Antipsychotic Polypharmacy: Are Two Ever Better Than One?

How do we account for the widespread use of combination treatment with antipsychotics? The prevalence of antipsychotic polypharmacy is currently estimated to be between 30% and 40%, despite a lack of supporting evidence. In this issue of the *Journal*, Essock and colleagues (1) make a major contribution with the first controlled trial examining polypharmacy with antipsychotics other than clozapine. In this 6-month open-label randomized trial, remaining on polypharmacy was superior to switching to monotherapy with respect to the primary endpoint, all-cause discontinuation; participants were twice as likely to discontinue treatment after switching to monotherapy. However, the two treatment groups did not differ in symptoms or side effects assessed by blind raters, except for a modest (roughly 1%) weight gain associated with polypharmacy and modest (roughly 2%) weight loss that followed the switch to monotherapy.

Given the many possible combinations of antipsychotics and lack of a clear rationale to favor any single combination, Essock and colleagues used an "all-comers" design to randomly switch participants from polypharmacy to monotherapy. This approach allowed them to study most, if not all, potential antipsychotic combinations and captured polypharmacy as it is practiced in the community. The primary endpoint, all-cause discontinuation, is a highly meaningful outcome that reflects both tolerability and effectiveness from the shared perspective of clinician and patient. Essock and colleagues note, however, that in the context of unblinded treatment, all-cause discontinuation may have introduced a bias in favor of polypharmacy. Unfortunately, it is not possible to gauge the effect of this potential bias; for example, it may have been offset by limiting enrollment to patients who were not optimally treated with polypharmacy. The observed superiority of maintaining polypharmacy over switching to monotherapy under open-label conditions reflects the experience of clinicians and patients when attempting to simplify antipsychotic regimens but may not tell us much about the true value of antipsychotic combination treatment.

"Polypharmacy does not produce side effects; it is the specific drugs and doses that matter."

A recent meta-analysis of 19 studies involving 1,229 subjects, conducted by Correll and colleagues (2), found a significant advantage for antipsychotic polypharmacy relative to monotherapy on measures of efficacy and all-cause discontinuation. Of interest were two predictors of superiority with polypharmacy: antipsychotic combinations that included clozapine were more likely to be superior, as were combinations that were initiated simultaneously (rather than adding the second drug in patients unresponsive to monotherapy). Most of the positive studies were conducted in China. While the advantage of polypharmacy over monotherapy in these studies could merely reflect a higher additive antipsychotic dose with polypharmacy, the meta-analysis by Correll and colleagues did not support this explanation.

Combining medications with differing mechanisms of action is standard practice for the treatment of refractory patients with hypertension, epilepsy, and many other medical conditions. Among antipsychotics, clozapine is the only agent that appears to possess a different, albeit unknown, mechanism of action and thus is the only agent

that would seem appropriate for combination treatment in refractory patients. Whereas the antipsychotic effect of other antipsychotics is directly linked to antagonism of dopamine D_2 receptors, clozapine achieves superior antipsychotic efficacy with substantially lower D_2 occupancy (3). Kapur and colleagues (4) demonstrated that addition of a high-potency selective D_2 blocker (haloperidol) to clozapine raises D_2 occupancy to a level associated with maximal antipsychotic effect. In theory, this approach might improve antipsychotic response in some patients who do not respond fully to clozapine and was shown to be effective in two placebo-controlled trials (5, 6) but was ineffective in several others (2). This hypothesis has two important caveats: it would be expected to work only if the second antipsychotic is prescribed at a dose sufficient to achieve optimal D_2 occupancy and only in patients with psychosis that is at least partially responsive to optimal D_2 blockade. Many patients who receive clozapine treatment do so only after displaying minimal or no response to D_2 blockers, thus making combination treatment unlikely to be of substantial benefit. Studies that were found to demonstrate added efficacy from polypharmacy in the meta-analysis by Correll and colleagues (2)—those in which clozapine was initiated simultaneously with a second antipsychotic agent in acutely exacerbated patients—may have examined individuals with psychosis more likely to be responsive to D_2 antagonism.

Because the antipsychotic combinations studied by Essock and colleagues are not known to differ in therapeutic mechanism, they would not be expected to improve efficacy in combination treatment relative to monotherapy prescribed at an optimal dose. The absence of change in symptom ratings after switching to monotherapy is consistent with this expectation, although participants commonly cited increased symptoms as their reason for discontinuation of monotherapy. If the combinations studied by Essock and colleagues were to improve outcome, enhanced tolerability would seem a more likely explanation. When side-effect profiles of two drugs differ, combined treatment with a reduced dose of each drug might reduce dose-related side effects while maintaining efficacy by additive D_2 blockade. Alternatively, an added drug might improve tolerability and adherence by directly reversing side effects of the first drug; for example, a sedating antipsychotic at bedtime might counteract an activating antipsychotic agent taken in the morning, and addition of aripiprazole may reduce prolactin levels or metabolic side effects (7, 8). However, this explanation for participant preference of polypharmacy was not supported because side effects did not differ following the switch to monotherapy.

As noted by Essock and colleagues, concerns about polypharmacy include the risk of increased side effects, poor adherence, higher mortality rates, and cost. Results from their study did not support concerns about side effects other than weight gain. Polypharmacy does not produce side effects; it is the specific drugs and doses that matter. For example, weight gain might result from polypharmacy that adds olanzapine, whereas switching from polypharmacy to olanzapine monotherapy at a higher dose might also be associated with weight gain. Both side-effect liability and cost vary considerably among agents. The evidence linking polypharmacy to mortality is inconclusive, with several early studies finding an association not replicated by recent studies (9, 10). However, higher doses of antipsychotics in general have been associated with increased cardiac mortality (11), and polypharmacy that results in a high additive dose should be avoided for this reason.

What can clinicians take away from this rather confusing literature? Clearly monotherapy, when tolerated and effective, is optimal. When patients fail to respond to an adequate dose of an antipsychotic, clozapine is the only option with established efficacy. However, relatively few patients remain on a single antipsychotic for long (12), and adherence is often poor even when patients choose to remain on monotherapy. In other words, treating people with schizophrenia may require trials of several antipsychotics in order to find one that is well-tolerated at an effective dose. In some patients, combination treatment may be preferred after all other reasonable options have failed.

In such patients, combination treatment using the lowest possible dose of each drug should be evaluated in a systematic, time-limited trial, and the evidence for benefit should be clear and well-documented if the combination is to be continued. As always, clinician judgment combined with patient preference must take over when treatment algorithms fall short.

References

1. Essock SM, Schooler NR, Stroup TS, McEvoy JP, Rojas I, Jackson C, Covell NH; Schizophrenia Trials Network: Effectiveness of switching from antipsychotic polypharmacy to monotherapy. Am J Psychiatry 2011; 168:702–708
2. Correll CU, Rummel-Kluge C, Corves C, Kane JM, Leucht S: Antipsychotic combinations vs monotherapy in schizophrenia: a meta-analysis of randomized controlled trials. Schizophr Bull 2009; 35:443–457
3. Kapur S, Zipursky RB, Remington G: Clinical and theoretical implications of 5-HT_2 and D_2 receptor occupancy of clozapine, risperidone, and olanzapine in schizophrenia. Am J Psychiatry 1999; 156:286–293
4. Kapur S, Roy P, Daskalakis J, Remington G, Zipursky R: Increased dopamine D_2 receptor occupancy and elevated prolactin level associated with addition of haloperidol to clozapine. Am J Psychiatry 2001; 158:311–314
5. Josiassen RC, Joseph A, Kohegyi E, Stokes S, Dadvand M, Paing WW, Shaughnessy RA: Clozapine augmented with risperidone in the treatment of schizophrenia: a randomized, double-blind, placebo-controlled trial. Am J Psychiatry 2005; 162:130–136
6. Shiloh R, Zemishlany Z, Aizenberg D, Radwan M, Schwartz B, Dorfman-Etrog P, Modai I, Khaikin M, Weizman A: Sulpride augmentation in people with schizophrenia partially responsive to clozapine: a double-blind, placebo-controlled study. Br J Psychiatry 1997; 171:569–573
7. Henderson DC, Fan X, Copeland PM, Sharma B, Borba CP, Boxill R, Freudenreich O, Cather C, Evins AE, Goff DC: Aripiprazole added to overweight and obese olanzapine-treated schizophrenia patients. J Clin Psychopharmacol 2009; 29:165–169
8. Kane JM, Correll CU, Goff DC, Kirkpatrick B, Marder SR, Vester-Blokland E, Sun W, Carson WH, Pikalov A, Assuncão-Talbott S: A multicenter, randomized, double-blind, placebo-controlled, 16-week study of adjunctive aripiprazole for schizophrenia or schizoaffective disorder inadequately treated with quetiapine or risperidone monotherapy. J Clin Psychiatry 2009; 70:1348–1357
9. Baandrup L, Gasse C, Jensen VD, Glenthoj BY, Nordentoft M, Lublin H, Fink-Jensen A, Lindhardt A, Mortensen PB: Antipsychotic polypharmacy and risk of death from natural causes in patients with schizophrenia: a population-based nested case-control study. J Clin Psychiatry 2010; 71:103–108
10. Tiihonen J, Lönnqvist J, Wahlbeck K, Klaukka T, Niskanen L, Tanskanen A, Haukka J: 11-Year follow-up of mortality in patients with schizophrenia: a population-based cohort study (FIN11 study). Lancet 2009; 374:620–627
11. Ray WA, Chung CP, Murray KT, Hall K, Stein CM: Atypical antipsychotic drugs and the risk of sudden cardiac death. N Engl J Med 2009; 360:225–235
12. Lieberman JA, Stroup TS, McEvoy JP, Swartz MS, Rosenheck RA, Perkins DO, Keefe RS, Davis SM, Davis CE, Lebowitz BD, Severe J, Hsiao JK; Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) Investigators: Effectiveness of antipsychotic drugs in patients with chronic schizophrenia. N Engl J Med 2005; 353:1209–1223

DONALD C. GOFF, M.D.
LISA DIXON, M.D., M.P.H.

Address correspondence to Dr. Goff (goff@psych.mgh.harvard.edu). *Editorial accepted for publication March 2011 (doi: 10.1176/appi.ajp.2011.11020314).*

In the last 3 years, Dr. Goff has served as a consultant or advisor to Abbott Laboratories, Astra-Zeneca, Biovail, Bristol-Myers Squibb, Cypress, Dainippon Sumitomo, Eli Lilly, Endo Pharmaceuticals, Forest Laboratories, H. Lundbeck, Hoffman-La Roche, Indevus Pharmaceuticals, Merck, Organon, Ortho-McNeil-Janssen, Pfizer, Proteus, Schering-Plough, Solvay, Takeda, Vanda, Wyeth, XenoPort, and Xytis; he has served on data safety and monitoring boards for Otsuka and Wyeth; and he has received research funding from GlaxoSmithKline, Janssen, Novartis, and Pfizer. Dr. Dixon receives an investigator-initiated grant from Ortho-McNeil Janssen Scientific Affairs, LLC; she has also consulted with Ortho-McNeil on the design of a study to assess the effectiveness of risperidone in the treatment of individuals with schizophrenia who have been released from jail or prison. Dr. Freedman has reviewed this editorial and found no evidence of influence from these relationships.