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REGULAR RESEARCH ARTICLE

Clozapine Treatment Is Associated With Higher Prescription Rate of Antipsychotic Monotherapy and Lower Prescription Rate of Other Concomitant Psychotropics: A Real-World Nationwide Study

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Abstract

Background: Although clozapine is effective for treatment-resistant schizophrenia (TRS), the rate of clozapine prescription is still low. Whereas antipsychotic monotherapy is recommended in clinical practice guidelines, the rate of antipsychotic polypharmacy is still high. There is little evidence on whether a clozapine prescription influences changes in the rate of monotherapy and polypharmacy, including antipsychotics and other psychotropics. We therefore hypothesized that the rate of antipsychotic monotherapy in patients with TRS who were prescribed clozapine would be higher than that in patients with schizophrenia who were not prescribed clozapine.

Methods: We assessed 8306 patients with schizophrenia nationwide from 178 institutions in Japan from 2016 to 2019. We analyzed the psychotropic prescription data at discharge in patients diagnosed with TRS and with no description of TRS (ND-TRS) based on the diagnosis listed in the discharge summary.

Results: The rate of antipsychotic monotherapy in the TRS with clozapine group (91.3%) was significantly higher than that in the TRS without clozapine group (45.9%; $P < 2.0 \times 10^{-16}$) and the ND-TRS without clozapine group (54.7%; $P < 2.0 \times 10^{-16}$). The rate of antipsychotic monotherapy without any other concomitant psychotropics in the TRS with clozapine group (26.5%) was significantly higher than that in the TRS without clozapine group (12.6%; $P = 1.1 \times 10^{-6}$) and the ND-TRS without clozapine group (17.0%; $P = 5.9 \times 10^{-6}$).

Conclusions: Clozapine prescription could be associated with a high rate of antipsychotic monotherapy. Patients will benefit from the correct diagnosis of TRS and thus from proper clozapine prescription.

Significance Statement

Clozapine is effective for treatment-resistant schizophrenia (TRS). However, the rate of clozapine prescription is low, and the rate of polypharmacy of psychotropics, including antipsychotics, is high in many countries. This real-world nationwide study revealed that the prescription of clozapine had almost no occurrence of antipsychotic polypharmacy compared with TRS and with no description of TRS without clozapine. Furthermore, the prescription of clozapine was associated with a higher prescription rate of antipsychotic monotherapy without other concomitant psychotropics than other groups. This may be associated with a reduction in the risks of psychotropic polypharmacy and may play a key role in reducing long-term all-cause mortality. We found that the prescription of clozapine was associated with a high prescription rate of lithium in this study. There may be domestic standards for white blood cell count in Japan, and applying global standards may result in a gradual decrease in lithium prescriptions.

Keywords: Treatment-resistant schizophrenia, lithium, polypharmacy, guideline, EGUIDE

Introduction

Schizophrenia is a chronic and complex disease with a prevalence of approximately 0.5%–1.0% (Simeone et al., 2015). Many guidelines recommend antipsychotic monotherapy as a first-line treatment for schizophrenia (Galletly et al., 2016; Remington et al., 2017; Barnes et al., 2020; Keepers et al., 2020; Japanese Society of Neuropsychopharmacology, 2021). Antipsychotics are effective in improving symptoms of schizophrenia; however, approximately 30% of patients with schizophrenia do not respond

to antipsychotics and develop treatment-resistant schizophrenia (TRS) (Kane et al., 2019). TRS is defined as an insufficient response to or insufficient tolerance to antipsychotics (Yasui-Furukori et al., 2022).

Clozapine is the only licensed antipsychotic for TRS, and clozapine monotherapy is the recommended treatment for TRS in most guidelines (Galletly et al., 2016; Remington et al., 2017; Barnes et al., 2020; Keepers et al., 2020; Japanese Society of Neuropsychopharmacology, 2021). Compared with other antipsychotics, clozapine has significant efficacy for overall symptoms, positive symptoms, and negative symptoms in the short term and significant efficacy for positive symptoms in the long term (Siskind et al., 2016); however, clozapine can cause many adverse effects, such as hypersalivation, tachycardia, constipation, glucose intolerance, weight gain, seizure, myocarditis, and pneumonia (Barnes et al., 2020; Japanese Society of Neuropsychopharmacology, 2021; Leon et al., 2022). In particular, neutropenia, including agranulocytosis, is a serious adverse effect of clozapine that can cause death (Matsui et al., 2020). A recent meta-analysis of clozapine use reported that the prevalence of neutropenia was 3.8%, the prevalence of agranulocytosis was 0.9%, and the mortality due to agranulocytosis was 2.1% (Myles et al., 2018). As a countermeasure against these adverse effects, patients treated with clozapine are registered and monitored in many countries by the Clozaril Patient Monitoring System (CPMS) (Matsui et al., 2020). These adverse effects represent one of the reasons why the rate of clozapine prescription is still low in many countries (Bachmann et al., 2017).

Antipsychotic polypharmacy is sometimes used in daily practice, such as in patients with insufficient improvement on antipsychotic monotherapy. Antipsychotic polypharmacy is associated with an increased risk of many adverse effects, such as extrapyramidal symptoms (EPSs) and hyperprolactinemia (Barnes et al., 2020; Japanese Society of Neuropsychopharmacology, 2021). Because of these adverse effects, antipsychotic polypharmacy is not recommended in guidelines (Galletly et al., 2016; Remington et al., 2017; Barnes et al., 2020; Keepers et al., 2020; Japanese Society of Neuropsychopharmacology, 2021). Nevertheless, the rate of polypharmacy is still high in several countries (Yang et al., 2018; Toto et al., 2019; Ayenew et al., 2021). We started the Effectiveness of Guidelines for Dissemination and Education (EGUIDE) Psychiatric Treatment Project in 2016. The purpose of the EGUIDE project was the dissemination of guidelines for the treatment of schizophrenia and major depressive disorder through educational programs. Furthermore, we investigated the effectiveness of our educational programs (Takaesu et al., 2019; Numata et al., 2021) as well as real-world prescribing patterns and treatment styles associated with nonadherence to the guidelines by assessing prescription rates at discharge for inpatients with schizophrenia or major depressive disorder (Ichihashi et al., 2020; Iida et al., 2020; Hashimoto et al., 2021). Regarding TRS, we reported that institutions with a low TRS examination rate had a low clozapine prescription rate (Yasui-Furukori et al., 2022).

To our knowledge, there is little real-world evidence regarding whether the prescription rates of monotherapy and polypharmacy, including not only antipsychotics but also other psychotropics, differed between patients with TRS who were and were not prescribed clozapine. We hypothesized that the prescription rate of monotherapy for patients with TRS who were prescribed clozapine would be higher than that for patients with schizophrenia who were not prescribed clozapine, and we investigated the characteristics of prescribed pharmacotherapy at discharge between these groups.

METHODS

Patients

This study was a continuous, nationwide, cross-sectional study. We performed this study as part of the previously reported EGUIDE project (Takaesu et al., 2019; Iida et al., 2020; Hashimoto et al., 2021; Numata et al., 2021; Furihata et al., 2022; Yasui-Furukori et al., 2022). We recruited psychiatrists beginning in October 2016. All participants provided written informed consent after the chief researcher had fully explained the procedures at the institution. We gathered the medical record information of patients at each institution with opt-out consent. Ethical approval was obtained from the ethics committees of the National Center of Neurology and Psychiatry (B2020-106) and each participating university, hospital, and clinic. The study procedures were conducted according to the Declaration of Helsinki. The protocol of this study was registered in the University Hospital Medical Information Network registry (UMIN000022645).

We gathered data from each participating institution from April to September of each year from 2016 to 2019 using a standardized data collection method in which participating institutions' medical records were checked and the data were manually entered into an Excel sheet. The data manager then double-checked the data. We gathered the data of 8306 patients diagnosed with schizophrenia at discharge from 178 institutions. We recorded all types and doses of prescribed psychotropics, such as antipsychotics, antidepressants, anti-Parkinson drugs, hypnotics and anxiolytics, mood stabilizers/antiepileptics, and other types of drugs, at both admission and discharge, as we reported previously (Hashimoto et al., 2021; Furihata et al., 2022). We calculated the dose of psychotropics using psychotropic dose equivalence, such as the chlorpromazine equivalent, imipramine equivalent, biperiden equivalent, and diazepam equivalent (Inada and Inagaki, 2015). We also recorded information on the diagnosis at discharge, modified electroconvulsive therapy during each hospitalization, and the number of rehospitalizations for the patients. We defined lithium, sodium valproate, carbamazepine, and lamotrigine as mood stabilizers in this study because they were approved as mood stabilizers in Japan. In this study, we included patients who were prescribed antipsychotics at discharge from their first hospitalization for schizophrenia during the data collection period.

Finally, we analyzed a total of 7186 patients from 177 institutions. We show the characteristics of the patients in Table 1.

Procedure

The definition of TRS of the Clozapine Appropriate Use Committee in Japan was applied in this study. An insufficient response was defined when symptoms did not respond to more than 2 adequate doses of antipsychotic therapy (i.e., >600 mg of chlorpromazine equivalent per day) (Inada and Inagaki, 2015), including more than one of the atypical antipsychotics for at least 4 weeks (Yasui-Furukori et al., 2022), for adequate periods of time with adequate medication adherence. Insufficient tolerance was defined when more than 2 types of atypical antipsychotics were taken as monotherapy, but the dose of any of the antipsychotics could not be increased to an adequate dose because of the occurrence of adverse effects, such as EPSs (Matsui et al., 2020).

Table 1. Characteristics of Patients

Variables	TRS with clozapine	TRS without clozapine	ND-TRS without clozapine	P^1	P^2	P^3
n	426	414	6346			
Female (%)	n = 236 (55.4)	n = 235 (56.8)	n = 3465 (54.6)	1.0	1.0	1.0
Age (y)	41.6 (11.8)	45.8 (14.3)	46.2 (15.8)	1.4×10^{-4}	1.1×10^{-8}	1.0
Prescription clozapine at admission (%)	n = 189 (44.4)	n = 8 (1.9)	n = 7 (0.1)	$< 2.0 \times 10^{-16}$	$< 2.0 \times 10^{-16}$	2.4×10^{-6}
Mean dose of clozapine at admission (mg/d)[4]	364.6 (175.6)	370.3 (168.2)	332.1 (192.1)	1.0	1.0	1.0
Electroconvulsive therapy during hospitalization (%)	n = 36 (8.5)	n = 100 (24.2)	n = 264 (4.2)	1.8×10^{-9}	4.1×10^{-4}	$< 2.0 \times 10^{-16}$

Abbreviations: ND-TRS, no description of TRS; TRS, treatment-resistant schizophrenia. Values are expressed as the mean (SD) except for (%). Fisher's exact test or the Mann–Whitney U test was adjusted by Bonferroni's correction for post hoc analyses, and $P < 6.2 \times 10^{-4}$ (0.05/81) was defined as significant.
[1]Comparison between the TRS with clozapine and TRS without clozapine groups using the Mann–Whitney U test or Fisher's exact test with Bonferroni correction.
[2]Comparison between the TRS with clozapine and ND-TRS without clozapine groups using the Mann–Whitney U test or Fisher's exact test with Bonferroni correction.
[3]Comparison between the TRS without clozapine and ND-TRS without clozapine groups using the Mann–Whitney U test or Fisher's exact test with Bonferroni correction.
[4]The mean dose of clozapine in patients for whom clozapine was prescribed at admission.

Patients with TRS were those for whom the diagnosis at discharge was listed as TRS in the discharge summary. Patients without TRS listed in the discharge summary were classified as having no description of TRS (ND-TRS) because we could not determine whether the possibility of TRS was considered for each patient. We analyzed whether patients were prescribed clozapine at discharge. All patients prescribed clozapine at discharge had been diagnosed with TRS. We compared the data of patients with TRS who were prescribed clozapine, patients with TRS who were not prescribed clozapine, and patients with ND-TRS who were not prescribed clozapine.

In this study, we defined antipsychotic monotherapy as the prescription of a single antipsychotic regardless of concomitant use of other psychotropics, and we defined psychotropic monotherapy as the prescription of a single antipsychotic without concomitant use of other psychotropics.

We compared the prescription rate of antipsychotic monotherapy and the dose of antipsychotics among the 3 groups, and we compared the mean number of types of psychotropics prescribed and the prescription rate of psychotropic monotherapy among the 3 groups. In addition, we compared the prescription rate and the prescribed dose of other psychotropics, such as anti-Parkinson drugs, antidepressants, anxiolytics, and hypnotics, and each mood stabilizer among the 3 groups.

Statistical Analysis

We performed statistical analysis with SPSS 22.0 software (IBM Co., Armonk, NY, USA) and EZR 1.54 software (Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria) and a modified version of R commander designed to add statistical functions for biostatistics (Kanda, 2013). We used the Shapiro–Wilk test as a test of normality. To compare the TRS with clozapine group, TRS without clozapine group, and ND-TRS without clozapine group, Fisher's exact test was used for categorical variables (such as sex, prescription rate of monotherapy, prescription rate of electroconvulsive therapy, and prescription rate of each psychotropic), the Kruskal–Wallis test was used for continuous and ordered variables (such as age, number of types of psychotropics prescribed and dose of each psychotropic prescribed), and $P < 1.9 \times 10^{-3}$ (0.05/27) was considered statistically significant. Then, Fisher's exact test and the Mann–Whitney U test were adjusted by Bonferroni's correction for post hoc analyses, and $P < 6.2 \times 10^{-4}$ (0.05/81) was defined as significant. The lower limit of detection of EZR was 2.0×10^{-16}. Descriptive statistics are expressed as the mean ± SD.

RESULTS

Patient Characteristics

The number of patients was 426 in the TRS with clozapine group, 414 in the TRS without clozapine group, and 6346 in the ND-TRS without clozapine group, and there was no significant sex difference among the groups (Table 1).

Prescription Rate of Antipsychotic Monotherapy and Psychotropic Monotherapy

We show the prescription rates of psychotropics at discharge in Table 2. The prescription rate of antipsychotic monotherapy in the TRS with clozapine group (91.3%) was significantly higher than that in the TRS without clozapine group (45.9%; $P < 2.0 \times 10^{-16}$) and the ND-TRS without clozapine group (54.7%; $P < 2.0 \times 10^{-16}$) (Fig. 1).

The mean number of all types of psychotropics prescribed in the TRS with clozapine group (2.5 ± 1.3/d) was significantly lower than that in the TRS without clozapine group (3.8 ± 1.9/d; $P < 2.0 \times 10^{-16}$) and the ND-TRS without clozapine group (3.4 ± 1.9/d; $P < 2.0 \times 10^{-16}$) (Fig. 2A). The prescription rate of psychotropic monotherapy in the TRS with clozapine group (26.5%) was significantly higher than that in the TRS without clozapine group (12.6%; $P = 1.1 \times 10^{-6}$) and the ND-TRS without clozapine group (17.0%; $P = 5.9 \times 10^{-6}$) (Fig. 2B).

Prescription Rates of Anti-Parkinson Drugs, Antidepressants, Anxiolytics and Hypnotics, and Mood Stabilizers, Especially Lithium

The prescription rate of anti-Parkinson drugs in the TRS with clozapine group (11.0%) was significantly lower than that in the TRS without clozapine group (35.3%; $P < 2.0 \times 10^{-16}$) and the ND-TRS without clozapine group (29.5%; $P < 2.0 \times 10^{-16}$) (Table 2). The prescription rate of anxiolytics and hypnotics in the TRS

Table 2. Prescription of Psychotropics at Discharge

Variables	TRS with clozapine	TRS without clozapine	ND-TRS without clozapine	P^2	P^3	P^4
Mean dose of clozapine at discharge (mg/d)	344.8 (163.9)					
Antipsychotic monotherapy (%)	n = 389 (91.3)	n = 190 (45.9)	n = 3469 (54.7)	$< 2.0 \times 10^{-16}$	$< 2.0 \times 10^{-16}$	1.9×10^{-3}
Mean dose of total antipsychotics (mg/d)[1]	716.4 (357.6)	886.6 (591.2)	687.8 (464.8)	1.4×10^{-3}	1.8×10^{-3}	2.8×10^{-12}
Mean no. of all types of psychotropics (n/d)	2.5 (1.3)	3.8 (1.9)	3.4 (1.9)	$< 2.0 \times 10^{-16}$	$< 2.0 \times 10^{-16}$	1.4×10^{-5}
Antipsychotic monotherapy without concomitant other psychotropics (%)	n = 113 (26.5)	n = 52 (12.6)	n = 1079 (17.0)	1.1×10^{-6}	5.9×10^{-6}	5.2×10^{-2}
Prescription rate of anti-Parkinson drugs (%)	n = 47 (11.0)	n = 146 (35.3)	n = 1870 (29.5)	$< 2.0 \times 10^{-16}$	$< 2.0 \times 10^{-16}$	4.4×10^{-2}
Prescription rate of anxiolytic and hypnotics (%)	n = 213 (50.0)	n = 295 (71.3)	n = 4218 (66.5)	8.8×10^{-10}	4.8×10^{-11}	1.4×10^{-1}
Prescription rate of antidepressants (%)	n = 23 (5.4)	n = 39 (9.4)	n = 566 (8.9)	1.0×10^{-1}	3.8×10^{-2}	1.0
Prescription rate of mood stabilizers (%)	n = 163 (38.3)	n = 106 (25.6)	n = 1506 (23.7)	2.6×10^{-4}	3.5×10^{-10}	1.0
Prescription rate of lithium (%)	n = 118 (27.7)	n = 21 (5.1)	n = 340 (5.4)	$< 2.0 \times 10^{-16}$	$< 2.0 \times 10^{-16}$	1.0
Prescription rate of mood stabilizers except lithium (%)	n = 60 (14.1)	n = 92 (22.2)	n = 1265 (19.9)	6.9×10^{-3}	8.9×10^{-3}	7.8×10^{-1}

Abbreviations: ND-TRS, no description of TRS; TRS, treatment-resistant schizophrenia. Values are expressed as the mean (SD) except for (%). Fisher's exact test or the Mann–Whitney U test was adjusted by Bonferroni's correction for post hoc analyses, and $P < 6.2 \times 10^{-4}$ (0.05/81) was defined as significant.
[1]Presented as chlorpromazine equivalent.
[2]Comparison between the TRS with clozapine and TRS without clozapine groups using the Mann–Whitney U test or Fisher's exact test with Bonferroni correction.
[3]Comparison between the TRS with clozapine and ND-TRS without clozapine groups using the Mann–Whitney U test or Fisher's exact test with Bonferroni correction.
[4]Comparison between the TRS without clozapine and ND-TRS without clozapine groups using the Mann–Whitney U test or Fisher's exact test with Bonferroni correction.

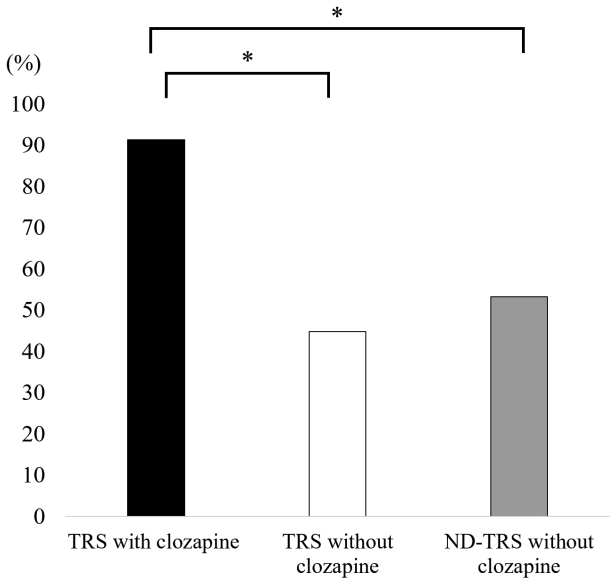

Figure 1. The prescription rate of antipsychotic monotherapy at discharge. The prescription rate of antipsychotic monotherapy at discharge in the treatment-resistant schizophrenia (TRS) with clozapine group was significantly higher than that in the other groups. Fisher's exact test adjusted by Bonferroni correction. *$P < 6.2 \times 10^{-4}$ was defined as significant. ND-TRS, no description of TRS.

with clozapine group (50.0%) was significantly lower than that in the TRS without clozapine group (71.3%; $P = 8.8 \times 10^{-10}$) and the ND-TRS without clozapine group (66.5%; $P = 4.8 \times 10^{-11}$) (Table 2). There was no significant difference in the prescription rate of antidepressants among the groups (Table 2). There was no significant difference in the prescribed mean doses of anti-Parkinson drugs, antidepressants, or anxiolytics and hypnotics among the groups (supplementary Table 1). The prescription rate of mood stabilizers in the TRS with clozapine group (38.3%) was significantly higher than that in the TRS without clozapine group (25.6%; $P = 2.6 \times 10^{-4}$) and the ND-TRS without clozapine group (23.7%; $P = 3.5 \times 10^{-10}$) (Table 2). The prescription rate of lithium in the TRS with clozapine group (27.7%) was significantly higher than that in the TRS without clozapine group (5.1%; $P < 2.0 \times 10^{-16}$) and the ND-TRS without clozapine group (5.4%; $P < 2.0 \times 10^{-16}$) (Table 2). There was no significant difference in the prescription rate of mood stabilizers except lithium among the groups (Table 2). There was no significant difference in the mean dose of lithium prescribed among the groups (supplementary Table 1).

Discussion

The main results of this study were that the prescription rates of antipsychotic monotherapy and psychotropic monotherapy in the TRS with clozapine group were significantly higher than those in the other groups. The prescription rates of other psychotropics in the TRS with clozapine group were significantly lower and the prescription rate of lithium was significantly higher than those in the other groups.

To the best of our knowledge, we are the first to reveal that the TRS with clozapine group had almost no prescription of antipsychotic polypharmacy compared with both the TRS without clozapine group and the ND-TRS without clozapine group in a large nationwide sample. These findings are supported by a recent small study (n = 62) reporting that the prescription rate of antipsychotic monotherapy was significantly increased after the prescription of clozapine (Akamine et al., 2021). A recent meta-analysis reported that compared with antipsychotic monotherapy, antipsychotic polypharmacy in schizophrenia did not show efficacy in high-quality, double-blinded, randomized controlled trials (Galling et al., 2017). This

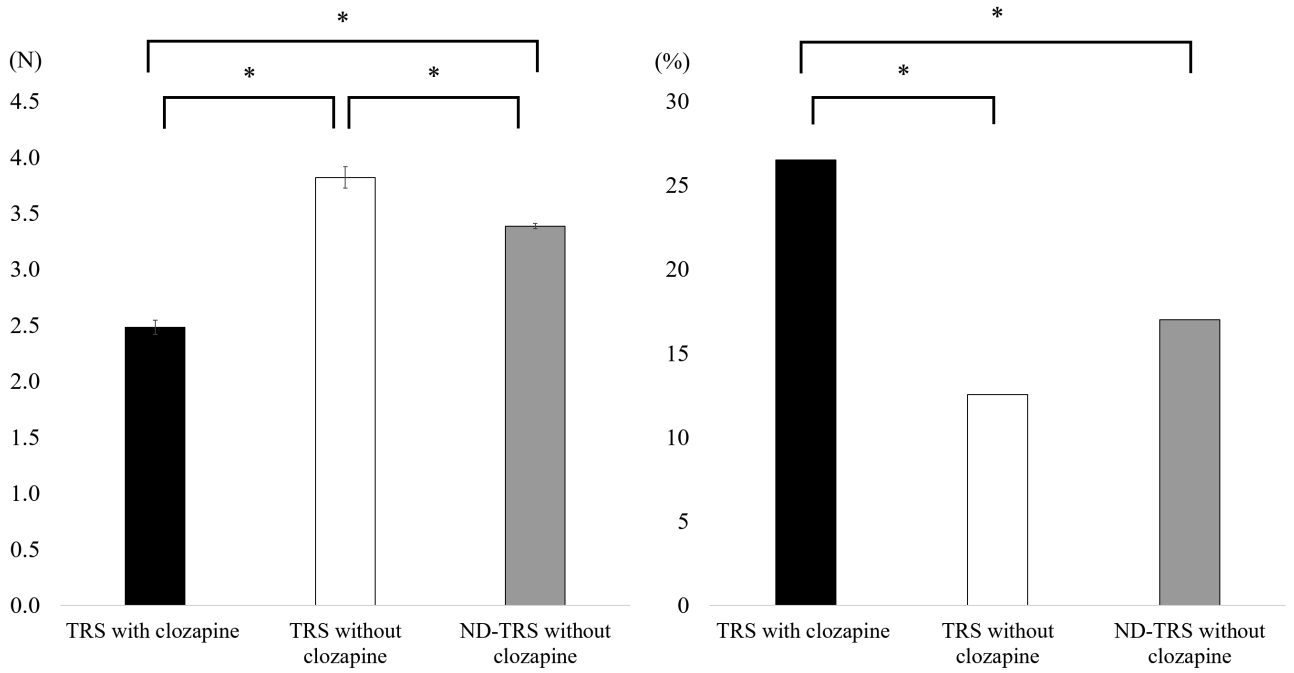

Figure 2. The mean number of psychotropics prescribed and the prescription rate of antipsychotic monotherapy without other concomitant psychotropics at discharge. (A) The mean number of all types of psychotropics prescribed at discharge in the treatment-resistant schizophrenia (TRS) with clozapine group was significantly lower than that in the other groups. On the other hand, the mean number of all types of psychotropics prescribed at discharge in the TRS without clozapine group was significantly higher than that in the other groups. (B) The prescription rate of antipsychotic monotherapy without other concomitant psychotropics in the TRS with clozapine group was significantly higher than that in the other groups. Error bars show the mean (SE). The Mann–Whitney U test or Fisher's exact test adjusted by Bonferroni correction. *$P < 6.2 \times 10^{-4}$ was defined as significant. ND-TRS, no description of TRS.

meta-analysis also reported that aripiprazole for augmentation was associated with prolactin reduction and weight loss. In addition, a nationwide cohort study reported that as antipsychotic polypharmacy, clozapine with aripiprazole was associated with the lowest risk of hospitalization in patients with schizophrenia, followed by clozapine monotherapy (Tiihonen et al., 2019), although there was a lack of evidence on whether polypharmacy with more than 3 types of antipsychotics was effective. Future studies on aripiprazole augmentation with clozapine are needed to clarify the improvements to adverse effects of clozapine, such as weight gain. Although it is unclear what treatment options are prioritized for TRS, a 12-month follow-up study in the United Kingdom reported that the prescription rate of clozapine in patients with TRS was only 2.4%, but the prescription rate of antipsychotic polypharmacy, instead of clozapine, in patients with TRS was approximately 46.9%; the prescription rate of >3 antipsychotics was approximately 9.1% (Stokes et al., 2020). In Japan, as in the United Kingdom, there is a strong tendency to choose multiple antipsychotic medications for the treatment of TRS (Yang et al., 2018; Yasui-Furukori et al., 2022). This could be for several reasons. One reason is that there are still few clozapine-licensed facilities and clozapine-licensed doctors in Japan because clozapine became available in 2009, later than in other countries. The second reason is that polypharmacy in Japan may be related to the traditional oriental herbal therapeutic concept in which a mixture of many ingredients is the best prescription (Inada and Inagaki, 2015). The other reason is that there may still be some psychiatrists who do not sufficiently utilize evidence-based clinical practice guidelines for treatment. We need to disseminate the guidelines for the treatment of schizophrenia through educational programs such as the EGUIDE project.

Antipsychotic polypharmacy may be considered in some clinically limited situations; however, clozapine monotherapy for TRS should at least be attempted before antipsychotic polypharmacy is prescribed.

We also revealed for the first time, to our knowledge, that there was a significantly higher prescription rate of psychotropic monotherapy in the TRS with clozapine group than in the TRS without clozapine group and in the ND-TRS without clozapine group. In addition, significantly lower prescription rates of anti-Parkinson drugs and anxiolytics and hypnotics in the TRS with clozapine group than in the TRS without clozapine and ND-TRS without clozapine groups were found, which is in line with a previous study reporting that the prescription rates of benzodiazepines and anti-Parkinson drugs were significantly decreased after the prescription of clozapine (Akamine et al., 2021). A recent meta-analysis reported that only clozapine treatment was significantly associated with a decrease in the prescription rate of anti-Parkinson drugs (Huhn et al., 2019). Continuous prescription of clozapine was shown to significantly reduce long-term all-cause mortality compared with continuous prescription of other antipsychotics (Vermeulen et al., 2018). Furthermore, many factors, such as an increase in the number of antipsychotics, anti-Parkinson drugs, and benzodiazepines prescribed, were associated with an increased risk of neuroleptic malignant syndrome (Guinart et al., 2021) and with potential risks, including drug-drug interactions (Yasui-Furukori and Shimoda, 2020). Although a previous study in Europe reported that the prescription rate of psychotropic polypharmacy increased from 2000 to 2015 and that 44.7% of patients received

more than 3 psychotropics, the prescription rate of clozapine did not change over time (Toto et al., 2019). These findings support the results of this study. Based on our findings and the findings of the literature mentioned above, an increase in the prescription of psychotropic monotherapy could be associated with a reduction in the risks of psychotropic polypharmacy and might play a key role in reducing long-term all-cause mortality associated with the prescription of clozapine.

We also found a higher prescription rate of lithium in the TRS with clozapine group than in the other groups. Although clozapine with concomitant lithium for augmentation is not recommended in guidelines (Barnes et al., 2020; Japanese Society of Neuropsychopharmacology, 2021), lithium is reported to lead to the proliferation of granulocytes, increase production of white blood cells (WBCs) and reduce the risk of neutropenia (Hager et al., 2002). In addition, lithium has widely been reported to prevent or treat neutropenia during clozapine treatment (Adityanjee, 1995; Boshes et al., 2001; Kanaan and Kerwin, 2006; Brunoni et al., 2008; Suraweera et al., 2014; Aydin et al., 2016), although concomitant lithium does not always prevent agranulocytosis (Valevski et al., 1993). Furthermore, there may be a domestic factor that would increase the concomitant use of lithium in this study. All Japanese clozapine users are also registered in the CPMS, but there are some differences between Japan and other countries (Nielsen et al., 2016; Myles et al., 2019; Matsui et al., 2020; Yasui-Furukori et al., 2022). The criteria for the initiation of clozapine treatment are stricter in Japan. The WBC count in Japan must be >4000/mm^3 compared with >3500/mm^3 in many other countries (Yasui-Furukori et al., 2022). Furthermore, leukopenia is defined as a WBC count <3000/mm^3, and this definition is higher than that in many other countries (e.g., <3500/mm^3) (Inada et al., 2018). However, applying global standards to the CPMS in Japan may result in a gradual decrease in lithium prescription.

In this study, the number of patients in the ND-TRS without clozapine group was much higher than the number of patients in the other groups. We previously reported that there was a significant correlation between the prescription rate of clozapine and the diagnosis rate of TRS (Yasui-Furukori et al., 2022). Beck reported that 56% of patients had been diagnosed with TRS, and 52% of patients who had been diagnosed with TRS had never been prescribed clozapine (Beck et al., 2019). Although the evidence for the efficacy of clozapine is strong (Siskind et al., 2016; Vermeulen et al., 2018; Huhn et al., 2019; Tiihonen et al., 2019), many TRS patients have not been prescribed clozapine (Bachmann et al., 2017). The correct diagnosis of TRS is a worldwide problem. Furthermore, previous studies reported that there were many barriers to using clozapine for TRS, such as adverse effects and the lack of knowledge and confidence of clinicians (Kelly et al., 2018; Farooq et al., 2019). In Japan, in addition to these barriers, there are Japan-specific barriers. One factor is the criteria of WBC count for the initiation of clozapine, which we described above. A second factor is that excessive caution is urged for diabetic patients taking clozapine in Japan. This can be because olanzapine and quetiapine, which have similar pharmacological profiles to clozapine, are contraindicated in diabetes patients in Japan. Furthermore, in Japan, patients must be hospitalized at the time of clozapine initiation. In addition, there are still insufficient numbers of clozapine-licensed facilities and clozapine-licensed doctors (Yasui-Furukori et al., 2022). These factors are Japan-specific barriers to clozapine use in Japan. Worldwide, we should consider education and emphasis on the importance of correctly diagnosing TRS and correctly prescribing clozapine.

This study has several limitations. First, this was a cross-sectional study, and we could not clarify the causal relationships between the prescription rate of clozapine and an increase in antipsychotic monotherapy. However, in this study, the sample size was relatively large, and we analyzed control data (i.e., data from the TRS without clozapine group). Second, there may be selection bias and sampling bias because, in this study, all participating institutions voluntarily cooperated, were not selected randomly, and did not include all patients within the study period. However, we standardized the method of data collection and gathered nationwide data from Japan. Because all inpatients during the sampling period were included, the sampling bias was low, although there was institutional bias. Third, we did not assess the clinical symptoms and severity of schizophrenia using rating scales such as the Positive and Negative Syndrome Scale or the Brief Psychiatric Rating Scale. Fourth, we could not assess why the TRS without clozapine group was not prescribed clozapine or why clozapine was not continued, such as due to inefficacy or severe adverse effects such as neutropenia. Further prospective clinical studies, including randomized controlled trials, are needed to clarify these causal relationships in detail. Fifth, the number of patients in the TRS groups was relatively small, and some TRS patients may have been included in the ND-TRS without clozapine group because we analyzed the data based on the medical records from each institution. Thus, we could not strictly distinguish whether schizophrenia that was not described as TRS was not TRS. However, the prescription rate of clozapine was much lower in Japan than in other countries; furthermore, we previously reported that the low prescription rate of clozapine was correlated with the low diagnosis rate of TRS (Yasui-Furukori et al., 2022). Hence, these data could reflect real-world evidence. Therefore, in the future, we should emphasize the importance of correctly diagnosing TRS to adequately prescribe clozapine, such as through educational programs like the EGUIDE project.

In conclusion, the findings from our analysis suggested that the prescription of clozapine for TRS could be the ideal antipsychotic therapy as indicated by the guidelines. Therefore, clinicians should appropriately diagnose TRS and constructively consider the prescription of clozapine for the treatment of TRS.

Supplementary Materials

Supplementary data are available at *International Journal of Neuropsychopharmacology (IJNPPY)* online.

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Interest Statement

The authors declare no conflicts of interest.

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