

# Antipsychotic Polypharmacy, Part 1: Therapeutic Option or Dirty Little Secret?

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

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**Issue:** *Although clinical trials of new antipsychotics prove their efficacy as monotherapies, up to half of the patients receive 2 antipsychotics at the same time.*

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## If at First You Don't Succeed, Try, Try Again

The 3 new antipsychotics—risperidone, olanzapine, and quetiapine—are transforming the treatment of schizophrenia and other psychotic illnesses.<sup>1</sup> These new atypical antipsychotic agents have now replaced so-called conventional antipsychotics such as haloperidol and chlorpromazine because clinical trials confirm that atypical antipsychotics have a better safety and efficacy profile than conventional antipsychotics. Clinical experience reveals that some patients respond better to one of these agents than to another, sometimes dramatically.<sup>2</sup> It is unclear why this occurs, and it is impossible to predict who will respond optimally to which one of the 3 atypical agents. Thus, the standard of practice is now to try each of the 3 agents sequentially if any fails to provide an acceptable therapeutic response.<sup>3</sup>

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*From the Clinical Neuroscience Research Center in San Diego and the Department of Psychiatry at the University of California San Diego.*

*Reprint requests to: Stephen M. Stahl, M.D., Ph.D., Editor, BRAINSTORMS, 8899 University Center Lane, Suite 130, San Diego, CA 92122.*

## What Is a Satisfactory Treatment Response to an Atypical Antipsychotic?

Atypical antipsychotics improve psychotic symptoms, but patients with psychotic illnesses, especially schizophrenia, rarely become “well.” Thus, even in a patient with the “usual response” to an atypical antipsychotic, clinicians feel pressured to prescribe another atypical antipsychotic in an attempt to gain an even greater reduction of symptoms. On the other hand, many patients continue to experience

improvement for many months after initiation of treatment with an atypical antipsychotic.<sup>4</sup> These contrasting responses result in competing priorities of trying to get a better outcome, perhaps with a different drug, and trying to give each atypical antipsychotic an adequate trial. It can indeed be difficult for patients, families, and prescribers to sit and “watch the pot boil” month after month without switching to another atypical antipsychotic, hoping for the full clinical effect of the first agent to kick in.

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## Take-Home Points

- ◆ Antipsychotic monotherapy is the recognized standard for treatment of psychotic illnesses
- ◆ Inadequate treatment responses to an atypical antipsychotic can lead to appropriate use of 2 antipsychotics, particularly a conventional antipsychotic to “top-up” an atypical antipsychotic
- ◆ Polypharmacy with 2 expensive atypical antipsychotics can result from “getting caught” in cross-titration between 2 antipsychotics before adequate trials of monotherapies have been attempted and does not currently seem to be justified

### Antipsychotic Polypharmacy? Not in My Practice

If satisfactory outcomes—however defined—do not result from atypical antipsychotic monotherapy, then a trial of clozapine, a conventional antipsychotic, or combinations of antipsychotics may be indicated.<sup>3</sup> Since antipsychotic polypharmacy is recommended only as a last resort, one might think that it would be used only in the sickest of the sick, and be rare. However, the results of several recent surveys show that antipsychotic polypharmacy may be prescribed for up to a fourth of outpatients<sup>2</sup> and up to a half of inpatients.<sup>5</sup> Why, then, are there essentially no studies, controlled or otherwise, of this common clinical practice? The lack of study and debate about this phenomenon seems remarkable considering how common this practice is. Have we discovered a dirty little secret that there is widespread failure to follow practice guidelines, with prescribers commonly acting irrationally and spending unjustifiably in such a large proportion of their patients? Or does atypical antipsychotic monotherapy fail to meet the needs of a large proportion of patients, which the use of 2 concomitant antipsychotics can fill?

### Conventional Antipsychotic “Lead-In” and “Top-Up”

Antipsychotic polypharmacy thus seems to be something everybody does and nobody admits.

The results of recent prescription audits of antipsychotics suggest that the use of 2 antipsychotics simultaneously can be both justified and unjustified. For example, atypical antipsychotics are often not considered to work as quickly or as robustly as conventional antipsychotics in patients

who are acutely psychotic.<sup>1,2</sup> Thus, for patients deemed too sick to begin oral monotherapy with an atypical antipsychotic, conventional antipsychotics such as haloperidol or loxapine may need to be administered acutely and perhaps even intramuscularly while an atypical antipsychotic is begun; i.e., a conventional antipsychotic “leads in” the atypical antipsychotic, with overlapping administration and then discontinuation of the conventional antipsychotic. Such patients may also require p.r.n. oral or intramuscular single doses of a conventional antipsychotic (“top-up” the atypical antipsychotic) to quickly quell agitation and aggressive behavior and head off incipient decompensation.

Such uses of conventional antipsychotics with atypical antipsychotics do not account for the majority of antipsychotic polypharmacy, however. Surveys<sup>2,5</sup> show that many patients stabilized on an atypical antipsychotic receive daily augmentation with a conventional antipsychotic. One of the few, if only, published studies on this phenomenon is an open case series in which clozapine partial responders were successfully augmented with the conventional antipsychotic loxapine.<sup>6</sup> Controlled studies of chronic antipsychotic augmentation of other antipsychotics are sorely needed.

### The “Cross-Titration” Trap

When switching between 2 antipsychotics, it is most common to titrate the first drug down while simultaneously titrating the second drug upward. This can create a quandary for the clinician when the patient appears to respond in the midst of “switching horses” halfway across the

stream. Do you go back to the first drug, continue with the cross-titration, or just stay trapped while giving 2 expensive atypicals at the same time without trying the second agent on its own? This trap is probably best to avoid, because it is not clearly effective and certainly is not cost-effective, even though no studies of the usefulness of staying trapped in cross-titration have been performed.

### Summary

Antipsychotic polypharmacy is a surprisingly frequent occurrence that can be both justified and unjustified, depending on how it is used. To the extent that this phenomenon has been unrecognized and is not being studied, it is a “dirty little secret.” To the extent that careful clinicians have uncovered a useful strategy for boosting the effectiveness of available antipsychotic monotherapies, it represents an opportunity to improve the outcomes of patients with psychotic illnesses.

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