Aaron van Dorn (00:07):

Welcome to AJP Audio for December 2022. I'm Aaron van Dorn. Today on the podcast I spoke with Dr. Rebecca Price, associate professor of psychiatry and psychology at the University of Pittsburgh. Dr. Price and colleagues investigated the use of a novel automated digital intervention to extend the duration of the antidepressant effects of a single dose of ketamine. Afterwards, I speak with AJP editor-in-chief, Dr. Ned Kalin, about the last issue of the year and what draws it together. Dr. Price, your study looked at the use of ketamine to treat depression in conjunction with an automated computer based intervention. How did you arrive at the idea to pair ketamine injections with active automated self association training?

Dr. Rebecca Price (00:40):

Well, at the really big picture level, we were aiming to develop new treatments that provide a combination of benefits we viewed as lacking currently within our healthcare system options. So namely, we want to develop treatments that are rapid, having a therapeutic onset ideally within hours or days, also efficient, so they would be a limited time investment for patients and practitioners, but have an enduring effect so that you can, over the longer haul, help people feel better, go on with their lives as uninterrupted as possible, and really reduce the burdens and the costs for patients going to seek treatment for depression. And finally, we wanted to focus on approaches that are not resource intensive for the settings where care is being provided. So for example, making use of digital therapeutics is a great way to ensure that there won't be much in the way of resources that need to be provided in order for a person to access that therapy, and potentially anybody with a device of any kind can access such a therapy.

(01:55):

And so this is really important because there's so much need for care for depression and other psychiatric conditions, but this need or this demand really currently far outpaces the supply. These are the kind of principles that we were coming from, and of course we've known for decades that for some patients suffering from depression, a single infusion of ketamine can get that rapid criterion met, so you can see that rapid ability to quickly reduce symptoms within the space of a few hours or one day, even in some cases when other slower acting treatments for depression haven't helped. But the effects of one single infusion ketamine are typically short-lived, and then returning for infusions over and over again to keep that relief going is not necessarily efficient, nor is it necessarily low on the resources that are needed. We wanted to take that as a starting point, but try to solve some of those problems.

(02:50):

From that goal, we drew from the neuroscience literature telling us that ketamine might quickly open up a window of opportunity by rapidly restoring a healthier state of the brain where new therapeutic associations might be readily learned. That was the hypothesis. And more specifically, in our own prior work in patients who had received a single infusion of ketamine, we observed rapid shifts in implicit associations regarding one's self and how one associates the concept of me, myself, with other clinically relevant concepts. And of course we know a core feature and very prominent symptom of depression is quite often this very devastatingly low level of self-worth or self-esteem indicating negative self associations. So we pulled all that background together and came up with this idea to try to use the single infusion of ketamine as a window of opportunity to strengthen associations between the idea of me and positive information and attributes.

Aaron van Dorn (03:55):

What did the computer based intervention consist of? How was it administered?

Dr. Rebecca Price (03:58):

We were drawing on decades of psychology research around something called evaluative conditioning, which is a form of classical conditioning or Pavlovian conditioning, and we developed, by drawing on that literature, some simple but highly systematic and repetitive exercises delivered on a computer screen. These were basically trying to efficiently build up self-worth and help people learn this basic idea that you're worth something, but doing that by simple pairings on the computer screen, some of which were delivered so briefly that they would be below the level of conscious perception, so lipping the letter I and positive words for just 17 milliseconds at a time, doing that repetitively over and over. Other aspects of it used very similar pairings but presented for half a second where you clearly could recognize what you would see on the screen. And then lastly, we also used a pictorial form by taking photos of each patient and pairing those up on the computer screen with smiling photos from standardized photo sets that are used as stimuli in a lot of psychology experiments.

(05:18):

Each of these had a game-like aspect to it where what the patients were asked to do had to do with what we think of as an incidental task, like, "Just click as fast as you can when you see a photo," or, "Press a button to tell us whether the word you see starts with a vowel or a non-vowel." So they're tending to a different task, but as they're attending to that other task, what they're really receiving is these repetitive systematic pairings of self-related stimuli and positive stimuli.

Aaron van Dorn (05:52):

Your study featured a number of comparator arms, including ketamine injections along with a sham intervention and saline injections, along with the computer intervention you were just discussing. How did the various arms compare? How long did the effects of the ketamine plus intervention treatment last?

Dr. Rebecca Price (06:04):

We found in this very first study to look at this that by doing these simple computer exercises following the ketamine infusion, we could extend the antidepressant effect of that one infusion for at least a month, whereas in the individuals who received ketamine but didn't receive our active computer exercises, they actually received identical exercises just minus the therapeutic content. So they were doing those exact same tasks on the computer, but their stimuli would've been not relevant to yourself and not as positively skewed, just a variety of mostly neutral cues. And so in that comparison group, we saw what we typically see in ketamine studies, which is a rapid onset of depression relief and then a gradual return of depression symptoms over the next one or two weeks. And so by about 10 to 12 days in our protocol, the people who just got ketamine, they were no longer showing a benefit relative to the saline group.

(07:09):

And the saline group also did receive the active version of the training task, so that allows us to be confident that there was something special about the combination of ketamine and the cognitive training exercises. So if you had just one without the other, if you had just the cognitive exercises or if you had just the ketamine infusion, neither of those were giving you this lasting relief from depression out to the one month mark. And we're now digging into other data that's not yet published, not included in this paper for AJP, but we did follow the patients with self-report surveys for a much longer period over a year, and it's looking that we actually have at least three months of benefit that we're seeing in those self-report depression scores from this very efficient package of infusion followed by four days of the computer exercises.

Aaron van Dorn (08:04):

Are there immediate clinical implications for your findings?

Dr. Rebecca Price (08:06):

Unfortunately, I would say no, not really. One thing that's been tremendously encouraging to me in the wake of publishing these findings has been the number of both patients and providers reaching out and wanting to know if they can start using this approach in their ketamine or S-ketamine treatments that they're already receiving and do that right now today. So this is really an important validation for us as a study team, as researchers, to know that this idea, this type of approach that we thought might fill a gap within what is available seems to be resonating with people out there who are battling depression and on the front lines, and offer something that they feel they are currently lacking. But I unfortunately have to tell those people, "No, this isn't quite ready for primetime. I can't tell you right now whether there are certain pieces of what we did in this experiment that are really the essential ingredients. I don't have a version of it that's ready to roll out and send your way."

(09:08):

And I've gotten some really interesting questions about, "For my upcoming ketamine infusion, should I bring a photo of myself and of other people smiling?" But I simply can't tell you that, because I don't know if, for instance, the subliminal blips of the words that we did repetitively was really the important ingredient that made it all work. I certainly would think that the degree to which we repeated these trials hundreds and hundreds of times in rapid succession doesn't take a lot of time, but on the computer screen, you can do these really rapid repetitions. That may have been a very important ingredient that would be hard for people to replicate out on their own. Although, I'll say it doesn't sound like something that could possibly hurt to try exposing oneself to positive information, but I certainly don't have the data to tell you that those kinds of things outside of our research context will help at this time, and I'm very hopeful that we will move in that direction and be able to offer something that's useful in real world clinic settings in the relatively near future.

Aaron van Dorn (10:18):

What were the limitations of your study?

Dr. Rebecca Price (10:19):

We allocated all of our resources in the study towards the two comparator arms that we thought were most essential, that being the people who got ketamine without the digital training exercises and people who got the training exercises without ketamine, but we did not have the fourth group that belongs in this design, which is the people who would get saline followed by the sham version of the training. And so this limits our ability to say one way or another whether the training exercises alone may have been doing anything helpful for the patients, because the saline arm, all of them got the real training exercises. So we have a conservative comparison where everybody in our study got at least one intervention, but there are certain questions we can't answer when it comes to understanding the effects in relation to no intervention at all. Also, it's important to highlight that this is a relatively small sample of 154 patients, the first ever test of this intervention.

(11:35):

There are certain criteria that made one eligible for our study, which are not necessarily perfectly generalizable to real world clinical settings, so a very important limitation to address will be to test how this may work in more diverse patients in every sense, heterogeneous diagnoses, more racial and ethnic

diversity than what we had in our sample, et cetera, just to understand whether this could be helpful much more broadly to a larger range of individuals out there suffering.

Aaron van Dorn (12:14):

You discussed it a little bit earlier, but what's next for your research?

Dr. Rebecca Price (12:17):

One area where we're already attempting to expand and have an ongoing clinical trial is in the area of addressing urgent suicidal needs from patients who have a high risk for suicidality. So we are interested in whether a similar type of intervention might be helpful to rapidly reduce suicidal thoughts, and then hopefully keep suicide risk at bay over a more protracted length of time. That's one more immediate direction that we're headed, but we also, as you mentioned, definitely see our next step being to validate whether this approach actually adds real benefit to the treatment that people are already accessing and receiving out in real world clinical settings.

(13:11):

But thinking more broadly about psychiatric diagnoses, and even specific patient profiles of symptoms and thought patterns, what we did here was very, very distilled and very expressly focused on just self-worth and self-esteem, but of course, there are many other patterns of thought that can become quite negative and rigid in the context of depression as well as anxiety, as well as eating disorders, et cetera. So I think that there is a tremendous potential for similar techniques to these to be expanded into more of a repertoire of modules that one might apply in trying to help a given patient with a given presentation.

Aaron van Dorn (13:58):

Dr. Price, thank you for taking the time to speak with us today.

Dr. Rebecca Price (14:00):

Thank you so much for having me. It was a pleasure.

Aaron van Dorn (14:02):

Up next, Dr. Ned Kalin. Dr. Kalin, welcome to the last AJP Audio for 2022.

Dr. Ned Kalin (14:07):

Thank you. It's a pleasure to be with you.

Aaron van Dorn (14:08):

This month, AJP looked at new therapeutic approaches to treatment involving digital technology, fMRI neurofeedback, and psycho-pharmacology. Earlier in this episode, I spoke with Dr. Rebecca Price regarding her and her colleagues' paper, which integrated several of those approaches by investigating the duration of antidepressant effects of a single infusion of ketamine coupled with an automated digital intervention. What can you tell us about that?

Dr. Ned Kalin (14:28):

Thanks, Aaron. This is a particularly interesting and exciting issue because it really gets into clinically relevant treatment issues, and the paper by Price and co-authors looking at how to prolong the effects of ketamine infusion is particularly interesting. In this paper, what the authors did was basically look at a cognitive therapeutic intervention, which was an automated intervention called automated self-association training and paired that with one ketamine infusion in individuals that suffered from depression. They did a controlled trial where they compared three conditions, one ketamine infusion with this psychotherapy, one ketamine infusion with a sham type of psychotherapy, and then a saline infusion with this automated self-association training psychotherapy. And what they found was one ketamine infusion, when it was administered with the sham psychotherapy, had positive effects but the effects weren't very long lasting, as we know from ketamine. And that's one of the issues in the field with ketamine is how often do you have to give it to maintain a response if you give it repeatedly, and how can we better maintain the acute response over time from the ketamine infusion?

(15:46):

The group that got ketamine plus the psychotherapy not only had an acute improvement in the depression, but that improvement was maintained over the course of the study, which was a 30 day assessment period. So that's exciting, because unlike ketamine alone, by adding in the psychotherapeutic intervention, it looked like the two treatments, ketamine plus the psychotherapy, enabled a prolonged response in individuals with depression. They also looked at a group that just got the psychotherapy alone and got a saline infusion instead of ketamine infusion, and that group actually got somewhat better and stayed better over time, but the amount of improvement was not nearly what was observed with the combination of ketamine plus the psychotherapy. So this is exciting because it suggests a non-pharmacological way of prolonging or maintaining a ketamine response.

(16:41):

Now, how that's working is a whole other story. It could be that ketamine is increasing neuroplasticity and therefore allowing the psychotherapeutic intervention to have more of an effect, but it also could be that these are just synergistic effects and that it really doesn't have anything to do with increasing neuroplasticity. That remains to be determined in future studies. Alan Schatzberg from Stanford wrote a really nice editorial on this paper that gets into the important issue of long-term maintenance of initial ketamine responses and how to think about other approaches to prolong ketamine responses.

Aaron van Dorn (17:18):

We have three additional papers in the issue that look closely at psycho-pharmacology. Let's start with a paper by Santos et al on the use of oral naltrexone with sexual and gender minority men with mild to moderate alcohol use disorder.

Dr. Ned Kalin (17:28):

So this is a paper that has findings that are not surprising, but are quite important from the standpoint of the population that was studied. And so this is a study looking at how to reduce binge drinking in individuals that have moderate levels of alcohol dependent symptoms. But what's important here is that the study group was 120 sexual and gender minority men, and this is a group that has been relatively understudied. And the authors of this paper argue that binge drinking in this group could be particularly relevant because it may be associated with more risky behaviors, and also more risky related sexual behaviors, and possibly lead to greater likelihood of acquiring sexually transmitted diseases, for example, HIV. So in this particular study, the design was to use oral naltrexone, 50 milligrams, versus placebo, but to do this in a way that is called targeted treatment. In this particular case, the participants

in the study over the 12 week study period were instructed to take the naltrexone when they expected that they were going to have episodes of heavy drinking or they were doing a lot of alcohol craving.

(18:50):

And what the authors found was that the treatment group, the naltrexone group, reduced binge drinking significantly over this period of time, and also reduced measures of alcohol craving as well. But interestingly enough, despite the effects that naltrexone had on alcohol consumption, the naltrexone group did not report significant differences from the placebo group in relation to engaging in risky related sexual behaviors. So while naltrexone reduced binge drinking, the link that the authors were trying to make between binge drinking and risky sexual behaviors, that link was not changed even though naltrexone had an effect. So not surprising findings, but important study in this population that has been understudied.

Aaron van Dorn (19:38):

Grilo and colleagues also investigated a pharmacological intervention, this time among patients with binge eating disorder.

Dr. Ned Kalin (19:43):

So again, both substance use disorders, like alcohol use disorder and binge eating disorder, we can think of as related to alterations in the reward related circuitry, or addictive types of disorders. And in this particular study, the investigators examined the combination of naltrexone and bupropion together versus behavioral weight loss therapy in treating binging disorder patients that also had comorbid obesity. A couple things to note. First of all, binge eating disorder is thought to be the most common eating disorder. Lifetime prevalence is thought to be around 3.5% with a greater prevalence in women than men. This frequently occurs with obesity, but the authors point this out that the obesity that's associated with binge eating may have a very different pathophysiology than the obesity that we think of as just more general obesity. What the study looked at, then, was four interventions in relatively small groups of people, roughly 35 per group. The first intervention was behavioral weight loss therapy plus placebo, the second intervention was bupropion-naltrexone combination, the third treatment group was bupropion-naltrexone with behavioral loss therapy, and the fourth group was placebo.

(21:04):

And what the authors found was that both the bupropion-naltrexone combination and behavioral weight loss therapy independently were effective for reducing binge eating, and what they found was that for the naltrexone group remission rates for binge eating were around 31%, for the behavioral weight loss group it was about 37%, and for the combination, a combination of naltrexone, buproprion, and weight loss therapy, about 57%. Now, even though the combination was greater than either one of the active treatments alone, this was not significantly greater, and the authors concluded that there was really no significant advantage of using the combination. But what's interesting about this is that the behavioral weight loss intervention group also showed more dramatic and significant weight reductions as far as their obesity went, and this started at two months of treatment and continued. And that magnitude of that effect was not seen in the naltrexone-bupropion alone group.

(22:13):

So it appears that both treatments can be helpful for a binge eating disorder, but for those individuals that have significant weight problems or obesity that's associated with it, which is common, it appears that the behavior weight loss therapy may be more effective than the combination of naltrexone and bupropion. So this is good data for clinicians to think about how to select treatments for their patients

that are struggling with eating disorders, and in this particular case, specifically binge eating disorders associated with obesity.

Aaron van Dorn (22:45):

Next up, Taipale and colleagues looked at the effectiveness of antipsychotic treatments on reducing work disability. What did they find?

Dr. Ned Kalin (22:51):

This is another interesting study. The findings are, I would say, expected, but again, what's interesting about this study, it's done in a very large Swedish population studying over 20,000 individuals that had a first episode non-effective psychotic episode, and these individuals were followed longitudinally from between four to 11 years. And what the investigators did is that they looked at work related disability in relation to when these individuals were taking and when they were not taking their antipsychotic medication. And one of the strong features of this study is that the measures of disability were actual objective measures in a sense of sickness absence or receiving a disability pension from the government, so these were measures of disability that were not just asking the question, "How disabled do you feel," or, "What can you do or can't do," but really a bit more objective measures of disability. And the analyses that were performed in those individuals that were taking in psychotic medications, and looking at them longitudinally to understand when they were on the medicines, how much disability did they have, and when they were off the medicines, how much disability do they have.

(24:06):

When individuals took their antipsychotic medication, the risk of disability was decreased by about 35%. Importantly, when they looked at longer term disability over a 90 day period, this was reduced by about 45%. So they also found that when individuals were on the long acting injectable antipsychotic formulations, that they were likely to do better than when not. Again, not particularly surprising, but a very well done study. A large sample, longitudinal data with really strong measures of disability, looking within individuals and demonstrating the importance of adherence to antipsychotic medication. And in particular, the advantage, again, that we know about of the use of long-acting injectable formulations. So another important, clinically relevant piece of information.

Aaron van Dorn (24:54):

Finally, we have an interesting paper that was looking at the efficacy of using functional MRI neurofeedback as the clinical and cognitive measure in children with ADHD.

Dr. Ned Kalin (25:01):

This is an interesting paper, and it actually is a negative finding, and we decided to publish this because we think that it's important to not only publish findings that are positive, but also, in well done studies, to publish findings that are negative, that are not positive. And this is looking at neurofeedback in children with ADHD. And there's been a push over the recent years to do neurofeedback in the MRI scanner, which enables the possibility of teaching individuals how to begin to regulate the activity of different brain regions. And the idea is that if we can identify brain circuits that are involved in the pathophysiology of an illness, and if the function of these circuits is altered, then perhaps we can actually teach individuals how to modulate the function, up-regulate or down-regulate, for example, the activity of that particular circuit. Now, there's nothing new about neurofeedback, and actually in the editorial that's contributed by Dr. James McGough from UCLA, he discusses the history of the use of various types of neurofeedback for ADHD.

(26:18):

But what's new here is doing this in the MRI scanner, and without going into the details, the researchers taught, basically, the participants how to up and down-regulate the function of a region in the frontal cortex called the right inferior frontal cortex, which has been implicated in ADHD, and also has been implicated in various processes, including cognitive control processes. They also had a really good control comparator, which was a sham group in the scanner where they were doing the same type of task and manipulation, but did not get accurate feedback about manipulating this particular part of their brain. The findings were basically that when the individuals were followed up at one week and six months, the boys that were in the active group, and also the boys in the sham group, both showed initial improvements in ADHD symptoms. But over time, and over a six month period, these reductions in symptoms went away, that is both groups went back to where they were before. So really no sustained effect of either treatment.

(27:31):

So that's the negative finding that this particular neural circuit or brain region focused neurofeedback training mechanism did not have a positive effect on reducing symptoms over time in ADHD individuals any greater than the sham group. What was interesting was that these individuals actually did learn to modulate activity of that region, and actually there was increased activity in this brain region that was detected in individuals that received this act of treatment. But even though they had these brain changes, it was not associated with any symptom changes. So it's a negative finding, like I said, that suggests that this particular neurofeedback approach is not effective for ADHD.

(28:15):

It does not mean that all other methods might not be effective. There are a variety of other neural circuits and other ways of thinking about neurofeedback in the scanner for this population and other populations that may be effective. But we wanted to get this out there as an example of a really well done study that has a negative finding, which is eye-opening. And then, as I mentioned, the editorial by Dr. McGough not only talks about the history of neurofeedback and ADHD, which goes way back, but also he calls the question as to whether this approach is really going to be a feasible and effective approach for ADHD patients.

Aaron van Dorn (28:53):

Well, Dr. Kalin, thank you once again for taking the time to speak with us.

Dr. Ned Kalin (28:56):

You're very welcome. Take care.

Aaron van Dorn (28:57):

That's it for AJP Audio for 2022, but be sure to check out the other podcasts from the APA at psychiatryonline.org. In the latest episode of Psychiatric Services From Pages to Practice, Dr. Dixon and Dr. Berezin talked to Dr. Nathaniel Morris about what involuntary psychiatric hospitalization means for patients and practitioners. All the best to you and yours, and I hope you'll join us once again in the new year.

(29:16):

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