“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.

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-HT2 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
Are Antipsychotics With Multiple Therapeutic Mechanisms Better Than Selective D₂ Antagonists?

peridone, and most recently, olanzapine. Others likely to be marketed soon include quetiapine, sertindole, zilprasidone, 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-HT₃/D₄ 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 superiority 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.◆

REFERENCES

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