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Challenges with Effective Diagnosis and Management of Bipolar 1 and 2 Depression

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Dr. Goldberg:
Well, hello, everybody. Welcome to our presentation today on Bipolar Disorder. I'm Dr. Joe Goldberg. I'm a Clinical Professor of Psychiatry at the Icahn School of Medicine at Mount Sinai in New York. I'm joined by my longtime friend and colleague, Dr. Manpreet Singh, who's a Child, Adolescent, and Adult Psychiatrist at Stanford University in California.

And so really, today we're going to try to wrestle with two core questions that go through the minds of really all clinicians who treat mood disorder patients where there's a concern about Bipolar Disorder. One is how do you make the right treatment decisions for those patients? What's evidence based and what's not so evidence based? And what's likely to work? And what's likely to be nonhelpful or detrimental? Preceded by the all-important question of, how do you make the best diagnosis you can?

So here's a condition where we don't have a lab test biomarker, definitive way of knowing this, this is the diagnosis, it's a clinical diagnosis. So that means that we're bringing to bear our knowledge base about cross-sectional symptoms, symptoms over time, family history, longitudinal course, past treatment response, and really sort of framing argument. As I will sometimes say, patients seldom, if ever, come in with a clear message board over their head saying, 'Hi, I have Bipolar 1 Disorder, now in the depressed phase, and proceed right to treatment', we're often trying to tease apart lots of different kinds of symptoms around mood, around cognition, impulsivity, sleep-wake cycle changes, so everything really starts with a careful diagnostic assessment.

So Manpreet, what do you do when the patient does not have the sign over their head with their ICD code, or otherwise an unambiguous history? We sometimes get an unambiguous history. But before you delve right in and jump to treatment, how do you think about, I want the greatest clarity diagnostically as I can?

Dr. Singh:
Well, I couldn't agree with you more, Joe. Bipolar Disorder, I would say is one of the most complicated diagnoses, in part because it's episodic, so patients don't always present with all of the symptoms that they're struggling with. And so, you have to really do a deep dive, not just about what's in your face and presenting at your door, but also looking backwards in history and also collecting collateral information.

At the heart of it, though, is a relationship with a patient. A trusting relationship, where you can work towards understanding the fundamental issues that are most functionally impairing for the patient. I use that as a way to prioritize my treatment planning, as well as to build trust and engagement with a patient. So starting at the core, with a patient's experience, I think can do you no wrong, and then you take things from there.

Yeah, so I mean, we want to start with U.S. FDA approved - while we're practicing in the U.S., approved medications, so that we can at

least start from a strong evidence-based perspective. I tried to use that, particularly in the youth populations, because there is still some fairly significant concerns about safety and long-term impact of treatment. Nevertheless, I think that in youth, and to some degree, were afraid to use medications that have worked really effectively, even if they have only recently been approved down to age 7. For example, lithium is an exceptionally effective medication, and early treatment with lithium can be very beneficial to impact potentially the positive course of the Bipolar Disorder over time. The issue with prevention is another reason to get the medication right, early on, and then think about strategies for maintenance treatment. So I use the second generation antipsychotics and the mood stabilizers, in particular, lithium, in part because I know that I can get good effective mood stabilization in an acute phase. And then in terms of longer-term management, though the evidence is still emerging in terms of their long-term efficacy and impact on preventing and prophylactic against relapse, what we generally believe is, is that people should remain on their medication at least 6 months, if not more, to be able to get that prophylactic effect. And the idea being in the discussions with patients, is to prevent recurrence of mood episodes, which in it of themselves can be very neurotoxic.

Dr. Goldberg:
Studies have shown that risk for relapse is the first 3 to 6 months. Once you've made it to that 6-month mark, anything that comes along is considered a new episode or a recurrence. So we will often say to patients, one of the goals is to put the flames out, make sure nothing's going to ignite again, and then get you to the 6-month mark and, basically, as you say, don't mess with success If the patient's doing well in those 6 months, you want to get them to day 180. It's like those car insurance places where if you go 10 years without an accident, you're now statistically a safer driver. So I really strive to tell the patient, let's just get you well, keep you well, with whatever is working.

Now, here's the catch, class effects. You know, if somebody says any old atypical antipsychotic has antidepressant properties, or for that matter, any anticonvulsant has mood-stabilizing properties, we make a scrunchie face and we hear that, right? How come?

Dr. Singh:
Anecdotally. Yes, because we think that some medications are more antidepressant genic or manicogenic, or whatever the case may be, it's all a wash in my view. We don't have the comparative effectiveness studies to really pin down which medications work for which patients. Those are required, in my view for precision-based psychiatric treatment. What do you think about that?

Dr. Goldberg:
So I think class effects are very interesting. I learned this lesson with the anticonvulsants, when drugs like valproate and carbamazepine came along, and then lamotrigine, there became this broad assumption that any anticonvulsant must have mood value. And curiously, that's where the trail ended. No other anticonvulsant besides the three I mentioned, has been shown to treat mania or depression. There really is not a class effect. The same as anticonvulsants don't all do the same thing when it comes to generalized seizures versus absence seizures. Breath of spectrum is very drug specific.

Same with a typical antipsychotics. So many have been studied and shown not to have antidepressant properties. Interestingly, at least a couple out there have been shown to not have antimanic properties. So you can't just make a class effect decision in your head and just sort of randomly pull things, you know, off the shelf, you have to talk about the ways in which there's an evidence base to support a particular drug.

Some drugs have been shown to work in multiple domains. For instance, the compound cariprazine, has evidence both in mania and depression. So does quetiapine, bimodal efficacy in both mania and depression. Olanzapine has a notably larger effect in mania than depression, but actually does have some antidepressant properties. And then some of the other newer compounds, lurasidone, lumateperone, both had been shown, or at least I should say both have been studied deliberately in the depressed phase. So we don't know as much about their antimanic value; it's more the absence of information rather than the evidence of absence.

Will they work by modally? Will they work long term? That's an important question that we don't have the answer to, and this is why I think good clinicians want to keep up with the literature and be informed about the breadth of spectrum of compounds. What's an adequate dose? An adequate duration? Has the drug been studied, say in Bipolar 2 Depression, not just Bipolar ? There's actually only two FDA approved drugs in Bipolar 2 Depression, that's lumateperone and quetiapine, and everything else is kind of an experiment. So I think having a good working knowledge of the evidence base from clinical trials helps us establish credibility with patients. So we're not just saying, 'Oh, well, subjectively, let's try this,' fostering the trial and error concept, as opposed to saying, 'This has been shown to work. This has not been shown to work. Here's why I think what I think, and let me help you make the best decision from among the available viable options in terms of their efficacy, their potential side effects, and what works best for you.'

Dr. Singh:
And I couldn't agree more about the point of using the evidence base to guide some of your initial discussions. Quetiapine is a good example of this. I don't know if you knew this, Joe, but in kids, we've had multiple failed trials of quetiapine and quetiapine extended

release for Bipolar Depression, just haven't separated from placebo. Now, do we need more data to help us understand why it's not working? Of course we do. And certainly, it's a very effective medication as an antimanic in kids. So what are those developmental differences? Why are kids not showing a signal detection there in those trials? It's a very important question, which is why we end up reverting to the ones - medications that are FDA approved for Bipolar 1 Depression in kids, namely, olanzapine, fluoxetine, and lurasidone. Cariprazine is undergoing phase 3 trials right now for kids.

And hopefully, we'll learn more about other agents, because that's clearly an unmet need for kids, particularly since earlier in the stages of bipolar evolution, mixed states are often very common. And so treating both the juxtaposition of mania and depression, as well as the prevailing mood state and whether it's mania or depression individually, is there very, very important and getting patients quickly to you euthymic states, becomes a kind of an imperative, if you will.

Dr. Goldberg:
Absolutely. So let me see if I can succinctly wrap up the highlight points that we tried to make here today. So I really want to encourage clinicians to almost adopt the mindset of an investigator or a detective, not just say, well, we could do this or this or this, but to really spend the time, devote the effort and the energy on the front end to establishing as clear a diagnostic impression as possible. For all the reasons we've talked about, Bipolar Disorder and it's comorbidities often have very heterogeneous presentations. Most people with this condition actually have more than just one diagnosis. So you may very well be identifying somebody with Bipolar 2 Disorder, with comorbid ADHD, with comorbid Substance Use Disorder. And so, our work is cut out for us to make as clear and explicit a description of what we think is going on, and what's supported by the family history in the course over time, and what prior treatments have been tried and been successful or not. And certainly, knowing what the patient's priorities are. We talk a lot about patient-reported outcomes these days. And what I think the patient needs may or may not correspond to what they think they need. So we want to get some convergence about that.

And once we've gone through that exercise, and eliminated things that are not relevant, and identified things that are, and talked about the ways in which every patient is like a snowflake with their uniqueness, then we can talk about what is evidence based in terms of pharmacology options. We should do no different with psychotherapy options, frankly, when we're talking about the cognitive dimensions or the interpersonal dimensions, or the impulse control dimensions, but we're tailoring the treatment to a given patient. Of the pharmacologies that are FDA approved, they differ, as we've said, in their breadth of spectrum. Do they treat both highs and lows? Do they have preventative data? Do they work in Bipolar 1 and Bipolar 2? Or just one versus the other? Do they have data in combination with other treatments that have shown synergy as opposed to just hodgepodge randomness? How is the tolerability of agents? How do we help patients understand the potential for side effects and how to navigate them? The time course? There's a lot that goes into this. But the payoff in my view, is the fruits of your labors will be well rewarded on the back end. Once you've gone through this exercise and diagnostic clarification and focusing on the pros and cons of viable evidence-based treatments, we can really craft regimens that have strong rationales and likelihoods for seeing successful outcomes. And as I tell my patients, the one thing I can promise you is a rationale for what I'm going to propose, and that's really the cornerstone of shared decision-making and treatment alliance.

Anything you want to add to that?

Dr. Singh:
No, you bet. I think that we can't do wrong by making sure that we take the patient's functionally impairing symptoms at heart and really understand how we can build an alliance and utilize that to guide our treatment.

Dr. Goldberg:
Well said.

Well, thank you all for joining us today. We hope this conversation and view about perspectives has been helpful to you as practitioners in your work with patients and we'll see you next time.

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