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Drs. Shekhar, McKinzie, and Felder Reply

TO THE EDITOR: Dr. Pomara suggests that the clinical efficacy of xanomeline treatment for improving cognitive deficits in schizophrenia patients in our study (1) may not have been a result of sustained M_1 receptor agonist properties, as hypothesized by Dr. Lieberman et al. (2), but rather a result of chronic agonist-induced desensitization and downregulation of cortical M_1 receptors. Although M_1 receptor desensitization contributing to the clinical efficacy of xanomeline is certainly possible, which is supported by some of the evidence cited by Dr. Pomara, such a hypothesis is difficult to test directly. On the other hand, it is equally possible that direct agonist effects of xanomeline may contribute to cognitive benefits for the following reasons.

First, the postmortem studies by Crook et al. (3) measured 3H-pirenzapine binding, a ligand that is not a highly selective M_1 receptor antagonist and does not distinguish high versus low affinity states of the M_1 receptor. Second, muscarinic M_1 receptors appear to have a high receptor reserve requiring only a 15% occupancy to attain full signal transduction, suggesting that a significant decline in receptor number can possibly occur without causing functional consequences (4). Thus, the conclusion by Crook et al. that reductions in M_1 receptor density in limbic regions were a result of hypercholinergic state has not been directly tested and remains speculative.

Interestingly, preclinical testing of another M_4 receptor agonist, BuTAC, demonstrated that it possesses antipsychotic-like properties similar to xanomeline. However, unlike xanomeline, BuTAC is an antagonist at the M_1 receptor and does not exhibit efficacy in spatial learning in rats. This may support the hypothesis that the cognitive benefits of xanomeline may well be the result of its agonist properties at the M_1 receptor. Unfortunately, utilizing direct orthosteric agonists of receptors, it is difficult to conclude whether the effects of chronic administration of the drug are a result of continued agonism or desensitization of its receptors. Recently published data using muscarinic receptor potentiators further support a role for M_1 and/or M_4 positive modulation, rather than antagonism, as the primary mechanism driving antipsychotic efficacy (5, 6). With positive modulators, M_1 and M_4 receptors would be less sensitive to downregulation as a result of the allosteric mechanism of action. Indeed, positive allosteric modulation would be less prone to desensitization and would preserve spatial and temporal regulation of M_1 receptor activation (4). Therefore, based on the high receptor reserve for the M_1 receptor, and most likely for M_4 receptor, and evidence based on recent M_1 and M_4 selective positive allosteric modulators, it is unlikely that orthosteric agonist-mediated desensitization is the sole explanation for muscarinic-based mechanisms of antipsychotic therapeutics.

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Risperidone-Associated Increase in Triglyceride Levels

TO THE EDITOR: Second-generation antipsychotics are frequently associated with metabolic adverse effects, such as weight gain and elevations of triglyceride or total cholesterol levels (3). Although minor changes in lipid levels have previously been reported during risperidone treatment (2), we observed the following case of pronounced risperidone-induced hypertriglyceridemia.

"Mr. A" was a 27-year-old man who suffered from DSM-IV paranoid schizophrenia for 9 years and had been previously treated with perazine and flupentixole. Upon his hospitalization, the patient presented with normal triglyceride (97 mg/dl) and total cholesterol (121 mg/dl) levels

(body weight: 98 kg; body mass index: 30.25 kg/m^2). His exacerbated psychotic syndrome remitted after risperidone was increased to 8 mg per day (serum level: 6.4 µg/L). His scores on the Positive and Negative Syndrome Scale (PANSS) were as follows: positive subscale, 9; negative subscale, 11; and global psychopathology subscale, 19. After 12 weeks, we observed an exceptional increase in his triglyceride levels, up to 627 mg/dl, and a marked rise in his total cholesterol levels, up to 249 mg/dl. Mr. A's uric acid level was slightly elevated, at 8.1 mg/dl. His fasting serum leptin was 14 µg/L, and his insulin level was 11 mU/L. His C-peptide level was 0.78 nmol/L, and his HbA1c level was 5.4%, both of which were normal. The patient's body weight increased to 112 kg (body mass index: 34.57 kg/m^2). After switching to aripiprazole, 45 mg per day, he experienced no change in body weight. However, significantly lower triglyceride and total cholesterol levels were observed during the subsequent 8 weeks (triglyceride level: 263 mg/dl; total cholesterol level: 104 mg/dl). Unfortunately, the patient's symptoms worsened, with a PANSS global psychopathology subscale score of 60, a positive subscale score of 29, and negative subscale score of 39.

After intensive consultation, Mr. A agreed to the reintroduction of risperidone, 8 mg/day, and his psychosis remitted (PANSS scores: positive subscale=10; negative subscale=8; global subscale=18), but his lipid levels re-increased (triglyceride level: 512 mg/dl; total cholesterol level: 278 mg/dl), with his body weight at 114 kg and a body mass index of 35.18 kg/m^2. Consequently, we suggested adding bezafibrate, a fibrate drug for reducing hyperlipidemia.

Although other studies have described risperidone-induced increases in triglycerides levels of 20% (2), our patient experienced an elevation of 600%. We were unable to detect excessive eating behavior or abnormal leptin levels or glucose metabolism. The general explanations of second-generation antipsychotic-induced metabolic disturbances implicate the antiserotonergic and antihistaminergic effects of drugs such as clozapine and olanzapine (3). However, risperidone interacts particularly with serotonin 5-HT_{2A} receptors—and only to a lower extent with 5-HT_{2C} receptors—and the drug has very low affinity to histamine H_1-receptors, rendering observations in our patient somewhat unexplained.

In light of recommendations to switch patients with second-generation antipsychotic-induced hypertriglyceridemia to risperidone (1), careful individual decisions appear to be necessary. We recommend general metabolic monitoring and dietary consultation for patients with psychotic disorders.

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Extreme Elevation of Creatinine Phosphokinase Levels in Neuroleptic Malignant Syndrome Associated With Atypical Antipsychotics

TO THE EDITOR: Neuroleptic malignant syndrome may develop subsequent to treatment with typical or atypical antipsychotics (1). An elevated level of creatinine phosphokinase is not required for a DSM-IV diagnosis of neuroleptic malignant syndrome, but it is common. During the past 5 years, creatinine phosphokinase has typically been reported at levels between 1,000 U/l and 10,000 U/l in cases of neuroleptic malignant syndrome (2, 3). A creatinine phosphokinase level of 800,000 U/l was reported for a patient who was being treated with a conventional antipsychotic (3). We report a case involving the use of the atypical antipsychotic clozapine and a creatinine phosphokinase level that exceeded 390,000 U/l.

"Mr. N" was a 28-year-old man with schizophrenia who believed that he existed within a video game and that he originated from another galaxy. He was treated for 5 months with risperidone, 6 mg/day, aripiprazole, 30 mg/day, and valproate, 1,000 mg/day. To reduce symptoms, clozapine was increased to 400 mg/day over 15 days, overlapping with risperidone for 10 days and with valproate briefly.

The patient complained of weakness, stiffness of the neck, diarrhea, and dysphagia. He manifested fever (101.1 °F), tachycardia (120 beats/min), hypertension (146/65 mmHg), and tachypnea (25 breaths/min). His physical examination revealed muscle weakness and pain upon palpation of his extremities. Treatment with clozapine was discontinued. The patient's creatinine phosphokinase level was 1,500 U/l. His cardiac fraction increased to 25.6 ng/dl, and his troponin levels increased to 18.6 ng/dl, with EKG changes suggestive of myocardial infarction.

Mr. N's fever later returned (102.2 °F); his creatinine phosphokinase level was 392,623 U/l; his white blood cell count was 18.7; and myoglobinuria was noted. However, the patient's serum creatinine level was normal. Bromocriptine and lorazepam were administered. The patient was hydrated, developed pulmonary edema, was intubated, and required restraints to prevent self-extubation. A CT scan showed pulmonary embolism, and a muscle biopsy was nonrevealing. A complete physical recovery ensued, but the patient's psychosis persisted.

In our patient, clozapine may not have been the sole cause of neuroleptic malignant syndrome, since risperidone (2) and aripiprazole (2), despite their discontinuance, may have contributed. In addition, the concomitant use of valproate (4) and lithium (1) has been reported as a risk factor.

Some authors have noted that patients being treated with atypical antipsychotics may present with atypical features of