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Managing Bipolar 1 and 2 Depression: Using Approved Treatments Safely and Effectively

Announcer:
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Dr. Singh:
Hi, I'm Manpreet Singh. I'm at Stanford University. And I'm joined by my dear friend, Dr. Joseph Goldberg from the Icahn School of Medicine at New York. And we're going to be talking today about optimizing treatment of Bipolar 1 and Bipolar 2 depression. We're going to try to weigh the safety, efficacy, and novel mechanisms that are on the horizon for both approved and unapproved treatments for bipolar depression.

And we're going to try here to go beyond the diagnosis and move towards a more in-depth discussion about tailoring treatments towards more personalized, N of 1 if you will, studies so that we can be more effective in helping patients receive the kind of care that they are most seeking. Certainly, the current landscape of treatments can - we can basically assume only lead to a partial response at best and have sub-optimal risk-benefit profiles. It's not always a one-size-fits-all, but it's also kind of taking the lesser of evils in some ways. So we have to do a little bit of in-depth, you know, digging, if you will.

And longer-term management is also complicated by poor insight. So people don't necessarily believe that they have the symptoms that they have over time, that's part of the mania symptom complex, poor insight, but also have difficulties trusting clinicians when they're undergoing many trials of treatments that are largely ineffective or result in poor treatment response.

It's also true that lithium may be underutilized, especially early in the course, even though it has terrific anti-suicidal properties.

So when you see a patient, Joe, coming into your clinic that might have some, say, for example, risk factors for overweight, obesity, or cardiovascular risk, how might you consider that patient, for example, in contrast to the college students that I see who might present closer to their first episode of mania, normal weight, and have just been effectively mood stabilized by lithium? Give me a sense of how you tailor your treatments.

Dr. Goldberg:
Right, right, right, right. So you may not like what you're about to hear, but I'm going to propose that in the initial assessment, you want to be as lavish and extensively descriptive as possible. You want to paint a picture in your head of everything that you think is pertinent, and everything that's pertinently absent for a given patient. So that doesn't just mean, I have a 21-year-old, depressed bipolar patient who's anxious, how should I treat them? I mean, that's like an opening move in chess, it tells you nothing about the game board and where to go from there. So you know, what are the things you want to know? Premorbid functioning. Sudden change from normalcy or gradual descent into non-normalcy? Was there a prodrome going on? If so, what was involved? Is this just about mood or other things as well? We know people with Bipolar Disorder usually have other psychiatric or substance use comorbidities. So that 21-year-old, depressed, bipolar patient who's smoking cannabis every day, and who's borrowing their friend's Xanax and their cousin's Adderall, and who's having panic attacks and thinks they might have ADHD and as a history of trauma, and is about 20 pounds overweight and has

poor body image, and maybe restricting and binge eating at other times, you have a much more complicated picture in store than just to say, well pick a medicine off the shelf. So, as you say, every patient is an N of 1. And these are just some examples of the things that go into our calculus in deciding what's going on.

I would say, it's not so simple to say, did you make the diagnosis? It's really, have you comprehensively evaluated the patient? For all of their diagnoses so that you can say, with some level of confidence, here's the current pathology, here's what the past histories look like, here are the risk factors. So as you point out, metabolic risk is non-trivial. Many of our treatments, some more than others, pose liabilities and hazards for aggravating weight gain or metabolic dysregulation. Some of our treatments are very high risk with regards to cognitive dysfunction or sedation, antihistaminergic effects, alpha-1 blocking effects, anticholinergic effects. So someone who's very concerned about cognition, I'm not going to want to jump down the path of an antihistamine, anticholinergic drug, they'll come in and say, you know, 'I think I need amphetamine,' and I'll say, 'well, maybe we should reduce your benzodiazepine load and your alcohol use and really try to - and cannabis does not help cognitive functioning at all.'

Dr. Singh:
Yeah.

Dr. Goldberg:
So you're really trying to sort of make a very clear picture of what's going on. Someone who's got very high rates asks for extrapyramidal side effects, and this can sometimes stratify along racial ethnic lines, or youth, or someone who had a bad experience with a medicine before if they were rapidly dosed with something, became acathectic.

So I spend a lot of time really trying to pin down what do I think is going on. What's the context of what's been going on? What's the past treatment been? And let's not repeat our mistakes. And then we can kind of start almost with a fresh slate in describing here's what's going on for you, here are the comorbidities, and here are the pharmacologies that have some basis in evidence for knowing the likelihood of working for the kinds of symptoms you have, separate from here the pharmacology options that are not as evidence based. How's that for a starting point?

Dr. Singh:
I like the way you think. And I do agree that optimization requires us to think very deeply about the individual characteristics of our patients. And it's still unfortunately true that patients continue to experience long delays in accurate diagnosis, timely treatment, and also suffer along the way significant functional impairments, both social and occupational, from recurrent episodes, whether they're manic or depressed. And frankly, depressed phases of illness, along with mixed features, and co-occurring anxiety and substance use, make it really difficult to achieve remission, and continue to plague our patients and us, frankly, in our treatment engagement process.

Cognitive impairment is also difficult to treat. And there are certainly some medications that may exacerbate cognitive impairment. So maybe we steer away from those medications that are maybe overly sedating. I think of quetiapine in those contexts or other medications that might slow a patient down during the day. Or think about dosing strategies that might actually be more optimal for a patient for medications that are more sedating, dosing them towards the evening, versus during the day. And find medications, rational combinations that might actually optimize a patient's treatment so that they're not off-roading, and using substances recreationally to try to manage the residual symptoms that they seem to not be able to effectively get coverage for with their current treatments.

Dr. Goldberg:
I want to amplify if I could, you're calling out about cognition. You know, patients with Bipolar Disorder will often self-diagnosis as, 'I have ADD.' And what they may not know is that cognitive dysfunction is part of what gets inherited in Bipolar Disorder.

Dr. Singh:
Yep.

Dr. Goldberg:
The unaffected siblings of people with Bipolar Disorder are about a half a standard deviation below the normal population on measures of attentional processing and executive function. So for those of us who study these kinds of things, it's very intriguing to ask, well, you know, what's a comorbidity, and what's sort of part of the illness? And now here, we can actually tie in a little bit of mechanism. There are certain medicines that we know could exacerbate cognitive dysfunction. You mentioned antihistaminergic drugs and anticholinergic drugs. Benzodiazepines do not help cognition. But there are certain medicines that we have reason to think could and, in fact, may even have been shown to have some potential benefits. So for example, drugs that block the 5-HT7 serotonin receptors, such as lurasidone, suggest themselves as maybe having value. And we have a colleague, who published a very interesting study with lurasidone in euthymic bipolar patients demonstrating improvement in global cognitive functioning.

Dr. Singh:

Right.

Dr. Goldberg:
Maybe that reflects mechanism around this 5-HT7 receptor, it's certainly something to be aware of and mindful of. Another receptor system of interest is in the dopamine circuitry, the D3 receptors, that we know drugs like cariprazine have a very strong binding affinity for, may actually have some value in reward processing, in anhedonia, in the ways in which patients attach salience to certain things, in the environment more so than others. So someone who's quite withdrawn, apathetic, can't concentrate, anhedonic, before they say, 'Gee, Doc, could I have a methylphenidate prescription?' Before you say, 'okay, sure,' you might say, 'well, let's dig a little deeper here. I mean, if what you're describing is impaired cognitive function, in say in reward circuitry, we might want to think about the potential value of a D3 partial agonist, such as cariprazine, maybe a 5-HT7 antagonist, such as lurasidone, or eliminating co-therapies that might be aggravating these things.'

So these are some of the ways in which we can craft pharmacology regimens to an individual patient, and also not just sort of taken face value a self-reported diagnosis without digging a little deeper.

Dr. Singh:
Well, what I love about what you've described is that we can actually convey some hope to our colleagues here about the novel mechanisms that are on the horizon, that not only may be more diverse in terms of their functional coverage. You mentioned some of the others, but I would just add 5-HT to antagonism and D1 that have implications for the glutamatergic system and AMPA. And novel mechanisms may address unmet needs of patients compared to the current treatment armamentarium, not just by being novel in terms of their targeting, but also maybe have more favorable side effect profiles. So you don't have the weight gain and sedation that you get from D2 antagonism.

And the other sort of, I guess, thing that we're all striving for is having our medications potentially be disease modifying. We're unsure if any of them will be, or currently are. But could we imagine that medications are not just helping us stabilize patients acutely, but actually have more long-term, pro-cognitive, neurotrophic, disease-modifying brain health kinds of impacts that we're really seeking for patients' long-term well-being.

So thank you so much for this very interesting discussion. And I hope the colleagues in the air are also appreciating our discussion and look forward to further conversations with you in the future. Joe, thanks so much.

Dr. Goldberg:
Likewise, thank you all for joining us today.

Announcer:
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