Optimal Dosing of Risperidone and Olanzapine in the Maintenance Treatment for Patients With Schizophrenia and Related Psychotic Disorders: A Retrospective Multicenter Study

Yusaku Yoshimura 1,2, Toshihiko Takeda 1, Yoshiki Kishi 3, Toshiki Harada 4, Akira Nomura 5 Kenji Washida 1,2, Bunta Yoshimura 3, Kojiro Sato 3, Yuji Yada 3, Shozo Aoki 2.

1. Department of Psychiatry, KawasakiMedical Graduate School, Kurashiki, Japan

2. Zikei Hospital, Okayama, Japan

3. Okayama Psychiatric Medical Center, Okayama, Japan

4. Taiyo Hills Hospital, Ochiaicho-Abe, Takahashi, Japan

5. Momonosato Hospital, Imadate, Kasaoka, Japan.

ABSTRACT

We conducted a retrospective multicenter study to determine the optimal tolerability dose ranges of risperidone (RIS) and olanzapine (OLZ) administered during schizophrenia maintenance phase. Two-year continuation rates of prescription at discharge were retrospectively examined using patient records. Adult patients with schizophrenia and related psychotic disorders, receiving antipsychotic monotherapy with RIS or OLZ at discharge, were included. The primary outcome measures were the time to treatment discontinuation and 2-year continuation rates at four modal dose ranges of each drug. We estimated the optimal tolerability dose ranges by comparing the continuation rates at various modal doses. Of 648 patients, 344 received RIS and 304 received OLZ. RIS 2-year continuation rates at four daily modal dose ranges were significantly different (0.5–2.5 mg: 46.0%, 3.0–5.0 mg: 40.0%, 5.5– 7.5 mg: 30.0%, 8.0–10.0 mg: 28.0%), with significant difference favoring RIS lower doses (0.5–5.0 mg) than higher doses (5.5–10.0 mg). In contrast, there were no significant differences among OLZ four modal dose ranges (2.5–7.5 mg: 49.1%, 10.0–15.0 mg: 42.6%, 17.5–22.5 mg: 40.9%, 25.0–30.0 mg: 39.0%). The time to treatment discontinuation significantly favored OLZ over RIS. However, it did not differ significantly between RIS lower doses and OLZ lower doses. In conclusion, it is suggested that the optimal tolerability dose range during maintenance treatment is 0.5–5.0 mg per day for RIS and 2.5–30 mg per day for OLZ and that RIS lower doses is comparable with OLZ lower doses.

Keywords: antipsychotic treatment, olanzapine, risperidone, schizophrenia, treatment discontinuation, optimal dosing

INTRODUCTION

Schizophrenia management generally involves a long-term administration of antipsychotic drugs. However, long-term maintenance treatment with antipsychotic drugs can result in discontinuation because of lack of efficacy, intolerability, or patients' decisions. Antipsychotic effectiveness studies examining the time to treatment discontinuation have shown high discontinuation rates for antipsychotic treatment. The Clinical Antipsychotic Trials of Intervention Effectiveness Study (Lieberman et al., 2005) reported that 74% of patients with chronic schizophrenia discontinued their study medication before 18 months. The European First Episode Schizophrenia Trial (Kahn et al., 2008) reported that 42% of subjects discontinued the prescribed antipsychotic before 12 months. Furthermore, it was suggested that medication discontinuation can lead to a negative outcome (Keith and Kane, 2003; Lacro, 2002; Lieberman, 1996) and that schizophrenia relapse is related to progressive decrease in brain volume and deficits and dysfunction in neuronal regulation (Kasai et al., 2003; Lieberman et al., 1997). Therefore, clinicians need to have treatment strategies in place for managing and optimizing antipsychotic drugs during long-term maintenance treatment. These strategies include continuous treatment with the optimal doses of each antipsychotic during the maintenance phase. Continuous treatment at therapeutic doses is an important goal for the effective management of schizophrenia in the maintenance phase; however, clinical evidence concerning therapeutic doses during the maintenance phase is limited.

Although several randomized antipsychotic effectiveness trials with stringent inclusion and exclusion criteria have been conducted (Lieberman et al., 2005; Johnsen et al., 2010; McEvoy et al., 2007), applicability and generalizability of these results may be limited. Moreover, the outcomes from naturalistic observational effectiveness studies in routine schizophrenia treatment are important in informing the clinicians about optimal antipsychotic drug treatment in everyday clinical practice. Therefore, effectiveness outcomes in schizophrenia patients in naturalistic pragmatic settings are of increasing interest to clinicians (Kilian R, 2012; Kroken RA., 2014; Zarin et al., 2005).

The concept of overall effectiveness of antipsychotic drugs includes several factors such as efficacy, safety, and tolerability. Treatment discontinuation has been regarded as an appropriate indicator of overall effectiveness in schizophrenia (Haro et al., 2007). Previous effectiveness studies revealed the superiority of olanzapine (OLZ) over risperidone (RIS) and other atypical antipsychotic drugs in terms of the time to discontinuation of the treatment (Beasley et al., 2007; Haro et al., 2007; Lieberman et al., 2005). However, evidence regarding the relationship between the maintenance doses and the treatment continuation of these treatment in the maintenance phase is sparse.

During hospitalization, schizophrenia patients usually receive acute-phase treatment, which includes antipsychotic initiation and switching in some cases. Thus at discharge, in most cases, patients are treated with effective antipsychotics as per their conditions in the acute phase. Furthermore,the antipsychotic drug doses are titrated from an initial dose to the therapeutic dose based on patients' clinical response and tolerability, and acute psychotic symptoms are treated to the extent that patients can be discharged from hospital to the community. Therefore, by examining the continuation rates of antipsychotic drugs at discharge and the maintenance doses of each drug, the overall effectiveness of each drug in the stabilization or maintenance phase and its association with maintenance doses can be assessed with little influence of acute treatment on the outcomes in naturalistic pragmatic settings.

To evaluate the overall effectiveness of RIS and OLZ and to estimate the optimal tolerability dose range of each drug in the stabilization or maintenance phase in real-life routine practice conditions, we conducted a retrospective, observational, multicenter study and examined the 2-year continuation rates of the two drugs after discharge.

METHODS

Subjects and Study Design

This was a 24-month, historical cohort, multicenter study of antipsychotic medications used for the stabilization or maintenance treatment of schizophrenia following acute inpatient treatment at psychiatric hospitals.

Using a historical cohort design, we screened all patients who were discharged from four psychiatric hospitals located in Okayama Prefecture, Japan, between January 2004 and December 2012. Data were obtained retrospectively from medical records or by contacting the treating specialists. Eligible patients were 16–60 years of age; had received a clinical diagnosis of schizophrenia, schizophreniform disorder, and schizoaffective disorder according to the International Classification of Diseases, version 10 (WHO, 1992) by the treating psychiatrists in a routine clinical setting; were receiving antipsychotic monotherapy with RIS or OLZ at discharge; and had received outpatient treatment at the same facility where they received inpatient treatment.

Patients were excluded if they had received a diagnosis of organic mental disorders; were referred to other outpatient facilities after discharge; or were prescribed long-acting injectable antipsychotics. Mood stabilizers, benzodiazepines, antidepressants, and anticholinergic medications were permitted. We excluded patients with antipsychotic polytherapy; however, we permitted another antipsychotic if it was prescribed at the chlorpromazine equivalent doses of 25 mg or less (Gardner et al., 2010, Kane et al., 2003) and was used as a sleep aid.

The study protocol was approved by the Institutional Review Board at each site (the Ethics Committees of Kawasaki Medical Graduate School, Zikei Hospital, and Okayama Psychiatric Medical Center) and was conducted in accordance with the Declaration of Helsinki.

Measurements

We hypothesized that there are significant differences in the treatment continuation rates between RIS and OLZ and also among different maintenance doses of RIS or OLZ. The primary outcome measures were the time to treatment discontinuation of each drug and the 2-year continuation rate of monotherapy with each drug at various modal doses after discharge.

Our criteria for treatment discontinuation included: (1) the change of initial antipsychotic, (2) addition of a second antipsychotic at the chlorpromazine equivalent doses of more than 25mg, (3) hospital admission for psychosis exacerbation, and (4) other reasons such as loss to follow-up or death. The cause of the change of initial antipsychotic or addition of a second antipsychotic was categorized as either lack of efficacy, intolerability, or patients' decision.

To determine the modal dose range of each drug in the stabilization or maintenance phase after discharge, daily doses were recorded throughout the study. We regarded the modal dose as the maintenance dose of each drug for each patient. We calculated the chlorpromazine equivalent doses of each drug and stratified patients into four dose categories accordingly. In this way, we compared the 2-year continuation rates at four different modal dose ranges for each drug [RIS (0.5–2.5 mg, 2.5–5.0 mg, 5.5–7.5 mg, and 8.0–10 mg per day) and OLZ (2.5–7.5 mg, 10–15 mg, 17.5–22.5 mg, and 25–30 mg per day)]. Furthermore, we compared the continuation rate of RIS lower doses (0.5–5.0 mg) with that of its higher doses (5.5–10.0 mg) and that of OLZ lower doses (2.5–15.0 mg) with that of its higher doses (17.5–30.0 mg).

In addition to demographic variables, we recorded the illness duration, anticholinergic medication use, index hospitalization duration, and antipsychotic doses at discharge.

Statistical Analyses

Groups were compared for categorical outcomes with Pearson's Chi-square (χ^2) test, or Fisher's exact test, and

continuous variables with a Mann–Whitney U test. The time to treatment discontinuation was estimated from the Kaplan–Meier curves.

Comparisons of the survival curves were performed using the log-rank test. Pearson's Chi-square test was used to compare the 2-year continuation rate of monotherapy with each drug. The medication modal maintenance dose for each subject was calculated as the dose that the subject received for the most number of days. The significance level for the results was set at $p < 0.05$.

RESULTS

Subject and Illness Characteristics

A total of 648 patients were included in this study; 344 were treated with RIS and 304 with OLZ.

There were no significant differences between the RIS and OLZ treatment groups in terms of gender and mean illness duration. The mean baseline age in the RIS group was significantly higher than that in the OLZ group (Mann–Whitney U test, $z = -2.26$, $p = 0.023$). Furthermore, the mean duration of previous hospitalization in the RIS group was significantly longer than that in the OLZ group (Mann–Whitney U test, $z = 3.87$, $p = 0.00011$).

The concurrent use rate of anticholinergic drugs was 57.4% in the RIS group and 29.1% in the OLZ group, with a significant difference between the two groups ($\chi^2 = 39.5$, df = 1, $p = 3.3 \times 10^{-10}$). There was a significant difference between the two groups in terms of the concurrent use of another antipsychotic (CP equivalent ≤ 25 mg) as a sleep aid ($\chi 2 = 26.0$, df = 1, $p = 3.4 \times 10^{-7}$) **(Table 1).**

The Discontinuation Rates for Specific Reasons

The discontinuation rates because of the lack of efficacy, intolerability, patients' decision, or hospital admission during the observation period did not differ significantly between the two groups **(Table 2).**

Table 1. Baseline characteristics of patients.

	Risperidone (N = 344)	Olanzapine (N = 304)	p
Male sex, n (%)	174 (50.3)	167 (54.9)	0.24
Age at discharge (years)	38 (16–60)	35 (16–60)	0.024 [a]
Illness duration (years)	7 (0–40)	6 (0–44)	0.48
Recent-onset illness (≤5years), n (%)	135 (39.2)	136 (44.7)	0.16
Baseline mean dose, mg per day ± SD	4.8 ± 2.5	16.6 ± 7.0	
Index hospitalization duration (weeks)	9 (1–660)	12 (1–536)	0.00011 [a]
Concurrent use of anticholinergic drugs, n (%)	186 (54.1)	90 (29.6)	3.3×10^{-10} [b]
Concurrent use of another antipsychotic as a sleep aid (CP equivalent ≤ 25 mg), n (%)	79 (23.0)	25 (8.2)	3.3×10^{-7} [b]

[a] Statistically significant with $p < 0.05$ based on Mann–Whitney U test.

[b] Statistically significant with $p < 0.05$ based on χ^2-square test.

Results are expressed as number (percent), mean ± SD, or median (minimum–maximum). SD: Standard deviation, CP: chlorpromazine.

Table 2. Outcome measures of effectiveness.

	Risperidone (N = 344)	Olanzapine (N = 304)	p
Two-year continuation of treatment, n (%)	128 (37.2)	130 (42.8)	0.15
Time to discontinuation of treatment (weeks)	44 (0–104)	76 (0–104)	0.010 [a]
Discontinuation for any reason, n (%)	216 (62.8)	174 (57.2)	0.15
Change of initial antipsychotic, n (%)	77 (22.4)	54 (17.8)	0.14
Addition of a second antipsychotic, n (%)	38 (11.0)	36 (11.8)	0.75
Lack of efficacy, n (%)	47 (13.7)	35 (11.5)	0.41
Intolerability, n (%)	54 (15.7)	46 (15.1)	0.84
Patient's decision, n (%)	14 (4.1)	9 (3.0)	0.45
Hospitalization for psychosis exacerbation, n (%)	83 (24.1)	62 (20.4)	0.26
For other reasons, n (%)	17 (4.9)	22 (7.2)	0.22
Lost to follow-up, n (%)	17 (4.9)	20 (6.6)	0.37
Completed suicide, n (%)	0 (0)	2 (0.7)	0.13
Maximal dose received, mg per day ± SD	5.2 ± 2.5	17.5 ± 7.2	
Mean modal dose, mg per day ± SD	4.3 ± 2.4	15.0 ± 7.3	

[a] Statistically significant with $p < 0.05$ based on Mann–Whitney U test.

Comparison of Different Modal Dose Ranges

There was a significant difference in the 2-year continuation rate among four different modal dose ranges of RIS ($\chi^2 = 10.4$, df = 3, p = 0.016). RIS 2-year continuation rates were 46.0% for 0.5–2.5 mg, 40.0% for 3.0–5.0 mg, 30.0% for 5.5–7.5 mg, and 28.0% for 8.0–10.0 mg per day. The 2-year continuation rate of RIS lower doses (0.5–5.0 mg) was higher than that of RIS higher doses (5.5–10.0 mg) ($\chi^2 = 9.70$, df = 1, p = 0.0018) because of the high hospitalization rate in the latter. There was a significant difference in the discontinuation rate due to hospitalization for psychosis exacerbation between the two groups in favor of RIS lower doses over RIS higher doses ($\chi^2 = 6.05$, df = 1, p = 0.014) **(Figure 1).** With regards to the rate of the use of anticholinergic drugs there was a significant difference among the four dose ranges of RIS (40.6% for 0.5–2.5 mg, 48.8% for 3.0–5.0 mg, 69.9% for 5.5–7.5 mg, and 71.7% for 8.0–10.0 mg per day, $\chi2 = 21.5$, df = 3, $p = 8.2 \times 10^{-5}$).

With regard to OLZ, there were no significant differences in the continuation rate among four modal dose ranges. OLZ 2-year continuation rates were 49.1% for 2.5–7.5 mg, 42.6% for 10.0–15.0 mg, 40.9% for 17.5–22.5 mg, and 39.0% for 25.0–30.0 mg per day. No statistically significant difference was found between OLZ lower doses (2.5–15.0 mg) and higher doses (17.5–30.0 mg) in terms of the 2-year continuation rate ($\chi^2 = 0.595$, df = 1, p = 0.44) **(Figure 2).** There was a significant difference in the use of anticholinergic drugs among the four dose ranges of OLZ (20.0% for 2.5–7.5 mg, 24.3% for 10.0–15.0 mg, 33.3% for 17.5–22.5 mg, and 48.8% for 25.0–30.0 mg per day, $\chi2 = 11.81$, df = 3, p = 0.0080).

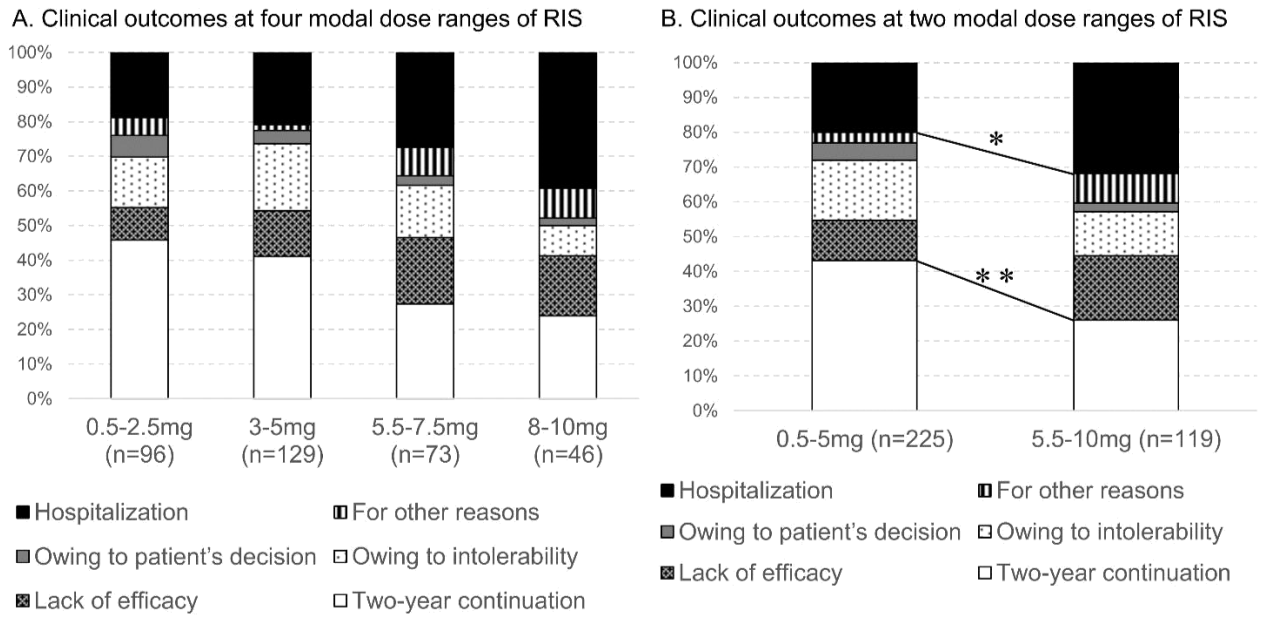

Fig. 1. Distribution of clinical outcomes at four modal dose ranges (A) and two modal dose ranges (B) of risperidone over the 2-year period after discharge from hospital.

*p < 0.05 and **p < 0.01 indicate significant differences based on Chi-square test.

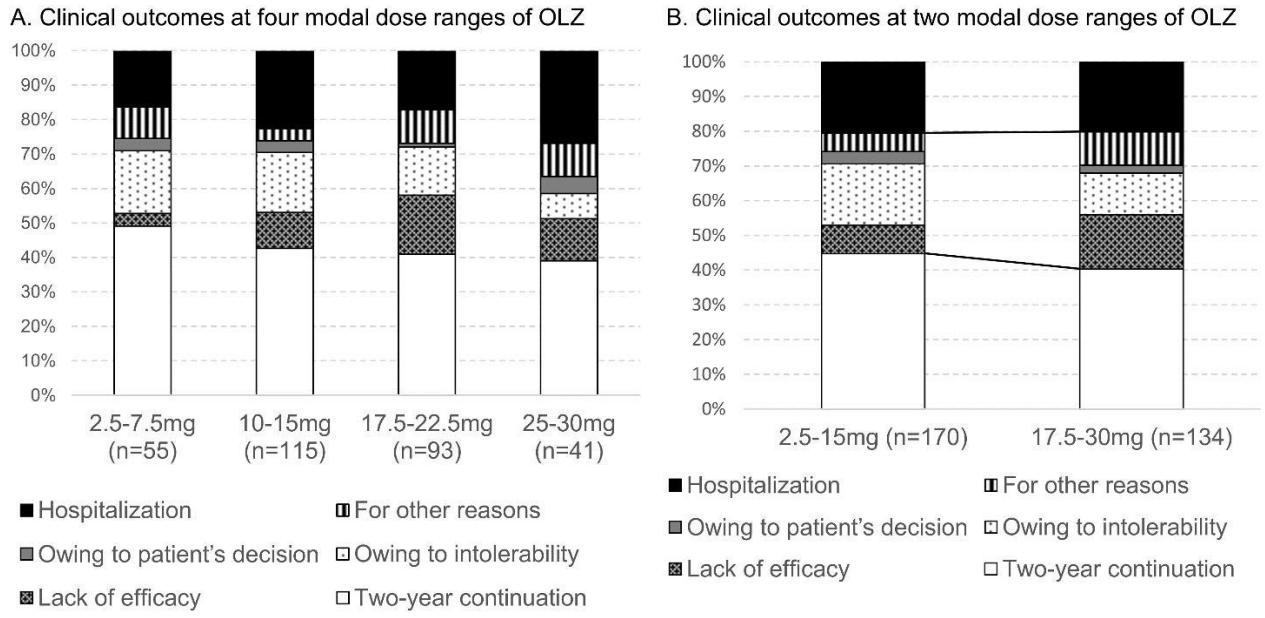

Fig. 2. Distribution of clinical outcomes at four modal dose ranges (A) and two modal dose ranges (B) of olanzapine over the 2-year period after discharge from hospital.

Kaplan–Meier Survival Analysis

The mean modal dose (s.d.) for patients treated with RIS and OLZ was 4.3 (2.4) mg per day and 15.0 (7.3) mg per day, respectively. With regards to time to discontinuation (for any reason) there was a significant difference between the two groups in favor of the OLZ group over the RIS group (log-rank $\chi^2 = 4.73$, df = 1, p = 0.030) **(Figure 3A).**

To allow the comparisons of changes in outcome measures in terms of the dosage of each drug, patients were stratified by modal dose after discharge [lower dose (RIS: 0.5–5.0 mg, OLZ: 2.5–15 mg) or higher dose (RIS: 5.5– 10 mg, OLZ: 17.5–30 mg)].

The mean modal dose (s.d.) for patients treated with RIS and OLZ lower doses were 2.8 (1.1) mg per day and

9.4 (3.7) mg per day, respectively. The mean modal doses for patients treated with RIS and OLZ higher doses were 7.1 (1.4) mg per day and 22.2 (3.6) mg per day, respectively.

Although the time to treatment discontinuation differed significantly between RIS and OLZ higher doses in favor of the OLZ group (log-rank χ^2 = 6.38, df = 1, p = 0.012), no significant differences were found between the patients treated with RIS and OLZ lower doses (log-rank χ^2 = 1.22, df = 1, p = 0.27) **(Figure 3B, 3C).**

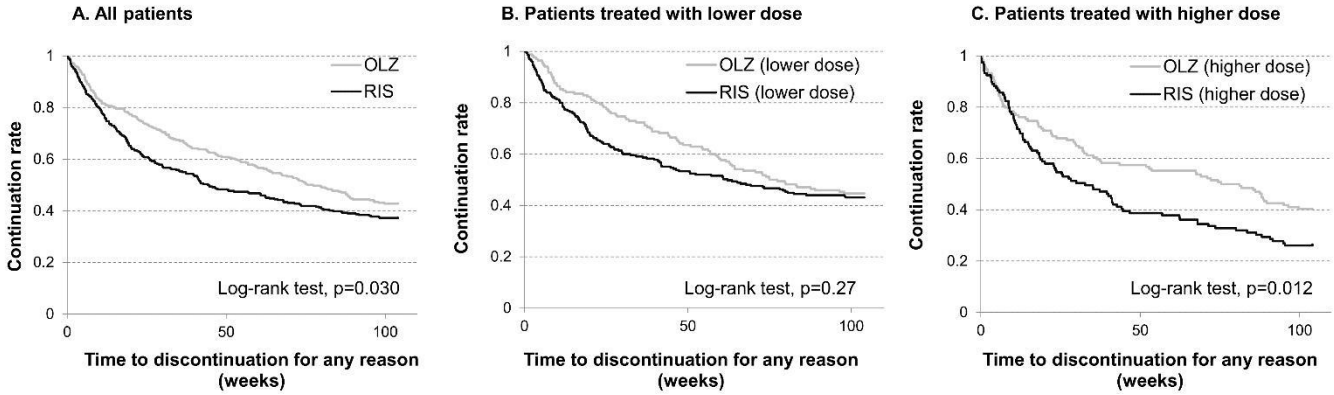

Fig. 3. Kaplan–Meier survival analysis of the time to discontinuation of risperidone and olanzapine antipsychotic monotherapies after discharge from hospital.

(A) Analysis of all patients, (B) Analysis of patients treated with lower doses (RIS: 0.5–5.0 mg, OLZ: 2.5–15 mg), (C) Analysis of patients treated with higher doses (RIS: 5.5–10 mg, OLZ: 17.5–30 mg).

DISCUSSION

The objective of this study was to compare the overall effectiveness of RIS and OLZ in terms of the maintenance doses based on the two year continuation rates and to explore the optimal tolerability dose range of each drug in the stabilization and maintenance phase of schizophrenia and related psychotic disorders. Our results indicated that OLZ showed significantly lower risks for all-cause treatment discontinuations than RIS among the patients treated with higher doses (RIS: 5.5–10 mg/day; OLZ: 17.5–30 mg/day), whereas there was no significant differences between the lower doses of two drugs. Several previous effectiveness studies (Beasley et al., 2007; Haro et al., 2007; Dossenbach et al., 2004; Lieberman et al., 2005) showed greater effectiveness of OLZ than RIS in terms of the time to treatment discontinuation. However, these studies included patients treated with higher doses of the two drugs and did not compare the effectiveness from the perspective of the dosage. In the light of our results, it is suggested that the superiority of OLZ is attributed to the difference of these two drugs in the overall effectiveness at higher doses.

Although evidence about the therapeutic doses required for long-term maintenance treatment is limited, some short-term studies have examined the efficacy and safety of RIS or OLZ higher doses. According to a review of 18 fixed-dose studies, RIS at daily doses of ≥6 mg produced no additional benefit and only increased the frequency of extrapyramidal adverse effects (Ezewuzie, 2006). With regard to OLZ high doses, several case series and open label studies reported that OLZ was frequently used at doses exceeding 20 mg per day, especially for severely ill or treatment-refractory patients, and described a favorable risk-benefit ratio (Dossenbach, 2000; Karagianis, 2003; Mountjoy et al., 1999; Thomas et al., 2008). Although double-blind clinical studies examining OLZ doses higher than 20 mg per day are limited, these doses are helpful in patients with higher levels of psychopathology in a randomized, double-blind, fixed-dose study (Kinon, 2008). Our results suggest that even if patients are successfully treated with higher doses (5.5–10 mg/day) of RIS in the acute phase, the treatment continuation rate

after discharge in the maintenance phase is alarmingly low if they need the higher dose of RIS subsequently. In contrast, it is suggested that OLZ higher doses (17.5–30 mg/day) has balanced effectiveness in the maintenance phase in terms of continuation rate after discharge.

To explore the optimal tolerability dose ranges of the two drugs in the maintenance phase, we compared the 2-year continuation rates of the two drugs at various modal dose ranges after hospital discharge. During acute phase and subsequent stabilization phase, the dose of each antipsychotic drug is titrated from an acute dose to a maintenance dose according to the patient's beneficial and adverse effects in order to optimize the effectiveness of each drug for each patient. Therefore, it can be assumed that the modal dose of the maintenance phase in this study is the dosage adapted to each patient with the optimal balance of efficacy and tolerability for the maintenance treatment. In other words, each patient can be assumed to belong to the modal dose range that is best suited to the patient's condition in the maintenance phase in terms of efficacy and tolerability. Under this assumption, it can be argued that the comparison of the treatment continuation at the different modal doses can give us information regarding the long-term outcome of treatment with different doses and thus it can enable us to explore the optimal tolerability dose ranges in naturalistic pragmatic settings.

In this study, the continuation rate of the higher doses of RIS (5.5-10mg per day) was alarmingly low (26.1%), which suggests that more than 5mg RIS is outside the optimal tolerability dose range, if we define optimal tolerability doses as being not less than approximately 40% of the 2-year continuation rate. This is probably because more than 5-mg RIS does not have the optimal balance of efficacy, safety, and tolerability in most patients in the long-term maintenance treatment. In fact, adjunctive anticholinergic use rate in patients treated with RIS higher doses was approximately 70%, which suggests that the higher doses of RIS caused extrapyramidal side effects such as Parkinsonism, akathisia and dystonia in the majority of the patients. Moreover, the side effects induced by anticholinergic drugs might negatively affect the patient outcomes. In contrast, the continuation rates of the higher doses (17.5–30 mg per day) of OLZ was 40.3% and comparable with OLZ lower dose ranges, which suggests that even OLZ higher doses are included in the optimal tolerability dose ranges. Thus, OLZ higher dose was shown to have balanced effectiveness in terms of safety and tolerability. Based on our 2-year continuation rate analysis, the optimal tolerability dose ranges in the stabilization and maintenance phase are suggested to be 0.5–5.0 mg per day for RIS and 2.5–30 mg per day for OLZ.

Several reviews on RIS or OLZ optimal doses for schizophrenia treatment have been reported (Ezewuzie et al., 2006; Kasper et.al., 1998; Lane et al., 2000; Williams et al., 2001), and several guidelines recommend the optimal doses of antipsychotic drugs (Buchanan et al., 2010; Kane et al., 2003; Lehman et al., 2004). Kane et al. (2003) explained that in maintenance treatment, RIS optimal doses are 2.0–4.5 mg per day for first-episode patients and 3.5–5.5 mg per day for multi-episode patients, whereas OLZ optimal doses are 10.0–20.0 mg per day for first-episode patients and 12.5–22.5 mg per day for multi-episode patients. Buchanan et al. (2010) recommended the daily dosage of second-generation antipsychotic medications for an acute symptom episode as 2–8-mg RIS and 10–20-mg OLZ and the maintenance dosage as the dose effective for reducing positive psychotic symptoms in the acute phase of treatment. However, empirical evidence as to optimal doses during the maintenance phase is limited.

As per our results, RIS optimal tolerability dose range in the maintenance phase was found to be 0.5–5.0 mg per day, which is slightly lower than the doses recommended in the guidelines. In contrast, OLZ optimal tolerability dose range in the maintenance phase was found to be 2.5–30 mg, which is broader than the dose ranges recommended in the guidelines, and more than 20 mg per day of OLZ was not less effective in terms of treatment continuation rate. It was thought that the superiority of OLZ over RIS may be limited in patients treated with higher doses of the two drugs as the continuation rate of RIS used in the optimal tolerability dose range was comparable with OLZ. Therefore, the maintenance dose of RIS in long-term treatment should be carefully

considered.

Limitations and Conclusions

This was a retrospective study and we were unable to evaluate several prognostic factors, such as illness severity, number of illness and hospitalization episodes, and treatment-resistant schizophrenia evaluation due to the lack of information recorded. Although all patients were treated to the extent that they did not need inpatient care and were able to be discharged to the community and it can be assumed that their overall mental health status are similar, there may be the possibility that more severely mentally ill patients were treated with higher doses of RIS. Another limitation is that the optimal tolerability dose range was estimated under the assumption that patients were treated at the doses properly adjusted according to beneficial and adverse effects. However, the doses of drugs might not necessarily be adjusted with the optimal balance of efficacy and tolerability in some cases. Besides, the influence of other concurrent psychotropic drugs such as mood stabilizers, antidepressant and benzodiazepines was not considered in this study. A further limitation is that our study was conducted in only psychiatric hospitals. Therefore, selection bias may exist and the results may not be widely applicable to the general population. Despite these limitations, this study provided the useful suggestion regarding the optimal tolerability dose ranges in the maintenance treatment based on the two year continuation rates in naturalistic pragmatic settings.

In our retrospective multicenter study of 2-year treatment continuation after hospital discharge, the optimal tolerability dose range in the stabilization and maintenance treatment for patients with schizophrenia and related psychotic disorders was suggested to be 0.5–5.0 mg per day for RIS and 2.5–30 mg per day for OLZ. Although the time to treatment discontinuation significantly favored OLZ over RIS in the total study population, RIS used in the optimal tolerability dose range was comparable with OLZ. Therefore, RIS dosage in long-term maintenance treatment should be given more attention.

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