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Comparative Effectiveness of Blonanserin and Paliperidone in 93 In-patients with Acute- to Maintenance-phase Schizophrenia

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ABSTRACT

When initiating treatment for acute-phase schizophrenia, careful consideration needs to be given to which drug will be used in the subsequent maintenance phase. Since blonanserin (BNS) and paliperidone (PAL) are both first-line treatments for acute-phase schizophrenia, our study retrospectively investigated the treatment continuation rate, dose levels, use of concomitant medications, clinical effects, and adverse drug reactions in 93 acute-phase schizophrenia patients receiving either of the monotherapies (BNS: n=40, PAL: n=53) to assess the treatment benefit of these drugs in acute- to maintenance-phase schizophrenia. The efficacy endpoints included the clinical global impression of severity (CGI-S), the clinical global impression of improvement (CGI-I) and the global assessment on function (GAF) scores assessed at Weeks 4, 8, 12, 24, and 52 after treatment initiation. Patients requiring involuntary hospitalization accounted for 75% of the BNS group and 90% of the PAL group and mostly comprised patients who had good social function before onset but relapsed because of poor drug adherence and hence received no residual benefit from their earlier treatment, as well as patients who were experiencing their first episode of schizophrenia. There were differences between the treatment groups in gender, age, and duration of illness. Notably, the BNS group had a higher proportion of females than the PAL group. In both groups, the CGI-S and CGI-I responses were affected by treatment in a majority of the patients who continued treatment, and the GAF score at Week 52 recovered to levels comparable to the pre-onset level in patients continuing treatment. The treatment continuation rate in this study (assessed by the Kaplan-Meier method) was 85% in the BNS group and 77% in the PAL group at Week 8 and 60.9% in the BNS group and 50.9% in the PAL group at Week 52. After Week 24, the number of dropouts in the BNS group decreased while the PAL group still had dropouts due to hyperprolactinemia-related adverse drug reactions. Treatment of schizophrenia requires careful selection of drugs in the acute phase that will ensure a good long-term prognosis and good drug adherence in the maintenance phase, and from this perspective, the results of this study suggest that BNS and PAL could be first-line drugs for the entire duration of treatment, from the acute phase to the maintenance phase.

Keywords: CGI, GAF, blonanserin, paliperidone, schizophrenia

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INTRODUCTION

Schizophrenia is a chronic disorder that is associated with impairments in social and occupational functioning owing to the recurrence and relapse of psychosis. Antipsychotic treatment should be continued indefinitely, even for patients who have achieved remission from the acute phase. However, poor drug adherence can easily lead to recurrence/relapse, which eventually results in re-hospitalization. This indicates that there are two crucial targets for schizophrenia treatment: induction of remission in the acute phase and

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continued drug adherence in the maintenance phase for the prevention of recurrence/relapse. A high treatment continuation rate in the maintenance phase can be achieved by using antipsychotics that afford therapeutic effects in the acute phase and that maintain their therapeutic effects in the maintenance phase. The drugs must also be well-tolerated.

Comparative studies on the effects of antipsychotics that have been conducted include efficacy studies evaluating symptomatic improvement as an endpoint [2, 18, 21] and studies of effectiveness based on endpoints relevant to the clinical setting, such as the treatment continuation rate/rehospitalization rate [12, 13]. In Japan, however, only a few comparative studies on the effects of antipsychotics have been conducted that followed subjects in sufficient numbers in the clinical setting from treatment initiation in the acute phase through to the maintenance phase.

We retrospectively studied acute-phase schizophrenia patients who were admitted to Kusatsu Hospital from October 1, 2010 to May 31, 2013 and were started on monotherapy with either blonanserin (BNS) or paliperidone (PAL), and compared the benefits of these two drugs.

PATIENT POPULATION AND STUDY METHOD

1. Patient population

The study enrolled 93 patients with acute-phase schizophrenia (DSM-IV) who were admitted to Kusatsu Hospital from October 1, 2010 to May 31, 2013. The patients were started on monotherapy with either BNS or PAL (BNS: n=40, PAL: n=53) in accordance with the criteria presented in Table 1. Ethical standards were maintained by having a primary physician or a pharmacist provide patients and/or their legal guardians with a thorough explanation of the fact that the antipsychotics would be administered within the approved dosage and mode of administration as well as of the indications and common adverse drug reactions of the drugs. In addition, this study was approved by the Ethics Committee of Kusatsu Hospital.

2. Introduction of BNS and PAL

BNS therapy was initiated according to the instructions in the package insert, i.e., treatment was as a rule initiated postprandially at an oral dose of 4 mg b.i.d. The dose was adjusted within a range of 4 to 24 mg, and the drug was administered orally q.d. or b.i.d. postprandially. PAL treatment was also initiated based on the package insert, i.e., at an oral dose of 6 mg, q.d. postprandially in the morning, as a rule. When necessary, the dose could be adjusted in increments of 3 mg/day, with intervals of at least 5 days between adjustments, up to the maximum dose of 12 mg/day.

Both groups were started on monotherapy, but the concomitant use of the following drugs was allowed when necessary: adjuvant drugs such as sodium valproate (VPA), benzodiazepine anxiolytics (Bz) such as lorazepam, and hypnotics such as flunitrazepam. The use of injectable antipsychotics was allowed in the acute phase.

3. Assessment method

In our study, the following items were assessed in an attempt to demonstrate the benefits (efficacy and safety) of BNS and PAL across the entire treatment period from the acute phase to the maintenance phase. Starting from treatment initiation in the acute phase, the patients were followed for 1 year; the acute-phase assessments were performed at Week 8 and the maintenance-phase assessments were performed at Week 52.

Information was collected on patient demographic variables including age, gender, duration of illness, and type of hospitalization. After treatment initiation, the dose level of each drug and the changes over time, the concomitant medications, and the changes in the doses of drugs as chlorpromazine equivalents (CP-conversion dose) were evaluated. The CP-conversion doses were calculated according to the conversion table for antipsychotics (Inada, Inagaki 2011 edition) [9].

The efficacy endpoints included Clinical Global Impression-Severity (CGI-S), Clinical Global Impression-Improvement (CGI-I), and Global Assessment of Functioning (GAF); assessments were performed at Weeks 4, 8, 12, 24, and 52 after treatment initiation.

Patients whose treatment was discontinued were followed as “treatment discontinuation for any cause” for the sake of calculating the treatment continuation rate.

Safety was assessed by determining changes in body weight and laboratory test results (blood glucose and triglyceride). Unless other action was required, the adverse drug reactions and adverse events were simply observed during the study period.

4. Analyses

Statistical analysis was performed using IBM SPSS (Statistical Package for Social Science) ver. 21, with a

relative risk of less than 5% being considered significant in every statistical process.

(1) CGI-S, CGI-I, and GAF

The CGI-S score was graded on a 7-point scale with 1 being "normal, not at all ill" and 7 being "Among the most extremely ill patients." The CGI-I score was graded on a 7-point scale with 1 being "very much improved" and 7 being "very much worse," and the GAF score was graded on a 1-100 ordinal scale. Intra- and inter-group comparisons were performed using the Wilcoxon signed-rank test and the Wilcoxon rank sum test, respectively. Statistical analyses were performed at initiation of treatment with either BNS or PAL and at Weeks 4, 8, 12, 24, and 52.

Table 1. Enrollment criteria

Hospitalized acute-phase schizophrenia patients
Treatment initiated with either BNS or PAL monotherapy
No current use of oral antipsychotics at the initiation of drug therapy in the acute phase
Injectable antipsychotics are allowed at the initiation of drug therapy in the acute phase
No restrictions on concomitant drugs

(2) BNS and PAL treatment continuation rate

The treatment continuation rate was analyzed by survival analysis with discontinuation as an event. The observation period for patients discontinued from treatment was defined as the number of days until discontinuation, whereas that for patients who continued was the number of days through Week 52, or 364 days. The treatment continuation rate was estimated by the Kaplan-Meier method and comparisons between the drugs were performed by the Log-Rank test.

(3) Body weight and laboratory tests

Body weight and laboratory findings (blood glucose) were compared by paired t-tests before and after the initiation of treatment with BNS or PAL.

RESULTS

1. Patient demographics

The dispositions of the study patients (N=93) are presented in Table 2. Intergroup comparisons showed that the patients in the BNS group were significantly older (p=0.009) at treatment initiation and that the duration of illness at treatment initiation was significantly longer (p=0.037) in the BNS group than in the PAL group. No intergroup differences were found in the sex ratio, the type of acute phase (first or relapse episode), the history of psychiatric treatment, the disposition of the type of hospitalization as specified in the Mental Health Welfare Law, the CGI-S score (mean), the GAF score (mean), or the highest GAF score in the last year (mean).

Table 2. Patient demographics

	BNS (n=40)	PAL (n=53)	Intergroup comparison
Age (±SD)	46.2 ± 15.0	39.3 ± 12.5	*P*=0.009 (t-test)
Gender			n.s. *P*=0.064 (χ^2 test)
Male	12	26	
Female	28	27	
Duration of disease (±SD)	13.2 ± 12.1	9.3 ± 8.8	*P*=0.037 (t-test)
First onset/Relapse	12/28	11/42	n.s.
Type of hospitalization			n.s.
Measures instituted	5 (12.5%)	4 (7.5%)	
Medical protection	25 (62.5%)	44 (83.0%)	
Voluntary	10 (25.0%)	5 (9.4%)	
CGI-S	5.9	6.1	n.s. (t-test)
GAF	28.3	29.0	n.s. (t-test)
GAF: Max in the past year	67.1	65.1	n.s. (t-test)

2. Dose levels of BNS and PAL and changes therein, and changes in the rate of the concomitant use of antipsychotics/adjuvant drugs

Figure 1 shows the mean dose levels of BNS and PAL. BNS was administered at 8.6 mg/day, 12.7 mg/day, and 10.5 mg/day at treatment initiation, Week 8, and Week 52, respectively. PAL was administered at 5.8 mg/day, 7.4 mg/day, and 7.1 mg/day at treatment initiation, Week 8, and Week 52, respectively. Comparison of the CP-converted doses in these treatment groups showed that PAL was administered at significantly higher doses than BNS at all the observation time points (p<0.001).

Figure 2 shows the changes in the rate of concomitant use of antipsychotics and adjuvant drugs. The rate of concomitant use of antipsychotics was 7.5% with BNS, which was higher than that with PAL at Week 4, but this was followed by a decline that resulted in no

concomitant use of antipsychotics starting from Week 24. Meanwhile, the rate of the concomitant use of antipsychotics with PAL increased starting from Week 4. The rate of the concomitant use of adjuvant drugs (VPA, Bz, antiparkinson agents, and hypnotics) was higher with BNS at all the observation time points.

Table 3 shows the concomitant dose level (mean maximum dose level) for adjuvant drugs. During the entire observation period, the rate of the concomitant use of antipsychotics was higher with PAL, whereas the rate of the concomitant use of adjuvant drugs was higher with BNS. The maximum concomitant dose levels for Bz and antiparkinson drugs were higher with PAL but the levels for VPA and hypnotics were similar with both drugs.

3. Clinical assessments

(1) CGI-S, CGI-I, and GAF scores

Figure 3 shows the changes in the CGI-S score. The CGI-S score included dropouts from assessment at all time points. The mean CGI-S scores significantly improved at Week 4 in both treatment groups ($p<0.001$), followed by a rapid decrease up to Week 8. A continued decline was observed for the BNS group from Week 12, whereas no such trend was observed for the PAL group. The mean CGI-S score after Week 12 was significantly lower in the BNS group than in the PAL group.

The mean change in the CGI-S score significantly improved in each group at Week 4 ($p<0.001$), followed by a rapid decrease until Week 8. A further decrease was observed in the BNS group at Week 12, while the PAL group exhibited a more mild decrease. At Week 52, the BNS group exhibited a significantly larger change in the mean CGI-S score than the PAL group (Figure 4).

Figure 5 shows the changes in the mean CGI-I score over time. The BNS group had more moderate or better improvements from Week 12, but there were no significant differences between the groups at all the assessment time points.

Figure 6 shows the changes in the GAF score. The mean GAF score includes dropouts from assessment at all time points. At Week 52, the endpoint recovered to a near-baseline (pre-onset) level in both groups. The GAF score was significantly higher in the BNS group than in the PAL group only at Week 12; there were no significant differences between the groups at the other assessment time points.

(2) Treatment discontinuation, reasons for treatment discontinuation, and the treatment continuation rate

The treatment continuation rates in 40 patients on BNS and 53 patients on PAL were calculated by the Kaplan-Meier method (Figure 7).

In the BNS group, 6 patients were classified as "treatment discontinuation for any cause" at Week 8, and the "treatment continuation rate" was therefore 85.0%. At Week 52, 16 patients were classified as "treatment discontinuation for any cause," and the treatment continuation rate was therefore 60.0%. In the PAL group, 12 patients were classified as "treatment discontinuation for any cause" at Week 8, and the "treatment continuation rate" was therefore 77.3%. At Week 52, 27 patients were classified as "treatment discontinuation for any cause" and the "treatment continuation rate" was therefore 50.9%. No significant differences were observed in the treatment continuation rate between the BNS and PAL groups at Weeks 8 or 52.

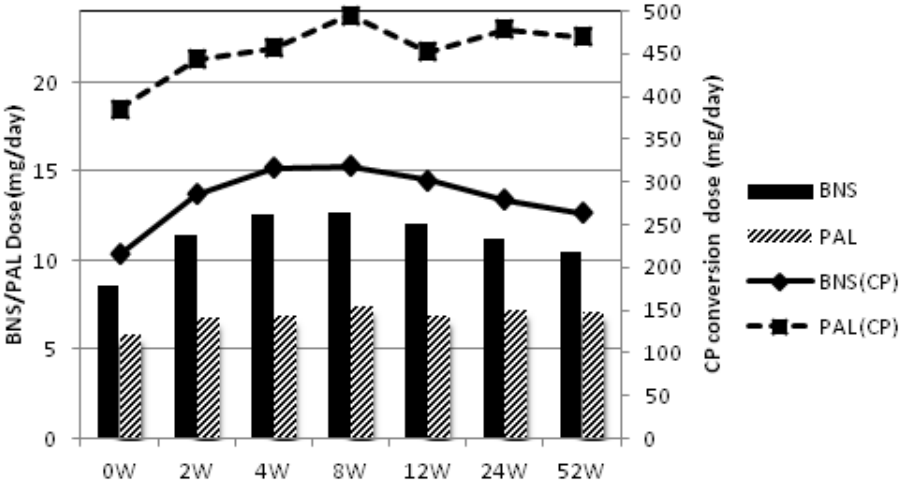

Figure 1. Changes in the doses of BNS and PAL over time.
CP: chlorpromazine-converted dose

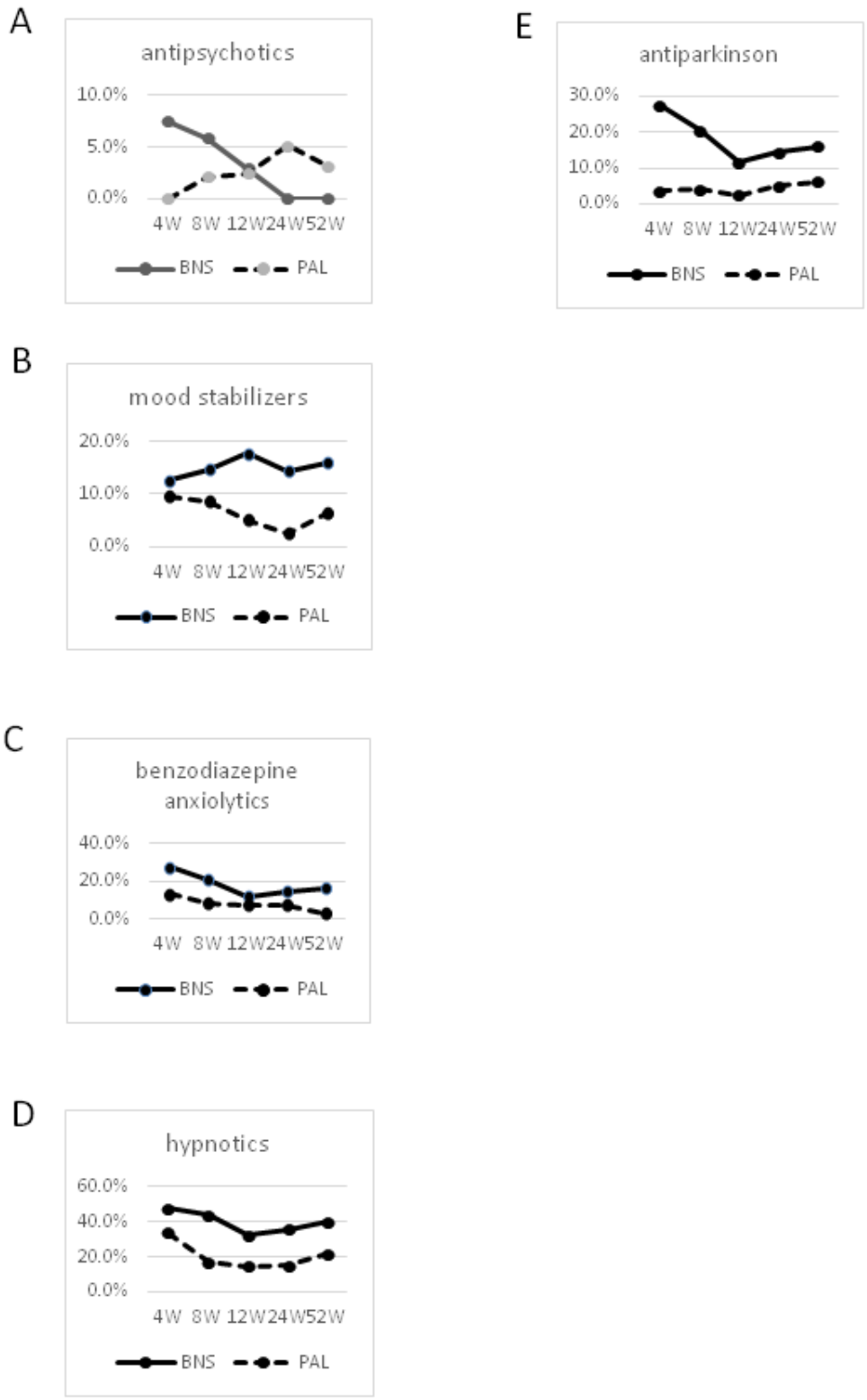

Figure 2. Changes in the rates of concomitant use of adjuvant drugs. A: antipsychotics; B: mood stabilizers; C: benzodiazepine anxiolytics; D: hypnotics; E: antiparkinson drugs

Table 3. Use of adjuvant drugs

mg/day	BNS	PAL
Antipsychotics (chlorpromazine equivalent dose)	130 ± 105	500 ± 141
Sodium valproate	700 ± 352	686 ± 195
Benzodiazepine anxiolytics (lorazepam equivalent dose)	1.23 ± 0.41	2.79 ± 0.57
Hypnotics (flunitrazepam equivalent dose)	2.00 ± 1.23	1.95 ± 0.85
Antiparkinson drugs (biperiden equivalent dose)	2.50 ± 0.55	2.50 ± 0.58

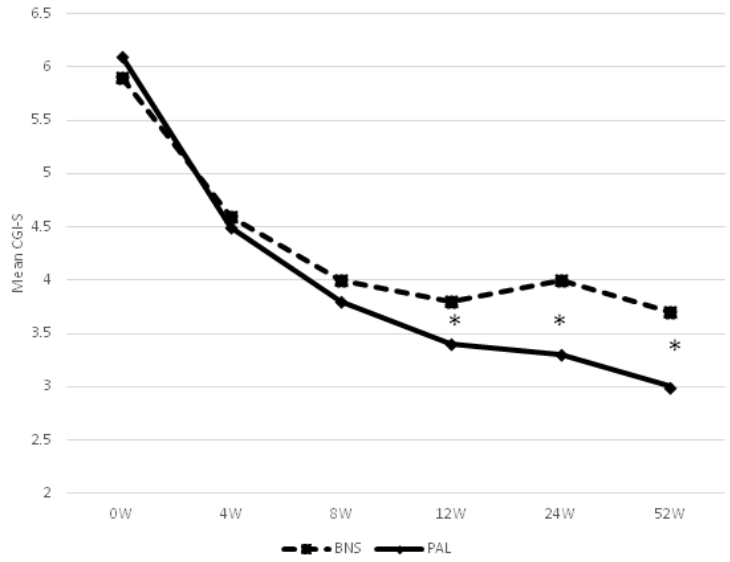

Figure 3. Comparison of mean CGI-S scores with BNS and PAL over time. *p<0.05

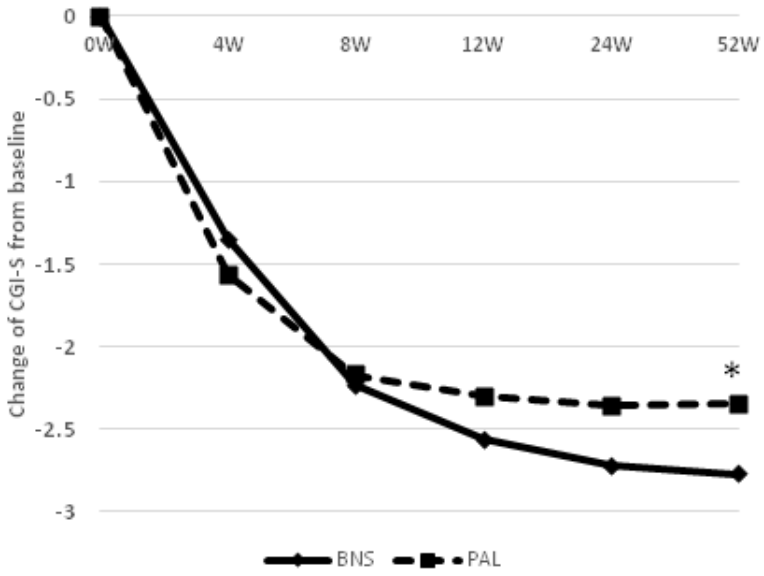

Figure 4. Comparison of the changes in the CGI-S scores from baseline with BNS and PAL over time. *p<0.05

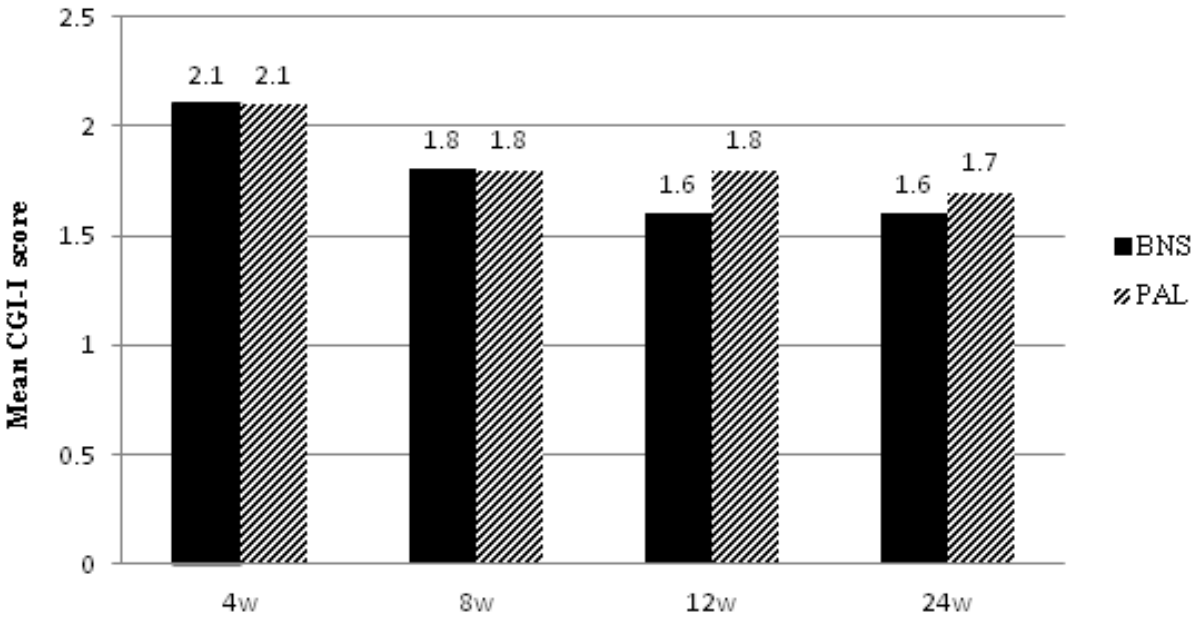

Figure 5. Comparison of the mean CGI-I scores with BNS and PAL over time

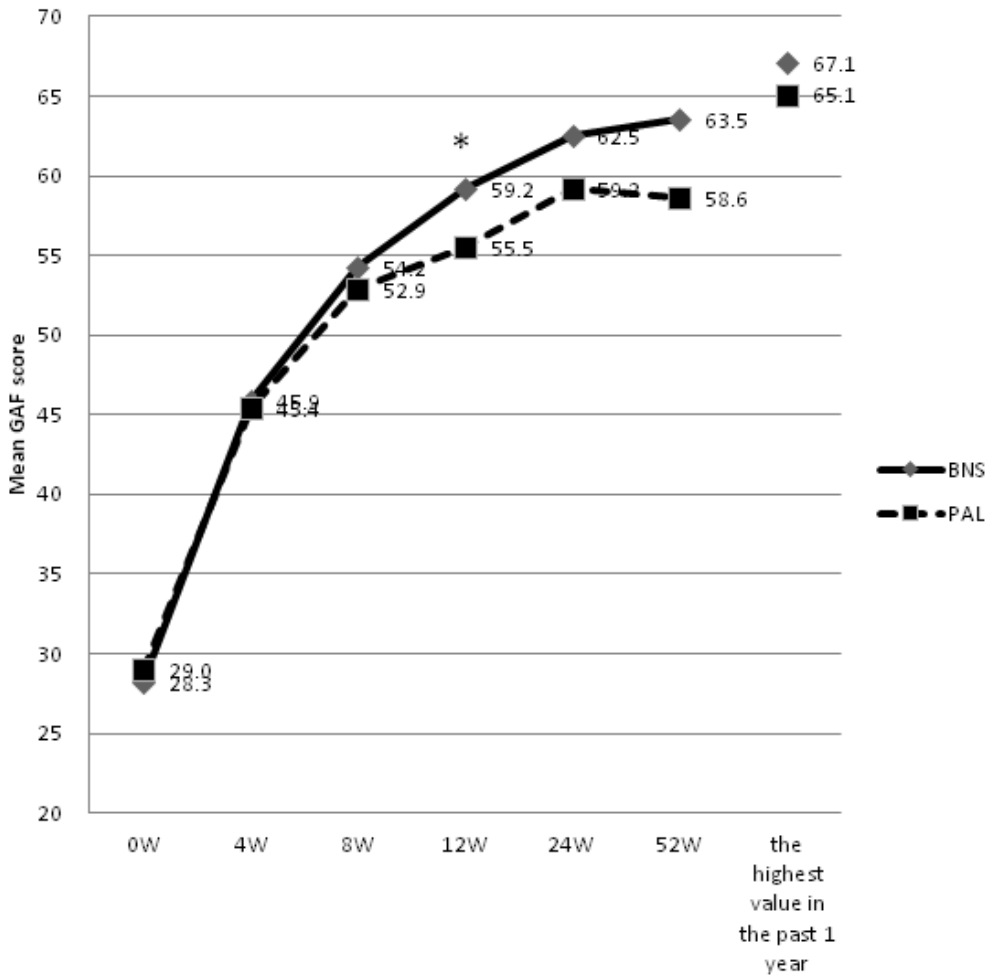

Figure 6. Comparison of the mean GAF scores with BNS and PAL *p<0.05

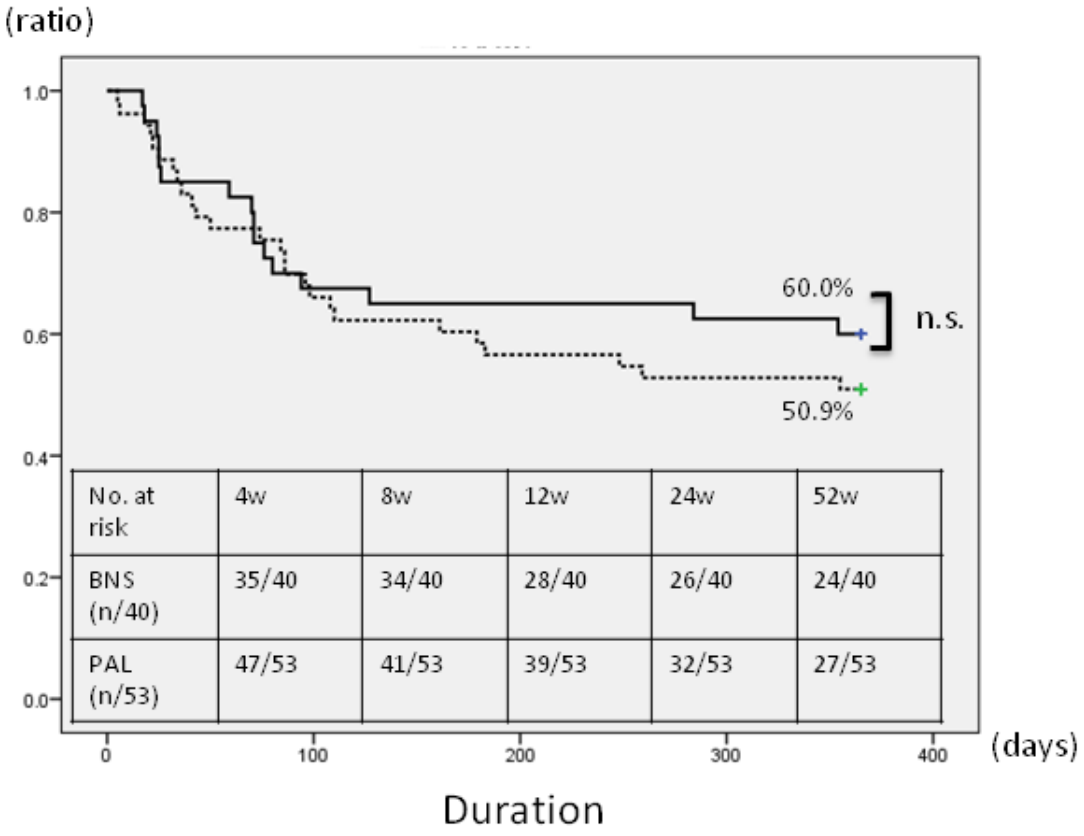

Figure 7. Comparison of the treatment continuation rates with BNS and PAL. The log rank test was used to compare the continuation rates. n.s.: not significant

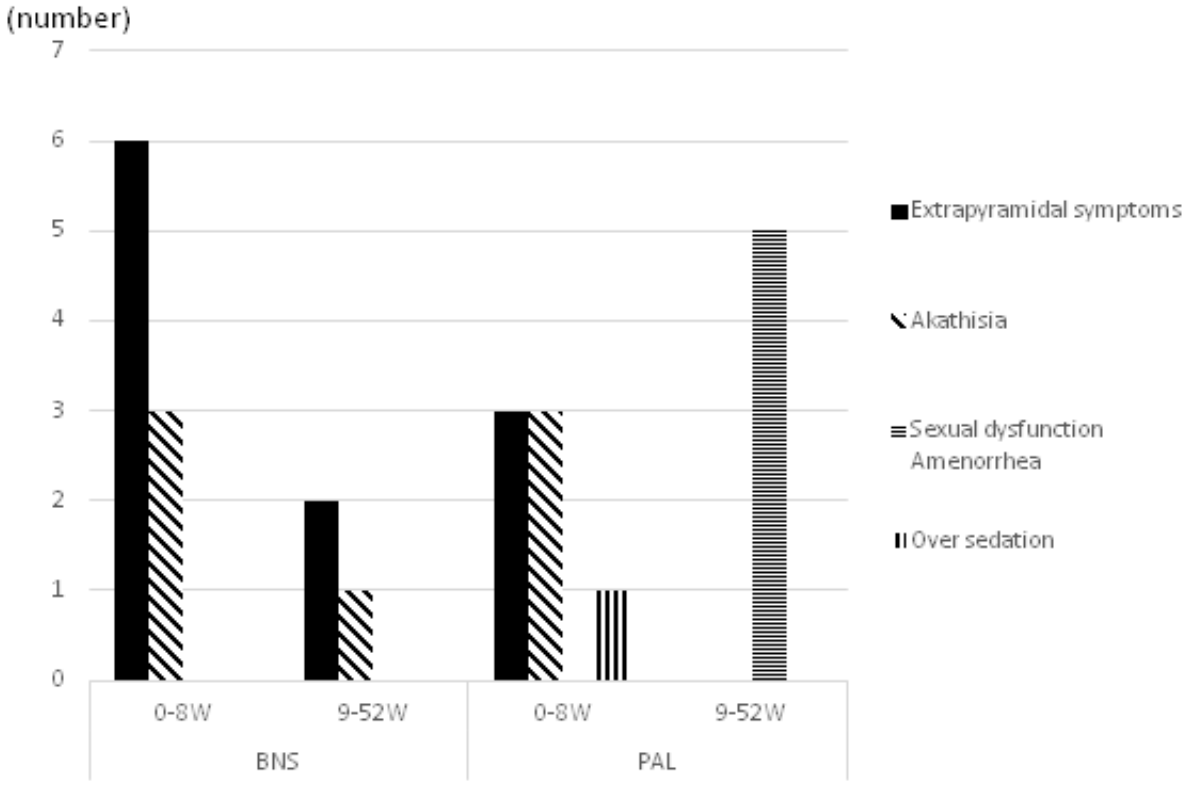

Figure 8. Incidence of adverse drug events with BNS and PAL over time

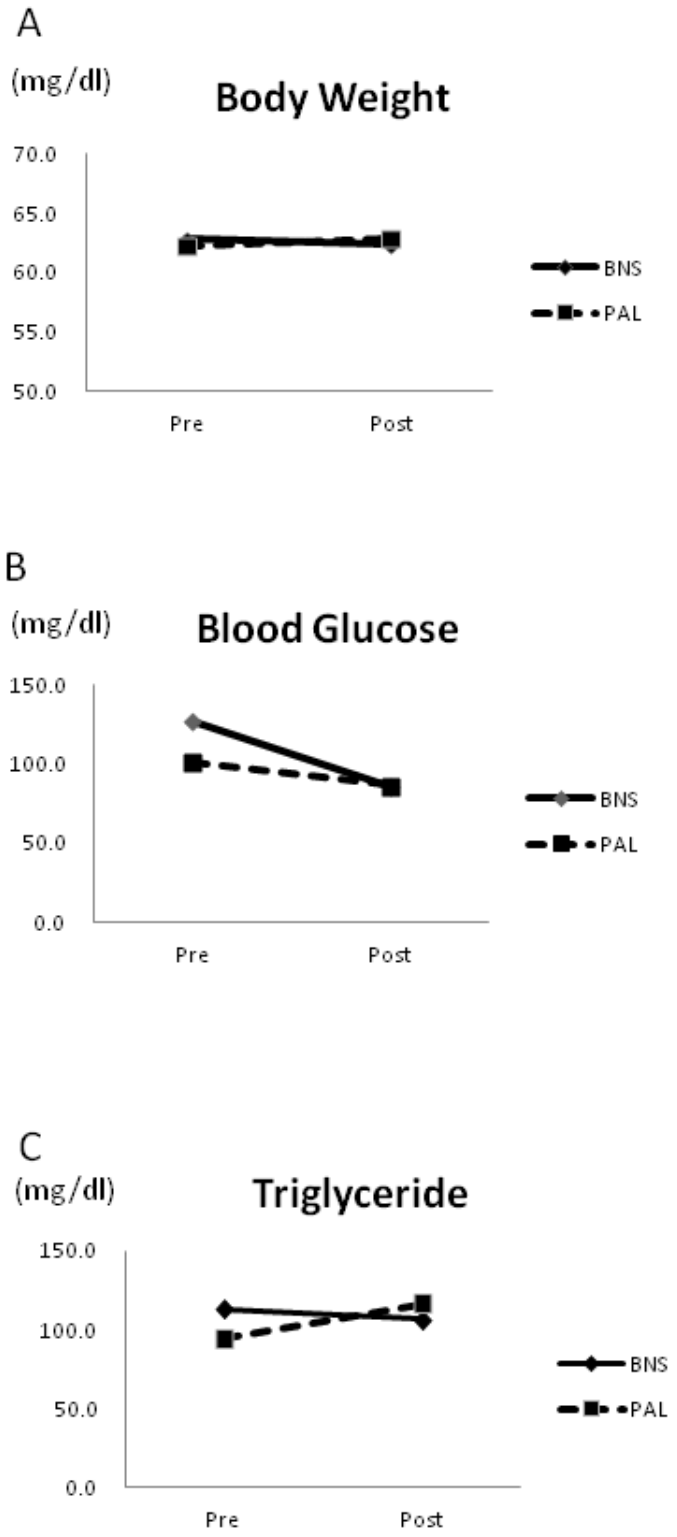

Figure 9. Changes in body weight, blood glucose, and triglycerides. A: Body weight; B: Blood Glucose; C: triglyceride

4. Safety

(1) Adverse drug reactions and adverse events

Figure 8 presents data on the adverse drug reactions/ adverse events observed in this study. During the entire observation period, 8 patients (20%) and 4 patients (10%) in the BNS group had extrapyramidal symptoms (EPS) and akathisia, respectively. In the PAL group, extrapyramidal symptoms were reported in 5 patients (9%), akathisia in 3 patients (6%), sexual dysfunction/amenorrhea in 5 patients (9%), and oversedation in 1 patient (2%). The disposition of adverse drug reactions/adverse events by observation time point showed that 6 patients had extrapyramidal symptoms and 3 patients had akathisia in the BNS group, and that 3 patients had extrapyramidal symptoms, 3 patients had akathisia, and 1 patient had oversedation in the PAL group in the period until Week 8 (the acute phase). In the period from Week 8

to Week 52 (the maintenance phase), extrapyramidal symptoms were reported in 2 patients and akathisia in 1 patient in the BNS group and sexual dysfunction/ amenorrhea was reported in 5 patients in the PAL group. Neither of the treatment groups had unknown adverse drug reactions/adverse events that were not listed in their package inserts.

(2) Body weight/laboratory tests

Figure 9 shows the changes in body weight and laboratory test results (triglycerides and blood glucose). Neither of the treatment groups had significant changes in their laboratory values between before and after administration.

DISCUSSION

The choice of antipsychotics for acute-phase schizophrenia patients is critical. In the acute phase, positive symptoms, negative symptoms, affective symptoms, and cognitive function deteriorate, and social function is compromised. Hence, treatment should aim at alleviating the symptoms and restoring social function. The treatment approach during the acute phase must foresee the subsequent maintenance phase and ensure the achievement of treatment goals that are tailored to the circumstances of the individual patient and that ultimately lead to patient recovery.

Antipsychotics have been compared in the past for their efficacy in the acute phase based on indices of improvement and the treatment continuation rate. Hatta et al. [5] studied 78 patients admitted to the emergency psychiatric ward who were randomly assigned to receive risperidone (RIS), olanzapine (OLZ), quetiapine (QTP), or aripiprazole (ARP) to investigate the treatment continuation rates for 8 weeks. The results showed that the treatment continuation rates for RIS and OLZ were significantly superior to those of the other two drugs. Ishizuka et al. [8] conducted an 8-week multicenter randomized parallel-group study in 130 schizophrenia inpatients and outpatients with markedly acute flare-up using OLZ and PAL, and found that the treatment continuation rate was significantly higher with PAL than with OLZ.

Tsutsumi et al. [22, 23, 24] published detailed reports of one-year follow-up from the acute phase to the maintenance phase in patients administered second generation antipsychotics (SGA) for the treatment of acute-phase schizophrenia, although the reports focused only on a BNS monotherapy group. Edoardo et al. [3] conducted a 6-week placebo-controlled double-blind study in acute-phase schizophrenia patients in which the researchers demonstrated the efficacy of PAL; reportedly the effect was maintained until Week 52. These two reports suggest that BNS and PAL may be first-line drugs for acute-phase treatment; however, there are no reports thus far that directly compare the use of BNS and PAL for the entire period from the acute phase through the maintenance phase.

Our hospital recommends the oral administration of SGA monotherapy for the treatment of acute-phase schizophrenia. The use of injectable antipsychotics is allowed only in the case of severe psychomotor excitability, and patients should be switched to oral SGAs as soon as remission from a state of excitement and agitation is achieved. In this context, SGA therapy is usually chosen depending on the condition of the individual patient, while BNS and PAL are also often introduced as the first-line therapy.

We compared the benefits of BNS and PAL, which are the common choices in the clinical setting for acute-phase treatment that are employed in our hospital, based on the CGI-S, CGI-I, and GAF scores, as well as on the treatment continuation rate during the period from the acute phase to the maintenance phase. The purpose of this study was to verify if BNS and PAL can be used as first-line SGAs for the treatment of acute-phase schizophrenia, and can also be considered for use in the maintenance phase.

1. Drug selection at therapy initiation

In this study, 78 patients required involuntary hospitalization, accounting for 83.9% of the entire study population (93 patients). The CGI-S scores at the initiation of BNS and PAL monotherapy were 5.9 and 6.1 and the GAF scores were 28.3 and 29.0, respectively. These scores were comparable to those reported by Ishizuka et al. [8] and Hatta et al. [5], and provide evidence that BNS or PAL had been used in patients with severe symptoms. Our study investigated SGA oral administration in an acute-phase patient group by excluding patients manifesting severe symptoms such as psychomotor excitability in an attempt to ensure tailored drug choice. This study included an enrolment criterion that allowed the use of injectable antipsychotics in the early stages of hospitalization. Injectables were used at treatment initiation in 12.9% of the entire study population (12/93 patients), and the disposition data show that injectables were used by 4 patients in the BNS group (2 of whom received haloperidol (HPD) and 2 of

whom received levomepromazine) and by 8 patients in the PAL group (2 of whom received HPD and 6 of whom received levomepromazine). These injections were administered to patients with involuntary admission only once or twice on the first day of hospitalization.

Acute-phase schizophrenia treatment requires that consideration be given to the treatment that will be administered in the maintenance phase, and antipsychotic monotherapy is therefore preferable. On the other hand, the possibility that monotherapy treatment may fail to achieve the desired level of sedation should also be considered. We believe that monotherapy with either BNS or PAL can be administered in hospital wards that are equipped to handle emergency/acute-phase treatment as long as hospital staff are knowledgeable, adequate treatment support structures are in place, adjuvant drugs such as VPA/Bz are available for use, and the temporary concomitant use of antipsychotics is possible.

2. Comparison of the efficacy of BNS and PAL based on the CGI-S, CGI-I, and GAF scores

The patient demographic data showed that although the two groups did not differ in the extent to which severity/social function impairment affected the GCI and GAF scores, the duration of illness was significantly longer in the BNS group than in the PAL group. The patients in the BNS group were older than those in the PAL group. The changes over time in the CGI-S scores indicate that there was an immediate response to treatment as evidenced by both the mean values and the mean changes in both groups through Week 8, although the mean CGI-S score was significantly lower in the BNS group starting from Week 12 (Week 12: $p=0.047$, Week 24: $p=0.036$, Week 52: $p=0.022$). There was a slight difference between the groups in the mean change in the CGI-S starting from Week 12, with a significantly larger change being seen in the BNS group at Week 52 ($p=0.035$). The mean CGI-I score for moderate or better improvement exhibited similar changes in both treatment groups until Week 8 and, although not significant, the BNS group exhibited moderate or better improvement starting from Week 12. Comparable increases in the GAF score were found in both treatment groups through Week 8; the BNS group exhibited a significantly larger increase than the PAL group only at Week 12 ($p=0.049$). The BNS group exhibited slightly greater changes in the GAF scores. These results show that BNS and PAL yielded sufficient treatment responses in the acute phase through Week 8 and demonstrate that these drugs can be used as first-line drugs for the treatment of acute-phase schizophrenia. However, slight differences were observed between the groups starting from Week 12 (the start of the maintenance phase). These differences can be explained by the pharmacological profiles of the drugs. Specifically, BNS has a lower affinity to receptors other than dopamine and serotonin, and thus exerts relatively less of a sedative effect. PAL, on the other hand, can exert antagonistic effects on adrenaline $\alpha1$, $\alpha2$, and histamine H1 receptors as well as on dopamine and serotonin receptors, and it therefore has a relatively more potent sedative effect. In the maintenance phase, it appears that agents with sedative effects may often contribute to functional enhancement.

From a hemodynamic perspective, Furukori et al. [4] reported peak/trough blood levels of BNS and PAL of 1.13 and 1.21, respectively, demonstrating that both drugs have excellent hemodynamic stability. These data suggest that stable improvement can be achieved and, in fact, this study found that both drugs have such properties. Regarding the transport of antipsychotics into the brain, Arakawa et al. [1, 20] reported that antipsychotic D2 receptor occupancy in the temporal lobe and pituitary gland was determined in a study using positron emission tomography (PET). The pituitary gland exists outside the blood brain barrier (BBB), and the brain/pituitary (B/P) ratio calculated from the D2 receptor occupancy in the temporal lobe and the pituitary gland showed that the percentage crossing the BBB was 3.88 for BNS and 1.61 for RIS. This suggests that BNS may have considerable ability to distribute to the brain. Since PAL is an active metabolite of RIS and has lower BBB permeability than RIS [15], the transport of BNS into the brain appears to be superior than that of PAL. In this study, the PAL group exhibited stagnant or deteriorating improvement in schizophrenia after Week 12 in some patients, and this might have contributed to the worsening results found in the PAL group data. In other words, BNS and PAL transport in the brain differ slightly, and this difference might have contributed to the differences in improvement in the CGI-S, CGI-I, and GAF scores.

3. BNS and PAL dose levels

As of April 1, 2013, our hospital had 1,471 patients (including both inpatients and outpatients) who were receiving antipsychotics, of whom 1,121 patients (76.2%) had been started on monotherapy. The mean CP-converted dose being received by these patients was 651.7 mg in the inpatients and 436.6 mg in the

outpatients, and the overall mean was 456.2 mg; these doses are significantly lower than the nationwide mean reported by Yoshio et al. [26]. This study enrolled a large number of involuntarily hospitalized patients in both treatment groups who had been treated at doses lower than those used for patients admitted to our hospital.

The starting dose of BNS was 8.6 mg/day, and this was subsequently increased to between 10.5 mg/day and 12.7 mg/day over 52 weeks. Comparison of the change in the dose at Week 8 from treatment initiation to that in the results reported by Tsutsumi et al. [22] found that the change in the dose in this study was approximately 3 mg lower on average. The changes in the dose from Week 8 to Week 52 indicated the beginning of the maintenance phase; these dose changes were similar to those reported by Tsutsumi et al. The PAL group received doses ranging from about 6 to 7 mg at all assessment time points over the 52 weeks of the treatment period; likewise, the change in the dose approximately 2 mg less in the report by Ishizuka et al. [8]. A study on PET [20] reported that the therapeutic window was 12.2 to 22 mg for BNS and 6 to 9 mg for PAL [17], and the dose levels in this study were closer to the lower boundary of the therapeutic window in both treatment groups. The dose levels used in this study were lower than those reported thus far, although the focus was on acute phase, and this was attributable to the fact that the study enrolled patients who had good baseline (pre-onset) social function but who relapsed because of poor drug adherence and non-compliance and hence had no residual effects of their prior treatment or who were patients experiencing their initial onset of the disorder, and that patients with medication-resistant hallucinations/ delusions were not enrolled. Ninomiya et al. [16] studied the long-term efficacy/safety of BNS in initial-onset schizophrenia patients, and reported that the mean dose level was 2.9 mg/day at treatment initiation and 5.6 mg/day during 1 year of treatment. Moreover, Üçok et al. [25] reported that they used a PAL dose level of 6.42 mg/day for initial-onset schizophrenia patients, which was a dose similar to the PAL dose level used in this study. Notably, their study enrolled a large number of patients whose treatment had been discontinued for a long time, and who were therefore presumably almost equivalent to initial-onset patients and thus could be regarded as quasi-drug-naïve at treatment initiation, and this may explain why they were afforded efficacy even at relatively lower doses. In this study, 4 patients in the BNS group and 8 patients in the PAL group received injectable antipsychotics during acute-phase treatment, and the effects of this on the subsequent BNS and PAL dose levels may have been minimal. When selecting the antipsychotic dose, a balance between efficacy and safety needs to be kept in mind, and the overall condition of the patient and the target symptoms should be identified before the dose level is decided. Thus, prescribing a high dose level of an antipsychotic based solely on the apparent severity of the patient's symptoms should be avoided. In addition, co-medical staff vigilance and a systematic treatment environment will also help prevent high doses of multiple drugs from being administered and thus help in the effort to prescribe an optimal dose level.

The comparison of the CP-converted doses in both treatment groups revealed that PAL had significantly higher CP-converted doses than BNS at all assessment time points. This may be explained by the formulation specification of the drugs used for both treatment groups. The minimal specification for BNS was the 2 mg tablet, which is equivalent to a CP-converted dose of 50 mg, and which thereby enables very fine dose adjustments. Meanwhile, the minimal specification for PAL was the 3 mg tablet, which is equivalent to a CP-converted dose of 200 mg. The benefit of PAL is that it does not require such fine dose adjustment as RIS, whereas a possible shortcoming of PAL could be that it has a wider adjustment range. Antipsychotic dose adjustment should ideally be performed based on close observation of the patient's overall condition and taking into consideration the therapeutic window plus estimations of D2 receptor occupancy.

4. Positioning of adjuvant drugs and concomitant antipsychotics

The rate of concomitant use of VPA, Bz, and hypnotics was consistently higher in the BNS group than in the PAL group throughout this study. The results are considered to accurately reflect the receptor affinity profile of both drugs. BNS is an SGA with a less potent sedative effect reflecting its clinical pharmacological profile and often requires concomitant use of an adjuvant drug [13]. This study allowed the primary psychiatrists to concomitantly administer either VPA or Bz for marked anxiety, irritability, or psychomotor excitement. PAL has potent antagonistic effects against adrenaline α1 and α2 and histamine H1 receptors [14], and this difference in receptor profiles might have been the

reason for the difference in the rate of concomitant use of adjuvant drugs.

Tsutsumi et al. [22, 23, 24] reported that the treatment continuation rate with BNS in acute-phase schizophrenia patients varied with the use of adjuvant drugs. Moreover, Heres et al. [19] reported that in the PERTAIN study, which investigated the efficacy of PAL in acute flare-up schizophrenia patients, Patients with a higher disease severity at baseline were about twice as likely to be treated concomitantly with a Bz. The results of this study and preexisting data reveal different rates of the concomitant use of adjuvant drugs, but the concomitant use of adjuvant drugs in acute-phase treatment is a common approach irrespective of the type of antipsychotic. The ideal "acute-phase treatment with consideration given to the maintenance phase" should encompass the concomitant use of adjuvant drugs and primary antipsychotics to treat the acute phase of schizophrenia as well as adjustment of the adjuvant drug to a minimal level in the maintenance phase.

In this study, the concomitant use of antipsychotics was observed in some patients in each group. The rate of concomitant use was 7.5% in the BNS group at Week 4; the use of antipsychotics declined longitudinally, and eventually, from Week 24 on, no antipsychotics were used. In contrast, the rate of concomitant use of antipsychotics in the PAL group increased longitudinally starting from Week 8. Nevertheless, the rate of concomitant use was minimal in both treatment groups. The PAL group exhibited a lower rate of increase or a decrease in the mean CGI and changes over time from Week 12, and some patients in the PAL group received antipsychotics in addition to incremental PAL dose adjustments to achieve further improvements and prevent further deterioration in their condition. Since the use of multiple antipsychotics in acute-phase treatment is somewhat controversial, efforts to prevent acute-phase patients from withdrawing from treatment are critical. Flexible regimens allowing the minimal concomitant use of antipsychotics for symptomatic control may be required at times to help patients withdrawal from antipsychotics when their conditions improve. In this study, the rate of the concomitant use of PAL with antipsychotics peaked at Week 24, and then declined by Week 52, indicating that the use of concomitant antipsychotics was a temporary measure.

The rate of the concomitant use of antiparkinson drugs was consistently higher in the BNS group throughout the study. The incidence of akathisia/extrapyramidal symptoms during this study was higher with BNS, and this is thought to accurately reflect its clinical pharmacological profile and high affinity for dopamine D2 receptors. Treatment with antipsychotics requires strategies to ensure that akathisia/extrapyramidal symptoms do not emerge, which can be achieved only by optimal dose titration for individual patients. In addition, when akathisia/extrapyramidal symptoms occur, they need to be treated appropriately by the concomitant use of antiparkinson drugs or β blockers; importantly, the concomitant use of these drugs needs to be discontinued once the symptoms resolve.

5. Treatment continuation rate

In this study, the "treatment continuation rate" was 85.0% in the BNS group and 77.3% in the PAL group, and there was no significant difference between the groups at Week 8. These percentages were comparable to data from existing reports from Japan [5, 8, 22], which supports the validity of the results of this study. Moreover, the treatment continuation rate at Week 52 was 60.0% in the BNS group and 50.9% in the PAL group; therefore, there was no significant difference between the groups, and these percentages were comparable to the treatment continuation rates found with amisulpride and ziprasidone in EUFEST and slightly higher than the results reported by Tsutsumi et al. [11, 24].

These results suggest that BNS and PAL can equally ensure treatment continuation, and can yield a treatment continuation rate comparable to that of other antipsychotics.

6. Impacts on adverse drug reactions/adverse events, body weight/laboratory test results

This study showed that neither BNS nor PAL affects body weight. BNS has been proven to affect body weight slightly, as reported by Ishigaki et al. [7] and numerous clinical studies, and the repeatability of this finding was demonstrated in this study. This may be explained by the fact that BNS has the lowest affinity for histamine H1 receptors among SGAs. Hirayasu et al. [6] reported that the incidence of body weight gain was 19.7% with PAL, suggesting that continued treatment with PAL may result in body weight gain. Although significant body weight gain, a common adverse drug reaction mentioned in the package insert, was not observed in this study, caution is required in long-term administration. In addition, no elevations in laboratory test results such as triglycerides or blood glucose levels were found in either treatment group. These findings may support

the contention that neither BNS nor PAL is likely to contribute to metabolic disorders, as has already been reported, and it therefore appears that these SGAs could be relatively safe in schizophrenia patients with comorbid obesity or diabetes mellitus.

In this study, PRL-related disorders were seen only in the PAL group. Despite the fact that BNS and PAL have equally potent binding affinity to dopamine D2 receptors, the mechanism whereby PAL affects PRL may be explained by the fact that BNS is more likely to be transported into the brain and thus less likely to affect the pituitary gland, as demonstrated by the PET study [1, 20] described earlier in this paper. Transport into the brain is dictated by the compound properties of the antipsychotic, i.e., the molecular weight and lipophilicity [15]. The molecular weight of PAL was 426.48, higher than the molecular weight of BNS (367.50), and the log P (log 1-octanol/water partition coefficient), representing the lipophilicity of PAL, was -0.38 (pH 5.0) and 1.02 (pH 7.0), which was smaller than that of BNS [3.43 (pH 5.5) and 4.59 (pH 8.3)] [10], suggesting that PAL is less likely than BNS to pass the BBB. The pituitary gland is located outside the BBB, and in response to elevated blood PAL concentrations, the D2 receptors in the tuberoinfundibular dopamine pathway are inhibited, resulting in elevated blood PRL levels. Caution must be exercised in the long-term use of antipsychotics by periodically monitoring the blood PRL level.

SUMMARY

Both BNS and PAL were proven to offer benefits for acute-phase schizophrenia patients from the acute phase to the maintenance phase. Of note, for patients with excellent social function prior to onset, BNS can be superior in the maintenance phase.

The primary limitations of this study include the retrospective nature of the investigation as well as the absence of the use of PANSS, BPRS, or DIEPSS for symptomatic assessment, which would have enabled the study to assess drug efficacy for psychiatric symptom and extrapyramidal symptom severity. Moreover, although the treatment continuation rate was estimated by the Kaplan-Meier method, this approach requires continued observation until the onset of an event to estimate the event incidence, and should therefore be employed for data obtained from prospective studies. Medical research often involves retrospective designs, and the Kaplan-Meier approach is often employed. The results of this statistical analysis approach need to be interpreted carefully.

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