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Partial Response in Major Depressive Disorder Treatment: Are We Doing Enough?

Announcer:
Welcome to ReachMD.

This medical industry feature, titled “Partial Response in Major Depressive Disorder Treatment: Are We Doing Enough?,” is sponsored by Otsuka Pharmaceuticals and Lundbeck.

Here’s your host, Dr. Charles Turck.

Dr. Turck:
As depression continues to be highly prevalent in the United States,[1,2] are we doing enough to gain symptom relief for patients with major depressive disorder and unresolved symptoms? How can we address these symptoms for patients who haven’t yet felt the full benefit of their current treatment?

This is ReachMD, and I’m Dr. Charles Turck.

Joining me to discuss unresolved symptoms for patients with major depressive disorder are Dr. Rakesh Jain and Dr. Clay Jackson. Dr. Jain is a Clinical Professor in the Department of Psychiatry at Texas Tech University School of Medicine in Permian Basin. Dr. Jain, thanks for being here today.

Dr. Jain:
Well thank you, Dr. Turck, for the warm welcome. And I’m looking forward to this conversation with you and Dr. Jackson.

Dr. Turck:
And Dr. Jackson is a Clinical Assistant Professor of Family Medicine and Psychiatry at the University of Tennessee College of Medicine in Memphis. Dr. Jackson, it’s great to have you with us.

Dr. Jackson:
It’s really great to be here and just welcome our learning community together as we explore how to help patients with these symptoms.

Dr. Turck:
To start us off, let’s get a better understanding of major depressive disorder, or MDD for short. Dr. Jain, what can you tell us about the prevalence and burden of this disorder in the United States?

Dr. Jain:
Yes, so major depressive disorder is the most common diagnosis seen by psychiatrists in the U.S,[1] affecting 8.4 percent of adults in 2020 alone.[2] That’s more than 20 million people, and overall, it’s more prevalent in women and is most common in patients ages 18 to 25.[2] And unfortunately, the COVID-19 pandemic has only exacerbated the issue.[3]

On top of that, MDD has been strongly associated with conditions like anxiety disorders,[4] substance abuse disorders,[5] and various chronic pain disorders.[6]

And we can’t talk about burden without mentioning the economic toll MDD has taken in the United States, upward of $326 billion US dollars in 2018, which was up 37.9 percent from 2010.[7]

So, while traditional antidepressants are commonly used for first-line treatment, unresolved symptoms are also common, leading to significant psychosocial and occupational functional impairment.[8,9]

In fact, I regularly see patients in my practice with concentration difficulties and symptoms of anxiety, among other symptoms, which all have a direct effect on my patients' functioning.

Dr. Turck:
And turning to you now, Dr. Jackson, let's dive deeper into unresolved symptoms. What challenges do these symptoms pose for patients with MDD?

Dr. Jackson:
In order to understand the effects of unresolved symptoms on patients' prognoses or functioning, one must first recognize them.

In my practice, I find that one of the most efficient means of uncovering unresolved symptoms is the use of validated scales and screeners. These tools help me to identify unresolved symptoms in MDD sooner rather than later. And in my opinion, clinicians should consider implementing them into their practices to eventually help patients achieve remission.[1] This should be every clinician's goal when treating MDD patients.

In research or academia, the Montgomery-Asberg Depression Rating Scale, or MADRS, along with the Hamilton Depression Rating Scale, or HAM-D, can both be used to help detect MDD symptoms. But we use the nine-item Patient Health Questionnaire, or PHQ-9, depression scale more commonly.

Now, remission has been defined as the absence of depressive disorder—or a score of less than five—according to the PHQ-9.[10] If we're using the HAM-D we look for attainment of virtually asymptomatic status—or a score of less than or equal to seven on the Ham-D—for at least two consecutive weeks.[11]

And looking beyond the scales, in my experience there's also a good correlation when a patient subjectively reports that they're back to normal.

So we've clarified the meaning of remission. Now, *response* has been defined as a 50 percent or greater reduction in symptoms.[12] But even individuals considered to be in response may still experience unresolved symptoms.

Common unresolved MDD symptoms include irritability, anxiety, [13] concentration and cognitive difficulties, low energy levels, depressed mood, and/or sad affect.[13] If left unresolved, these symptoms may also negatively affect patients' functional status.[13]

And MDD patients who have unresolved symptoms have an increased risk of a relapse.[11,14,15]

Dr. Turck:
So, Dr. Jackson, you mentioned partial responders to treatment. Turning to you, Dr. Jain, how is a partial response defined, and how common is it for patients to not achieve remission?

Dr. Jain:
It's very common, because only about 28 percent of patients treated with a single antidepressant achieve remission.[16]

So, it's common to see a partial response in patients, which has been defined as only a 25 to 50 percent reduction in depressive symptoms.[17]

As a result, we're seeing a significant unmet need in MDD treatment, which can lead to ongoing functional impairment,[18] low adherence to therapy,[19] and low rates of follow-up.[20]

Now to adequately assess a partial response, we can look to the clinical practice guidelines, such as those from the American Psychiatric Association, or APA for short. This guideline suggests that it takes four to eight weeks to conclude if a treatment is producing a partial response or no response at all. If at least a moderate improvement is not observed within this timeframe, then diagnosis, side effects, and treatment plan should be reassessed,[21] which we'll talk about a little later.

Dr. Turck:
Thanks, Dr. Jain. Coming back to you now, Dr. Jackson, are there certain characteristics that have been shown to predict non-response or non-remission in a patient?

Dr. Jackson:
Absolutely, so we have baseline predictors available at the onset of treatment, which include sociodemographic qualities, symptom

presentation and comorbid conditions.[22]

We also have process predictors that are based on information gathered during treatment, and these include change in symptom severity, treatment-related side effects, and patient adherence.[22]

Dr. Turck:
For those just joining us, this is ReachMD.

I'm Dr. Charles Turck, and today I'm speaking with Drs. Rakesh Jain and Clay Jackson about unresolved symptoms in patients with major depressive disorder.

So, Dr. Jain, once you identify a patient with a partial response, what do the next steps in treatment look like, and what tools do we have to support these next steps?

Dr. Jain:
Well, if the patient has no response or a partial response to antidepressants, guidelines recommend that clinicians should optimize current medication dosage or switch antidepressant therapy to within or outside of class mechanism of action, or augment with another treatment regimen.[21]

Guidelines also recommend beginning psychotherapy, that is of course if the patient isn't already in therapy. This can include interpersonal psychotherapy, cognitive-behavioral therapy, or psychodynamic psychotherapy.[21]

We should also consider the importance of all three neurotransmitters—norepinephrine, serotonin, and dopamine—relevant to the pathophysiology of major depressive disorder, as some therapies target just one or two.

But in particular, let's consider norepinephrine. Dysregulation of the noradrenergic system is associated with a wide variety of psychiatric symptoms. For example, some of the ones we talked about such as hyperarousal, irritability,[23] low energy,[24] and concentration difficulties,[25] can be unresolved symptoms that we see in patients who are modulated by norepinephrine. There are also alpha-adrenergic receptors that can modulate the noradrenergic tone, and this impacts the level of norepinephrine activity that are available in the brain.[25]

Some atypical antipsychotics, or AAPs, have selective alpha-2 adrenergic antagonism that work to increase norepinephrine levels,[26,27] or they have selective alpha-1 adrenergic antagonism that may work to block the action of excessive norepinephrine levels.[28] Therefore, it's important to consider the range of AAPs available when considering treatment options for your patients.

Dr. Turck:
Thanks Dr. Jain. Now I understand you also have a hypothetical case to share with us today?

Dr. Jain:
I indeed do. We have a hypothetical patient case that demonstrates how we could possibly target all neurotransmitters—specifically norepinephrine, in addition to serotonin and dopamine—by augmenting the treatment plan.

So this is a 37-year-old female diagnosed with major depressive disorder one year ago. She was on an SSRI and complained of unresolved symptoms including irritability, anxiety and inner tension, and concentration difficulties. This patient's current treatment is an SSRI that addresses one neurotransmitter, serotonin.

The proposed plan is to continue SSRI treatment to maintain the clinical benefits this patient is experiencing. However, we must consider how we can address her unresolved symptoms. And we can augment treatment with an AAP to these symptoms.[29]

As we discussed earlier, unresolved symptoms can be attributed to the dysfunction of multiple neurotransmitters. In this case, this patient's irritability may be caused by *high* norepinephrine levels that engage alpha-1b receptors. At the same time, her lack of concentration may be related to *low* norepinephrine levels, which are modulated by the alpha-2c receptor.[26,27]

So by adding an AAP treatment that addresses all three monoamines with both selective alpha-1b and alpha-2c antagonism, we may be able to better address this patient's variety of symptoms.[27]

Dr. Turck:
So, we're almost out of time for today, but I'd like to close with your thoughts on improving the patient experience from diagnosis to treatment. Dr. Jackson, what can you share with us?

Dr. Jackson:

So full remission is my aspirational treatment goal, but we have challenges and barriers in getting there, as we've discussed today.

In my opinion, it's imperative that we partner with our patients throughout every step of treatment to better understand treatment responses and to detect unresolved symptoms early, and then choose the most appropriate care path. Patient buy-in is important for success, not least because it may drive adherence.

Dr. Turck:
And Dr. Jain, we'll end with your final thoughts.

Dr. Jain:
Sure. I would like to add that remission is considered a gold standard of care, and achieving a better quality of life is just as important for patients with MDD.[21]

If we can also help return patients to more normal psychosocial and occupational situations, in my opinion, that should be our ultimate goal. And we can achieve this by really considering the pharmacology of different treatment options when managing partial response, as we saw with our patient case. We know that SSRIs and SNRIs target one or two of the major monoamines, so it's important to consider treatments that may address the full monoamine profile.

Dr. Turck:
That's a great way to round out our discussion on this topic.

I want to thank my guests for helping us better understand partial response in patients with major depressive disorder. Dr. Jain, Dr. Jackson, it was great speaking with you both today.

Dr. Jain:
And it was very good to be with both of you, thank you.

Dr. Jackson:
It's been a joy to be a part of this conversation and we wish all of our colleagues well in treating your patients.

Announcer:
This program was sponsored by Otsuka and Lundbeck. If you missed any part of this discussion, visit Medical Industry Features on ReachMD.com, where you can Be Part of the Knowledge.

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