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New Hope Emerging in the Treatment of PTSD in Women: Overcoming Suboptimal Outcomes

Announcer:
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Dr. Goldberg:
Well, hello everyone. Welcome to our presentation today entitled ***New Hope Emerging in the Treatment of PTSD in Women Overcoming Suboptimal Outcomes***. I'm Dr. Joe Goldberg. I'm here today with my colleague, Dr. Roger McIntyre. We are both psychiatrists, psychopharmacologists, clinician researchers who've long been interested and involved in emerging trends and studies in psychopharmacology.

PTSD is often an underappreciated, neglected area, especially in women. So it's a real pleasure for Roger and myself to be with you here today. We're going to be tag-teaming our presentation as we go through the following objectives. You can read these here as we'll talk about, really, the highlight points we hope to draw to your attention. Very pragmatic about recognizing PTSD, what it is, what it isn't, how to understand it epidemiologically, what's protective against PTSD. And then we'll talk a lot about treatment, especially emerging treatments for PTSD.

Our disclosure statements appear here.

And let's begin. So post-traumatic stress disorder, very similarly defined, both in the Diagnostic and Statistical Manual of Mental Disorders, the DSM-5, and in the ICD-11. I’m going to draw your attention to a couple of main points. First, so you have to have had an exposure to an actual or threatened, well, depending on where you're looking, either threatened death, serious injury, or sexual violence, or an extremely threatening or horrifying event or series of events. So people call this the A Criterion. And the important point here is that it's a fundamental threat to one'sl safety and well-being. So there's a little bit different than saying, “I underwent a hardship”; “I lost a job”; “I lost a relationship.” Those are traumas, but the so-called A Criterion speaks to a direct threat to one's fundamental being and welfare.

Followed then by these 4 domains that we speak of: intrusive thoughts; avoidance of experiences that might conjure up recollections or associations to the incident event; changes in cognition and mood – that was a revision in the last edition of our nosology, the DSM-5, calling out the ways in which people with post-traumatic stress disorder can have mood dysregulation, mood symptoms, and changes in how they think about things; and then arousal and reactivity, or hyper sort of reactivity. And that's, in many ways, it kind of a cuts across many diagnoses sort of phenomenon, being hypervigilant to the environment, kind of an expectancy that something is going to just come out of nowhere and jump out of the bushes. It's not unique to PTSD. We see that phenomenon in mood disorders. We see it in psychotic disorders. We see it in substance use disorders. But an important concept is, these are the 4 domains that cohere, that we want to ask about and think about.

Roger is going to give us some more information in a few minutes about duration, but to make a diagnosis of PTSD, the symptoms have to be present for a month or longer. Shorter than a month is something called acute stress reaction, or acute stress disorder, which can morph into PTSD. Roger will tell us more about that. The symptoms have to be distressing, they have to impair functioning, and they're not the direct result of some physiological or substance-induced etiology.

So here's some information about epidemiology. It's interesting. I think PTSD is the one ailment in all of psychiatry where there has to be an etiology or a precipitating cause. When people have a major depression, tell me if I'm wrong, Roger, you have a major depression, say, well, from what? You say, from brain circuitry, that you don't have to have a reason to be depressed, but in PTSD, you have to have the A Criterion. That's interesting. You could walk around this earth with the vulnerability to PTSD and never have an A Criterion hit you over the head and so the syndrome never expresses itself. If you want to think of it as like multiple hits, someone who's got a biological susceptibility to PTSD, which we consider an abnormal reaction to a highly stressful event, that vulnerability will then present itself, we see, in about 6% to 7% of the population. You can see some stratification here by age.

We talk about military and civilian forms of PTSD, and there's some differences in the types of trauma that might occur. So for instance, as you can see on this slide, within veterans, there are higher rates in women than in men that seem to be associated with some predisposing factors, such as a history of child abuse, childhood abuse, interpersonal violence, and particular stressful life events. That's not to say that every woman who joins the military and becomes deployed, who has history, personally, of childhood abuse or interpersonal violence is a setup for PTSD, but let's just say she is at a higher risk than, say, a male counterpart.

Let's delve a little bit more into some of these 4 domains. So first, again, trauma, so exposure to an actual or threatened death, serious injury, or sexual violence in one of the following ways. As you can see, you have to be directly exposed. So that means I didn't just read about it in the newspaper. I didn't get it secondhand because my friend was a victim of some violent crime. It's not something I watched on television, unless monitoring something on a screen is part of your job. So you have to witness it up close and personal. It's got to happen to you directly. And then it leads to these 4 domains.

PTSD, in some ways, is an overlearned emotional response. So you get these intrusive thoughts, distressing thoughts. It's almost like the opposite, in my mind, of like a positive experience. You have a wonderful encounter with someone, a very charismatic teacher, or a very positive emotional experience and you remember it with a positive affective valence, this would be an aversive experience with a negative affective valence, and you've kind of overlearned it, so it comes up again and again and again.

And any associative cues find their way of intruding into your head, which can then lead to behaviors such as avoidance. So if my tormentor, attacker, I don't know, had a mustache or wore a blue shirt, any associative cue, just like in traditional operant conditioning or aversive learning paradigms, any associative cue can evoke that same autonomic response, so I'll avoid it. I'm not going to walk down that street ever again. I get the heebie-jeebies if I have to be in the company of anything or anyone that reminds me of the event. So I'll tiptoe, and I might not even realize consciously why I'm doing that.

So now we see that the various cognitive domains that can be impacted, that can range from, well, a kind of a quasi-amnestic experience, or almost what might be called a dissociative phenomenon. That is, I just can't remember the details; I sort of checked out. I start to formulate negative beliefs or expectations about myself. What's the next shoe that's going to drop? Almost an expectancy bias for an inevitable aversive condition that's going to come along my way.

And then I start to form ideas and beliefs and thoughts about self-blame and others, things cognitive psychologists would call cognitive distortions. And then that can lead to persistent negative emotional states, fear, horror, guilt. And then we kind of get a setup for the potential for depression to come into the picture, and if someone goes on to meet the full criteria for a major depressive episode affecting sleep and appetite, we can see high comorbidity of major depressive disorder with PTSD and so on.

And then lastly, so hyperarousal. I'm hypervigilant. So think of the zebra on the African plains who's been attacked before and just can't quite let their guard down enough to be able to be in the moment, mindful, grazing, because the slightest startle evokes a hyperarousal response. And in PTSD, as I said before, it's kind of an overlearned response to an aversive experience. You can see many of the things described here, irritability, anger outbursts, self-destructive behavior, hypervigilance, exaggerated startle response, trouble concentrating. It's important to think of this, I think, as a constellation, because no one of these is pathognomonic. Anger outbursts happen with lots of disorders. Reckless behavior happens with a lot of disorders. All of these could be, well, if taken out of context, understood without the trauma component that would be defining of PTSD.

Symptoms have to go on, as I said, for at least a month to make this diagnosis. But for most people, both men and women, they'll go on for more than 3 months, in fact, sometimes even more than 6 months. And in fact, in half of cases, it can go on for 2 years. Now, this is a natural course. It doesn't quite take into account the impact of treatment, much less effective treatment. But as I say, this could become a chronic condition. And most chronic psychiatric conditions that persist become debilitating and start to accrue all kinds of bad

things. It becomes the new normal. You adapt to it. You can imagine how it affects your relationships, your work function, your social functioning, and so on. So some people can remain symptomatic indefinitely.

We have some predictors of worse outcomes here, and I think this is a transition over to Roger, since he's going to be talking a bit more about differential diagnosis and what predisposes people to PTSD. Roger, from this list, anything you would particularly call to attention? We did highlight female. Women who have PTSD tend to fare more poorly for perhaps a variety of reasons. Anything you'd want to call out here as we move on to some of these additional elements?

Dr. McIntyre:
Joe, what really sort of struck me about this particular topic of duration, we're talking about a condition, PTSD, that's very, very severe; yet, for most people, it takes years to be detected. And for most people, this is a long-duration illness. This is not just a brief excursion, this is a chronic problem. And as we know, Joe, this often is a segue into other medical and mental disorders as well.

Dr. Goldberg:
Let's press forward. Roger, you want to pick up here?

Dr. McIntyre:
Absolutely. So the differential diagnosis, Joe, and you really sort of spoke to this so clearly with respect to acute stress disorder. Part of this is just simply counting up days of the month. Acute stress disorder, by definition, is a condition of disturbance that looks a whole lot like PTSD, but it's a duration differentiation. In other words, it's less than a month. And it's true that many people, after a traumatic event, will have what looks like PTSD, full-blown PTSD, but it abates, say, after a period of time, say, a month. So that's acute stress disorder.

Joe, what I might also add to the differential diagnosis in this context of PTSD is thinking about complex PTSD. Now, complex PTSD is not necessarily a diagnosis that's in DSM-5, but it is a diagnosis that is kind of familiar.

What's the definitional difference? Well, I think, fundamentally, it's similar to PTSD. I think there are some differences that are more than nuanced, insofar as an emphasis on more repeated, long-term trauma. It's not uncommon for us, for example, to see people who, for example, as children, there's been repetitive physical abuse or harm, sexual abuse that's taking place over months and years. And I think phenomenologically, again, I think that I don't really see what's called the zone of delimitation from PTSD. In other words, I don't see a lot of daylight between this and PTSD. But there are some aspects that are phenotypically emphasized more in complex PTSD, that being the tremendous disturbance in identity, identity regulation, identity diffusion, identity concepts. A lot of these folks, in fact, would have character disorders, some people with PTSD, but often being referred to experts for assessment around dissociation, personality problems.

And, Joe, you and I both know that we are referred many patients, query bipolar disorder, when it turns out they may have bipolar disorder, they may not, but they have tremendous affective dysregulation and impulsivity, lability of their mood and cognition behavior that looks a little like bipolar disorder. But it may be, but it may not be; it may be complex PTSD. So there's some aspects that are slightly different here with acute stress as well as complex PTSD.

Dr. Goldberg:
I'd underscore dissociation. When I hear that word, it's a very complicated and difficult phenomenon. It's hard to treat. Complex PTSD, I think, is extremely hard to treat pharmacologically. We want to recognize it when someone's been repeatedly exposed to sexual abuse or physical abuse, emotional abuse. So back to you, sorry.

Dr. McIntyre:
Yeah, absolutely. And, Joe, you spoke to this with respect to trauma. And just to put some numbers on this, we do know that there's a large percentage of the population. This is global. This is not delimited to Western, high-income countries that are exposed to a traumatic event, and it depends on how trauma is defined. But you can see that the majority of people are exposed to some type of traumatic event at least once in their lifetime. And some studies might report women more so; some report men more so. But we do also know that multiple traumatic events also occurs. This doesn't just seem to be a retrospective recall bias. This seems to be validated with some nice methodologic approaches. So unfortunately, traumatic experiences are common.

Joe, you kind of alluded to this. Given this incredible exposure, this pathogenic, what we call, exposomic, this exposure to trauma, it really is interesting as to who goes on to have a psychopathology like acute stress or PTSD and who goes on to not have these problems. In other words, the resiliency aspect. And I find this extremely interesting.

Joe, you mentioned that trauma is not synonymous with PTSD. I completely agree. And I've been equally interested in how people, from a trajectory perspective, end up with PTSD, while others, in fact, don't. Now, I think that, of course, trauma is broadly defined. The likelihood of going on to PTSD, you talked about it, Joe, with respect to some of the risk factors.

And of course, not all traumas are created equal; there's different types of trauma. And age of exposure is also, I think, another issue. Clearly, trauma in the form of a sexual trauma at the age of 8 by a parent is a different type of trauma than, for example, age 30 or 40, for example, loss of a loved one, things of that nature. But what we can say is, is that trauma is common, repetitive trauma is extremely common, but most people do not go on to have PTSD.

Dr. Goldberg:
If I can just add to that. I fully agree. The people that write about resilience talk about the notion of post-traumatic growth and the idea that you expose someone to manageable conflicts and situations that is not defeated, horror, helpless ones, but problem-solving. This is let your kids stumble, let them face adversity, let them learn how to solve challenges and to help guide them toward how to make solutions and make things work so that what could seem to be traumatic actually turns out to be a resiliency-building experience. So it's a fascinating area, what differentiates the capacity for resilience and growth, as opposed to going down this path of intrusive thoughts and negative cognitions and so on.

Dr. McIntyre:
And you know what's also interesting with that, Joe, how often I've asked patients, have you ever had a traumatic experience? If patients come back and say, well, how do you define that? And it's a reminder that what is, in quotes, traumatic to one person is not interpreted as traumatic necessarily to another person. So maybe it's in addition to the exposure, it's the interpretability of that threat by the lived experience that affects the risk, if you will, for PTSD.

Clearly, sex differences exist with respect to exposure prevalence. There's no question about that. And obviously there's going to be differences with respect to the types of trauma. So I think we think about it broadly. I like the way you articulated that Criterion A, it could be death, it could be threat to the integrity of oneself, and we typically think about combat, of course, that's obviously very significant. But civilian-type traumas are common and they are broadly defined.

Let's also not forget, one of the most common traumatic exposures is loss of a loved one. That is a traumatic event for many people. It may or may not go on to PTSD, but is certainly very, very common.

Dr. Goldberg:
Indeed.

Dr. McIntyre:
Now with respect to risk factors, again, broadly defined, I think I like to have sort of a way of classifying risk factors. Sociodemographic, we spoke to. There's also so-called anamnestic or personal history-type risk factors. Probably the one that is most replicated is prior history of trauma, but there's also other aspects. For example, people talk about temperament and temperamental dimensions, and some people have more of a liability, if you will, to maladaptive stress responses, in quotes, by nature, if you will.

And then we also know, in fact, that there is family history. For example, there's this really interesting topic, Joe, about generational PTSD, which is talked about; it brings up biological aspects. In other words, is there an inheritance of PTSD at the epigenetic level, if you will? Is that passed on through generations? Sort of a nidus of risk for the next generation, so to speak? I think it's always difficult to fully suss out how much of this is, in quotes, biologic versus the environmental propagation. But I think we're also becoming really interested in what are the molecular and cellular effects of trauma, that is, aspects of epigenetics, and is that also, in fact, passed through generations?

Now, with respect to the pathophysiology of PTSD, Joe, I mean, you know this well, this is a complex topic. We would love to have parsimony and simplicity, a nice one size fits all. As they say, it's complicated. But we do have really comprehensive so-called biology of stress research findings. I mean, the lead effector or candidate is the disruption in the HPA axis. When I was trained as a resident, I was told that people have too much cortisol; that's what leads to PTSD. That's not untrue, but I think it's become a little more complicated. Some people actually have too little cortisol. Some have dysregulated circadian rhythms and cortisol. Some have a bit of some of the above, if you will. So I think, for me, I sort of see it as a dysregulated cortisol system, if you will. And some people are increased, some are decreased, others and/or have altered circadian rhythm. That's a stress response.

Second, and this is related, is alterations in the inflammatory system. In other words, the inflammatory system has evolved as a stress response system. It is activated when it detects threat.

Thirdly, the catecholamine system, of course, comes to mind. But broadly monoamines, we know that there's those different categories of symptoms you talked about, Joe, for example, aspects of mood dysregulation. Well, we could think that's all 3 neurotransmitters, serotonin, norepinephrine, dopamine, but maybe serotonin comes to mind. That hypervigilance, that hyperarousal, that on-guardedness, clearly that speaks to aspects of noradrenergic drive or overdrive. And then many people have that cognitive numbing, that real sort of

numbing cognitively. You could maybe say, well, overly simplistic explanation would be dopamine. And there may be some modicum of truth to that.

It extends on, because when you have a system, when the brain is so activated, it means there's a hyperenergetic load on the brain cells, and that then means there could be oxidative stress and mitochondrial dysfunction as well.

So there's not a simple explanation, but this fits neatly into what's called allostatic load. What the heck is allostatic load? Well, we know that, as organisms, we adapt to stress. PTSD is a maladaptive stress response, which means our resiliency has been over-, if you will, burdened by this momentum of trauma, biology of trauma, so we're not adapting. And so allostatic stress is sort of like wear and tear. So we have this biological perturbation, many effectors like I described. The end result is it begins to wear and tear, not just the integrity of brain cells, but also the integrity of our physical health. This is probably why so many of our patients who present to us actually present with not only PTSD, but medical comorbidity, eg, obesity, diabetes, metabolic syndrome rates are considerably higher in our patients who live with PTSD.

Now, with respect to a more detailed dynamic model, it's one thing just to list the various, what we call, effectors, or I call them suspects in the suspect line that cause PTSD. But I think, in fact, we would step back and say, isn't this a dynamic system? Of course it is. And I think rather than saying cortisol is increased or decreased, it probably is a bit more helpful to say that the hypothalamus, the pituitary, right down to the adrenal, there is a feedback loop system. And the prevailing view today is that there seems to be something altered or abnormal about the feedback loop. And that feedback loop, which is wonderfully engineered under a normal set of circumstances, is a delicate interplay. In situations of PTSD, there's, for example, altered sensitivity to the feedback, resulting in the peripheral alterations in cortisol that we see. That's why, for me, I find it may be more accurate to say we've got a dysregulated cortisol axis, rather than too much or too little.

Now, there's been many lines of research. There's been a triangulation of evidence on this, really arriving at, that A, it's complicated, and there's many different systems that are at play that lead to this maladaptive system. I think in many ways, what we've done, Joe, as you know, is we sort of worked backwards over the years. We've tried to find therapeutics that are helpful for PTSD as maybe providing a little insight on the biology of PTSD. And we also have lots of great clinical work and translational research, highlighting, for example, dysregulation in the catecholamine system, or the monoaminergic system, as I made reference to. And I think, in fact, that along with many other suspects, for example, we think about disturbances and glutamate/GABA excitation/inhibition balance, that's been implicated. We talk about maybe peptides are altered. For example, maybe there's disturbances in everything from neuropeptide Y to endorphins right down to oxytocin. And all of these observations are not mutually exclusive. I think what we can say is, is that we have evolved to elicit a very robust stress response for survival and integrity of body. And because of that, it shouldn't surprise anyone that so many of these very sort of primordial systems are involved in the stress response.

Dr. Goldberg:
And what's particularly nasty is with the re-experiencing and reliving, you just keep strengthening the synaptic connections in the maladaptive way. It's like an evolutionary survival mechanism that's gone awry.

Dr. McIntyre:
Absolutely.

Dr. Goldberg:
So as you mentioned, Roger, lots of neurotransmitter systems, neuropeptide systems involved, complex; there is no one single a-ha. If it was all about serotonin, we would have solved this long ago.

Let us shift gears for a moment. We've been talking a lot about pathophysiology, and we're going to say a bit in a few moments about treatment. Let's talk about screening. So underscoring again, trauma does not equal PTSD, but it is a prerequisite for it. So how do you screen for this? Well, there's a few standard scales that are commonly administered. Probably the best one that's known is something called the PCL-5. It's a 20-item self-report measure. There are different versions for civilian and military exposures to trauma. There's also, in primary care, a PTSD screen called the PC-PTSD-5. All of these screen for trauma but then go beyond just, have you had trauma? This bottom bullet here talks about trauma scales and dissociation and trauma symptoms. And again, one could use these scales at the bottom to screen for trauma, but the PCL-5 tends to be the one that's most commonly used.

Here are some sample questions from it. So again, it talks about not just trauma, but also the sequelae. So repeated disturbing memories, disturbing dreams, you can have nightmares, reminders, strong physical reactions, avoidant behaviors. Really key, these 20 questions, in various ways to the criteria in the DSM. We have some scoring information shown on the right. And the thing about screens, again, is they're screens; they're not definitions. So if you score above a threshold of about 31 or so, it's probable PTSD. And what does that mean? If you're a clinician, it means you say, I've got a positive screen. Now I've got to delve in deeper. I've got to do a

clinical interview. I've got to assure there's no confounding factors. I probably want to think about psychiatric comorbidities, like mood disorders, substance use disorders, and things like that. So the screen is the entry point into the system.

Let's talk about treatment. And here's a sobering factor. Roger, when we do mood disorder research and we use the term response, how do we define response in, like, depression?

Dr. McIntyre:
Usually a 50% or greater improvement from baseline.

Dr. Goldberg:
Yeah. Does it not blow one's mind to think how low the bar has been set in PTSD to say, well, so Ms. Jones, the good news is you're a responder to treatment. The bad news, you're 20% better than when you started out. It is a statement, I think, to how far we have yet to go to accomplish more efficacious treatments. At the same time, yes, that's certainly a step in the right direction, but hardly cause for celebration. It takes a while to even judge that 20% to 30% improvement. Here, let's try this treatment, 3 months from now, you may be 20% better.

I don't think we want to impart a dismal message to patients, but at the same time, I think we want to be realistic in saying this is a hard problem to treat. It's probably a multimodal problem to treat. A pill is probably not going to fix it all, but pharmacology paired with the right kind of psychotherapy can be very efficacious. But when patients say, “How long till I'm better and how long till this kicks in,” I think we want to remind them just that this is a challenge. It's going to take some expertise.

Plus, we don't have a lot of FDA approved treatments. We have 3. Does that not bother you that in all these years, we have paroxetine, sertraline, 2 SSRIs, and we have 1 device that's FDA cleared, repetitive transcranial magnetic stimulation. And guidelines will tell us that the first-line treatment in PTSD, you can certainly use pharmacologies, but behavioral interventions such as prolonged exposure therapy, eye movement desensitization reprogramming, which is basically a variant of exposure therapy that, in the hands of a properly trained clinician, conjures up memories, and you kind of try to unlearn them. It's almost like extinction behavior in either classical conditioning or operant conditioning. So if you really want to get savvy on PTSD, go read about behavioral conditioning and operant conditioning, because without that, medications alone don't do a whole lot.

Roger, can you speak to the current practice guidelines from the VA. Here they are. I'm going to just put them up. What do you think of these?

Dr. McIntyre:
Yeah, absolutely. In the clinical practice guidelines, they provide decision support. It's a way to be a bit more consistent, a bit more appropriate. We hope it improves the quality and the cost effectiveness of care. The VA has a guideline, and it's a practice guideline circa 2023. And the way that the recommendations are listed is they're listed as a first line. So you alluded to this, Joe, paroxetine, sertraline, and maybe venlafaxine, which venlafaxine is recommended; it may not have an FDA indication. Those are recommended full stop, strong statement, and unequivocal.

Thereafter the word insufficient comes up quite a bit. Insufficient evidence. I'll just say, I'll keep it brief, Joe, insufficient evidence for most other things, it seems.

Now, there is, in fact, insufficient evidence for or insufficient evidence against. And the guidelines, in fact, go in different directions here. I won't go into all the details, but I think maybe just to keep it topical, Joe, there's so much talk these days about psychedelics and their role in PTSD. We've recently heard, for example, that MDMA has been rejected by the FDA in its application for an approval in PTSD, combined with psychotherapy. The current guidelines, in fact, at the VA, are recommending – they're saying that the evidence to recommend, there's no really good evidence to recommend for or against psilocybin in that context. That's a different, obviously, type of psychedelic.

What I thought was also interesting, Joe, and this is certainly something I'll just maybe reflect out loud on. Most people referred to me with PTSD are prescribed benzodiazepines. They tell me that their clinician has suggested cannabis. I hear this all the time. I don't agree with that, by the way. And yet, it seems like in the guidelines from the VA there's no recommending against that, which is really interesting. What also sort of caught my eye, Joe, is the suggestion against using prazosin or guanfacine in the treatment of PTSD. That caught my eye.

But there is, in fact, I think, an appetite that emerges from these guidelines for new therapeutics. My goodness, 3 treatments. Again, we're not trying to be defeatist and discouraging, but clearly, when you see discouraged against, insufficient evidence against it, it leads you to say, we need new therapeutics.

Dr. Goldberg:

For sure. I can think of a list of, I think, 12 medical conditions that will get you a medical marijuana card, and PTSD is on that list. People call and say, “Can I see you to get a medical marijuana card,” because the cannabis supposed to be good for PTSD. You have to step back and say, but there's no research to support that. So that arrived by fiat. So from an evidence-based standpoint, it is a slim list.

Here's that slim list, right? So as you heard Roger and I both were saying, so 2 SSRIs and one SNRI are the best study. Let's take a bit of a deeper dive into the alpha-adrenergic realm, and then we're going to talk about some emerging data with atypical antipsychotics.

So here's some meta-analysis data on using antidepressants for PTSD. Roger, can you talk about this? I'm so upset looking at these data. I just can’t

Dr. McIntyre:
Yeah, I agree, Joe, this is not satisfactory. This is wholly inadequate. When you look at the standardized mean differences, in other words, the effect size of paroxetine and sertraline, it's quite modest. I'll keep it positive. It's modest at best. And clearly that is something we're going to need to improve upon. And I think, in fact, there's a recognition this is the case. Clinicians so often encounter people who've been there, done that, not benefiting. What do I do next? So I think that there's a need for first-line therapeutics. There's clearly a need for how can we boost benefit?

Now, Joe, when I think about treating PTSD, I sort of approach it the way I treat most mental disorders. You can sort of say, Okay, how do I treat this condition en bloc? In other words, just treat the condition. But when we talk about treating dyslipidemia, we think to ourselves, am I treating the cholesterol, the LDL, the HDL, what am I treating? So taking a more dimensional approach is how medicine usually works, and we’ve kind of been late to this, but psychiatry is getting more into sort of breaking down diagnostic constructs and breaking down what are the key targets, and maybe some medications could be symptomatically benefit for some dimensions, but maybe not as good for others.

And when I think about the adrenergic therapeutics, clonidine, guanfacine, which is,these are agents that are presynaptic or the postsynaptic, prazosins, trazodones, these are medications that people know well, help some symptoms of PTSD, for example, may be helpful in insomnia in some patients and nightmares, these are drugs that target and modulate the adrenergic system. So I suppose in some, maybe a little more charitable. I think if we just try to conquer the entire PTSD phenomenon with one treatment, that seems pretty aspirational, but maybe there's treatments that are better able to target select symptoms. And the adrenergic therapies, I think is a good illustration of that.

Dr. Goldberg:
Two quick comments here. So alpha agonists and alpha antagonists, they do different things. So as you mentioned, Roger, the postsynaptic alpha-1 blockers like prazosin, trazadone, seem to be specifically helpful for nightmares and sleep phenomena, not for the autonomic hyperarousal. It’s interesting.

So this Murray Raskind study in *The New England Journal* that we cite here, which is a pretty good study to look at, his group was the first one that said prazosin could be helpful for nightmares. But then when they did their follow-up study, it wasn't. And they argued that there are a lot of chronic PTSD patients in that sample, and they suggest maybe an alpha-1 blocker is more useful in acute onset, rather than lingering, smoldering, chronic. It's a hypothesis they used to explain why prazosin didn't do a whole lot.

And then on the presynaptic side, we have alpha-2 agonists. So clonidine, guanfacine. I'm not as dismal as the VA is here. I mean, I think it certainly speaks to the pharmacologic mechanism of fight or flight and downregulation of autonomic hyperarousal. I think the problem here is just it's a lot of anecdotal case reports, and there hasn't really been a good, big randomized trial that's controlled for all these variables. So jury's out, I think.

And last point. Remember a few years ago there was that study that said, hey, if you get exposed to a trauma and you give them beta-blockers within like hours of the exposure, you'll block the memory consolidation. It was a very kind of sexy idea. And I remember ER psychiatrists carrying that paper in their back pocket in the ER when I was a trainee. That didn't seem to pan out with longer studies. So I think it's an interesting hypothesis, but I wouldn't go around doing it full stock.

Dr. McIntyre:
Yeah, absolutely, Joe. I mean, there's been so much attention given to the psychedelics, which, of course, is a large, polysemous, multi-definitional construct. It could include serotonergic psychedelics like psilocybin, but it could also include the so-called entactogen and pathogen MDMA. And MDMA, methylenedioxymethamphetamine, along with psychotherapy, has recently been reviewed by FDA. And I think that the FDA’s decision to reject the application, I don’t think it was just a closed door; I think was more work is needed. I don't think there was any questions about the theoretical background, the conceptual background. There are questions about the data, the interpretability, some of the data, how it was gathered. And there's been other methodological aspects, I think. So I think that was really

an issue with the package, but it wasn't like the end of the story.

Dr. Goldberg:
Yeah, it's hard to not break the blind. You're either going to have a psychedelic experience or.... So I think the methodology is what really got criticized more than the treatment itself. So stay tuned there.

So let's talk about atypical antipsychotics. Here's a meta-analysis from, well, 10 years ago. At that time, 9 randomized trials, olanzapine, risperidone, quetiapine, ziprasidone, and I believe this meta-analysis came out before – there was a large multisite trial of quetiapine published in the *American Journal of Psychiatry*. It's an off-label use, but it actually did have a pretty substantial effect. So due to some lag in the literature here. And also raises the question of whether there may not be class effects among atypical antipsychotics, as is often the case. These are multimodal, poly-mechanistic drugs, and they may not, as a class, all work for the same things.

On the whole, and I think why the VA was kind of meh, is, yeah, this sort of a smallish effect size, a little bit better with intrusion, not so good with avoidance, maybe a little better with hyperarousal. So this is a bit of an older meta-analysis, doesn't really take into account some of the newer data.

Here's the newest of the new, just recently published. Preclinical data suggesting that one of the dopamine partial agonists, brexpiprazole, in preclinical studies, seems to have some efficacy when introduced soon after a traumatic experience for diminishing the expression of, let's say, maladaptive fear responses when looked at in the laboratory, may promote more normal fear memory than the hyperarousal, startle kind of phenomenology.

So brand new. In humans now, we have a randomized clinical trial of brexpiprazole plus sertraline for PTSD. So have a look. These were data that were just recently presented at a meeting but not yet published. So we're getting kind of a quick initial look. Three 11-week randomized trials, flexible dosing of brexpiprazole or placebo, and it's sertraline. Sertraline, that FDA-approved drug with an effect size of 0.12 in adults with a variety of PTSD symptoms that were there for over 6 months. So as you can see, if you augment sertraline with brexpiprazole, you get a significantly greater effect than with just either brexpiprazole alone or sertraline alone or placebo. That's quite newsworthy. First trial on the left. On the right, just looking at brexpiprazole with sertraline versus sertraline alone, boy with this paltry effect size of sertraline alone, what to say? There is some effect, but, wow, this really enhances the effect significantly greater.

Dr. McIntyre:
Joe, do you think that this is unique to sertraline with brexpiprazole? Or would this benefit possibly be extrapolated to other SSRIs, other antidepressants?

Dr. Goldberg:
It sure invites that speculation, doesn't it, Roger? So I would love to test your hypothesis as to see what would the augmentation value be with, say, something like venlafaxine or, to make that more modern, desvenlafaxine. Who knows about things like a newer serotonergic drug like vortioxetine, which may have some procognitive effects. Roger McIntyre, you may know, wrote about that.

So I think this invites clinicians who are thinking in neuroscientific terms to use their judgment and their thinking. It's not random; it's not throw it against the wall and see what sticks. These are the data that we have. Can't wait to see it published, and I hope it's going to inspire that kind of empiricism that'll really answer these questions better.

Third trial, looking at brexpiprazole at different doses. And just missed significance at these different doses of 2 mg versus 3 mg. But certainly, the sertraline with placebo in this arm seemed to have a somewhat larger effect, 17-point drop on the CAPS-5 compared to about 11 or 13 drop here. So don't know if this is more of a failed trial, the sertraline worked better, but this stands side by side with the 2 previous studies that I showed you.

Roger, do you want to take us home with the odds and ends of additional treatments?

Dr. McIntyre:
Yeah, absolutely, Joe. So TMS, of course, has many different ways it's delivered, including, of course, the rTMS, the familiar is also different, accelerated models. There's also theta-burst and so on. But rTMS, you mentioned, Joe, earlier, does have the FDA acknowledgement with respect to its use. Meta-analytic data supported, again, different modalities of TMS. You can see listed based on the frequency, some were theta-burst stimulation.

So TMS, which is looking even more interesting these days, as an add on in the antidepressants in MDD, is also showing some data in PTSD. So that's obviously an alternative treatment that we need to consider.

In addition, there's also a variety of more sort of mechanistically informed, hypothesis-driven type approaches. I won't go into all of them, Joe. Stemming from dysregulated HPA axis, can you modulate that through some systems? Also looking at glutamatergic modulation,

antioxidant, the list goes on. But I think what we would say is, is that interesting, certainly academically sound, based on good guiding principles around the current models of the pathophysiology. But I can't say any of these are sort of really fit for purpose in everyday clinical practice, pharmacologically.

Dr. Goldberg:
Comforting to know that there's ongoing research, though, and interesting hypotheses. As you said in the very beginning, there isn't just like one mechanism that's at play; we cast a wide net.

Dr. McIntyre:
One area just on that just final comment, Joe, is the GABA glutamate situation. I do wonder whether or not we'll begin to see – so we have some preliminary RCTs with ketamine in this area, that might be something also you'll hear more about.

Evidence-based psychotherapy, I think if I was to start off the discussion, trauma-focused psychotherapy clearly comes to mind as a first-line therapy, eg, cognitive behavioral therapy in that area. But there's other types of psychotherapies, and maybe not used as much or accessible as much, like EMDR, eye movement desensitization reprocessing, there's mindfulness, there's support, there's group therapy.

I might also mention, Joe, that what's really interesting, part of this is an attempt to improve access and availability, is so-called virtual therapies, or augmented reality, virtual reality therapies; they look interesting. They're under development right now, among other things, for PTSD. So we'll see where that goes as well. But psychotherapy clearly has to be considered a Level 1 treatment.

Dr. Goldberg:
Said in one sentence, your hippocampus influenced by the amygdala has to unlearn and extinguish an overlearned aversive response.

So summarize for us, would you, Rog?

Dr. McIntyre:
Sure. I mean, PTSD, clearly, it's common. It's clearly a debilitating condition. It's a condition that is very persistent in many people. Too often it's not detected and diagnosed. And I think, frankly, some clinicians might say, "Well, I haven't been screening for it. Not as many treatments available," but we do have a call, a clarion call to screen for it, we talked about screening tools to consider, be familiar with the DSM criteria. And also, what I might say is, yes, it's been a couple of decades since we've had an FDA pharmacotherapy, sertraline and paroxetine are approved. We talked about rTMS. But there is, in fact, now, excitement on the horizon and hope, because there are new therapeutics that are being looked at, not just pharmacologic, but as I alluded to, things like augmented reality, virtual reality. In the interim, CBT is certainly tried, tested, and true. And we look forward to hearing what new treatments could be provided.

Dr. Goldberg:
It's always a pleasure chatting with you about these things. I hope you all out there have found this as engaging and informative and useful as I think Roger and I both have. So I want to thank you all for joining us today. Roger, any final comments? I'll give you the last word.

Dr. McIntyre:
Okay, great, Joe. Personally and professionally, always great to work with you, and thanks to our colleagues for joining us.

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