Transcript Details

This is a transcript of a continuing medical education (CME) activity accessible on the ReachMD network. Additional media formats for the activity and full activity details (including sponsor and supporter, disclosures, and instructions for claiming credit) are available by visiting: https://reachmd.com/programs/cme/the-evolving-role-of-rapid-acting-agents-for-the-treatment-of-mdd/13090/

Released: 12/23/2021
Valid until: 12/23/2022
Time needed to complete: 15 minutes

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

The Evolving Role of Rapid-Acting Agents for the Treatment of MDD

Announcer:
Welcome to CME on ReachMD. This activity, entitled “The Evolving Role of Rapid-Acting Agents for the Treatment of MDD” is provided by Prova Education.

Prior to beginning the activity, please be sure to review the faculty and commercial support disclosure statements as well as the learning objectives.

Dr. Thase:
While occasional feelings of sadness are not uncommon, these emotions tend to be fleeting for most people and usually pass within minutes or a few days. At a darker end of the spectrum, sadness that won’t lift is one of the cardinal symptoms of depression, which is one of the leading global causes of disability. Depression can cause a multitude of symptoms, many of which are associated with impairment, and if not treated appropriately, this can go on for months or even years. Are you treating your depressed patients optimally?

This is CME on ReachMD, and I’m Dr. Michael Thase.

Dr. Parikh:
And, hi, I’m Dr. Sagar Parikh.

Dr. Thase:
So, Sagar, welcome and let’s dive right in. So when we think about what differentiates normal sadness or a normal reaction to a very sad and upsetting event, we want to separate it from a clinical diagnosis and then associate that with how the illness adversely affects the quality of our life and our health and so forth. So I’m thinking, Sagar, can you help us make a differentiation in terms of, say, neurobiology or in terms of when you treat or when you don’t treat?

Dr. Parikh:
Well, for me, you know, the issue of treatment and indeed the differentiation of, like, an adjustment disorder with depressed mood versus a true clinical depression really hinges on how much it impairs the person’s life. You know, Michael, you said that disability is a leading consequence of depression and, you know, when we think about depression, who does it hit? First of all, it starts young, you know, it starts early in life. Secondly, it often recurs. And really, the biggest challenge I think we have is that there’s a triple delay. There’s a delay in finding a treatment that works because we don’t have biomarkers to match treatments to individuals. A second delay is that when we do find something that works, it works on symptoms, but those symptoms often take many weeks to fully resolve. And then the third delay is that there’s a gap or there’s a delay, an additional delay between symptom improvement and restoration of functioning. So with these 3 delays it’s a tough battle for a patient, and it’s a tough battle for a clinician.

Now, why are there these delays? Well, some things are public health related, but others are because of the nature of the illness. It’s heterogenous; there are multiple neurotransmitter systems involved. We’re familiar with the usual suspects, you know, serotonin, dopamine, norepinephrine, but sometimes we overlook what is actually the number one neurotransmitter in the CNS and that’s glutamate. And glutamate and its evil twin, GABA, are really important modulators of all kinds of systems in the brain. And, you know, I

wonder if expanding our targets for action in drugs could possibly help us address these delays.

Now, you're an expert on mechanisms, Michael. Could you tell me what else we can do with this?

Dr. Thase:
Well, yes, I think you've driven home a good point and that is going back to really Nobel Prize-winning discoveries in the 1950s and the key relationship that serotonin and norepinephrine have with modulating stress and of course depression is a kind of adverse response to a sustained or uncontrollable or loss-generating kind of stress. We had antidepressants that were tailored and targeted while first discovered accidentally but then subsequently refined and improved upon to modulate those stress responses through serotonin and norepinephrine mechanisms. And so that got us to being able to treat maybe 6 or 7 out of 10 depressed people reasonably well and in the modern era with reasonably good tolerability and safety.

But as we can see in this schematic, norepinephrine and serotonin are only part of a broad and elegant system, and these systems really function in an interrelated way, almost like neural circuits. And so as you mentioned, GABA and glutamate represent 2 fast reactive components to this kind of modulation and whereas conventional antidepressants may take weeks to do their job, there are some medications that directly target the GABA and glutamatergic components of this system and can exert effects within hours or overnight even.

Sagar, which ones do you normally start with?

Dr. Parikh:
Well, you know, I think I'm on the cusp of wondering if I should change. And the reason I say that, before I get into specific agents is – you know what? I think we're almost at a tipping point or at a launch of a new era that resembles what happened when Prozac hit the market in the late 1980s. You know, just this month in the *American Journal of Psychiatry*, we saw a report of a study of a specialized form of TMS [transcranial magnetic stimulation] which given multiple times per day produces impressive remission rates within a week or 2. We've been hearing the story for the last 10 years about IV ketamine, which produces often dramatic remission results, even 24 hours post the first infusion and a more durable kind of remission after several infusions.

We're hearing about psilocybin, which also seems to be relatively fast-acting with a significant improvement after 1 week and, you know, perhaps a peak after 3 weeks. And now we've heard in the past few years something about neuroactive steroids. We know about the FDA-approved brexanolone for postpartum depression. There's also an oral version known as zuranolone. And these agents, neuroactive steroids, work on the systems that you were just alluding to, GABA and glutamate. And so what I'm seeing is a paradigm shift. We used to say, you know, start an antidepressant, 4 to 8 weeks is when you'll see a significant response. In the elderly, wait a little longer. I don't think our consumers, our patients, are going to be accepting that 5 years from now when we have multiple treatments that have results in 2 to 3 weeks.

Dr. Thase:
Yeah. Of course, ketamine is a schedule 3 drug, and planting an IV and observing an infusion over 90 minutes or 2 hours, including the recovery time, is a labor-intensive intervention, whereas ketamine is a generic drug. The cost of the drug itself is not pricey, but with the procedure is complex and can be costly. Esketamine is FDA-approved for intranasal delivery but is still associated with the need for safety monitoring across a 2-hour office visit. And the medication you mentioned a moment ago, brexanolone, likewise is intravenous infusion. But there are the possibilities of moving from intravenous to internasal to oral delivery, and a drug that is in phase 3 of development, zuranolone, is one such example of that. I think the neurosteroids, you jokingly referred to GABA as the evil twin of glutamate, but I think it's more like the yin and the yang.

For those just tuning in, you're listening to CME on ReachMD. I'm Dr. Michael Thase, Professor of Psychiatry at the University of Pennsylvania's Perelman Medical School and the Corporal Michael J. Crescenz Veterans Affairs Medical Center, where I'm broadcasting from today. Joining me today is Dr. Sagar Parikh from the University of Michigan, and we're discussing the evolving role of rapid-acting agents for the treatment of major depressive disorder, or MDD.

Dr. Parikh:
Well, Michael, you know, you referred to a couple of the newer agents, brexanolone and zuranolone. You know, like with all new compounds, I think it's a mixed bag of studies, mostly promising but, you know, occasionally some things that cause us to try and pause and understand it more fully. What's your take on zuranolone?

Dr. Thase:
So there are several really interesting things about zuranolone because it is the first of the rapid-acting antidepressant treatments that is going to be delivered in oral form. And I think secondly it is in phase 3, and phase 3 is nearing, if not completed, for the treatment of postpartum depression. But wrapping up, still a few studies ongoing in major depressive disorder. And those studies have included both

first-line treatment and treatment-resistant depression.

Now, in postpartum depression, there are 2 or more unequivocally positive studies, so I think that that will be getting to us maybe within the next year, year and a half for that FDA-approved indication. For the major depressive disorder diagnoses, there are a mixture of both positive and negative studies in both major depressive disorder and in treatment-resistant depression. And so this will get a lot of scrutiny from the FDA. But I think the kind of most exciting thing about this is not only is the mechanism of action novel, the way the treatment is provided is unique in the sense that you are looking at a 2-week run-up of therapy and then followed by an observational period that can go on for not just weeks but even months. So this is a treatment that has been directed towards intermittent delivery of medication so that some people might only take it for a couple weeks a couple times a year. So quite different. It does have a unique side effect profile as well, mostly sedation because the drug does come out of the GABA-modulating family. But none of the usual kind of nuisance side effects often associated with antidepressants such as sexual side effects, for example.

Dr. Parikh:
Well, Michael you know, it makes sense that if these are newer compounds with different mechanisms of action, the way we deliver them shouldn't be the same old, same old, you know? We know that ketamine is delivered, if it's IV, often twice a week for a few weeks. We know that esketamine is twice per week often for 4 weeks. And finally, we're seeing the literature on psilocybin, which might be just once every 6 months, a single dose. So it's quite understandable that new agents with new mechanisms will have different ways of how much we give and how long we give.

Dr. Thase:
So, Sagar, before we close, I think it's important to touch on strategies that strengthen our relationship with patients. Even the most effective medication is not so helpful if the patient doesn't trust the indication, isn't confident that the doctors made the right choice, or if the patient's actually not taking the medication. What techniques have you found to be useful in communicating with your depressed patients?

Dr. Parikh:
Well, you know, shared decision-making has been well established across medicine as both a contemporary way of relating to patients as well as an effective way. You know, if you are able to talk to the patient, get them to help choose a treatment, they're more likely to adhere to that treatment and more likely to do well.

So how do you have shared decision-making? Well, it's important to be able to provide the patient the right kind of information so that they can meaningfully engage in a discussion. You know, what are the side effects; what are the benefits; how does this work; when will it stop working? All of these kinds of questions. Now, you know, we are doomed to get these information sheets when we go to the pharmacy and fill a prescription, so that's kind of like, you know, toxic information in my view. So we need to provide relevant and accurate and appropriately nuanced information. So there are a couple of patient resources that I try to use. One, of course, is the CANMAT patient and family guide to depression treatment. This is a about a 30-page magazine-size booklet that's available for free download as a PDF from the CANMAT website, and it's written by patients for patients with medical supervision. So it talks to patients in a very friendly language, how to prepare for a meeting with your clinician, how to tally or monitor your symptoms, what are the treatments, medications, psychotherapy, neuromodulation?

Other sites include our very own Michigan Depression Toolkit, a free website which also provides this kind of information. So giving patients the information, I often try to say, "Here are the 2 treatments or the 3 treatments that I think are the best for you," and ask them, "Which do you want to hear about first?" and then go through then sequentially. So really trying to collaborate in the decision-making, I think, is critical.

Dr. Thase:
Sagar, why don't we put up the links to these 2 valuable sites so that our participants can jot them down? And you're too modest about your relationship with CANMAT. CANMAT is a nationally representative group of mood disorders experts in Canada. Sagar is now an expat and is here with us on our side of the border, but the CANMAT group, I think for 3 generations of guidelines now, have been putting out really useful, wonderful, and comprehensive practice guidelines about the care of and the treatment of people with depression.

I want to suggest one other resource, and we'll add this to the graphic, and that is the Depression and Bipolar Support Alliance. One of its many functions is serving as a clearinghouse for pamphlets and information about living with mood disorders and the treatment of mood disorders.

So this has really been a fantastic conversation. But before we wrap up, Sagar, can you share one take-home message for our audience?

Dr. Parikh:
I think the overall message is we are at a time when there are lots of exciting new treatments. And these new treatments are really based on a deeper understanding of neuroscience, new mechanisms of action, so we should be prepared to look for and understand the newer treatments, number one. And we should, put our seat belts on because we're not going to be treating people and waiting for 8 weeks. We're going to be asked by our patients and indeed ourselves can we do better? Can we get results in 2 to 3 weeks? So that is the paradigm shift that's coming.

Dr. Thase:
Well thanks. I think that's a wonderful take-home message. I would say that even as we have new and hopefully more effective or differently effective treatments become available in the coming years, that the process of engaging with your patient and providing good care that makes use of both symptom-level data and side effect data and incorporates those in the visits along with sharing the process of decision-making to foster the collaboration really will help ensure that we get our best possible outcomes.

So unfortunately, that's all the time we have today. So I want to thank the audience for listening in and thank you, Dr. Parikh, for joining me and sharing all of your valuable insights. It was great speaking with you today and really a privilege to have the chance to provide this continuing medical education event.

Dr. Parikh:
Thank you, Michael.

Announcer:
You have been listening to CME on ReachMD. This activity is provided by Prova Education.

To receive your free CME credit, or to download this activity, go to ReachMD.com/Prova. Thank you for listening.