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ReachMD
www.reachmd.com
info@reachmd.com
(866) 423-7849

Addressing Unresolved Symptoms of Major Depressive Disorder

ReachMD Announcer:
Welcome to ReachMD.

This medical industry feature, titled "Addressing Unresolved Symptoms of Major Depressive Disorder," is sponsored by Otsuka and Lundbeck.

Here's your host, Dr. Charles Turck.

Dr. Turck:
About two out of three patients with major depressive disorder have unresolved symptoms following first-line antidepressant treatment.[1] Maybe this is because we're only looking at part of the puzzle. Could augmentation therapy be the solution?

This is ReachMD, and I'm Dr. Charles Turck. Joining me to explore the role of augmentation therapy in patients with major depressive disorder, or MDD for short, is Dr. Rakesh Jain, who is a Clinical Professor in the Department of Psychiatry at Texas Tech University School of Medicine at the Permian Basin.

Dr. Jain, welcome to the program.

Dr. Jain:
I am so happy to be with you and our colleagues, Dr. Turck. And what an important topic we are going to be discussing.

Dr. Turck:
Well to start, Dr. Jain, can you give us some background on the neurobiology of MDD?

Dr. Jain:
I'd be happy to. So, the pathophysiology of MDD is multifactorial; and while it's not fully understood, we know that dysfunction amongst monoamine neurotransmitters plays a significant role.[2-4]

We typically think of serotonin and dopamine as monoamines involved in major depressive disorder, but it's also important to consider how norepinephrine may play a significant role.[5]

And any dysfunction within each of these neurotransmitter pathways may be associated with symptoms of MDD.[5] For example, noradrenergic hypoactivity can lead to low energy and concentration difficulties, whereas hyperactivity can lead to irritability and agitation.[6-8]

Overall serotonin hypoactivity may affect mood and anxiety.[3,6]

And reduced dopaminergic activity may be associated with pessimistic thoughts.[9]

Now, these three monoamines are closely linked to each other, and their pathways overlap each other within regions of the brain.[5] This interconnection allows for the neurotransmitters to work together through a wide variety of mechanisms. But because of this, the dysfunction of one monoamine pathway can cause dysfunction in another.[4,5,10-12]

All of these interactions between neurotransmitters may also contribute to other MDD symptoms.[5]

So, an effective strategy for treating patients with MDD could be to balance all three monoamines without under- or over-activating these systems.[13]

Dr. Turck:
Now what symptoms of MDD are associated with these monoamines, and what do we want to be mindful of when targeting these neurotransmitters?

Dr. Jain:
Well, first, norepinephrine, or NE for short, contributes to mood, as well as modulates arousal and attention to stimuli.[7]

Noradrenergic system dysregulation is associated with an array of symptoms, including low energy, concentration difficulties, and depressed mood with noradrenergic hypoactivity. And in a hyper-noradrenergic state, patients may experience symptoms of hyperarousal, irritability, agitation, and aggression. And an individual may experience symptoms from hypo- and hyper-noradrenergic states at the same time.[6-8]

And so, in treating MDD we should aim for balance in norepinephrine levels to prevent noradrenergic overactivation leading to symptoms such as hyperarousal.[8]

Then there's the hypoactivity of serotonergic systems which is thought to contribute towards anxiety and mood in patients with MDD.[3,6]

So modulating the serotonergic system is also important in MDD treatments that aim to address serotonergic hypoactivity and suboptimally treated symptoms of depression.

Finally, there's dopamine, also known as DA, which is thought to mediate aspects of mood, motivation, attention, and reward.[13]

In MDD, the DA system is generally thought to be hypoactive.[2]

This is associated with sadness, anhedonia, and pessimistic thinking.[2,6,9]

Dr. Turck:
So now that we've reviewed the monoamine profile in MDD, let's talk about how antidepressant treatments work within these systems. Dr. Jain, what can you tell us about this?

Dr. Jain:
So, first-line treatment options, such as SSRIs and SNRIs, only target one or two members of the monoamine profile. And there's no currently available first-line antidepressant treatment that can target all three of the major monoamines.[14-16]

And this is a worthy consideration because, unfortunately, about 50 percent of patients with MDD continue to have unresolved symptoms following treatment with antidepressant medications.[17-19] Actually, in about one-third of patients, these treatments fail to produce even a partial response—where a partial response is defined as reduction in depressive symptoms by 25 to 50 percent.[20,21]

So, partial targeting of the monoamine profile could be one reason why many patients continue to experience unresolved symptoms with standard antidepressant treatments.[22]

And because these neurotransmitters are interconnected, it may be particularly important to consider targeting the full monoamine profile when treating patients with either no response or partial response to antidepressant therapy.[5]

Dr. Turck:
For those just tuning in, you're listening to ReachMD.

I'm Dr. Charles Turck, and today I'm speaking with Dr. Rakesh Jain about augmentation therapy for patients with major depressive disorder.

Now that we know more about the low rate of symptom response to antidepressant treatment, let's take a look at these patients who continue to have MDD symptoms. Dr. Jain, can you tell us about the burden of unresolved symptoms in partial- and non-responders?

Dr. Jain:
Oh absolutely, Dr. Turck. It's a great question. But before I do so, I want to take a look at some of these unresolved symptoms. Some of them include an ongoing depressed mood, irritability, anxiety, lack of concentration, and low energy levels.[23-27]

Unfortunately, patients struggling with unresolved symptoms may experience a significantly worse prognosis due to higher risk of recurrence, relapse, and hospitalization. These patients are also at risk for a much lower quality of life and symptoms, such as an

increased risk of comorbidities, loss of productivity, financial strain, poor social functioning, and, most importantly, a high suicide risk.[14,19,23,28]

Dr. Turck:
With this information in mind, what are some strategies that have been shown to help improve patient outcomes for partial- and non-responders?

Dr. Jain:
Well, one strategy that is to tailor your treatment approach to your patient.

And for partial-responders or non-responders to standard antidepressant treatment, you can tailor their pharmacotherapy by adjusting their dose, switching medication, combining treatment, and augmentation.[14,29]

First, for some partial responders, optimizing the current antidepressant treatment may point to increasing or decreasing the dose based on your patient's improvement and tolerability.[29] However, evidence suggests that dose escalation is no more effective than continuing a lower dose.[30,31]

Now let's take look at switching antidepressant treatments. Studies have shown a similar efficacy in patients with MDD after switching antidepressants or continuing with the current medication. In fact, in one study, nearly 75 percent of patients who switched their antidepressant failed to achieve MDD remission.[32,33]

So another option is combination therapy, where a second antidepressant can be added to the current treatment.[14] This is an option worth considering because evidence supports combination treatment in providing symptom improvement over monotherapy, especially when the combination includes complementary monoamine profiles.[34,35]

And finally, there's augmentation therapy, which is similar to combination therapy. For instance, an FDA-approved atypical antipsychotic can be added to antidepressant treatment. Like combination therapy, this strategy aims to improve symptoms over monotherapy by complementing the antidepressant's monoamine profile.[14]

Dr. Turck:
With that said, let's dig a bit further into the concept of augmentation. Does this strategy provide any advantages over combination therapy or switching?

Dr. Jain:
So this treatment strategy doesn't reduce any benefit the patient gains from the current antidepressant therapy. Instead, augmentation with an agent that complements the antidepressant's monoamine profile has the potential to improve response to the patient's current antidepressant treatment.[22]

Augmentation with atypical antipsychotic medications, in particular, is the most studied adjunctive therapy. Many randomized controlled trials and meta-analyses have shown its efficacy in treating unresolved symptoms.[36,37]

So, possible advantages of augmentation therapy include the potential to maintain the therapeutic benefit of the first-line agent, avoid withdrawal symptoms due to switching medications, counteract the antidepressant side effects, target all three MDD-related monoamines, enhance the antidepressant effect, and even increase remission rates.[14,15,19,22]

On the flip side, the possible disadvantages of augmentation can include increased pill burden, the risk of additional side effects, and potential stigma associated with antipsychotics.[13,19,38]

I will note that the atypical antipsychotic medications have varying levels of binding affinity to different neurotransmitter receptors. So the unique affinity profile of each medication can help guide treatment choice based on symptom and side effect management.[39]

Dr. Turck:
Now, we're almost out of time for today. So Dr. Jain, are there any key takeaways you'd like to leave with our audience?

Dr. Jain:
Yes, there are a few. So, the currently available first-line antidepressant treatments for MDD only target one or two of the major monoamine pathways—norepinephrine, serotonin, and/or dopamine.[14] And as we discussed, dysfunction in one of these neurotransmitters can lead to dysfunction within the other monoamines.[4,5,12]

Unfortunately, most patients don't respond at all, or only partially respond, to standard antidepressant treatments, which places them at

higher risk for poor outcomes, such as comorbidities and suicide.[14,19,23,28]

So with all of that in mind, MDD treatment options that increase function but avoid overactivation of all three of the major monoamines may benefit these patients in managing their unresolved symptoms.[5,13]

And augmenting a patient's treatment plan by adding a complementary atypical antipsychotic medication to the current antidepressant therapy could address all three main MDD neurotransmitters of the monoamine profile.[22]

For partial responders and non-responders to first-line antidepressant treatments, augmentation with atypical antipsychotics offers potential benefits to patients, including improvements in both symptom reduction and risk management.[36,37]

Dr. Turck:
With those final takeaways in mind, I want to thank my guest, Dr. Rakesh Jain, for helping us better understand the unique profile of atypical antipsychotic medications and their impact in augmentation therapies in major depressive disorder.

Dr. Jain, it was great speaking with you today.

Dr. Jain:
It was great speaking with you as well on a topic of such great importance.

ReachMD 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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