

AJP Audio – Dr. Charles Nemeroff – January 2025

Aaron van Dorn ([00:07](#)):

Welcome to AJP Audio for January, 2025. I'm Aaron Van Dorn. The January issue of AJP is a special issue focusing on the use of psychedelics in psychiatry. The issue has articles focused on everything from clinical potential of psychedelics in the treatment of psychiatric disorders to potential avenues for further study and potential harms and concerns for psychedelic therapy and research. For this episode of the podcast, American Journal of Psychiatry editor-in-Chief Dr. Ned Kalin sat down with issue guest editor Dr. Charles Nemeroff of the University of Texas at Austin to talk through the issue and discuss what it has to offer readers.

Dr. Ned Kalin ([00:38](#)):

Well, I'm really pleased today to be able to have with us Dr. Charlie Nemeroff, who is a good friend and colleague, and also an international leader in the area of psychopharmacology and biological psychiatry. We've had the pleasure of having Charlie be a lead in the special issue that will be presented in January related to psychedelic drugs and their therapeutic effects, which is obviously very timely. And we felt that AJP is ready to take this on and that the field is really at the point where important points could be made and are really worthy of us highlighting them in the American Journal of Psychiatry. So Charlie, thank you for doing this. I want to introduce Charlie and why don't you say a few words about the special issue, Charlie, and then we'll get into some of the specific papers and what they say and what they mean.

Dr. Charles Nemeroff ([01:26](#)):

Well, let me just start off and say that I was delighted to be invited with my colleague Greg Fonzo, to serve as editors of this special issue of the American Journal of Psychiatry on psychedelics. And the reason I'm excited about it is because we know that we have to bring scientific rigor to a field that is somewhat ahead of its skis, that there is much publicity about psychedelics in the lay media and on the internet, constant bombardment of individuals who are discussing their personal experiences. It's remarkable and an emerging database about the potential utility of these medications for the treatment of psychiatric disorders. So we thought it was an appropriate time to launch an issue and give the readers of the journal a sort of state-of-the-art view of where we are in psychedelic medicine.

Dr. Ned Kalin ([02:27](#)):

Thank you for that, Charlie. I think we have a really great diversity of papers ranging all the way from some special articles, some reviews, some data papers and some commentaries. But why don't we start off with the paper that was authored by Roger McIntyre. This is related to an overview about some of the methodological considerations and ideas about future research related to psychedelic treatments.

Dr. Charles Nemeroff ([02:52](#)):

Well, Roger provided a wonderful overview and raised a number of seminal questions that remain to be answered in the field of psychedelic medicine. And in particular, Roger reminded us that all of the scientific data that we have have come from relatively rigorously controlled clinical trials in which subjects are very carefully screened for inclusion in clinical studies and then monitored very closely. And he raises a number of issues first about the potential widespread availability of psychedelics in unsupervised non-clinical settings. The fact that we don't know a lot about long-term safety of these very powerful medications. We really don't yet understand the mechanism of action of these medications that we have some ideas about them. And we really need to do a better job of trying to

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understand who within a particular psychiatric diagnosis might be helped by psychedelic medicines. And if so, which ones? Because there are many different drugs that are classified as psychedelic.

Dr. Ned Kalin ([04:06](#)):

Speaking of different drugs, there's been a recent interest, Charlie, in some of the more rapidly acting and shorter acting drugs, there's a paper that's a review paper by Johannes Ramaekers that gets into more detail about some of these potential treatments on the horizon.

Dr. Charles Nemeroff ([04:24](#)):

This is a very interesting manuscript because it's largely focusing on what's called 5-MeO, which is 5-methoxy-N,N-dimethyltryptamine and it's relative DMT dimethyltryptamine. These are extremely short-acting psychedelics and they have a length of action depending on the dose that could go from 30 minutes to an hour or maybe even 90 minutes. And the question is whether ultra short-acting psychedelics have the same kind of therapeutic benefit as the longer acting drugs such as psilocybin, which lasts say six to eight hours. And there's relatively little data on ultra-fast acting psychedelics. And in fact, there's even controversy about whether one has to have a so-called psychedelic experience in order for these drugs to produce their therapeutic effects. So a lot more study needs to be done in this area.

Dr. Ned Kalin ([05:28](#)):

Yeah, I know this is an area of a lot of interest from the standpoint of new drug development with drugs that may be interacting with the 5-HT_{2A} receptor and not having psychedelic effects and wondering whether or not they have efficacy. So it'll be more to come that's going to be exciting.

([05:44](#)):

The next paper that we wanted to talk about is a paper that really gets into the potential harms and adverse effects of these treatments. All of us in psychiatry have been excited about the potential, but also most of us have been very wary about potential side effects and harms that could occur. And this is a paper by Sharmin Ghaznavi. You want to tell us a little bit about that paper, Charlie?

Dr. Charles Nemeroff ([06:08](#)):

Yeah, so the senior author is Jerry Rosenbaum, who is the former chair at Mass General on the head of their psychedelic center. And it is a well-written and thoughtful piece about caution in the area of psychedelic medicine. And what this group points out is that there have been case reports of individuals outside of a clinical setting who have ingested psychedelics and have had concerning adverse events including psychotic episodes that last for a considerable amount of time, manic episodes, what we used to call when Dr. Kalin and I were in training and working in the emergency room, bad trips. And we know very little about what the characteristics are of individuals who are at risk for such adverse events. They also raise issues related to potential abuse liability of these agents. I will say that it's very important to understand that psychedelic medications are not like opiates. They don't have dependence liability, they're not like chronic use of benzodiazepines. No one would ever suggest that psychedelic doses of these medications should be taken on a regular basis and certainly not on a daily basis, but I think the caution is not unwarranted.

Dr. Ned Kalin ([07:42](#)):

Thanks, Charlie. The next two papers, Charlie, you were actually quite involved with, and one of these is a review on psilocybin and the other is a review on MDMA. As you know, these are probably the leading candidates that are closest to clinical utility, but tell us a bit about each of those and the reviews that you were involved with.

Dr. Charles Nemeroff ([08:01](#)):

So in terms of psilocybin, it has certainly been studied in more randomized controlled trials than any other agent. Of course, the issue with controlled trials with psychedelics is that blinding is a problem so that most people who take a psychedelic know that they got the active treatment and did not get the placebo. And so that's an important and very pragmatic concern about interpreting results with psychedelics. Having said that, there've been multiple trials in depression, which have shown a superior antidepressant effect compared to placebo. There has also been studies in other disorders including alcohol use disorder in which there was a very large effect of psilocybin in reducing heavy drinking days. There are also studies done in patients with metastatic cancer who showed long-lasting benefits of psilocybin treatment in terms of the depression and anxiety. So there will be more to come in this area, but we would have to say the results are absolutely promising.

([09:17](#)):

In terms of MDMA, which is a different class of psychedelic, it's called an entactogen or an empathogen, it has very different subjective effects than the classic psychedelics like LSD or psilocybin. It has largely been studied in post-traumatic stress disorder, and no one I think would disagree that the magnitude of the therapeutic efficacy of MDMA in PTSD is larger than almost any other clinical trial that has involved psychedelics. Maybe the psilocybin alcohol study would match it, but several randomized controlled trials that demonstrated efficacy in PTSD, which obviously is a urgent need because of the lack of effective treatments to get patients into remission. So there'll certainly be more to come with that agent. As you know, the FDA recently did not approve the submission of MDMA for approval for the treatment of PTSD. There are a number of reasons for that. Certainly the efficacy in the trials look very solid, but the FDA is requiring more information. I'm certain that additional studies will ensue.

Dr. Ned Kalin ([10:45](#)):

Charlie, I wonder if you could just say a few words about the psychotherapies that have been suggested to be important in relation to these treatments.

Dr. Charles Nemeroff ([10:53](#)):

So Ned, there's a lot of controversy about this and the field is somewhat divided, and I've been on one side of this argument, which has to do with the question of where is the special sauce here that results in clinical efficacy? Is it the drug or is it the therapy or is it the combination? And I've argued in a paper you published in the American Journal previously that the special sauce is the drug and that psychotherapy can be helpful and it could be addition. But I don't like the term psychedelic assisted therapy because it implies that all the drug is doing is assisting the efficacy of psychotherapy.

([11:40](#)):

And as you know, not included in this issue is a study recently done with LSD without any psychotherapy showing robust efficacy in patients with generalized anxiety. So I think the jury is out about the therapy. I think the important thing to say is that the therapy that's used in psychedelic trials is not what we generally understand to be evidence-based psychotherapy. It's not cognitive behavior therapy, it's not cognitive processing therapy. It's a different kind of social support psycho-education, integration as it's called, and we need more research in this area.

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Dr. Ned Kalin ([12:24](#)):

Thank you, Charlie, that was a nice overview and a nice discussion about the current issues related to the psychotherapy.

([12:31](#)):

The next paper is a paper that is authored by Scott Aaronson, and this gets a little bit into more detail specifically about treating patients. And in this particular case, these are patients that have fairly resistant depression from the standpoint of other treatments that were tried. Do you want to make a few comments about that paper?

Dr. Charles Nemeroff ([12:49](#)):

This is really an interesting paper. Scott Aaronson heads a psychedelic center at Shepherd Pratt affiliated with the University of Maryland. And what he did was pick the most severely treatment resistant patients that you can imagine. These are patients who failed multiple previous treatments, including ECT. And there were 12 patients in the study, and he treated them with a single dose of psilocybin and found dramatic reductions in Madras depression severity scores. I mean, really a remarkable open study. So it's an open study, you have to take it with a grain of salt. But the bottom line is they had three sessions before the treatment with the therapist using the sort of standard kind of psycho-education integration and then a single dose of 25 milligrams of psilocybin. And there was a very robust antidepressant response. I think, Ned, what you and I are most interested in is what is the durability of this effect? How long will it last? Because as we've seen with ketamine and esketamine, you get a very transient effect, but it doesn't persist. And the question here is whether psilocybin will have a much more robust and persistent effect.

Dr. Ned Kalin ([14:17](#)):

The next paper also is a clinical paper with potential relevance. And this is a paper that appears to be a secondary analysis of data that was collected in examining the effects of psilocybin and psychotherapy combined with that in relation to alcohol use disorder treatment. It's a paper by Brock Pagni. Basically one of the claims here is that there are actual changes in some personality traits over time.

Dr. Charles Nemeroff ([14:45](#)):

Yeah, absolutely. So there's a large study done by Michael Bogenschutz and Steven Ross group at NYU, and they looked at 84 patients that they randomized to either psilocybin or to an active control, which was diphenhydramine. And they also received 12 weekly psychotherapy sessions, and there was a long-term follow-up to 24 weeks. And what they reported is using the very best measure of personality, the NEO personality inventory, that they found very long-lasting changes that were towards normalization of personality traits in alcohol use disorder, which are a pretty remarkable finding.

Dr. Ned Kalin ([15:31](#)):

It's quite interesting from the standpoint of the actual impacts potentially on personality. Charlie, the final paper is a paper that deals with getting back to psychological support and perhaps assisted psychotherapy. And it's a paper that is specifically focused on the Compass-sponsored clinical trials. And I think this gets at some of the issues that you're raising a little bit earlier about the psychotherapy and the psychedelic-assisted approaches.

Dr. Charles Nemeroff ([16:02](#)):

Well, I think this is coming out of the Compass group and they're trying to understand the nature of the psychotherapy that they're providing, this very manualized psychotherapy, and what are the components of the psychotherapy that are associated with the therapeutic response. So I think it was a very reasonable contribution to the field. It's just one step towards trying to understand what is the minimal type of psychotherapy in the broadest sense that will be necessary. And we're not in any way suggesting that patients ought to be dosed with drug and not be monitored closely. But the question is in terms of the, not only the acute dosing, but in the aftermath of the experience, what's the best kind of therapy if you want to use that term in the integrative phase? And so this is the Compass's group's manualized psychotherapy treatment.

[\(17:06\)](#):

Ned, the last thing I wanted to mention to you was the issue of biomarkers of psychedelic-induced neuroplasticity, which was summarized by David Olson. And the short version of this is that human imaging studies, as well as preclinical models are being used to determine the mechanism of action of psychedelics. And there's burgeoning evidence that these medications increase neuroplasticity, and it may well be that that is their primary mechanism of action, but a lot more work will need to be done.

[\(17:43\)](#):

The last thing I would say is if psychedelic medications can be useful either in doses that do not produce hallucination, that is microdoses, could be taken every day or alternately analogs of these medications without any hallucinogenic properties could be administered, they might represent novel therapeutic approaches. But obviously we need more research in order to investigate this.

Dr. Ned Kalin [\(18:16\)](#):

But Charlie, thank you for taking the time to talk to us about these papers. This is an exciting issue. It's very, very timely. I think we've got a lot to look forward to in this area as things move forward, I want to particularly acknowledge your efforts, Charlie, and those of Greg Fonzo also at the University of Texas. It's been a pleasure to work with you, and we're excited to hear responses from our readership about this issue. So again, thank you very much, Charlie.

Dr. Charles Nemeroff [\(18:41\)](#):

Thank you, Ned.

Aaron van Dorn [\(18:43\)](#):

That's all for this first episode of AJP Audio for 2025. I hope you'll stick with us for the rest of the year. We'll be back next month with a new episode. But in the meantime, be sure to check out the other podcasts on offer from the APA, including the Medical Mind Podcast, which continues a series on mental health pathfinders with a recent episode talking with APA CEO and Medical Director, Dr. Makita Wills. Check that out and all the other podcasts the APA offers at psychiatryonline.org or wherever you get podcasts.

Announcer [\(19:09\)](#):

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