Antipsychotic Polypharmacy, Part 2: Why Use 2 Antipsychotics When 1 Is Not Good Enough?

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Last month's CORNER article examined the potential reasons and rationales for and concerns about the combined use of antipsychotics.[1] This article will review the evidence regarding the efficacy and safety of antipsychotic polypharmacy in the treatment of schizophrenia.

Does Antipsychotic Polypharmacy Lead to Enhanced Efficacy?

Besides a number of open-label studies and case series,[2–4] remarkably few randomized controlled trials have compared antipsychotic monotherapy with antipsychotic polytherapy. To date, only 6 controlled studies[5–10] published in English investigated the efficacy of antipsychotic cotreatment, providing inconclusive evidence. In 5 trials,[5–9] a high-potency D_2 antagonist was added to clozapine in refractory schizophrenia patients. While 2 of these studies reported superiority of adding either sulpiride or risperidone to clozapine,[5,6] the other 3 did not show superiority of adding risperidone to clozapine.[7–9] In the latest study,[10] aripiprazole or placebo was added to clozapine for 8 weeks. While there was no difference in the reduction of the Positive and Negative Syndrome Scale total score, aripiprazole augmentation was significantly superior regarding negative symptoms measured by the Positive and Negative Syndrome Scale and the Scale for the Assessment of Negative Symptoms.

These contradictory results may be due to different trial methodologies. For example, a trial duration of 10 weeks or longer has been reported to mediate the superiority of antipsychotic cotreatment.[11] On the other hand, the overall negative results may also reflect a ceiling effect of antipsychotic action in clozapine nonresponders. In a recently completed meta-analysis without language restrictions,[12] 19 randomized controlled trials (N = 1216) of antipsychotic combinations were analyzed. Across these studies, antipsychotic cotreatment was superior to monotherapy regarding study-defined efficacy, as well as regarding 2 Clinical Global Impressions-Improvement scale thresholds.[12] However, the data were highly heterogeneous and there was a potential publication bias against studies with negative outcomes, which limited the degree to which these data could inform clinical practice and guidelines.

Is Antipsychotic Polypharmacy Safe?

Several studies reported increased nonserious side effects in combination groups, including extrapyramidal side effects and greater anticholinergic use, increased dyskinesia, mild akathisia, hyperprolactinemia, and hypersalivation.[13] It is unclear whether combined antipsychotic use is possibly associated with an increased risk for serious adverse events, such as increased rates of diabetes[14] and death from cardiac causes.[15,16] While concerning, the findings in these 3 uncontrolled and cross-sectional studies could also be explained by prescriber or cohort effects, in that more chronically and severely ill patients who have more risk factors for adverse cardiac outcomes are predisposed to receive antipsychotic polypharmacy. This possibility is supported by a study[17] in which the finding of a significantly higher rate of metabolic syndrome in the antipsychotic polytherapy group (N = 100) compared to the monotherapy group (N = 264) was lost after controlling for traditional cardiovascular risk factors that were more prevalent in the combination group.

Can Antipsychotic Polypharmacy Improve Tolerability?

Several studies suggest that adding an antipsychotic with less adverse event potential to one with greater adverse event potential in certain areas may lead to a reduced side effect burden. Findings have included decreased rates of hypersalivation, sedation/hypersomnia, hyperprolactinemia, and relevant improvements in weight and/or metabolic indices.[10,13] While at least some of this side effect–sparing effect could be related to clozapine dose reduction,[18,19] lower side effect rates were also observed when the dose of the first antipsychotic, namely clozapine, was not reduced.[10,20]

Next Steps

Results from several ongoing or completed randomized controlled studies are hoped to further inform clinical practice regarding the potential benefits and risks associated with antipsychotic cotreatments. These include 2 recently completed, 16-week, double-blind, placebo-controlled, multicenter trials of aripiprazole augmentation. In one study[21] (N = 207), aripiprazole or placebo was added to clozapine after inadequate response and a weight increase of at least 2.5 kg. In the other trial[22] (N = 323), aripiprazole or placebo was added to risperidone or quetiapine after inadequate psychotic symptom response despite at least 4 weeks of monotherapy. Ongoing studies include 1 placebo-controlled augmentation study[23] of clozapine with aripiprazole lasting 8 weeks including a 6-month and 12-month follow-up phase (projected N = 61). Moreover, 2 active controlled augmentation studies compare the addition of aripiprazole or haloperidol to clozapine over 12 months (projected N = 216)[24] or the addition of ziprasidone or risperidone to clozapine (duration not mentioned; projected N = 24).[25]

In addition, studies are required that examine the most utilized cotreatment strategies, including nonclozapine second-generation antipsychotic combinations with each other or with a first-generation antipsychotic. To exclude the possibility of insufficient dosing in the monotherapy arm, studies may need to monitor serum antipsychotic levels and include a "high dose" lead-in phase, a "high dose" monotherapy arm, or both a therapeutic dose combination group and a reduced dose cotreatment arm.[13] Finally, the continued need for 2 antipsychotics in patients who are improved and stable on antipsychotic polytherapy should be explored by randomly discontinuing the antipsychotic that was prescribed first and that was augmented with a second antipsychotic due to insufficient response, and allowing for blinded dose optimization of the antipsychotic that was introduced second. Such data are currently collected in a patient subgroup as part of a federally funded study entitled "Effectiveness of Switching Antipsychotic Medications."[26]

Conclusions

Antipsychotic polypharmacy is common in the treatment of schizophrenia. Controlled efficacy and safety data are mostly lacking, particularly for nonclozapine combinations. Antipsychotic polypharmacy may be useful in certain

scenarios, but more studies are needed to determine the magnitude of effects regarding efficacy and tolerability, and the unique contribution of specific combination treatments. The (largely unknown) risks and benefits of antipsychotic cotreatment have to be weighed against the known effectiveness of clozapine for refractory schizophrenia. Although hard to design and conduct, high-quality, longer-term, controlled cotreatment and discontinuation studies in patients treated with antipsychotic combinations are needed to provide sufficient evidence that could guide clinical practice.

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