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The characteristics of discharge prescriptions including pro re nata psychotropic medications for patients with schizophrenia and major depressive disorder from the survey of the “Effectiveness of guidelines for dissemination and education in psychiatric treatment (EGUIDE)” project

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Abstract

Background: Several guidelines recommend monotherapy in pharmacotherapy for schizophrenia and major depressive disorder. The content of regular prescriptions has been reported in several studies, but not enough research has been conducted on the content of pharmacotherapy, including pro re nata (PRN) medications. The purpose of this study was to evaluate the content of pharmacotherapy, including PRN medications, and to clarify the relationship with regular prescriptions.

Methods: We used data from the “Effectiveness of Guidelines for Dissemination And Education in psychiatric treatment” (EGUIDE) project to investigate the presence or absence of PRN psychotropic medications at discharge for each drug category. We compared the PRN psychotropic prescription ratio at discharge by diagnosis for each drug category. The antipsychotic monotherapy ratio and no prescription ratio of other psychotropics for schizophrenia at discharge and the antidepressant monotherapy ratio and no prescription ratio of other psychotropics for

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major depressive disorder at discharge were calculated for each regular prescription, including PRN psychotropic medications, as quality indicators (QIs). Spearman's rank correlation test was performed for QI values of regular prescriptions and the QI ratio between regular prescriptions and prescriptions including PRN medications for each diagnosis.

Results: The PRN psychotropic prescription ratio at discharge was 28.7% for schizophrenia and 30.4% for major depressive disorder, with no significant differences by diagnosis. The prescription ratios of PRN antipsychotic medications and PRN antiparkinsonian medications were significantly higher for schizophrenia. The prescription ratios of PRN anxiolytic and hypnotic and PRN antidepressant medications were significantly higher for patients with major depressive disorder. For both schizophrenia and major depressive disorder, the QI was lower for discharge prescriptions, including PRN medications, than for regular prescriptions. QI values for regular prescriptions and the QI ratio were positively correlated.

Conclusions: Considering PRN psychotropic medications, the monotherapy ratio and no prescription ratio of other psychotropics at discharge decreased in pharmacotherapy for schizophrenia and major depressive disorder. A higher ratio of monotherapy and no prescription of other psychotropics on regular prescriptions may result in less concomitant use of PRN psychotropic medications. Further studies are needed to optimize PRN psychotropic prescriptions.

Keywords: Depression, EGUIDE, Pro re nata, Psychotropic, Schizophrenia

Background

Schizophrenia and major depressive disorder are serious chronic disorders that cause impaired social functioning [1, 2], and pharmacotherapy is an important part of their treatment. Several guidelines recommend monotherapy with antipsychotics for schizophrenia [3, 4] and monotherapy with antidepressants for major depressive

disorder [5–8]. The “Effectiveness of Guidelines for Dissemination and Education in psychiatric treatment” (EGUIDE) project is a nationwide multicenter study launched in Japan in 2016 [9]. The EGUIDE project is an educational program for psychiatrists on guidelines for schizophrenia and major depressive disorder, and the content of inpatient treatment is quantified as a quality indicator (QI) and evaluated over time [10–19]. A QI is an indicator for quality of care by assessing the structure, process, and result of medical care and helps to assess whether a patient's care is consistent with the evidence-based standard of care [20]. The results from the EGUIDE project show monotherapy rates at discharge and concomitant rates of other psychotropic medications as QIs of treatment [10, 11]. For example, the antipsychotic monotherapy ratio in the inpatient treatment of schizophrenia in Japan is approximately 60%, and the antidepressant monotherapy ratio in the inpatient treatment of major depressive disorder in Japan is approximately 60%. However, these QIs were calculated for regular prescriptions that are taken daily on a regular basis.

In the psychiatric field, pro re nata (PRN) psychotropic medications are often used “as needed” for psychiatric symptoms such as agitation and insomnia, in addition to regular pharmacotherapy. It has been reported that PRN psychotropic medications are prescribed to 70–90% of patients hospitalized for psychiatric disorders [21,

22]. Moreover, the study from the EGUIDE project reported that the PRN psychotropic prescription ratio was approximately 30% for inpatients with schizophrenia and major depressive disorder, even for discharge prescriptions [15]. Previous studies on the frequency of PRN psychotropic medication use have been limited to local settings, at a single or a few facilities, and to a wide range of psychiatric diagnoses. A study in an adolescent acute psychiatric ward reported that the average use of PRN psychotropic drugs was 0.35 times/day (standard deviation (SD)=0.60) [23]. In addition, a single-center study on 205 patients admitted for the treatment of schizophrenia reported that the use of PRN psychotropic drugs was 0–4.18 times/day, with a mean of 0.48 times/day (SD=0.73) [24]. These reports suggest that PRN psychotropic medication is a frequently used treatment. Therefore, QIs, such as the monotherapy ratio, should be evaluated not only for regular prescriptions but also for pharmacotherapies, including PRN psychotropic medications. There is no high-quality evidence on the effectiveness of PRN psychotropic medications, and PRN psychotropic drug use is based on clinical experience and habits [25]. Furthermore, it has been suggested that PRN psychotropic drug prescriptions are at risk of leading to polypharmacy and high-dose prescribing [15, 26, 27]. It has also been suggested that the use of PRN psychotropic medications may in fact prolong hospital stay and increase readmission rate [24]. Thus, PRN psychotropic

medications are widely used without sufficient evidence to recommend their use, and factors related to their prescription need to be clarified.

In this study, we aimed to reevaluate the pharmacotherapy of inpatients with schizophrenia and major depressive disorder at discharge in Japan, including the use of PRN psychotropic drugs. The data from the EGUIDE project were used to examine the content of prescriptions that included PRN psychotropic drugs for each drug category.

Methods

This study was a continuous, nationwide, cross-sectional study. This study was approved by the ethics committees of the National Center for Neuropsychiatry and Neurology (approval number B2022-004) and the participating EGUIDE sites. This study was conducted in compliance with the Declaration of Helsinki and its amendments. The study protocol was registered in the University Hospital Medical Information Network Registry (UMIN000022645). We created a dataset of the treatment at discharge between April and September of each year from 2016 to 2020 from the 240 hospitals that participated in the EGUIDE project. Using this dataset, a pharmacotherapy survey was conducted, including PRN psychotropic prescriptions, on patients with diagnoses of schizophrenia and major depressive disorder discharged from each facility between April and September of the first year of participation in the EGUIDE project. Patients were able to opt out of the purpose and procedures of the study and refuse study participation. We gathered the medical record information of patients at each institution with opt-out consent. Diagnoses of schizophrenia and major depressive disorder were made according to the Diagnostic and Statistical Manual of Mental Disorders 5th edition [28]. For patients who were hospitalized multiple times, only the treatment of the first hospitalization was included. Patients whose discharge prescriptions were unknown were excluded from the study. In addition, we excluded patients with schizophrenia who did not have regular prescriptions of antipsychotics at discharge and patients with major depressive disorder who did not have regular prescriptions of antidepressants at discharge. Prescription data of 2498 patients who were diagnosed with schizophrenia and 1022 patients who were diagnosed with major depressive disorder (MDD) were gathered from 97 institutions.

We investigated the age at discharge and sex of the patients and the presence or absence of PRN psychotropic prescriptions at discharge for each psychotropic drug category. We performed t-test and χ^2 tests on the

association between each diagnosis and age; and sex. We then performed χ^2 tests on the association between each diagnosis and PRN psychotropic prescription ratio at discharge for each psychotropic drug category.

In addition, QI values for regular prescriptions at discharge and for prescriptions including PRN psychotropic drugs at discharge were calculated. Additional file 1: Tables S1 and S2 show the specifics of QIs in this study. Furthermore, the ratio of QI values for prescriptions, including PRN medications, to QI values for regular prescriptions was calculated. Spearman's rank correlation test was performed on QI values for regular prescriptions and the QI ratio between regular prescriptions and prescriptions including PRN medications for each diagnosis. Because we performed the analysis 7 times throughout this study, the significance level of 5% was set at 5.5×10^{-3} (0.05/9) with Bonferroni correction due to multiple testing. All statistical analyses were performed using IBM SPSS Statistics 26.0 (IBM Co., Armonk, NY, USA) and Excel (Microsoft, Redmond, WA, USA).

Results

The PRN psychotropic prescription ratio at discharge for each drug category and demographic data for the patients are shown in Table 1. There was no difference in the PRN psychotropic prescription ratio between schizophrenia and MDD. For each psychotropic category, the PRN antipsychotic prescription ratio was significantly higher for schizophrenia than for MDD ($p = 4.9 \times 10^{-9}$, $df(1) = 34.22$). The PRN anxiolytic and hypnotic prescription ratio was significantly higher for MDD than for schizophrenia ($p = 2.0 \times 10^{-3}$, $df(1) = 9.51$). The PRN antidepressant prescription ratio was significantly higher for MDD than for schizophrenia ($p = 9.4 \times 10^{-6}$, $df(1) = 19.63$). The PRN antiparkinsonian prescription ratio was significantly higher for schizophrenia than for MDD ($p = 1.5 \times 10^{-4}$, $df(1) = 14.42$).

The PRN prescription ratios by drug category for patients with PRN psychotropic prescriptions at discharge are shown in Additional file 1: Table S3. Among patients with schizophrenia, more than half had PRN antipsychotic prescriptions and PRN anxiolytic and hypnotic prescriptions, whereas less than 10% had PRN antidepressant prescriptions and PRN antiparkinsonian prescriptions. Among patients with MDD, more than half had PRN anxiolytic and hypnotic prescriptions, whereas less than 10% had PRN antidepressant prescriptions and PRN antiparkinsonian prescriptions.

In addition, Tables 2 and 3 show the QI values for regular prescriptions, prescriptions including

PRN medications, and the QI ratio between regular prescriptions and prescriptions including PRN medications.

A positive correlation was found between QI values for regular prescriptions and the QI ratio for schizophrenia [$r_s=0.965$, $p=1.8 \times 10^{-3}$] (Fig. 1A). A positive correlation was also found between QI values for regular

prescriptions and the QI ratio for MDD [$r_s=0.963$, $p=2.0 \times 10^{-3}$] (Fig. 1B).

Discussion

This is the first study to investigate PRN psychotropic prescriptions at discharge in inpatient treatment of schizophrenia and MDD by drug category. PRN

Table 1 Demographic and clinical data

| | Schizophrenia (n = 2498) | Major depressive disorder (n = 1022) | p-value |
|---|--------------------------|--------------------------------------|-----------------------|
| Age (mean ± SD) | 45.63 ± 15.60 | 58.65 ± 17.26 | 1.1×10^{-98} |
| Sex (female, n, %) | 1354 (54.2) | 666 (65.2) | 2.4×10^{-9} |
| PRN psychotropic prescription ratio (n, %) | 718 (28.7) | 311 (30.4) | 0.32 |
| PRN antipsychotic prescription ratio (n, %) | 443 (17.7) | 101 (9.9) | $*4.9 \times 10^{-9}$ |
| PRN anxiolytic and hypnotic prescription ratio (n, %) | 465 (18.6) | 237 (23.2) | $*2.0 \times 10^{-3}$ |
| PRN antidepressant prescription ratio (n, %) | 13 (0.5) | 22 (2.2) | $*9.4 \times 10^{-6}$ |
| PRN antiparkinsonian prescription ratio (n, %) | 55 (2.2) | 4 (0.4) | $*1.5 \times 10^{-4}$ |

As the level of significance, $p < 5.5 \times 10^{-3}$, was within the 5% significance level, based on the Bonferroni correction, it was considered in the multiplicity of the tests

PRN pro re nata, SD standard deviation

* $p < 0.05$, after the Bonferroni correction

Table 2 QI values for patients with schizophrenia

| QI (n = 2498) | QI values for regular prescriptions | QI values for prescriptions including PRN | QI ratio between regular prescriptions and prescriptions including PRN |
|---|-------------------------------------|---|--|
| Antipsychotics monotherapy ratio (n, %) | 1404 (56.2) | 1266 (50.7) | 0.902 |
| Antipsychotics monotherapy ratio without any other psychotropics (n, %) | 429 (17.2) | 344 (13.8) | 0.802 |
| No prescription ratio of anxiolytics and hypnotics (n, %) | 847 (33.9) | 727 (29.1) | 0.858 |
| No prescription ratio of antidepressants (n, %) | 2295 (91.9) | 2292 (91.8) | 0.999 |
| No prescription ratio of mood stabilizers and antiepileptics (n, %) | 1857 (74.3) | 1857 (74.3) | 1.00 |
| No prescription ratio of antiparkinsonian drugs (n, %) | 1755 (70.3) | 1732 (69.3) | 0.987 |

PRN pro re nata, QI quality indicator

Table 3 QI values for patients with major depressive disorder

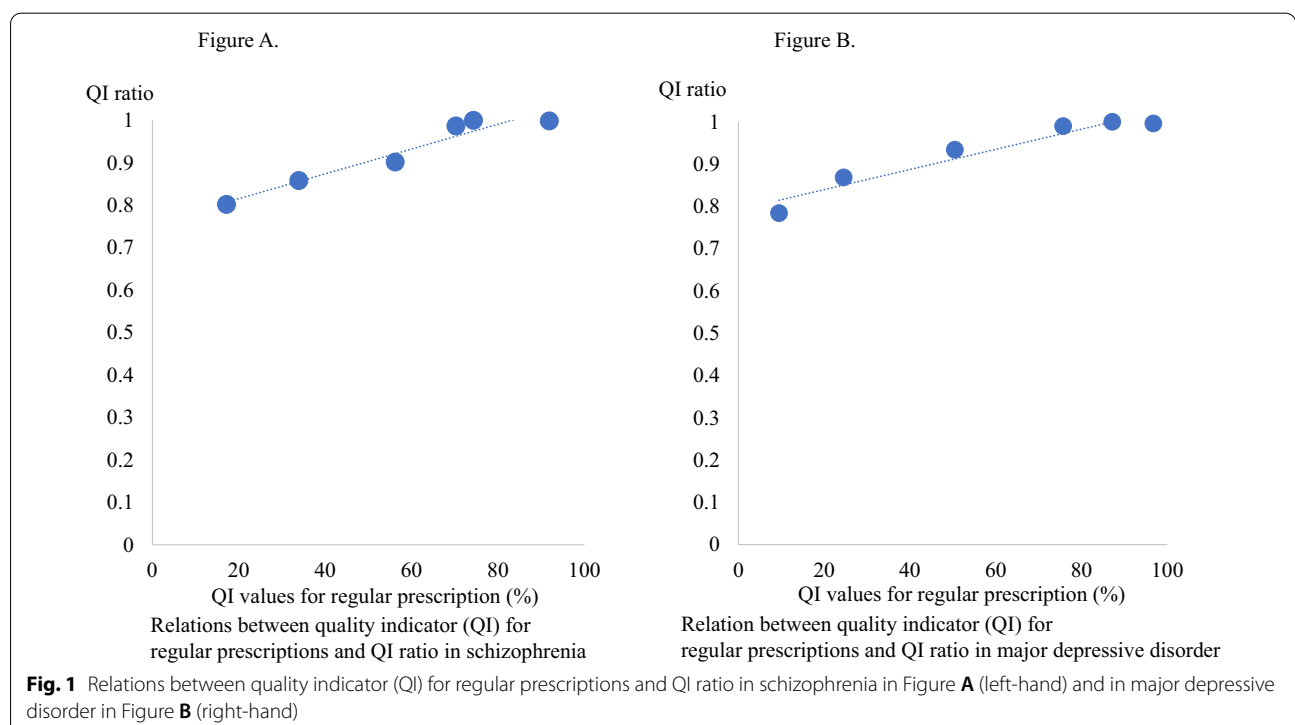
| QI (n = 1022) | QI values for regular prescriptions | QI values for prescriptions including PRN | QI ratio between regular prescriptions and prescriptions including PRN |
|---|-------------------------------------|---|--|
| Antidepressant monotherapy ratio (n, %) | 774 (75.7) | 766 (75.0) | 0.990 |
| Antidepressant monotherapy ratio without any other psychotropics (n, %) | 97 (9.5) | 76 (7.4) | 0.784 |
| No prescription ratio of anxiolytics and hypnotics (n, %) | 251 (24.6) | 218 (21.3) | 0.869 |
| No prescription ratio of antipsychotics (n, %) | 516 (50.5) | 482 (47.2) | 0.934 |
| No prescription ratio of mood stabilizers and antiepileptics (n, %) | 891 (87.2) | 891 (87.2) | 1.00 |
| No prescription ratio of antiparkinsonian drugs (n, %) | 999 (96.8) | 985 (96.4) | 0.996 |

PRN pro re nata, QI quality indicator

psychotropic medications were prescribed at discharge to 28.7% of patients with schizophrenia and 30.4% of patients with MDD. There were no significant differences in the PRN psychotropic prescription ratio by diagnosis. On the other hand, the PRN antipsychotic prescription ratio and PRN antiparkinsonian prescription ratio were significantly higher for patients with schizophrenia than for those with MDD. The PRN anxiolytic and hypnotic prescription ratio and PRN antidepressant prescription ratio were significantly higher for patients with MDD than for patients with schizophrenia. This difference suggests that PRN psychotropic medications in certain drug categories are more likely to be prescribed depending on the diagnosis. Generally, antipsychotics are prescribed for SZ and antidepressants for MDD [3–8]. Therefore, it is obvious that the kind of prescribed medication depends on the diagnosis. It has been reported that PRN antipsychotic medications aimed at calming acute agitation are more common for patients with schizophrenia [26]. For this reason, PRN antipsychotic prescriptions might be more common for patients with schizophrenia than for those with MDD. PRN antidepressant medications were prescribed at low rates for both schizophrenia and MDD, possibly because antidepressants have fewer sedative effects [29, 30] and take time to develop their effects [31]. In addition, the guidelines for patients with SZ do not recommend prescribing antidepressants for SZ [3, 4]. Nevertheless,

PRN antidepressants were prescribed to some SZ patients in this study. Therefore, education and dissemination of guideline-based treatment is required for PRNs as well. Since anticholinergics are widely used for the treatment and prevention of extrapyramidal symptoms produced by antipsychotics, especially acute dystonia [32], the PRN antiparkinsonian prescription ratio may have been higher for schizophrenia than for MDD. Insomnia is a frequent symptom in both schizophrenia and MDD [33–35] and may be one reason for the high PRN anxiolytic and hypnotic prescription ratio for both disorders.

In this study, the QI values decreased with the inclusion of PRN prescriptions for all QIs except no prescription ratio of mood stabilizers and antiepileptics. A previous study suggested that the polypharmacy ratio increases when PRN prescriptions are included [36], and a similar trend might be observed in this study. Furthermore, a positive correlation was found between QI values for regular prescriptions and the QI ratio for both schizophrenia and MDD. This means that higher QI values for regular prescriptions indicate a smaller reduction in QI values for prescriptions including PRN medications. Higher QI values for regular prescriptions indicate that there are fewer concomitant medications in that drug category on regular prescriptions, and a smaller reduction in QI values for prescriptions including PRN medications indicates fewer PRN prescriptions in that drug category. In other words, these results suggest



that drug categories that are less likely to be used in combination on regular prescriptions are less likely to be prescribed as PRN medications. Despite several guidelines [3–8] recommending monotherapy for the treatment of schizophrenia and MDD, in clinical practice, both schizophrenia and MDD are treated with multiple psychotropics [37–39]. PRN psychotropic prescriptions are habitually practiced without sufficient evidence [25], and the need for guidelines on the proper use of PRN medications has been pointed out [24, 40, 41]. The results of this study suggest that promoting monotherapy as recommended in the guidelines, taking PRN medications into consideration, may lead to a reduction in PRN psychotropic prescriptions, which in turn may lead to an improvement in the QI value of each drug category. It has also been noted that PRN psychotropic medications for hospitalized patients may continue to be prescribed without regular monitoring of their use, and the need for education of health care providers regarding PRN psychotropic medications has been noted [24]. The EGUIDE project reported that educational programs on guidelines improved the clinical knowledge of participants [9], and there is a need to accumulate evidence on PRN psychotropic medications and provide appropriate education regarding PRN medications in the future.

Limitations

There are several limitations in this study. First, this study did not assess the severity of psychiatric symptoms using a rating scale such as the Positive and Negative Syndrome Scale or the Hamilton Depression Rating Scale. Since treatment for patients with SZ and MDD may be influenced by the severity of the patients [3–8], further studies are needed taking into account the severity of illness. Second, this study examined only the presence or absence of PRN psychotropic prescriptions at discharge and did not assess the frequency of PRN medication use during hospitalization or the amount used per visit. Therefore, further studies are needed taking into account the frequency of PRN use during hospitalization and the amount of PRN used per visit. Third, the data in this study were collected from medical institutions that voluntarily participated in the survey, approximately half of which were university hospitals, which limits the generalizability of the results.

Conclusion

Regarding PRN psychotropic medications, the monotherapy ratio and no prescription of other psychotropic medications ratio at discharge decreased in the pharmacotherapy for schizophrenia and MDD. A

higher ratio of monotherapy and no prescription of other psychotropics on regular prescriptions may result in less concomitant use of PRN psychotropic medications. Further studies are needed to optimize PRN psychotropic prescriptions.

Abbreviations

df: Degrees of freedom; EGUIDE: The effectiveness of guidelines for dissemination and education in psychiatric treatment; MDD: Major depressive disorder; PRN: Pro re nata; QI: Quality indicator.

Supplementary Information

The online version contains supplementary material available at <https://doi.org/10.1186/s12991-022-00429-8>.

Additional file 1: Table S1. Definition of Quality Indicators for patients with schizophrenia in this study. **Table S2.** Definition of Quality Indicators for patients with major depressive disorder in this study. **Table S3.** PRN prescription ratio at discharge by drug category.

Acknowledgements

The authors thank the following psychiatrists belonging EGUIDE members.

Author contributions

YK and NY-F were critically involved in collecting and analyzing the data, and wrote the first draft of the manuscript. KIn and KW were critically involved in the design of the study and contributed to the interpretation of the data and writing of the manuscript. NHase, KId, Klc, NHash, HH, YS, YI, and HM, were involved in analyzing the data and contributed to the interpretation of the data and the writing of the manuscript. HYamad, HI, KOH, YY, KOg, SN, JI, TT, SO, FK, RF, TO, MM, HK, MT, CK, AH, KA, HYamag, MK, TN, MU, TK, SK, JM, and KM, were involved in and contributed to the participant recruitment process and data collection, and the data interpretation. RH supervised the entire project, and was critically involved in data collection, design, analysis and interpretation of the data. All authors approved the final version of the manuscript and agree to be accountable for all aspects of this work. All authors read and approved the final manuscript.

Funding

This work was supported by the Japan Agency for Medical Research and Development (AMED) under Grant Number JP16dk0307060, JP19dk0307083, and JP22dk0307112, JSPS KAKENHI Grant Number JP21K17261, the Health and Labor Sciences Research Grants (H29-Seishin-Ippan-001, 19GC1201), the Japanese Society of Neuropsychopharmacology, the Japanese Society of Mood Disorders, the Japanese Society of Clinical Neuropsychopharmacology, and the Japanese Society of Psychiatry and Neurology. The funders had no role in the study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Availability of data and materials

The datasets generated and/or analyzed during the current study are not publicly available due to privacy and ethical restrictions (i.e., we did not obtain informed consent on the public availability of raw data) but are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

This study was approved by the ethics committees of the National Center for Neuropsychiatry (approval number B2022-004) and Neurology and at the participating EGUIDE sites.

Consent for publication

Not applicable.

Competing interests

The authors declare no conflict of interest.

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Received: 1 September 2022 Accepted: 16 December 2022

Published online: 26 December 2022

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