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Emerging Perspectives: The Potential Role of Xanomeline Trospium Across the Bipolar Spectrum

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Dr. Rubio:
This is CE on GLC Education. Hello, I am Jose Rubio, and here with me today is Dr. Sunny Tang.

In this episode, we look at the big picture: the potential for muscarinic therapies to work across the entire bipolar spectrum. In previous episodes, we have reviewed the course of illness in bipolar disorder, the areas of unmet need, and the treatment of the various disease states in bipolar disorder, and how muscarinic agents might interact with the putative mechanisms of mania and cognitive dysfunction in bipolar disorder. We'll discuss here the potential of muscarinic agents as a complement to our current tools to address mood, psychosis, and cognition simultaneously.

Dr. Tang, looking ahead, where do you see xanomeline-trospium fitting into the real-world treatment algorithm for bipolar disorders?

Dr. Tang:
Well, I want to stress first that the trials are still ongoing, so we'll really need to see what comes out of those trials in terms of the endpoints that are met and the tolerability and safety and all of that. So we'll really have to see what the evidence shows before we have a clear answer in terms of understanding how xanomeline-trospium will be fitting into the real-world treatment algorithm, as you mentioned.

In terms of comparing xanomeline-trospium with existing treatments, we discussed earlier when we talked about the underlying neurocircuitry involved in bipolar disorder that xanomeline-trospium, in terms of being a muscarinic M1/M4-selective agonist, is very mechanistically promising because it fits in terms of acting on the dopamine circuits with other effective antimanic agents that we know of even though the dopamine targeting in this case is indirectly.

And we also know, you mentioned in the last episode, Dr. Rubio, that cognition is a major area of sustained impairment affecting functional outcomes in bipolar disorder, and cognition is also interesting as a potential pharmacologic target because of this impairment and because we know from earlier studies that M1/M4 muscarinic circuits might have an effect on this area.

I think an important area to also note is the safety profile of xanomeline-trospium compared to established treatments. There's an absence of metabolic disruption, which means that it has an advantage over those other pharmacologic agents in this very critical area

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that affects long-term health outcomes, and we anticipate that the therapeutic window is likely going to be wider than a lot of mood stabilizers like lithium, for example, where you have to get levels for the mood stabilizer to make sure that it's remaining in a narrow therapeutic window.

And with xanomeline-trospium, there is nausea and vomiting, on the other hand, and some cholinergic-related side effects that we will have to contend with or potentially consider and think about in terms of evaluating this as a real-world treatment.

So, Dr. Rubio, what do you think are the most critical takeaways for a clinician who's looking to integrate these novel neurobiological concepts into their practice?

Dr. Rubio:
Yeah, I mean, I concur with your big-picture assessment of the state of the field. And again, I also want to emphasize that xanomeline-trospium received FDA approval in September 2024 for schizophrenia; it's not FDA-approved for bipolar disorder. There are the two phase 3 trials, BALSAM-1 and BALSAM-2, that are currently undergoing to study the efficacy for acute mania and mania with mixed features in bipolar disorder, and the results will be critical in determining whether the translational promise holds.

That being said, the rationale is compelling. So why is the rationale compelling? Well, every effective antimanic agent, lithium, valproate, all the atypical antipsychotics, they ultimately modulate dopaminergic transmission, and xanomeline-trospium fits this pattern through a fundamentally different mechanism. So rather than D2 blockade directly, it works indirectly through the M1 and M4 pathway into the dopamine synthesis capacity. And this means that it targets the same hyperdopaminergic state in the associative striatum that's driving mania and psychosis, but without the D2 blockade that causes extrapyramidal syndromes, hyperprolactinemia, tardive dyskinesia.

The other advantage is that cognition is an area of unmet need. As discussed in the Episode 4, there's no currently approved bipolar treatment that's targeting cognition, so xanomeline-trospium could position itself different because if the promise from the schizophrenia trials hold also in bipolar disorder, it could have some precognitive effects in bipolar disorder as well. That being said, I want to be clear: there's not a specific indication—FDA indication—for cognition. We have post hoc data, but those post hoc data are quite compelling.

So the positioning in the treatment algorithm, while we await the results from the BALSAM trials, are some potential niches. This could be helpful for patients who cannot tolerate metabolic burden from the currently approved treatments, patients that have prominent cognitive impairment, or patients that then could consider xanomeline-trospium as an adjunct to lithium or valproate if those 2 drugs are having some efficacy issues.

So for the first time, we have a mechanistically informed agent that could potentially address mood, psychosis, and cognition across the bipolar spectrum, and that is very promising given the current state of the field.

Dr. Tang:
Yes, well, thank you so much. I think our time is up, and this has been a fantastic discussion. Thank you so much for listening.

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