

# Antipsychotic Polypharmacy: Squandering Precious Resources?

Stephen M. Stahl, M.D., Ph.D.

**Issue:** *Using 2 antipsychotics at the same time is perhaps the most expensive, most widely practiced, yet least evidence-based therapeutic option in psychiatry today.*

## Blending an Antipsychotic Nectar

Atypical antipsychotics represent a major advance in psychopharmacology, based on compelling evidence that monotherapy with atypical antipsychotics has superior benefits over monotherapy with conventional antipsychotics.<sup>1-3</sup> Despite becoming the most expensive drugs in psychiatry and for many health care systems, atypical antipsychotics have now largely replaced conventional antipsychotics due to the perceived greater efficacy of the atypicals.<sup>4</sup> An especially expensive clinical utilization of these already expensive drugs is to combine them with another antipsychotic (polypharmacy) in an attempt to further enhance their efficacy.<sup>5,6</sup> Although only case reports and clinical anecdotes but no well-designed studies suggest that polypharmacy may be beneficial in some patients, this prac-

tice can occur in up to half of inpatients and a quarter of outpatients, contributing substantially to the overall costs of these drugs.<sup>3-6</sup>

## What's Wrong With Antipsychotic Polypharmacy?

Several potentially good reasons exist for using 2 antipsychotics at the same time, even in the absence of controlled studies of its benefits, including use in acute settings where rapid response is mandated and use in switching from one drug to another where cross-titration can be the best tolerated transition.<sup>5,6</sup> A more controversial use of antipsychotic polypharmacy, however, is the long-term maintenance of a patient on 2 agents as an approach to treating those with partial or no response to monotherapies.

One barrier to long-term antipsychotic polypharmacy for such patients is the possibility that it will sabotage the best proven advantages of atypical antipsychotic monotherapy, namely, to reduce motor side effects and potentially prevent tardive dyskinesia. Theoretically, all antipsychotics act to control positive symptoms of psychosis by blocking dopamine D<sub>2</sub> receptors.<sup>1</sup> Atypical antipsychotics supposedly do this without causing motor side effects because they com-

pletely block D<sub>2</sub> receptors in limbic areas controlling psychosis while incompletely blocking the D<sub>2</sub> receptors in extrapyramidal areas controlling motor side effects.<sup>1,3</sup> Incomplete blockade of the extrapyramidal receptors can become complete by giving 2 atypical antipsychotics, a conventional antipsychotic with an atypical antipsychotic, or high doses of 1 atypical antipsychotic. Since it's impossible to block more than 100% of the D<sub>2</sub> receptors controlling psychosis, further drug addition might only lead to more blockade of the wrong D<sub>2</sub> receptors, with a net clinical effect not much different from treatment with conventional antipsychotic monotherapy, but with a net economic effect that can be more than 20 times the cost of conventional antipsychotic monotherapy.<sup>4</sup> On the other hand, attempting to attain better symptom relief, especially in cognition and enhanced functional outcomes, by combining those pharmacologic properties of the atypical antipsychotics other than their ability to cause differential dopamine receptor blockade<sup>1</sup> has some hypothetical appeal if as yet no proven theoretical foundation.

## Clinical Judgment vs. Clinical Trials

Various health care systems report that long-term antipsychotic polypharmacy for all types of antipsychotics in-

*BRAINSTORMS is a monthly section of The Journal of Clinical Psychiatry aimed at providing updates of novel concepts emerging from the neurosciences that have relevance to the practicing psychiatrist.*

*From the Neuroscience Education Institute in Carlsbad, Calif., and the Department of Psychiatry at the University of California San Diego.*

*Reprint requests to: Stephen M. Stahl, M.D., Ph.D., Editor, Brainstorms, Neuroscience Education Institute, 5857 Owens Street, Ste. 102, Carlsbad, CA 92009.*

volves between 10% and 25% of patients given antipsychotics.<sup>2,4</sup> Among patients receiving either risperidone, olanzapine, or quetiapine within the California Medicaid Program, approximately 5000 of them, or 4.4%, receive 2 of these 3 agents simultaneously for more than 60 days.<sup>4</sup> This practice persists despite the fact that no controlled trials and fewer than a dozen case reports of such combinations are reported in the literature.<sup>4</sup> Continuing such high-cost prescribing practices for the few, without better documentation of its benefits, may lead payors to radically restrict access to atypical antipsychotics for the many due to the perception of squandering a precious resource. This action, taken without supporting evidence, would be a regrettable development in psychopharmacology.

Proper studies of antipsychotic polypharmacy are thus long overdue. There is an obvious lack of commercial incentive for one company to study its drug by augmenting it with a competitor's drug, and there is a continuing lack of academic interest in funding what would obviously be quite complex clinical studies of antipsychotic polypharmacy. Nevertheless, if no controlled studies of antipsychotic polypharmacy are conducted, then the benefits perceived by those who prescribe 2 antipsychotics for thousands of patients will not be systematically assessed, nor will the theoretical risks of motor side effects of this practice be evaluated. Furthermore, alternatives to antipsychotic polypharmacy must be compared with long-term antipsychotic polypharmacy, including the relative value of this high-cost practice. To recommend whether long-term antipsychotic polypharmacy fits into the

**Table 1.**  
**Alternatives to Long-Term Atypical Antipsychotic Polypharmacy**

1. Trial of every available monotherapy
2. Extend monotherapy treatment periods before giving up
3. Divalproex augmentation
4. Switch to conventional monotherapy
5. Trial of some agents at higher doses if no side effects at therapeutic doses
6. Clozapine

treatment guidelines for psychosis, and at what point it should be used, these important gaps in our knowledge must be filled.

#### **What Are the Alternatives to Polypharmacy and Why Look for Them?**

The clinician is currently caught in a dilemma between doing the best for each patient based on anecdotally observed benefits of antipsychotic polypharmacy in some cases and the lack of controlled evidence that this option has benefits, that its high costs are justified, and that it might theoretically cause the same motor side effects as conventional antipsychotics. Fortunately, there are several options to antipsychotic polypharmacy to consider while we await the evidence for the risks, benefits, and value of long-term antipsychotic polypharmacy to materialize (Table 1).

One alternative to using 2 drugs at once is to try every monotherapy first, including each of the 4 first-line agents (risperidone, olanzapine, quetiapine, and ziprasidone) and soon a fifth new agent (aripiprazole). Another alternative is to recognize that many patients do not respond quickly and that a 4- to 6-week trial of any monotherapy may be inadequate for them. Thus, retesting a monotherapy

for 16 to 20 weeks may show delayed benefits, especially on cognition and rehabilitation, that were not present in previous short-term trials of the same agent.

Another option to polypharmacy is to try high doses of some monotherapies (particularly olanzapine and quetiapine) in partial responders who have no side effects at therapeutic doses. This option is only beginning to be investigated and is another area requiring much further study. A model for how atypical antipsychotic polypharmacy studies could be conducted is the recent report suggesting enhanced antipsychotic efficacy of divalproex in schizophrenia when it was added to either risperidone or olanzapine.<sup>7</sup> Finally, there may indeed be patients who do better on conventional antipsychotics and should be switched to one of these agents. ♦

#### **REFERENCES**

1. Stahl SM. *Essential Psychopharmacology*, 2nd ed. New York, NY: Cambridge University Press; 2000
2. Stahl SM. Selecting an atypical antipsychotic by combining clinical experience with guidelines from clinical trials. *J Clin Psychiatry* 1999;60(suppl 10):31-41
3. Meltzer HY. Mechanism of action of atypical antipsychotic drugs. In: Davis KL, Charney D, Nemeroff CL, et al, eds. *Neuropsychopharmacology: The Fifth Generation of Progress*. New York, NY: Elsevier; In press
4. Drug Utilization Review Board of California Medicaid Program. Dept Health Services, Med-Cal Division. Sacramento, Calif. 2001
5. Stahl SM. Antipsychotic polypharmacy, pt 1: therapeutic option or dirty little secret? *J Clin Psychiatry* 1999;60:425-426
6. Stahl SM. Antipsychotic polypharmacy, pt 2: tips on use and misuse. *J Clin Psychiatry* 1999; 60:506-507
7. Casey DE, Daniel D, Tracy K, et al. Improved antipsychotic effect of divalproex combined with risperidone or olanzapine for schizophrenia. Presented at the World Assembly of Mental Health, 26th Biennial Congress of the World Federation for Mental Health; July 22-27, 2001; Vancouver, BC, Canada