 4). Common adverse events (incidence rate ≥20%) in both the BNS01 and BNS02 studies were insomnia, anxiety, somnolence, nasopharyngitis, hyperprolactinemia, malaise, and dizziness. Most adverse events occurred within 8 weeks after the initiation of treatment: 82.9% (266/321; BNS01) and 90.2% (55/61; BNS02). One case of death was observed in each study: suicide unrelated to blonanserin (BNS01) and recurrent breast cancer with unknown causality (BNS02). Other serious adverse events were reported in 5.6% of patients (18/321; BNS01), including hallucination, delusion, anxiety, nervousness,
depression, asthenia, malaise, akathisia, gait abnormal, somnolence, insomnia, stupor, anorexia, vomiting, accidental ingestion, coma, malignant neoplasm, hemoptysis, pathological fracture, brain contusion, and subarachnoid hemorrhage, and in 8.2% of patients (5/61; BNS02), including delusion, hallucination, nervousness, and anemia. The total numbers of adverse events were 3741 (BNS01) and 678 (BNS02), but no sedation was observed, and severe events were observed in 2.35% (85/3741; BNS01) and 4.1% (28/678; BNS02) of patients.

**Extrapyramidal symptoms**

Common extrapyramidal adverse events included akathisia (19.3%, 62 patients), tremor (19.0%, 61), bradykinesia (15.3%, 49), and dyslalia (10.3%, 33) in the BNS01 study and akathisia (34.4%, 21), tremor (27.9%, 17), and bradykinesia (16.4%, 10) in the BNS02 study. The incidence of extrapyramidal adverse drug reactions was 35.8% (115/321; BNS01) and 52.5% (32/61; BNS02) (Table 4).

**Laboratory data**

One patient in each study without laboratory data was excluded from the analysis. Abnormal changes in the laboratory data were reported in 212/320 patients (66.3%; BNS01) and 37/60 patients (61.7%; BNS02). Blood prolactin concentrations significantly decreased from baseline and were returning to normal with each visit in both studies. The mean changes from baseline at last observation carried forward were $-4.7 \pm 21.36$ ng/mL (BNS01) and $-7.1 \pm 17.20$ ng/mL (BNS02). The mean weight did not change significantly from baseline during the treatment period in any of the studies. No specific abnormal changes in the laboratory tests were observed in relation to the dose or duration of blonanserin treatment, and the results are shown in Table 3.
no clinically relevant electrocardiographic abnormalities were found in any of the studies.

**Efficacy**

The PANSS total score was lower than baseline at each visit. Each PANSS subscale score (positive, negative, and general psychopathology subscale scores) decreased from baseline during the treatment period (Table 5).

In the combined subgroup of both study participants who used concomitant first-generation antipsychotics (note that the concomitant use of SGAs was prohibited), the mean change from baseline in PANSS total score (SD, 95% CI) was $-6.3$ ($16.4$, $-8.2$ to $-4.5$), which was not much different from the change observed in the overall population of each study (Table 5).

**Discussion**

In the both long-term studies, the 28-week completion rate for oral blonanserin treatment was about 80%. The types of adverse events were similar to those in the preceding 8-week randomized, active-controlled studies. Long-term blonanserin use did not increase the risk of extrapyramidal symptoms or weight gain but reduced the dose of antiparkinsonian drugs, minimally affecting functioning. In both studies, the PANSS total score, positive score, and negative score were decreased at the last observation carried forward compared with those at baseline. These results suggest that oral blonanserin is useful for long-term treatment of chronic patients with schizophrenia when the appropriate management of clinical symptoms and adverse drug reactions are applied.

In the BNS01 study, concomitant antipsychotic use was allowed except for SGAs, and most patients (89.1%) used concomitant antipsychotics at least one point during the study. In comparison, concomitant antipsychotics were limited in the BNS02 study—only haloperidol (up to 12 mg/day) was allowed, and blonanserin monotherapy was attempted by increasing its dose and tapering haloperidol. As a result, the concomitant use of antipsychotics was minimal.

Even though a clinical study is under a specific treatment, the results of the BNS02 study are closely similar to those of SGA monotherapy as the dose was adjusted according to the severity of the psychiatric symptoms. SGA monotherapy was recommended at the time the BNS02 study was performed; however, polypharmacy was still mainly adopted in clinical practice. In the BNS02 study, > 70% of patients received only blonanserin, and 27.9% of patients concomitantly used haloperidol.

| Table 4 (continued) |
|---------------------|
| System organ class  |
| Preferred term (adverse events) | BNS01 study | BNS02 study |
|                     | $N=321$ | $N=61$ | |
|                     | $n$ (%) | $n$ (%) |
| Pharyngitis         | 28 8.7 | 4 6.6 |
| ALT (GPT) increased | 28 8.7 | 3 4.9 |
| Rhinitis            | 27 8.4 | 6 9.8 |
| Chest pain          | 24 7.5 | 4 6.6 |
| Upper respiratory tract infection | 23 7.2 | 5 8.2 |
| Weight increased    | 23 7.2 | 5 8.2 |
| Arthralgia          | 22 6.9 | 1 1.6 |
| Gamma-glutamyltransferase increased | 21 6.5 | 2 3.3 |
| Hypotension         | 21 6.5 | 4 6.6 |
| Fungal skin infection | 20 6.2 | 3 4.9 |
| Pain                | 19 5.9 | 0 0.0 |
| Purpura             | 18 5.6 | 1 1.6 |
| Cough               | 18 5.6 | 2 3.3 |
| Hypertension        | 18 5.6 | 1 1.6 |
| AST (GOT) increased | 17 5.3 | 3 4.9 |
| Conjunctivitis      | 16 5.0 | 0 0.0 |
| Accommodation disorder | 12 3.7 | 9 14.8 |
| White blood cell count increased | 10 3.1 | 8 13.1 |
| Extrapyramidal adverse drug reactions | 115 35.8 | 32 52.5 |

**Table 5** Change from baseline in PANSS scores (LOCF)

| Category              | BNS01 study | BNS02 study |
|-----------------------|-------------|-------------|
|                       | $N=315$ | $N=59$ | |
|                       | Baseline, | Baseline, | Baseline, | Baseline, |
|                       | Mean [SD] | Mean [SD] | Mean [SD] | Mean [SD] |
|                       | Change from baseline, Mean [SD] | 95%CI lower, upper | Change from baseline, Mean [SD] | 95%CI lower, upper |
| Total                 | 79.4 [24.6] | −64 [16.0] | −8.2, −4.7 | 69.9 [22.5] | −88 [19.0] | −13.8, −3.9 |
| Positive              | 16.0 [6.7] | −09 [4.8] | −1.4, −0.3 | 14.9 [5.8] | −17 [6.1] | −3.3, −0.1 |
| Negative              | 23.9 [8.1] | −24 [4.5] | −2.9, −1.9 | 19.8 [7.8] | −29 [3.9] | −3.9, −1.9 |
| General psychopathology | 39.8 [12.9] | −31 [8.7] | −4.1, −2.2 | 35.2 [11.6] | −43 [11.5] | −7.3, −1.3 |

PANSS positive and negative syndrome scale, LOCF last observation carried forward, SD standard deviation, CI confidence interval
suggests that blonanserin monotherapy is a potentially effective, safe, and tolerable long-term treatment for patients with schizophrenia.

The continuation rates at 28 weeks were high in both studies: 82.2% (BNS01) and 78.7% (BNS02). In the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) study, a large-scale and long-term clinical study of SGAs for schizophrenia, the withdrawal rate was approximately 40–60% at 6 months and approximately 50–70% at 12 months [20]. These results suggest that the continuation rate of blonanserin treatment was not inferior to those of approved drugs. In addition, even if blonanserin was used in combination with other antipsychotic drugs, the discontinuation rate was not higher than that observed with blonanserin monotherapy. Therefore, this indicates that there is no major safety concern regarding combination therapy of blonanserin together with antipsychotic drugs. The post-hoc efficacy analysis of these two studies demonstrated that > 80% of patients continued blonanserin for 28 weeks in both studies. The remission rate in patients receiving blonanserin for 52 weeks was 30.3% (47/155; BNS01) and 50.0% (19/38; BNS02), suggesting improved efficacy after long-term blonanserin treatment [21].

The types of adverse events were similar to those in the previous 8-week randomized, controlled studies of blonanserin in Japan [22–25]. Most of the events occurred within 8 weeks, and there was no increase of adverse events or new emergence of late-onset-type events due to long-term administration. One suicide occurred during the BNS01 study, which was considered unrelated to blonanserin by the investigator. Almost all patients experienced adverse events, while only a few of them experienced events that resulted in the discontinuation of blonanserin treatment. Common adverse events found in these two studies, including insomnia, anxiety, and hyperprolactinemia, are commonly observed with other antipsychotics or in patients with schizophrenia [16] and were not late onset or refractory.

In the BNS01 study, the incidence of extrapyramidal adverse drug reactions was 35.8%, which was similar to that in Japanese 6–12-month studies of other SGAs [26–32]. In a network meta-analysis that compared oral blonanserin and other antipsychotics (e.g., aripiprazole, clozapine, clozapramine, haloperidol, olanzapine, mosapramine, paliperidone, perospirone, quetiapine, and risperidone), blonanserin exhibited a lower risk of extrapyramidal adverse drug reactions than that of haloperidol but a higher risk than those of olanzapine and quetiapine; there were no distinct differences with other antipsychotics [33]. The risk of akathisia was higher with blonanserin than olanzapine, and there were no clear differences with other antipsychotics.

In the BNS02 study, the incidence of extrapyramidal adverse drug reactions was 52.5% and did not increase with treatment duration, despite the concomitant use of haloperidol. In the BNS01 study, 92.5% of patients were initially taking antiparkinsonian drugs, and 21.4% of these patients were able to discontinue or reduce these drugs, while approximately 8% required increased doses. Similarly, in the BNS02 study, 91.8% of patients were initially taking antiparkinsonian drugs, and 39.3% of these patients discontinued or reduced these drugs, while < 20% required increased doses. Although anticholinergic drugs may cause cognitive impairment and unpleasant peripheral anticholinergic side effects, they are commonly used to treat extrapyramidal symptoms [34, 35]. Since cognitive impairment obstructs the recovery from schizophrenia, anticholinergic drugs should be ideally avoided during the treatment of schizophrenia. Animal studies have suggested that dopamine D3 receptor antagonists suppress extrapyramidal symptoms induced by the continuous administration of haloperidol [36]. Thus, the reductive mechanism of antiparkinsonian drugs concomitantly used with blonanserin might relate to its inhibition of the D3 receptor.

It has been reported that treating schizophrenia with SGAs represents a risk for weight gain, metabolic syndrome, and cardiovascular events [37]. Weight gain is also known to be a possible consequence of discontinuing antipsychotic medication. The incidence rates of adverse weight gain observed with long-term blonanserin treatment were 7.2% (BNS01) and 8.2% (BNS02). A low incidence rate of weight gain (5%) was also observed in a 52-week study involving 200 Japanese patients received blonanserin transdermal patches [38]. A network meta-analysis demonstrated that blonanserin had the lowest risk for weight gain [33]. The low incidence of weight gain might be attributed to the receptor selectivity of blonanserin: a potent affinity for the dopamine D2 and D3 and serotonin 5-HT2A receptors and low or negligible affinity for the 5-HT2C, 5-HT1A, and H1 receptors, which are involved in SGA-induced weight gain [39].

In both studies, the PANSS total score, positive score, negative score, and general psychopathology score decreased from baseline during the treatment periods, which indicates that the efficacy of blonanserin regarding psychiatric symptoms of schizophrenia was sustained during long-term treatment. Considering that 82.2% (BNS01) and 67.2% of patients (BNS02) exhibited negative symptom dominance, the effect of blonanserin is interesting. The limitations of this review include the following: the two studies reviewed had no comparators because of the open-label design; although the setting of the BNS01 study was close to polypharmacy, the
combinations with risperidone, quetiapine, perospirone and olanzapine have not been studied yet.

It is reported that blonanserin improves verbal fluency and executive function (cognitive function), as assessed by the Brief Assessment of Cognition in Schizophrenia, Japanese-language version, as well as daily living and work skills (social function) as measured using the Life Assessment Scale for the Mentally Ill in patients with acute-phase schizophrenia [40]. In addition, blonanserin add-on therapy for refractory schizophrenic patients reduces the total dose of antipsychotic drugs and improves psychiatric symptoms, enhancing both function, as measured by the Social and Occupational Functioning Assessment Scale, and subjective well-being, as measured by the Subjective Well-being under Neuroleptic Scale [41]. These results do not follow/evaluate genetic vulnerability or changes in neuroanatomical markers, but at least suggest that treatment with blonanserin improves schizophrenia-related functional disability, and we hope that comprehensive treatment of schizophrenia, using blonanserin, will be useful in terms of improving stigma and discrimination.

In addition, in a multicenter, randomized, rater-blinded study on adjunct antipsychotic treatment for schizophrenic and dopamine-supersensitive psychotic patients, blonanserin improved psychiatric symptoms and reduced the amount of prior antipsychotics; the blonanserin monotherapy rate at the endpoint was 26.3% [18], similar to another retrospective study [17]. In the above-mentioned studies, many cases used blonanserin in combination with prior SGAs.

Recently, a new formulation of blonanserin, the transdermal patch, has been approved in Japan, which has the advantages as follows: easy supervision, no first-pass metabolism that can affect plasma levels of oral blonanserin, lower incidence of overall or extrapyramidal adverse events compared with oral blonanserin possibly due to more stable plasma blonanserin levels over long periods [42], and sustained positive patients’ attitudes (assessed by drug attitude inventory 10-item version and patient-questionnaire) to the medication with transdermal patch during long-term treatment [38].

Furthermore, blonanserin was approved in Japan for the treatment of schizophrenia in adolescents, making it the only atypical antipsychotic in Japan for the indications for adolescents with schizophrenia. It is expected that blonanserin can contribute to early medical access for patients with early psychosis.

Taken together, blonanserin, both used as monotherapy or in combination with other antipsychotics, exhibits long-term efficacy against positive and negative symptoms in patient populations who have mostly chronic and predominantly negative symptoms. Such therapy does not exhibit safety issues that would cause poor treatment adherence.

Conclusions
Sustainable efficacy of blonanserin is useful for long-term continuous use in chronic patients. It is considered to be a promising treatment option for eliminating or reducing polypharmacy while managing adverse drug reactions appropriately. Given the high continuation rate in various settings, including monotherapy or combination therapy with other antipsychotics, blonanserin may possibly fit both the current real-world clinical setting and the currently recommended approach to antipsychotic medication. In addition, because blonanserin is the only atypical antipsychotic for adolescent schizophrenia approved in Japan, it is expected that blonanserin can contribute to early access to medical intervention for patients with early psychosis. Furthermore, a new formulation of blonanserin, the transdermal patch, was approved in Japan for the treatment of schizophrenia [42]. This new option is further expected to contribute to the treatment adherence in the continuous treatment of patients with schizophrenia.

Abbreviations
PANSS: Positive and Negative Syndrome Scale; SGA: Second-generation antipsychotic agent.

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Authors’ contributions
MM and TK took responsibility for the data collection and interpretation of data as a chief investigator each for the two studies reviewed. HN wrote the first draft of the manuscript including literature searches. YI finalized the manuscript. All authors had full access to all study data, had final responsibility for the decision to submit for publication, took part in either drafting or revising the manuscript. All authors read and approved the final manuscript.

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Availability of data and materials
Data sharing is not applicable to this article as no data sets were generated or analyzed during the current study. In addition, information about public data sharing was not included in the informed consent form of the two studies included in this review.

Declarations
Ethics approval and consent to participate
The study protocols of the two studies included in this review were approved by the institutional review board at each study site. Written informed consent was obtained from all participants.

Consent for publication
Not applicable.
Competing interests

MM reports personal fees from Meiji Seika Pharma, Otsuka pharma, Shionogi Pharma, Sumitomo Dainippon Pharma, Eli Lilly, Pfizer, Janssen, and Astellas, outside the submitted work. HN and YI are the employees of Sumitomo Dainippon Pharma Co., Ltd. TK reports personal fees from Otsuka, Janssen, Sumitomo Dainippon Pharma, Meiji Seika Pharma, Eisai, Daiichi Sankyo, Merck Sharp & Dohme, and FUJIFILM Toyama Pharmaceutical; other from Sumitomo Dainippon Pharma, HISAMITSU PHARMACEUTICAL, and Takeda Pharmaceutical, outside the submitted work.

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