Aaron van Dorn (00:07):

Welcome to AJP Audio for October 2024. I'm Aaron van Dorn. Today on the podcast I spoke with Dr. Bodyl Brand, a postdoctoral researcher at the University of Oxford and a co-author on a paper in the latest issue of the American Journal of Psychiatry. Looking at the impact of menopausal hormone therapy on psychosis relapse in women of menopausal age with schizophrenia or schizoaffective disorder.

(00:26):

After the conversation with Dr. Brand, we'll again speak with AJP Editor-in-Chief Dr. Ned Kalin. Who will walk us through the rest of the October issue of AJP, which takes a close look at the clinical import and basic science touching on schizophrenia spectrum disorder and psychosis.

(00:39):

Dr. Brand, while women diagnosed with schizoaffective disorder, or SSD, initially have a less severe clinical picture than men. After the age of 45, women with SSD face a greater frequency of psychosis relapse than men of the same age. It's been speculated these changes in disease course might be linked to the decline of estrogen production that leads to menopause. Your study aimed to look at the impact of menopausal hormone therapy, or MHT, in women diagnosed with SSD in a Finnish cohort. What did you find?

Dr. Bodyl Brand (01:05):

First of all, to briefly summarize our findings, we found that menopausal hormone therapy was associated with a 16% reduced relapse risk to psychosis when compared to non-use. And to provide a little bit of background, we know that in every woman, estrogen levels dramatically decline around menopause. And we also know that antipsychotic effectiveness in preventing relapse to psychosis declines around menopausal age in women with SSD.

(01:31):

And we also know that estrogen addition can improve symptoms and cognition in women with SSD, but that has only been tested in pre-menopausal women before menopause. Before the study, we didn't know whether estrogen-based menopausal hormone therapy, I'll just call it MHT from now on, can help to prevent a psychosis relapse after or around menopause.

(01:53):

So we studied the effectiveness of MHT in preventing relapse psychosis in a nationwide Finnish cohort study of women with SSD. And we included women aged between the age of 40 and 62 who were prescribed MHT during the follow-up period, which was between 1994 and 2017. We examined the exposure to MHT using a within-subject design, meaning that each individual function does their own control. And by that way, we compared periods of MHT use with periods during which no MHT was used within the same individual.

(02:28):

Our study population consisted of 3,488 women who used MHT during the follow-up period. And as I said, we found as a main finding that MHT use, any MHT type, was associated with 16% reduced relapse risk compared to non-use. And we also stratified our results by the age at which MHT was started. Dividing these women into three groups, women between the age of 40-49, women between the age of 50-55, and 56 to 62. And we found that in this older age group, menopausal hormone therapy was not effective in preventing relapse, while it was in the younger age groups.

Aaron van Dorn (03:08):

Cardiovascular disease is the leading cause of death for women with schizoaffective disorder. And menopausal hormone therapy was first used in the 1960s, but its use dropped around the turn of the century following several studies that linked it to increases in the incidence of heart disease, stroke, and breast cancer.

(03:23):

Although later studies indicated that later initiation of MHT is associated with reduced all-cause mortality and the risk of heart disease and reduced risk of heart disease and diabetes. That said, use of antipsychotics is also associated with an increase of cardiovascular disease and obviously comes with its own set of side effects. How should clinicians weigh these factors when setting out a course of treatment for women with schizoaffective disorder?

Dr. Bodyl Brand (03:43):

Well, now first of all, I'm not a clinician myself, so I always find it difficult to tell clinicians what they should do or what I think they are doing. But I can imagine that there is a scenario that a woman in her late 40s, early 50s who has been stable on antipsychotics for years, because women are relatively more stable on antipsychotics when they are younger, when she suddenly starts to experience a worsening of her symptoms.

(04:08):

I can imagine that the first thing that comes to mind for a clinician is to increase the dose of the antipsychotic medication. But by doing that, we might be missing a crucial piece of the puzzle because the onset of menopause with its significant hormonal changes, could be playing a major role in this symptom exacerbation that we see around this age. And I think that's a factor that's frequently overlooked in clinical practice.

(04:31):

And you might think that by increasing the dose that makes sense because it might decrease the symptoms. It seems logical. But our previous research tells a different story than that because we showed that higher doses do not effectively prevent relapse. And while they do increase the risk for side effects. For example, metabolic side effects, osteoporosis, cardiovascular side effects as you mentioned.

(04:54):

And I think that's particularly worrisome for female patients of menopausal age who are already at an increased risk for cardiovascular disease, metabolic diseases. And our study provides evidence that augmentation with MHT might provide a better strategy for relapse prevention, rather than increasing the dose. And as you mentioned, MHT can not only reduce psychotic relapse risk, but it can also provide relief for a wide range of health conditions to which these women become more vulnerable around menopause. And that could avoid the need for multiple treatments for many separate problems. For example, statins for metabolic diseases.

(05:33):

And besides the potential antidepressants effect, MHT has consistently shown to reduce central adiposity. And when it's initiated on time, which is not longer than 10 years after menopause, it also reduced all-cause mortality and the risk of diabetes, osteoporosis, dementia, and coronary heart diseases. And it can also possibly reduce the risk of colon cancer risk.

(05:58):

I think these properties might be particularly valuable for female patients with SSE because cardiovascular diseases are the leading cause of death in women with SSE, followed by colon cancer. And also osteoporosis and metabolic diseases are very common in this patient population.

Aaron van Dorn (06:16):

You mentioned earlier that women who are going through menopause at a period of low estrogen level, are at a greater risk of psychosis relapse. That's also true that women who are going through periods of their menstrual cycle with low estrogen levels are also at greater risk of psychosis relapse. So the question would then follow, what is the active mechanism that is causing estrogen to prevent these? Do we have any idea?

Dr. Bodyl Brand (06:37):

Yeah, I think that's a very interesting question. That is, I'm very interested in answering that. I think it's very complex and there are multiple ways by which estrogen can be protective on the brain and can also have an effect on, interact with the effects of antipsychotic medication.

(06:53):

For example, in the brain, studies have found that in pre-menopausal women in one study, they found that women only require half of the dose of olanzapine than men, and they attribute these findings to the protective effect of estrogen on the brain. And they think that estrogen has an antipsychotic-like effect on the brain.

(07:10):

How this exactly works, as far as I know, is not entirely understood, but it could be that estrogen is involved in dopamine regulation. So we see that in psychosis, the dopamine regulation, dopamine is dysregulated. And we also see that estrogen has regulating effect on the dopamine neurotransmission. At a point when estrogen levels decline, there might be more dopamine dysregulation, which might make them more vulnerable to psychosis. But I think that more research is currently being done and needs to be done on this topic.

Aaron van Dorn (07:44):

Your study found that variations on MHT effectiveness based on the type of administration of the estrogen use, but also with the specific drugs they were paired with. Were these differences significant?

Dr. Bodyl Brand (07:53):

Yes, indeed. We looked into the difference of different formulations because there are a lot of different types of MHT and we were of course curious about the difference in effectiveness of these different formulations. Just for a little bit of background, all MHT formulations contain a certain form of estrogen, which could either be estradiol or estriol. But could also be estradiol that is derived from animal pregnant mares.

(08:18):

But the ones that most commonly use is estradiol. And these estrogens can either be administered alone or in combination with a progestogen. And these combined formulations, so combined with a progestogen, typically consists of estradiol, which is responsible for the estrogenic effects, and that is then combined with any specific type of progestogen. And these progestogens all vary in their effects on progesterone receptors. And they can also have an effect on androgen receptors in the brain and even on other receptors that are involved, for example, in the stress system in the brain.

(08:48):

There's one odd one out, that is tibolone, which has estrogenic, progestogenic, and androgenic effects on its own. So we started with comparing estrogen-only formulations with the combined ones, and we found no clear difference in their effectiveness. And we also compared transdermal and oral formulations, which also had a similar effectiveness, although the effect of and transdermal formulations was a bit more heterogeneous. But it might also be because it was a smaller group of women using these transdermal formulations.

(09:20):

We then compared also the specific formulations and then specifically all the types of different progestogens. And our results suggest that different formulations have varying effects. And we found that estriol, tibolone, and estrogen combined with dydrogesterone didn't lower the risk of relapse, while all the other formulations did.

(09:41):

And a specific one that I would point out is dydrogesterone because this one is currently most commonly prescribed. And is one of the first choices, at least in the Netherlands, for treating menopausal hormone therapy. Because it is most similar to the natural hormone progesterone and it has fewer side effects in the body.

(09:59):

So that's one that has a preference, but we didn't find any beneficial effects of these compounds. So it might be that this specific type of compound have different effects in the brain. But I think that more studies are needed for this to confirm this because it was a small group that we were comparing.

Aaron van Dorn (10:15):

You mentioned you're not a clinician of course, but are there immediate clinical implications for your study?

Dr. Bodyl Brand (10:19):

Yes, I think there are some direct clinical implications coming forth of our findings. Because our study shows that an already existing pharmacological treatment, MHT, which is already on the market since the 1960s as you mentioned, can reduce the risk of relapse in a very vulnerable population of psychosis patients. And the fact that it is already on the market means that it's safe and that it has been checked for side effects. And that the ones that are on the market can be safely prescribed to these women, taking into account certain, all the contraindications of course.

(10:51):

And I think more generally in clinical practice, this study shows that we could be paying more attention to the possible impact of the menopause on the manifestation of psychosis. And that if the condition worsens around menopause, consideration could be given to use MHT. Of course, by again taking into account the contraindications. So it might be a signal to psychiatrists and clinicians that it might be a viable option if other things not work. And might be something that can be tried before heightening the antipsychotic dose.

Aaron van Dorn (11:27):

What were the limitations of your study?

Dr. Bodyl Brand (11:29):

So yeah, starting I would like to prefer start with several strengths.

Aaron van Dorn (11:34):

Sure.

Dr. Bodyl Brand (11:34):

Because I think that a major strength of our study was its naturalistic and observational design, which enables generalization to real world settings. For example, if you look at RCTs at randomized clinical trials, they usually only represent only up to a fifth of the real world individuals with schizophrenia spectrum disorders as a consequence of eligibility criteria, and that limits their translatability.

(11:59):

And we really researched a group of patients, we didn't have any exclusion criteria. It was really a natural population, so to say. And also if you look at case series or other non-randomized studies, they might encounter indication bias. As, for example, women that opt for MHT might be expected to display a more initiative compared to non-users. And our within individual analysis tackles these issues of comparing between individuals and avoiding the differences between individuals of symptom severity or reasons to start MHT as we use within subject design.

(12:38):

However, there might also be very complex time-varying covariates for which we could not effectively address. For example, the interplay between hormones antipsychotics and the individual physiology is very complex and it is very difficult to address all these interactions between these things.

(12:57):

And we also, for example, it's difficult to say if it might be the case that long-term use of MHT might have different effects than short-term use. And that's also something that we were not able to account for.

(13:10):

And of course there might be individual variability. Some women might respond differently to MHT because of changing factors that we could not capture in the study. For example, due to lifestyle changes.

(13:22):

And there are some other drawbacks of our study, for example, that we use age to estimate menopause. And the lack of information about the clinical measures others than hospitalization. We didn't had any scores on symptom severity, for example, or on which symptoms were most clearly elevated. And for which symptoms it was most effective. We only had the relapse, yes or no, so to say.

Aaron van Dorn (13:47):

You've touched on this briefly earlier, but there is a lot about menopausal hormone therapy, and indeed the effects of estrogen augmentation more broadly, that we don't know about yet. What avenues of further study are needed in this area?

Dr. Bodyl Brand (13:58):

So yes, I think this was the first study to systematically investigate the potential benefits of estrogen augmentation within a population of women with SST of menopausal age. And now that we have this evidence from an observational cohort study, I think for this field, the next step would be to conduct the clinical trials, testing MHT in peri and-or post-menopausal women with SST.

(14:22):

Because these studies are needed before it can really be officially translated into clinical guidelines. We need this evidence from clinical trials. And as I mentioned before, there are a lot of clinical trials on estrogen augmentation in pre-menopausal women with psychosis. But there aren't any in peri-menopausal or post-menopausal women, which makes it complicated to have a really strong body of evidence. So again, I think the next step is to conduct well-powered clinical trials to see if these beneficial effects can be confirmed in these studies.

(14:53):

And furthermore, I think it's important that we gain a clear understanding on the differences in effectiveness of different formulations of MHT. Because the one I talked about, dydrogesterone wasn't effective, while another one was much more effective, levonorgestrel. So I think this is something that also needs to be figured out.

(15:12):

And I think for now we should be keeping in mind that there is not a one-size-fits-all approach and that different MHTs might have different effectiveness. But I think that's certainly an area that needs more research. And I think there is also a lot of uncertainty about the long-term effects of MHT, not only on mental health effects, but also on the somatic problems.

(15:33):

And that often leads clinicians to prescribe MHT only for a limited period of time, for five or 10 years. And although the current state of literature suggests that there are no direct disadvantages to use MHT for more than 10 years, as long as it's well-monitored and it started on time, it would be beneficial to have more solid evidence for this.

Aaron van Dorn (15:54):

And speaking of further areas of study, what's next for your research?

Dr. Bodyl Brand (15:57):

So yes, over the past few years I have worked with great pleasure and learned a lot of things in the research group of Professor Iris Sommer at University of Groningen in the Netherlands. I recently completed my PhD there, of which this paper was a part of. And the broader topic of my PhD was to understand the impact of sex and sex hormones on the treatments of psychosis.

(16:20):

During my PhD, I also had the pleasure to work with Heidi Toppel and the research group from the Karolinska Institute, and this study as a result of that, together with other studies. And a few months ago, I started a postdoc at the University of Oxford within the group of Philip McGuire and Robert McCutcheon.

(16:37):

And here I definitely want to continue on improving care for women with psychosis because I think there are still many steps to be taken to understand how psychosis affects women differently than men and how we can address these differences. And my goal overall is to better understand why women

have an increased vulnerability to psychosis during hormonal transition phases such as the menopause, and also during certain periods during the menstrual cycle, et cetera. All these periods in life that are specific to women.

(17:13):

And this with the overarching goal to intervene more effectively during these phases by adapting our treatments strategies.

Aaron van Dorn (17:24):

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

Dr. Bodyl Brand (17:24):

Thank you. It was a pleasure.

Aaron van Dorn (17:24):

Up next, Dr. Ned Kalin. Dr. Kalin, welcome back to AJP Audio for October 2024.

Dr. Ned Kalin (17:29):

Thank you, Aaron. It's a pleasure to be here.

Aaron van Dorn (17:30):

The October issue of AJP takes a close look at matters surrounding schizophrenia spectrum disorder and psychosis. First up, we have the featured article for this episode from Dr. Brand and colleagues, looking at the effectiveness of menopausal hormone therapy and preventing relapse in women with schizophrenia or schizoaffective disorder. What can you add?

Dr. Ned Kalin (17:47):

Aaron, this is a really interesting study with important clinical implications. It's a study that was done with a Finnish database, a large database. And it was examining within a subject, that is within one woman over time, whether or not the prescription of hormone replacement therapy during the perimenopausal period was associated with a decreased risk to have relapses or psychotic episodes in women that already had a history of schizophrenia or schizoaffective disorder.

(18:17):

The design here is that the investigators looked at the risk when women were either on or off hormone replacement therapy within the same person over time. What's interesting is that we already know that menopause is a period of risk for women from the standpoint of a variety of psychiatric symptoms. And women that have schizophrenia or schizoaffective disorders are more likely to have relapsing episodes during that period. And sometimes their anti-psychotic medications are thought not to work as well during this period.

(18:49):

So there's something about the hormonal changes in women that make them more vulnerable during this period, and we've known that for a long time. What this study shows is that if women are taking hormone replacement therapy, and in this case what they identify was that it was either estrogen alone or estrogen with progesterone. That that significantly reduced the risk by about 16% of the likelihood of women with these illnesses having a relapse that required hospitalization.

(19:18):

What's also interesting is that they found that the hormonal therapy was more effective when it was started earlier in women. If it was started between 40 and 55, there was a decrease in hospitalization for psychosis. But they didn't find that effective if the hormonal replacement therapy was started around 56 years of age and all the way up to 62 years of age.

(19:38):

So interesting finding, clinically relevant. And speaks to the need to really consider using estrogen and estrogen with progesterone in women that have this risk. The editorial that was accompanying this was really quite good. And also pointed out that in this study, unfortunately, a low percentage of menopausal women was schizophrenia spectrum disorders receive hormonal replacement therapy. So suggesting that not only is this helpful, but also it's more or less overlooked in women with these illnesses.

Aaron van Dorn (20:09):

Next we have an article from Partanen and colleagues, looking at the burden of ileus and pneumonia and individuals with schizophrenia who were treated with the anti-psychotic clozapine.

Dr. Ned Kalin (20:17):

This is an interesting and also clinically relevant study and focuses in on clozapine in I think a rather unique way. And what's important about this study, again, interesting enough, it's done from a Finnish database, the Finnish bio bag, in which there is a large group of patients with schizophrenia that were taking clozapine.

(20:40):

They identified 2,100, roughly 2,100 schizophrenic patients taking clozapine. And they compared their long-term outcome to roughly 2,000 individuals that had schizophrenia or were treated with other medications.

(20:57):

Now, we've known for a long time that clozapine is associated with many side effects, but the trade-off has been that clozapine is really probably the best, not probably, is the best antipsychotic medication for treating treatment-resistant schizophrenia and is approved by the FDA for that. The unique aspect of this study was that these patients were followed for up to 25 years taking this medicine. And on the median number of years the patients were taking clozapine was about eight years.

(21:27):

And what they found was that there were a number of side effects that we're well aware of, that were increased and increased likelihood of having them if you're treated with clozapine. And these ranged from cardiovascular types of related effects. To neutropenia, which is a serious side effect, but occurs in much lower frequency. And in fact, neutropenia and agranulocytosis are probably one of the reasons, while rare, why clozapine is not used as much as perhaps it should be.

(21:55):

They focused in, however, on gastrointestinal hypomotility. And the sort of the worst case of this as our clinicians know is ileus, when our bowel stops functioning, basically. It's associated with severe constipation and other types of GI side effects. And what they highlight was that there were significantly increased incidence of ileus and also of pneumonia in patients that were taking clozapine. The risk of this was also associated with a significantly greater risk of actually dying.

(22:30):

The findings then sort of in summary show that the ileus and pneumonia were associated with clozapine administration, frequently go overlooked over time. And the relative likelihood of this occurring was in older patients 50 years and older. And importantly, these were associated with a greater risk of dying.

(22:49):

So as more specifically in the 2,100 individuals taking clozapine, there were 79 cases of ileus and 12 associated deaths. And 408 cases of pneumonia and 24 associated deaths. So again, not totally new knowledge from the standpoint of knowing about side effects. But new knowledge from the standpoint of emphasizing ileus and pneumonia as being occurring with greater frequency in patients taking clozapine. And greater risk of individuals over 50 years of age. And importantly, greater risk of dying in individuals that develop those adverse events.

Aaron van Dorn (23:25):

Is that knowledge something clinicians will be able to use to help treat and prepare for it? Or is this another aspect that they need to consider when prescribing the drug?

Dr. Ned Kalin (23:32):

Both of those are true. I think it's important to consider that when prescribing the drug. But also important to monitor for early signs of these adverse events and obviously to take them quite seriously because they can portend very bad outcomes including death.

Aaron van Dorn (23:46):

Following that, we have a paper from Moran and colleagues investigating the risk of incident psychosis in mania with amphetamines, such as those prescribed in the US to treat ADHD.

Dr. Ned Kalin (23:54):

Another important paper. And again, we've known that stimulants can be associated with the induction of psychosis or mania. This study was a study that was done from a database from a clean hospital in Boston, looking at in-patient admission records for all patients between 2005 and 2019. Between the ages of 16 and 35, they were admitted for their first hospitalization for psychosis or manic symptoms.

(24:22):

So they took this cohort of about 1,300 patients that were admitted to the hospital for psychosis or mania. 1,300 of the patients, I should say, had been prescribed amphetamines one month prior to admission. There's also, they had a comparison group of about 2,700 comparison patients that were admitted for depression and anxiety disorders.

(24:43):

And basically they compared the likelihood of being prescribed amphetamines one month prior to admission in both of these groups. And what they found was is that 10% of the individuals that were admitted across the entire sample, had been prescribed amphetamines in the month prior to admission. So both the patients with psychosis with mania, and also the comparison group to patients with depression and anxiety.

(25:09):

But there was roughly a two-fold greater prescription rate in the group that went on to develop psychosis and mania compared to the control group. So those that developed psychosis or mania were two times as likely to be prescribed stimulants prior to their hospitalization.

(25:26):

So the authors concluded that the odds ratio, or the risk, relative risk, was about 2.7 times greater for developing psychosis or mania when taking prescribed amphetamines in the month prior to hospitalization. This is very important clinically because we use stimulants a lot. They're prescribed a lot. The likelihood of prescribing them has increased over the years.

(25:49):

But importantly, there was a dose response effect. So that at the lower doses, the likelihood of developing psychosis or mania was much less at the dose equivalents that were around 30 milligrams of extra amphetamine a day, where the odds' ratio was now almost up to 5.3 times. So lower doses, much less risk. Higher doses, considerable risk.

(26:11):

The other interesting observation that methylphenidate, which also is a stimulant but has somewhat of a different mechanism of action, was not seen to be associated with the induction of psychosis or mania. However, it's important to point out that the patients that were taking methylphenidate were taking relatively lower doses. And so there wasn't this higher dose range to really examine whether higher doses of methylphenidate would in fact induce psychosis like dextroamphetamine or other amphetamine related compounds.

Aaron van Dorn (26:41):

Gallucci colleagues took a look, neurocircuitry and therapeutic targeting of depressive symptoms in patients with schizophrenia spectrum disorders.

Dr. Ned Kalin (26:48):

This is less directly clinically applicable, but has really important clinical implications. And I think has the potential to be really interesting from the standpoint of its clinical applications.

(27:00):

This is a group that was very interested in trying to tease out the neural correlates of negative symptoms versus depression in patients with schizophrenia spectrum disorders. Depression is very common in patients that have schizophrenia or schizoaffective disorders, and so are negative symptoms.

(27:19):

Distinction is not always clear, but in general, negative symptoms have to do with the lack of motivation to engage in activities, what we call a flattened affect, an amotivational type of attitude. But depression on the other hand, is more characterized by sad mood, by a lack of interest in positive activities, and a sense of not really being able to enjoy things.

(27:45):

Sometimes they're hard to sort out. So what these investigators did was they took 157 individuals with schizophrenia spectrum disorders, and importantly a subset of these individuals, roughly 70 of them, were also in a study looking at responsivity to transcranial magnetic stimulation, and I'll come back to that in a minute.

(28:04):

What they did is they took all the symptoms and they did what's called a latent variable analysis. I won't go into the details of that. But where they were able to categorize the symptoms of these patients into three variables that reflected the symptoms. The first one was reflecting general depressive symptoms. The second one was reflecting the so-called negative symptoms. And the third latent variable was more related to some specific depressive symptoms like guilt and early morning awake.

(28:33):

They then took these latent variables and tried to correlate them with resting functional brain activity. So they asked the question, "What brain circuits are most correlated with these different variables?" And what they found was is that different brain circuits were correlated with these different variables.

(28:49):

So more specifically, some brain circuits were correlated with the depressive symptom variables. And other brain circuits, and actually some it in a different direction even, were correlated, for example, with the negative symptom. Supporting the idea that negative symptoms and depression have a different neural basis, and also supporting the notion that these are really distinct symptom patterns.

(29:14):

Now to further examine this and to also support this view, as I mentioned, they had 70 individuals in the study that had undergone transcranial magnetic stimulation that was applied bilaterally to the prefrontal cortex, the dorsolateral prefrontal cortex. And that was one of the brain regions that was associated with a general depression variable.

(29:36):

So the hypothesis would be that those individuals, in those individuals, that would get better and that perhaps negative symptoms would not get better. Because the different neural circuits than those that were targeted with the TMS were thought to be related to the negative symptom. And that's in fact what they found.

(29:56):

They found that the bilateral application and the dorsolateral prefrontal cortex of TMS seemed to help the depressive symptoms in these individuals, but did not seem to help the negative symptoms. Further demonstrating that there are distinct neural variables and correlates associated with these different symptom patterns.

(30:14):

And also beginning to sort of pave the way for selective treatments that may get at the different symptoms. And the idea that different types of neuromodulation in different sites may actually be effective for both types of symptoms.

Aaron van Dorn (30:29):

And finally, we have a paper from Arion and colleagues investigating a layer three pyramidal neurons in the cellular level in primates and looking at its implications on schizophrenia.

Dr. Ned Kalin (30:38):

So, Aaron, this is a very interesting paper. It's a basic science paper. And as you may know, one of the themes that I've had in my role as the editor-in-chief of The Journal, is to bring more basic and translational science when appropriate into the journal. So that it can help support some of the clinical findings and clinical issues that are so important to our clinicians and scientists in the field.

(31:05):

And this is an example of a paper that really gets at the prefrontal cortex as it may relate to schizophrenia. And as it may relate to the working memory deficits that are seen in individuals that suffer from schizophrenia. So we've known for a very long time the patients with schizophrenia and schizoaffective disorder have cognitive alterations. And a lot of these have to do with their ability to problem solve and use their executive function. And also we know that their working memory is also not as efficient as individuals that don't have this illness.

(31:42):

The work by Arion and all in this issue of The Journal, tries to get at understanding better the different cell types in the dorsolateral prefrontal cortex that may underlie these memory deficits in individuals that develop schizophrenia. The dorsolateral prefrontal cortex we've talked a lot about. That's the region of the brain that has a lot to do with memory and executive function.

(32:07):

It's also part of the brain that is the interface between cognition and emotion. And it's a critical target, as we know from the standpoint of much of our TMS work actually. So what Arion and colleagues did is they actually used a rhesus monkey model. The reason they used rhesus monkeys is because rhesus monkeys have brains that are very similar to humans, especially in the prefrontal cortical regions.

(32:31):

Rodent species on the other hand, do not have a very well-developed prefrontal cortex and are not as good a model to use to understand human brain, especially in relation to the prefrontal cortex and cognitive functions. And what these investigators did is that they examined in detail how genes were working in very specific brain cells in the dorsolateral prefrontal cortex.

(32:57):

And without going into great detail, the brain cells that they selected are brain cells that have been associated with working memory. And also have been demonstrated to be altered in the way they're connected to other cells in post-mortem brains from schizophrenic subjects.

(33:12):

So we know that the brain cells that the researchers pick, which are called pyramidal cells, they're excitatory neurons in a specific layer of the cortex, and this is layer three of the cortex, are particularly interesting. Because A, they're associated with a pathophysiology of schizophrenia. And B, they're associated with cognitive working memory, which we know is altered in individuals with schizophrenia.

(33:35):

And in a very in-depth kind of analysis, the investigators looked at the development over time from prepuberty to puberty to adulthood in different cell types in this brain region. And what they found was is that there were different developmental trajectories that related to how the genes were working in these different cell types that are important.

(33:59):

And so this is important from a basic understanding of the cells that underlie working memory. But as importantly, they found that one of the types of cells had a maturational time course that was very similar to the onset of schizophrenia. And they suggest, and this is just a suggestion, that those cells may be the ones that are particularly relevant to the alterations that are occurring with working memory in schizophrenic subjects.

(34:26):

And their work has highlighted some of the genes in those cells that are involved with development, which could be genes that are also involved with the development of cognitive deficits in individuals that develop schizophrenia. And also potentially could serve as treatment targets for new molecules that might act on those genes that have been identified to be relevant.

(34:48):

So it's very basic neuroscience, but it's very interesting and important and relevant in relation to thinking about how we think about schizophrenic individuals developing working memory problems. And understanding more about the basic neurons in brains that may be contributing to these deficits. And also opening up new ideas about molecular treatment targets.

Aaron van Dorn (35:11):

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

Dr. Ned Kalin (35:13):

You're welcome. Thanks, Aaron.

Aaron van Dorn (35:15):

That's all for this month's AJP Audio, but be sure to check out the other podcasts offered by the APA.

(35:20):

In the most recent episode of Psychiatric Services From Pages To Practice, Dr. Dixon and Dr. Berezin speak with Dr. Maggi Price of Boston College's School of Social Work to discuss gender-affirming psychotherapy or GAP. A comprehensive evidence-informed and human-centered set of practices focusing on the treatment of transgender youth, developed by Dr. Price and colleagues.

(35:36):

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Speaker 4 (35:41):

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