To: US_NS_Staff
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From: CN=Paula T Trzepacz/OU=AM/O=LLY
Subject: Great articles from Psych News on diabetes & antipsychotics!

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----- Forwarded by Paula T Trzepacz/AM/LLY on 07/08/2002 04:26 PM -----

Marni Lemons
07/08/2002 11:01 AM

To: USZYPREX
cc:
Subject: Great articles from Psych News on diabetes & antipsychotics!

The following are two articles from the current issue of Psychiatric News -- the first reports extensively on the diabetes issue and the second on the weight management data we presented at the APA. The first article quotes Dr. John Buse, Dr. Les Citrome and Dr. John Newcomer, explaining that the risk of diabetes appear to be related to the underlying mental illness and that the risk seems to cross antipsychotic agents (see highlights). Dr. Newcomer says diabetes is tied to weight gain, but goes on to say that the perceptino that one antipsychotic causes diabetes more than others is incorrect. The doctors also recommend screening of these patients.

We worked very closely with Jim Rosack, the reporter, to positively impact the story and are very please with the result. Originally, he intended to report simply on the link between Zyprexa and Clozaril and diabetes.

Marni

Psychiatric News

Clinical and Research News

Studies Close In on Diabetes, Psychiatric Illness Link

Jim Rosack

Researchers are striving to shed light on the puzzling link between severe and persistent psychiatric illness, psychotropic medications, and diabetes.

A significant volume of recent data, including several reports of new research presented at APA's annual meeting in May, is helping some researchers begin to form what they believe is a solid hypothesis explaining the persistent link between psychiatric illness and problems with glucose regulation.

Many researchers suspect that psychotropic medications, antidepressants and antipsychotics in particular, may be aggravating an underlying predisposition or risk for developing diabetes. Although some researchers suspect the drugs' actions on 5HT1A receptors play a role in the interaction, no one believes the mystery is close to being solved.

"In psychiatry, we prescribe a host of medications that are known to carry a liability of weight gain," said John Newcomer, M.D., an associate professor of psychiatry at Washington University School of Medicine in St. Louis. "This weight gain is almost surely predominantly an increase in adiposity—the degree of body composition made up of fat, or adipose, tissue. We've known for years now, since the 1970s, that an increase in adiposity can be associated with an increase in insulin resistance," Newcomer, who has studied the question extensively, told *Psychiatric News.*

The first report of a suspected link between psychiatric illness and diabetes was published in 1926, well before the advent of psychotropic medications. A significant number of reports have followed, especially after the explosive development of psychotropic medications in the last few decades. This has led both clinicians and researchers to ponder what part of the link is inherent to the disease process and what part is played by medications.

Newcomer explained that if a patient has baseline insulin resistance, the amount of fat the patient deposits into adipose tissue from energy taken in from a meal tends to increase. Adipose tissue itself secretes two hormones, leptin and resistin (characterized for the first time about a year ago), both of which can contribute to increased insulin resistance.

"The drugs that cause the most weight gain, then, would cause the largest shift in insulin resistance, bringing out an overexpression of diabetes," Newcomer explained.

Yet it's not that simple, he warned. There are many reports of patients developing diabetes when taking psychotropic drugs, even when they don't show significant weight gain. And in many cases, the onset of diabetes is within months of starting the drug, rather than the years that diabetes experts would predict in a nondiabetic and otherwise healthy individual.

Add to that the numerous reports of diabetes in patients with schizophrenia that were published before the development of modern psychotropic medications, and a confounding question emerges: Which came first, an inherent risk to develop diabetes along with psychiatric illness (possibly because of a baseline elevated insulin resistance) or the known contribution of psychotropic medications to the development of diabetes?

Data Don't Explain Differences

The data are indeed conflicting, but there is a perception in the field, Newcomer said, to think that the highest risk of developing diabetes while on a psychotropic medication occurs with the antipsychotics, particularly clozapine or olanzapine. But that perception may not actually be on target, he noted.

"I think all this rank-order stuff is still really up in the air," he said.

"When I look at the preponderance of data," agreed John Buse, M.D., Ph.D., "there simply doesn't seem to be any major difference between antipsychotic therapies and the incidence of diabetes."

Buse is an associate professor of medicine and chief of the Division of General Medicine and Clinical Epidemiology at the University of North Carolina. "My advice to psychiatrists," Buse, a diabetes expert and director of the UNC Diabetes Care Center, told *Psychiatric News*, "is to recognize that with people who have severe and persistent disease—particularly schizophrenia, but also severe psychotic depression and bipolar disorder—there may be simply a higher risk of those people developing diabetes than the general population, regardless of their medication profile."

Recent Reports

Several recent reports have examined the issue. In May both Britain's Medicines Control Agency and the Japan's Health and Welfare Ministry issued diabetes-related alerts regarding olanzapine. The British agency cited 40 "reports of hyperglycemia, diabetes mellitus, or exacerbation of diabetes" including four that resulted in ketoacidosis and/or coma, and one resulting in a patient's death. Japan reported two deaths of patients with existing diabetes who were prescribed olanzapine and seven other patients who had "loss of consciousness or coma" while taking the drug.

Reports have recently been published that review the FDA's MedWatch system for reporting adverse events in the U.S. involving several antipsychotics and diabetes. These reports note that from 1990 to 2001, there were 242 accounts of new-onset diabetes and 54 reports of worsening of existing diabetes for patients taking clozapine. Most of the cases developed within six months of starting the

drug, and 25 patients died as a result of diabetic complications.

A new report on MedWatch data presented at last month's Endocrine Society meeting in San Francisco reviewed risperidone. It identified 83 newly diagnosed cases and 40 patients with pre-existing diabetes that worsened after being started on the drug between 1993 and 2001. There were five deaths of patients taking risperidone tied to diabetic complications.

Elizabeth Koller, M.D., a medical officer in the Division of Metabolic and Endocrine Drug Products at the FDA, cowrote the MedWatch reports as an individual researcher rather than as an FDA official. Koller wrote in the risperidone report that "these data, along with similar reports of hyperglycemia with olanzapine, clozapine, and quietiapine, suggest that antipsychotic use may unmask or precipitate diabetes in psychotic patients. Causality cannot be ascertained because of the nature of these data and absence of control groups. While the number of such cases in the literature and in MedWatch attributed to clozapine or olanzapine are greater than those with risperidone, no conclusions can be made until direct prospective studies of causality and relative risk are done."

"Patients, and even physicians, hear these kinds of reports," Buse commented, "and they just freak out." He reiterated that the topic is actually very complex, and only solid research will help answer the questions.

In the March *Archives of General Psychiatry,* Newcomer reported the results of a study looking at glucose regulation in 48 patients with schizophrenia. The study was funded primarily through grants from NIH and NARSAD, using no industry funding.

Newcomer's study was a blinded look at modified oral glucose tolerance tests to compare glucose regulation in patients receiving placebo, a "typical antipsychotic," or risperidone, clozapine, or olanzapine.

All patients in the study were nondiabetic and had already been receiving antipsychotic medications, avoiding what Newcomer described as the "tendency to flip into diabetes in the first few months of taking the drugs."

The study concluded that subjects taking olanzapine and clozapine had significant increases in blood glucose after receiving a dose of the drug compared with those receiving a typical antipsychotic or placebo. Risperidone-treated patients showed glucose elevations that were significant compared with placebo, but not significantly different from the typical antipsychotic group.

A second recent analysis, independent of industry funding, was presented at the APA annual meeting. The data are from a study published in the February *American Journal of Psychiatry*, by Jan Volovka, M.D., Ph.D., chief of the clinical research division at the Nathan S. Kline Institute for Psychiatric Research in New York, and his colleagues.

That report detailed a double-blind, head-to-head efficacy trial of clozapine, olanzapine, risperidone, and haloperidol. The new research presentation at the annual meeting described changes in glucose and cholesterol in patients taking the four medications. The trial studied patients who had failed on previous treatments.

"One of the take-home messages was that there were only 14 outliers [of 101 patients studied] who had elevations of glucose levels above 125 mg/dl," Leslie Citrome, M.D., M.P.H., told *Psychiatric News.* Citrome, a co-author on both the *AJP* report and the annual meeting presentation, is director of the Clinical Research and Evaluation Facility at Nathan Kline and clinical professor of psychiatry at New York University.

"Of those 14, six were taking clozapine, four were taking olanzapine, three were taking risperidone, and one received haloperidol," Citrome said.

"Whenever I initiate treatment for patients with schizophrenia," Citrome said, "I always want to do a comprehensive medical workup." He often finds, he said, that this patient population has received little if any comprehensive medical care. "These patients do have a higher risk of a number of medical conditions, including diabetes." He regularly orders lab tests including baseline liver enzymes as well as fasting glucose, cholesterol, and lipid levels.

By screening for diabetes at the outset, Buse noted, psychiatrists can catch it early and avoid the troubling scenarios in the case reports, regardless of which antipsychotic drug the patient may need.

"If there is a difference between these drugs, I at this point couldn't tell you which of the drugs has the greatest diabetes risk—other than clozapine," Buse concluded. "But the difference between the one with the greatest risk and the one with the least risk is small in comparison to the absolute risk of developing diabetes that is associated simply with having a severe psychiatric illness."

Newcomer added, "The patient may well be at risk. But then we [as psychiatrists] have the responsibility to ask whether or not there is an iatrogenic contribution—a modifiable degree of risk that we add. When we cause an increase in weight or adiposity, we're going to see some very predictable changes in glucose regulation."

Psychiatric News

Weight Management Cuts Risk Of Antipsychotic-Related Diabetes

Jim Rosack

New research suggests that comprehensive weight management can help alleviate the risk of developing diabetes while taking antipsychotic medications.

In response to recent critical reports linking its $2.5 billion a year antipsychotic olanzapine (Zyprexa) to diabetes and diabetic complications resulting in some deaths (see story on facing page), **Eli Lilly and Company has been busy researching ways to break the link or at least to alleviate its severity.**

A report of research funded by Lilly and presented at APA's 2002 annual meeting in May suggests that patients who take antipsychotics may be able to reduce their risk of glucose-regulation problems by controlling weight gain through dietary changes and exercise.

Recent warnings from British and Japanese regulators about the link between olanzapine and severe diabetes prompted Lilly in May to strongly defend its drug's safety history, saying that any "report suggesting a causal relationship between Zyprexa and blood-sugar problems was not an accurate reflection of the European Union or Japanese labeling or even current scientific evidence."

Researchers have long thought that olanzapine causes weight gain in roughly one-third of patients who take it, with some of those patients gaining in excess of 25 pounds. That weight gain may increase the risk of developing type 2 diabetes.

"Managing weight gain is a challenge for many Americans, especially those with severe and persistent mental illness," said Franca Centorrino, M.D., director of the Bipolar and Psychotic Disorders Outpatient Program at McLean Hospital and Harvard Medical School.

Centorrino presented data at the APA annual meeting indicating that patients who took olanzapine, risperidone, clozapine, or ziprasidone and participated in a weight-management program were able to decrease their body mass index (BMI) and their weight.

At baseline, patients' average BMI was 36.6, with a corresponding average weight of 231.4 pounds. Each patient had gained at

least 10 pounds while on antipsychotic therapy. The patients participated in weekly dietary counseling and twice-weekly group exercise including treadmill, step machine, biking, and rowing and were followed for 24 weeks.

Over 90 percent of the patients, Centorrino reported, experienced an average decrease in BMI of 2.1 points, on average losing 13.1 pounds. **Patients taking olanzapine saw the largest reduction, followed by patients taking clozapine or risperidone (about half the reduction seen with olanzapine).** Patients taking ziprasidone saw the smallest reduction in both BMI and weight, as would be expected since patients taking ziprasidone on average do not gain a significant amount of weight.

"Dependably managing schizophrenia with appropriate medication should be the first priority for physicians and their patients. Once their symptoms and lives are under control, patients can then implement simple lifestyle changes to help manage weight gain, and stay on the treatment that works best for them," said Centorrino in a press briefing.

A second study looked at the long-term benefits of the weight-management program. In a six-month follow-up study, Betty Vreeland, M.S.N., an advanced practice nurse at the University of Medicine and Dentistry of New Jersey, also found that nutritional counseling and regular exercise resulted in weight loss for patients on antipsychotic therapy.

"Our program was successful," Vreeland said in a press release, "because patients were very satisfied with the program and found it easy to follow. Ninety-eight percent of patients said they felt better in general, now eat healthier, exercise more, and have found better ways to cope with stress."

In addition, patients in both studies were able to lower their resting heart rates, blood pressure, cholesterol, and triglycerides by the end of the studies.

Managing weight not only reduces risk of diabetes, it also helps patients remain compliant with their medication, according to a Pfizer-sponsored study released at the annual meeting.

In a survey of 300 U.S. psychiatrists, completed for Pfizer (which makes the Geodon brand of ziprasidone) by Roper Starch Worldwide, 90 percent of those responding said they believe that weight gain is the most likely side effect to cause patients to stop taking their medication. The survey indicated that not only does weight gain affect compliance, but psychiatrists believe it affects patients' self-esteem as well and adversely impacts patients' quality of life.