Aaron van Dorn (00:07):

Welcome to *AJP Audio* for March 2025. I'm Aaron van Dorn. Today on the podcast I spoke with Dr. William Horan, a researcher at Bristol Myers Squibb. Dr. Horan and colleagues have a paper in the March issue of the American Journal of Psychiatry, looking at Xanomeline and Trospium, a recently approved monotherapy for the treatment of schizophrenia that has a novel mechanism of action and its potential cognitive benefits. Afterwards, I'll once again speak with Dr. Ned Kalin, AJP Editor-in-Chief, about the rest of the March issue and what draws it together. Dr. Horan, your study looked at the impact of Xanomeline and Trospium monotherapy on cognitive impairment in patients with acute schizophrenia using pooled data from two, phase three clinical trials. What did you find?

Dr. William Horan (00:45):

Well, in this study, we sought to confirm findings from an earlier phase two placebo controlled study, that was in about 125 acutely symptomatic people with schizophrenia. We found that treatment with KarXT, while it wasn't associated with cognitive improvement in the full sample, it was associated significantly compared to placebo on an exploratory cognitive endpoint in a subgroup of people with schizophrenia. Specifically a subgroup that came in with at least moderate impairment at baseline, and that was defined as having at least one standard deviation below healthy normative standards on a cognitive battery. What we found in our recently published study confirmed those earlier results. So we combined data from two phase three trials. It was a much larger sample, about 350 patients, and as in the phase two trial, although we didn't see any improvements on an exploratory cognitive endpoint, in this case, the CANTAB battery, which was developed by Cambridge Cognition. We did again find that among the subsample of people who came in with at least moderate impairment at baseline, they did show an improvement compared to placebo.

(02:12):

And again, impairment was defined as scoring at least one standard deviation or worse, compared to healthy normative standards from a reference sample. So the results were really very similar across the phase two and phase three data sets. The magnitude of the effect was quite comparable, so about a Cohen's D effect size of 0.50 in the phase two, compared to 0.54 in the phase three. And there were also minimal correlations with changes in symptoms, and that was either assessed by the PANS total score or positive or negative symptom subscales, along with changes in cognition. Suggesting that they were not tightly coupled to changes in clinical symptoms overall. So what we're seeing here is a consistent story, and it's encouraging because it's the first time a monotherapy for the treatment of schizophrenia has shown a replicable cognitive benefit.

Aaron van Dorn (03:15):

Prior to the FDA approval for Xanomeline and Trospium monotherapy, which bind to the M1, M4 muscarinic receptors, all the previously approved antipsychotic medications for the treatment of schizophrenia bound to the D2 receptor. What is the difference between the mechanism of action in these treatments important?

Dr. William Horan (03:29):

Well, right, as you said, for decades we've been using antipsychotics that all shared this single mechanism, which with a few minor nuances and qualifications, all focus on blockade of dopamine D2 receptors, post-synaptic dopamine D2 receptors. So on the positive side, those medicines are helpful in controlling positive symptoms for many people with schizophrenia. On the negative side, however, they don't fully treat positive symptoms for all patients. In addition, they come with a number of distressing

side effects, and those include things like lethargy or lack of energy, extrapyramidal side effects or movement problems, which can even include tardive dyskinesia, metabolic syndrome, and in some cases quite large weight gain. Also, they don't effectively treat the cognitive symptoms or the negative symptoms.

(04:31):

And those are really the key drivers of long-term challenges in daily life functioning for people with schizophrenia. So while they have some key benefits, these drugs that we've used for decades also come along with these troubling side effects and they don't really impact cognitive and negative symptoms. KarXT is really a fundamentally new approach to targeting schizophrenia. It focuses on a different neurotransmitter system, the acetylcholine neurotransmitter system, and specifically muscarinic M1 and M4 receptors in the brain. So it acts without directly blocking D2 dopamine receptors at all. What's exciting about that is, you can get potentially effective control of positive symptoms, potentially also cognitive and negative symptoms without experiencing all the troubling side effects that go along with those traditional dopamine D2 receptor blockers.

Aaron van Dorn (05:39):

As you mentioned, traditional antipsychotic medications have had some severe side effects that can limit their clinical effectiveness in treating patients with schizophrenia. How does the side effect profile of Xanomeline and Trospium monotherapy compare traditional antipsychotic medications?

Dr. William Horan (05:53):

Well, the safety and tolerability profile of KarXT has been established now across acute and long-term trials up to 12 months. And it does have some side effects that go along with its cholinergic mechanism of action. And in the phase three trials, these were predominantly GI-related symptoms. So things like nausea, upset stomach, constipation, and some vomiting. Now they tend to occur very early when people are starting on the medicine and titrating up, and they tend to be relatively short-lived. So people habituate to them as they continue with treatment. It's also worth noting that in those trials we did not see a high incidence of those typical side effects that are associated with dopamine D2 blockers, the lethargy, weight gain, metabolic changes and movement disorders. So Cobenfy doesn't carry a boxed warning and it does not have atypical class warnings and precautions. However, it does have some warnings and precautions, and they include things like risk of urinary retention, risk of use in patients with hepatic impairment and a few others along those lines.

Aaron van Dorn (07:20):

As we mentioned earlier, Xanomeline and Trospium monotherapy was approved by the FDA last September, increasing the armamentarium for schizophrenia treatment for clinicians. But do your findings have any immediate clinical relevance for that clinicians treating these patients should consider?

Dr. William Horan (07:33):

Well, at this stage, Cobenfy is indicated for the treatment of schizophrenia in adults. So the key immediate relevance is that this medicine can provide effective positive symptom control without the distressing side effects that are associated with the drugs that we've typically used. Now, as mentioned earlier, cognition was evaluated as an exploratory measure in the phase two and phase three trials, and cognition data was not included in the approval package for KarXT and it's not included in the label. So at this stage, while we're very encouraged by the consistent cognitive improvements and also some

negative symptom improvements seen across the phase two and phase three trials, the jury is still out and we need additional research to really get a handle on whether it can help with those aspects of schizophrenia as well.

Aaron van Dorn (08:31):

Beyond clinical relevance, what further research is required in this area? Both with Xanomeline and Trospium and with schizophrenia treatment research in general?

Dr. William Horan (08:38):

So as we discussed, our evaluation of KarXT's impact on cognition was exploratory in nature. And the data generated was intended to inform potential future hypothesis testing efforts, rather than support an indication or be included in the label. So to support a label for cognition, we would really need to use a different type of design and different participants. We would need to enroll participants with predominant cognitive symptoms who are in a stable phase of the illness, not in the midst of an acute psychotic episode, and target cognitive symptoms as the primary outcome. So we continue to explore next steps to try to collect that type of data for KarXT as it relates to cognitive impairment and schizophrenia. And at this stage, the field has been trying for decades to identify a medication for cognitive impairment and we just haven't so far. If we can move this forward and collect the data that we need, it would be a wonderful addition to the clinician's toolbox if we could identify a cognitive enhancing drug.

Aaron van Dorn (09:58):

What were the limitations of your research?

Dr. William Horan (10:00):

There were several. The trials that were the basis of this research were short-term trials, about five weeks. And they were in acutely symptomatic people, so they were in the midst of an episode of psychosis. And it's challenging to isolate cognitive changes from other changes in symptoms that occur in that context.

Aaron van Dorn (10:25):

Of course.

Dr. William Horan (10:26):

Some other limitations, the battery that we used, it focused on four key cognitive domains in schizophrenia, but it didn't cover all seven of the domains that are prescribed in the matrix consensus guidelines for CIS trials and schizophrenia. We also didn't include a measure of functional capacity or functioning to get at whether any changes in cognition had functional implications, or were functionally meaningful. And of course, these were just placebo-controlled studies, so there was no comparison to other antipsychotics to see how they compare to each other.

Aaron van Dorn (11:05):

What's next for your personal research?

Dr. William Horan (11:07):

Well, there are a couple of different areas that I'll mention. The first one is in addition to looking at standard measures of clinical symptoms and cognition, we've been doing some qualitative research on participant experience with taking KarXT. And this involves conducting in-depth interviews with them to hear about what their challenges are when they come into the study as related to positive negative cognitive symptoms, and things like quality of life and treatment satisfaction. And then we follow them up to six months to ask how the treatment has impacted those things either favorably or unfavorably. We've started to present some of that data at conferences and it provides some real insight into what taking this medication is like for people with schizophrenia.

(12:01):

And I can tell you from the data that we've looked at so far, many report challenges with cognition, and they report favorable effects on those challenges as they continue with the medication. Another area that we're looking into is, what other indications or conditions might KarXT be helpful with? So in addition to using KarXT as a monotherapy in schizophrenia, there's an ongoing trial looking at KarXT as an adjunctive treatment for schizophrenia. Also, looking at whether it might be helpful for treating psychosis in people with Alzheimer's disease, and then some additional directions as well, things like potentially bipolar mania. Or within Alzheimer's disease, whether it could help potentially with things like agitation or even cognitive impairment, which of course is so central to Alzheimer's disease.

Aaron van Dorn (13:00):

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

Dr. William Horan (13:02):

My pleasure.

Aaron van Dorn (13:03):

Up next Dr. Ned Kalin. Dr. Kalin, welcome back to AJP Audio for March 2025.

Dr. Ned Kalin (13:08):

Thank you, Aaron. It's good to be here.

Aaron van Dorn (13:09):

This month on the podcast I spoke with Dr. William Horan, Dr. Horan and colleagues looked at a new novel antipsychotic treatment of patients with schizophrenia that utilizes a different mechanism of action from other available treatments. What can you tell us about it?

Dr. Ned Kalin (13:21):

So Aaron, this is an interesting study examining not only the established antipsychotic properties of this newly approved treatment for schizophrenia, but also continuing to look at and confirm that this drug also has positive effects on improving cognition in individuals that are suffering from schizophrenia. The drug itself is KarXT or it's also known as Cobenfy. It's a M1, M4 muscarinic agonist with a peripheral antagonist. And the actual chemicals or drugs are Xanomeline and also Trospium. This combination allows for the brain stimulation of muscarinic receptors to activate them, and at the same time inhibiting these types of receptors in the periphery outside the brain. And the reason that this is proven to be useful is because in the past drugs that would activate muscarinic receptors would have really bad side effects from the standpoint of a whole host of physiological effects.

(14:25):

And so this combination has allowed the ability to activate muscarinic receptors in the brain, which appear to have or do have some antipsychotic effects, and at the same time blocking the typical peripheral side effects of these kinds of drugs by using this antagonist of the system that only works peripherally and doesn't get into the brain. So it's a very clever approach. And this has recently been improved as a new mechanism. It's not a dopaminergic mechanism, at least not directly for this treatment of psychotic symptoms and for being effective in schizophrenia. But also, the drug has been explored from a standpoint of its so-called pro-cognitive effects, which basically means enhancing cognition. This drug has already been studied in some earlier work that was done in some of the phase two trials that suggested that it had positive effects on cognition. And this is now an analysis of about 150 patients that received the drug and roughly 150 patients that did not, who were acutely psychotic, looking at whether or not this improved cognition.

(15:31):

The bottom line is that the researchers found that it did, but only in those individuals that already had significant cognitive alterations of baseline. This I think is an important point that it did not further enhance cognition in individuals with schizophrenia, that already had relatively normal cognitive functioning. But this is important because cognitive functioning is a hallmark of psychotic disorders, alterations of cognitive functioning, and has been linked to social outcomes and functional outcomes. And so this looks like it will not only target the psychotic symptoms, but will help cognition in those individuals that already have this impairment. And importantly, it looks like, although it's hard to establish this, that these effects seem to be somewhat independent of the effects of the drug on the psychotic symptoms. I think that this is a real opportunity to think about not only improving psychotic symptoms, but also cognitive functioning in our patients that are suffering from schizophrenia.

Aaron van Dorn (16:28):

Has this drug has a lower side effect profile than traditional antipsychotics? Is this something that's going to supplement traditional antipsychotic medicines that act on dopamine receptors or is it something that's going to be used in conjunction with them?

Dr. Ned Kalin (16:39):

Right now it looks like this will be used independently of those drugs. It does have a different side effect profile. I wouldn't say it has less side effects. It has different side effects, but it certainly does not seem to have some of the most concerning side effects that we see with the dopamine blockers such as tardive dyskinesia. It remains to be seen, this drug hasn't been used all that much over time in many, many more individuals. What kind of things come out? But by and large, it really does work by a different mechanism, which is great to have in our armamentarium so that if the typical or atypical antipsychotic drugs, which mostly work by blocking dopamine, two receptors don't work in an individual, that this could be another treatment strategy. And also, as you alluded to, the side effect profile is extremely different. And also now because of these, what looks like to be these positive effects on cognition may be another added benefit of this strategy using this medicine.

Aaron van Dorn (17:34):

Next we have a review from Levenstein and colleagues looking at the use of ketamine as an antidepressant.

Dr. Ned Kalin (17:38):

This is an important paper because this paper pulls together preclinical and clinical research data that begins to try to talk about the complex mechanisms that may be mediating the antidepressant effects of the use of sub-anesthetic doses of ketamine. So I think almost everybody now is aware of the potential of sub-anesthetic ketamine, as a rapid-acting antidepressant agent, and also perhaps as an anti-suicidal agent. The initial studies suggested that the major mechanism of action was mediated through antagonism of the NMDA receptor affecting the excitatory neurotransmitter systems, and there's still absolutely considerable data that's related to that. This paper also delves into the evidence that supports opiate mechanisms as also being important in mediating some of the effects of ketamine and probably working in conjunction with some of the NMDA antagonist effects. And so this paper really brings that to the fore and opens up a variety of questions, including thinking more deeply about how opiate mechanisms themselves may be pathways into novel antidepressant treatments.

Aaron van Dorn (19:00):

Fal Tolecus and colleagues also have a review, this time a meta-analysis looking at Esketamine also for the treatment of depression.

Dr. Ned Kalin (19:05):

So this is a nice complement to the paper we just talked. Also talking about ketamine, in this case it's Esketamine is an enantiomer of ketamine. So ketamine when it's administered is what we call a racemic mixture. It has two different enantiomers that are mirror images of each other chemically. This is the one that's thought to be more potent. Esketamine. And of course, what's different here is that instead of administering it intravenously, this is a preparation that's been approved for intranasal administration, and has been used quite avidly in the field. It was initially approved by the FDA for treatment resistant depression and also as an add-on basically to other antidepressant treatments and perhaps as an anti-suicidal treatment. More recently, it's been approved by the FDA for using it alone by itself in the treatment of depression.

(19:56):

This is another really important paper I think, because it takes a look at the entire literature in which clinical trials have been done pitting esketamine against other drugs or looking at esketamine just over time in relation to placebo. The outcome of this meta analysis is important because it suggests that while esketamine is effective, the effect may not be as strong as was initially thought or purported. It looks like that the effects also may be relatively short-lived. So in this particular meta analysis, the magnitude of the effects that were found were on the order of what we see with some other adjunctive treatments for depression. So for example, a number of antipsychotic drugs have now been established to be effective as an adjunct to improving the way an antidepressant works. And so the effects of esketamine look to be along that magnitude, but of somewhat concern, this meta-analysis strongly suggests that the effects are relatively short-lived.

Aaron van Dorn (20:57):

Next, we have an article from Couture and colleagues looking at another novel depression treatment. This time, space transcranial direct current stimulation.

Dr. Ned Kalin (21:03):

This is a very preliminary study, and I'll start off by saying the findings need to be taken with a grain of salt because of its preliminary nature. Nonetheless, we thought it was interesting to publish in the journal because of the potential that this treatment has. So this is now using direct current stimulation

with small little electrodes on the front of the brain. What's really nice about this is it's easy to do. It's relatively inexpensive. It could be done at home, so it's a treatment that may have wide applicability at some point, if it's effective. And there have been a number of studies looking at this as a treatment for depression, some of which have suggested that it works and others of which suggested that it doesn't. So the data's quite mixed. And the motivation for this study was to try to see if the application of this treatment could be more effective by modifying how often it was given. Giving it more frequently within a day.

(22:01):

And so in this particular study, the investigators used this direct cranial stimulation over the front of the brain five times a day with 20-minute intervals over a five-week period for a total of 50 applications. And I should say that this was an open-label study, so individuals knew they were getting it. The doctors were using it, knew they were using it, and there was no comparator group. And what they found was that this was a relatively safe treatment with a few side effects. The 28 patients with major depression that underwent this, most of them were also on other medications for depression. What the investigators found was that there was roughly a 29 or 30% reduction in symptoms at four weeks of administration. Side effects were minimal, but were consistent headaches, 68%, some skin dermatitis where the electrodes were roughly two-thirds of the individuals reported that as well. So this looks like it had somewhat of an effect. It looks like it could be useful, but again, caveats to emphasize our open-label study, relatively small sample and more work really needs to be done, which was highlighted in the editorial that accompanied this paper.

Aaron van Dorn (23:18):

Next we have a paper from Stern and colleagues looking at the impact of the drug Ondansetron, on patients with obsessive-compulsive disorder.

Dr. Ned Kalin (23:24):

So the first-line treatment for OCD is psychotherapy. That is a exposure and response prevention psychotherapy, and also SSRIs and doses that are higher than those usually used to treat depression. Despite those treatments that we have, we still have an individual obviously, that suffer from this illness and we need, as we do throughout all of our treatments, better treatments. This is an attempt to augment the effects of SSRIs, or even to see if a drug that affects the serotonin system in a different way is effective. So the drug that was used is Ondansetron. It's a 5-HT3 or serotonin three receptor antagonist. It's commonly used for nausea, commonly used in patients that are getting chemotherapy for example. But it has properties on the serotonin system. And what's particularly interesting about the system that this affects the five 5-HT3 receptor, is that there is some work that has suggested that that receptor is involved with our internal processing and sense of urges and feelings.

(24:31):

And one of the things that happens in people with OCD is that they will get some internal sensations that they perceive, or internal urges that are somatosensory, physical in a way, and that they feel like they have to behave or act on them sometimes. So that was the rationale for this. This drug has been explored in other studies at lower doses in relation to OCD with mixed effects. And so these investigators wanted to give this drug at higher doses that have generally been tried in the past. So they gave 24 milligrams a day of Ondansetron to individuals with OCD, and also they could have had a tick disorder as well, which is very related. They basically looked at whether or not the symptoms got better, but also whether there were changes in brain systems that are known to be associated with this

premonitory sensations that individuals with OCD sometimes have and sometimes trigger or thought to trigger some of the OCD related behavior.

(25:28):

This particular study, again, it was a small study, but in this case it was a double-blind randomized design, over four weeks that compared 24 milligrams of Ondansetron per day to placebo. And there were 27 individuals were in the group that got Ondansetron, and this was compared to 24 individuals that got placebo. Now about half the patients were taking SSRIs or other psychotropic medications. That turns out to be important as we look at the results. And then they also did functional brain imaging with fMRI before and after the study to see whether or not there was a reduction in the activation of some of these areas of the brain that are thought to be related to these premonitory sensation experiences that individuals have that may trigger OCD symptoms. Overall, the investigators did not find a positive effective of Ondansetron on reducing symptoms, but they did find that in the subset of individuals, roughly half, that were taking SSRIs or other medications, that there was a significant reduction in symptoms.

(26:31):

So this suggests that perhaps, and again it's a small sample, perhaps adding Ondansetron at this dose into an SSRI may actually augment its efficacy. They also didn't find hypothesized effects on decreasing activation of regions like the insulin, the sensory motor cortex, which are these regions that I've been alluding to that have to do with interoception, sensations that may be perceived early on in the processing of sensations and so on. But they did find that, again in the individuals that had concomitant SSRIs on board and also got Ondansetron, that they were getting some effects in these systems that they hypothesized to be effective. So again, small study, this case double-blind, a high dose of Ondansetron, perhaps effective in helping augment SSRIs from the standpoint of reducing OCD symptoms. And also some evidence that some of the brain networks that are related to sensations internally, may also be dampened down with this high dose in conjunction with SSRIs.

Aaron van Dorn (27:35):

And finally, there's a priority data letter from McGirr and colleagues also looking at obsessive-compulsive disorder this time using D-cycloserine in conjunction with intermittent theta-burst stimulation.

Dr. Ned Kalin (27:45):

So one of the things that characterize some of the papers in this issue are that they're pretty exploratory and somewhat preliminary, but also really interesting on the standpoint of new treatments and new ideas about how to move forward to better help our patients and impact their symptoms in positive ways. And this is another study along those lines. D-cycloserine was initially brought forward as an antibiotic, actually an anti-tubercular agent. And it was discovered that this drug also had effects on neuroplasticity by its interactions with a site, a glycine site on the NMDA receptor, which is a receptor system that we know is related to neuroplasticity. So for many years now, psychiatric researchers have been exploring the addition of this drug to various treatments, especially psychotherapeutic treatments that may actually enhance the efficacy or augment the efficacy of the primary treatment by increasing various neuroplastic processes. This particular study combined D-cycloserine with a potent transcranial magnetic stimulation protocol. This is theta-burst stimulation, which we've talked about in the past, which has been demonstrated to be effective for depression.

(29:01):

It capitalizes on naturally occurring theta rhythms in the brain, and we know that because of the way that it works, that it can be delivered in shorter epics than typical repetitive transcranial magnetic stimulation. So combining ITBS with D-cycloserine in patients with OCD. So another OCD study. And again, ITBS itself is thought to be a perhaps more neuroplastic than regular TMS. And the researchers in this study targeted the medial prefrontal cortex and the anterior cingulate cortex because these are regions that are thought to be more amenable to reducing symptoms related to OCD. Very small study. There were four groups of OCD patients. The four groups were Sham, TBS plus placebo... Sham, TBS plus d-cycloserine, TBS plus placebo, and TBS plus D-cycloserine. And none of the groups were greater than 10 individuals per group. Okay, so small study. It turns out that in this case, TBS was administered five days a week over a four-week period, and about an hour or so before the administration of TBS, the participants took a pill that contained D-cycloserine or a placebo.

(30:18):

And it turned out that the combination group, ITBS plus DCS had a significantly greater symptom improvement compared to the three other treatments, which was what? Hypocypothesis. So this is early preliminary evidence, again, suggesting that DCS combined with TBS may be a more effective treatment and a strategy, especially for patients that haven't been responsive or very responsive. Now, what's interesting here is that none of these treatments impacted the comorbid depressive symptoms that these patients has, which is a little bit surprising because TBS itself is a treatment for depression. So that's a question about why that didn't happen, could be because of where this was applied. It was applied in a different region of the brain, that was typically applied in patients [inaudible 00:31:04] with depression. And there's a really nice accompanying editorial by Dr. Joshua Brown from Harvard and Dr. Noah Phillips, who's an expert in this area from Brown University, that talk about this as a potential new treatment and also talk about some of the concerns in relation to the preliminary nature of the data.

Aaron van Dorn (31:21):

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

Dr. Ned Kalin (31:23):

You're welcome. It's a pleasure, Aaron.

Aaron van Dorn (31:25):

That's all for this month's episode of AJP Audio, but I hope you'll join us next month for more of the best research psychiatry has to offer. I also hope you'll check out the other podcasts the APA has to offer. Over on the Medical Mind podcast, they have a Psych News special report on the complexities of medication management and psychiatry. You could find that and more over at psychiatryonline.org or wherever you get podcasts.

(31:45):

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