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### Navigating the Limitations of Current BD Therapies

#### Announcer:

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#### Dr. Tang:

This is CE on GLC Education, and I'm Dr. Sunny Tang. Here with me today is Dr. Jose Rubio. In this episode, we're discussing unmet needs in the treatment of bipolar disorder. And while established therapies like lithium and atypical antipsychotics remain the clinical mainstays, they also may be difficult to tolerate over the long term and can impose some significant side effects. So we'll explore why addressing these side effects is often as much of a clinical challenge as controlling the mood symptoms themselves, and why residual symptoms can continue to limit recovery despite available therapies.

So, Dr. Rubio, what are the key challenges associated with current FDA-approved pharmacologic options for managing bipolar disorder?

#### Dr. Rubio:

I will start with lithium, which is perhaps one of the older drugs that we have in our armamentarium. It's a great drug. It's very effective. It's underutilized, and it still remains a cornerstone of bipolar disorder maintenance.

However, there are some challenges associated with lithium use. So one is that it requires strict therapeutic drug monitoring. There's a narrow therapeutic index, and there might be short-term and long-term issues with its use. You could acutely induce toxicity, and that's why there's this narrow therapeutic index in the short term. You can also have side effects that are within plasma levels that are adequate; you could still experience tremor, polyuria, polydipsia. And then in the long term, there are some chronic damage that could occur in the kidneys or the thyroid. So there are some challenges to its use.

Then we have atypical antipsychotics. So the atypical antipsychotics are widely used for mania and maintenance but carry significant metabolic issues. These are, of course, as you probably know, weight gain, dyslipidemia, increased risk of metabolic syndrome, type 2 diabetes, and then it's a problem because patients may not stay on the drug over the long term once they notice that they are having all of these side effects early, within weeks of starting treatment.

There's one particular gap in the treatment of bipolar disorder, which is relative to depression. So bipolar depression, as we discussed on the first episode, is where patients spend most of their symptomatic time. However, there are some FDA-approved treatments for bipolar depression. As of today, those are quetiapine, lurasidone, lumateperone, cariprazine, and olanzapine and fluoxetine combination. So these are drugs that are available, but obviously they all have side effects, as we have discussed. Being antipsychotics, they do have issues with metabolic side effects. Standard antidepressants are not effective, so that's not an option that we have for

these patients. And unfortunately, many patients still experience residual symptoms when they are on these treatments.

Also, I would like to mention some side effects that happen with these drugs that are concerning, particularly tardive dyskinesia. People with bipolar disorder are at high risk for tardive dyskinesia, and this is something that can have quite disabling consequences.

And last but not least, I would like to mention the cognitive gap. So cognition, as we are going to discuss in Episode 4, is a big part of what drives morbidity in bipolar disorder. There are no drugs that are effective against cognitive dysfunction in bipolar disorder, and that remains a big challenge.

So the picture is that we have tools, but those tools are incomplete, either because of tolerability and/or insufficient efficacy.

**Dr. Tang:**

So how do these safety and tolerability concerns impact our ability to achieve functional recovery, rather than just symptomatic remission?

**Dr. Rubio:**

I want to be very clear that remission and recovery are not exactly the same thing. So symptomatic remission means that the affective symptoms, whatever we measure with the YMRS, the MADRS, is under control. So the patient is symptomatically stable. But that is different from the patient being able to return to work, to have relationships, to engage socially. That is what we refer to as functional recovery. And the data shows that only 30% to 40% of patients achieve functional recovery, and this gap between recovery and symptom remission is really where our therapies fall short.

The side effects themselves could undermine function, so sedation, cognitive blunting that patients may experience with antipsychotics, that could be detrimental to their recovery. Weight gain, metabolic changes, that's going to erode physical health, self-esteem. And importantly, when side effects are difficult to tolerate, the patients may discontinue the drug. And if they discontinue the drug, they are at risk for relapse and then having another episode. So this can build up over the long term.

And I think that, really, cognition is key. Without addressing cognitive function, functional recovery is very difficult. So I would say that we have to redefine the treatment goals, and I think that we have to prioritize occupational functioning, quality of life, cognitive performance, patient-reported outcomes. These are things that I feel we should really emphasize when we are discussing what are the goals that we have for the treatment for our patients.

**Dr. Tang:**

Yes, those are some really important considerations and priorities for sure. Thank you so much.

**Announcer:**

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