- *Essential Psychopharma*Stahl*ogy* -

Let Them Eat Generics

Can one atypical antipsychotic substitute for another?

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Vive la France

In the 18th century, the French aristocracy was out of touch with its citizens, who eventually stormed the Bastille and overturned the king during the French revolution. In an act of contempt for the rank and file, Marie Antoinette was famously quoted as saying, "Let them eat cake," and lost her head to the guillotine as a result.

In the 21st century, some of our formulary committees may be getting out of touch with the rank and file prescriber, trying to save money based on the false assumption that there are no important differences among atypical antipsychotics. In an act that may be intended as fiscal prudence, but could be the result of poor understanding of the clinical science, some are increasingly saying, let them eat generics, let them eat Haldol, or let them eat whatever is on sale this month.

What does the evidence say?

Atypical antipsychotics have both pharmacologic similarities and proven pharmacologic differences.[1,2] On one hand, all five of the first-line atypical antipsychotics—risperidone, olanzapine, quetiapine, ziprasidone, and aripiprazole, as well as the second-line agent clozapine—are dopamine D2 antagonists as well as serotonin 5-HT_{2A} antagonists. This makes them all distinguishable from conventional antipsychotics and members of a single class that have antipsychotic actions without profound extrapyramidal side effects. Thus, they are all atypical antipsychotics.

On the other hand, none of these agents share the same secondary binding properties, and they have profound differences in the additional neurotransmitter receptors to which each of these agents binds compared to the others in this class.[1,2] Differences in secondary binding properties are the leading hypotheses to explain the differences that clinicians commonly see when a patient responds better to one of these agents than to another or tolerates one of these agents better than another.

Is the absence of evidence, evidence of absence?

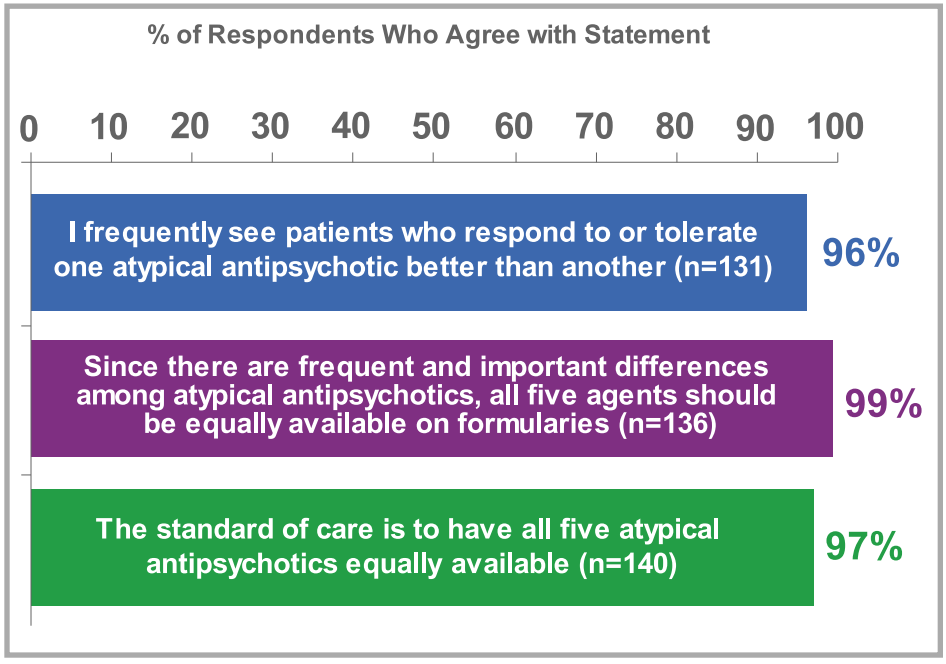
Consistent and predictable efficacy differences among the first-line atypical antipsychotics have been difficult to demonstrate in large clinical trials. Those that have been reported have not always been replicated, which may be due in part to differences in the doses of the different agents being compared.[3] This has led some to assume that since multicenter trials have not yet proven efficacy advantages of one atypical antipsychotic over another, that no such differences exist. But is the absence of evidence the evidence of absence? Furthermore, differences in tolerability among the atypical antipsychotics are readily demonstrable, especially in terms of weight gain and probably also in terms of risk of diabetes, sedation, akathisia, hyperprolactinemia, orthostatic hypotension, and other side effects.[4,5]

What do the rank and file think?

Often, the full benefits of a new class of therapeutics are not discovered until such new drugs have been used in clinical practice for a number of years. Thus, there is not only evidence-based prescribing, but also prescribing-based evidence. Doses for all atypical antipsychotics identified in controlled trials have needed to be adjusted in clinical practice.[3,4] Use of atypical antipsychotics in bipolar mania and bipolar depression has been an unexpected new efficacy benefit. Most dramatic are the very large and frequent differences that are seen from one patient to another in response and tolerance to different drugs in this class.

Clinical practitioners readily recognize the differences that one agent in this class can make, compared to another, for individual patients. These responses are not predictable, and no one agent is clearly superior in all cases.[3,4] Selecting the best atypical antipsychotic for an individual patient remains

Survey of Clinical Practitioners on the Class of Atypical Antipsychotics



an art, an iterative trial-and-error process, not a science. This process cannot proceed without access to all agents in this class. There is perhaps no single drug class in all of psychiatry, and perhaps all of medicine, where there are as many differences among the members of the class than there are for the atypical antipsychotics. To demonstrate this phenomenon of perceived differences among the drugs in this class, a recent survey of 407 mental health practitioners who were high prescribers of atypical antipsychotics found that 96% frequently see patients who respond better to one atypical antipsychotic than to another, who tolerate one atypical antipsychotic over another, or both (See figure).

Off with their heads

Despite these findings, a disturbing number of formulary committees are beginning to restrict access to members of this class of atypical antipsychotics based purely on cost. Rather than stating that they simply cannot afford to give all options to patients, some may disguise this financial motive as a scientific one, incorrectly stating that all atypicals are the same anyway, so why not use the cheapest one? The common drug formulary committee for the Department of General Services in the state of California has recently taken this stand, despite the disagreement of experts and an open formulary policy for the state's Medicaid program.

When mental health practitioners were asked whether these drugs were the same and whether the least expensive should be used, or if their differences justified all being available, 99% agreed that they should all be available. (See figure). Furthermore, these practitioners strongly agreed that the standard of care was to keep all agents available (See figure).

The bottom line—Formulary committees beware! Clinicians do not appreciate being forced to practice below the standard of care. So far, the rank and file prescribers are hesitant to protest, and no Robespierre has yet emerged to lead the revolt and storm the Bastille, perhaps remembering that he, too, eventually was guillotined. Nevertheless, scientific evidence, clinical practitioner consensus, treatment guidelines, pharmacologic rationale, and common sense all speak for keeping all five, first-line atypical antipsychotics available for our patients. Let them eat cures, not cake!

Take-Home Points

1. A growing body of data and the overwhelming opinion of prescribers is that the five atypical antipsychotics—risperidone, olanzapine, quetiapine, ziprasidone, and aripiprazole—are all different from each other.
2. These differences are not as apparent in multicenter trials of large groups of patients as they are in clinical practice. In these smaller settings, patients are treated one at a time and are frequently observed to respond better to one atypical antipsychotic than to another. Patients especially tend to tolerate one atypical antipsychotic better than another.
3. Nevertheless, there is a movement to save money by removing the most expensive of these agents from formularies in the flawed assumption that one atypical antipsychotic can substitute for another.
4. Best practices currently require that all five, first-line atypical antipsychotics are available. Formulary committees that say "let them eat the cheapest" may find that prescribers will storm their Bastille and decapitate their decisions to return best treatment options to the masses.

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Publication Information

PsychEd Up—ISSN:1553-8907 (print), 1553-8915 (online)—is published monthly by NEI Press.