What Makes an Antipsychotic Atypical?

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Issue: *"Atypical" as applied to an antipsychotic can mean different things to different experts. To clinicians it can connote "low extrapyramidal side effects" or "good for negative symptoms"; to a pharmacologist, "5-HT$_2$ and D$_2$ receptor antagonism"; to a marketer, "new and different"; and, to an economist, "expensive."*

A flood of new antipsychotics is generating improved treatments for schizophrenia but tangled terminology for clinicians. All of the newer antipsychotics since clozapine have been lumped into a new therapeutic class often referred to as "atypical"[1–4] (Table 1). This includes not only risperidone, olanzapine, and quetiapine, but also sertindole (marketed only outside the United States) and ziprasidone (expected to be approved in the United States soon). Lumping all of the new agents together helps to distinguish them as a class from most of the older conventional antipsychotics, which are clearly less tolerated and possibly less effective, especially for negative symptoms.[1–5] These new agents must distinguish themselves from the older generic agents if they hope to support price premiums.

However, by considering all of the new drugs as one class, differences among newer drugs are obscured. Thus, there are also attempts to distinguish 1 new agent from another. So far, the results are intriguing, even controversial.[6–8] It is already clear from anecdotal use—if not yet from controlled clinical trials—that individual patients can show dramatic differences in efficacy as well as tolerability from 1 of the newer agents to another. Furthermore, as new standards in pharmacology and clinical evaluations are applied to the older agents, some surprising findings among those agents are beginning to emerge (Table 2).[9]

All new and old antipsychotics improve positive symptoms and are also D$_2$ receptor antagonists.[4] All new antipsychotics block 5-HT$_{2A}$ receptors as well and have fewer extrapyramidal side effects (EPS) at low doses than the conventional antipsychotics have at standard doses.[1–9] One atypical antipsychotic (quetiapine) has no more EPS than placebo.[8] So far, at least 2 antipsychotics (olanzapine and risperidone) have shown greater efficacy than a conventional antipsychotic for negative symptoms, and 2 (olanzapine and quetiapine) do not raise prolactin like the conventional drugs do.[6–8] Early indications are that ziprasidone may cause less weight gain compared with all other new and old agents.[1–3]

How many, if any, of the "atypical" properties are due to 5-HT$_2$ antagonism remains a quandary, although it is a good bet that it is this

Take-Home Points

- There are multiple definitions for an atypical antipsychotic.
- The "atypical" concept is dependent upon dose: less is more.
- Some atypicals may be more atypical than others.
- Even some conventional antipsychotics may be atypical.

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Table 1. Types of Antipsychotics

Atypical Antipsychotics	
	Clozapine
	Risperidone
	Olanzapine
	Quetiapine
	Sertindole (not available in the United States)
	Ziprasidone (Food and Drug Administration–approval pending)
	Loxapine?
Examples of Conventional (Typical) Antipsychotics	
	Phenothiazines
	Butyrophenones
	Thioxanthenes

Table 2. What's in a Name?

Drug	Type	Property
Clozapine	Unusual atypical	More efficacy but agranulocytosis
Quetiapine	Most atypical	Lowest extrapyramidal side effects?
Olanzapine, risperidone	More atypical	Better for negative symptoms?
Risperidone	Atypical yet typical?	Elevates prolactin
Ziprasidone	Atypical atypical?	Less weight gain?
Loxapine	Atypical atypical? “Cinderella” antipsychotic	Will $5\text{-}HT_2$-binding prove atypical at low doses?
All	Typical atypical	Dose-dependent atypical properties (less is more)

mechanism that reduces EPS of these drugs at low doses.[10] On the other hand, there are at least 16 receptors where 1 or more of the new drugs interact.[1–3] No 2 drugs have an identical profile, suggesting that therein lies the explanation for some of the differences clinicians are observing from 1 drug to another, particularly in certain patients. These ancillary pharmacologic properties, in addition to $5\text{-}HT_2$ and D_2 antagonism, include binding to D_1, D_3, and D_4 receptors; to $5\text{-}HT_{1A}$, $5\text{-}HT_{2C}$, $5\text{-}HT_3$, $5\text{-}HT_6$, and $5\text{-}HT_7$ receptors; to α_1, α_2, H_1, and muscarinic cholinergic receptors; and to serotonin and norepinephrine reuptake pumps.[1–9]

It is well known that many of the old antipsychotics bind α_1, muscarinic, and histamine receptors in addition to D_2 receptors[4]; however, what is not so well known is that a few traditional antipsychotics also bind to the $5\text{-}HT_{2A}$ receptor just like the new antipsychotics.[9] These include loxapine as well as chlorpromazine and thioridazine.[9,11] Positron emission tomography studies of loxapine in schizophrenic patients confirm its significant $5\text{-}HT_2$ binding properties, but chlorpromazine does not seem to bind to $5\text{-}HT_2$ receptors except at high doses.[9,11] Thus, is loxapine the “Cinderella” antipsychotic waiting to be invited to the low-dose atypical antipsychotic ball? Given these provocative data plus the current lack of availability of an intramuscular dosage formulation for any new antipsychotic, another look at this less expensive agent, both orally and in its available parenteral form, appears to be in order.

Research on the antipsychotics is proceeding at a fast and furious pace; some of these preliminary distinctions among agents may be lost and yet others proved. No matter what we end up calling the new antipsychotics, it is clear that they represent a significant advance in therapeutics for schizophrenia. ◆

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