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**Subject:** Psych News reports on labeling issue - Extensively quotes John Newcomer

The following article, by Jim Rosack, currently appears on the *Psychiatric News* web site. Rosack has extensively interviewed Dr. John Newcomer on his feelings about the FDA label change. Newcomer is critical of the fact that the FDA did not address weight gain in its recommended labeling. At the end of the article, Newcomer issues a call to the ADA to issue a consensus on the issue. See highlights.

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**Clinical & Research News**

**FDA to Require Diabetes Warning On Antipsychotics**

**Jim Rosack**

**Choosing to sidestep the issue of differences in weight gain among the different medications, the new warnings appear to put the entire class on equal footing for risk of diabetes.**

In a series of letters delivered in mid-September, the U.S. Food and Drug Administration (FDA) disclosed to makers of atypical antipsychotic medications that it will require each drug maker to relabel its product to include warnings regarding risk of hyperglycemia and diabetes mellitus.

**Communications between the FDA and drug makers are usually considered privileged and proprietary—those considered to be sensitive are rarely disclosed. However, the receipt of the letters was made public by Eli Lilly and Co., maker of olanzapine (Zyprexa).**

**The makers of each of the other atypical antipsychotics, clozapine (Novartis's Clozaril), risperidone (Janssen's Risperdal), quetiapine (AstraZeneca's Seroquel), ziprasidone (Pfizer's Geodon), and aripiprazole (Bristol-Myers Squibb/Otsuka's Abilify) all confirmed to Psychiatric News the receipt of similar letters requesting the new warning language. None, however, was willing to make copies of its letter available.**

The Lilly letter was disclosed in a press release and posted on the company's Web site.

The FDA letter to Lilly, signed by Russell Katz, M.D., director of the agency's Division of Neuropharmacological Drug Products, noted that "after reviewing the available data pertaining to the use of atypical antipsychotic medications and diabetes mellitus adverse events, we have concluded that the product labeling for all atypical antipsychotics should be updated to include information about these events."

The letter continued, "While we acknowledge that the relationship between atypical antipsychotic use and diabetes mellitus adverse events has not been completely described," the agency will require all atypicals to carry the broad new warnings (see box on page 26 for the agency's proposed language for the warnings). "Increased attention to the signs and symptoms of diabetes mellitus may lead to earlier detection and appropriate treatment and thus reduce the risk for the most serious outcomes," the letter advised.

**The public release of the letter by Lilly was considered a bold move by pharmaceutical-industry analysts, who regarded the FDA warnings as controversial and having significant potential to alter prescribing patterns. Olanzapine, analysts noted, is tied to reports of weight gain and diabetes more often than are other atypical antipsychotics.**

The issue is certainly not a new one. Case reports of diabetes and diabetic complications associated with atypical antipsychotics have been known for many years. However, significant debate has occurred in both the research and clinical arenas as to how strong the association is, and what factors—if any—are likely to predict which patients will be at increased risk.

One central issue in the controversy is the role played by weight gain as a factor in increasing a patient's risk for developing diabetes. Endocrinologists have long held that obesity is a key factor increasing the risk of diabetes in the general population. A significant body of epidemiological research has attempted to answer the question in patients taking antipsychotics, with somewhat conflicting results.

Many psychiatrists familiar with the issue now believe that weight gain fostered by antipsychotic medications does play a central role in elevating the risk of diabetes in their patients.

**"Both case-report literature and published FDA MedWatch analyses indicate that about 75 percent of the cases of new-onset type II diabetes associated with drugs like clozapine and olanzapine occur in the setting of obesity and substantial weight gain," said John Newcomer, M.D., an associate professor of psychiatry at Washington University School of Medicine in St. Louis.**

**"That leaves 25 percent, though," Newcomer told Psychiatric News, "who develop diabetes without weight gain, and these are the difficult cases to figure out."**

**Newcomer has published several research studies on the risk of diabetes in patients taking atypical antipsychotics.**

**Several studies have indicated that patients gain the most weight on olanzapine and clozapine, while patients taking risperidone and quetiapine gain less. Patients taking ziprasidone or aripiprazole generally do not gain weight, and may even lose weight.**

**While cases of diabetes have been reported among patients taking all of the six medications in question, some studies indicate that the highest number of cases appears to be in patients taking olanzapine and clozapine.**

Olanzapine maker Lilly several years ago acknowledged that weight gain is a known risk factor for diabetes and began a line of research geared to help patients reduce the amount of weight they gain while on the drug—either through pharmacological means or via diet and exercise. Some data have been published that suggest that weight gain can be limited in patients with schizophrenia taking olanzapine.

### **FDA's Stance**

**"The FDA was in a very difficult position," Newcomer noted. If the agency had done nothing, it would have been accused of being nonresponsive. If the FDA ordered selective labeling—only certain drugs within the class—then the agency "would really have been on the spot to justify that position."**

**In ordering warnings across the entire class of atypicals, however, Newcomer believes the agency may have been trying for the middle ground—not wanting to single out one medication. Yet by avoiding the weight issue, he said, the FDA appears to have**

**caught the ire of a number of specialists familiar with the issue.**

**"Clearly, the NIH [and] the [American Diabetes Association] say that weight gain is a major risk factor for diabetes mellitus and that it should be watched. Yet there is little mention of it in the FDA warning," Newcomer said.**

In addition, he maintains that the warning could have been more specific on what physicians should do if a patient develops serious diabetic complications, as well as how patients taking atypical antipsychotic medications should be monitored to catch any impairment in glucose control early. Newcomer also believes that "the FDA could have identified that there are differences in short- and long-term weight gain among the individual medications that are already detailed in the package inserts and should be considered as part of monitoring and treatment decisions."

### **Looking for Answers**

In its letter to Lilly, the FDA "acknowledge[s] that additional labeling changes may be required as new information becomes available. Areas that require additional research include, but are not limited to, identification of subpopulations at greatest risk for diabetes mellitus adverse events, exploration of the relative risk for diabetes mellitus adverse events among the different antipsychotics, and evaluation of potential mechanisms of action."

Each of the companies involved continues to pursue these and other research questions in an attempt to resolve the issue, and most of the companies told Psychiatric News that they will review the requested labeling changes and work out final language with the FDA.

Endocrinologists are intimately involved in attempting to answer key questions as well. The American Diabetes Association (ADA) has scheduled a November 19 consensus development conference to address the relationship between antipsychotic medications and diabetes.

Newcomer is a member of the ADA consensus panel's planning committee. (He noted that the final consensus committee will be made up of endocrinologists and senior psychiatrists who—like himself—have no research or financial interest in the companies that make the medications at issue.) The ADA conference is currently targeted at primary care physicians and endocrinologists, Newcomer said, who have not yet heard much about the diabetes problems that psychiatric patients are encountering. However, the results of the conference will have obvious relevance beyond those fields.

**APA is also working on the issue, having established an antipsychotics and diabetes subcommittee under the Corresponding**

**Committee on Research on Psychiatric Treatments. Newcomer also is on this subcommittee.**

**"What remains to be seen is whether the ADA comes out with a consensus statement that is in line with or different from the FDA's language," Newcomer said. "Will there be any clarity to the monitoring and treatment recommendations? APA's subcommittee will watch this very closely and will be in a position to add to or clarify the ADA statement, so that we get the most accurate and complete information out in a timely manner."**

The FDA's letter to Lilly is posted on the Web at [http://www.lilly.com/pdf/2003\\_9\\_17\\_fda\\_letter.pdf](http://www.lilly.com/pdf/2003_9_17_fda_letter.pdf).

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