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From Trials to Practice: Evaluating Xanomeline-Trospium Chloride for Schizophrenia

Ashley Baker:
This is *NeuroFrontiers* on ReachMD, and I'm psychiatric nurse practitioner Ashley Baker. Here with me today to discuss the efficacy and safety of xanomeline-trospium chloride as a schizophrenia treatment is Dr. Steven Paul. Not only is he a Professor of Psychiatry and Neurology at Washington University in Saint Louis, but he's also the co-founder and Board Chair at Seaport Therapeutics in Boston. Dr. Paul, welcome to the program.

Dr. Paul:
Thank you, Ashley. It's great to be here.

Ashley Baker:
To start us off, Dr. Paul, can you explain the mechanism of action of xanomeline-trospium and how it differs from traditional antipsychotic medications?

Dr. Paul:
Xanomeline-trospium chloride is a completely new and novel approach to treating schizophrenia. It's a combination of two medicines: xanomeline, which gets into the brain and stimulates two of the five muscarinic receptors preferentially, and trospium chloride, which blocks muscarinic receptors but only in the periphery. It doesn't get into the brain.

And so therefore, we can get the beneficial therapeutic effects of xanomeline, which have been shown in several studies, without the adverse events associated with peripheral stimulation of these receptors. So these two drugs are combined in the same capsule and are now used to treat schizophrenia.

There have been three pivotal placebo-controlled trials of xanomeline-trospium chloride that have been carried out. They're very positive trials, and these trials form the basis of the approval by the FDA for treating schizophrenia here in the United States. And the mechanism, as I alluded to, is really quite unique.

All of the other antipsychotic drugs that we use—the typical and atypical antipsychotics—work primarily by blocking dopamine receptors, particularly the D2 subtype of dopamine receptor; and so arguably, xanomeline-trospium is the first novel antipsychotic medicine launched in the U.S. in over 70 years since chlorpromazine, or Thorazine, was introduced in the 1950s.

And on the basis of the trials that had been conducted in psychotic individuals with schizophrenia—these are inpatient, placebo-controlled trials—the drug performed really well. We saw very strong efficacy comparable to what is seen with the very best antipsychotic medicines used today but, importantly, without many of the adverse events associated with the current standards of care, namely things like sedation or somnolence, no weight gain, no extrapyramidal motor symptoms or akathisia, and no hyperprolactinemia. So there's a very unique profile available now to patients.

Ashley Baker:
Dr. Paul, can you tell us more about how xanomeline-trospium chloride differs from current treatment options?

Dr. Paul:
Yes. As I indicated, it does differ considerably in that it's not a dopamine D2 receptor blocker, so you don't get many of the side effects associated with blocking these dopamine receptors. Now importantly, it does have its own set of side effects that are due to its own unique pharmacology. In some cases, patients experience a little nausea and vomiting, and in others, they can experience some of the

anticholinergic effects: dry mouth, constipation, etc. So those are adverse events that one needs to look out for clinically.

Based on the clinical trials that have been conducted to date, these are usually mild to moderate in severity, and they actually seem to go away nicely over the course of a couple of weeks, so patients don't really stop their medicine as a result of them. They sort of dose right through them, and over time, the drug has been shown to be very well tolerated.

Ashley Baker:
With that in mind, are there any other safety considerations that we should think about with this treatment option?

Dr. Paul:
Great question, Ashley. Yes. Xanomeline-trospium is almost exclusively metabolized by the liver, so in patients that have any kind of liver impairment or insufficiency, one has to be very careful. In fact, it's a good thing for doctors to make sure patients' livers are healthy and able to metabolize the drug, and so sometimes, we order liver function tests just before we put patients on the medicine. And in the case of patients who have some known hepatic insufficiency of some sort, one has to be very careful with this medicine.

Beyond that, the medicine is well tolerated. The anticholinergic effects of the trospium can, in some individuals, also cause some urinary issues like urinary retention. So that would be another adverse event that would need to be monitored very closely.

Ashley Baker:
For those just tuning in, you're listening to *NeuroFrontiers* on ReachMD. I'm psychiatric nurse practitioner Ashley Baker, and I'm speaking with Dr. Steven Paul about the treatment option xanomeline-trospium chloride for patients with schizophrenia.

So considering its efficacy and safety profile, Dr. Paul, let's zero in on the integration of xanomeline-trospium chloride into treatment protocols. Who is an appropriate patient for this approach?

Dr. Paul:
Another great question, Ashley. I think that almost any patient that has schizophrenia and is experiencing psychotic symptoms—the so-called positive symptoms of the disorder (hallucinations, delusions, etc.) —would be a good candidate for this medicine, especially people who perhaps have been on other medicines in this general class and have, for example, had excessive weight gain or experienced extrapyramidal motor symptoms or akathisia. Because this medicine is really devoid of those adverse events, they would be excellent candidates as well.

There are some ongoing trials right now to explore the combination of xanomeline-trospium chloride with other antipsychotics that patients might be on: the traditional typical and atypicals. The hope there is to see some added benefits given that the mechanism is different from the older drugs, and so theoretically, at least, it might be possible to see even better efficacy if you add them together. Those studies are underway. We should know later this year how they come out, whether in fact there is added improvement or added benefit in people that don't respond totally well or adequately to the current standards of care; that will be another patient population, for example.

Ashley Baker:
And once we select an appropriate patient and begin treatment, how can we monitor and manage adverse events?

Dr. Paul:
Great question. So the adverse events that occur that are related to xanomeline and trospium occur early, and so very early on in treating a patient with xanomeline-trospium, you want to monitor them very carefully. And in fact, what you can do is titrate the medicine a little bit. In fact, the medicine normally is titrated. It's in three dosage forms: 50/20, 100/20, and 125/30. These are capsules with different amounts of each of these two medicines. And you start with the 50/20, which is the low dose, and over time, you get some attenuation of side effects, and then you bump the dose to the next dose and monitor for side effects. And then if patients are not having those side effects—some nausea, some vomiting, or some of the GI side effects—you can go to the highest dose. It turns out that if you just slow down the titration a little bit and prolong the time that a patient is on those lower doses, you can circumvent many of the side effects.

So I think there's a lot we still need to learn about how this drug is used in the real world, but we have some options here that I think are going to be very beneficial in how it's used in patients.

Ashley Baker:
Now, given everything we discussed today, Dr. Paul, do you have any final thoughts on xanomeline-trospium chloride and its impact on the schizophrenia treatment landscape?

Dr. Paul:

Well, I'll mention two. The first is it's still in the early days, and my experience in this area of research is that it usually takes a couple years before we truly understand the benefits and risks of any new medicine once it's in the general population and once many more patients receive the medicine. Then we really get a sense of how effective it is and what are the side effects, etc. But number two is that this medicine does offer patients something that the current drugs just don't offer them. It offers them very robust efficacy without those troublesome side effects of weight gain and extrapyramidal side effects. Probably, this drug has no risk, for example, of tardive dyskinesia, which is a permanent neurological side effect of long-term treatment with antipsychotic drugs. If it turns out that xanomeline-trospium is effective in treating the cognitive symptoms and the negative symptoms along with the positive symptoms, it will represent a real breakthrough for the treatment of schizophrenia.

Ashley Baker:
Well, with those final thoughts in mind, I want to thank my guest, Dr. Steven Paul, for joining me to discuss xanomeline-trospium chloride as a treatment for schizophrenia.

Dr. Paul, it was great speaking with you today.

Dr. Paul:
Same here, Ashley. Thank you.

Ashley Baker:
For ReachMD, I'm psychiatric nurse practitioner Ashley Baker. To explore this and other episodes, visit ReachMD.com/NeuroFrontiers, where you can Be Part of the Knowledge. Thanks for listening.