

## Introduction

# What Makes an Antipsychotic Atypical?

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The term *atypical antipsychotic* has caused a good deal of debate and confusion, because its meaning has evolved over time, and those with different perspectives on this issue tend to define this term differently.<sup>1</sup> To a pharmacologist, it can mean “serotonin-2A (5-HT<sub>2A</sub>)-dopamine-2 (D<sub>2</sub>) antagonist” or “multiple simultaneous neurotransmitter binding activities.” To a prescriber, it can mean “low extrapyramidal symptoms” or “reduction of negative symptoms.” To a marketer, it may mean “new and different.” To a formulary committee with a short-term orientation, an atypical antipsychotic often means “expensive,” but to a pharmacoeconomist with a long-term orientation, it can mean “cost-effective.” Each of these aspects of atypical antipsychotics is discussed in the articles that are included here.

Elliott Richelson, M.D., provides an overview of the pharmacologic binding activities, and other activities, that may define an atypical antipsychotic, including antagonism of 5-HT<sub>2A</sub> receptors and D<sub>2</sub> receptors. He has also discovered, and reports here for the first time, that loxapine and its hydroxylated and demethylated metabolites are all serotonin-dopamine antagonists with higher affinities for 5-HT<sub>2A</sub> receptors than for D<sub>2</sub> receptors.

Gary Remington, M.D., Ph.D., F.R.C.P.C., and Shitij Kapur, M.D., Ph.D., F.R.C.P.C., review the positron emission tomography (PET) evidence for the in vivo binding characteristics of a number of antipsychotic drugs, from the prototypical conventional antipsychotic haloperidol to the atypical antipsychotics clozapine, risperidone, olanzapine, and quetiapine to the serotonin-dopamine antagonists loxapine and amoxapine. They debate the evidence for the potential clinical relevance of varying amounts of occupancy of 5-HT<sub>2A</sub> receptors and D<sub>2</sub> receptors by all 7 of these drugs.

Larry Ereshefsky, Pharm.D., then applies the pharmacologic and pharmacokinetic considerations raised in the articles by Dr. Richelson and by Drs. Remington and Kapur to the selection of an antipsychotic drug. He places loxapine midway in the pharmacologic spectrum from haloperidol to risperidone.

I review 5 different serotonin-dopamine antagonists, namely, clozapine, risperidone, olanzapine, quetiapine, and loxapine, and assess whether they are atypical, providing clinical pearls and dosing tips for all 5. This review combines the empirical evidence from clinical practice experience with guidelines from clinical trials as a strategy for selecting an antipsychotic drug. In my analysis, I conclude that loxapine is unusual, but not atypical, and may have a niche for use as an augmenting agent to atypical antipsychotics in patients with unsatisfactory treatment responses.

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*The closed symposium “What Makes an Antipsychotic Atypical?” was held in Dallas, Tex., May 6–7, 1998, and was supported by an unrestricted educational grant from Watson Laboratories, Inc.*

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Loxapine is a bit of an enigma, since it is a serotonin-dopamine antagonist, yet considered to be a conventional or typical antipsychotic. William M. Glazer, M.D., reviews the evidence that loxapine may have some atypical features, particularly at lower doses; he also proposes studies that will be necessary to characterize the clinical features of loxapine according to modern research standards in schizophrenia, since this drug was developed using older methodologies in the 1970s.

By conducting a retrospective review of the treatment responses of patients taking loxapine, Herbert Y. Meltzer, M.D., and Karuna Jayanthilake, M.A., research the possibility that loxapine may be atypical at low doses. They report, surprisingly that antipsychotic efficacy is present at low doses (less than 50 mg/day), which are less than the recommended doses of 60 to 100 mg/day (maximum = 250 mg/day given in 2 divided doses).

Finally, Peter F. Buckley, M.D., reviews the use of antipsychotics, both typical and atypical, in the management of agitation and aggression. He provides guidelines for treatment of intermittent problems with intramuscular administration of typical antipsychotics such as loxapine and haloperidol; he also gives suggestions for managing persistent problems with the first-line atypical antipsychotics risperidone, olanzapine, and quetiapine, and if these fail, clozapine.

#### REFERENCE

1. Stahl SM. What makes an antipsychotic atypical? [BRAINSTORMS] J Clin Psychiatry 1998;59:403-404