

ANTIPSYCHOTICS: TO COMBINE OR NOT TO COMBINE?

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SUMMARY

Antipsychotic monotherapy is strongly recommended in the treatment of schizophrenia. However, antipsychotic polypharmacy (APP) is common in clinical practice, and appears to be related to illness severity and duration, treatment-refractoriness, hospitalization status, duration of hospitalization, geographic region and age. Given the high number of different antipsychotic combinations reported in the literature and prescribed in clinical practice, there are perhaps more differences than similarities between such combinations. While the majority of combinations increase side-effect burden, limited evidence suggests benefits of certain combinations. Until more data are available, APP should be reserved for difficult-to-treat patients, with careful consideration of pharmacodynamics properties and doses of each drug, as well as close monitoring.

Key words: antipsychotic polypharmacy (APP) - treatment of schizophrenia

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INTRODUCTION

In spite of growing number of antipsychotics in clinical practice, treatment of schizophrenia remains to be a challenge every day. Patients with schizophrenia exhibit marked interindividual variability in their responses to antipsychotics, and some of them have poor response to several antipsychotics, or even no response at all. Common strategy in management of these difficult-to-treat patients is the combination of psychoactive drugs.

Antipsychotic polypharmacy (APP) refers to the co-prescription of more than one antipsychotic drug for a given patient, and differs from augmentation, which is the addition of other psychoactive drugs to current antipsychotic regimen. It was reported 40 years ago that polypharmacy in psychiatry represents an example of a "legitimate" but unnecessary use of psychotropic agents (Sheppard et al. 1974). Although this article was published long before the introduction of second generation antipsychotics (SGAs), APP still remains a common issue in clinical practice.

RATES OF APP

In spite of recommendation for monotherapy given at the maximal tolerated dose (Goodwin et al. 2009), APP is widely prescribed. It has been investigated in epidemiological studies, with both cross-sectional and longitudinal design, cross-sectional studies in different in-and out-patient populations, retrospective chart analyses, as well as in randomized controlled trials. The prevalence of APP in schizophrenia spectrum disorders differs in different settings. It appears to be related to illness severity, treatment-resistance, hospitalization

status, duration of hospitalization, geographic region, duration of illness, and age (Correll & Gallego 2012, Gallego et al. 2012a, Novick et al. 2012, Xiang et al. 2012, Kristiansen et al. 2013, Soukas et al. 2013, Teo et al. 2013). The highest use of APP was reported in treatment-refractory patients who were receiving ECT, where it was reported in 72.2% of patients (Kristiansen et al. 2013). Moreover, patients who were treatment-resistant were more likely to be on APP compared to non-resistant patients (Teo et al. 2013). Literature review indicates that APP is prescribed for patients who are difficult to treat with standard antipsychotic monotherapy (Correll & Gallego 2012). Some patients may need antipsychotic doses higher than maximally recommended. These patients will often get two instead of one antipsychotic. The use of APP appears to be related to hospitalization. The frequency of APP prescription was 51.6% in the sample of hospitalized Asian patients older than 55 years (Xiang et al. 2012). In a total 16,083 of Finish patients with schizophrenia, who were at least once hospitalized, the prevalence of APP was 46.2%, and the longer the duration of schizophrenia, the more common the APP (Soukas et al. 2013). In this large epidemiological sample, APP was also associated with long hospitalizations (Soukas et al. 2013). Patients who were on APP were also reported to have received higher antipsychotic doses (Procyshyn et al. 2010, Xiang et al. 2012). The prescription of APP was further associated with younger age, greater illness severity, acuity, complexity, chronicity, refractoriness, and, interestingly, with male sex (Correll & Gallego, 2012). The largest study of APP prevalence rates and correlates, which included 147 studies with 1,418,163 participants, 82.9% of whom were diagnosed with schizophrenia, reported a global median of 19.5% of

patients who were receiving APP (Gallego et al. 2012a). However, this study also revealed substantial regional differences, in terms that pooled APP rates were lower in North America (16%) compared to both Asia (32%) and Europe (23%) (Gallego et al. 2012a). Among antipsychotics, quetiapine is most commonly used in polypharmacy combinations (Essock et al. 2011, Correll & Gallego 2012). While olanzapine was found to have the highest monotherapy rate throughout 12 months (66.8%), quetiapine had the lowest (43.4%) (Novick et al. 2012). Similarly, 61.5% olanzapine-treated patients received antipsychotic monotherapy in Japanese out-patients (Ye et al. 2012). On the contrary, olanzapine showed the highest rates of use in polytherapy in Catalonia (37.1%) (Bernardo et al. 2012). However, unlike the former studies, the latter study analysed all out-patient antipsychotic prescription, which was not limited only to schizophrenia (Bernardo et al. 2012). In this study, 27.0% of patients treated with LAI (Long acting injectable) antipsychotics, were also receiving oral antipsychotics (Bernardo et al. 2012). Another study reported even higher use (46%) of concomitant oral and LAI antipsychotics (Aggarwal et al. 2012). Unlike oral antipsychotics, a combination of two different LAI antipsychotics appears to be very uncommon (Bernardo et al. 2012).

RISKS AND BENEFITS OF APP

In spite being commonly prescribed, relative risks and benefits of APP are largely unknown (Correll & Gallego 2012). Patients with schizophrenia who switched from APP to monotherapy, decreased their body mass index (BMI) compared to those who stayed on APP, and, in turn, increased their body mass index (Essock et al. 2011). Majority of patients (69%) were able to tolerate switching from polypharmacy to monotherapy, with no worsening of their symptoms (Essock et al. 2011). However, the other one third of patients in the Essock et al. 2011 study, needed to return to APP (Stahl 2013). Compared with antipsychotic monotherapy, concomitant use of 2 or more antipsychotics was not associated with increased mortality (Tiihonen et al. 2012). Interestingly, the use of antidepressants was associated with less frequent antipsychotic polypharmacy (Gallego et al. 2012a, Soukas et al. 2013), and with markedly decreased suicide deaths (Tiihonen et al. 2012). General risks and benefits of drug combinations are provided in table 1.

Based mostly on uncontrolled and observational studies, there is some evidence that APP carries an increased side effect burden compared to monotherapy (Gallego et al. 2012b). The strongest evidence was reported for Parkinsonian side effects and anticholinergic use, followed by increased prolactin levels (Gallego et al. 2012b). However, given the high number of different antipsychotic combinations reported in the literature and applied in clinical practice, there are

perhaps more differences than similarities between such combinations. For example, while most antipsychotic combinations result in weight gain (Essock et al. 2011, Gallego et al. 2012b), others may actually result in weight loss (Henderson et al. 2009, Fan et al. 2013). One analysis of prescription database for antipsychotics, has revealed 198 different combinations of two antipsychotics, with the most frequent being the combination of first generation antipsychotics (FGAs) and SGAs (Bernardo et al. 2012). Twenty different antipsychotic combinations were reported in overall 40 patients in phase 3 of Catie trial, who had relatively severe psychopathology and who stopped their previous medication due to inadequate therapeutic effect (Stroup et al. 2009). Combinations of specific antipsychotics are provided in table 2.

Interestingly, most studies reported that aripiprazole augmentation was associated with a decrease in certain side effects (Gallego et al. 2012b).

Table 1. Potential risks and benefits of APP

Risks	Benefits
Increased adverse effects burden (weight gain, sexual dysfunction, dry mouth)	Longer time to all-cause discontinuation
Greater anticholinergic treatment	Targeting broader range of symptoms
Higher total health service costs	Improvement of symptoms
Higher total daily dose of antipsychotics	

Henderson et al. 2009, Molina et al. 2009, Procyshyn et al. 2010, Essock et al. 2011, Baandrup et al. 2012, Gallego et al. 2012a, Gallego et al. 2012b, Hashimoto et al. 2012, Fan et al. 2013

PHARMACOKINETIC AND PHARMACODYNAMIC INTERACTIONS OF APP

Drug combinations can give rise to pharmacokinetic and/or pharmacodynamic interactions. Combining different drugs must consider substrate, inhibitor, and inducer properties for the cytochrome P450 (CYP) isoenzymes of each given drug. Although most, but not all antipsychotics are substrates for CYP enzymes, they are usually not likely to significantly influence CYP activity. For example, neither risperidone nor haloperidol had significant effects on quetiapine pharmacokinetics (Potkin et al. 2002). Risperidone did not influence clozapine pharmacokinetics (Chetty et al. 2009).

On the other hand, pharmacodynamic interactions do occur and could be both beneficial and harmful. In fact, beneficial interactions are believed to increase the efficacy of such a combination. Harmful actions of combined drugs can induce adverse reactions, as provided in table 3.

Table 2. Certain combinations of antipsychotics

Antipsychotic combination	Study population	Results	Reference
Olanzapine and aripiprazole	Overweight and obese patients with schizophrenia and schizoaffective disorder, treated with stable dose of olanzapine, double-blind study	↓ in weight, BMI and tryglicerydes	Henderson et al. 2009
Olanzapine and amisulpride	Schizophrenic patients partially responsive to olanzapine, open-label study	Improvement in symptoms of schizophrenia	Molina et al. 2009
Clozapine and aripiprazole	Patients treated with clozapine, double-blind study	Improvements in glucose tolerance test, ↓ in plasma LDL, ↓ in LDL particle numbers, ↓ in the lean mass	Fan et al. 2013
Clozapine and sertindole	Patients treated with clozapine for at least 6 months with no sufficient response, double-bind study	No improvement, no change in metabolic paramethers, 12-millisecond QTc prolongation	Nielsen et al. 2012
Clozapine and SGAs	Analysis of 14 double-blind studies	Modest benefit	Taylor et al. 2012
Quetiapine or risperidone and aripiprazole	Patients stabilized on risperidone or quetiapine, double-blind study	No improvement in efficacy, ↓ in prolactin levels in risperidone-treated patients	Kane et al. 2009
Olanzapine or clozapine and ziprasidone	Patients on clozapine or olanzapine, with diabetes, impaired fasting glucose, or insulin resistance, open study	No changes in weight, BMI, cholesterol levels, or fasting glucose, no changes in efficacy	Henderson et al. 2009

Table 3. Pharmacodynamic interactions potentially causing adverse events

Effect on receptors	Consequences of the blockade	Antipsychotics with high affinity
Potent dopamine D2 antagonism in striatal area	EPS	Fluphenazine, Haloperidol, Risperidone
Dopamine D2 antagonism in hypothalamic infundibular system	Hyperprolactinemia	Amisulpride, Haloperidol, Sulpiride, Risperidone, Paliperidone, Zotepine
Histamine H(1) antagonism	Weight gain, sedation	Clozapine, Olanzapine, Quetiapine
Acetylcholine M(1) antagonism	Anticholinergic side effects such as dry mouth, constipation, cognitive impairment	Clozapine, Olanzapine, Quetiapine
Alpha-1 adrenoceptor antagonism	Orthostatic hypotension, tachycardia	Asenapine, Chlorpromazine, Clozapine, Iloperidone, Risperidone, Sertindole, Ziprasidone

Bymaster et al. 1996, Torre & Falorni 2007, Minzenberg & Yoon 2011, He et al. 2013

The addition of a high potency dopamine D2 antagonist to a low potency antagonist and broad-receptor spectrum antipsychotics like clozapine or quetiapine is the logical combination to treat different symptoms. Preclinical study suggests that, unlike risperidone and chlorpromazine, quetiapine did not potentiate the cataleptogenic activity of haloperidol, suggesting that the combined administration of quetiapine with haloperidol did not aggravate EPS (Tada et al. 2004). Mechanisms of action other than D2 blockade, and hence other combinations of antipsychotics with different receptor profiles might be more relevant for negative, cognitive, affective symptoms (Goodwin et al. 2009), or insomnia. Since there is a great heterogeneity of antipsychotics in binding to different receptors, definition of potentially treatable therapeutic targets in particular patients is important when considering APP (Stahl et al. 2013). Measuring plasma concentrations, i.e., therapeutic drug monitoring (TDM), is valuable to adjust antipsychotic dose when

adverse events or lack of efficacy are suspected. Pharmacogenetic studies suggest that certain gene variations, such as those of dopaminergic system, might help predict the development of acute EPS (Živković et al. 2013).

Although numerous studies have investigated APP, due to differences in methodology, study population, geographical region, and many different combinations, it is difficult to draw simple conclusions. Since majority of studies were cross-sectional (Gallago et al. 2012a), data regarding long-term APP are scarce. It cannot be excluded that some APP in those studies was either part of cross-titration or transient in acute care settings. On the other hand, the risk for some adverse effects, such as tardive dyskinesia or metabolic syndrome, increases with long-term treatment. In addition, few studies of APP reported psychopathology ratings or adverse effects, highlighting another under-researched area (Gallego et al. 2012a). Namely, as it was reported 40 years ago, the use of polypharmacy is similar in kind to

developing a new generation of treatment forms, essentially investigational with insufficient evidence available regarding compatibility, dose response factors, side effects and relative efficacy (Sheppard et al. 1974). While switches to monotherapy can be accomplished successfully for the majority of patients (Essock et al. 2011), it should be first-line treatment of schizophrenia. Monotherapy should be given at the maximal tolerated dose and at least two antipsychotics of different action/tolerability and clozapine should be given as a monotherapy before a combination is considered (Goodwin et al. 2009). Guidelines are based on the highest levels of evidence, which are double-blind clinical trials. Study population in those trials is strictly selected. Those trials are necessary, but only represent the tip of the iceberg of patients with schizophrenia. Real world psychiatrists, in turn, treat all schizophrenic patients, including those who do not respond to numerous monotherapies, who have uncontrolled impulsivity, violence, aggression and active substance abuse, who are increasingly housed long-term on forensic units or prisons following commission of violent crimes, and/or who may have borderline, affective, and even antisocial psychopathic features (Stahl 2013). While there is only limited evidence to support the combination of two or more antipsychotics in schizophrenia, further evidence from well conducted clinical trials is needed.

It should be noted, however, that APP is not limited to schizophrenia spectrum disorders. It has also been reported in patients with bipolar disorder (16.9%), and major depression (14.3%) (Procyshyn et al. 2010). Several properties of SGAs other than D2 antagonism, such as effects on different serotonin and nor-epinephrine receptors and transporters, as well as partial D2 agonism, are proposed to contribute to their antidepressant activity (Šagud et al. 2011).

CONCLUSION: TO COMBINE OR NOT TO COMBINE?

There are no easy answers to this simple question. Antipsychotic monotherapy is strongly recommended in the treatment of schizophrenia. However, each patient is different. Severe psychopathology and/or treatment resistance justify some reasonable combinations of antipsychotics. While numerous combinations are prevalent in clinical practice worldwide, safety and efficacy reports of those combinations are scarce. Experts agree that more data are needed in sufficiently powered, randomized controlled trials. Furthermore, it has recently been suggested that, rather than continuing to deny APP to anyone, guidelines should define which patients are the candidates for APP (Stahl 2013). Until then, using the existing knowledge, careful treatment consideration and monitoring of any individual patient would help us to maximize benefit and minimize harm of antipsychotics.

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