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The Next Frontier: Addressing Persistent Cognitive Impairment in Bipolar Disorder

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Dr. Tang:
Hi, this is CE on GLC Education, and I'm Dr. Sunny Tang. Here with me today is Dr. Jose Rubio.

So bipolar disorder is often defined by its mood episodes, but for nearly 40% of our patients, the primary burden is actually a global cognitive impairment. So in this episode, we're focusing on cognition as a vital therapeutic topic, and we'll explore how muscarinic agents could address these persistent deficits in memory and executive function to improve real-world occupational outcomes.

So, Dr. Rubio, we know that many patients never return to their baseline cognitive function who are experiencing bipolar disorder. So how might some muscarinic-targeted therapies address these cognitive trait deficits?

Dr. Rubio:
Well, let me start by saying that mood episodes define the diagnosis, but cognitive impairment is the strongest predictor for occupational disability. So even when patients achieve symptomatic remission, meaning that they are euthymic, they may not be able to return to work or to maintain relationships.

Now, not everyone experiences this cognitive symptom. So there are 3 distinct subgroups that show us different profiles of cognitive impairment, and this has been well replicated in research. About 30% to 50% of patients are going to be cognitively intact, meaning that their performance is comparable to healthy controls across all domains of cognition. And interesting, in some cases there might be superior social cognition.

Now, there are about 29% to 33% of patients that may have some selective impairment, meaning that they have moderate deficits in some aspects of cognition, not in all of them. For instance, they may have some impaired processing speed, attention, etc. And then there are between 20% and 40% of patients that have severe cognitive impairment across all cognitive domains. That would be similar to what you see in schizophrenia, and these are patients that have the greatest functional disability.

So why are M1 receptors a reasonable target? Well, M1 receptors in the prefrontal cortex and hippocampus, they mediate cognitive functions. For instance, M1 receptors in the DLPFC, in the dorsolateral prefrontal cortex, sustain persistent neuronal firing during working memory tasks, and in the hippocampus they are related to long-term potentiation. So this creates a compelling mechanistic rationale. So if the M1 tone is insufficient in the circuits, then M1/M4 agonists could directly enhance the neural processes for these

patients.

And there's already some proof of concept in post hoc data from the schizophrenia studies. Individuals with baseline cognitive impairment treated with xanomeline improved at better rates in cognition than those with placebo. And critically, these cognitive gains were independent of improvements in psychotic symptoms, meaning that they were not disease-specific; they were genuine procognitive effects.

So these subgroups are not just descriptive; they could be actionable. If cognitive clusters can be identified early, they could guide how we decide treatment for patients.

Dr. Tang:
So how could identifying these cognitive clusters early in treatment perhaps help us personalize approach using muscarinic agents?

Dr. Rubio:
So, again, these are not just a theoretical description, but something that we can use in the clinic. So I would start by saying that we should do screening for cognitive function. So the International Society for Bipolar Disorders, they recommend routine cognitive testing. There are some tools that are as quick as 15 minutes, and they have sufficient sensitivity and specificity. For instance, the Screen for Cognitive Impairment in Psychiatry, the SCIP, and that is something that could give us information about whether there are any domains that are being affected by cognitive impairment.

And then if we are able to identify patients, particularly those that have the global impairment, that 40%, those are going to be the best candidates for procognitive agents. As we saw in the schizophrenia trials, there might be some cognitive potential in schizophrenia. So the question is, does that replicate to patients with bipolar disorders?

In the BALSAM trials of xanomeline in bipolar disorders, we will be able to check whether this is a pattern that is confirmed or not. So hopefully, if this replicates, this could have an impact in the algorithm of the treatment of bipolar disorders because, for the first time, we would have a tool that has a procognitive effect. Remember that many of the antipsychotics, they may induce some impairments in cognition, so this would allow us to focus on treating the cognition first, and that should have an effect on functional outcomes, which is an unmet need at the present time.

Dr. Tang:
Yeah, absolutely. This sounds like a very promising and important area that we'll see some input and data from soon. Thank you so much.

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