Clinical Psychopharmacology and Neuroscience - Manuscript Submission

- Manuscript ID: CPN-22-984
- Title: Influence of psychotropic pro re nata drug use on outcomes in hospitalized patients with schizophrenia
- Running Title: Influence of psychotropic pro re nata drug use
- Article Type: Original Article
- KeyWords: hospitalization, hospital readmission, polypharmacy, pro re nata, psychotropic drugs, schizophrenia

Abstract

Objective

In the treatment of patients with schizophrenia, *pro re nata* (PRN) drugs are commonly prescribed for medical indications such as agitation, acute psychiatric symptoms, insomnia, and anxiety. However, high-quality evidence supporting the use of PRN medications is lacking, and these drugs are administered on the basis of clinical experience and habits. Therefore, the actual use of psychotropic PRN drugs and its influence on the patients' outcomes need to be investigated.

Methods

This study included 205 patients who underwent inpatient treatment for schizophrenia. We investigated the prescription of psychotropic drugs before admission and at discharge, as well as the dosing frequency of PRN drugs during hospitalization. We also examined the influence of psychotropic PRN drug use on hospitalization days, antipsychotic polypharmacy, and readmission rates.

Results

Patients who used psychotropic PRN drugs during hospitalization had significantly longer hospitalization days ($p = 7.5 \times 10^{-4}$) and significantly higher rates of antipsychotic polypharmacy ($p = 2.4 \times 10^{-4}$) at discharge than those who did not use psychotropic PRN

drugs. Moreover, a higher number of psychotropic PRN drugs used per day was associated with higher readmission rates within 3 months of discharge ($p = 4.4 \times 10^{-3}$).

Conclusion

Psychotropic PRN drug use is associated with prolonged hospitalization, antipsychotic polypharmacy, and increased readmission rates in inpatients with schizophrenia. Therefore, psychiatric symptoms should be stabilized with regularly prescribed medications without the extensive use of psychotropic PRN drugs. Moreover, a system for monitoring and reexamining PRN drug use needs to be established.

Keywords: hospitalization, hospital readmission, polypharmacy, *pro re nata*, psychotropic drugs, schizophrenia

Introduction

In clinical practice in the field of psychiatry, *pro re nata* (PRN) drugs are commonly prescribed for medical indications such as agitation, acute psychiatric symptoms, insomnia, and anxiety [1-3]. PRN drugs are prescribed to 70%–90% of patients hospitalized for mental illnesses [4,5].

Antipsychotic drugs are the mainstay of pharmacotherapy for schizophrenia. The effectiveness of these drugs becomes evident at 2–4 weeks after their administration. Partly because of this delay, PRN drugs may be needed for immediate effects in acute-stage treatment. In situations requiring urgent action, such as during episodes of violence and aggression, PRN medications may be beneficial because they can be used immediately. However, the use of PRN drugs has associated risks. PRN drug use can result in polypharmacy, high-dose prescriptions, and a rapid increase in medication doses [6,7]. As polypharmacy leads to increased adverse events [8,9], it may be detrimental to patients. Hence, warnings are issued against undirected administration of PRN drugs [6,10]. In addition, the risk of overreliance on pharmacological treatment among health-care providers has also been reported [11,12], leading to the avoidance of nonpharmacological interventions and a reduction in nursing skills. PRN medications

have also been reported to increase the risk of double drug administration, which constitutes a medical malpractice [13, 14].

Despite the risks associated with PRN medications, these drugs are currently used at a high frequency. However, high-quality evidence supporting the use of psychotropic PRN medications is lacking, and these drugs are administered solely on the basis of clinical experience and habits [11]. Therefore, the actual use of psychotropic PRN drugs needs to be investigated and the influence of psychotropic PRN drug use on the patients' treatment and outcomes needs to be clarified. This study retrospectively investigated the prescription of psychotropic PRN drugs and their actual use in hospitalized patients undergoing treatment for schizophrenia, as well as the influence of psychotropic PRN drug use on pharmacotherapy at discharge and on patient outcomes.

Methods

We investigated the medical records of 215 patients admitted to the Department of Neuropsychiatry, Kitasato University East Hospital, between April 1, 2018, and March 31, 2020, for the treatment of schizophrenia. This study was approved by the Kitasato University Hospital Ethics Committee (approval no. B20-170, date of approval: September 23, 2020) and was conducted in accordance with the ethical standards of the

Declaration of Helsinki. As this was a retrospective observational study using existing medical information, signed informed consent was not obtained from the patients. We excluded one patient who died and three patients with missing data. Six patients admitted for maintenance electroconvulsive therapy were further excluded because they were discharged without any additional therapeutic intervention during hospitalization. The remaining 205 patients (84 men and 121 women; mean age, 44.87 ± 13.82 years) were included in the analysis.

Data collection

We investigated the patients' demographic data, hospitalization days, hospital admission type (voluntary or involuntary), number of prior admissions to the psychiatric department, regularly prescribed psychotropic drugs at discharge, psychotropic PRN drugs prescribed before admission and at discharge, total number of psychotropic PRN drugs used during hospitalization, presence or absence of seclusion and restraint during hospitalization, and readmissions within 3 months of discharge.

Statistical analyses

We calculated the percentage of patients with psychotropic PRN prescriptions before

admission and at discharge, as well as the percentage of patients who used psychotropic PRN drugs at least once during hospitalization.

The patients were categorized into two groups based on whether they used psychotropic PRN drugs at least once during hospitalization. We performed χ^2 tests to examine differences in the percentage of patients in the two groups according to sex, psychotropic PRN prescription ratio before admission and at discharge, seclusion or restraint during hospitalization, involuntary admission, and antipsychotic polypharmacy at discharge. Antipsychotic polypharmacy was defined as the presence of two or more antipsychotic prescriptions. The Mann–Whitney U-test was performed to assess age, number of prior admissions to the psychiatric department, and hospitalization days. Furthermore, the McNemar test was performed to analyze the psychotropic PRN prescription ratio before admission and at discharge.

We calculated the number of psychotropic PRN drugs used per day by dividing the total number of PRN drug doses by the number of hospitalization days (mean, 0.48 ± 0.73; range, 0–4.18). Logistic regression analysis was performed with readmissions within 3 months after discharge as the dependent variable. In the logistic regression analysis, 41 patients with unknown outcomes were excluded. Of the patients, 23 were readmitted and 141 were not readmitted. Sex, age, number of prior admissions to the

psychiatric department, hospitalization days, number of psychotropic PRN drugs used per day, seclusion or restraint during hospitalization, and involuntary admission were set as independent variables.

The significance level of 5% was set at 5.0×10^{-3} by Bonferroni correction for multiple testing with 10 tests. The Statistical Package for the Social Sciences software (version 26.0; IBM SPSS Inc., Armonk, NY, USA) was used for statistical analyses.

Results

Demographic and clinical data

Table 1 presents the demographic and clinical data of the study patients. The patients were divided into two groups according to whether they used psychotropic PRN drugs at least once during hospitalization. Age, sex, number of prior admissions to the psychiatric department, hospital admission type, and psychotropic PRN prescription ratio before admission and at discharge were compared between the two groups. A total of 140 (68.3%) patients used psychotropic PRN drugs at least once during hospitalization. No significant differences were found in age, number of prior admissions to the psychiatric department, and hospital admission type between the two groups. The female ratio of patients with psychotropic PRN drug use during hospitalization was significantly higher

than that of patients without psychotropic PRN drug use during hospitalization ($\chi^2[1] = 14.24$, $p = 1.6 \times 10^{-4}$). The psychotropic PRN prescription ratio before admission in patients with psychotropic PRN drug use during hospitalization was significantly higher than that in patients without psychotropic PRN drug use during hospitalization ($\chi^2[1] = 19.54$, $p = 9.8 \times 10^{-6}$). Among the 205 patients, 80 (39.0%) were prescribed psychotropic PRN drugs before admission and 138 (67.3%) at discharge. The psychotropic PRN prescription ratio at discharge was significantly higher than that before admission ($\chi^2[1] = 38.68$, $p = 5.0 \times 10^{-10}$).

Of the 140 patients who used psychotropic PRN drugs at least once during hospitalization, 123 (87.9%) were prescribed psychotropic PRN drugs at discharge. In contrast, of the 65 patients who did not use any psychotropic PRN drug during hospitalization, 15 (23.1%) were prescribed psychotropic PRN drugs at discharge.

Comparison of patient outcomes according to psychotropic PRN drug use

Table 2 shows the results of the comparison of outcomes between patients who used psychotropic PRN drugs during hospitalization and those who did not. The antipsychotic polypharmacy ratio at discharge in the group that used psychotropic PRN drugs was 68 (48.6%), compared with 14 (21.5%) in the group that did not use psychotropic PRN drugs.

In addition, the number of hospitalization days in the group that used psychotropic PRN drugs was 88.29 ± 71.17, compared with 58.95 ± 46.86 in the group that did not use psychotropic PRN drugs. Patients who used psychotropic PRN drugs were significantly more likely to have antipsychotic polypharmacy at discharge ($\chi^2[1] = 13.52$, $p = 2.4 \times 10^{-4}$) and had a longer hospital stay than those who did not use psychotropic PRN drugs ($u = 3218.00$, $p = 7.5 \times 10^{-4}$). No significant difference in seclusion or restraint during hospitalization was observed between the two groups. The results of the logistic regression analysis are presented in Table 3. Readmission within 3 months after discharge was associated with the number of psychotropic PRN drugs used per day (odds ratio, 2.140; 95% confidence interval, 1.268–3.611; $p = 4.4 \times 10^{-3}$).

Discussion

Prescription and actual use of psychotropic PRN drugs

This is the first study to investigate the actual use of psychotropic PRN medications in inpatients with schizophrenia. Of the 205 inpatients with schizophrenia included in this study, 140 (68.3%) used PRN drugs during hospitalization. We found that the percentage of patients prescribed psychotropic PRN drugs at discharge increased to 67.3%, compared with 39.0% of patients who were prescribed psychotropic PRN drugs before admission

(Table 1). Psychotropic PRN drugs are highly likely to be administered to patients during the first 4 days of hospitalization [4]. The prescription of psychotropic PRN drugs during hospitalization may have increased as a means of calming patients with agitation and of counteracting the behavioral disorders observed during the acute stage. The female ratio of patients who used psychotropic PRN drugs during hospitalization was higher than that of patients without psychotropic PRN drug use during hospitalization. Insomnia is more common among women [15], and the use of psychotropic PRN drugs to improve insomnia may be related to this result. In addition, since previous studies have shown that PRN prescriptions for depression are more prevalent in women [16], it is possible that a similar trend may exist in schizophrenia. The results of our study do not provide adequate insight into the reasons for sex differences in PRN use. Therefore, further research on sex differences in PRN use is needed.

The psychotropic PRN prescription ratio before admission in patients with psychotropic PRN drug use during hospitalization was higher than that in patients without psychotropic PRN drug use during hospitalization (Table 1). This result suggests that PRN drugs prescribed before admission are more likely to be continued after hospitalization. In addition, 87.9% of patients who used psychotropic PRN drugs during hospitalization received psychotropic PRN prescriptions at discharge. This finding suggests that most of

the psychotropic PRN drugs prescribed during hospitalization were continued at discharge. Moreover, 23.1% of patients who did not use psychotropic PRN drugs during hospitalization were prescribed PRN drugs at discharge (Table 1). These results suggest that PRN drug prescriptions may be made automatically without considering the patients' preference or how the drug is actually used.

Although the treatment guidelines for schizophrenia in various countries mention the use of PRN drugs to manage excitement/agitation and behavioral disorders during the acute stage, they do not mention the long-term use of PRN drugs [17-22]. In contrast, the guidelines for schizophrenia published by the British Association for Psychopharmacology [23] recommend periodically reexamining the clinical indications, dosing frequency, doses, therapeutic effects, and adverse events. The guidelines on violence and aggression [24] discuss long-term PRN drug prescriptions and recommend not automatically prescribing PRN drugs on admission. Furthermore, they suggested that PRN drug use should be reexamined weekly; if PRN drugs were not used after the previous reexamination, discontinuation should be considered.

Despite these recommendations, the results of this study suggest that health-care providers were unable to regularly examine the psychotropic PRN prescriptions during hospitalization, thus allowing the longer administration of PRN drugs. Therefore,

appropriate prescriptions and use of psychotropic PRN drugs should be closely monitored by periodically evaluating the patients' conditions after admission and adjusting the medications accordingly.

Influence of psychotropic PRN drug use on patient outcomes

Among patients with schizophrenia who underwent inpatient treatment in Japan, 57.1% received monotherapy with an antipsychotic drug at discharge [25]. In our study, 40.0% of the patients received polypharmacy of antipsychotic drugs at discharge and 60.0% received monotherapy with an antipsychotic drug at discharge. This result suggests that the antipsychotic prescription status of our study patients was similar to that reported in previous Japanese studies. Antipsychotic polypharmacy at discharge was observed in 48.6% of patients who used psychotropic PRN drugs at least once during hospitalization, compared with 21.5% of patients who did not use such medications (Table 2). This result suggests that psychotropic PRN drug use may be involved in antipsychotic polypharmacy. Previous studies in Japan have also suggested that psychotropic PRN prescriptions affect polypharmacy [16].

Furthermore, our study showed that a higher number of psychotropic PRN drugs used per day was associated with higher readmission rates within 3 months of discharge (Table

3), and that patients who used psychotropic PRN drugs had a significantly longer hospital stay than those who did not use such drugs (Table 2). A previous study has shown that patients with schizophrenia have high readmission rates: 13.4% within 1 month of discharge, 38.9% within 1 year of discharge, and 64.1% within 4 years of discharge [26]. Patients in whom the expected treatment reaction or remission goal was not achieved at discharge had approximately twice as high recurrence rates [27]. The results of these studies and those of the present study suggest that patients who use psychotropic PRN drugs take a longer time to recover from psychiatric symptoms and show an insufficient response to treatment even at discharge. For the maintenance treatment of schizophrenia, intermittent drug administration has a higher risk of recurrence and readmission than continuous administration [28]. Many guidelines and algorithms do not recommend intermittent drug administration [29]. Merely performing symptomatic treatment with PRN drugs during periods of symptom aggravation may increase the risk of recurrence and readmission. Therefore, drug therapy adjustment aimed at stabilizing psychiatric symptoms with regular prescriptions seems to be crucial whenever possible.

Considerations in psychotropic PRN drug use

This study suggests that although psychotropic PRN drug use does not improve

outcomes in inpatients with schizophrenia, PRN drug prescriptions tend to increase at discharge. Therefore, precise guidelines for the use of psychotropic PRN medications are required [4,10]. Educational programs focusing on guidelines for pharmacotherapy of schizophrenia have enhanced the clinical knowledge of psychiatrists [30]. Although no established evidence on PRN drug use exists, organizing the content of guidelines on PRN treatment in various countries, establishing precise guidelines, and raising public awareness through educational programs may help in the appropriate prescription of PRN drugs.

Therapists must not merely encourage patients to use PRN drugs for acute psychiatric symptoms; rather, they should consider using nonpharmacological psychological interventions. Psychological interventions are potential alternatives to PRN drug therapy [31,32]. Even when managing patients with agitation, initially using verbal interventions is preferable before drug therapy. Moreover, increasing the patient's willingness to be assisted through trust building with the therapist can help prevent subsequent episodes of excitement and agitation [33]. However, few psychological interventions have been used as alternatives to psychotropic PRN drugs [34]. Some studies have shown that reducing the dose of PRN drugs and attempting to discontinue and replace them with psychological interventions can reduce the patients' violence and aggression, as well as the need for

movement or activity restrictions [35-37]. Because patients are often concerned that the long-term use of PRN drugs may inhibit other efforts to cope with psychiatric symptoms or eventually lead to dependence, they need more detailed knowledge about PRN drugs [38]. Therefore, therapists are encouraged to consider that the evidence on PRN drugs is insufficient thus far and to share the decision-making process about psychotropic PRN drug use with patients by discussing possible alternative methods, including psychological interventions [39].

When prescribing psychotropic PRN drugs, therapists should exercise caution to avoid polypharmacy. Decisions about the use of PRN drugs are based on a complex process that includes the patient's preferences and the views of other professionals. Thus, a system that adequately monitors the process leading to PRN drug use, periodically reviews the prescription and use of PRN drugs, and thoroughly considers the need for adjustments to regularly prescribed medications is needed [14, 40]. The findings of our study suggest the possibility that PRN drugs have continued to be prescribed without any specific aim or periodic monitoring. Therefore, it is necessary to formulate and adopt a system for periodic reexamination of patients taking PRN drugs while clarifying the process leading to PRN drug use during hospitalization for the treatment of acute-stage schizophrenia.

Limitations

One limitation of this study was that the analysis was performed without direct assessment of symptom severity. Another limitation was that drug therapy and adherence after discharge were not evaluated, which could have affected the readmission rates. Additionally, as the number of patients in this study was small, additional data collection and verification are required. As this study was a retrospective analysis conducted at a single facility in Japan, the results may not be generalizable to all patients with schizophrenia. Therefore, the differences in the use of PRN drugs among different institutions and countries should be examined in the future. Furthermore, this study did not investigate the type or dosage of the PRN drugs used; hence, future studies collecting and analyzing these data are needed to identify the influence of PRN drugs on the treatment of patients with schizophrenia.

Conclusion

Our findings suggest that psychotropic PRN drug use is associated with antipsychotic polypharmacy, prolonged hospitalization, and increased readmission rates in inpatients with schizophrenia. Thus, psychiatric symptoms should be stabilized with regularly prescribed medications without the extensive use of psychotropic PRN drugs. Moreover,

a system for monitoring and reexamining PRN drug use needs to be established.

Acknowledgments: We would like to thank Editage (www.editage.com) for English language editing.

Conflicts of interest: The authors declare that they have no conflicts of interest relevant to this article.

Data availability statement: The data supporting the findings of this study are available from the corresponding author on reasonable request.

Authors' contributions: Yoshitaka Kyou was critically involved in data collection and analysis and wrote the first draft of the manuscript. Satoru Oishi and Ken Inada were critically involved in the study design and contributed to data interpretation and manuscript writing. Takeya Takizawa was involved in data analysis and contributed to data interpretation and manuscript writing. Yuki Yoshimura, Itsuki Hashimoto, Ryutaro Suzuki, Reina Demizu, Tsuyoshi Ono, Yuka Noguchi, and Tomohiko Kimura were involved in the patient recruitment process and data collection, as well as contributed to

data interpretation. Hitoshi Miyaoka supervised the entire project; contributed to data collection; and was critically involved in the design, analysis, and interpretation of data. All authors read and approved the final manuscript.

Ethics approval: This study was approved by the Kitasato University Hospital Ethics Committee (approval no. B20-170) and was conducted in accordance with the ethical standards of the Declaration of Helsinki.

References

1. Friedman R, Nurenberg JR, Birnbaum S, Schleifer SJ. *Using structured clinical feedback to encourage alternatives to use of "P.R.N." medication in a state psychiatric hospital. J Psychiatr Pract 2012;18:381–387. doi: 10.1097/01.pra.0000419823.69914.c7.*

2. Morkunas B, Porritt K, Stephenson M. *Experiences of mental health professionals and patients in the use of pro re nata medication in acute adult mental healthcare settings: a systematic review. JBI Database System Rev Implement Rep 2016;14:209–250. doi: 10.11124/JBISRIR-2016-003167.*

3. Srivastava A. *Limited evidence for the effectiveness of p.r.n. medications among psychiatric inpatients. J Psychiatr Pract 2009;15:193–201. doi: 10.1097/01.pra.0000351879.52883.10.*

4. John AB, Karina L, Neil H. *A best-evidence synthesis review of the administration of psychotropic pro re nata (PRN) medication in in-patient mental health settings. J Clin Nurs 2008;17:1122–1131.* https://doi.org/10.1111/j.1365-2702.2007.02236.x.

5. Krystle M, Vinita A, Ilan F, Renee T. *Descriptive analysis of pro re nata medication use at a Canadian psychiatric hospital. Int J Ment Health Nurs 2017;226:402–408.* https://doi.org/10.1111/inm.12265.

6. Fujita J, Nishida A, Sakata M, Noda T, Ito H. *Excessive dosing and polypharmacy of antipsychotics caused by pro re nata in agitated patients with schizophrenia. Psychiatry Clin Neurosci 2013;67:345–351.* https://doi.org/10.1111/pcn.12056.

7. John AB, Karina L, Neil H. *Mental health professionals' psychotropic pro re nata (p.r.n) mediation practices in acute inpatient mental health care: a qualitative study. Gen Hosp Psychiatry 2007;29:163–168.* https://doi.org/10.1016/j.genhosppsych.2006.12.005.

8. Gallego JA, Nielsen J, De Hert M, Kane JM, Correll CU. *Safety and tolerability of antipsychotic polypharmacy. Expert Opin Drug Saf 2012;11:527–542. https://doi.org/10.1517/14740338.2012.683523.*

9. Kim JJ, Pae CU, Han C, Bahk WM, Lee SJ, Patkar AA, et al. *Exploring Hidden Issues in the Use of Antipsychotic Polypharmacy in the Treatment of Schizophrenia. Clin Psychopharmacol Neurosci. 2021; 19(4):600-609.* doi: 10.9758/cpn.2021.19.4.600.

10. Michael FH, Harvey AW. *Pro re nata medication for psychiatric inpatients: time to act. Aust N Z J Psychiatry 2008;42:555–564. https://doi.org/10.1080/00048670802119804.*

11. Douglas-Hall P, Whicher E. *"As required" medication regimens for seriously mentally ill people in hospital. Cochrane Database Syst Rev 2015;7:CD003441. https://doi.org/10.1002/14651858.CD003441.pub3.*

12. Krystle M, Vinita A, Ilan F, Renee T. *Analysis of non-pharmacological interventions attempted prior to pro re nata medication use. Int J Ment Health Nurs 2018;27:296–302. https://doi.org/10.1111/inm.12320.*

13. Mohammad SA, Mohammed A-S, Amal A, Abdulrhman A, Mubarak A, Mohammed A, *et al.* PRN Medications Ordering Practice at a Large Intensive Care Unit in Saudi Arabia. *J Intensive Crit Care 2016;2:26.* DOI:10.21767/2471-8505.100044.

14. Robert DN, Peter F, Richard K. *Examining trends in the administration of "as needed" medications to inpatients with behavioral and psychological symptoms of dementia. Am J Alzheimers Dis Other Dement 2015;30:247–256. https://doi.org/10.1177/1533317515585924.*

15. Voderholzer U, Al-Shajlawi A, Weske G, Feige B, Riemann D. *Are there gender differences in objective and subjective sleep measures? A study of insomniacs and healthy controls. Depress Anxiety 2003;17:162–172. https://doi.org/10.1002/da.10101.*

16. Ichihashi K, Kyou Y, Hasegawa N, Yasui-Furukori N, Shimizu Y, Hori H, *et al. The characteristics of patients receiving psychotropic pro re nata medication at discharge for the treatment of schizophrenia and major depressive disorder: a nationwide survey from the EGUIDE project. Asian J Psychiatr 2022;69:103007. https://doi.org/10.1016/j.ajp.2022.103007*.

17. Hasan A, Falkai P, Wobrock T, Lieberman J, Glenthøj B, Gattaz WF, *et al. WFSBP Task Force on Treatment Guidelines for Schizophrenia. World Federation of Societies of Biological Psychiatry (WFSBP) guidelines for biological treatment of schizophrenia—a short version for primary care. Int J Psychiatry Clin Pract 2017;21:82–90. https://doi.org/10.1080/13651501.2017.1291839*.

18. Galletly C, Castle D, Dark F, Humberstone V, Jablensky A, Killackey E, *et al. Royal Australian and New Zealand College of Psychiatrists clinical practice guidelines for the management of schizophrenia and related disorders. Aust N Z J Psychiatry 2016;50:410–472. https://doi.org/10.1177/0004867416641195*.

19. Elizabeth K, Amina YU, Clare T, Tim K. *Management of psychosis and schizophrenia in adults: summary of updated NICE guidance. BMJ 2014;348:g1173. https://doi.org/10.1136/bmj.g1173*.

20. Gary R, Donald A, William H, Zahinoor I, Thomas R, Michael T. *Guidelines for the pharmacotherapy of schizophrenia in adults. Can J Psychiatry 2017;62:604–616. https://doi.org/10.1177/0706743717720448*.

21. Japanese Society of Neuropsychopharmacology. *Japanese Society of Neuropsychopharmacology: "Guideline for Pharmacological Therapy of Schizophrenia." Neuropsychopharmacol Rep 2021;41:266–324. https://doi.org/10.1002/npr2.12193*.

22. American Psychiatric Association. *Practice Guideline for the Treatment of Patients with Schizophrenia. 3rd ed. Washington, DC: American Psychiatric Association; 2019*.

23. Barnes TR, Drake R, Paton C, Cooper SJ, Deakin B, Ferrier IN, *et al. Evidence-based guidelines for the pharmacological treatment of schizophrenia: updated recommendations from the British Association for Psychopharmacology. J Psychopharmacol 2020;34:3–78.* https://doi.org/10.1177/0269881119889296.

24. National Institute for Health and Care Excellence. *Clinical Guidelines. Violence and aggression: short-term management in mental health, health and community settings; 2015. Retrieved: April 17, 2022. https://www.nice.org.uk/guidance/ng10.*

25. Ichihashi K, Hori H, Hasegawa N, Yasuda Y, Yamamoto T, Tsuboi T, *et al. Prescription patterns in patients with schizophrenia in Japan: first-quality indicator data from the survey of "Effectiveness of Guidelines for Dissemination and Education in psychiatric treatment (EGUIDE)" project. Neuropsychopharmacol Rep 2020;40:281–286.* https://doi.org/10.1002/npr2.12122.

26. Christopher GH. *Five-year rehospitalization experience of a state-wide cohort of persons with schizophrenia. Soc Psychiatry Psychiatr Epidemiol 2019;54:861–870.* https://doi.org/10.1007/s00127-018-1650-7.

27. Schennach R, Riedel M, Obermeier M, Jäger M, Schmauss M, Laux G, *et al. What happens with schizophrenia patients after their discharge from hospital? Results on outcome and treatment from a "real-world" 2-year follow-up trial. Eur Arch Psychiatry Clin Neurosci 2020;270:661–670. https://doi.org/10.1007/s00406-019-01055-4*.

28. Stephanie S, Mouhamad M, Nicola M. *Intermittent drug techniques for schizophrenia. Cochrane Database Syst Rev 2013;7:CD006196. https://doi.org/10.1002/14651858.CD006196.pub2*.

29. Takeuchi H, Suzuki T, Uchida H, Watanabe K, Mimura M. *Antipsychotic treatment for schizophrenia in the maintenance phase: a systematic review of the guidelines and algorithms. Schizophr Res 2012;132:219–225. https://doi.org/10.1016/j.schres.2011.11.021*.

30. Takaesu Y, Watanabe K, Numata S, Iwata M, Kudo N, Oishi S, *et al. Improvement of psychiatrists' clinical knowledge of the treatment guidelines for schizophrenia and*

major depressive disorders using the 'Effectiveness of Guidelines for Dissemination and Education in Psychiatric Treatment (EGUIDE)' project: a nationwide dissemination, education, and evaluation study. Psychiatry Clin Neurosci 2019;73:642–648. https://doi.org/10.1111/pcn.12911.

31. Dennis CD. *Encouraging alternatives to seclusion, restraint, and reliance on PRN drugs in a public psychiatric hospital. Psychiatr Serv 2005;56:1105–1108. https://doi.org/10.1176/appi.ps.56.9.1105.*

32. Lisa AM, Dror B-Z, Elizabeth C-S, Mary FB, Matthew JF. *Mobile mindfulness intervention on an acute psychiatric unit: feasibility and acceptability study. JMIR Ment Health 2017;4:e34. https://doi.org/10.2196/mental.7717.*

33. Richmond JS, Berlin JS, Fishkind AB, Holloman GH Jr, Zeller SL, Wilson MP, *et al. Verbal de-escalation of the agitated patient: consensus statement of the American Association for Emergency Psychiatry Project BETA de-escalation workgroup. West J Emerg Med 2012;13:17–25. https://doi.org/10.5811/westjem.2011.9.6864.*

34. Janette C, John AB, Amanda RR. *Exploration of therapeutic interventions that accompany the administration of p.r.n. ('as required') psychotropic medication within acute mental health settings: a retrospective study. Int J Ment Health Nurs 2007;16:318–326.* https://doi.org/10.1111/j.1447-0349.2007.00487.x

35. Smith GM, Davis RH, Altenor A, Tran DP, Wolfe KL, Deegan JA, *et al. Psychiatric use of unscheduled medications in the Pennsylvania state hospital system: effects of discontinuing the use of P.R.N. orders. Community Ment Health J 2008;44:261–270.* https://doi.org/10.1007/s10597-008-9126-y.

36. Gregory MS, Donna MA, Robert HD, William S. *Correlation between reduction of seclusion and restraint and assaults by patients in Pennsylvania's state hospitals. Psychiatr Serv 2015;66:303–309.* https://doi.org/10.1176/appi.ps.201400185.

37. Ross F, Jeffry RN, Shira B, Steven JS. *Using structured clinical feedback to encourage alternatives to use of "P.R.N." medication in a state psychiatric hospital. J Psychiatr Pract 2012;18:381–387.* https://doi.org/10.1097/01.pra.0000419823.69914.c7.

38. Bernadette M, Kylie P, Matthew S. *Experiences of mental health professionals and patients in the use of pro re nata medication in acute adult mental healthcare settings: a systematic review. JBI Database Syst Rev Implement Rep 2016;14:209–250. https://doi.org/10.11124/JBISRIR-2016-003167.*

39. Kirsi H, Lauri K, Eila R-T, Minna L, Olavi L, Mari K. *Patient participation in pro re nata medication in psychiatric inpatient settings: an integrative review. Int J Ment Health Nurs 2018;27:536–554. https://doi.org/10.1111/inm.12427.*

40. Lesley B, Dianne W, Karen H. *Nurses' attitudes towards the use of PRN psychotropic medications in acute and forensic mental health settings. Int J Ment Health Nurs 2018;27:168–177. https://doi.org/10.1111/inm.12306.*

Table 1. Demographic and clinical data

	With psychotropic PRN drug use during hospitalization (n = 140)	Without psychotropic PRN drug use during hospitalization (n = 65)	All (n = 205)	*p*-Value
Age (years, mean ± SD)	44.44 ± 14.06	45.78 ± 13.35	44.87 ± 13.82	0.71
Sex (female ratio; n, %)	95 (67.9%)	26 (40.0%)	59.0%	[a]1.6×10^{-4}
Number of prior admissions to the psychiatric department (mean ± SD)	3.98 ± 4.87	2.83 ± 3.79	3.61 ± 4.58	0.05
Hospital admission type (involuntary admission; n, %)	102 (72.9%)	51 (78.5%)	74.6%	0.39
Psychotropic PRN prescription ratio before admission (n, %)	69 (49.3%)	11 (16.9%)	80 (39.0%)	[a]9.8×10^{-6}
Psychotropic PRN prescription ratio at discharge (n, %)	123 (87.9%)	15 (23.1%)	138 (67.3%)	[a]3.5×10^{-20}

As the level of significance of $p < 5.0 \times 10^{-3}$ was within the 5% significance level based on Bonferroni correction, it was considered in the multiplicity of tests.

[a]$p < 0.05$ after Bonferroni correction.

PRN, *pro re nata*; SD, standard deviation

Table 2. Comparison of patient outcomes according to PRN drug use

	With PRN drug use during hospitalization (n = 140)	Without PRN drug use during hospitalization (n = 65)	All (n = 205)	*p*-Value
Seclusion or restraint during hospitalization (n, %)	63 (45.0)	33 (50.8)	96 (46.8)	0.44
Polypharmacy of antipsychotic drugs prescribed at discharge (n, %)	68 (48.6)	14 (21.5)	40.0	[a]2.4×10^{-4}
Hospitalization days (mean ± SD)	88.29 ± 71.17	58.95 ± 46.86	78.99 ± 65.78	[a]7.5×10^{-4}

As the level of significance of $p < 5.0 \times 10^{-3}$ was within the 5% significance level based on Bonferroni correction, it was considered in the multiplicity of tests.

[a]$p < 0.05$ after Bonferroni correction.

PRN, *pro re nata*; SD, standard deviation

Table 3. Factors related to readmission

	Odds ratio	95% CI		*p*-Value
		Lower limit	Upper limit	
Readmission within 3 months after discharge				
Sex (female)	0.987	0.375	2.596	0.98
Age	1.024	0.988	1.061	0.19
Number of prior admissions to the psychiatric department	0.928	0.814	1.057	0.26
Hospitalization days	1.001	0.994	1.008	0.73
Number of PRN drugs used per day for psychiatric symptoms	2.140	1.268	3.611	[a]4.4×10^{-3}
Seclusion or restraint during admission	1.507	0.488	4.649	0.48
Involuntary admission	1.068	0.322	3.542	0.92

As the level of significance of $p < 5.0 \times 10^{-3}$ was within the 5% significance level based on Bonferroni correction, it was considered in the multiplicity of tests.

[a] $p < 0.05$ after Bonferroni correction.

CI, confidence interval; PRN, *pro re nata*