"Awakening" From Schizophrenia: Intramolecular Polypharmacy and the Atypical Antipsychotics

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Issue: *Clever combinations of pharmacologic mechanisms may enhance the efficacy of antipsychotic drugs and alter the course of schizophrenia.*

Is the ideal antipsychotic a soloist or a member of a large ensemble? The earliest antipsychotic melody of D_2 receptor antagonism was embedded in a cacophony of jackhammering antihistamines, screeching anticholinergics, and droning α-antagonists.[1] This molecular noise is somewhat filtered by high-potency antipsychotics, but the emerging dopamine antagonist theme song is too loud, grating on nerves, especially extrapyramidal ones.[1]

Just when we thought that better auditory filtering was the answer for tuning the off-pitch conventional antipsychotics, along came clozapine, where multiple simultaneous pharmacologic mechanisms serendipitously harmonize to improve antipsychotic efficacy.[2] Of course, a few bad notes of sedation and weight gain and even seriously dissonant chords of seizures and agranulocytosis are mixed in as well. Nevertheless, the clozapine story has encouraged us to look for molecules that can deliver three new therapeutic dimensions for those with schizophrenia: (1) robust efficacy for symptoms that the old antipsychotics cannot treat, such as negative symptoms and cognitive dysfunction; (2) help for those whose positive symptoms are refractory to classical antipsychotics; and (3) interruption of the downhill course of progressive loss of social functioning, which far too many patients experience.

The new atypical antipsychotics have attempted to put together the right blend of pharmacologic mechanisms and eliminate the misfits in order to compose an even better symphony than the one played by clozapine, so the new atypical antipsychotics are each creating their own unique ensembles of mechanisms. There are more than a half dozen atypical antipsychotics, including three already marketed in the United States, namely clozapine, ris-

Take-Home Points

- Removal of some pharmacologic properties (e.g., antihistamine) from an antipsychotic can improve tolerability but not efficacy
- Addition of other pharmacologic properties (e.g., 5-HT_2 antagonism) to an antipsychotic can improve tolerability and possibly efficacy as well
- A new therapeutic goal of the emerging atypical antipsychotics is to mix a pharmacologic nectar of multiple neurotransmitter receptor actions that can reliably trigger "awakenings" from schizophrenia and arrest the downhill course of illness

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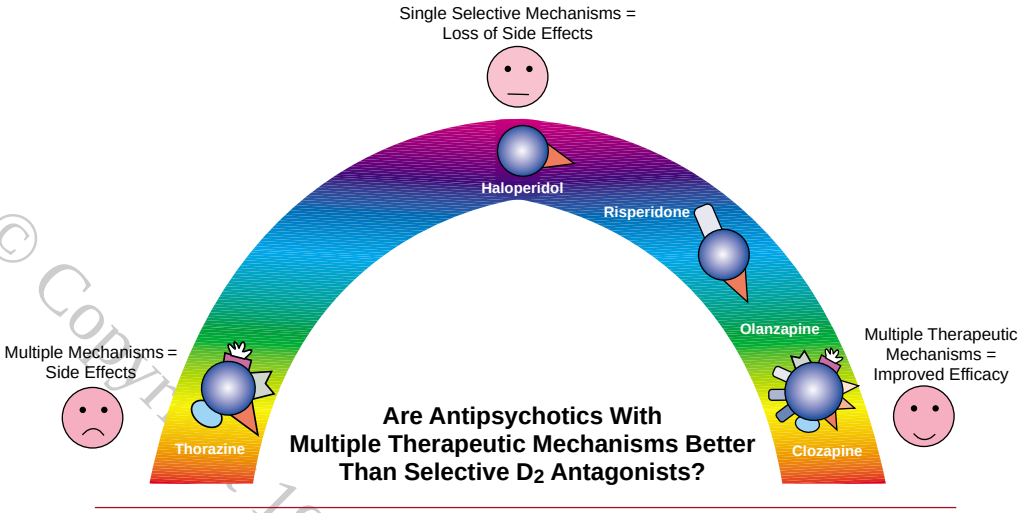

peridone, and most recently, olanzapine. Others likely to be marketed soon include quetiapine, sertindole, ziprasidone, and even iloperidone.[3,4]

Are these agents all *me-too*'s that merely play "same song, second verse," or do some represent truly distinct molecular symphonies? Only by listening to each agent as it enters clinical practice will we ultimately be able to tell which agent will be preferable and for which patients.

Essentially, no one disputes that a 5-HT_2/D_2 duet (also known as serotonin-dopamine antagonists or SDAs) is a highly desired component in the orchestra of an atypical antipsychotic.[1,4] In fact, all the atypical antipsychotics share this pharmacologic feature, which is thought to explain findings of reduced extrapyramidal side effects and at least slightly improved negative symptoms emerging from the clinical trials of all members of this class.[1–5] However, it is too early to tell whether the new atypical antipsychotics will capture clozapine's undisputed superior efficacy for schizophrenic patients refractory to classical neuroleptics in molecules that have fewer side effects.

The phenomenon of "awakenings" in an Oliver Sachs' sense is the dramatic improvement seen in some schizophrenic patients taking clozapine and the restoration of lost souls to near normal existence. This is virtually unknown in association with the classical antipsychotics. Awakenings were first seen anecdotally during clinical trials with clozapine and are now reported occasionally with the newer antipsychotics as well.[6] The fact that dramatic and highly restorative clinical efficacy can be seen at all heartens us to hope that getting the pharmacology just right will render this phenomenon more widely reproducible.

Finally, the atypical antipsychotics may help interrupt the downhill course of psychotic illness, which is a feature of too many schizophrenic patients.[7,8] If preventing relapse in fact arrests the illness at the point when treatment is instituted, this would be a tremendous therapeutic advantage for the atypical neuroleptics.

Each new agent has a relatively unique combination of multiple therapeutic actions, and only time will tell whether any cocktail is better than another. But do we need a string quartet of pharmacology for some patients, an intramolecular brass ensemble for others, or a psychopharmacology jam session of rock and roll to help still more? Just as individual tastes in music differ, so may the responses of the wide range of suffering neurobiological mechanisms in the schizophrenias. Nevertheless, after a long slumber, innovation in therapeutics for schizophrenia is again awake and active. ◆

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