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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