



# 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<sup>1</sup> 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.<sup>2</sup>

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.<sup>3</sup>

Number of antipsychotics used and psychotropic drug loading in patients with schizophrenia in Japan was the greatest among Asian countries.<sup>4</sup> In addition, Qiu et al<sup>5</sup> 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.<sup>6</sup> In addition,

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combining aripiprazole with clozapine was associated with the lowest risk of rehospitalization, indicating that certain types of polypharmacy may be feasible in the treatment of schizophrenia.<sup>7</sup>

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.<sup>8</sup> Polypharmacy increases the risk of extrapyramidal syndrome and elevation of plasma prolactin concentration,<sup>9</sup> except aripiprazole.<sup>10</sup> Furthermore, anticholinergics were frequently used for patients who underwent polypharmacy.<sup>11</sup>

Several cohort studies have suggested a significant association between antipsychotic daily dose and mortality.<sup>12,13</sup> 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) monooxygenases and/or uridine diphosphate-glucuronosyltransferases (UGT).<sup>14</sup> 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)<sup>15</sup> and 2.50 (95% CI, 1.46-4.30).<sup>16</sup> However, later studies have reported no association between mortality and antipsychotic polypharmacy.<sup>17</sup> Tiihonen et al demonstrated that compared with antipsychotic monotherapy, concomitant use of 2 or more antipsychotics was not associated with increased mortality (HR, 0.86; 95% CI, 0.51-1.44).<sup>17</sup> Although the principal outcome measure, time to all-cause discontinuation, indicated superiority for monotherapy over polypharmacy for the majority of (oral and depot) second-generation APs (SGAs), a significant overall advantage of polypharmacy was detected for mortality and hospitalization.<sup>18</sup> The risk of natural death did not increase with the number of concurrently used antipsychotic agents compared with the corresponding risk associated with antipsychotic monotherapy (adjusted odds ratio [OR] = 1.48 [95% CI, 0.89-2.46]; 2 antipsychotics: OR = 0.91 [95% CI, 0.61-1.36]; 3 or more antipsychotics: OR = 1.16 [95% CI, 0.68-2.00]).<sup>19</sup>

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

Norio Yasui-Furukori has been a speaker for Otsuka Pharmaceutical Co., Ltd., Mochida Pharmaceutical Co., Ltd., Dainippon-Sumitomo Pharmaceutical Co., and MSD Co. Kazutaka Shimoda has received research support from Novartis Pharma KK, Dainippon Sumitomo Pharma Co., Astellas Pharma Inc, Meiji Seika Pharma Co., Ltd., Eisai Co., Ltd., Pfizer Inc, Otsuka Pharmaceutical Co., Ltd., Daiichi Sankyo Co., and Takeda Pharmaceutical Co., Ltd., and honoraria from Eisai Co., Ltd., Mitsubishi Tanabe Pharma Corporation, Takeda Pharmaceutical Co., Ltd., Meiji Seika Pharma Co., Ltd., Janssen Pharmaceutical KK, Shionogi & Co., Ltd., Dainippon Sumitomo Pharma Co., Daiichi Sankyo Co., and Pfizer Inc. The funders did not have any role in data collection or in the study design, analysis, decision to publish, or preparation of the manuscript. The remaining authors declare that they have no competing interests to report.

## 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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