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Bringing Bipolar I to Light: Connecting on Diagnosis & Treatment Challenges

Narrator:
Welcome to CME on ReachMD. This activity titled Bringing Bipolar I to Light: Connecting on Diagnosis and Treatment Challenges is provided by Forefront Collaborative and supported by an educational grant from Otsuka America Pharmaceutical, Inc. and Lundbeck. This replay of a live broadcast focuses on how we can overcome challenges in the diagnosis and treatment of bipolar I disorder. Here is your moderator, Dr. Roger McIntyre.

Dr. McIntyre:
Hello, I'm Roger McIntyre, Professor of Psychiatry and Pharmacology at the University of Toronto. Greetings virtually from Toronto, Canada. I'm very glad you could join us for our program, not just joining myself but also my two colleagues, who will be presenting with me, who I'm going to introduce in just one moment.

This is a very difficult time. I call it the triple threat, not just the public health crisis but the economic and the mental health crisis. We're already hearing that people with serious illness like bipolar disorder are not only more susceptible to the infection and complications of COVID-19, but more recently we are hearing about increased mortality in people with serious mental illness. The time could not be greater than now for us to be having a conversation that we'll have tonight, which will be largely focused on how can we keep patients better in the long-term.

To engage in this conversation with me, I want to introduce my colleagues. They begin with Dr. Amy Becher-Smith. Dr. Amy Becher-Smith is the Assistant Professor of Clinical Practice at The Ohio State University in the College of Nursing in Columbus, Ohio. Amy, welcome.

Dr. Becher-Smith:
Thank you so much. Hello, everyone.

Dr. McIntyre:
Nice you could join us, Amy. And also a friend and colleague, Joe Goldberg in New York. Joe is at the Icahn School of Medicine at Mount Sinai in New York. Joe, warm welcome to you as well.

Dr. Goldberg:
Thank you, Roger. Amy, real pleasure to be here tonight.

Dr. McIntyre:
I want to, in fact, just move things along because we've got a very ambitious agenda tonight for you, and the agenda is going to cover broadly the management of bipolar disorder. We're going to start off with diagnosis, which I think is still the great unmet need in bipolar, arriving at a timely and accurate diagnosis. We're going to spend a lot of time on individualizing treatment with respect to thinking about patient phenotype, matching it to the treatment options. You're going to hear a lot about long-term treatment, especially focusing on adherence. The process will be didactic, but we're also going to have plenty of time for interaction. We're going to ask you for your

questions. We've got poll questions for you, and we've got a debate that will take place between Joe and I a bit later on. So, I'm looking forward to this. Let's get started if we can.

Okay, we're going to talk about the diagnostic challenges, and I'll keep this pithy because I think that the message will be very clear and unambiguous. The unmet need in bipolar disorder in 2020, 2021, remains getting the diagnosis accurate and making that diagnosis timely. Now, I'm not going to go through the DSM-5 criteria. We all know what it is. The defining feature of bipolar I disorder is the presence of at least 1 manic episode. The DSM-5 contains a list. We call it a polythetic list of criteria. You know the essential feature is a disturbance in mood, elevated, expansive, irritable, as well as increase in energy activity with additional symptoms reaching threshold. You know, I would not define bipolar disorder as the onset of mania, but that is at least a benchmark that many people have used for good purpose. As a pragmatism to that, if we use that as the benchmark of the onset, really, in fact, studies keep telling us it's about 5 to 10 years for people to be diagnosed, and people utilize healthcare services at a very high rate. It's often cited. There are several healthcare providers that have been consulted despite the fact the person has observable characteristics of bipolar disorder.

So, what is the takeaway message? The message is that for every patient with depressive—and I'm going to even add anxious symptoms—who presents in clinical practice at that first indexed visit or someone who comes back for repeat visits and is not doing well, the sleeves have to be rolled up. We have to be screening for bipolar disorder, always remaining vigilant for bipolar disorder, and always have that in the back of the minds of consideration.

With respect to the reasons we get lost—well, there are many reasons, one of which is, frankly, the system. We're all time poor. It takes time to really capture the phenomenology but also some of the key bipolar validators, which we're going to talk about: the age at onset, number of episodes, the illness trajectory, the response to treatment and family history. I think really one of the major reasons in my experience why patients referred are missed is because they just simply weren't screened. They weren't asked about it. That's clearly modifiable. Part of it is the challenge of trying to suss out bipolarity from some of the other comorbidity or other psychopathology, whether it be psychosocial pathology, whether it be trauma, comorbidities like anxiety, PTSD, ADHD, and certainly, these conditions not only occur at the time of presentation but often will precede the presentation of bipolar disorder. Often in psychiatry, once you get a diagnosis, it kind of sticks with you, and if a patient has been diagnosed, for example, with generalized anxiety or depression first, that sort of becomes their sort of familiarity, and that's the diagnosis we get biased on, so be careful of that. Never forget to think about bipolarity.

As it relates to overcoming these challenges—this is a great point for discussion—Joe and Amy, how can we overcome these challenges to improve this diagnosis of bipolar I disorder?

Dr. Becher-Smith:
I'll start. So I think one important thing is just taking the time to take the history, and having collateral information from family members is really important. I know one of... I treat a high population of substance use disorders, and typically, they're not even presenting until maybe they are ready for treatment, which can be a long time in the process of their substance use, so going back and really tracking back: When did these symptoms start? Are we self-medicating due to symptoms that are uncomfortable for them? And then, can they even remember what was going on or not? If you've been doing methamphetamine for 20 years, it's very hard to decipher if someone's been up or down or if they have an underlying bipolar or other mental illness. So, I think really taking that time. And it may not happen at that initial visit. It may be following visits after that, after they are stabilizing. And I think another point with that population is they don't tend to be very trusting of the medical professional. If you think they have been using illegal drugs for a long time, "I'm not going to disclose things to people". So really it is about that process of having them understand that we're here to help them and help them move forward with wherever they are in their lives and that not to fear disclosing certain information.

Dr. McIntyre:
Nice points. Joe?

Dr. Goldberg:
I'll agree, and I'll add that a lot of patients with bipolar disorder are not seen by a mental health professional usually. They may be seen in primary care settings. Their chief complaint may or may not be a tipoff if I come in and say, "I'm depressed" or "I'm having marital problems" or "I'm drinking too much." A lot of this is education for the first responders, essentially primary care clinicians, non-prescribing psychotherapists who are hearing about mood problems. Every mood disorder patient needs to be screened for both poles. That's in practice guidelines. It's just common sense. It's not just screening for both poles. It's screening for psychosis. It's screening for anxiety. It's screening for comorbidities. But psychiatrists often find themselves seeing more complicated patients nowadays, someone who's been through several treatments, someone who's been diagnosed with something else or something else, and so, if your practice is especially oriented toward complex mood disorders, you're trying to amass all the information that you're getting from your predecessors.

So, screening is really, really important in primary care. Things like the Mood Disorders Questionnaire, for example, as a screen will tell you there is a likelihood that this diagnosis exists. And when you have enough information to make you suspicious that bipolar disorder could be in the picture, this is where I think you have to roll up your sleeves and allocate the time on the front end that's needed to both pin down historical symptoms, course over time, age at onset, family history, get a collateral historian, ask patients to clarify terms if they come in and say, "I'm rapid cycling and I have ideas of..." You know, simple, simple terms.

Bipolar disorder is about recurrence. It's about on/off, on/off, on/off. Traditional approaches for depression may not be that successful, and so we're really looking at complex mood disorders, and we have to just know what those features are and put them together in terms of symptoms, in terms of course over time, family history, and you're really building a story kind of jigsaw puzzle.

Dr. McIntyre:
This is a great dashboard. Just to keep in mind, 75% of people with bipolar begin the illness before the age of 25, so this is a an early age at onset illness. I'm especially vigilant in women during pregnancy, postpartum, who have new onset or recurrent episodes of mood. And something I like to think about is what I call my 4 As. When a patient is depressed and says, "You know, Dr. McIntyre, I'm depressed and I'm anxious, I'm agitated, I'm angry, and I cannot pay attention"—"I'm anxious, agitated and angry, can't pay attention"—that sounds like a lot of mixed features going on there, and I get really suspicious of bipolarity—again, the features that Amy and Joe have also, I think, enumerated so far. So this is a great set of clues for the potential diagnosis.

You've heard us talk about screening. I was part of a group that helped validate the Rapid Mood Screener. It not only looks at phenomenology, like the MDQ, but it also, in fact, looks at bipolar validators, like prior number of episodes, age of onset. I suspect that that's why the Rapid Mood Screener has slightly better sensitivity, specificity, positive and negative predictive value, than does the MDQ, so it's a bit of an evolution, if you will, in terms of screeners. Comments? Joe? Amy?

Dr. Goldberg:
I think screening is very helpful as the first step, the same as we do elsewhere in medicine. A Pap smear does not mean you have cervical cancer, a high sed rate doesn't mean you have lupus, but this arouses our attention, so it's a really good first pass. If you're in a busy setting, a patient in the waiting room can fill out the MDQ, or now the Rapid Mood Screener, bring it in, and you go over it with the patient. So you don't just tally it and file it. You clarify.

We did some studies showing the MDQ makes an excellent semi-structured interview. We found very high positive predictive value with it as well as negative predictive value. So, if a patient scores below the threshold, don't belabor the point. The probability of seeing bipolar disorder then becomes very low. You can move on to the next thing. But this is really the starting point and the initiation of a conversation.

Dr. McIntyre:
Beautiful.

Dr. Becher-Smith:
Yeah, and I would add to Dr. Goldberg. I think what also helps—I use the MDQ—is psychoeducation is really highlighting some of those symptoms and putting them together, because a lot of times patients haven't even really thought of it or thought it through. This is their experience day-to-day they have had for years not knowing this may be abnormal and that it may be causing them suffering that they didn't quite realize, so I think it's a good teaching tool as well.

Dr. McIntyre:
You know, Amy, you are reminding me. I think the screening tools make us more contemplative. Often we are precontemplative, but this makes us more contemplative of bipolarity, which I think is a great nonspecific deliverable of those scales. Very quickly—it's a big topic, COVID-19—could you give us kind of a Wiki sort of a quick kind of how have you adapted to some of the diagnostic challenges during COVID-19?

Dr. Becher-Smith:
In my practice we actually never shut down. We were considered essential. I'm in a community mental health center, so a lot of our individuals are homeless, don't have phones, don't have telehealth, that type of thing, so that was really important to do. Fearful as staff members, but the patients are also fearful. It's caused a lot of relapse of substance use all over the place. That has been devastating. And just people, isolation, not knowing what to expect, anxiety, and that stress, whether they are on the medication that they are taking normally, they may start having more symptoms because of that stress, so staying in close contact, having them come in, increasing counseling, increasing groups as much as we can to keep safe, that's one thing that we really tried to do because more and more people, mental health or not, are feeling isolated, disconnected, and it's causing more mental health issues.

Dr. McIntyre:

Beautiful. Joe?

Dr. Goldberg:
I've had the experience that with high levels of acuity it gets very, very difficult when you're at such a distance to be able to get a handle on things, so if someone is floridly manic or for that matter suicidally depressed and they need a high level of care—they need a team; they need 24/7 monitoring and supervision; they need a washout of medicines; they need tox screens; they need a lot more than just a screen and a lot more than just a single individual—I'm finding that that's been very, very difficult. I'll have patients contacting me with complex psychopathology and, "Can I see you for a consultation?" and really the question becomes, Do you need an individual or a team? to get greater clarity on things.

And then in terms of fears about going in the hospital, where I am at Mount Sinai, I don't know if the second wave is coming, but New York was very successful in keeping the curve flat for quite a while, and now, for the first time in months, we're seeing increased cases. They'll go back and forth from the medicine unit to the inpatient psychiatry unit, and then we have to redesignate units as COVID units, so it just makes it much harder to do our job. It's challenging enough to get the family in and get the longitudinal history and clarified that this is not substance-induced and get the prior medication history, and now, on top of all of that, to have to worry about fears around COVID just makes it all the more challenging.

Dr. McIntyre:
It sure does.

Dr. Becher-Smith:
Just to add to that, the crisis in Ohio and Central Ohio just went way down. People aren't reaching out for help when they need it.

Dr. McIntyre:
Right.

Dr. Becher-Smith:
But you know they are at home, just not wanting to go out because they're worried about the virus.

Dr. McIntyre:
That's a great point. I agree. And thank you for both your comments. Not only has this been a terrible situation for the general population, especially with mental illness, but we've recently just conducted analysis where we're anticipating what I call the 1% rule. For every 1% increase in unemployment, a commensurate 1% increase in suicide, so it's really got to flatten curves and get ahead of the curve of suicide and worsening of mental health outcomes. I can't think of a more important segue now talking about individualizing. Joe, over to you, managing bipolar on the individual—to the individual lens.

Dr. Goldberg:
Thank you, Roger. So I want to talk about the idea of not treating the diagnosis but rather treating the patient, and by that I mean getting a real clear sense of what their presentation is, what the nature of their psychopathology is, and then choosing treatments that are really geared toward their particular constellation of symptoms, their unique profile.

I've broken things down here into 3 columns. The first one says Clinical Domains. These are things that you think about, knowingly or not wittingly: What am I treating? Am I treating their affective instability? Am I treating psychosis? Am I treating insomnia, suicidality, impulsivity? All the elements that go into this ailment, this condition, which can present in different ways during depression, during mania, during mixed states, during maintenance phases, balancing risks and benefits and side effects and keeping patients engaged, worrying about adherence, there are plenty of things to keep our attention busy and occupied here.

Now, in the middle column I've listed aside the likelihood that a particular treatment is going to work. Some of these are demographic features, like age or sex or race, ethnicity. Some of these are clinical factors, like age at onset, level of severity, proneness toward highs versus lows, chronicity. When you think about a particular patient, patients are like snowflakes; no 2 are alike. You can be having a manic episode, and it's your fifth episode, and you've had 3 more in the last year, so rapid cycling is evident, and your polarity proneness may be more indicative of highs versus lows, so you're getting kind of a vivid picture in your mind of who this unique patient is to then line this up with what kinds of treatments make the most sense.

On the last column we've listed pharmacologically mood stabilizers, antidepressants, antipsychotics, novel agents, hormonal therapies, immunomodulators. There is a whole range of things that we now think about in our pharmacopeia, and matching these up I would suggest is not simply how do you treat bipolar depression or how do you treat a mixed state but rather how do you put these modulators and mediators together in identifying the clinical domains that you're going after to then target the best treatment.

Let's take lithium as an example. Who's a good lithium candidate? I've listed here characteristics. It works especially well in the first few

episodes; may not work as well after you have had several episodes go by in time. It's not a drug you want to wait until somebody's been multidrug resistant because by then lithium may not work as well. Lithium is one of those drugs that does seem to have some familiality to it. If a first-degree relative of yours has bipolar disorder and lithium was helpful for them, there's about a two-thirds concordance that the same will be true for you. It's no guarantee, but it's another piece in the puzzle that you put in with this. Patients who tend to be more prone toward highs rather than lows fare better with lithium. Lithium is a better antimanic than an antidepressant drug, and unfortunately, a lot of our patients are more polarity prone towards depression than toward mania, which is why lithium doesn't always work as well as we might wish it would. Lithium tends to be especially helpful when manias are this more elusive, euphoric, expansive, grandiose kind of mania rather than the more dysphoric, irritable, mixed presentations that we often see, another reason why lithium may not always work as well as we wish. If you've had 4 or more episodes in the past year, lithium may not be as successful as if you haven't had many episodes in the last year. Lithium tends to work better when there is not a history or current active substance use in the picture. And we often think of lithium as having particular value for its anti-suicide, anti-impulsivity effect. So you can sort of run through this picture in your mind as you're deciding if the patient in front of you fits the profile more or less for lithium.

By contrast, I'll talk about some of the anticonvulsant mood stabilizers: divalproex and carbamazepine, both agents that we think of as having more impact on the mania side than on the depression side, like lithium, but some differences from lithium. Divalproex in particular may work better than lithium in multi-episode patients, may be more useful than lithium when there are mixed features present as opposed to pure euphoric manias. Divalproex has a very nice database for impulsive aggression across many diagnoses from bipolar disorder to traumatic brain injury, dementia, personality disorders. It may have a unique anti-aggressivity effect. It may be a little more robust than lithium, perhaps in some studies at least, when rapid cycling is evident. The 2 together, lithium plus divalproex, may be better than either one alone in rapid cycling.

There are some interesting data suggesting that in bipolar patients with active alcohol use disorder, liver enzymes permitting divalproex may actually have a direct effect in mitigating or reducing alcohol use, so that's another moderating factor that would go into your calculus in deciding if someone might be a good candidate for divalproex. It's a drug that we can orally load quite safely- 20 mg, 30 mg/kg is quite safe. Particularly in the patient setting when time is quite sensitive, you can get someone markedly better within 3 to 5 days. That's hard to do with a lot of agents.

On the flipside, it may not be so wonderful a choice in a woman of reproductive years because of risks of teratogenicity. There is some potential of polycystic ovarian syndrome. Side effects, it can have weight gain among some other concerns. So, one size does not fit all, but these are some of the profiling differences between the anticonvulsants and lithium.

Now, lamotrigine is the mirror image of all these. Lamotrigine is a mood-stabilizing drug that mainly exerts its effect from below on the depression symptoms. It has been shown and FDA approved to forestall the time until a next episode, particularly if it's a depressive polarity. It's sometimes used off label in acute bipolar depression, but the evidence base and the FDA indication is for maintenance prevention. There are some compelling evidence-based trials combining lamotrigine with lithium or with quetiapine in acute bipolar depression. I'll often think of it as a good copilot or a good adjunctive treatment in the setting of depression, particularly when there is depression polarity proneness, sort of a best supporting actor. I think it has a very useful niche in that particular kind of patient, not so evidence-based in the setting of manic or mixed episodes though.

Now, antidepressants, quite a controversial area here. Are they good? Are they bad? One of the questions that originally had come up was, do they switch patients into mania? Do they destabilize mood? That's a hypothesis that was articulated in the 1970s, but more recent studies would say that it's a fairly definable subgroup of bipolar patients at risk for destabilization of mood. Probably about 10–15% would be what metaanalyses tell us, so it's by far not the majority of patients. The bigger concern then switching to mania is, do they work? And here we have a mixed bag because a lot of antidepressants have never been studied. In fact, no antidepressant developed after 1999 has ever been studied in a randomized trial, placebo-controlled trial, for bipolar depression, so a lot of our data come from the earliest of the SSRIs, bupropion and then the tricyclics. There is no placebo-controlled data with any SNRIs, no data with mirtazapine or with the newer serotonin-modulating drugs.

With that in mind, you can make a profile here on the left. I have characteristics or moderators that might favor use of an antidepressant as a safer option. In a bipolar II, not a bipolar I patient, who has pure depression, no mixed features, no rapid cycling, no recent mania, no substance abuse, a very robust initial response without any signs of having gotten manic with an antidepressant before, this ends up being a fairly small sliver of the bipolar depression universe, because a lot of patients, as you see on the right, have mixed features when they are depressed—they have bipolar I, they have rapid cycling—and so candidacy for an antidepressant may pertain to a fairly small subgroup of patients, which is what brings us to the more evidence-based treatments for bipolar depression.

Second-generation antipsychotics as a class treat psychosis, but they vary in their psychotropic profile for mood. Some treat the depressed phase of illness. Cariprazine, lurasidone, quetiapine, olanzapine, fluoxetine, and the most recent drug, lumateperone, all

have at least 1, if not 2, randomized trials for bipolar depression, but some compounds have negative trials. Ziprasidone has only negative data. Aripiprazole acutely has negative data. A lot of drugs have no data, so there's a lot of diversity.

For maintenance purposes we have favorable data with aripiprazole, with risperidone, both of which are available as a long-acting preparation as well. Olanzapine has maintenance data. We have negative data with lurasidone and a lot of missing data, so we can't make a generalizable class assumption on does the drug work for mania? Psychosis? Depression? and maintenance? not to mention the varying adverse effect profiles, so one size again fits one.

Dr. McIntyre:
Okay. I think we have some questions coming in, and plenty of questions, actually. Let's bring them up here. Here is one for you. I'll pose one to Amy first. And it's not an easy question, Amy. This is a difficult one. This one took me about 10 years to figure out, so I'll give you 15 seconds. How do you differentiate substance abuse from bipolar disorder?

Dr. Becher-Smith:
Yeah, so it's complex and difficult, and it takes time, getting that timeline back to when the substances? What substance? At what age did you start? Where did you progress to? Have there been any long-term sobriety that you have had that we can monitor different symptoms? Did mood symptoms happen before use? And then sometimes it's just helping them with getting into recovery and continuing to monitor, so sometimes it's not very clear.

Dr. McIntyre:
Yeah, very good. I would say I agree with that. This is a very commonly encountered situation, and I think many clinicians are seeing an increase in substance abuse, in part because of the COVID-19 situation in their patients.

Dr. Becher-Smith:
We're getting to our debate. So the clinical topic debate will be on atypical long-acting injectable, or LAI, antipsychotics for bipolar I disorder, to use or not to use based on the evidence. So, Dr. Goldberg and Dr. McIntyre will be debating each other. We have some rules about this. Each of them will allow each other to talk and to present their arguments. They'll have 2 and a half minutes each to present and then a minute and a half to provide a rebuttal and closing statements. And we'll start. Dr. McIntyre will be in support, and Dr. Goldberg would oppose the use. We'll start with you, Dr. McIntyre.

Dr. McIntyre:
Okay. I guess I've got 2 and a half minutes.

Dr. Goldberg:
Tell us why, Roger.

Dr. McIntyre:
Well, the reasons that I would put forward as reasons to consider an LAI and why I think they are very appropriate, 3 and 2, 3 hard reasons and 2 theoretical reasons. Three hard ones:

- Patients often forget to take their medication. There is non-concordance with taking treatments according to best practices and what we recommend. And part of this, not all of this, but part of this is because of forgetfulness and things of that nature, so given the relapse recurrence proneness of bipolarity, it would make a lot of sense for a condition greatly affected by human nature, that is forgetting, to have that treatment. That's number one. The recurrence proneness is significant, and the more episodes that you have, the more likely you're going to have problems.
- We don't want patients hospitalized, and it turns out, based on the evidence, only lithium—one of Joe's favorite drugs—and long-acting injectables are the only 2 that have been shown to lower hospitalizations in some large studies. So the first reason is people forget. Second reason is that they have been shown to lower hospitalizations.
- And what's the third reason? Patient preference. Patients actually when asked, "Do you want to take a treatment every day or a treatment once a month?" and many patients will say, "Well, that seems like a trick question because the answer is obvious." But what I've noticed is many of my patients say to me, "Nobody ever talked to me about long-acting injectables." And I'm probably responsible because I never thought about talking about it with some of my higher-functioning patients before, so that's something, so patient preference.

So the 3 are human nature, second is hospitalization reduction, and thirdly is this whole patient preference.

Now, the 2 theoretical issues are maybe we can slow the progression of the illness. This illness progresses the more episodes you have, and that would be amazing. Disease modification would be a great set of words to use. And then finally, there's more comorbidity in people with more episodes—that is more drugs, alcohol, ADHD, binge, obesity, diabetes—so maybe, if we can prevent episodes, we

can prevent that Velcro effect, that sticking on of all these comorbidities.

So I'll leave it as that. And, Joe, look forward to hearing what you've got to say.

Dr. Goldberg:
Oh, Roger, where do I start? So I think the notion of a long-acting treatment is a brilliant one. I wish we had a long-acting lithium, a long-acting divalproex, a long-acting lamotrigine, but the reality is we have really 2, arguably 3 drugs to consider here. One is aripiprazole long-acting injectable, the other is risperidone long-acting injectable, and then olanzapine does have Relprevv that's long-acting. That's approved in schizophrenia, hasn't been studied in bipolar disorder, but for what that's worth.

So we're really talking about what is the value of aripiprazole or risperidone, and the main problem I have with either of those being the core treatment is they have each been shown to be very robust in treating or preventing mania but not depression. Now, the way the studies were done with those drugs, they weren't really fairly set up to give a full test of how good a job either drug could do for depression, but the fact remains we don't have any positive data with either of those agents to acutely treat bipolar depression or prevent bipolar depression. And as we've been saying, depression tends to be the most common mood state that we see in this disorder, so, for the most common mood state, we don't really have an efficacious strategy if we go with just a long-acting injectable. We have to come up with something else for when such patients get depressed. And then what do you do since the FDA-approved treatments for bipolar depression incorporate other atypical antipsychotics that do have antidepressant value? Do you add such a different SGA to the long-acting injectable SGA? Do you take away the long-acting SGA and replace it with the other atypical, or do you do something novel? So the depression piece I think is the biggest downside.

The other elements to this are many have said that mood stabilizers are really the core of long-term treatment, particularly lithium. They have been studied the longest. We don't really have multi-year data with any of the atypical antipsychotics, and before we commit a patient to very long-term, possibly indefinite use, we're balancing that against the risk of metabolic problems, adverse effects, tardive dyskinesia or other movement disorders, and we just don't have years and years of experience with that.

So those are really the main concerns that I would voice about using LAIs as the core of treatment for a majority of patients.

Dr. Becher-Smith:
Thank you, Dr. Goldberg. Dr. McIntyre, do you have a rebuttal?

Dr. McIntyre:
Very quick rebuttal. One of the difficulties we all find ourselves with patients when they come to us with bipolar disorder who are prescribed treatment and they are having symptoms, is it because they're not taking the medication according to recommendation, and/or is it because the treatments are not working as well? And if the patient is on a long-acting injectable and they are having breakthrough symptoms, I can safely conclude it's because of inefficacy. And in this world of known unknowns and unknown unknowns and known knowns, that is a very important known known that it is the treatment that's not working. That has impact on what I'm going to do, so that's another reason I would think about LAIs.

Dr. Becher-Smith:
Okay. Dr. Goldberg?

Dr. Goldberg:
And my rebuttal for earlier comments, which were, by the way, very eloquent and thoughtful, and I'll say more about them in my own words in a few to adherence. If a patient with say nonadherent to a drug that was ineffective, the presupposition is that one of these long-acting injectable compounds would be a better, more efficacious treatment. We need to clarify that. If the patient's nonadherence was because of side effect burden or metabolic syndrome or movement disorders, then that's a different reason for nonadherence. If the patient has been on multiple medicines, it would be nice to think that an LAI would replace. It's like those TV commercials for one appliance that replaces your whole... You've got 10 appliances in your kitchen, and you buy this one thing. I never found that to be so true. It would be lovely if we could say, "Forty percent of bipolar patients who take 4 or more psychotropic drugs..." If you could say, "A long-acting injectable will replace all that, sign me up," it's just we don't really know if that's true, and given the complexity of the phenotypes and the comorbidities, I can't say to you, "Take this long-acting injectable, but you're still going to be on 2 or 3 or 4 other medicines." So the tradeoff may or may not equate to a happier outcome. We don't know.

Dr. Becher-Smith:
Now we come to: What is your real opinion about atypical LAI antipsychotics for bipolar? Is this an appropriate treatment?

And I'll start with my experience. So I have a handful of individuals with bipolar I that have been successful and have chosen the route of an LAI. I found that when I do have discussions with people, most of the barrier is the injection and the needle, and people don't want to

be stuck, so my hope is down the line in the future that we'll have other long-acting ways to administer medications for individuals where they don't have that fear of being stuck.

Dr. McIntyre:
My own view is that I think that, for me, the biggest learning that I've taken away the last decade is don't presume that higher-functioning patients might not prefer a long-acting injectable. I had this bias it's only for more tertiary, more late-stage, very nonadherent patients. That's one point. The other one is—I think Joe touched on this—is that the reality is, when we see a lot of people with bipolar disorder, the treatments are not—no one treatment is a panacea, so I think about maybe there is a role for the LAI in treating these symptoms like preventing and delaying mania, and that might require some other treatment to be added to it, like a lithium or lamotrigine. The reality is we need to have thoughtful, contemplative, safe combination treatments probably in most patients.

Dr. Becher-Smith:
Thank you. Dr. Goldberg?

Dr. Goldberg:
So I couldn't disagree with me more.

Dr. Goldberg:
Look, the most common reason patients get hospitalized and they relapse is they stop their medicines, period. I mean, nonadherence is far and away the biggest reason.

Dr. McIntyre:
Yeah.

Dr. Goldberg:
And the data are very, very, very compelling with long-acting injectables. In fact, if you take side by side the oral aripiprazole maintenance data with the long-acting injectable, it is a much greater degree of wellness that's sustained over the course of a year with a long-acting injectable. So, if it's a question of patient's priorities and we're asking, "Well, how do you feel about a needle?" "How do you feel about getting rehospitalized?" "How do you feel about the risk of what happened the last time you had a manic episode?" One manic episode—I've seen this, you've seen this—can wipe out savings, can devastate lives, and so I fully agree with Roger. Having this as the backbone of treatment to forestall those kinds of disastrous outcomes kind of gives you a level playing field from which you can then talk about adding all kinds of things to further enhance outcome, but if someone's relapsing, getting rehospitalized, we've got to break the cycle, and LAIs are by far the best way to do that, no question.

Dr. Becher-Smith:
Thank you so much. So, overcoming the challenges of treatment adherence, we know with bipolar I, challenges with diagnosing, deciding on treatment and then adherence. Let's start with a definition of nonadherence, which we would define as a percentage of medication of less than 80%, so 1 to 2 days per week maybe of not taking those medications. Then we look at 2 different categories of intentional or unintentional. Intentional is someone voluntarily not taking medications, and unintentional means unplanned and unconscious behaviors that's causing them to not follow through with their treatment plan.

So, what are the consequences of nonadherence? We know that if we're not figuring out, and partly this is—and we'll get to this as we talk in our discussion—are we working with the patient to really understand how they are taking their medications, what they feel about their medications? And if we're not, then we may be increasing dosages that we don't need to, adding medications or making switches that we really don't know from one to another which one is working or not if they are not following through with the treatment plan. Obviously, decompensation, disease recurrence, hospitalization, suicide, lost productivity, and then healthcare costs, the more and more that we're in and out of the hospital using crisis, using substances, all of that is increased burden on the healthcare system.

How do you monitor for signs of treatment nonadherence? All right, so talking with Dr. Goldberg and Dr. McIntyre, this here—this slide presents different risk factors. So, how do you both monitor for nonadherence?

Dr. McIntyre:
Maybe I'll take the first response to that, and maybe I'll speak to just 1 dimension of that. And this is a fantastic framework, this slide, Amy, that helps us organize different considerations, so I'm just going to pull on one of those for me. In my progress note, I have it in there the percentage of time that people have taken their medication, and so, on every visit, every time, no exception, my working assumption is that the patient is taking it somewhere between 0% and 100%, and that's something that I have learned from my graduate students who did a lot of work on adherence and so on. So, in other words, it just becomes an open conversation to discuss this each and every time. Tactically, what I try to do is I really try to boost a patient's literacy around their illness and this treatment, this psychoeducation, psychoeducation, and then I try to create an environment with my patients where it's very open just to discuss this,

and frankly, I've been quite impressed by how much patients are wide open about how they don't want to take the treatment on these days. They are prn fiddling with their lithium on these days. They are giving themselves a little prn on this and so on. So I think that's how we work with people, and that's what I've done in my practice.

Dr. Becher-Smith:
Thank you. Dr. Goldberg, do you have some words?

Dr. Goldberg:
Do you know how if you ever go to the dentist and the dentist says, "So, you're flossing your teeth every day?" Does anybody ever look their dentist in the eye and say, "No, I'm not"? It just sort of breaks down the whole therapeutic alliance at that point. It's a loaded question. It's socially pulling for a certain response. So, for me, I'm a researcher and I'm a clinician, and this is one instance where I take off my researcher hat and I try to be a bit of an old-fashioned doctor, and I will say to the patient, "Look, we know that most people have a really hard time taking medicines for a variety of reasons. Most of them do at some point, and they often won't loop in their doctor in the dialogue. They may not want to take medicines for lots of reasons. Maybe they don't think they need them anymore. Maybe they don't like a side effect. Maybe there's a stigma. You can probably tell me better than I can tell you. I have one request of you—" patient "—which is, if you're like most people and there comes a time where you're thinking about wanting to either skip or stop or ghost me in the treatment, loop me in. I'm here to help. Tell me about it. I'm not here to judge. I'm not the dentist asking if you're flossing your teeth. I expect you don't floss your teeth, but I'd like to know why. Maybe I can help. If it's about a side effect, maybe you can counter the side effect. If it's about a sense of stigma, if it's about 'I don't think the drug is working,' let me try to help." So I really try to appeal to the therapeutic alliance. That's my own strategy for trying to address it is to normalize the experience for the patient and almost collude with them in such a way as to say, "If there's a problem with the medicine, please look to me for help. I'm not here to judge. I'm here to help."

Dr. Becher-Smith:
Absolutely. Thank you so much. What techniques do you use to improve treatment nonadherence? So we'll be looking at facilitators of adherence and looking at patient-focused modifications versus treatment provider, and I'll open this up for discussion. I just want to touch on a few things that the literature is telling us as we look more at patient-focused and provider modifications that we can take really moving toward that patient empowerment, allowing people to be part of the process to discuss different or have shared decision-making with them where you're collaborating with the patient. A lot of times when I'm seeing someone first off I'm going to present them maybe with a couple options that would be appropriate for them. "Hey, we could do this, and this is what the outcome would be. This is what the positive and negative side effects would be, or we could go with this." So I'm allowing them to have some say in the treatment, so they're going to be more apt to follow through with that if they think it's their own plan. So I think as we move forward and integrating as providers, looking at ourselves and how we can help individuals be more successful with their treatment plans.

Dr. Goldberg, do you want to... Or Dr. McIntyre, I'm sorry, would you like to comment on this?

Dr. McIntyre:
I'll keep my remarks very brief. I think that the facilitator is the process of openness. Again, I think that when it comes to adherence, engage in patient/clinician, mutually agreed upon therapeutic objectives, and I think that if you spend a lot of your time on that, that's a good return on the investment, and I have found tactically that helps me. What do they want from the treatment? What are their therapy objectives? And I try to work with them within that framework.

Dr. Becher-Smith:
Thank you so much. And Dr. Goldberg has a decision aid that he's going to present for us.

Dr. Goldberg:
In just a second.

Dr. Becher-Smith:
Okay.

Dr. Goldberg:
I was just going to say I think what Roger has described is motivational interviewing. It's helping the patient identify what's important to them. They need the locus of control on this. They need to at least feel the empowerment. Otherwise, it's going to feel like a struggle. "So, tell me your priorities. If your priorities are about avoiding weight gain, if your priority is about 'I don't want to be in the hospital again,' 'I don't want to ever go back to that depression,'" I keep notes and I'll say, "You know, remember when you told me 4 months ago the worst thing ever was this depression? And now you're telling me, 'I don't think I need this medicine anymore.' May I remind you of how bad this was? I hate to think of you suffering with these problems, and my worry for you if you do decide to stop this medicine is that you could wind up back where you were 4 months ago." So I really try to hone in on what the patients' priorities are and remind them of

them.

So, speaking of medicines, let me jump in. We've created for you here tonight this decision aid. This is a very condensed summary of all the kinds of medicines we're talking about: the mood-stabilizing drugs, second-generation antipsychotics. You're not going to be able to read this on the screen, but you can download this from the ReachMD website in the supplemental materials legibly, and this really goes through in some measure of concise but detailed way indications for medicines. Are they used in adults? pediatric? acute? mania? depression? maintenance treatment? long-acting injectables? short-acting IM formulations? the half-life of the drug? the evidence-based in bipolar depression? mania? mixed states? the maintenance? with or without rapid cycling? with or without anxiety? with or without substance abuse? side effect profile? So, as you're sitting with patients and thinking, "We have options. Let me be here for you as kind of the broker of information." You can sit down with a patient and kind of go through what their priorities are in terms of targets for efficacy, tolerability, and use this tool as kind of a guide or a menu to help you and the patient together arrive at some shared decision-making process that will help them realize what their own goals are.

Dr. Becher-Smith:
Questions.

Dr. Goldberg:
Questions.

Dr. McIntyre:
Okay, let me look here. I think in the interest of time, maybe a real... 2 short snappers. We've got time for 2 short snappers. Are there any apps that any one of you like to use at point of care with patients?

Dr. Becher-Smith:
You know, I do not have any. I've looked at the literature on that, and it doesn't seem to be that we have a lot. I'm sure that it is helpful in the world that we live in and technology that people will find apps that can help them remind them of their medication or appointments and things like that, but I don't know that we have the literature yet supporting apps to recommend.

Dr. Goldberg:
I don't have a specific app. However, I do like mood charting, particularly at points where we're starting a new medication and we're trying to get some sense as to whether it's having an impact or not. So I'm old-fashioned, I like paper and pencil, but I will tell some of my GenX patients or my millennials, "Look, you can do this on an app. And the key really is we're going to start a new medicine. We're going to start a new medicine, and we'd like to know is it working." Patients say, "Is this working?" "You'll find that out. You'll be tracking your mood day to day to day. You don't have to do this forever but long enough for us to get a sense, 'Gee, look at how many days of euthymia you have had. Look at how many days you have had excursions from high to low,'" and then we can compare 4 weeks ago to now and probably do some fancy numbers. Patients like hard data. I like measurement-based care. I put my researcher cap back on. So, if I can say to the patient, "Look, here are the numbers. You are 48% less depressed than you were a month ago. Now, let's talk about whether you want to stay with the treatment."

Dr. McIntyre:
Yeah, very good. And I would echo both of your comments. I don't have an app I rely on myself. Those are a work in progress with respect to validating them and showing that they improve health outcomes and/or are cost-effective, but I think it's the future, and we're in this virtual world, and perhaps one of the externalities, one of the unintended consequences of this terrible situation of COVID is we have maybe a more coherent, more accessible mental healthcare system with better embrace of affordable digital capabilities where broadband is available for all of our patients.

Amy, Joe, thank you for joining me for this discussion. We covered a lot of territory in a relatively short period of time, so thank you, and thank you for your wonderful insights and your input and having some of the fun with this back and forth. Really, I want to thank everyone for joining us for this program. These are obviously very unique times in so many ways, and really, in fact, for me, as I go to my clinic, which I will be again tomorrow, I think this program has touched on many aspects that for me still are front and center as priority to help our patients that we're so privileged to help. Get that diagnosis accurate and timely, try to be contemplative, move yourself from pre-contemplation to contemplation, think about the treatment options, inform yourself of the different profiles of efficacy, tolerability and safety. We talked a lot about long-acting injectables. There is a role. They are one component. There are many components. Patients should be made aware of the components that are available to them and combine them in a rational way. Think about some of the enablers and some of the facilitators that we talked about, always being cognizant of the barriers, and work with patients in a very collaborative care model.

Again, we have a lot to do. These are obviously very difficult times. I can't think of a more rewarding condition to treat than bipolar

disorder, and some of the tactics and some of the principles we put forward I do think increase the probability for success. So, thank you all, and I bid you all a very good evening.

Dr. Becher-Smith:
Thank you.

Dr. Goldberg:
Goodnight all.

Narrator:
You've been listening to a replay of a live broadcast about bipolar I disorder. This activity was provided by Forefront Collaborative and supported by an educational grant from Otsuka America Pharmaceutical, Inc. and Lundbeck. To receive your free CME credit or to download this activity, go to ReachMD.com/bipolartolight. This is CME on ReachMD. Be Part of the Knowledge.