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# Mixed Signals on Mixed Features: Clearing up Confusion in Patients with Major Depressive Disorder

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Welcome to CME on ReachMD. This activity entitled Mixed Signals and Mixed Features, clearly up confusion in patients with Major Depressive Disorder is provided by the University of Florida College of Medicine and Novice Medical Education, and is supported by an independent educational grant from Otsuka America Pharmaceutical Inc.

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Dr. McIntyre:
Welcome to this CME Webcast titled Mixed Signals and Mixed Features, clearing up confusion in patients with Major Depressive Disorder. I am Roger McIntyre, Professor of Psychiatry and Pharmacology at the University of Toronto, and I will be one of the speakers and facilitators, and I am joined by two very experts in this area; Holly Swartz and Mark Zimmerman. So, hi and I ask you to introduce yourself.

Dr. Swartz:
Thank you. I'm Holly Swartz. I'm the Director of the Depression and Manic Depression Prevention Program and Professor of Psychiatry at the University of Pittsburgh.

Dr. Zimmerman:
Thank you, Roger. I'm Mark Zimmerman. I'm the Director of Outpatient Psychiatry in the Partial Hospital Program at Rhode Island Hospital and Professor of Psychiatry and Human Behavior at Brown University.

Dr. McIntyre:
Thank you to both of you and great to have this opportunity to share and exchange thoughts around this topic. As mentioned today, we're going to be talking about mixed symptoms and mixed features uh that are specified in the DSM-5, one of the new specifiers, and its importance in identifying this phenomenology with respect to patients with Major Depressive Disorder. How does that guide treatment? How does that affect the sequencing of treatments in patients that we see? Upon completion of this educational activity, you should be able to review the DSM-5 Diagnostic Criteria for Mixed Feature specifier for Major Depressive Disorder. We're going to discuss rating scales. That is, rating scales that may assist us in identifying and measuring mixed features and maybe help us differentiate, if you will, Major Depressive Disorder from Bipolar Disorder. We're going to talk about the cautionary issue, with that being antidepressants and the destabilization of some patients with mixed features; we'll talk about that, and then we'll talk about how we can implement evidence-based medicine towards the overarching aim of really, in fact, looking at uh the best outcomes for our patients. So, why don't we start by looking at a patient's scenario that we should all be familiar with and I can, you know, say just anecdotally as a clinician, uh I see many, many people with major depression who have mixed features. This is Michelle. She is a 27-year-old who has been successfully treated for depression in the past with SSRIs and has no psychiatric hospitalization prior. She presents to the clinic with typical uh symptoms of depression like depressed mood and anhedonia as well as a decrease in appetite and difficulty sleeping. She reported spontaneously what I hear from so many patients; that is, I feel wired and I'm tired, making reference to the fact that her she's feeling agitated, there's a certain level of irritability, but also a sense of fatigue at least on exertion to carry out tasks. She has fleeting thoughts of uh death, of uh death of herself, but no active suicidal ideation or intent to harm herself or others. Again, she has these racing thoughts that are interfering with her ability to focus and concentrate, very distracted of late, and only sleeping a few hours at night and, on occasion, has been spending a lot of money online shopping during these times when she is feeling wired and tired. So, a scenario not uncommon. We hear this a lot. Uh, maybe Mark I'll start with you. Um, does this patient have Major Depressive Disorder with mixed features?

Dr. Zimmerman:
The short answer is yes, according to DSM-5. There has been a significant change from DSM-4 to DSM-5. In DSM-4, you could only diagnose a mixed type of uh of picture when someone met full criteria for a manic episode and depressive episode, and it was under the rubric of Bipolar Disorder. DSM-5 introduced for the first time a specifier that applies to depressive episodes for Major Depressive Disorder or Bipolar Disorder. So, this case is an example of someone who has a history of major depressive episodes, has current symptoms of Major Depressive Disorder and also some of the features that specified in DSM-5 characteristic of mixed features. Decreased need for sleep, she's not feeling uh the need to sleep, and not feeling the need to sleep the next day. She's spending money recklessly and excessively. Uh, you also mentioned some features that aren't necessarily in the DSM that have also been characteristic of mixed features such as irritability and agitation.

Dr. McIntyre:
Right. That's a nice point Mark, because you you were very clear in identifying and listening to the symptoms. My experience when I see these types of patients, I refer to it as the 5 AAAs. They're often anxious, agitated, they can't pay attention, very angry, and often have anhedonia, and none of these features actually find themselves into the criteria for mixed features. So, there's a disconnect between what DSM allows and what the phenomenological studies are reporting out in terms of what's most common in this presentation.

Dr. Zimmerman:
I think the authors of the DSM specifier were most concerned with over diagnosis and over inclusiveness, so they prioritize specificity over sensitivity and that's why they focus on non-overlapping symptoms, features that are characteristic of manic and hypomanic episodes but are not characteristic of depressive episodes.

Dr. Swartz:
And yet some of these um other symptoms the uh irritability and agitation, which we all agree are so common from a clinical standpoint and are yet and are not included as specifiers, I think are good clinical clues uh because we see them so commonly even if we can't count them in the symptoms we often want to use those as indicators that we want to dig more deeply to see if this patient might, indeed, be experiencing a mixed episode.

Dr. McIntyre:
You know, just to put some percentages on this, we recently published uh a paper showing that about 25% of patients with major depression come to my clinic or the Cleveland Clinic in Ohio with major depression actually fulfill the DSM-5 criteria for mixed features. My question for you Holly, is distinguishing major depression from bipolar. Um, many people might be saying, well aren't these patients just eventually going to declare themselves as bipolar anyways? Is this not just splitting hairs? What what do you think? Are they all going to become bipolar or?

Dr. Swartz:
Yeah, no, it's a great question and it's an important question. Um, I think first it's it's probably useful to um talk about again numbers. So, approximately somewhere between 13 and maybe 20% of individuals will eventually go on to be diagnosed with Bipolar Disorder. So, a significant minority, so not all, but a significant percentage of these individuals will will perhaps go on to to to develop the full syndromal criteria for Bipolar Disorder. But this is not the same thing as Bipolar Disorder. And so, maybe it's useful to think about the difference between the way we think about Affective Disorder um using categorical diagnoses versus thinking about a more spectrum approach to understanding uh affective disorders. Because um, when we think about the DSM-4, as you alluded to Mark, um originally diagnoses were really siloed so we had um very discreet uh categories for mixed mixed episodes and they were housed within the bipolar uh within the bipolar category. But, um, perhaps it might be more useful to think about mood disorders on a spectrum and this is what the mixed episode specifier are helping us to do. So, at one end of the spectrum, if you will, we've got pure, unipolar depression. At the other end of the spectrum we've got Bipolar I Disorder with Syndromal Mania and in between we have these intermediary phenotypes which include things like Bipolar II Disorder and, of course, Unipolar Disorder with mixed episodes. And so, um, mixed uh Major Depressive Disorder with mixed features is not Bipolar Disorder, per se, from a categorical standpoint, but probably resides somewhere along this bipolar spectrum.

Dr. Zimmerman:
Right. And related to the spectrum concept is the controversy, if you will, of categories versus dimensions. So, we talk about subthreshold symptoms assuming we know what the threshold should be and it may well be individuals with two such features should be considered as having Bipolar Disorder. We just don't know.

Dr. McIntyre:
That's an interesting point. Many colleagues watching the program might be saying to themselves, if not aloud, I'm busy, I see a lot of patients, why should I anguish about identifying mixed features in this patient? What's the relevance of this? And my immediate response to that is, well there's implications for, first of all, prognosticating the patient, in terms of setting a care plan. There could be implications for the comorbidity this patient might be at risk for and/or currently is manifesting. It could also have implications for suicide risk, and it's been my experience, this patient population very likely reports suicidal ideation. Fortunately, our patient is not right now, but this population is particularly susceptible to suicidality. Mark, any comments on that?

Dr. Zimmerman:
And lastly, is treatment implications. Uh, to prevent suicidality. That's right. Uh, individuals with mixed features are at increased risk for

uh suicidality or a history of suicide attempts. Their prognosis is poor. Following individuals over time, they do not do as well. They not only have comorbidities uh across anxiety disorders but also substance use disorders, personality disorders, so there is a fair amount, a great amount of comorbidity in individuals with mixed features compared to individuals without mixed features.

Dr. Swartz:
So, I think what you point out is really important. So, back to our patient Michelle, this is somebody that we really would be concerned about, so we would be concerned about risk for suicide. We would be really concerned about um her prognosis over time. We'd be concerned about the the possibility uh that she would have, as you pointed out, additional comorbidities that we would need to address in her her care.

Dr. McIntyre:
One of the tactics or one of the principles of care is really to introduce measurement and rating scales and screening tools, Mark, you've been an international leader in this area, walk us through how you think about, you know, the the implementation of scales to try and maybe sauce out Major Depression from Bipolar with mixed features versus not.

Dr. Zimmerman:
Given the time pressures that clinicians face, they're not able they don't have the time to assess things as thoroughly as they would like. So, we, over the past decade or so, have developed a number of self-report scales that can be used to monitor individuals and other scales have been developed to screen individuals for histories of pathologies, including a history of Bipolar Disorder. So, there are scales such as the Mood Disorder questionnaire, the MDQ, while not tied specifically to assessing Major Depressive Disorder or depressive episodes with mixed features, can help alert the clinician to the possibility of someone having a history of Bipolar Disorder. In terms of ongoing treatment and ongoing monitoring, to the best of my knowledge, uh we're the only ones who have developed these self-report scale to assess not only the symptoms of depression but also the symptoms that are characteristic of the mixed features. So, that's one aspect. We we regularly have patients fill out self-report scales in our uh clinical practice. But, in terms of monitoring, uh what needs to be done special; if you're treating someone with depression, you should be asking about the symptoms and the criteria at every visit. And, if you ask about them at every visit, for someone who is on a treatment or during the course of their treatment, having emerging symptoms of bipolarity, that will be picked up. If you ask someone about their mood, not only would they say they're not depressed, if they're having emerging manic or hypomanic symptoms, they'll talk about the mood elevation or the irritability that they may have. You ask them about sleep. If you ask them about interests, they will not only deny the characteristic features of depression but will talk about the opposite features that are characteristic of mixed features. So, I think it's important to be thorough in your assessment of the defining features of depression and you will then identify the emergence of mixed features if, in fact, they are emerging.

Dr. McIntyre:
Uh Mark, did you want to mention the name of your scale because it's the only one that's out there.

Dr. Zimmerman:
Sure. I I suppose I'm not the best of promoters. Uh, we developed first a depression scale, the Clinically Useful Depression Outcome Measure or Outcome Scale, or the CUDOS, and then we developed a mixed feature specifier add-on to that. So, it's the CUDO-SEM, which is available anybody who emails me uh I send it to clinicians. There is no charge. There's no licensing fee.

Dr. Swartz:
But I think the point that you make, which is so important, is that if you're in the business of treating depression, you're also in the business of looking for hypomanic symptoms. Um, and those two things cannot be distinguished from each other, you have to do them both.

Dr. Zimmerman:
Absolutely.

Dr. McIntyre:
You know, one of the other points I wanted to bring up is the topic of what I call below the neck health, in other words, physical health. And, there is now a uh really a replicated body of evidence now that indicates, doesn't suggest, indicates that people who have mixed features are more prone to having overweight and obesity, more prone to having perhaps cardiovascular disease and metabolic syndrome. We know this mood disorder population is already differentially affected by obesity, diabetes, cardiometabolic risk, but there's something about patients with mixed features that puts them at particularly high-risk and this is another reason why I think it's particularly relevant to sauce this out because that is an additional clarion call to really pay close attention to risk factors around cardiometabolic conditions because we're taking care of patients below the neck and so-called above the neck and why I think this is also relevant. Now, just coming back to herself, Holly, here's a person who is, in fact, going through mixed symptoms and, to be clear, there's no hypomanic episode or manic episode that would declare Bipolar II or Bipolar I, respectively. This person has hypomanic symptoms woven into depression with no prior hypomania or mania. What implications, you know, Mark's talked about the CUDO scale and the mixed features, what does this mean for for really treatment as you see it?

Dr. Swartz:
The question about how to treat individuals with Major Depressive Disorder and mixed features is a complicated one and I think we're just now finding a road map. But, one of the things that we know is that um having the presence of these mixed features uh predicts a poor response to antidepressant medications. And so, Michelle is a good example, she's been treated with an antidepressant and has

not responded well, and this is a typical presentation. Yeah. Um, and so, we would want to think about some alternatives and uh we would uh want to consider, for instance, in some of the treatment guidelines, the alternatives such as uh second generation antipsychotics, which are recommended for individuals with with these presentations or perhaps combining antidepressants with other treatments such as second generation antipsychotics or potentially mood stabilizers. So, um, again, the the treatment um studies are uh just beginning to to point the way but it seems like using alternatives to antidepressant monotherapy uh would be would be the way to go with somebody like Michelle.

Dr. McIntyre:
I mean I agree with you mostly, Holly, and I think for me, my experience has been for many decades doing this now that people who got these mixed features in depression just don't do as well on conventional antidepressants and there is a body of literature now that would really align with my own impression, it sounds like it's your impression. There are some guidelines that have now been created. There has been a recent expert consensus guideline with Dr. Steve Stahl who was the first author, there's international guidelines that have been created. There's also the Florida guidelines, they've been updated every second year, and we're now beginning to see mention that in Major Depressive Disorder with mixed features, to your point, perhaps some of these people might do better. That is, safely and effectively treated with atypical agents or some other agent that would be thought of more for a bipolar patient like a lithium or lamotrigine. Mark, your thoughts?

Dr. Zimmerman:
Uh, you know, those are the suggestions right now. There's, unfortunately, a paucity of data uh addressing the issue which is just beginning to emerge. Uh, but, thus far, there is some encouraging data on the use of second generation antipsychotics as first line treatment and that's what some of these guidelines are recommending. Others are more circumspect and conservative in saying we don't have enough data at this point to uh differentiate treatment recommendations between those with Major Depressive Disorder with and without mixed features.

Dr. McIntyre:
You know, what I have maybe agonized maybe more than I should of about, is I often will see people where I, frankly, cannot ascertain whether their diagnosis is best explained by Bipolar II Disorder with depression being the predominant presentation or they have Major Depressive Disorder with mixed features. And, you know, we we go through the list of symptoms and I I, you know, and use rating scales and still sometimes I find myself still not that certain where my patient actually fits in. And, over the years, impressionistically, I have found that for many of these adults where I'm more confident that they have major depression with mixed features, that I'm better on using some of these atypical agents, but your point's well-taken. In fact, I can only think of one large randomized control study ever done uh with an atypical in major depression with mixed features, and I wouldn't call that uh uh huge uh uh wealth of data. But, that was a certainly a result that's in keeping or is in line with what we are impressionistically left with that atypical seem to help these patients.

Dr. Swartz:
Yeah, I mean I think your point about the differential diagnosis between Bipolar II Disorder and Depression with mixed features is a really interesting one, and I think um the treatment literature in Bipolar II Disorder um tells a slightly different story. So, we have data showing that some folks with Bipolar II Disorder do as well with an antidepressant as well as mood stabilizer like lithium. And, it's it's an interesting um area to think about just because I think um, in many respects, they are close cousins and often difficult to differentiate between the two. Um, and so, I think, again, this is an area where we need more information because it is curious that folks with Bipolar II Disorder, some of them at least, will do well with antidepressant monotherapy and yet the data point to a different um treatment outcome for individuals with Major Depression and mixed features.

Dr. McIntyre:
Right. Absolutely.

Dr. Zimmerman:
And, as the data emerges we may well go more quickly to mood stabilizer agents. Maybe not completely replace the traditional antidepressant first, but use uh mood stabilizers, second generation agents as augmentation medications. And there has been increasing literature demonstrating an FDA approval for a number of medications as augmenting agents for antidepressants.

Dr. Swartz:
Before we get into that, I just want to just point out that not all antidepressants are equal. Um and that it does seem like medications the selective serotonin re-uptake inhibitors are mostly what we're talking about here rather than the tricyclic antidepressants that we would all recommend staying away from which seem to have worse outcomes in individuals on the Bipolar spectrum.

Dr. McIntyre:
You know, as I'm reflecting on our conversation, it almost feels like history repeating itself because it wasn't that long ago that lithium was very often prescribed actually for many people with major depression with recurrent episodes. And, and this is still not uncommon in many parts of the world like Europe and so on, and I think what's happened is that we've recognized there's a subset of people with major depression who have mixed features, according to DSM-5, who, in fact, uh really just don't do well enough with our conventional antidepressants. Key points though, atypicals have adverse events and we would encourage people to be familiar with that, ranging from sedation to EPS and tardive dyskinesia and, in some cases, there's weight gain and metabolic disruption. So, this is a risk-benefit analysis that everyone has to do and I think we can all agree this patient population is not only affected by other medical problems but also many other psychiatric problems. And so, I I think that there's going to be a larger quantity disease management, multi-

dimensional approach to managing this condition. So, Mark, a patient like this uh uh we're going to consider different types of treatment, how would you really think about monitoring this patient?

Dr. Zimmerman:
Not only is it important to monitor clinical features and symptoms, it's important to monitor by by chemical, biological uh parameters uh metabolic profile. Need to monitor, although patients will readily self-monitor their weight and may well complain about any weight gain, and there are differences amongst medications regarding risk of weight gain, but it's also important to get some laboratory measures to monitor sugar levels, to monitor cholesterol levels, uh to monitor triglyceride levels, so monitoring goes beyond just simply uh symptom assessment.

Dr. McIntyre:
With that in mind, what I'd like to do is, in fact, bring today's uh meeting to a close. It's obviously only an opportunity to scratch the surface on this very interesting and complex topic of mixed features in Major Depressive Disorder and really, in fact, it's important for us as practitioners to not forget that this is a common phenotype. This is a common condition uh with estimates ranging but approximately 1 in 4 individuals with Major Depressive Disorder, in fact, meeting the DSM-5 criteria for mixed features specifier. Why is it relevant? It's relevant because mixed features in an adult with major depression has prognostic implications, has implications for comorbidity, has implications for suicidality, and also implications for treatment selection and that segues into my final point which is, at the end of the day, what do we do to help these patients. At the end of the day, there's still, in fact, in Mark's point earlier, really a need for more resurge because this is really a fairly new entity, a new nosological entity in the DSM-5, and there clearly is a need for more rigorous research. But what's there is giving us reasons to believe that in some of these patients, using some of the atypical antipsychotics or other agents that are more conventionally thought of as mood stabilizing, like lithium or lamotrigine, is, in fact, is identified in some of the recent expert consensus statements as well as guidelines. And, again, these guidelines will evolve their iterative but our hope is over the next five to ten years we'll have much more rigorous literature to guide treatments for patients presenting with this very, very common phenotype. I want to thank both Holly and Mark for joining me here today and thank you all for joining us for this webcast.

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