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Antipsychotic drug warnings indicate need for better communication between endocrinologists, psychiatrists

In January, the FDA issued a warning about adverse metabolic effects for adolescents taking the second-generation antipsychotic drug olanzapine. The revised labeling for olanzapine, which is FDA-approved for the treatment of schizophrenia and bipolar disorder in adolescents and adults, states that clinicians should consider the increased potential for weight gain, hyperlipidemia and long-term adverse effects for adolescents.

In 2003, the FDA issued a warning for second-generation antipsychotics, including olanzapine (Zyprexa, Eli Lilly) and risperidone (Risperdal, Janssen), among others, citing an increased risk for diabetes and hyperglycemia. The FDA stated that glucose levels should be monitored in patients with diabetes, at risk for diabetes or with symptoms of hyperglycemia. Concurrently, the American Diabetes Association and American Psychiatric Association recommended glucose and lipid testing for all patients started on second-generation antipsychotics.

Now, the latest FDA warning adds to the issue surrounding metabolic risks associated with these drugs.

“The adverse effects caused by these new second-generation antipsychotic drugs are without a doubt problematic,” **Daniel Hartung, PharmD, MPH,** assistant professor of pharmacoeconomics at Oregon State University, told *Endocrine Today*.

Such warnings and recent data indicate a greater need for communication between endocrinologists and psychiatrists in monitoring weight gain, glucose and other lipid levels, experts said.

“Communication between endocrinologists and psychiatrists — and among all physicians — is critical in the management of a patient’s psychiatric disorders and the adverse effects of their medication,” said **Howard R. Belkin, MD, DDS, JD,** a psychiatrist at Beaumont Hospital, Royal Oak, Mich.

Elaine Morrato, DrPH, MPH, found that the FDA warning for second-generation antipsychotics did not increase metabolic screening rates.

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Dan Meyers / University of Colorado School of Medicine

Endocrine Today interviewed leading researchers in the field to discuss the results of recent studies, potential issues with the current FDA advisory system and methods to improve communication between endocrinologists and psychiatrists.

Metabolic risks ignored

Despite warnings, recent study results have indicated that physicians may not be screening users of second-generation antipsychotics for elevated glucose and cholesterol levels.

Elaine Morrato, DrPH, MPH, assistant professor in the department of health systems, management and policy at the University of Colorado, Denver, and colleagues conducted two studies "to see to what degree the 2003 FDA warnings were adopted."

In a study published in *Archives of Pediatric and Adolescent Medicine* in April, Morrato and colleagues concluded that more effort is needed to ensure that patients who receive second-generation antipsychotics are screened for diabetes and dyslipidemia and monitored for adverse drug effects. They analyzed Medicaid claims data from California, Missouri and Oregon on 5,370 children aged 6 to 17 years without diabetes who were taking second-generation antipsychotics and 15,000 children without diabetes who were taking albuterol but no antipsychotics.

Glucose screening was performed in 31.6% of children treated with second-generation antipsychotics vs. 12.6% treated with albuterol. Lipid testing was performed in 13.4% of children taking antipsychotics vs. 3.1% taking albuterol. The case incidence of glucose and lipid disorders was higher in children treated with antipsychotics vs. albuterol (8.9 per 1,000 children vs. 4.9 per 1,000 children and 9.7 per 1,000 children vs. 4.6 per 1,000 children).

Their findings reflect clinical practice patterns one year after recommendations from the ADA and American Psychiatric Association called for metabolic screening of patients receiving second-generation antipsychotics regardless of age or underlying diagnosis.

"The results suggest that work is still needed to improve metabolic monitoring of children receiving antipsychotic medication," Morrato told *Endocrine Today*.

A study published in *Archives of General Psychiatry* in January also examined laboratory claims data from Medicaid programs in California, Oregon and Missouri between 2002 and 2005 — before and after the 2003 FDA warning. Morrato and colleagues compared glucose and lipid monitoring trends in 109,451 patients receiving second-generation antipsychotics with a control cohort of 203,527 patients receiving albuterol but no antipsychotics.

Again, they found that the FDA warning was not associated with an increase in blood glucose and cholesterol screening (1.7%; *P*=.02). Initial testing rates for patients using antipsychotics were low; glucose testing was at 27% and lipid testing was at 10%.

Although new prescriptions for olanzapine declined during the warning period (annual share decline, 19.9%; *P*<.001), the researchers found that prescriptions of the lower-risk drug aripiprazole increased (share increase, 12.1%; *P*<.001). This may be attributed to the elimination of prior authorization in California during the same time frame, according to the researchers.

“I suspect that it is easier, and therefore faster, to switch prescribing practices following a drug warning, particularly if safer alternatives are available, than it is to increase complexity in medical care by adding extra monitoring,” Morrato said.

Daniel Hartung

According to Hartung, also a researcher for this study, “the results demonstrate that the way we communicate risk information to clinicians needs to be re-evaluated for some types of messages.”

The conclusion does not necessarily indicate that physicians are ignoring governmental and industry recommendations, Belkin said, adding that the data were four- to eight-years-old when the study was published.

“During those intervening years, the knowledge among psychiatrists that there is a relationship between the use of second-generation antipsychotics and weight gain, hyperlipidemia and increases in blood sugar, anecdotally, has become common knowledge,” Belkin said.

“Clinical experience with these medications, discussions with patients, other psychiatrists and physicians seem to have made the use of screening and monitoring tests for the adverse effects of these medications relatively common. It appears, from discussions with physicians, that screening and monitoring tests are now routinely performed prior to and during the administration of second-generation antipsychotics,” he said.

FAST FACTS

Issues of Concern

1 The FDA issued a warning in January 2010 about adverse metabolic effects associated with olanzapine.

2 The American Diabetes Association and American Psychiatric Association recommend glucose and lipid testing for all people starting second-generation antipsychotics.

3 A 2010 study showed that glucose screening was conducted in just 32% of children who took antipsychotics.

Warning, revised labeling

The FDA warning and revised labeling for olanzapine states that clinicians should consider the increased potential for weight gain, lipid disorders and potential long-term effects.

Eli Lilly, the manufacturer of Zyprexa, sent a letter to physicians in January detailing the amount of weight gain associated with the drug. The proportion of study participants reporting significant weight gain was greater in adolescents compared with adults.

After 24 weeks of treatment with olanzapine, the percentage of adults who gained at least 7% of their baseline body weight was 89%. Further, 55% of adolescents gained at least 15% of their baseline body weight and 29% gained at least 25% during long-term exposure to olanzapine, according to information provided in the letter.

The letter further stated that clinically significant elevations in triglycerides have been observed in adolescents taking olanzapine. These elevations are reportedly as high as 500 mg/dL, which is “extremely high,” according to Belkin.

Howard R. Belkin

“These weight gains are clearly clinically significant and undesirable,” he said. “Physicians are urged to consider these long-term risks to adolescents and consider alternative treatments before prescribing olanzapine.”

Second-generation antipsychotics are a heterogeneous class of drugs and that extends to efficacy and adverse effects, according to Hartung.

“Not only do some of these agents have the propensity to exacerbate metabolic profiles, they can also lead to potentially life-threatening arrhythmias and have been linked to an increased risk for death in elderly patients,” Hartung said. “Some of these risks are manageable and can be acceptable when treating certain serious chronic mental illnesses, such as schizophrenia; however, when the drugs are used for conditions in which the effectiveness is uncertain or unlikely to be positive, the risk-benefit equation becomes unacceptable.”

The FDA warning also states that the safety and efficacy of olanzapine has not been established in children aged younger than 13 years.

However, Morrato and colleagues found that one-quarter of new prescriptions for second-generation antipsychotics were filled for children, according to data from the aforementioned study published in *Archives of General Psychiatry*. Although olanzapine was not the most commonly prescribed antipsychotic among children in the study, the numbers were still “considerable,” Morrato said. Among children initiating antipsychotic therapy, the most commonly prescribed antipsychotic was risperidone (50.5%). New prescriptions for children aged 6 to 12 years totaled 60.7%, and new prescriptions for adolescents aged 13 to 17 years totaled 39.1%.

“I was struck by the number of children who are using these medications,” Morrato said. “Many psychiatrists and primary care physicians would not necessarily think about screening a 14-year-old for diabetes. Yet, there are studies coming out that suggest these younger patients experience the same metabolic adverse effects as adults. This is a vulnerable group, and the long-term consequences of second-generation antipsychotics in children and adolescents are unknown.”

Targeting the warnings

A study published in the January issue of *Archives of Internal Medicine* examined the effect of an FDA warning about antipsychotics in elderly patients with dementia and behavioral disturbance. The FDA issued an advisory warning in 2005, citing an increased risk for death in this patient population taking antipsychotics.

Data show a small decline — about 20% — in atypical usage among elderly patients with dementia, according to **Ray Dorsey, MD,** assistant professor of neurology at the University of Rochester Medical Center. However, Dorsey and colleagues noted that the study raised larger issues about communication between patients and providers and appropriate prescribing.

“We found that the FDA advisory did lead to a substantial decline in atypical use among the elderly with dementia, although tens of thousands of patients continue to receive these agents despite little evidence of their efficacy and substantial safety concerns,” **G. Caleb Alexander, MD,** assistant professor of medicine at the University of Chicago and a researcher for the study, said in an interview.

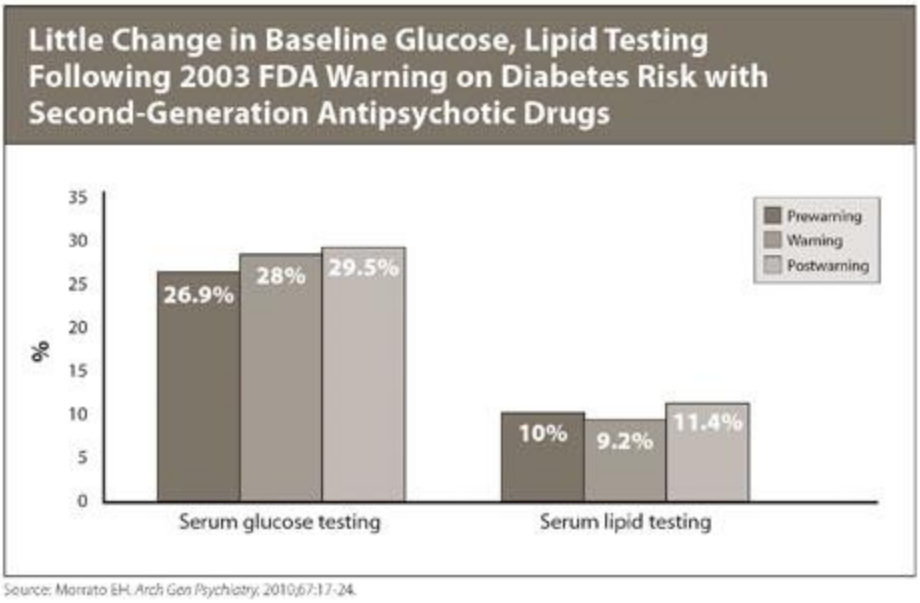
Alexander and Dorsey said given the reliance on FDA advisories to communicate new information about drug safety, more systematic research is needed to understand the effect of advisories.

“We suggest that the specificity and impact of warnings could be enhanced by targeting the warnings to physicians such as geriatricians and psychiatrists, in this case, and patients and potentially caregivers who are most likely to be affected by the warning,” Dorsey told *Endocrine Today*.

Moreover, the approach should be akin to the ways in which pharmaceutical companies target physicians who are most likely to prescribe and patients who are most likely to use or benefit from a drug. The same approach could be used to communicate safety information and risks, Dorsey said.

Other means of communicating risk beyond "Dear Provider" letters and posting of advisories on the FDA's website may be needed. In addition, Dorsey said, the target audience should be expanded beyond prescribers to patients directly.

"Pharmaceutical firms could be responsible, including financially, for communicating safety risks that emerge after a drug is approved, and regulators could ensure and assess the effectiveness of such communications," Dorsey said.



Source: Morrato EH. *Arch Gen Psychiatry.* 2010;67:17-24.

Inadequate testing

This is not the first time that adherence of the FDA guidelines regarding metabolic testing and antipsychotic drugs has been called into question.

A small study published in the June 2007 issue of *BMC Psychiatry* examined monitoring practices in primary and secondary care to determine how often patients treated with antipsychotics were having their BMI, glucose and lipids checked.

Paul Mackin, MD, PhD, a National Institute of Health Research clinician scientist and psychiatrist at Newcastle General Hospital, England, examined the burden of cardiovascular risks in patients with severe mental illness taking second-generation antipsychotics. Despite clear recommendations about monitoring this patient group, the results were not positive, he said.

"We found that monitoring was inadequate, despite the generally poor metabolic status of these patients," Mackin said.

Of the 106 community-treated psychiatric patients from across northeast England, 53% had hypertriglyceridemia and 31% had hypercholesterolemia — but only 7% received lipid-lowering therapy. Recording of measures of adiposity occurred in 0% of patients, and less than 50% of patients had neither blood glucose nor lipids monitored during the follow-up period.

"It's difficult to be certain about the reasons for these findings, but it would appear that lack of awareness on the part of the clinicians may be a key issue. Who should be responsible for monitoring is also an unresolved problem. Should it be the general practitioner or the psychiatrist?" Mackin said.

With robust evidence to show that some of these drugs carry serious metabolic adverse effects, there should be no excuse for lack of monitoring, he said.

“However, I do not think that doctors are willfully ignoring warnings such as these,” Mackin said.

There is a need for better communication between primary and secondary care to ensure that clinicians and patients know who is taking responsibility for checking for the emergence of metabolic adverse effects associated with second-generation antipsychotics, he said.

“We are getting better at this, but there is still a long way to go,” Mackin said.

Increased need for communication

Endocrine Today interviewed experts who said communication between endocrinologists and physicians is critical to manage a patient’s medication for psychiatric disorders.

Ned M. Weiss, MD, an endocrinologist at Abington Memorial Hospital, Pennsylvania, said discussion between the two specialties is essential, and endocrinologists have a responsibility to guide their colleagues in psychiatry to recognize the metabolic abnormalities associated with these medications and guide patients to the appropriate settings for therapy and follow-up.

“The endocrinology community should be proactive in this effort,” Weiss said.

“Clinical trials of various lifestyle interventions may help some of these patients avoid the serious sequelae of the metabolic syndrome. I have had some success using meal replacements in these patients as a way to help them control their body weight. However, my sample size is small and follow-up is difficult. Nevertheless, this approach, as well as others, is needed in larger settings so that we can have more outcomes data that can help drive clinical decisions in the office setting,” he said.

Morrato said the current data highlight the challenges between cross-consulting and collaboration.

“This is a case in which psychiatrists may not typically be trained to monitor for diabetes and endocrinologists may not typically be trained to monitor for mental health disorders,” Morrato said. “For patients taking antipsychotics, it is important that both health care professionals are involved in patient care decision-making. However, unless there is well-integrated care, it can place more ownership and burden on patient to manage information between the different specialties.”

Some experts said second-generation antipsychotics are beginning to be prescribed for other psychiatric disorders, such as severe anxiety, obsessive-compulsive disorder, depression and sleep disorders.

Moving forward

Sun H. Kim, MD, an assistant professor of endocrinology, gerontology and metabolism at Stanford University School of Medicine, said when analyzing these studies it may not be fair to say many doctors “ignore” the FDA warnings.

“Many doctors, especially psychiatrists, are aware and concerned about the side effect profile of antipsychotic medications,” Kim said.

The main issue, according to Kim, is that patients who are treated with antipsychotic medications are primarily seen by psychiatrists who feel more comfortable, and rightly so, with managing psychiatric problems than metabolic problems such as high glucose and cholesterol levels.

“Therefore, there might be some hesitance to order these tests,” Kim said, adding that these issues are somewhat unfortunate, as emerging evidence suggests that individuals with psychiatric problems are more at risk for metabolic/medical problems regardless of their antipsychotic therapy.

“I would love to see a model in which patients with psychiatric problems are taken care of in a system where both psychiatric and medical issues are addressed in one clinic by a team of physicians,” Kim said.

As far as the current FDA advisory system, Alexander said he would not characterize it as “broken.”

“Nevertheless, there are a number of ways that the advisory system might be strengthened. These include more sophisticated efforts to reach high-volume prescribers of the therapies in question, as well as greater efforts to systematically measure the effect of advisories on a number of outcomes,” Alexander said.

“Ultimately, the advisory system is all about trying to improve drug safety, and yet we know relatively little about the true impact that advisories have,” he said. – *by Angelo Milone*

POINT / COUNTER

Is there a lack of communication between endocrinologists and psychiatrists regarding metabolic screening of second-generation antipsychotic users?

For more information:

- Dorsey ER. *Arch Intern Med.* 2010;170:96-103.
- Morrato EH. *Arch Gen Psychiatry.* 2010;67:17-24.
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