

## Antipsychotic Medications: Present and Future

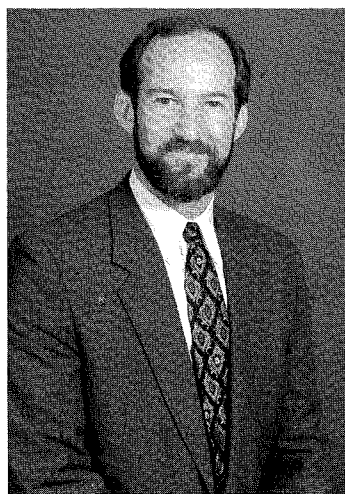
*An interview with Lawrence Jay Cohen, PharmD, BCPP, FASHP, FCCP; Professor of Pharmacy, Psychiatry, and Behavioral Sciences, at the University of Oklahoma, Colleges of Pharmacy and Medicine; Director, Clinical Pharmacology Services, Oklahoma Department of Human Services/ Developmental Disabilities Services Division, Oklahoma City, Oklahoma.*

### Introduction

*An expert in psychopharmacology, Dr. Cohen is well qualified to comment on the value of the newer, atypical antipsychotics and how they compare to conventional neuroleptics.*

*The author of numerous peer-reviewed articles about atypical antipsychotics, Dr. Cohen also lectures frequently about these agents. Dr. Cohen has received numerous awards and appointments and is a reviewer for several psychiatric and pharmacotherapeutic journals.*

*Dr. Cohen earned his PharmD at the University of Southern California, where he also completed his post-doctoral training in psychopharmacology.*



Lawrence Jay Cohen, PharmD

### Changes in Treatments

**AJMC:** *You've specialized in psychopharmaceutics for 20 years. Since you obviously have first-hand experience with both conventional and newer antipsychotic medications, you're qualified to comment on the differences between the two. What are your observations? What types of changes have you noticed in patients taking the newer drugs?*

**Dr. Cohen:** The main differences I have seen relate to efficacy and side-effect profile. The newer drugs have a dramatically lower frequency of extrapyramidal side effects (EPS), including dystonic reactions, akathisia, and pseudoparkinsonism, and dyskinesia. These side effects have been notorious for causing noncompliance. In

patients with psychiatric disorders, as well as those with mental retardation and geriatric dementia, we see less cognitive impairment with the newer drugs. With the newer atypicals, there is also less of a need for anticholinergic drugs, so there are fewer anticholinergic effects, which may also help to contribute to improved cognition.

### Deciding If and When to Switch

**AJMC:** *In treating psychotic patients or in consulting with other clinicians who treat them, how do you go about determining if someone should be switched from a conventional antipsychotic to one of the newer, atypical agents?*

**Dr. Cohen:** That's easy. I don't believe patients should be switched just because newer drugs are available. If a patient is stable and functioning reasonably well on an antipsychotic, I wouldn't interfere. However, if there is a problem or a reduction in activity or functional level, I would consider a switch. You have to weigh the risk of making someone unstable against improvement that may or may not happen with a newer drug. The decision to switch should be made on a case-by-case basis. In the future, many more patients will be started on the newer drugs because of better side-effect profiles. This in turn will lead to better compliance, which should help keep people out of inpatient facilities.

**AJMC:** *What advice would you give about successfully and safely making a switch?*

**Dr. Cohen:** Dr. Peter Weiden is really the expert on this. My sense is that it is important for clinicians to know that even though a drug is essentially out of the patient's bloodstream, there can still be negative reactions. If the old medication is discontinued rapidly and the new medication is started rapidly, the patient may experience withdrawal symptoms that could be misperceived as an exacerbation of the illness or as side effects of the new drug. Clinicians need to be aware that pharmacologic actions can persist for a while. Some patients have been *marinating*—so to speak—in their drugs for a long time, and pharmacologic actions can continue at the receptor level for a long time after a drug is withdrawn.

### The Importance of Reduced Side Effects

**AJMC:** *Four atypical agents are now available—clozapine, risperidone, olanzapine, and quetiapine. One advantage is that they cause fewer problems with tardive dyskinesia and EPS. Has that been true in your observation*

*of patients over the years? How important is this?*

**Dr. Cohen:** It's very important. With every year of exposure to conventional antipsychotic drugs, the risk of tardive dyskinesia is increased<sup>1</sup>; one study found that the increase is as much as 5% per year.<sup>2</sup> People who develop movement disorders like tardive dyskinesia, tardive dystonia, and tardive akathisia often have further deterioration, such as an inability to swallow or ambulate. In elderly patients, late-onset dyskinesia can interfere with independent functioning and require a higher level of care, which means spending more money, making this an even more important issue. The newer atypical agents are known to cause significantly less tardive dyskinesia and EPS. An important corollary is that the lifetime risk of late-onset (tardive) dyskinesia should be lower as well; there are fewer data on late-onset tardive dyskinesia and EPS with the newer drugs, because we don't yet have lifetime follow-up data.

**AJMC:** *Clearly the patients themselves would benefit by experiencing fewer problems with dyskinesias and EPS. Who else would benefit? Caretakers? Clinicians? Hospitals? Society at large? How so?*

**Dr. Cohen:** Obviously, these symptoms compromise functional ability. Fewer symptoms would benefit patients, in that they would be more likely to remain independent and require less help. This would clearly benefit caretakers.

Fewer, less frequent symptoms would be helpful to clinicians, too. Sometimes EPS can mimic other conditions—for example, akinesia looks a lot like depression—which can lead to inappropriate drug treatment. In addition, akathisia may be mistaken for aggression or agitation, resulting in additional medication being used. Society at large benefits by having to spend less money to care for the patient. In any considera-

tion of pharmacoeconomics, it is important to look at *all* the costs involved in individual care, including direct and indirect costs, such as lost productivity and lost days from work for patients and caregivers. The goal of treatment is to get people stabilized and functioning so they can be as independent as possible.

### Distinguishing Between the Atypicals

**AJMC:** *What do you think the major differences are between clozapine, risperidone, olanzapine, and quetiapine? Are there any significant differences in terms of efficacy, effects on negative and positive symptoms, side effects, and patient satisfaction?*

**Dr. Cohen:** There are really no studies on this yet, so my comments are based on personal observations. Clinically, these drugs are more similar than they are different, although there are some differences in their pharmacology and side effect profile.

Clozapine differs from the other three drugs in several ways. It requires a weekly blood test, which is a major drawback, especially for geriatric or mentally retarded patients. Although all four drugs cause some weight gain, significant weight gain is a problem with clozapine. Significant drooling is another problem, especially for bed-ridden patients who might aspirate. There is a high risk of seizures with clozapine as well. However, no significant increase in serum prolactin has been found with clozapine, and the drug does not appear to cause tardive dyskinesia and may even improve it. Clozapine is effective in treating both positive and negative symptoms. Its main advantage is that it is highly effective for patients who are refractory to other medications.

Risperidone is as effective as clozapine for both positive and negative symptoms. However, at higher doses it causes more EPS than clozapine, and may not be as effective for negative symptoms.

As with all of these drugs, there is some weight gain, and risperidone causes an increase in serum prolactin levels.

Olanzapine seems to be highly effective for both positive and negative symptoms, and at low doses, it does not seem to cause EPS. It also does not appear to cause a persistent elevation of serum prolactin. Olanzapine does cause some degree of weight gain. At high doses, it seems to be more sedating. Olanzapine produces a transient increase in hepatic

*"In the future, many more patients will be started on the newer drugs because of better side-effect profiles. This in turn will lead to better compliance, which should help keep people out of inpatient facilities."*

— Lawrence Jay Cohen, PharmD

transaminase levels that normalizes within 30 to 45 days. Although the chemical structure of olanzapine is similar to that of clozapine, the drug acts differently. For example, the pivotal trial of olanzapine included 32 patients who developed agranulocytosis on clozapine, but none of them developed it on olanzapine.

The newest drug is quetiapine, an interesting drug with similar efficacy for positive and negative symptoms compared to the other new drugs and a low incidence of EPS. It appears to cause EPS in the placebo range along the entire spectrum of dosing. Again, there is some weight gain. No increases in serum prolactin levels have been reported. An adverse event of concern with quetiapine is cataracts, which were found in a long-term dog study, but not in primates. To date, there have been no reported cases in humans. As a precautionary measure, the drug company suggests that patients have a slit-lamp or other ophthalmic exam before starting the drug and every six months thereafter.

They are currently conducting a study to clarify the drug's effects in humans.

### Selecting an Atypical Antipsychotic

**AJMC:** *Once a clinician has decided to put a patient on one of the newer atypical agents, how should he or she go about choosing which one? How do you go about deciding if a patient is a candidate for clozapine, risperidone, olanzapine, or quetiapine?*

**Dr. Cohen:** That's a tough question. It boils down to prescriber preference and side effect profile. You could almost flip a coin to choose among risperidone, olanzapine, or quetiapine. Clozapine falls into a category of its own because of the need for weekly blood tests, the risk of seizures, and its proven efficacy in patients who are refractory to other antipsychotic drugs. Sometimes the answer is easy—the provider often just has to use whatever's on the formulary.

**AJMC:** *In making this decision, does it make a difference if the person is an inpatient or outpatient?*

**Dr. Cohen:** With clozapine, being an inpatient is beneficial, because it is easier to test the blood and monitor the patient. With the other three drugs, it's a toss-up. The important thing is, wherever patients are when the drug is started, they need to be able to continue on that drug when they move to another level of care. If you can't assure continuity of care across levels, then you shouldn't tinker with the treatment.

**AJMC:** *You said that sometimes providers have to use whatever is on the formulary. You have a lot of experience setting up and managing formularies. In considering which antipsychotics to add to a formulary, which ones would you choose if you had to restrict the choices to two or three?*

**Dr. Cohen:** My feeling is that I would prefer not to restrict the formulary. In my view, all the new drugs should be added, then periodically reassessed, say every 6 months. I would advise having the prescriber "buy in" up front on periodic reassessment and elimination of drugs that don't work well for a particular population. Reassessment should be a dynamic, active process. The key is to continue the patient on the drug if the response is favorable. It's a major mistake to take patients off a drug that is working when changing to a new medication on formulary, but unfortunately, this does happen.

If it were mandated that I choose two or three drugs, then I'd want to find a different world to live and practice in. The incremental cost of having choices is not really huge. But it is costly if you change large numbers of patients from typical to atypical antipsychotic agents.

### Cost Effectiveness

**AJMC:** *In the age of managed care, cost effectiveness is an important consideration. Clearly the newer antipsychotics are more expensive than conventional neuroleptics. Yet clinicians and pharmacists seem to believe they are cost effective. Do you agree with this?*

**Dr. Cohen:** These medications are cost effective in ways that we have already touched on, such as improving patients' functional level so they can be more independent, keeping them outside of institutional environments, and enabling them to return to work or increase their productivity.

Superior outcomes need to be demonstrated to justify these drugs to legislatures and decision-making bodies. We need to show there is a payback in terms of return to work or return to the tax base. I think the payback is there. The olanzapine-versus-haloperidol study showed that at three different time points, a significantly greater number of

patients taking olanzapine were able to return to work.<sup>3</sup> This suggests that the drug is cost effective. It will be important in the future to have similar types of studies for the newer antipsychotics.

**AJMC:** *If you had unlimited funds at your disposal to launch any studies you would like, what might some of them be? What kinds of studies are needed to conclusively distinguish between conventional neuroleptics and the newer atypical antipsychotics?*

**Dr. Cohen:** It is a challenge to conduct the type of studies needed. These studies would show the ability of the newer drugs to influence people's lives in terms of return to work, consumption of fewer resources, and the ability to make it on their own. You would have to gather data in real time on both direct and indirect costs of care, and assess patients' functional levels over time to see if the costs of the drugs are justified and are a means to an end.

### Pipeline Agents

**AJMC:** *Is there anything exciting in the pipeline for treatment of psychosis?*

**Dr. Cohen:** Always! The first possibility is years away, but the next round of novel compounds may well be drugs that work on the glutamate system. The idea for this research came from the observation that the street drug PCP, which acts on the glutamate system, has effects that mimic the positive (NMDA receptors) and negative symptoms and disorganization symptoms of schizophrenia. Researchers are studying drugs that work to reverse the effects of PCP.

Another important area for development is different dosage formulations of

antipsychotics. We need rapid-acting, injectable medications for acute treatment in the emergency room, a depot long-acting medication that can be in-

*"Another important area for development is different dosage formulations of antipsychotics. We need rapid-acting, injectable medications for acute treatment in the emergency room, a depot long-acting medication that can be injected perhaps once a month for patients who have problems being compliant, and a wafer formulation that dissolves in the mouth for patients who can't swallow."*

— Lawrence Jay Cohen, PharmD

jected perhaps once a month for patients who have problems being compliant, and a wafer formulation that dissolves in the mouth for patients who can't swallow.

### ... REFERENCES ...

1. Glazer WM, Morgenstern H, Doucette JT. Predicting the long-term risk of tardive dyskinesia in outpatients maintained on neuroleptic medication. *J Clin Psychiatry* 1993;54:133-139.
2. Kane JM, Woerner M, Weinhold P, et al. Incidence of tardive dyskinesia: Five year data from a prospective study. *Psychopharmacol Bull* 1994;20:39-40.
3. Hamilton SH, Genduso L, Revicki DA, Johnstone BM. Medical resource use and socioeconomic outcomes for olanzapine compared with haloperidol in the treatment of schizophrenia and other psychotic disorders. Presented at the 1997 annual meeting of the American College of Clinical Pharmacy. November, 1997; Phoenix, AZ.