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www.reachmd.com

info@reachmd.com

(866) 423-7849

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Profile and Role of Emerging Treatment Options: MOA, Safety and Efficacy, and Identifying the Patients Who May Benefit

### Announcer:

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### Dr. Goldberg:

Hello, everyone. This is CME on ReachMD. I'm Dr. Joe Goldberg. I'm here today with my good friend and colleague, Dr. Roger McIntyre. Hello, Roger.

### Dr. McIntyre:

Joe, good to be with you again.

### Dr. Goldberg:

A pleasure. So now we've discussed available clinical data that support different emerging treatment options in PTSD and their current investigational status. And now, in this episode, we're going to take a deeper look at some of the unique mechanisms of action of these treatment options and the ways in which their mechanisms of actions impact their safety and their efficacy.

So, Roger, can you get us started in thinking about how to adjust mechanism of action of some of the emerging agents to treat PTSD?

### Dr. McIntyre:

Absolutely, Joe. Happy to do so. I'll try to keep it coherent and brief. First of all, I think what we start off with is PTSD is a complex disorder with many different mechanisms of serving the dimensions of psychopathology that define the condition. We have plenty of in vitro pharmacology with the medications. In some cases, we have preclinical work with animals and some translational work with human beings that provide a reason to believe that these mechanisms I'm going to briefly describe could be at play.

For example, the combination of brexpiprazole/sertraline, which has now completed a phase 3 development program in PTSD, involves, obviously, sertraline, which is a serotonin and, to some extent, a dopamine reuptake inhibitor. Brexpiprazole is interesting. It is multimodal, it's affecting receptors, primarily serotonin, norepinephrine, and dopamine. And, Joe, remember a quick check of the psychopathology of PTSD involves aspects of mood, anxiety, intrusion, avoidance, and hypervigilance. And so all of these phenomenological characteristics map on to those monoaminergics, which is, in fact, targeted, at least the receptors are, with brexpiprazole in combination with sertraline.

MDMA and psychedelics, larger conversation. So I guess I'll keep it brief, Joe. This is based on a theory that these treatments can really fast-track signal transduction mechanisms that facilitate genesis and differentiation and plasticity of circuits within the amygdala and the hippocampus and other brain structures, subserving stress or aberrant stress responses. And these are very much investigational and many different groups in the public and private sector are looking at these. Other NMDA antagonists are similar, with respect to investigational agents, but it really converges on this plasticity model and trying to facilitate plasticity or learning processes in regions of

the brain that have been abnormal, if you will, in trauma.

Other types of therapeutics include things like fatty acid amide hydrolases, and we've got nicotinic acetylcholine receptor type 7 modulators. I think, in fact, what I would do, Joe, is just say, look, these are different mechanisms affecting different aspects of either cellular reactivity, cellular neurogenesis and differentiation. The thesis here is that PTSD rests on an abnormal fear response that has been learned. And are there ways to modulate that learning process and, as a consequence, alleviate the symptoms and towards the unlearning or relearning process affecting cellular systems implicated in memory and cellular and neurogenesis, and so on.

So it's an exciting set of features. We certainly need new therapeutics, and I think the future looks very hopeful.

**Dr. Goldberg:**

It's a fascinating area for study when you think about, from preclinical studies, for instance, with brexpiprazole looking at the impact on hippocampal learning and aberrant responses to fear versus normal memories. We're really trying to help regulate consolidated memories that are overlearned from an aversive response. So to the extent pharmacologies can potentially augment behavioral approaches, we might really actually get the mechanism of what causes this illness, not just make symptoms better.

Well, this has been a great discussion, Roger. I want to thank you so much for that very concise and very thorough overview of mechanisms. Hope you found this helpful as you think about PTSD and try to understand it better. We're out of time for now, but we hope to see you again soon. So thanks for joining.

**Dr. McIntyre:**

Thanks, Joe. Take care, everybody.

**Announcer:**

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