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Antipsychotic Polypharmacy in Schizophrenia: Why Not?

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Antipsychotic polypharmacy (APP), defined as the use of 2 or more antipsychotics, is common in schizophrenia, with a global median rate of 19.6% (interquartile range, 12.9%–35.0%), although substantial variations exist between treatment settings, regions, populations, and prescribers.[1] Reasons for APP are diverse and include trying to enhance antipsychotic efficacy or targeting different symptoms or symptom domains that are insufficiently addressed by antipsychotic monotherapy, including anxiety, insomnia, aggressive/impulsive behaviors, or negative symptoms.[2] APP has also been associated with the desire to lower the dose and/or reduce side effects of the original antipsychotic, the process of ongoing or aborted cross-titration, combination of different antipsychotic formulations, and prescriber and/or patient/family preference.[2] Interestingly, clinicians who prescribe more APP tend to be more experienced, see more patients per week, continue the APP regimen of prior prescribers, and have a preferred APP choice, although different clinicians disagree on specific top APP choices.[3]

This frequency of APP is particularly relevant considering that current treatment guidelines essentially recommend antipsychotic monotherapy both after the first episode and for treatment maintenance in schizophrenia patients across the illness trajectory, arguing that the level of evidence to support APP, regarding both its efficacy and its safety, is insufficient.[4–6] In case of treatment resistance, the cornerstone of treatment is clozapine.[7] Unfortunately, clozapine remains heavily underutilized, with approximately a 5% rate of use, despite the fact that 25%–40% of patients with schizophrenia would be candidates for it[8]; however, as with APP, clozapine utilization varies greatly across regions, settings, and prescribers.[9] APP is recommended in treatment guidelines only after multiple failed monotherapy attempts, including clozapine, and careful consideration of the pharmacokinetic, pharmacodynamic, and adverse effect profiles of the two antipsychotics that are to be combined.[4–6]

What Is the Evidence From Controlled Clinical Trials?

In a first comprehensive meta-analysis of 19 randomized controlled trials (RCTs) including 1,216 patients with schizophrenia that compared APP with antipsychotic monotherapy,[10] APP was associated with a 24% lower risk of treatment failure/nonresponse, translating into a number needed to treat of 7. However, greater efficacy of APP was influenced by studies conducted in China, lasting > 10 weeks, with combinations including clozapine as well as APP initiated from the start of treatment, which did not allow to address the question of whether adding a second antipsychotic is helpful when a patient fails to respond to antipsychotic monotherapy. At the same time, another meta-analysis focusing exclusively on APP in RCTs involving clozapine concluded that advantages of APP were restricted to the 14 open-label studies for symptom reduction and 10 open studies for reducing the risk of treatment failure, whereas neither of these two key outcomes favored APP involving clozapine in any of the 6 meta-analyzable blinded RCTs.[11]

The most recent and updated meta-analysis of 31 RCTs comparing APP with antipsychotic monotherapy in schizophrenia[12] again showed only efficacy advantages of APP in open-label or low-quality studies (symptom reduction, measured as standardized mean difference [SMD] = −0.83; 95% CI, −1.16 to −0.50; $P < .0001$). In open/low-quality studies, APP was also superior to AP monotherapy regarding study-defined treatment response (risk ratio [RR] = 1.30; 95% CI, 1.04 to 1.64; $P = .024$). In contrast, higher quality, blinded RCTs did not appear to show any advantage of APP over monotherapy for the treatment of schizophrenia symptoms, measured both as a continuous outcome (SMD = −0.30; 95% CI, −0.78 to 0.19; $P = .23$) and when assessing treatment responder status (RR = 0.99; 95% CI, 0.72 to 1.39; $P = .99$). These findings were replicated in high-quality studies for APP including clozapine regarding symptom reduction (SMD = −0.30; 95% CI, −0.78 to 0.19; $P = .23$) and response status (RR = 1.01; 95% CI, 0.78 to 1.33; $P = .92$). Interestingly, augmentation strategies based on adding aripiprazole to a D_2 antagonist were associated with negative symptom improvement, even in high-quality studies (SMD = −0.41; 95% CI, −0.79 to −0.03; $P = .036$). Surprisingly few adverse effect differences emerged, including more prolactin elevation, but less insomnia when combining 2 D_2 antagonists, but also reduced prolactin levels and body weight when combining a D_2 partial agonist with a D_2 antagonist.[12] A reduction of body weight and cardiometabolic risk factors when aripiprazole is added to clozapine has been described before,[13] but data in that meta-analysis were limited by the short study durations, relatively few studies and patients, and emergence of agitation/akathisia with this APP combination.

However, the authors of the most recent comprehensive meta-analysis[12] of APP acknowledged that it would be possible that patient subgroups potentially benefiting from APP the most might not be enrolled in randomized trials and, especially, in blinded studies, as they were too sick or had limited illness insight. This suggestion seems to be supported by a study of 127 patients with schizophrenia stabilized on APP who were randomized to stay on APP or be switched openly to antipsychotic monotherapy, with the remaining antipsychotic being chosen jointly by the physician and patient.[14] At the end of the 6-month assessment period, 86% of the patients

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randomized to remain on APP were still taking both medications vs only 69% of those assigned to switch to monotherapy. Thus, compared to APP, 17% more patients converted to antipsychotic monotherapy stopped that treatment. Notably, most monotherapy discontinuations entailed returning to the original APP. Although anxiety about being switched openly to antipsychotic monotherapy could have biased the results against the monotherapy switch, these results seem to support the idea that a subgroup of people with schizophrenia may benefit from APP.

What Is the Evidence From Large, Nationwide Cohorts?

To avoid randomization bias (ie, selection of patients agreeing to an RCT), enhance generalizability of the data, and allow for long-term follow-up and large numbers of patients, nationwide database studies can be very helpful. A recent such nationwide Finnish cohort study[15] observed 62,250 patients with schizophrenia during the use of 29 different antipsychotic monotherapy and APP types and found that, altogether, any APP was associated with a 7%–13% lower risk of psychiatric rehospitalization vs any antipsychotic monotherapy. Clozapine was the only monotherapy among the 10 best treatments. Notably, these findings were confirmed for all-cause hospitalization, as well as for mortality, where clozapine (rank 13) and olanzapine (rank 15) were the only two monotherapies among the top 15 treatments reducing mortality significantly vs no antipsychotic treatment. Other sensitivity analyses were consistent with the primary outcomes.

The Disconnect Between Efficacy and Effectiveness

This apparent disconnect between meta-analyses of double-blind and open-label studies and between RCTs and cohort studies is not unique to APP, but part of an observed discrepancy between clinician perception and evidence-based research, as well as between efficacy and effectiveness. Notably, similar incongruities have been observed for the evaluation of efficacy of long-acting injectable antipsychotics (LAIs) and of clozapine wherein meta-analyses of RCTs did not show superiority of LAIs vs oral antipsychotics[16] or of clozapine vs other second-generation antipsychotics,[17] while mirror-image[18] and cohort[19,20] studies did show superiority. One potential explanation for this disconnect could be related to the aforementioned selection bias, in that sicker patients or those at higher risk for a poor outcome (in whom LAIs, clozapine, and APP might be especially effective) are underrepresented in RCTs that suffer from multiple exclusion criteria and that focus on efficacy,[21] while clinicians are more interested in effectiveness for a broader and possibly more representative sample of patients in need of alternative treatments that go beyond many first-line approaches.

Nevertheless, it is also possible that clinicians may abort antipsychotic switches when patients improve and that this time coincidence favors continuation of APP in stabilized patients who might have remained improved/stable, even if the antipsychotic switch had been completed. The fact that as many as 69% of patients with schizophrenia on APP were able to tolerate the switch to and remain on antipsychotic monotherapy[14] indicates that likely more patients receive long-term APP than might be necessary.

Conclusion

Data on APP indicate that, in high-quality RCTs, evidence for superior efficacy vs antipsychotic monotherapy is scant (possibly with the exception of reductions in negative symptoms when combining a partial D_2 agonist and a D_2 antagonist). Moreover, about 2 out of 3 patients on APP may be safely converted to antipsychotic monotherapy, but a subgroup of maybe 1 out of 6 patients might benefit from continued APP. Additionally, the most recent Finnish, nationwide database study[15] suggested that APP may be associated with significantly lower psychiatric hospitalization risk due to any psychiatric and nonpsychiatric reasons and may also reduce mortality more than treatment with antipsychotic monotherapy. More importantly, to reduce the risk of psychiatric hospitalization, except for the aripiprazole + clozapine combination, no APP appeared to be superior to clozapine alone. Taken together, the combination of a partial D_2 agonist with a D_2 antagonist could be desirable for some patients, but data to support other combinations are lacking. Nevertheless, in principle, when considering combining antipsychotics, it would make most sense to combine agents with different pharmacodynamic dopamine actions, such as combining a full antagonist with a partial agonist, or a tight D_2 binding agent with one with less potent D_2 binding (such as quetiapine or clozapine). Similarly, combined antipsychotics should not double up on the same dopaminergic and/or extradopaminergic activity and related adverse effect(s), including sedation, insomnia, weight gain, Parkinsonism, akathisia, prolactin elevation, and QTc prolongation. Rather, antipsychotics with complementary adverse effect profiles should preferentially be combined. However, clinicians may also need to consider combining an antidepressant with an antipsychotic instead, as this combination was superior to antipsychotic polytherapy for prevention of hospitalization in a large US Medicaid database study.[22] Additionally, antidepressant augmentation of antipsychotic treatment may improve negative symptoms.[23,24]

Given the established effectiveness of clozapine for treatment-refractory psychotic symptoms,[20,25] the risks and uncertainties regarding the efficacy of APP[2] have to be weighed against the well-established risk/benefit ratio of clozapine treatment. However, due to the considerable adverse effect profile of clozapine[26] and clinicians' tendency to reach for APP before or instead of using clozapine,[27] the search for new treatments and treatment mechanisms that can improve outcomes in patients who only insufficiently benefit from antipsychotic monotherapy[28,29] has to continue and be a primary objective for schizophrenia research.

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