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Evolving Pharmacologic Intervention for Methamphetamine Use Disorder: A Focus on ADAPT-2

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Dr. Shoptaw:
This is CME on ReachMD, and I'm Dr. Steven Shoptaw. Today, my colleague, Dr. Madhukar Trivedi and I will be discussing the evolving landscape of pharmacologic intervention for methamphetamine use disorder. Our focus will be evidence from the ADAPT-2 clinical trial, recently published, supporting that the combination of extended-release naltrexone and high-dose bupropion can reduce methamphetamine use for patients with moderate to severe methamphetamine addiction. Dr. Trivedi, welcome.

Dr. Trivedi:
Thank you very much, Steve. These important data from ADAPT-2 offer clearly a good therapeutic advance for methamphetamine use disorder, and hopefully we can now take it to the clinic. The U.S. attention toward addiction, obviously has focused largely on opioids in the last several years, with good reason. On the other hand, the recent National Center for Health Statistics data reported the rate of overdose deaths involving stimulants increased ten times between 2009 and 2019. So this prevalence of meth misuse is common in the western U.S. This drug is now endemic to the hill country and the rust belt cities, where the opioid epidemic rages. More recently, a morbidity/mortality weekly report from the CDC estimated among adults reporting use of methamphetamine, about 53% had meth use disorder. So this current level of use and addiction to methamphetamine among American adults is beginning to be at a high that has not been seen for almost a decade and a half. Given the size of this problem, Dr. Shoptaw, what are the treatments that are currently available for people who want to stop their methamphetamine use?

Dr. Shoptaw:
Madhukar, that's a great question. Up until today we've not been able to answer the question, other than to say behavioral therapies are the only treatments that show evidence for reducing methamphetamine use – things like contingency management, cognitive behavioral therapy and motivational interviewing. It remains that there are no FDA-approved treatments for methamphetamine use disorder, but over the last twenty years, we've seen randomized placebo controlled trial outcomes show some signals of efficacy, either in post hoc analyses or in subgroup analyses. Now, naltrexone is one of these, and bupropion is another. So, one of the things that the ADAPT-2 trial was built on is the rationale of combining these two medications – naltrexone and bupropion, that have a hint of efficacy – to set the dose at the highest levels possible and give the combination medication every opportunity to show a sign of efficacy in reducing methamphetamine use.

So, there was other things that are going on that supported the rationale. Number one – the high dose. Number two – the idea of some early preliminary work showing that the combination was tolerable and that it had some indication of efficacy, and that leads us to today's discussion about the ADAPT-2 trial. In designing the ADAPT trial, the team was very mindful of several issues that had plagued previous trials. One is the heterogeneity of the illness, and how it presents at baseline. We decided to focus on severe users of

methamphetamine, documented by 18 or more days of methamphetamine use at baseline, requiring people to provide two urine drug screens that were positive for methamphetamine within a 10-day period at baseline to document severe methamphetamine use. Small sample sizes. This trial had 403 participants in it. It was fully powered to show any signal of efficacy. There was no question that at the end of the study, we would know what happened when you used this medication combination. High placebo responses. Many of the medication trials up until this time have suffered from people showing unexpectedly high responses to placebo. In the sequential parallel comparison design that was used in this trial, initial randomization to placebo was enriched with a 3:1 response ratio of placebo to active medication to account for the high placebo response in prior trials. Ill-defined attention to retention. We paid a lot of attention to retention and to medication adherence during the trial. And then finally, poorly-defined outcome measures. This trial was designed to show that there was a treatment response, and in fact, that's the primary outcome – a response. That is, being able to provide three or more urine-negative samples in the two-week period – weeks five and six, and weeks 11 and 12, in the trial.

Dr. Trivedi, what're your thoughts are about the preparation and implementation of the ADAPT-2 trial.

Dr. Trivedi:
So I think, Steve, you captured it – what we were running into when we were designing this study is that the field had imagined that there are no pharmacological treatments available because there were a whole lot of studies that had not succeeded in the past.

A number of these things went into the design of this, and then we really were very mindful of the challenges you just raised. So all of these issues were focused on, in order to get to that point.

And I think that maybe it is probably best for me to go through a little bit of the results from this.

So we have enrolled 403 participants in Stage 1, and this was an adaptive study design called Sequential Parallel Comparison Design. Any of you interested in the nuances of this design can read it up in our New England Journal of Medicine paper. But the bottom line is, that at the end of the Stage 1, and then at end of Stage 2, we really evaluated people who had significant benefit in their methamphetamine use. And we found that about, on an average, about 16.5% of the people in the combination group, naltrexone and bupropion, and only 3.4% in the placebo group in the first phase got response. And in the second stage, it was even higher, so that we got 11%, 11.4% of people doing very well on the combination, as opposed to only 1.8%. So we basically, in a nutshell, were able to accomplish the task of reducing the unnecessary placebo response, and our number of the people who got better on the combination was almost ten times better than what happened on placebo. And in addition, we did a number of secondary data analyses that included percentages of urine samples testing negative, reductions in craving, reductions in depressive symptoms, improvement in self-evaluations of treatment effectiveness.

So two things about the outcomes. Our primary outcome measures were met. The second thing is the consistency of the findings across all of the secondary outcomes.

So, I think that, not surprising, we are pleased with the results, and this gives us now a bona fide, real leverage to say there is a pharmacological intervention available for this population.

So Dr. Shoptaw, I think having talked about some of the results, maybe give your perspective on what you feel the magnitude and the impact of this is, and also how do we then disseminate this so that this becomes available to patients.

Dr. Shoptaw:
Thanks Madhukar. I think that these results are incredibly exciting. I think it's important to remember that the number needed to treat – that is, the number of patients needed to be treated with this medication combination to show an effect – to see the effect is nine. So, out of every nine patients, one on average is going to show the effect that you mentioned. We need to think about using the combination to treat a panel or a population of patients, not figuring out which one is going to respond. This is a treatment that works. Our charge, as you mentioned, is to figure out how we use it. That on average, the population of patients with this severe methamphetamine use disorder are going to benefit if we treat the population with the medication combination. One of the questions that comes up is, you know, is this a relevant number needed to treat? Is the number needed to treat of nine relevant? Well, by comparison, Vivitrol – that is the extended-release naltrexone part of this formulation – is approved for use for reducing heavy drinking days for alcohol use disorder, and the number needed to treat is twelve. So it's in the same neighborhood.

Dr. Trivedi:
Sorry to interrupt, Steve, but I think that this number needed to treat part is something I'm so glad you are getting into the details. As you know, NICE guidelines in the U.K. will use number needed to treat of less than ten as a trigger for people to change clinical practice. It always needs remembering that the number needed to treat of nine is in the realm of other treatments.

Dr. Shoptaw:

And building on your point, Madhukar, the FDA is apparently very comfortable in approving medications for addictions that have outcomes that don't include absolute abstinence. Vivitrol is approved for use for reducing heavy drinking days in alcohol use disorder, so, I would think that the opportunity to have this be an FDA-approved product soon, or in our future, is there. I think the challenge is, how do we get our field to get this out there, and I think that there's some important questions that come to mind about that, whether that's getting this combination on to formularies, so that people can, prescribe the medication to patients in front of them.

Next we need to ensure that there's equity in access to this combination approach. We understand that the private insurance market may adopt this quickly, but the idea of being able to get it into FQHC's and other settings where people who may have either limited or no health insurance would be able to access this medication combination. And finally, what we need to do is to think about making access available for people who are in 12-step, or other behavioral therapies, because we know that medications are only a piece of the treatment answer that people are, and need, to engage behaviorally as well as medically in their treatment recovery process.

Dr. Trivedi, what is your perspective about the barriers that we face in getting this out in the field?

Dr. Trivedi:
I think we have to really focus on the science, is my biased view. The evidence is overwhelming that this works. Our task is to really get providers, patients, demanding. I mean, I think that in most cases in the United States, treatments that get paid for by payers is often a combination of science and what the society demands. So we just have to be convincing our partners in all aspects of society to understand that the risk of not treating methamphetamine use disorder remains and continues to get worse.

Dr. Shoptaw, what do you think is our next steps, now that we know about the results from ADAPT-2?

Dr. Shoptaw:
So, one of the most important things I'm encountering as I move in our field, is that we first need to get agreement that it is time to consider pharmacotherapy as the foundation for methamphetamine use treatment. This pharmacotherapy combination works. For people who respond to it, they don't have to think about doing anything or changing their behavior. It just works. That provides a nice foundation for moving forward. But that doesn't mean that clinicians and providers are going to line up to the prescription pad and make this available to people. There are many people who feel differently about the role of pharmacotherapy in stimulant use disorder treatment. We need to engage our field in a discussion to talk about this issue, to get in line, to bring people in line to agree that this effect is important, and we need to move this medication forward. We see a 15-18% reduction in methamphetamine use with this medication. Is that significant? I think it is. I definitely think so. Next, we need to talk about how to provide the care. We don't need any more silos of care. We need actual interactive, integrative treatments. So the idea of bringing this as a foundation of medication for stimulant use disorder treatment, it's agenda-setting, and it's what we need next.

Well, this has certainly been a fascinating conversation. But before we wrap up, Madhukar, do you have any take homes? One take home message that you want our audience to remember?

Dr. Trivedi:
I think that the methamphetamine use disorder is a serious illness and has fatal outcomes, and that this combination is a pharmacological option that should be discussed with patients, and payers to insure that patients are allowed to have this as an option in their treatment program.

Dr. Shoptaw:
I agree with that. And I also think it is time for us as a field to begin the discussion of considering medication as a foundation for treatment of stimulant use disorder.

Unfortunately, that's all the time we have today. So I want to thank our audience for listening in, and thank you, Dr. Madhukar Trivedi, for joining me and sharing all of your valuable insights. It was great speaking with you today.

Dr. Trivedi:
Thanks a lot, Steve.

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