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Pathophysiology and Pharmacologic Rationale of Emerging Agents for the Treatment of PTSD

Announcer:
Welcome to CME on ReachMD. This episode is part of our MinuteCE curriculum.

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Dr. McIntyre:
This is CME on ReachMD and I'm Dr. Roger McIntyre. Hear with me today is a good friend and colleague, Dr. Joe Goldberg. Joe, welcome.

Dr. Goldberg:
Thank you, Roger. Hello everybody. Thanks for joining us today.

Dr. McIntyre:
Joe, let's discuss some of the data supporting each of the emerging or combination of agents as potentially useful in treating PTSD.

Dr. Goldberg:
Sure. So as we acknowledge and know, the 2 FDA-approved treatments for PTSD, 2 SSRIs, sertraline and paroxetine, have limited data in terms of robustness, and data with venlafaxine, there's also acknowledged in some practice guidelines as being useful. But the monoaminergic antidepressants are either under studied or underwhelming in their performance, which leads us to look for newer things.

So a couple of areas of particular interest. One is the class of drugs we broadly speak of is atypical antipsychotics. If you looked at a meta-analysis from 10 years ago, you'd find modest enthusiasm for the overall impact of some of the older atypical antipsychotics.

But if you looked at data in the last 10 years, you'd see some interesting things. There are some emerging data with newer second-generation antipsychotics that may speak to a more targeted value in the symptoms of PTSD. One in particular, one of the partial agonists at the D2 dopamine receptor, a drug, brexpiprazole, has recently been shown in some large, randomized trials to augment the effects of sertraline, one of the FDA-approved treatments to treat PTSD, with a fairly large effect size and with a significant difference from either placebo or looking at sertraline alone. So that's very encouraging.

Do you know that when studies are done looking at response in PTSD, they set the bar rather low. You've got to be 20% to 30% better than when you started out. So imagine if you had any medical ailment and you're 20% better, and that's deemed response, speaking to our historical treatments as having modest benefits. So as something newer comes along, such as the study I just mentioned, it arouses a great deal of interest.

A second area of interest is the whole realm of psychedelic medicine, and the potential for modulating the serotonin 2a receptor. There are ongoing studies with psilocybin, with synthetic derivatives that may have value in the domains of PTSD.

And one psychedelic drug in particular that recently went to the FDA is MDMA, so-called entactogen. It was studied as an augmentation

to psychotherapy. That is to say, it's not just, here, take MDMA and that's it, but rather as a facilitator of the work that's done in psychotherapy to try to extinguish some of the overlearned aversive responses to traumatic experiences.

So it's a complicated data set. At the end of the day, the FDA's advisory panel voted 10 to 1 to not approve the package that was submitted. But if one looks at what went on, it wasn't so much about the drug itself as much as about limitations of how the study itself was conducted. For example, there was no so-called active placebo. You were either taking a drug that could produce some psychedelic experiences or a placebo, and that probably compromised the blind for some patients, if not most or all.

The second was, there was a great deal of homogeneity in the sample in terms of not having diversity of patients. Racial ethnic diversity and groups for whom we don't really know as much about the safety as well as efficacy of this drug. So the FDA basically asked the manufacturer, do more studies, come back to us. We put this on hold for now.

There are some novel compounds that are of interest. I'll just briefly mention these for the sake of completeness. So NMDA receptor antagonists, more broadly than just ketamine, are getting interest. There's a molecule known as NYX783 that is investigational. Fatty acid amide hydrolase modulators, a class known FAAH drugs have some very preliminary research that are being looked at. And then, alpha-7 nicotinic cholinergic receptor drugs are also an area that's beginning to get some research interest. So basically, we're looking at targets that go beyond just monoamines, as we're hoping to get better effects and maybe more than just a 20% or 30% improvement from baseline, as research moves along quite briskly in the world of treatment of PTSD.

Dr. McIntyre:
Joe, fantastic. And these new investigational therapeutics are so interesting. They really remind me of a larger motif in psychiatry about identifying mechanistically informed and more targeted therapeutics. As you say, hopefully we can improve upon the effect sizes that we've seen with, for example, sertraline and paroxetine in PTSD.

Well, our time is up. Thanks for the great discussion, Joe. Thanks to all of our audience for tuning in.

Dr. Goldberg:
Thanks everyone. See you next time.

Announcer:
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