Understanding the Tolerability Profile of Xanomeline-Trospium Combination for the Treatment of Schizophrenia

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In this issue of JCP, Kaul and colleagues[1] report on the safety and tolerability of xanomeline-trospium chloride combination for the treatment of schizophrenia based on pooled results from three similarly designed 5-week studies conducted in patients experiencing an acute exacerbation of their illness. Xanomeline-trospium combination was approved for use in adults with schizophrenia in 2024 by the US Food and Drug Administration and represents a new approach to managing the symptoms of psychosis. The mechanism of action is thought to be by central muscarinic M1 and M4 receptor agonism via xanomeline, which in turn selectively decreases the release of dopamine in the part of the human striatum thought responsible for the production of hallucinations and delusions.[2,3] This is a different strategy from postsynaptic dopamine D2 receptor blockade, the mainstay of how schizophrenia has been treated for the past seven decades. By avoiding dopamine D2 receptor blockade, the "collateral damage" of drug-induced movement disorders and prolactin elevation can be circumvented. Avoidance of blockade of serotonin, adrenergic, and histamine receptors can also reduce the risk of sedation, weight gain, and metabolic abnormalities that can be problematic with the use of traditional treatments. Of note, the package insert for xanomeline-trospium combination does not contain the word "antipsychotic" and is devoid of the class-level warnings and precautions, including the boxed bolded warning regarding mortality in elderly demented patients with psychosis, found across the board for the older agents.[4] Efficacy for the acute treatment of schizophrenia appears robust.[5] So, what's the catch?

Xanomeline's peripheral promuscarinic actions can lead to adverse gastrointestinal effects such as nausea and vomiting. In a small study of xanomeline alone in people with schizophrenia, patients were initiated on 25 mg TID, and stepwise titrated up to 75 mg TID over the course of 4 days; 70% of the participants receiving xanomeline experienced nausea or gastrointestinal distress and 60% experienced vomiting.[6] Most of these adverse reactions were of mild or moderate severity, were transient, and did not result in discontinuation of treatment for any patient. However, a 60% rate of vomiting is unacceptable under most conditions. Fortunately, when xanomeline is combined with the peripherally restricted antimuscarinic agent trospium, the observed rates of promuscarinic gastrointestinal adverse effects are substantially reduced.[1] The dosing schedule for xanomeline/trospium in the acute studies started at 50 mg xanomeline/20 mg trospium BID and increased to a maximum of 125 mg xanomeline/30 mg trospium BID by the end of the first week based on tolerability, with about 80% of the participants receiving xanomeline/trospium achieving the highest dose.[5] The rate of nausea reported for the xanomeline-trospium group was 18.5% (vs 3.8% for the placebo group) and that for vomiting 13.5% vs 1.7%, respectively. Cholinergic side effects generally began within 2 weeks of starting medication and were transient and mild or moderate in intensity. Having an antiemetic agent available may be helpful where this is a specific concern for the individual patient being treated. It is possible that gastrointestinal side effects are dose related and/or may be related to the speed of titration. Instructions contained in product labeling permit a slower titration rate than that done during the clinical trials. Still unknown is the optimal dose—xanomeline/trospium 50/20, 100/20, and 125/30 mg BID were not evaluated using a fixed dose clinical trial design. Also unanswered are the outcomes of once daily dosing. Patients with treatment-resistant schizophrenia or first-episode psychosis were not included in the trials.

Trospium is a potent antimuscarinic agent and is used for the treatment of overactive bladder.[7] It can lead to constipation and other anticholinergic effects, as observed in the acute studies of xanomeline-trospium combination with rates of constipation 17.1% for the xanomeline-trospium group vs 6.1% for the placebo group. Trospium does not easily cross the blood-brain barrier; thus, trospium does not negate the therapeutic effects of the

centrally acting xanomeline. However, combining xanomeline-trospium with other anticholinergic agents (including some antipsychotics such as olanzapine) may be problematic because of additive peripheral anticholinergic effects, as well as unpredictable central effects.

It is noted that trospium is not well absorbed in the presence of food,[2] resulting in the prediction that nausea and vomiting can be especially problematic if xanomeline-trospium is taken with a meal.

The observation of hypertension and tachycardia with xanomeline-trospium has led to the recommendation of assessing heart rate at baseline and as clinically indicated during treatment.[2] The product label also recommends assessing liver enzymes and bilirubin prior to initiating treatment and as clinically indicated.[2]

The short duration of the studies included in the analysis of safety and tolerability among acutely ill patients begs the question of longer-term safety and tolerability during maintenance treatment among clinically stable individuals. Data presented in poster form from two 52-week open label studies have shown that there are no unexpected findings, with safety and tolerability outcomes consistent with that observed during the acute studies.[8,9]

In the end, xanomeline-trospium combination offers treatment for schizophrenia like no other. The selectivity of muscarinic M1/M4 receptor agonism avoids movement disorders, prolactin elevation, sedation, weight gain, and metabolic disturbances. The challenge will be managing pro- and antimuscarinic effects in patients vulnerable to developing them.

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