

## DRUGS, PREGNANCY, AND LACTATION

### Atypical Antipsychotics

The reproductive safety of the older typical antipsychotics, such as haloperidol, is supported by extensive data that have accumulated over the past 40 years, at least with respect to teratogenic risk. Much of the data come from their use in treating nausea, particularly with prochlorperazine (Compazine). While long-term neurobehavioral data have been somewhat sparse, no particular indications of risk have been raised in more than 4 decades of use.

We have far less reproductive safety data on the newer "atypical" class of antipsychotics that have become widely used over the past decade because they lack some of the long-term side effects associated with the typical antipsychotics. These drugs—olanzapine (Zyprexa), risperidone (Risperdal), quetiapine (Seroquel), aripiprazole (Abilify), ziprasidone (Geodon), and clozapine (Clozaril)—are approved for schizophrenia; several are approved for acute mania as well.

But they are also being used widely across psychiatric disease states, including anxiety, agitation in the elderly, generalized anxiety disorder, and obsessive-compulsive disorder, and as adjunctive treatment of depression.

Because reproductive safety data on the atypicals have been sparse, clinicians are again faced with the difficult situation where a relatively new class of medicine is being used frequently. What data are available have been largely limited to manufacturers' accumulated case series or spontaneous reports.

To date, such information has not suggested any "signals" with respect to specific concerns regarding their use during pregnancy, but we can make only limited conclusions based on such information.

A study published in April—the first prospective study of the reproductive safety of the atypicals in the literature—provides some reassuring data regarding the risk of malformations, albeit in a relatively small sample. Investigators from the Motherisk Program in Toronto prospectively followed 151 women who took olanzapine, risperidone, quetiapine, or clozapine during pregnancy. All had taken one of these agents during the first trimester, and 48 were exposed throughout pregnancy. A total of 151 pregnant women who had taken a non-teratogenic drug also were followed.

In the atypical-exposed group, one child was born with a major malformation (0.9%), a rate lower than the 1%-3% background rate; compared with two (1.5%) babies in the control group, an insignificant difference.

Differences between groups in the rate of spontaneous abortions, still-

births, or gestational age at birth were not statistically significant. Women taking atypical antipsychotics did have significantly higher rates of low-birth-weight babies (10% vs. 2%) and therapeutic abortions (10% vs. 1%) (J. Clin. Psychiatry 2005;66:444-9).

As the authors point out, the sample was relatively small, the study was statistically underpowered, and long-term neurobehavioral outcomes were not evaluated.

The authors included the number of spontaneous reports of pregnancy exposures to atypicals, provided by the respective manufacturers, with the exception of newer agents. Among 242 olanzapine-exposed pregnancies, there was no increase of major malformations or other abnormal outcomes above baseline. Of 523 clozapine exposed pregnancies, there were 22 "unspecified malformations."

Of the 446 quetiapine-exposed pregnancies, 151 outcomes were reported, of which 8 were different congenital anomalies. Eight malformations were reported among the approximately 250 reports of pregnancies and lactation exposed to risperidone, but no pattern of abnormalities was noted.

If a patient can do without the medication, then it would be appropriate to discontinue it, but this is frequently not the case and these decisions have to be made on a case-by-case basis weighing the relative risks versus benefits.

For a patient planning a pregnancy who has a severe psychiatric illness and is maintained on an atypical antipsychotic to sustain functioning, switching to a typical antipsychotic may be prudent. But we often see women who present when they are already pregnant and on an atypical agent. At this point a switch may not be the wisest decision, if she is at a risk of relapse. For those women, the Motherisk data are not a guarantee of safety but do provide information that is at least moderately reassuring. Although this small study is encouraging, given the prevalence of reproductive-age women on these agents, it would be ideal if the industry performed postmarketing surveillance studies. Such studies may soon be mandated by the Food and Drug Administration in this post-Vioxx era, with increased emphasis on the safety of marketed drugs.

DR. COHEN directs the perinatal psychiatry program at Massachusetts General Hospital, Boston, which offers information about pregnancy and mental health at [www.womensmentalhealth.org](http://www.womensmentalhealth.org). He is a consultant to AstraZeneca, Eli Lilly, and Janssen, which make atypical antipsychotics.



BY LEE  
COHEN, M.D.

## Diabetes Risk From Atypical Antipsychotics Is Not Equal

BY SHERRY BOSCHERT  
San Francisco Bureau

SAN DIEGO — All atypical antipsychotics carry the same risks for the development of diabetes, according to the Food and Drug Administration, but some experts have a more nuanced view.

Everyone agrees that some atypical antipsychotics are more likely to cause weight gain than are other drugs of the same class. That's enough to make some experts outside the FDA believe that there's also a tiered risk for diabetes in patients who take these medications, Stephen M. Stahl, M.D., said at a psychopharmacology congress sponsored by the Neuroscience Education Institute.

Clozapine (Clozaril) and olanzapine (Zyprexa) cause the most weight gain among atypical antipsychotics. Risperidone (Risperdal) and quetiapine (Seroquel) inhabit a middle ground, and little or no weight gain is seen in patients on ziprasidone (Geodon) or aripiprazole (Abilify).

"As goes weight, so goes risk for diabetes," said Dr. Stahl of the University of California, San Diego. He has been a consultant for—or received financial support from—the companies that make olanzapine (Eli Lilly & Co.), quetiapine (AstraZeneca), and ziprasidone (Pfizer Inc.).

The divide between the FDA warnings and other expert opinions might be understood as a division between concern about acute hyperglycemic events and the development of diabetes over time, Ramachandiran Cooppan, M.D., said at the same session in a copresentation with Dr. Stahl.

Because there are not enough long-term data to rule out an increased risk for diabetes with all the atypical antipsychotics, and because they seem to have equal risks for causing acute hyperglycemic events, the FDA decided to err on the side of caution and place a blanket warning for diabetes risk on the whole class, said Dr. Cooppan of the Joslin Diabetes Center, Boston.

He has been a speaker or consultant for, or received grants from, the companies that make olanzapine and ziprasidone.

The useful point of the FDA warning is that "there is a myth out there that type 2 diabetes patients can't go into diabetic ketoacidosis. We need to change that,"

because up to 40% of people with type 2 diabetes can slip into diabetic ketoacidosis, he noted.

On the other hand, at the time that most case reports of acute hyperglycemic events emerged in patients on atypical antipsychotics, most psychiatrists were not screening patients for impaired glucose tolerance or other diabetes risk factors. "It doesn't take much weight gain to tip you over [into diabetes] if you're genetically predisposed," Dr. Cooppan said.

The American Diabetes Association guidelines on diabetes risk consider other factors that the FDA did not address, such as changes in lipids, blood pressure, or coagulation, he and Dr. Stahl said.

Comparisons of separate pharmaceutical company-sponsored studies suggest that aripiprazole can significantly reduce triglyceride levels in patients previously

treated with an atypical antipsychotic, and that clozapine and olanzapine are associated with the largest elevations in triglyceride levels, Dr. Stahl said. The triglyceride effects of other atypical antipsychotics fall be-

tween these two zones.

"We think that there may be a differential risk" for diabetes among atypical antipsychotics, but only time will tell, Dr. Cooppan said.

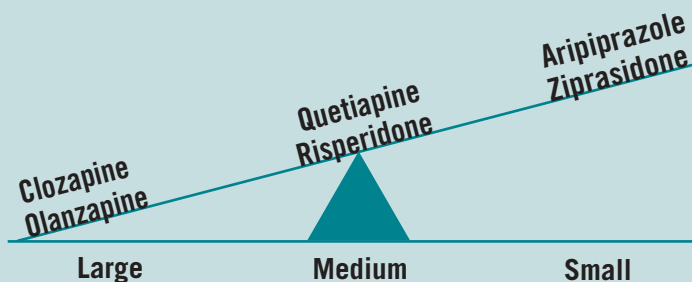
Dr. Stahl still uses clozapine and olanzapine when needed, despite their potentially higher risk for diabetes.

The important thing is to start balancing the benefits of the drugs with risk differentials when choosing therapy, he explained.

Physicians who prescribe these drugs must be prepared to monitor all severely mentally ill patients for diabetes risk factors regardless of the drug used, he emphasized.

On the front of each chart, put the patient's blood pressure, lipid levels, recent triglyceride level, weight or body mass index, and "maybe even a waist circumference" measurement. "People like us have leverage on our patients to get them to change their lifestyles," Dr. Stahl said. "None of [this] is very simple, but we should at least try." ■

### When It Comes to Weight Gain, All Atypical Antipsychotics Are Not Created Equal



Source: Diabetes Care 2004;27:596-601