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Review

REVIEW

Antipsychotic Polypharmacy: A Dirty Little Secret or a Fashion?

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Abstract

The term polypharmacy was originally coined to refer to problems related to multiple drug consumption and excessive drug use during the treatment of a disease or disorder. In the treatment of schizophrenia, polypharmacy usually refers to the simultaneous use of 2 or more antipsychotic medications or combined (adjunct) medications such as mood stabilizers, antidepressants, anxiolytics, or hypnotics in addition to single or multiple antipsychotics. Two decades ago, antipsychotic polypharmacy was criticized as being more expensive, having unproven efficacy, and causing more side effects. However, in recent years, antipsychotic polypharmacy has become more or less acceptable in the views of clinical practitioners and academic researchers. Results from recent reviews have suggested that the common practice of antipsychotic polypharmacy lacks double-blind or high-quality evidence of efficacy, except for negative symptom reduction with aripiprazole augmentation. We reviewed some representative studies that enrolled large numbers of patients and compared antipsychotic polypharmacy and monotherapy during the past decade. The results revealed that a certain proportion of select patients can benefit from antipsychotic polypharmacy without further negative consequences. Because most of the current treatment guidelines from different countries and organizations prefer monotherapy and discourage all antipsychotic polypharmacy, guidelines regarding the use of antipsychotic polypharmacy in clinical practice should be revised. On the basis of the findings of 2 large-scale studies from Asia and Europe, we also suggest ideal rates of various maintenance treatments of schizophrenia, which are as follows: antipsychotic polypharmacy, 30%; combined mood stabilizer, 15%; combined antidepressant, 10%; combined anxiolytics, 30%; and combined hypnotic, 10%.

Keywords: schizophrenia, combined medication, treatment guideline, high-dose antipsychotic, deprescribing

Introduction

The term polypharmacy was originally coined to refer to problematic prescriptions that entailed multiple drug consumption and excessive drug use during the treatment of a disease or disorder (Friend, 1959). In a recent systemic review, the most commonly reported definition of polypharmacy was a numerical definition of the prescription of a daily regimen of 5 or more medications to a patient; polypharmacy also connoted potentially inappropriate or unnecessary medications (Masnoon et al., 2017). Polypharmacy has been a concern among older individuals due to a greater risk of adverse drug reactions or negative clinical consequences, resulting from metabolic changes and reduced drug clearance associated with aging (Maher et al., 2014). The prevalence of polypharmacy has been increasing over the last few decades (Wastesson et al., 2018), and efforts of deprescribing medication have been reported in many studies (Scott et al., 2015; Salahudeen, 2018).

Antipsychotic Polypharmacy

Antipsychotic polypharmacy (APP) is commonly observed in the treatment of schizophrenia or other psychotic disorders. In an early 1970s survey of 4 states of the United States (Sheppard

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et al., 1974), the results revealed that New York psychiatrists most frequently prescribed a combination of 2 drugs, and some even prescribed 6 drugs at a time. Pennsylvania psychiatrists were the second most likely to prescribe multiple drugs, whereas those in California and Texas least frequently used combinations. The authors concluded that polypharmacy in psychiatry represented an example of a "legitimate" but unnecessary use of psychotropic agents. Currently, no consensus regarding the definition of APP is available; however, most of the research papers have referred to it as the simultaneous use of 2 or more types of antipsychotic medication. Commonly reported reasons for APP in clinical practice include unsatisfied efficacy of primary antipsychotics, rapid therapeutic response, severe course of illness, clozapine intolerance, cross titration, randomized controlled evidence, amelioration of side effects, treatment of comorbid conditions, economic concern, and skepticism toward the use of treatment guidelines (Ito et al., 2005; Barnes and Paton, 2011; Correll et al., 2011; Kishimoto et al., 2013; Lin et al., 2013; Malandain et al., 2018).

Prevalence of APP

In recent decades, many studies have reported the prevalence of APP in the treatment of schizophrenia. Gallego et al. (2012) presented a systematic review and a meta-regression of the global and regional trends of the prevalence of APP based on 147 studies from the 1970s to 2009. The median APP rate was 19.6%, with a wide variation across countries (interquartile range = 12.9–35.0%). APP rates did not differ between decades but differed between regions, with the rates being higher in Asia and Europe than in North America and in Asia than in Oceania. APP increased from 12.7% (1980s) to 17.0% (2000s) in North America, decreased significantly from 55.5% to 19.2% in Asia, and had nonsignificant changes in Europe (23%). The authors also found that APP was associated with a greater anticholinergic requirement, shorter observation time, greater illness severity, and lower antidepressant use. Recent reports have identified the prevalence of APP in different countries as follows: Nigeria, 70.4% (Igbinomwanhia et al., 2017); Arizona, United States, 27.1% (Boskailo et al., 2017); South Africa, 28.4% (Armstrong and Temmingh, 2017); Ethiopia, 28.2% (Tesfaye et al., 2016); China, 12.7%; and Japan, 19.9% (Qiu et al., 2018). In a recent survey, "Research on Asian Prescription Pattern (REAP)," that investigated 15 countries (Yang et al., 2018), the mean (SD) rate of APP in 3744 patients with schizophrenia was 42.2% (12.0%), with the highest rate in Vietnam (59.1%) and the lowest in Myanmar (22.0%).

Controversy of APP

APP has always been subject to debate. Two decades ago, it was criticized as being more expensive, having unproven efficacy, and causing more side effects (Stahl, 1999, 2002), whereas in recent years, it has become more or less acceptable in clinical practice and academic research (Stahl, 2012; Moore et al., 2017). Galling et al. (2017) presented a meta-analysis of 31 studies that compared APP and antipsychotic monotherapy (APM), with 20 of the comparisons involving clozapine add-on with other antipsychotics. The results revealed that antipsychotic augmentation was superior to monotherapy for total symptom reduction, but this result was only apparent in open-label and low-quality trials. The authors suggested that the common practice of APP in schizophrenia still lacks double-blinded or high-quality evidence of efficacy, except for negative symptom reduction with aripiprazole augmentation. The results of a meta-analysis on safety and tolerability issues by the same group (Galling et al., 2016) revealed that APP was similar to APM regarding intolerability-related discontinuation, and the incidence of 1 or more adverse events was lower with APP. However, the authors argued that these results were solely driven by open-label and efficacy-focused studies.

Because APP in clinical practice is still controversial, we reviewed some representative studies with large numbers of patients that compared APP and APM within the past decade.

Katona et al. (2014) reported a nationwide study from Hungary, comparing APP (n = 7901) and APM (n = 5480) with the principal endpoint being the time to all-cause treatment discontinuation during a 1-year observation period. They found that monotherapy was superior to APP for long-term sustained treatment, whereas APP had advantages in mortality and psychiatric hospitalizations, suggesting APP may be more efficacious during the exacerbation of psychotic symptoms. Tiihonen et al. (2019) ran a nationwide cohort study in Finland using the risk of psychiatric rehospitalization as a marker for relapse in the nationwide cohort of 62 250 patients with schizophrenia. The results revealed that combining aripiprazole with clozapine was associated with the lowest risk of rehospitalization, indicating that certain types of polypharmacy may be feasible for the treatment of schizophrenia. The authors further argued that because add-on treatments were started when monotherapy was no longer sufficient to control the worsening of symptoms, it was likely that the effect sizes of polypharmacy were underestimated. Interestingly, they suggested that although the results did not indicate that all types of polypharmacy were beneficial, the current treatment guidelines should modify their categorical recommendations discouraging all APP in the maintenance treatment of schizophrenia.

The results of a population-based, nested case-control study of 27 633 patients from Denmark revealed that the risk of natural death did not increase with the number of concurrently used antipsychotic agents compared with APM (Baandrup et al., 2010), while current use of benzodiazepine derivatives with long elimination half-lives (more than 24 hours) has been found to be associated with an increased risk of natural death in patients with schizophrenia treated with antipsychotics, suggesting that APP does not contribute to the excess mortality from natural causes in middle-aged patients with schizophrenia. Kadra et al. (2018) compared the risk of mortality in 10 945 adults on long-term APM (76.9%) vs APP (23.1%) in the United Kingdom and found a weak association between long-term APP use with all-cause mortality and natural causes of death after adjusting for a range of possible confounders and no significant association between APP and unnatural causes of death. The authors suggested that the effect of long-term APP on mortality was unclear, with limited evidence to indicate an association, even after controlling for the effect of dose. Kasteridis et al. (2019) compared the effect of APP and monotherapy in 17 255 patients in the United Kingdom using primary care medication record data of unplanned hospital admissions (all-cause), emergency department visits, and mortality as outcome measurements. The results revealed that APP was not associated with the increased risk of the 3 outcomes. The authors suggested that when clinicians considered APP necessary, health care utilization and mortality were not affected. Table 1 summarizes the results of these aforementioned studies.

Hatta et al. (2019) reported a real-world experience of 1543 acute exacerbation psychotic (87.6% schizophrenia) patients in Japan. Among all participants, there were 42.8%, 15.7%, and 3.6%

responders to an initial and a second and a third antipsychotic, respectively. For the other 552 patients, the response rate (Clinical Global Impression-Improvement [CGI-I] score ≤3) to APP was 89.8%. Compared with all patients, adverse events did not occur frequently in patients who were prescribed APP. The authors concluded that APP may be an option in acute-phase treatment for patients who do not respond to either an initial or a second antipsychotic.

A review of 12 systematic reviews on metabolic syndrome side effects and APP (Ijaz et al., 2018) obtained heterogeneous results, mostly with narrative syntheses and without pooled data, and was rated as low quality. An indication of a possible protective effect of drug combinations, including aripiprazole for diabetes and hyperlipidemias, was noted, and only 1 review reported an association between APP and hypertension. On the basis of the current evidence, the authors could not definitively conclude that APP increased the risk of metabolic syndrome in schizophrenia or that it was safe relative to APM. Table 1 presents the summary of these aforementioned studies.

Constantine et al. (2015) evaluated the risks and benefits of switching from 2 to 1 antipsychotic medication in a randomized controlled trial comprising 140 patients with schizophrenia or schizoaffective disorder. Participants who switched to APM experienced greater increases in symptoms than patients who did not switch. All-cause discontinuation rates during the 1-year trial were higher in the switching group than in the stay-on-APP group. The authors suggested that clinicians should be cautious in switching patients with chronic schizophrenia who are stable on APP. Further, APP discontinuation has challenges; therefore, adequate trials of evidence-based treatments such as clozapine and long-acting injectable antipsychotics should be undertaken in inadequately responsive patients with schizophrenia before moving to APP.

High-Dose Antipsychotics

In general, patients with schizophrenia respond to APM at standard doses, but a subset of patients require more heroic measures that included APP and high-dose monotherapy (Moore et al., 2017). In this special article, the authors suggested that if the treatment goal was to occupy a greater degree of D2 receptors to address treatment-resistant positive and aggressive symptoms, high-dose monotherapy was the preferred option compared with polypharmacy. Although APM at standard dosing levels was sufficient for the majority of patients, a subset required "unconventional" approaches such as APP and higher than normal dosing. High dosing ranges of second-generation antipsychotics were suggested in this article.

In the first REAP study (Sim et al., 2004), 17.9% of 2399 patients with schizophrenia were prescribed high-dose antipsychotics (defined as more than 1000 mg of chlorpromazine-equivalents per day), with Japan, Korea, and Singapore using higher doses than other countries. In the fourth REAP study (Yang et al., 2018), the average antipsychotic drug load (ADL) calculated by the sum of each antipsychotic's prescribe daily dose divided by defined daily dose (WHO, 2017) was 1.5, with the highest being 2.29 in Japan and the lowest being 1.00 in Indonesia. This phenomenon was similar to different prevalences of APP across countries. John and Dragovic (2015) reported a comparison of ADL between APP (n = 99) and APM (n = 130) in patients with schizophrenia in a public mental health service located in metropolitan Western Australia. The mean ADL was 2.64 for APP and 1.34 for APM, suggesting that APP was not associated with reduced dose of individual antipsychotics.

Deprescribing APP and High-Dose Antipsychotics

Most patients receive APP or high-dose antipsychotics during acute exacerbation. According to clinical judgment, the medication used should be simplified or tapered in the maintenance phase, yet many clinicians have been reluctant to adjust medication dosages, leading to a higher rate of APP or high- or mega-dose prescriptions of antipsychotics. Currently, a trend of "deprescribing" in general medicine is being observed, especially for older patients (Brodaty et al., 2018; Ulley et al., 2019). Deprescribing can be defined as a process of withdrawal or dose reduction of medications, which are considered inappropriate for an individual, to reduce adverse effects of multiple medications, including nonadherence (Reeve et al., 2017). Regarding the concern of APP, Matsui et al. (2019) presented a systematic review and meta-analysis comparing switching to APM vs staying on APP in schizophrenia. The study was based on 6 randomized controlled trials involving 341 patients and revealed a significant difference in discontinuation due to all causes in favor of staying on APP, with no significant differences in relapse, any psychopathology, neurocognition, extrapyramidal symptoms, or

Table 1. Summary of large-scale studies comparing antipsychotic polypharmacy and monotherapy

Study	Country	Patient no. (APM/APP)	Primary outcome	Results and recommendation
Baandrup et al., 2010	Denmark	27 633	Risk of natural death	No increase in the number of concurrently used antipsychotics
Katona et al., 2014	Hungary	5480/7901	Time to all-cause treatment discontinuation, mortality, and hospitalization	APM was superior to APP for long-term treatment, considering SGAs in treatment discontinuation. APP was associated with a lower likelihood of mortality and hospitalizations.
Kadra et al., 2018	United Kingdom	8421/2524	Mortality	APP effect on mortality was unclear, even after controlling the effect of dose.
Tiihonen et al., 2019	Finland	62 250	Rehospitalization	Combining aripiprazole with clozapine was associated with the lowest risk.
Kasteridis et al., 2019	United Kingdom	17 255	Unplanned hospitalization and mortality	Results supported APM, and for APP, health care utilization and mortality were not affected.

Abbreviations: APM, antipsychotic monotherapy; APP, antipsychotic polypharmacy; SGAs, second-generation antipsychotics.

bodyweight between the 2 groups. Because the quality of evidence was low to very low, the authors suggested that the findings should be considered preliminary and inconclusive. On the basis of international standards, the rate of APP and the dose of antipsychotics prescribed for schizophrenia in Japan have been considered to be unnecessarily high (Xiang et al., 2012; Yoshio et al., 2012). Yamanouchi et al (2014) evaluated a treatment reduction approach that reduces APP and high-dose rates of prescriptions through a randomized open study. After 12 or 24 weeks of adjustment, 23% of doses of antipsychotic medication was reduced and no differences in outcomes were observed between the dose reduction and observation groups.

In an open-label, single-arm prospective study by Graff-Guerrero et al (2015), the dopamine D2/3R occupancy before and after antipsychotic dose reduction (up to 40%) in late-life schizophrenia were compared. Dopamine D2/3R occupancy in the entire sample decreased by a mean (SD) of 6.2% (8.2%) following dose reduction (from 70% to 64%). Slight but significant symptomatic improvements and reduced adverse effects were noted. The authors suggested that the striatal dopamine D2/3 R occupancy threshold for antipsychotic therapeutic effects was lower (50%) in patients with late-life schizophrenia than in younger patients (65%), which has a significant implication for the management of this specific and ever-growing late-life schizophrenic population. Recently, Ozawa et al (2019) conducted a model-guided antipsychotic dose reduction study. In the study group, baseline doses were reduced to the doses corresponding to 65% D2 occupancy in 4 weeks, followed by treatment with this target dose and a 52-week follow-up. The doses of risperidone and olanzapine were reduced from 4.2±1.9 mg/d to 1.4±0.4 mg/d and 12.8±3.9 mg/d to 6.7±1.8 mg/d, respectively. Compared with the "no change" dose group (n=18), no significant differences in scores of the "change" dose group on the Positive and Negative Syndrome Scale and the Clinical Global Impression–Schizophrenia were evident. In addition, extrapyramidal symptoms were significantly improved in the dose reduction group.

The continual use of antipsychotic drugs by patients with schizophrenia, especially in first-episode cases, is still controversial. Omachi and Sumiyoshi (2018) conducted a review of the effects of reduction or discontinuation of antipsychotic drugs in patients with first-episode psychosis or schizophrenia based on 6 studies. The results suggested that although this strategy may be associated with higher relapse rates, it may improve cognition and social function. The authors suggested that the measures of functional outcome should be considered for deciding which strategy of antipsychotic treatments is beneficial in individual cases of first-episode psychosis or schizophrenia. However, Tiihonen et al. (2018) conducted a 20-year nationwide follow-up study on discontinuation of antipsychotic treatment in first-episode schizophrenia, and the results revealed that the lowest risk of rehospitalization or death was observed for patients who received antipsychotic treatment continually. With regard to the promotion of personalizing antipsychotic treatment (Wunderink, 2019), the authors suggested that instead of determining whether to maintain or discontinue antipsychotics, clinicians should ascertain the lowest effective dosage to optimally prevent both relapses and side effects and to allow optimal functional recovery.

Deprescribing should be considered after a careful assessment of the overall health of a patient, therapeutic goals, medication adherence in the current treatment regimen, and willingness to deprescribe the medicine. For the process of deprescribing, Salahudeen (2018) suggested that it was best performed by reducing medicines one at a time, with careful assessment, effort, commitment, and time. Endsley (2018) suggested the following 4-part process to deprescribe: review all current medications; identify any inappropriate, unnecessary, or harmful medications; plan deprescribing with the patient; and regularly review medications.

Combined Medication

Combined medication in treating schizophrenia refers to the use of 1 or more psychotropic drugs in addition to the primary antipsychotics due to limited effectiveness. Correll et al. (2017) presented a systemic overview of 29 meta-analyses on combined medications in the treatment of schizophrenia. A total of 42 combination strategies in 381 individual trials with 19833 participants were noted. The results revealed that 14 of 32 agents combined with antipsychotic drugs were significantly superior to controls, whereas none of the 5 pharmacological combinations with clozapine outperformed controls. The effect sizes were inversely correlated with the meta-analyzed study quality, reducing confidence in these recommendations; thus, the authors concluded that no single strategy can be recommended for patients with schizophrenia based on the current meta-analysis literature.

To treat schizophrenia in clinical practice, the most commonly prescribed add-on medications besides antipsychotics are other psychotropic drugs such as mood stabilizers, antidepressants, anxiolytics, and hypnotics. These drugs are administered to treat the peripheral symptoms of schizophrenia, such as agitated or aggressive behaviors, anxious or depressive mood, and insomnia. Although these drugs are widely used, the rate of this combined medication administration has been seldom reported.

In the fourth REAP survey (Yang et al., 2018), the rate of concomitant use of mood stabilizers was 14.0%, antidepressant was 12.0%, anxiolytics was 27.9%, hypnotics was 9.3%, and antiparkinsonians was 45.1%. In this study, the calculation formula of psychotropic drug load (PDL) was proposed to estimate the amount of psychotropic drugs consumed by a patient in a day. PDL is the sum of the daily dose of each psychotropic drug prescribed divided by its defined daily dose in the 5 pharmacological classes. The mean PDL in this study was 2.61, with the highest in Japan (4.13) and the lowest in Indonesia (1.16). This wide variation reflects the large differences in prescription pattern between countries.

Toto et al (2019) conducted a survey on 30908 inpatients with schizophrenia from Germany, Switzerland, Austria, Belgium, and Hungary. The results also revealed the rates of concomitant psychotropics used. The rates were as follows: antipsychotics 94.8%, tranquilizers (anxiolytics) 32%, antidepressants 16.5%, anticonvulsants 14.1%, lithium 2.1%, hypnotics 8.1%, and antiparkinsonians 16%. The polypharmacy rates (≥5 drugs) increased from 19% in 2000 to 26.5% in 2015, and psychiatric polypharmacy (≥3 psychotropic drugs) was noted in 44.7% of patients. These prescription patterns illustrate the clinical significance of APP and combined medication in the real world.

Tiihonen et al. (2012) conducted a study to link national databases of mortality and medication prescribed to 2588 patients with schizophrenia hospitalized in Finland to investigate all-cause mortality during the use of antipsychotics, antidepressants, or benzodiazepines. The results revealed that APP was not associated with increased mortality, and the combined use of antidepressant was also not associated with a higher risk of mortality and was associated with markedly decreased suicide

deaths. Interestingly, the combined use of benzodiazepine was associated with a substantial increase in mortality, and this was attributable to both suicidal and nonsuicidal deaths.

Conclusions

Currently, APP has become more acceptable than in previous decades, and more evidence-based studies have proved its benefit. On the basis of recent studies reviewed here, with open large patient groups, most results revealed that a certain proportion of select patients can benefit from APP without further negative consequences in general. Hence, APP in clinical practice should not be considered a dirty little secret anymore. Most current treatment guidelines from different countries and organizations prefer APM and discourage all APP; hence, such guidelines should be revised regarding the use of APP in clinical practice. Because APP should not be a fashion either, Stahl (2013) has proposed a dozen suggestions regarding the transition from APM to APP, and these suggestions can be applied as tentative guidelines for APP use at present.

As there is no consensus on the ideal rate of APP and the combined use of other psychotropic drugs, the conception of a Health Care Quality Indicator Project (Arah et al., 2006; Carinci et al., 2015) can be utilized. In this project, a set of indicators is developed by comparing data from different resources, and then the exact positions of these indicators can be learned by clinicians and health administrators to obtain consistent results. Thus, according to the 2 compatible results from Asia (Yang et al., 2018) and Europe (Toto et al., 2019) and previous reports of APP, we suggest the following approximated ideal rates of maintenance treatments in patients with schizophrenia: APP, 30%; combined mood stabilizer, 15%; combined antidepressant, 10%; combined anxiolytics, 30%; and combined hypnotic, 10%, with ADL approximately 1.5 and PDL approximately 2.0. A large discrepancy in the use of anticholinergics exists between Asia (Yang et al., 2018) and Europe (Toto et al., 2019) (45.1% vs 16%). This difference might be because Asian patients have been more susceptible to extrapyramidal side effects (Binder and Levy, 1981; Ormerod et al., 2008).

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