Recent trends in antipsychotic polypharmacy in the treatment of schizophrenia

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Abstract
Ichihashi et al reported that 43% of patients had antipsychotic polypharmacy. Number of antipsychotics used in patients with schizophrenia in Japan was the greatest among Asian countries. However, the antipsychotic polypharmacy rate in Japan decreased gradually. Recent systematic review, meta-analysis and meta-regression analysis demonstrated that antipsychotic augmentation was superior to monotherapy. However, several cohort studies have suggested a significant association between antipsychotic daily dose and mortality. In addition, most pharmacokinetic interactions with antipsychotics occur at the metabolic level and usually involve changes in the activity of the major drug-metabolizing enzymes involved in their biotransformation. Thus, avoidance of unnecessary polypharmacy, knowledge of the interaction profiles of individual agents, and careful individualization of dosage based on close evaluation of clinical response and possibly plasma drug concentrations are essential to prevent and minimize potentially adverse drug interactions in patients receiving antipsychotics.

KEYWORDS
antipsychotic polypharmacy, drug interactions, guidelines, Japan, schizophrenia

Ichihashi et al reported that 43% of 1164 patients (43% in 23 university hospitals, 54% in 12 national/public hospitals, and 33% in 9 private hospitals) had antipsychotic polypharmacy in "Effectiveness of Guidelines for Dissemination and Education in psychiatric treatment (EGUIDE)" project in 2016, which is a series of training courses for Japanese psychiatrists.

Antipsychotics are not always effective in schizophrenia patients. There are still patients with treatment-resistant schizophrenia (TRS), which has led to a growing trend of resorting to atypical antipsychotic polypharmacy due to fewer side effects. In addition, Qiu et al reported the difference in antipsychotic polypharmacy trends between China and Japan. The overall antipsychotic polypharmacy rate was higher in Japan than in China. However, the antipsychotic polypharmacy rate in Japan decreased gradually, and in 2014, the rate in Japan was similar to that in China. Japanese governments published a press release to draw attention to the polypharmacy of psychotropic agents in 2011 and have regulated medical service fees in patients treated with antipsychotic polypharmacy since 2014, just after national reports in 2011 published an antipsychotic polypharmacy rate of 28.8%-30.0% from 2005 to 2009.

A recent systematic review, meta-analysis and meta-regression analysis demonstrated that antipsychotic augmentation was superior to monotherapy regarding total symptom reduction, although the superiority was only apparent in open-label and low-quality trials and not in double-blind and high-quality trials. In addition,
COMMENTS

On the other hand, several guidelines consistently recommend monotherapy of antipsychotic agents. For example, the Maudsley Prescribing Guidelines in Psychiatry states that we should concern ourselves with the addition of an antipsychotic to another antipsychotic solely to increase efficacy. From a theoretical point of view, since all antipsychotics block D2 receptors (unlike antihypertensives, which use different mechanisms), there is limited rationale for additional antipsychotics. In addition, many clinical trials studying the side effects of polypharmacy have associated polypharmacy with an increased incidence of side effects, although most have been uncontrolled studies or observational studies. Polypharmacy increases the risk of extrapyramidal syndrome and elevation of plasma prolactin concentration, except aripiprazole. Furthermore, anticholinergics were frequently used for patients who underwent polypharmacy.

Several cohort studies have suggested a significant association between antipsychotic daily dose and mortality. It is natural that daily doses of polypharmacy tend to be higher than that of monotherapy. In addition, most pharmacokinetic interactions with antipsychotics occur at the metabolic level and usually involve changes in the activity of the major drug-metabolizing enzymes involved in their biotransformation, that is, the cytochrome P450 (CYP) mono-oxygenases and/or uridine diphosphate-glucuronosyltransferases (UGT). Therefore, even if the dose of antipsychotics is low, the plasma concentration of each drug may be high after polypharmacy, leading to a risk of mortality.

Mortality associated with antipsychotic polypharmacy has not yet been concluded. Previous reports have suggested that significant mortality risks are 2.46 (95% CI, 1.10-5.47) and 2.50 (95% CI, 1.46-4.30). However, later studies have reported no association between mortality and antipsychotic polypharmacy.

Thus, although evident disadvantage of antipsychotic polypharmacy has not yet been concluded, avoidance of unnecessary polypharmacy, knowledge of the interaction profiles of individual agents, and careful individualization of dosage based on close evaluation of clinical response and possibly plasma drug concentrations are essential to prevent and minimize potentially adverse drug interactions in patients receiving antipsychotics.

CONFLICT OF INTEREST
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AUTHOR CONTRIBUTION
NYF designed the study and wrote the initial draft of the manuscript. KS contributed to supervision of the draft.

DATA AVAILABILITY STATEMENT
Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

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REFERENCES
1. Ichiaisshi 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. Neuropsychopharmacology Reports. https://doi.org/10.1002/npr2.12122 (in press).
2. 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(10):642-8.
3. Mojtabai R, Olff M. National trends in psychotrophic medication polypharmacy in office-based psychiatry. Arch Gen Psychiatry. 2010;67(1):26-36.
4. Yang S-Y, Chen L-Y, Najoan E, Kallivayalil RA, Viboonma K, Jamaluddin R, et al. Polypharmacy and psychotropic drug loading in patients with schizophrenia in Asian countries: Fourth survey of Research on Asian Prescription Patterns on antipsychotics. Psychiatry Clin Neurosci. 2018;72(8):572-9.
5. Qiu H, He Y, Zhang Y, He M, Liu J, Chi R, et al. Antipsychotic polypharmacy in the treatment of schizophrenia in China and Japan. Aust N Z J Psychiatry. 2018;52(12):1202-12.
6. Galling B, Roldán A, Hagi K, Rietschel L, Walzyza F, Zheng W, et al. Antipsychotic augmentation vs. monotherapy in schizophrenia: systematic review, meta-analysis and meta-regression analysis. World Psychiatry. 2017;16(1):77-89.
7. Tiihonen J, Taipale H, Mehtälä J, Vattulainen P, Correll CU, Tanskanen A. Association of antipsychotic polypharmacy vs mono-therapy with psychiatric rehospitalization among adults with schizophrenia. JAMA Psychiatry. 2019;76(5):499–507.

8. Misawa F, Shimizu K, Fujii Y, Miyata R, Koshiishi F, Kobayashi M, et al. Is antipsychotic polypharmacy associated with metabolic syndrome even after adjustment for lifestyle effects? A cross-sectional study. BMC Psychiatry. 2011;11:118.

9. Gallego JA, Nielsen J, De Hert M, Kane JM, Correll CU. Safety and tolerability of antipsychotic polypharmacy. Expert Opin Drug Saf. 2012;11(4):527–42.

10. Yasui-Furukori N, Furukori H, Sugawara N, Fujii A, Kaneko S. Dose-dependent effects of adjunctive treatment with aripiprazole on hyperprolactinemia induced by risperidone in female patients with schizophrenia. J Clin Psychopharmacol. 2010;30(5):596–9.

11. Chakos MH, Glick ID, Miller AL, Hamner MB, Miller DD, Patel JK, et al. Baseline use of concomitant psychotropic medications to treat schizophrenia in the CATIE trial. Psychiatr Serv. 2006;57(8):1094–101.

12. Cullen BA, McGinty EE, Zhang Y, dosReis SC, Steinwachs DM, Guallar E, et al. Guideline-concordant antipsychotic use and mortality in schizophrenia. Schizophr Bull. 2013;39(5):1159–68.

13. Torniainen M, Mittendorfer-Rutz E, Tanskanen A, Bjorkenstam C, Suvisaari J, Alexanderson K, et al. Antipsychotic treatment and mortality in schizophrenia. Schizophr Bull. 2015;41(3):656–63.

14. Spina E, de Leon J. Metabolic drug interactions with newer antipsychotics: a comparative review. Basic Clin Pharmacol Toxicol. 2007;100(1):4–22.

15. Waddington JL, Youssef HA, Kinsella A. Mortality in schizophrenia. Antipsychotic polypharmacy and absence of adjunctive anticholinergics over the course of a 10-year prospective study. Br J Psychiatry. 1998;173:325–9.

16. Joukamaa M, Heliovaaara M, Knekt P, Aromaa A, Raitasalo R, Lehtinen V. Schizophrenia, neuroleptic medication and mortality. Br J Psychiatry. 2006;188:122–7.

17. Tiihonen J, Suokas JT, Suvisaari JM, Haukka J, Korhonen P. Polypharmacy with antipsychotics, antidepressants, or benzodiazepines and mortality in schizophrenia. Arch Gen Psychiatry. 2012;69(5):476–83.

18. Katona L, Czobor P. Bitter I. Real-world effectiveness of antipsychotic monotherapy vs. polypharmacy in schizophrenia: to switch or to combine? A nationwide study in Hungary. Schizophr Res. 2014;152(1):246–54.

19. Ray WA, Chung CP, Murray KT, Hall K, Stein CM. Atypical antipsychotic drugs and the risk of sudden cardiac death. N Engl J Med. 2009;360(3):225–35.

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