Aaron van Dorn (00:08):

Welcome to AJP Audio for March 2023. I'm Aaron van Dorn. The March issue of the American Journal of Psychiatry is focused on advances in the treatment of major depression. In this episode I spoke with Dr. Gary Sachs, Clinical Vice President at Signant Health and an Associate Clinical Professor of Psychiatry at Harvard Medical School.

(00:23):

Dr. Sachs and colleagues investigated the use of cariprazine, an atypical antipsychotic, as an adjunctive treatment, along with standard antidepressants for major depression. Afterwards, I spoke with AJP Editor-in-Chief, Dr. Ned Kalin, about the rest of the March issue and other papers touching on the treatment of major depression.

(00:38):

Dr. Sachs, your study looked at the effects of cariprazine, an atypical antipsychotic, and as an injunctive therapy in conjunction with antidepressants for the treatment of major depressive disorder. What did you find?

Dr. Gary Sachs (00:47):

We randomized patients with inadequate response to standard antidepressant treatment to add cariprazine, one and a half milligrams cariprazine, three milligrams for placebo, along with their current standard antidepressant treatment. It turned out that adding cariprazine, 1.5 milligrams, was significantly better than adding placebo to standard antidepressant medication. The trends for cariprazine three milligrams fell just short of the traditional 0.05 level of statistical significance. There's a lot to be learned about dosing these medications.

(01:21):

In prior studies, the lower dose had succeeded in some, but not all. And here what we're seeing is, the higher dose is succeeding in some, but not all, including this study. So I think it's important to distinguish between not statistically significant and coming to a conclusion that the higher dose actually is ineffective. And both doses were actually very well tolerated.

Aaron van Dorn (01:49):

Why is treating major depressive disorder in patients proven to be such a challenge for clinicians?

Dr. Gary Sachs (01:54):

Yeah, this is really a problem for a number of reasons, some of which really have to do with the diagnostic dilemmas due to our vocabulary, the limitations of DSM itself. You may know from the DSM-5 Field Trials that the test reliability for depression is actually shockingly low.

(02:14):

So we have a lot of problems there. The variability of the course, the lack of time that most psychiatrists have to do an adequate assessment. And a lot of the set and setting of clinical practice is disadvantageous to making a confident diagnosis and initiating treatment in a timely way.

Aaron van Dorn (02:33):

Why did you choose to look at cariprazine in conjunction with antidepressants?

Dr. Gary Sachs (02:37):

Well, this is a huge unmet problem. What do you do after a second or third standard antidepressant doesn't work? There's so many patients who have had that experience, and the evidence base, like the STAR*D study, it's pretty limited and generally discouraging.

(02:56):

STAR*D taught us that only about one in three patients respond to their initial treatment. So there's so many people who would benefit from knowing what is the next step, what is the next place we should go if we fall into that category, where the majority of patients with major depression actually will be, failing to respond to that first standard antidepressant treatment.

Aaron van Dorn (03:22):

Why in particular did you choose to look at using an atypical antipsychotic conjunction with more standard antidepressant medications that are usually prescribed?

Dr. Gary Sachs (03:30):

Well, you've captured a couple of things just in the words that you've used, Aaron. When we talk about antipsychotic or antidepressant, we're really talking about terms that have a lot more meaning as marketing terms than they do as capturing a realm of potential therapeutic meaning in terms of the actions of the medications that we can use. We have tool, like an SSRI, and we're going to call it an antidepressant, but I would argue that perhaps we could call these drugs atypical antidepressants because they differ in their mechanism, but they look like they're actually quite good treatments for depression.

(04:15):

So if you start looking at the known pharmacological activity of cariprazine, there's some impressive differences in terms of interaction with the D3 receptor. I don't know for sure how much that contributes to its activity here, but it does seem that it has a different mechanism. And that may well explain why patients who don't respond to one class of medications for their depression would respond to another.

(04:44):

The other thing that I think is really important about cariprazine is it's a more fault-tolerant medication due to its long half-life. Cariprazine and its metabolites will be present for a couple of days due to that long half-life, even if a patient were to miss consecutive doses, let's say, over a weekend. So that's a great attraction, to me anyway as a clinician.

Aaron van Dorn (05:11):

Speaking of that long half-life, one of the things that atypical antipsychotics are often associated with, it can be severe side effects. What side effects did you see with the use of cariprazine in conjunction with other antidepressants in your study?

Dr. Gary Sachs (05:23):

In the study itself, which was a six-week double-blind phase, the side effects were actually surprisingly small, and so the discontinuation rate due to adverse effects was extremely low.

(05:37):

The only adverse effects that were considered to be more frequent in the cariprazine treat groups, akathisia was just under 1% in the placebo group and about 5.3% in the 1.5 cariprazine group, and just

under 8% in the three milligram group. Akathisia is a relatively uncomfortable state to be in, wanting to be in motion, purposeless motion. And you'll see people who look like they're marching their legs while they're sitting in place or they're pacing back and forth, and they're just not sure even what the point is of doing that. There's no object in their behaviors. Nausea, 2.4 in placebo, about 8% with a 1.5, and 6.3 in the three milligram group. So all these are relatively low, but it's interesting that those were more frequent in the cariprazine group.

(06:42):

The other thing that people always focus on about adverse effects is average weight gain, and in all three groups over the course of the study, the average weight gain was less than a kilogram in those three groups. So a very desirable kind of adverse effect profile. Same thing with the lab work that was done. There was no indication of subjects being particularly prone to getting metabolic syndrome from cariprazine.

Aaron van Dorn (07:09):

What were the limitations of your study?

Dr. Gary Sachs (07:11):

Yeah, there's several important limitations to think of, and one, to go back to the adverse effect, is because of the long half-life, maybe if we had looked longer, we would've seen more differences I think. Short duration is one of them. The other important issue here is clinical trials use strict eligibility criteria. So we can't say necessarily this result is generalizable to all patients with treatment refractory depression. And in fact, the criteria for being in the trial, you had to have inadequate response to at least one and no more than three standard antidepressants. But as it turned out, the population that actually entered the trial, the majority had only had one inadequate response.

(08:02):

So I feel pretty good about saying for that group, cariprazine 1.5 milligrams did a great job. I don't know that we could say the same thing about people who have failed two or three or even more prior trials of standard antidepressant. That's a serious kind of problem. We have to be careful when we generalize those results.

Aaron van Dorn (08:25):

Are there clinical implications for the treatment of major depressive disorder in the short-term from your study?

Dr. Gary Sachs (08:29):

Yeah, I think it's really important for clinicians to recognize that now that we have a solid evidence base for this class of molecules, that we don't have to wait for subjects or patients to fail to respond to two or three agents in the standard antidepressant group.

(08:52):

Our patients are suffering and they're losing educational opportunities. Their relationships with their friends and family suffer. There's just a lot of loss occupationally, and we don't have to wait for that many trials. Now that we have this treatment, I think patients ought to be made aware, at the very least, that this option is available.

Aaron van Dorn (09:14):

What's next for your research?

Dr. Gary Sachs (09:15):

Aaron, as a methodologist, I'm really very interested in ways to improve the representativeness of the samples in clinical trials so we can generalize results appropriately. And that that's something that could involve improving diagnostic confidence in a number of different ways, so we've been working with methodologies for that.

(09:38):

But also for presenting patients with a better value proposition when they enter research. In this study that we're talking about, and in practically every study we've ever done, the assessment patients get is superb, yet we don't usually make that available to them after they leave the trial. And I think that would be a wonderful thing to be doing, and we're looking for ways to make that happen operationally.

Aaron van Dorn (10:05):

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

Dr. Gary Sachs (10:07):

Thank you very much, Aaron. Appreciate talking with you.

Aaron van Dorn (10:09):

Up next, Dr. Ned Kalin.

(10:11):

Hi, Dr. Kalin. Welcome to the March episode of AJP Audio.

Dr. Ned Kalin (10:13):

Good morning, Aaron. It's nice to be with you.

Aaron van Dorn (10:15):

The March issue of AJP takes a serious look at the important topic of depression. Earlier I spoke with Dr. Sachs about the use of cariprazine in the treatment of major depressive disorder. What can you tell us about that article?

Dr. Ned Kalin (10:25):

This is, it's an important paper that looks at cariprazine, which is a atypical antipsychotic, or second-generation antipsychotic, as an adjunctive treatment for depression. It's a Phase 3 study that went into actually the relatively recent approval of cariprazine for this purpose.

(10:44):

Cariprazine is interesting because it's got some interesting neurochemical effects with affecting the D3 and the D2 receptor, and also the 5-HT1A receptor. Its highest selectivity is for D3, which may be unique and may add to its antidepressant properties. Cariprazine joins a bunch of other second-generation antipsychotics that have been approved for this indication, including aripiprazole, quetiapine and brexpiprazole. And in this particular study, what the investigators found was that 1.5 milligrams of cariprazine was effective, and it had effects significantly greater than placebo when added to a current antidepressant, to enhance treatment responses in individuals with major depression.

(11:30):

This is interesting because the 1.5 milligram dose had the effect ... Actually the higher dose did not, and that's somewhat of a puzzle in this study, because I believe other earlier studies have shown that higher doses have been effective for as an adjunct for treatment depression. There was a 50% reduction in the MADRS score, the Marie Asberg Depression Rating Scale, in 44% of the cariprazine treated patients, as compared to 34 or 35% of the placebo treated patients. And when looking at remission rates, which is a MADRS score of less than 10, cariprazine at that dose was not significantly different than placebo, which is a little bit of a concern.

(12:15):

But overall it shows efficacy, adds another atypical neuroleptic to our armamentarium for treating refractory or difficult depression. Michael Thase from the University of Pennsylvania, an expert in this area, provides a really nice editorial that goes along with this paper that talks about the design, as well as the implications of the findings.

Aaron van Dorn (12:35):

Musliner and colleagues have an article looking at polygenic risk score and episode of polarity in individual with bipolar disorder. What can you tell us about that?

Dr. Ned Kalin (12:42):

This is interesting. One of the interesting things is thinking about bipolar disorder as not just one illness but having a lot of heterogeneity in the way it presents over an individual's lifespan. And anybody that treats bipolar patients knows that each one is an individual. Some patients have more manic episodes, other patients have more depressive episodes, some patients have more mixed states.

(13:05):

And so what the investigators here sought out to do was to try to understand whether there was a genetic signal that would be helpful in understanding the different presentations over a lifespan of an individual, or over a long-term of an individual. And in this case, what the investigators did is that they followed over 2,700 individuals that were genotyped and hospitalized for bipolar disorder. This actually occurred in a Denmark cohort. And then these individuals were followed up four, five years after the initial diagnosis to look at what types of episodes they had, whether they're manic depressive or mixed episodes.

(13:46):

And they did a polygenic risk scores, which we've talked about before, which is a culmination of the SNPs, that are risk SNPs, related to different illnesses. They did a polygenic risk scores for a variety of illnesses, including bipolar disorder, major depression and schizophrenia. And then asked to what extent were those genetic risk scores predictive of these different patterns or the different numbers of episodes, whether they were manic or depressive, that an individual had.

And the findings basically showed that they could find some significant associations between the polygenic risk scorers and these presentations and some of the findings include the bipolar and schizophrenia polygenic risk scorers were related to the number of manic episodes that an individual might have. Whereas the depression polygenic risk scorers were associated with depressive and mixed episodes, and actually negatively predicted manic episodes.

(14:40):

Now these are not large effects, and so this certainly couldn't be used clinically, but this again is a hint at the genetic underpinnings of bipolar disorder and a glimpse into how the genetic variation may relate to these different presentations over a life course. So much work needs to be done in this area. Not ready for clinical use, but very early leads suggesting that we can begin to understand, at a more basic level, why some people have different courses of bipolar illness.

Aaron van Dorn (15:10):

Next, Visontay and colleagues looked at alcohol consumption and how it relates to depression.

Dr. Ned Kalin (15:15):

This is an interesting study, and draws on a large cohort of individuals from the National Longitudinal Survey of Youth in 1979. The investigators in this study got data from over 5,000 individuals, beginning at an age between 29 and 37 years of age. And then these individuals are followed up for another number of years, all the way up to 41 to 49 years of age.

(15:38):

And what they did is they assessed at various time points across this span the amount of drinking that an individual did based on self-report. And also based on self-report, the amount of depressive symptoms and depression that that individual did. They used some sophisticated analytic methods that they assert can allow us to think about causal relations. I'm cautious about that because I think from a statistical standpoint, we really need to be careful about thinking about causal relationships, or A causing B, for example.

(16:11):

But nonetheless, what they found was is that individuals that had a reported consistent occasional and consistent moderate alcohol use, when compared to abstainers, were likely to have lower depression scores and less depression when they reached 50 years of age. In contrast, when compared to abstainers, individuals that were drinking above guidelines or heavier drinkers who were consistent in that pattern of drinking, actually had non significantly but higher depression symptoms.

(16:44):

So this is interesting. This suggests that moderate and occasional alcohol use is actually associated with less depression in this sample. Again, the investigators here try to draw a causal relation between alcohol, amount of drinking, and depression, but I think that that is, again, as I mentioned, should be cautiously interpreted.

Aaron van Dorn (17:05):

Dunlop and colleagues took a look at depression and remission between pharmacotherapy and psychotherapy.

Dr. Ned Kalin (17:10):

This is an interesting paper using functional brain imaging, in this case magnetic resonance imaging and what we call resting-state functional connectivity, to see if changes in those measures with treatment were reflective of different responses in relation to a psychotherapy, in this case CBT, versus medication therapy. This is data from a clinical study that was done in which 131 individuals were randomized to receive one of three treatments. It was either 16 weeks of CBT, duloxetine at 30 to 60 milligrams per day, or escitalopram at 10 to 20 milligrams per day.

(17:54):

What the investigators found was that there were some brain changes that were common across the treatments if individuals got better, this was basically into remission. They also found some brain changes or functional connectivity changes that were more specific to either the medication treatments, which they lump together, both the duloxetine and escitalopram in their analysis, or the psychotherapy treatments.

(18:21):

I think most interestingly, and what really resonates with what we understand and how we think about things, were some of the changes that were specific to cognitive behavioral therapy. And in this particular study, what they found was is that individuals that remitted had changes in the connectivity between what we call the executive control network and also the salience network and the affective network. And so what's interesting about this is that the executive control network involves various regions, including prefrontal cortical regions, which have a lot to do with decision-making, cognition, and the cognitive emotion regulation interface.

(19:01):

And so changes in the connectivity of the front of the brain, in part that's related to the executive control network, in relation to other regions of the brain that are encompassed in the affective network, some limbic regions and the salience network, other regions that have to do with vigilance, that suggests that those changes may reflect in some part what's happening with effective treatment. And we think of CBT or most psychotherapies, at least initially, as impacting regions that are accessible, conscious and cognitively oriented, such as the prefrontal cortex, the executive control network.

(19:39):

So that finding really fits and it's really quite interesting, from the standpoint of that being changes in those networks and their connectivity being associated with remission associated with CBT.

Aaron van Dorn (19:50):

And finally, Elbau and colleagues took a look at target selection for a repetitive transcranial magnetic stimulation for the treatment of depression.

Dr. Ned Kalin (19:56):

Yeah, so this is data from a clinical trial in which investigators were comparing different types of transcranial magnetic stimulation. In this case, they were comparing the application of TMS at 10 hertz versus theta burst. Which we've, I think, talked about in the past, which is a relatively new method that's being used. That is a way to begin to mimic some of the brain's intrinsic rhythms, at least thinking about that.

(20:24):

So the data from that was used, and the question that was asked was that, could functional connectivity measures, like we were talking in relation to the last paper, be predictive of outcomes from the standpoint of the magnitude of response with these different treatments? This question is built on a large body of work that's been ongoing, that has been attempting to use various methods to localize the best target to stimulate in the prefrontal cortex with transcranial magnetic stimulation. And a number of studies in smaller samples have strongly pointed to the strength of connectivity between the target region in the dorsal lateral prefrontal cortex, with a region in the anterior cingulate cortex called the subgenual anterior cingulate cortex.

(21:11):

This is an interesting region, because this is a region that's been implicated in depression. It's a region also that has been targeted with deep brain stimulation in some studies. And there's a whole variety of evidence at a neuroanatomical level as well to suggest that the connectivity of this region to both the prefrontal cortex and limbic structures, is important from the standpoint of this region being a hub in modulating these systems. These systems are also the systems that are frequently implicated in depression and anxiety disorders.

(21:41):

What the investigators did was they actually looked at, in this relatively large sample of 295 participants, looked at the strength of connectivity between where the stimulation site was and the subgenual ACC in each individual patient. Now it's important to keep in mind here in thinking about the results, that they tried to use the exact same location for each patient when they stimulated in the front of the brain, in the dorsal lateral prefrontal cortex. And this was based on other work that suggested that this region is an optimal region.

(22:16):

Nonetheless, even though they tried to use the same region, the strength of connectivity or functional connectivity between that region and the subgenual ACC would likely be different at an individual level, and that's what they measured. What they found was the relation between how strong the connectivity was between the stimulation site and the subgenual ACC, the strength of that was in fact predictive of outcome. However, they found that this is a very small effect, and actually quite smaller than what's been reported in other studies and in smaller samples.

(22:49):

Now there's one thing to keep in mind here, which is that in other studies, investigators will frequently try to find the spot in the dorsal lateral prefrontal cortex that is most connected to the subgenual ACC, and then actually stimulate that spot in each individual. And that really is quite different than what was done here, which was to use the same exact site to stimulate and then calculate how strong the connectivity was with the subgenual ACC.

(23:17):

What they found was is that while this was a significant effect, it only accounted for a small amount of how we think about the outcomes, that was 3% of the variance. Again, I think that this is probably an underestimate when we actually prospectively find the site that we're interested in and stimulate that site. Nonetheless, it's an interesting study. It's a large sample. And there's a really good editorial that accompanies this by Dr. Noah Philips and Dr. Shan Saddiqi from Harvard Medical School.

Aaron van Dorn (23:45):

Well, Dr. Kalin, thank you for putting the March issue into context for us.

Dr. Ned Kalin (23:48):

You're very welcome. It's a pleasure to be with you.

Aaron van Dorn (23:50):

You. That's all for this month's AJP Audio, but be sure to check out the other podcasts from the APA. This month on Psychiatric Services from Pages to Practice, Dr. Dixon and Dr. Berezin are looking into

measuring measurement, the use and barriers to utilizing measurement-based care by healthcare providers. That and much more at psychiatryonline.org or wherever you get your podcasts.

(24:08):

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