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A Portrait of Bipolar I Depression: Visualizing Improved Patient Care on World Bipolar Day

Announcer:
Welcome to CME/CE on ReachMD. This activity, titled “A Portrait of Bipolar I Depression: Visualizing Improved Patient Care on World Bipolar Day” is provided in collaboration by Forefront Collaborative and AKH, Inc., and supported by an educational grant from Allergan.

This replay of a live broadcast features a panel discussing how we can improve the diagnosis and treatment of bipolar I depression. Here’s your moderator, Dr. Joseph Goldberg.

Dr. Goldberg:
Well, hello, everyone, welcome to our presentation tonight on diagnosis and treatment of bipolar depression, happy Bipolar World Day, happy National Doctor Day glad you could be here with us this evening. I’m Dr. Joe Goldberg. I’m a Clinical Professor of Psychiatry at the Icahn School of Medicine at Mt. Sinai in New York. I’m joined today by my friends and colleagues Dr. Andy Nierenberg from Mass General Hospital, hello Andy.

Dr. Nierenberg:
Glad to be here. Thanks, Joe.

Dr. Goldberg:
An honor, privilege and pleasure. And my colleague, Dr. Larry Culpepper, who’s a Professor of Family Medicine at Boston University School of Medicine. Larry, welcome.

Dr. Culpepper:
My thanks. Glad to join you guys.

Dr. Goldberg:
You’ll note that our disclosures are available to you on the event page.

Our first presentation, we’re gonna call “A Call to Action - The Need for Earlier, More Accurate Diagnosis and Improved Treatment for Bipolar 1 Disorder”. So, I’m gonna begin just with some background and context for this presentation tonight. Imagine, if you will, a lifelong medical condition that robs people of their normal life expectancy by as much as 10 to 12 years, nearly tripling the chance of premature death due to all causes, all medical causes and on the slide you have in front of you, the standardized mortality ratios across age groups for people with bipolar disorder versus the general population, you see a substantial increase multi-full higher likelihood of all causes mortality compared to the general population in people that have bipolar disorder. This is a condition that typically strikes in youth, late adolescence, young adulthood, it collides precisely with the developmental milestones that we think of for achieving our educational, our social, our financial our work independence and our identities. It’s a condition that with help organization still counts as the number 6 cause of disability in the world.

If we could have the next slide, please, I think that shows the global burden of disease study where 5 of the top 10 causes of disability in the world are psychiatric and there’s bipolar disorder right in the middle. More often than not, bipolar disorder is a condition that’s accompanied by one or more other serious psychiatric conditions. Part of what makes this illness so challenging scientifically and

clinically is, is that it's seldom presenting all by itself. We see patients with bipolar disorder and alcohol or substance use disorders and anxiety disorders and eating disorders and medical comorbidities, as well as we'll discuss in just a moment.

Imagine that the morbidity from this illness isn't just one phase, it's not just manic episodes, it's hypo-manic episodes, it's depressed phases of the illness with the downside, the depressed phase of the illness being more common and more burdensome phase with regards to both morbidity and mortality, over time. 6 to 10 years, on average goes by from the initial onset of this illness until an accurate diagnosis and an accurate treatment plan is formulated a- and quite often, this can be a complex and chronic, yet highly treatable condition. So, one of our messages of optimism tonight, is when it's accurately recognized early on, the prognosis can be among the best of any psychiatric ailment, so one of our main objectives tonight, is to talk about early recognition, early intervention.

Before this program started, you may have seen a quotation from the author James Edgar Skye who's on slide, the slide you have right in front of you, now. He's someone who lives with bipolar disorder, has written about his lived experience, he's suffered with the burden of this condition, including the depressed phase we wish to thank him for sharing his experience and keep him in mind as we think about him and other patients as we go through our presentation tonight.

So, you know, the longer we wait to recognize a medical condition, any medical condition, the harder it is usually to treat. The prognosis becomes affected by durations of untreated

illness. That's true with cancer, it's true in infections disease, it's true in heart disease, it's true in just about all forms of serious mental illnesses. And so, the duration of untreated illness becomes its own important parameter. If that duration is as little as two years, we see suicide rates can become extremely elevated I think the next slide here, you can see this percentage of suicide attempts stratified by even just a two year delay from symptom onset 'til actual intervention, people with bipolar disorders have a substantially increased risk for suicide attempts or completion, especially during the depressed phase. So, you know, part of the challenge here is distinguishing unipolar from bipolar disorder, we'll talk about that, tonight to, to, to identify someone as having bipolar illness, you have to have had at least one lifetime mania or a hypomania. But again, the depressions are often dominant, and that's part of what makes the diagnostic challenge so difficult. Sometimes the patients doesn't advertise the history of a mania or a hypomania, they just present with depression, and so our task, as you'll have to, sort of, ferret through the history. This is why screening becomes so critical to minimize duration of untreated illness, to maximize the success rates by using appropriate treatments, also minimize some of the, the medical complications, people with bipolar disorder tend to be overrepresented with metabolic syndrome with hypertension, cardiovascular disease, smoking, sedentary lifestyles, and you know, when you think about it, if we can make effective interventions in their mental health, we might actually help them live longer and live better lives.

It's much easier to treat a first episode of any ailment than the umpteenth episode, whether that's a heart attack or epilepsy or bipolar disorder, so you wanna give great thought to the importance of early intervention, makes the outcomes far, far more favorable. This means, not just asking patients themselves about their histories and taking a longitudinal perspective, but also getting collateral historians to corroborate information. I always like to teach that it is worth the investment of time and energy to do a very thorough initial evaluation.

We start with screening, we'll talk about that more, tonight, but screening is, sort of, a gateway entry to identifying patients that are at risk for bipolar disorder. We'll be talking about some of the telltale signs, like early age at onset, or a family history, or highly recurrent brief depressions that come and go and come and go or not such great responses to antidepressants. These are some of the clues that tip us off of thinking someone with depression may actually not have unipolar disorder.

So, we're gonna be going through some cases tonight and a lot of questions and answers and for our next segment, I'm gonna turn things over to Dr. Culpepper.

Dr. Culpepper:
Why, thanks, Joe. And, we do have three cases. We're gonna, we actually, our viewers are gonna select one of the cases and we will follow that case through both segments of this evening. So, first, we'll discuss the diagnostic assessment of the patient recognizing diagnosing of the patient and then the second half of the evening we'll focus on treatment of the same patient.

So, it's a polling question and we have the three cases: Sam, who's a 27-year-old referred for psychiatric evaluation after threatening to knock the lights off of a colleagues; Anna, who's a 20-year-old patient referred by her parents for failure to thrive and C, David, who's a 50-year-old who's urged by his wife to seek help because of mood swings.

So, let's go to the, the poll thing, A) is Sam, he's you know, in for knocking the lights off, or almost knocking the lights off of a colleague, Anna, who's just not doing well according to her parents and David, whose wife wants him fixed wants help because of his mood swings, so which case do you want us to pursue this evening?

Dr. Goldberg:
And you'll be able to review-

Dr. Culpepper:
Unintelligible

Dr. Goldberg:
-all these cases yourselves.

Dr. Culpepper:
Aaahhh. Yeah.

Dr. Goldberg:
We have all these cases, so you'll be able to download the PDFs but we're gonna pick one tonight-

Dr. Culpepper:
Uh, oh.

Dr. Goldberg:
A tie.

Dr. Culpepper:
Aaahhh.

Dr. Goldberg:
Are all the votes in?

Dr. Culpepper:
Sam's pulling ahead.

Dr. Nierenberg:
Sam's pulling ahead.

Dr. Goldberg:
Alright. It's looking like Sam.

Dr. Culpepper:
Alright.

Dr. Goldberg:
Knocking out lights.

Dr. Culpepper:
OK. So, we're gonna move on to Sam. And Sam let me give you more information about Sam. He's a 24-year- 27-year-old, he's a single, aspiring actor. He was raised by his divorced mother along with his fraternal twin. He's had low grade depression and social phobias since childhood. He binge drinks before auditions and acting jobs or first dates, yeah, whenever he's under pressure and unfortunately it has become a sloppy drunk with predictable bad results. He's had supportive psychotherapy. He's had trials of SSRIs and NSRIs that have been quite adequate he's had benzodiazepine without benefit. He's had therapy and his therapy his therapist says his dramatic irritable outbursts are just his diva personality traits along with maybe his drinking. He was referred by his union manager for psychiatric evaluation after threatening to knock the lights out of a lighting technician. A little poetic justice, I guess. For making too much noise. Little bit more history

Dr. Goldberg:
A question.

Dr. Culpepper:
Yeah we have more history coming but all the following would help to corroborate a possible diagnosis of bipolar disorder, except which of the following? And again, this is a polling question: history of either bipolar disorder or panic disorder in his fraternal twin B) the presence of an alcoholic use disorder as a free-standing condition, C) a personal history of a suicide attempt, D) a personal history of a psychotic depression. So, which of these would help would not help colap- corroborate the possible diagnosis of bipolar disorder? Which one's not really supportive really doesn't help you with it?

Dr. Nierenberg:
Well, it's shifting a bit, huh?

Dr. Culpepper:
Yeah. Well, it seems like it-

Dr. Nierenberg:
Well, it's neck and neck with A and B, but it looks like D is still ahead.

Dr. Culpepper:
Yep.

Dr. Goldberg:
So, I get to review what we believe is true here? I hate to say it but the, the correct answer is actually B. Presence of an alcohol use disorder as a free-standing condition wouldn't in itself be so helpful as would the other items in differentiating bipolar disorder. So, a fraternal twin, be great to have a clone, right? Same DNA, although even there, it's not 100% concordance, but it's pretty high, 65 to 80%, fraternal twin, first degree relative, you still got pretty good data, maybe 10 to 25% informative about, about the genetics of this disorder. Suicide attempts, unfortunately can run in bipolar families and so that's, that's informative. And psychotic depressions, actually, tend to be a little more commonly seen in people that are risk for bipolar disorders, so while none of these is a clincher, they're all clues in the story and those three would stand out. Alcohol is certainly relevant, but it's not as directly informative.

Dr. Culpepper:
OK. So, let me give you a little bit more history. Got a consulting psychiatrist involved because of the referral and he or she contacted Sam's current psychiatrist to get more information. When the consultant asked about past symptoms, either of psychosis or of mania, hypomania, Sam's current psychiatrist interjected that Sam did not have bipolar disorder because when he administered the MDQ, or the Mood Disorder Questionnaire, the score was only 5.

So, another polling question: which of the following statements is true? So, that's not accepted. Which is true about making a diagnosis of bipolar disorder? Option A) is Sam's MDQ score below 7 means that he does not have bipolar disorder B) epidemiologic studies report prevalence rate for comorbid alcohol use disorder up to 90% of individuals with bipolar disorder, C) the MDQ may be a lesser level instrument, and patients with mood disorders with active alcohol or substance abuse disorders and D) it is not necessary to have a history of mania or hypomania to make a diagnosis of bipolar 1 or bipolar 2 depression. So, which of the following statements is true? Three of them aren't, which one does stand out as helping you make a diagnosis of bipolar disorder? And looks like, so far, we've got C.

Dr. Nierenberg:
Yep

Dr. Culpepper:
And that looks right to me.

Dr. Nierenberg:
That looks right to me, also.

Dr. Goldberg:
Yeah. If we can leave that up for just a sec, let's just briefly talk about these. So, what's the Mood Disorders Questionnaire? The MDQ is one of the screening tools that's been validated as a screen not a proxy for the diagnosis, but a screen, just like, well any other screen in medicine PICC screening test, doing a Sed Rate, doing a, a, a Pap Smear, it's informative, you want to screen in as many patients, you don't want to miss anybody but then you have to cone down deeper. So, somebody's scores above a 7 on the MDQ doesn't mean they have bipolar disorder, but it means that it's very likely they might. They score below it, it doesn't guarantee they don't, it just means it's less likely that they would. Alcohol use, as I said a little bit earlier, certainly is common in people with bipolars or it's not 9 out of 10, thought, it's a little bit on the high side, so it's not quite that high. Studies would say maybe 60% be the national comorbidity survey went up as high as 70%, thereabout, so it's not quite as high as that.

So Mood Disorder Questionnaire, is less reliable if there's active alcohol or substance use. Doesn't mean you can't use it, but it just means that it's awfully tough to differentiate somebody whose mood symptoms may conflict with active use. You have to go back in time and find a period where they were not contaminating their mood with alcohol or substances and about half the time that's tough to do and item D. So, yeah, if nothing else, for tonight, please leave here knowing that to call someone bipolar disorder, they have to have had at least one mania or hypomania, that's a necessary criteria and for membership in the bipolar club.

Dr. Nierenberg:

And, and those episodes of mania, hypomania, it's very helpful if they're unequivocal and if you have an informant who helped you to be able to define that.

Dr. Culpepper:
Yeah, so next question: we really have a number of screening tools, the MDQ, you've mentioned, the rapid mood screener, 6 questions much newer but as good as MDQ and two other longer instruments, so he what are limitations of these?

Dr. Nierenberg:
So, part of the limitations has to do with their positive predictive value and negative predictive value and particularly with the MDQ, it really picks up many more false positives than would be useful. But as Joe said, earlier, it's really very helpful to have something that at least prompts you to think about it and then go back to the history and see if somebody not only had the symptoms of mania or hypomania, but they happened at the same time. So you really want to, you want that to be able to have a network a crystal, if you will, of how all of those symptoms are related. So, it's, it's not a definitive test but it is a test that can help you look into the past history.

Dr. Goldberg:
This is where the dialogue with Sam's consulting psychiatrist gets a little spicy because if they consultant comes in and says, "Well, he can't have bipolar disorder because he didn't screen positive for it", we have to say, "You know, it's a screen, it doesn't completely negate the possibility", although it is true, the negative predictive value of these screens is pretty good. That means if you do score below the threshold, a fairly high chance you don't have the ailment, but if you score positive, it doesn't mean you do. But it means that, like you're saying, it's an ant- it's an entry point, it really guides your interview to, to pin down some of these criteria, clarify them longitudinally and get corroboration from a, from a third party, collateral historian.

Dr. Culpepper:
Yeah, I find you know, if both the patient and say, a spouse or a, a parent answers them in the queue with a low score I have a lot more confidence than if just the patient who may just not recognize, you know, the extremes of his own behavior.

Dr. Goldberg:
You give out these scales to a patient and then you go over it with the patients. The other things is we, we published a study saying, you know, fill, have the patient fill it out and don't' just put it in the chart, go over it with them (laughter) and make sure you understood what the questions mean. And when you use these scales as a semi-structured interview, the reliability is enormously high. We, we published data with, with sensitivity and specificity over 90% after you use it to affirm that when the scales says "racing thoughts" the patient didn't mean anxious ruminations of when you say "flight of ideas" it didn't mean anxiety, so it's very helpful to guide the interview.

Dr. Nierenberg:
And also, I sorry, I like to ask people if they say they have racing thoughts, say that if I was able to hear your thoughts, what would I hear? And have them try to recreate it, if they don't have it at the moment.

Dr. Culpepper:
Yeah. Yeah, for us in primary care, it, it also is these questionnaires, a lot of times, also really are some are __ (0:21:30.6) to identify things that we can explore further in our interview. And particularly when we have, you know say a patient and a spouse and they're very divergent that itself can often help us open up conversation that can be quite helpful to you know, the families.

Dr. Goldberg :
I think we have-

Dr. Culpepper:
Let's move on-

Dr. Goldberg:
-a question.

Dr. Culpepper:
Yeah.

Dr. Goldberg:
Speaking of questions. On our next slide.

Dr. Culpepper :
Yeah. (laughter). So, the consultant psychiatrist differential included bipolar 1 disorder in the depressive phase, possible with some mixed features are major depressive disorder with mixed features. So, the key point of differentiation between these two DSM-5

diagnoses is which of the following? So, these again are the polling questions: A) agitation and sleep disruption occurring bipolar depression but not major depression with mixed features, unipolar.

So, patients with unipolar major depression have never met the DSM-5 criteria for a hypomanic episode C) option is irritability is a unique to the mood disturbances in bipolar disorder but is not part of unipolar depression with mixed features, or D) in a patient with mixed features, irritability, distractibility and agitation are symptoms that can double count towards simultaneously defining both manic and hypomanic and depressive episodes.

So, let's see what people are thinking.

Dr. Goldberg:
They're going back and forth.

Dr. Culpepper:
Yeah.

Dr. Goldberg:
Looks like it's a split decision.

Dr. Culpepper:
Yeah. A and D, are coming up strong, but,

Dr. Goldberg:
Yep.

Dr. Culpepper:
D is pulling ahead a little.

Dr. Goldberg:
Maybe here's a good chance for us to say what MDD-MF even is 'cause some of our re- our attendees may not have even heard of this concept of major depression with mixed features. Andy, can you concisely tell us what is MDD-MF?

Dr. Nierenberg:
So, so major depressive disorder with mixed features is having some of the features of mania and hypomania but falls short of the diagnostic criteria. So, just a few of those.

Dr. Goldberg:
So, that would be like answer B, huh?

Dr. Nierenberg:
That would be like answer B (laughter).

Dr. Goldberg:
Yeah, and so it was really the DSM-5's effort to move our thinking toward a spectrum and the idea that you don't necessarily have just mania and just depression but that there are observations a lot of people who are manic and have even low-grade, mixed elements with the downside but more interestingly, there are patients who've never had a full mania or hypomania, but syndromal depression and as you say they may have some of the elements of the opposite pole. Now, the interesting question, is "What do they grow up to be?". If you follow them out, do many of them go on to have a course suggestive of bipolar disorder? Studies don't really give us definitive answers to that. Some studies may say 20% over 5 years may go on to qualify for the full syndromal conversion, but these are people that go on our, our watch lists.

Dr. Culpepper:
Yeah, so we really have a, you know, on the next slide a disagreement here. The consultants-

Dr. Goldberg:
That never happens in psychiatry (laughter).

(collective laughter)

Dr. Culpepper:
-consulting psychiatrist says bipolar 1 Sam's current psychiatrist says no, it's treatment resistant major depression, plus some anger management issues rather than the bipolar 1. So, how are you gonna resolve that?, Andy, what would you do next?

Dr. Nierenberg:
So, what I would do is go into dept both with the patient and their informant about the times that they might have had at least some of the symptoms of mania or hypomania and again make sure that they had the symptoms at the same time. Right, so that if it turned out that every once in a while he got angry and was irritable, but had no other symptoms of mania or hypomania, it would be, that would be against the diagnosis. But if he had a decreased need for sleep, along with the irritability and racing thoughts, and grandiosity, that was different than his usual self, then it would be more consistent with the diagnosis.

Dr. Goldberg:
Yeah, I'll, I'll second that. I want to remind our attendees that we have our polling questions open and our Q&A open so please submit your questions as you're hearing about these cases. Now, it's I think when Sam threatened to punch the lights out of the lighting technician, if I was interviewing Sam, I would want to know what was happening prior to that: did he not sleep the night before, has he been sleep-deprived? Actors have a high-risk profession, they have shoots overnight, is there any substances in the picture, I mean, you want context for these things. If Sam looks back and said, "I can't believe I said that, my mouth opened, the words came out with no filter", and there's a sense of impulsivity that's inconsistent with who Sam is, that, that's a little more comforting about the diagnosis than if Sam just says, "Well, he deserved it", and it, it wasn't impulsive, it was more of a deliberate kind of things, so you a- you almost want to get his perspective. It's almost like people that overspend when they're manic and you, you say, "Well, did you really need to buy 10 houses?" and if they say "Yes" (laughter), you wonder, as opposed to pe-, you know, buyer's regret, you say, "I can't believe I did that. Where was my thinking" because there's this notion of just loss of perspective when you're in the throes of a mania or a hypermania.

Alright, so I think with this, speaking of questions, we are up to our questioning. And let's see, a couple of questions and I'm just gonna, for the sake of time, give us one or two. So when we talked about screening before, we mentioned a Mood Disorders Questionnaire and someone's asking is other screening tool that's a little newer called the Rapid Moods Screener. This is a 6-item, it's like 6 minute, 6 item questionnaire that was, I think, just recently published this year by RS McIntyre that, that's nicely validated, it's a little faster, more streamlined, it's key to some of the core elements like racing thoughts that, that it helps to differentiate unipolar from bipolar disorder. If you score at least 4 items on this 6-point scale, it's got a pretty good predictive value of bipolar disorder, so whereas the Mood Disorders Questionnaire has about 13 items on it, you gotta score a 7 or higher, this is a little bit quicker you know, they're all, sort of, going after the DSM symptoms. And again, our job is to assure that patients are describing this as a constellation, not like Sam was angry on Thursday but then sleep deprived two weeks later but that these things fall together. So, we take these screens, and we use them to really guide our interview to try to come up with a rationale for the diagnosis.

Dr. Nierenberg:
I agree.

Dr. Culpepper:
Yeah, I mean they, they're sensitive in specificity are virtually the same for the MDQ and the, and the rapid screener. I find I still consider both useful. The Mood Disorder Questionnaire gives me a lot more items to go back and ask the patient more background.

Dr. Goldberg:
Mmmhmm.

Dr. Culpepper:
So, it really depends on how you use the screener in your practice with these patients. I think the one thing I would say is if you do pew-PHQ-9 and it's positive, you gotta go onto one of these. You know, you don't stop there. You've gotta go onto then think about bipolar.

Dr. Goldberg:
Mmmhmm. And indeed, every patient with syndromal depression, really needs to be screened for a history of mania or hypomania. One nice thing about these screening tools is they're self-administered, at least the Mood Disorders, actually they're both self-administered screens, so a patient can fill this ou tin the waiting room, bring it in, "Hello, Mr. Nierenberg, it's nice to meet you. Why don't you-OK I see what we're gonna be talking about for the next few minutes", so it really can help, you know, move things along. I, I find measurement-based care really helpful, especially when time is limited and we want to know what, where to, sort of, hone in and zero in and if patients scores zero on everything, we can move on to talk about other things. So-

Dr. Culpepper:
Yeah, and how to do it at the beginning of every episode, or every new episode of depression, really deserves if you've not diagnosed bipolar before, you've still gotta look at it further.

Dr. Goldberg:
Excellent point, Larry, a lot of things can happen over time and just because somebody may have not ever had a mania by age 21, they

come back 10 years later, and they're depressed, a lot of baseball gets played in the middle, so you want to be co- conscious of that.

Alright, so I think we're gonna move on at this point to our next segment. We're gonna hear now from Dr. Nierenberg on an overview of treatments recommended for bipolar 1 depression. Take it away, Andy.

Dr. Nierenberg:
Great, thanks, Joe. Next slide, please.

One of the things about bipolar depression is that there are only 4 FDA approved treatments. There's the olanzapine/fluoxetine combination, quetiapine, lurasidone, and cariprazine, so these are the big 4 currently approved by the FDA. It's quite remarkable that there are only 4 medications approved, but one of the things that, that I'll say again and again, you will see there's no antidepressant on this list, except fluoxetine in combination with olanzapine, otherwise, there's no monotherapy antidepressant and there's no current antidepressant that it approved alone for bipolar depression.

Next, please.

Let's go through each one of these, look at the data, they will all converge in that you'll see that there's a pattern that about 50% respond to the olanzapine/fluoxetine combination and you'll see around 50% in each of the following slides. What you will see is a difference in the placebo response rates and that's why you can't quite really directly compare these and none of these 4 have compared to, have compared to each other, at all, which is also quite remarkable. So, we can't currently just say "this medication is better for this type of treatment", but they do differentiate in terms of side effects, and we'll tell you about that, in a minute.

Next, please.

In terms of its use olanzapine/fluoxetine adjunctive with lithium or valproate and the big limitation, the big limitation is metabolic syndrome, it makes people very big and that is a problem with weight gain. What I want you to notice is the discontinuation rates on the right and the discontinuation rates with placebos is over 61%, keep that in mind and we'll compare that to the others as we go through this.

Next, please.

Then we have quetiapine, and you notice, again, it's about 50% response rates, whether you're giving 300 or 600. Now, one of the things that's, the, important to note, this does not tell you if you don't respond to 300, will you then respond to a higher dose at 600? We don't quite know that. This does not answer that question. But what it does show is that you will get more side effects with the 600, that we know when there's a direct head-to-head comparison.

Next, please.

So, it's approved for acute treatment of depressive episodes, also for maintenance and that's important the other side effects are, sort of, the usual side effects that you'll see with these, but also risk of metabolic syndrome makes people big, they don't like that. Placebo discontinuation rates about 40% or so and again, you can see why you can't quite compare them if the placebo rates are, are discontinuation, the discontinuation rates are so different.

Next, please.

Then we have lurasidone, look at that, it's again about 50% low dose range, 20 to 60, higher dose range, 80 to 120, doesn't tell you if you don't respond to the low dose, will you do better at the higher dose but again it's all around 50% or so.

Next, please.

Now, this is very important because in order to absorb it, gotta eat 350 calories. It approved adjunctive with lithium or valproate and here the side effects are quite different than what you've heard thus far. Here is can be activating with akathisia and extrapyramidal symptoms or it can actually cause somnolence. I think on average, and I would ask Joe and, and Larry to comment on it, it's about a third, a third, a third. One third won't have it, one third will get agitated, one third will get somnolent about that and then some GI side effects. But look at that placebo discontinuation rate, it's almost 10 times less than what was seen in the olanzapine/fluoxetine. That's why it's very hard to directly compare these.

Next, please.

And then you have the last one that has come on the market, which is cariprazine, about 50% whether you use the lower dose or the higher dose. There's another study that showed that the higher dose did not separate from placebo. So, here it's a little unclear if more is better. And it's unclear if you target 1.5 or try to target 3.0, also doesn't answer the question, "if you don't respond to 1.5, do you go up

to 3.0?", that is actually unknown.

Next, please.

It's approved as monotherapy and side effects, again, it can get agitated or you can have somnolence. I don't know if we have a good feel, yet, for the proportion who get agitated or, or somnolent. My guess, it's about again the third, third, third, maybe actually true. But look at that placebo discontinuation rate, it's tiny. It's on 2.5%. again, this is just a caution that you can't quite directly compare these and they haven't been directly compared.

Next, please.

This is a very nice summary that was put together by Les Citrome to try to put it all together, so in response around 50% for all of them weight gain, big for olanzapine, right, big weight gain, olanzapine/fluoxetine. With quetiapine, it also occurs but maybe not as frequently but the burden with quetiapine is sedation. Right, less so with olanzapine/fluoxetine but certainly less with lurasidone and cariprazine. So, this gives you some sense of how to indirectly compare them.

Next, please.

Now, the Canadian guidelines, which are considered among the best, but now they're three years old, so they probably have to get revised soon, and the internation Society of Bipolar Disorder Guidelines have these treatments these treatment recommendations and if you look at it, you glance at it, you'll see there's quetiapine and lurasidone and a secondary treatments were actually even cariprazine I don't, I that might be revised with with better data recently with maintenance you'll also see quetiapine and then you'll see lithium rise up. Lithium may be better for maintenance to prevent mania, and lamotrigine may be better to prevent depression.

Next, please.

And, the treatments that are clearly not recommended right, these are negative studies, include aripiprazole monotherapy, which is surprising because it is approved for the treatment of treatment-resistant depression, unipolar, ziprasidone, lamotrigine plus folic acid, although we can argue about that and a couple of other things. But what's really important is that antidepressant monotherapy, right, is not recommended and you may hear us say that again and again, it's just not (laughter) recommended, OK? These are also it's such a low probability that it's gonna help it makes sense to really think carefully before you turn to antidepressant monotherapy.

Next, please.

So, here are a couple of questions for you, about this, right? One, what is the one reason antidepressant monotherapy is not recommended for bipolar 1 depression? One is that it can trigger manic episodes and rapid cycling, it can trigger a depressive episode B), it can worsen a depressive episode C), in bipolar disorder, or antidepressant monotherapy can worsen anxiety D). Alright, so vote your conscious, vote frequently, let's see what you see. So, A) it's gonna cause manic episodes and rapid cycling, B) contribute to a depressive episode, C) antidepressant monotherapy can worsen or D) it can worsen anxiety. Let's see if we're able to get the results, here. We had a technical problem of getting that. Alright, so you're texting "REACHMD" to 22333 and you go A, B, C, or D. Looks like we're not getting through it, here and if we're not-

Dr. Goldberg:
Maybe the audience realized this is a complicated question-

Dr. Nierenberg:
This is a complicated question, that's right, so, so really the answer is A. Right, that, there's an increased risk that it can trigger a manic episode and rapid cycling, but also, as I said before, there's the risk that it can not work which is a probability and that's pretty much the problem.

Dr. Goldberg:
I would just like to underscore the last part when Dr. Nierenberg and I have had friendly debates on this topic before about the perils of antidepressants. Many clinicians presume that the main peril is, is answer A that can they trigger manic episodes or rapid cycling and as Andy quickly glossed over in his comment, that is a risk, but it's not a huge risk. The studies would say, maybe 12 to 18% or so of bipolar patients may have in the short run an aceeler- an induction of mania. Longer term, a little more data saying you may get more episodes over time but the even bigger risk with monotherapy is that no one's ever shown that antidepressants work so when someone asks you 'what's the biggest risk with an antidepressant' you know, it's somewhat of a risk that it can induce mania or rapid cycling. They haven't been shown to cause suicidality, there is not a database I'm aware of that says antidepressants will make bipolar patients more suicidal but really the biggest concern is it's got a very large number needed to treat. You have to give a lot of people an antidepressant before you see a benefit. So, the biggest risk is they don't work.

Dr. Nierenberg:
And I, I think also there's a big myth that somehow bupropion has a special status in working for bipolar depression. It turns out not to be true.

Dr. Goldberg:
Mythbusters.

Dr. Nierenberg:
Right.

Dr. Goldberg:
Right, so we move onto our next segment.

Dr. Nierenberg:
Alright, so, there are some treatments under investigation and out of these lumateperone is on the path to get approved while all these others maybe ketamine may or may not ever get approved for it or s-ketamine but certainly there's a lot of data to suggest it can work in the short term and long term. There's much less data for pramipexol modafinil, armodafinil and thyroid.

Next, please.

So, now we've gotta deal with treating Sam. And we've start out with a disagreement. Sam's current psychiatrist thinks he has treatment-resistant major depression plus anger management issues, not bipolar disorder. And he proposes a trial of olanzapine/fluoxetine combination saying it'll cover both bases. While the consulting psychiatrists says, well yeah, OFC would be reasonable for treatment resistant depression but it's metabolic baggage is huge and the liability from you know, for Sam from the metabolic consequences particularly over a longer term outweighs possible benefits. So, he instead suggests treating bipolar depression with you know, a treatment that's got a, a lower metabolic risk. So, next polling question: all of the following, evidence-based treatments for bipolar depression are associated with relative low weight gain during long-term clinical trials, except A) quetiapine, B) lamotrigine, C) lurasidone, or D) cariprazine. So, which of those does cause some weight gain? All of the following are associated with a little weight gain during long term trials, except which? Quetiapine, lamotrigine, lurasidone, cariprazine.

Dr. Goldberg:
Well, looks like we're having another technological glitch, so let's give 'em the answer, which is, A; A causes weight gain. Quetiapine is associated with weight gain and metabolic syndrome a little less than OFC, but it is associated with it.

Dr. Nierenberg:
Yep. And so, let's let's keep going. So, Sam did begin treatment with lurasidone, 40 mg a day and he did initially show some improved mood. But within a few months, he began drinking again, binging and became increasingly depressed. He reports that he cannot concentrate and thinks that he really has attention deficit disorder and would like to try taking a stimulant. You're skeptical about ADD and don't think a stimulant would help. He indicates that he is taking his meds, so he is adherent he's also in psychotherapy and he's attending AA meetings, so he's, he's trying he's pulling his part of the bargain, here. So, you're concerned about both his increased alcohol use and his worsening depression. And previously, Sam's dose of lurasidone was increased to 60 mg a day but he did encounter sedation and akathisia without really you know, any mood benefit. So, next question is the next polling, and we'll see if our tech works. Which of the following would be an evidence based next step in his treatment? A) discontinue the lurasidone and try an SSRI that he has not taken previously, B) switch from lurasidone to topiramate, C) insist that he retry a higher dose of lurasidone, or D) augment the lurasidone with divalproex? So-

Dr. Culpepper:
Well, it looks like we're getting answers, huh?

Dr. Nierenberg:
Yeah.

Dr. Culpepper:
Yeah.

Dr. Nierenberg:
We're getting answers.

Dr. Culpepper:
Interesting.

Dr. Nierenberg:
Yeah, Joe, what's,

Dr. Goldberg:
Yeah, so, so, you've, evidence-based would argue that an augmentation of lurasidone with divalproex might get you a little more bang for your buck, since the data with lurasidone both for monotherapy and augmentation and while there wasn't the head-to-head comparison of combo with mono, you know, it, it's an evidence-based combination. Going higher on the lurasidone dose doesn't really have an evidence-base. In fact, interestingly in the, in the flexible dose studies that were, that were done, se- seldom was the effective dose a whole bunch higher than the starting out dose. so, we don't really know if there's a clear dose relationship, at least for depression purposes with lurasidone. Adding topiramate. Nah. Topiramate has, has no data in bipolar disorder. There were five negative randomized trials in acute mania and no data in bipolar depression. It's got other properties of interest, it may help Sam lose weight, it may help, may help with is alcohol, there's some nice off-label data using topiramate as a, as an anti-craving drug, so it may actually have value for his alcohol, but it's not gonna do much for his mood. And try an SSRI that hasn't been taken, well, you know, we go back to the debate with the consulting psychiatrist (laughter) who sounds like he wants Sam to take another SSRI, is just, you know, we got this storyline and narrative going that, that Sam hasn't gotten better with antidepressants and there's enough data here to make us wonder about bipolar depression, so if Sam hasn't quite hit it off with lurasidone, one might think about a divalproex augmentation or one of the other evidence based bipolar depression treatments that Dr. Nierenberg has been telling us about.

Dr. Nierenberg:
Joe, would you also consider adding lithium instead of divalproex?

Dr. Goldberg:
Yes, so we, we can't have everything on the slide, but the, the database for lurasidone did identify the well-taken point augmentation of lurasidone with either divalproex or lithium and the think about lithium as a gold-standard drug and if Sam's early in his clinical career, lithium may work better before many episodes have gone by in time. One of our themes tonight is early recognition and lithium is a drug that may work especially well early on by the time you've got a bazillion episodes, the horse is long gone out of the barn. So, for sure, I'd think about lithium.

Dr. Culpepper:
Joe, Andy, with, with patients like this where you're, you know, you you're doing your best with them and obviously it's gonna be a little bit of a trial and error getting to the right medication for this patient, how long do you go, usually between making a shift, you know, assuming the patients, you know, in, you know, not decompensating how long do you go before you make another change? I mean, in depression we say, you know, a couple, up to three weeks for bipolar depression how long is a good enough sort of, interim trial study?

Dr. Nierenberg:
Well, I think it depends on the slope. It depends on whether they are gradually getting better and you're seeing some improvement or if they're, sort of, flat-lining with no improvement whatsoever. As every week goes by with no improvement whatsoever, I get increasingly nervous, and increasingly concerned. So, if you see zero, I mean, really zero improvement in three weeks, I'd really start to get worried. If there was some improvement in that time, then I would persist a little bit longer, but it's important to note that most of the studies were done at six weeks. No longer than eight weeks.

Dr. Goldberg:
And here's a little tidbit. There is some research to say, like, two weeks you'd like to see a noticeable effect or if you're using a rating scale at least a 20% improvement so if you're giving a patient, pick your favorite rating scale, PHQ's not really meant to be tract changes over time, people still use it but, you know, if you're a researcher using a, a MADRS or a QIDS or you could give a patient a Beck, but you can also just give them a visual analogue scale and rate your depression but some metric, you know, you wouldn't look at a blood pressure patient and say, "Are you feeling less hypertensive now?" (laughter). So, you'd like to see movement after two weeks and if you haven't seen anything at all, you ought to do something; you either change the dose, you augment, you can say I, you, you've had a noticeable improvement in two weeks you're on the right track, so slow and steady wins the race.

Dr. Nierenberg:
Yeah, agreed.

Dr. Goldberg:
So, excellent, it think we will turn to some questions now. We've got a few questions here. Why are antidepressants recommended for adjunctive use and not as monotherapies in bipolar depression? Dr. Nierenberg, you wanna comment on this?

Dr. Nierenberg:

So, it's only, only the combination (laughter) of olanzapine and fluoxetine that's it. I think we tend to reason, 'oh, OK, if it's olanzapine and fluoxetine can't it be some other antipsychotic and some other antidepressant?' not really that hasn't either been tested or shown to be particularly negative, when olanzapine/fluoxetine first came out. The company looked at some other combinations and they just didn't work as well. So, it's really important to know the only antidepressant that's been approved is in combination with olanzapine and that antidepressant is fluoxetine. No other antidepressant has ever shown efficacy.

Dr. Culpepper:
I think well a lot of times we think, 'well, gee, you know, augmentation you know, we had the STAR*D trial, it works you know, in unipolar depression, why not bipolar?', and I, I think the key there is recognizing that brains are different yeah and what's going on at the, the synapse yeah and you know, some of the neurochemistry of a bipolar affected brain, you know, is different and so you can't just use what, you know, about mono- unipolar depression in bipolar depression. It doesn't translate well.

Dr. Goldberg:
Yeah, I think it's also nice to be able to, to fall back on a database. You know, twenty years, thirty years ago, we didn't have a database. It was, it was much more prescribing-based evidence rather than evidence-based prescribing. Now we have clinical trials. We know that there are not class effects across all the second generation antipsychotics, just like there are not class effects across all anticonvulsants. So, some agents have very specific niche roles as we're talking about lamotrigine's niche role is more in the depressed phase, especially for stalling the depressed phase, not so much on the high side, lithium, as Andy alluded to is more on the management of the high side than the low side. Some of the SGAs are useful-

Dr. Culpepper :
Second-generation anti-psychotics-

Dr. Goldberg:
-sorry, than the typical antipsychotics. So, quetiapine, lurasidone, cariprazine have value on the depressed side. Other agents have not been shown to. Loraz- lumateperone, which Dr. Nierenberg mentioned is on the horizon has its two positive studies in bipolar depression. It's in front of the FDA now, so one of our questions was about what's in the pipeline and being looked at? It's always nice to tell patients there's a pipeline, and that things are coming along. It helps inspire optimism and the data with lumateperone, which is a very interesting compound, it's a very strong 5-HT2A antagonist, much, much more so than the D2 receptors, so might be a, kind of, a nice thing for patients that are especially sensitive to the striatal motor adverse effects of antipsychotic drugs. But what's really cool about the lumateperone data is it worked really well, not just in bipolar 1 depression, but even better in bipolar 2 depression, and while our discussion tonight is really on bipolar 1 depression, maybe we'll come back next time and we'll talk about bipolar 2 because only clotiapine has some data and now lumateperone will, so that broadens the breadth of spectrum and gives us more to hope for.

Dr. Nierenberg:
Yeah, and, and Joe I think it, Joe and Larry, I think it's important to point out that the most common treatment that people give is an antidepressant plus an antipsychotic other than OFC. So, we really, really don't know if that helps but we do know it's common and at the very least, people should rethink that.

Dr. Goldberg:
Yeah, there was that American Journal paper last year that talked about the up use of antidepressants as monotherapies and so here's an instance where clinical practice is divergent with (laughter) the evidence-based it's really orthogonal (laughter), so, the more that people are aware of the evidence-based, I think the more we'll be able to make informed decisions.

Dr. Culpepper:
Yeah, and, and I just you know, reiterate I think in, in primary care, we often say, 'oh I'm worried about metabolic so I'm gonna use aripiprazole, I know it's gonna be a, a little risk for metabolic, but we don't have a good database for aripiprazole in terms of demonstrating efficacy in bipolar disorder.

Dr. Goldberg:
In fact, we have a pretty bad database for-

Dr. Culpepper:
Yeah.

Dr. Goldberg :
A few negative randomized trials. So, imagine telling your patient, well I'm gonna give you something that might have some metabolic value but it's never been shown to work for your potentially lethal ailment. Here you go. So, we really gotta take all the pieces and put them, put them together.

This has been a wonderful discussion. I wish it could go on longer, but sadly we must wrap up. So, if I can ask us to move to our summary slides, bipolar depression is a greater burden source of morbidity and mortality for patients with bipolar 1 disorder as compared to the manic side. The manic side isn't nothing, but much of this complexity and chronicity that we talk about comes from the southern hemisphere of the illness. Early recognition, proper intervention, critical, critical, so for stalling progression, to educating patients to getting them partnering in their own treatment so we can avoid misdiagnoses and possibly even for stall some of the complications of the illness.

And do we have a next slide?

What can we do to improve diagnosis? Screen. Screen. Screen. Screen. Screen. Every, every depressed patient at every episode it's a, it's a fluid mosaic over the course of time. Be very mindful of the risk windows, young adulthood, patients with a family history, early age at onset of first depression highly recurrent brief depressions that come and go and come and go, psychosis during depression, non-response to anti-depressants, plate-detected, build a story, think about these screening tools and their pros and cons as Andy and other, we described, these are screens, so use them, give them out, go over them with your patients, go over them again with your patients, give them to the family members so you're, you're getting all the convergent data you possibly can, be aware of the 4 FDA-approved treatments for bipolar 1 depression that it's olanzapine/fluoxetine combination, quetiapine, lurasidone and cariprazine and we've talked about some of these more investigational treatments and be aware of guideline-based recommendations for bipolar 1 depression, although as Andy has said guidelines come and go, so we have to stay abreast of things.

And, with that, I'm gonna, I'm gonna wind us up and round, round us out. Wind us up- thank you all for joining. I hope this has been a helpful presentation for you it's been certainly an engaging one for me. I want to thank my friends and collogues, Andy Nierenberg and Larry Culpepper for, for keeping things very lively and moving and thought-provoking throughout our presentation.

Thank you all for joining our broadcast tonight focusing on bipolar 1 depression. You will receive an email shortly with more information about how to get your post-test evaluation and claim your free CME or continuing education credits. Thank you for your participation. We hope you have a great night. Stay safe.

Announcer:
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