

Letters to the Editor

Severe Hypertriglyceridemia Associated With Olanzapine

Sir: We report on the case of a male patient who developed extreme elevations in triglyceride levels after the initiation of olanzapine, but has subsequently been maintained on olanzapine through aggressive treatment with agents to combat this adverse effect.

Case report. Mr. A, a 42-year-old African American man, was diagnosed with schizophrenia, paranoid type (DSM-IV). Mr. A's history of psychiatric hospitalizations dates back to the age of 19. However, before that, he had a long history of illicit substance abuse, using marijuana at the age of 12 and alcohol regularly at the age of 14. Despite this, he obtained a high school diploma and took several hours of college-level coursework. Over the years, Mr. A has presented with a number of psychiatric symptoms such as poor grooming and hygiene, auditory and visual hallucinations, paranoid ideations, and irritable, threatening, assaultive behavior. He has been diagnosed with a number of schizophrenia subtypes since 1980, but has been managed with either thioridazine or haloperidol decanoate. A long history of medication noncompliance has led to numerous decompensations and hospital readmissions.

At the time of this admission to our facility, Mr. A weighed 190 lb (86 kg) and had a body mass index (BMI) of 31. Upon admission, Mr. A was on treatment with the following medications: lovastatin, 40 mg p.o. q.d., for hypertriglyceridemia; divalproex sodium, 500 mg p.o. q.a.m. and 750 mg p.o. q.h.s., for mood stabilization; thioridazine, 100 mg p.o. q.a.m. and 300 mg p.o. q.h.s., for psychosis; and propranolol, 10 mg p.o. t.i.d., for migraine headache prophylaxis. Due to formulary differences between our institution and the transferring institution, lovastatin was replaced by pravastatin, 20 mg p.o. q.d. At the time of admission, Mr. A was diagnosed with DSM-IV schizophrenia, paranoid type, and polysubstance dependence. In addition, he was diagnosed with hypertension and hyperlipidemia.

Mr. A's admission lipid panel had the following results: total cholesterol = 227 mg/dL, triglycerides = 313 mg/dL, high-density lipoprotein (HDL) = 42 mg/dL, and low-density lipoprotein (LDL) = 122 mg/dL. Additionally, his fasting blood glucose was 82 mg/dL, his serum creatinine was 1.2 mg/dL, and his aspartate aminotransferase (AST) was 22 U/L. As a result, pravastatin was discontinued 7 days after admission, and gemfibrozil, 600 mg p.o. b.i.d., was initiated in an effort to specifically lower triglycerides. In addition, Mr. A was placed on a Heart Healthy Diet. Serum valproic acid levels 2 and 3 months after transfer to our facility were 54 mg/L and 62 mg/L, respectively.

Thirteen weeks after initiation of gemfibrozil, repeat laboratory measures showed that Mr. A's total cholesterol was unchanged while his triglycerides were greatly improved at 134 mg/dL, his HDL was 38 mg/dL, and his LDL was increased at 162 mg/dL. During this time period, a gradual titration off of

thioridazine treatment was initiated because Mr. A complained of sedation and was exhibiting no overt signs of psychosis or aggression.

Nineteen weeks after admission, olanzapine, 5 mg p.o. q.h.s., was initiated and then increased to 15 mg p.o. q.h.s. over the course of a month to treat negative symptoms of schizophrenia. During the olanzapine titration, Mr. A continued to be tapered off of thioridazine treatment at a rate of 100 mg/week. During this time, divalproex sodium was slightly increased by 250 mg to a dose of 500 mg p.o. q.a.m. and 1000 mg p.o. q.h.s., and propranolol was switched to a long-acting dosage form of 60 mg/day because Mr. A continued to complain of migraine headaches.

Four weeks later, significant changes in Mr. A's lipid panel were observed. His total cholesterol increased slightly to 248 mg/dL; however, his triglycerides increased to 539 mg/dL, while his HDL was 27 mg/dL; his LDL was unable to be calculated. During this time, AST and alanine aminotransferase levels remained within the normal range and his serum valproic acid level was 71 mg/L.

After another month, a repeat lipid panel showed Mr. A's total cholesterol had increased to 375 mg/dL, the triglycerides were severely elevated at 5093 mg/dL, the HDL was 63 mg/dL, and the LDL was unable to be calculated. A repeat lipid panel was ordered to rule out laboratory error, but again the results showed grossly elevated triglycerides of 4045 mg/dL. His hemoglobin A_{1c} was markedly elevated at 11.9%, his fasting blood glucose was elevated at 394 mg/dL, and his serum amylase and lipase were within normal ranges at 58 IU/L and 24 IU/L, respectively. Following the repeat laboratory verification of abnormal lipid and glucose values, blood glucose meter readings indicated the glucose concentrations to be between 300 and 400 mg/dL for several days. Divalproex sodium, gemfibrozil, and propranolol were all discontinued. Fenofibrate, 201 mg p.o. q.d.; aspirin, 325 mg p.o. q.d.; quinapril, 10 mg p.o. q.d.; glyburide, 5 mg p.o. b.i.d.; and a sliding scale of regular insulin were all initiated. Interestingly, there were no significant objective or subjective physical findings other than a complaint of a headache during the period of time when the laboratory abnormalities were noted and medications were changed.

After 4 weeks with this treatment regimen, Mr. A was showing significant improvement in his laboratory values as his total cholesterol was down to 219 mg/dL, his triglycerides were down to 181 mg/dL, his HDL was 33 mg/dL, and his LDL was 150 mg/dL. His fasting blood glucose was down to 80 mg/dL. Subsequently, 3 weeks later, a taper of glyburide was initiated due to an episode of hypoglycemia, and glyburide was eventually discontinued after an additional 3 weeks. Approximately 8 weeks later, olanzapine was increased to 20 mg p.o. q.h.s. due to the development of auditory and visual hallucinations. Since that time, Mr. A has been maintained on olanzapine, 20 mg p.o. q.h.s.; aspirin, 325 mg p.o. q.d.; quinapril, 10 mg p.o. q.d.; fenofibrate, 216 mg p.o. q.d.; and atorvastatin, 10 mg p.o. q.d.

The most recent lab values (December 2001) show Mr. A's condition to be well controlled: total cholesterol = 139 mg/dL, triglycerides = 94 mg/dL, HDL = 40 mg/dL, LDL = 80 mg/dL, fasting blood glucose = 90 mg/dL, and hemoglobin A_{1c} = 4.9%. Mr. A's weight was down 19 lb (9 kg) from admission.

This case represents the great complexity of conditions that mentally ill patients may present with beyond the psychiatric realm. First, the development of significant hypertriglyceridemia demands exploration into potential causes. Abnormalities in lipid panels, hyperglycemia, and obesity have been associated with olanzapine and other atypical antipsychotic agents.¹⁻¹² Clearly, there may be an association between the development of hyperlipidemia, hyperglycemia, and obesity; however, the development of one does not always directly correlate with the development of another. This implies that there are multiple mechanisms of action for the development of one of these disorders in patients who receive atypical antipsychotics.

Recently, primary literature discussing atypical antipsychotic-associated metabolic changes has focused more on diabetes. Current theories for diabetes focus on the potential development of an islet cell toxic reaction, interference with non-insulin-mediated glucose utilization, and decreased insulin receptor sensitivity/insulin resistance.^{13,14} Weight gain secondary to antihistaminergic and serotonergic blockade has also been hypothesized as a source of diabetes development.^{14,15} One recently released publication reviewed the reports of diabetes mellitus developing or being exacerbated during treatment with olanzapine.¹³ Interestingly, a number of diabetes cases developed within the first 6 days of therapy, suggesting that weight gain is not the sole mechanism by which olanzapine-treated patients develop diabetes.¹³

The theories for atypical antipsychotic-associated hyperlipidemia are less well understood, but the condition is known to be more prevalent in obese patients. Both hyperlipidemia and hypertriglyceridemia are thought to be associated with insulin resistance.¹⁴ In extreme cases of hypertriglyceridemia, when a patient develops pancreatitis, the expected physiologic response is the decreased production of islet cells and decreased glucose utilization, further adding to the association between diabetes and hypertriglyceridemia.

In the case reported here, the only new medication that was introduced when the triglyceride and glucose elevations occurred was olanzapine. Mr. A did not experience significant changes in weight prior to or during the time period when the laboratory abnormalities were discovered. While one cannot rule out the dose increases of propranolol and divalproex sodium as being contributing factors, the patient had been on treatment with these agents, and abnormal lipid elevations are generally not considered a dose-related phenomenon. Additionally, patient compliance was a concern based upon his history of frequent noncompliance; however, a review of the medication administration record indicated that Mr. A was fully compliant and exhibited no behaviors suggestive of noncompliance.

While the underlying mechanisms are unexplained, it is possible that the combination of olanzapine with divalproex sodium and/or propranolol increases the propensity to develop diabetes, hyperlipidemia, or obesity.^{9,16} In addition, the effectiveness of the fibric acid derivative fenofibrate at reducing triglyceride levels provides hope that an agent is available that can successfully manage such extreme lipid panel changes associated with olanzapine use.

The authors report no financial affiliation or other relationship relevant to the subject matter in this letter.

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Nicotine-Induced Angiogenesis

Sir: Dr. Silver and colleagues' article¹ demonstrates the potential therapeutic value of nicotinic receptor modulation in reducing behavioral symptoms in Tourette's disorder. The authors explicitly clarify that side effects limit chronic usage of transdermal nicotine but fail to mention a most troublesome side effect—the fact that nicotine has been shown to induce angiogenesis and thereby accelerate the growth of tumors and atheroma.² These effects may occur in vivo as well as in vitro at nicotine concentrations that are pathophysiologically relevant. They should be taken into consideration when planning further research with transdermal nicotine and novel nicotine receptor modulating agents.

Dr. Schwartz reports no financial or other relationship relevant to the subject matter of this letter.

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Dr. Shytle and Colleagues Reply

Sir: We would like to thank Dr. Schwartz for drawing attention to the possibility that the chronic use of transdermal nicotine to treat Tourette's disorder could pose a potential risk that was not mentioned in our article.¹ As pointed out by Dr. Schwartz, a recent *in vitro* study found that nicotine induced angiogenesis and accelerated the growth of tumors and atheroma under laboratory conditions.² However, these authors stated that their findings raise particular concerns about the effects of chronic nicotine use in humans at risk for pathologic angiogenesis as opposed to those without such risks. For example, previous long-term exposure of healthy rats to nicotine did not alter cardiovascular structure or function.³ Moreover, short-term use of transdermal nicotine in humans with a history of cardiovascular disease did not increase ischemic events in a 10-week smoking cessation study.⁴

Nevertheless, the fact that activation of nicotinic receptors may induce angiogenesis and accelerate the growth of tumors and atheroma should raise concerns about recent attempts by pharmaceutical companies to exploit the therapeutic potential of nicotinic receptor agonists. Such interest has resulted in the research and development of several cholinergic nicotinic receptor medications now entering experimental clinical trials for Alzheimer's and Parkinson's disease as well as for chronic pain.⁵ While preclinical studies have suggested that these potential medications should have substantially improved side effect profiles relative to nicotine, results from early phase I and phase II clinical trials indicate that some of these ligands still appear to have clinically significant nicotine-like side effects.⁶ Because some of these new drugs, like nicotine, have mixed agonist/antagonist properties at different nicotinic receptor subtypes,⁷ it is becoming less clear whether receptor activation or inactivation is responsible for the therapeutic and/or adverse side effects. For example, it is possible that many of the adverse effects of nicotine are due to nicotinic receptor activation at cer-

tain subunits, while the therapeutic effects of nicotine are mediated by receptor inactivation at other subunits.⁸

In this regard, we recently reported that mecamylamine, a nicotinic receptor antagonist, given at low doses (2.5-7.5 mg/day), may be therapeutic for comorbid mood disorders in Tourette's disorder patients without the side effects obtained with nicotine therapy.⁹ In addition, recent evidence suggests that bupropion, which is effective in the treatment of attention-deficit/hyperactivity disorder, depression, and smoking cessation, functions as a potent nicotinic receptor antagonist.¹⁰ Thus, nicotinic receptor antagonists such as mecamylamine and bupropion may also be useful to treat certain nicotine-responsive neuropsychiatric disorders without nicotine-induced side effects.

The authors are inventors on patents owned by the University of South Florida that cover the use of mecamylamine and other nicotinic receptor antagonists for the treatment of nicotine-responsive neuropsychiatric disorders. These patents are licensed to Targacept, Inc., who owns the trade name and marketing rights to mecamylamine (Inversine).

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