Aaron van Dorn (00:07):

Welcome to AJP Audio for July 2024, I'm Aaron van Dorn. Today on the podcast I spoke with Dr. Lina Jonsson, Associate Professor in the Department of Psychiatry and Neurochemistry at the Institute of Neuroscience and Physiology at the Sahlgrenska Academy at the University of Gothenburg in Sweden. Dr. Jonsson and colleagues looked at the association of occupational dysfunction in hospital admissions with polygenic profiles in patients with bipolar disorder. Afterwards, AJP Editor-in-Chief Dr. Ned Kalin will walk us through the rest of the July issue. Dr. Jonsson, your study looked at people with bipolar disorder with occupational dysfunction when people are faced with difficulties performing tasks associated with work and life, and those with a history of hospital admissions with polygenic profiles. What did you find?

Dr. Lina Jonsson (00:45):

As you mentioned, we focused our analysis on both measures of occupational dysfunction and hospital admissions. There is a large group of patients that fail to regain functioning after bipolar disorder onset. And understanding the driving mechanisms is important to mitigate occupational dysfunction. Here, whether this in a bipolar disorder cohort called Svebyg that includes over 5,000 bipolar disorder patients and we use Swedish National Registry data to extract this information about hospitalizations and occupational dysfunctions. For those that might not be that familiar with the Swedish National Registry data, we have extracted information about psychiatric inpatient hospitalizations since the 1970s and had on average data during about 26 years between the ages 15 and 17 in the Svebyg cohort. The number of hospitalizations per year captures a lifetime estimates on disease intensity or illness severity. For occupational functioning, we had yearly records about employment and long-term sick leave since the 1990s and had there about 20 years of data between the ages 25 and 65 before the subjects concluded. And we could use this information to derive this long-term measures percentage of years that the subjects were employed or were long-term sick. We tested these outcomes in relation to so-called polygenic scores and we included polygenic scores for major psychiatric disorders, bipolar disorder, schizophrenia, depression, alcohol use disorder, and also educational attainment.

Aaron van Dorn (02:30):

Mm-hmm.

Dr. Lina Jonsson (02:31):

The polygenic scores for those that might not be that familiar with what polygenic scores are. This i a summarized estimated effect of many genetic variants for a specific trait in individuals and they are calculated based on previous large, so-called genome wide association studies. When we tested this, how these polygenic scores, so the polygenic liabilities associated with the outcomes, we show that the polygenic profiles differed for occupational dysfunction hospitalizations. More specifically, we could show that hospitalizations associated with the higher polygenic score for both bipolar disorders and these findings have been shown before. But in contrast, occupational functioning or these type of outcomes in bipolar disorder hasn't been that studied, especially when it comes to polygenic score analysis. And we found here that hospitalizations were associated with polygenic scores for bipolar disorder, schizophrenia, occupational dysfunction measures of employment and long-term sick leave associated with polygenic scores for schizophrenia, depression, ADHD, and also a lower score for educational attainment. And it's quite interesting how the polygenic profiles differed between these two outcomes. We followed up the analysis of occupational functioning in a control cohort and we also followed up the analysis of hospitalizations in the replication cohort called the Bipolar Disorder Research

Network, which is the bipolar disorder cohort from the UK, including approximately 4,000 subjects. And we can replicate the association between hospitalizations and polygenic scores, schizophrenia and bipolar in that cohort.

Aaron van Dorn (04:22):

Your study also found some polygenic liabilities associated with occupational dysfunction were also found in control subjects who similarly evinced occupational dysfunction. What does this suggest about grouping occupational dysfunction and hospitalization as characteristics of bipolar disorder?

Dr. Lina Jonsson (04:35):

I think it's very interesting that we see the same associations between the polygenic scores in control as we do in cases. And I think that it captures something that might not be specific only to bipolar disorder, but capture an underlying mechanisms or something that drives occupational dysfunction in general, not only in bipolar disorder. And it's something that might be important on a more general level as well. As I mentioned before, many patients fail to regain full functioning after disease onset and that it is sort of very important trying to understand in driving mechanisms for this. And I think that our findings in both cases and controls is one way to analyze these differences.

Aaron van Dorn (05:18):

Your study found significant crossover between the two groups only with schizophrenia spectrum disorder. What were the other conditions that you looked at that were associated with the two groups? You mentioned some of these earlier.

Dr. Lina Jonsson (05:29):

As you say, we found that polygenic score of schizophrenia associated with both occupational dysfunction and increased hospitalizations in bipolar disorder. This has been shown before as well. For example, for hospitalizations, others have shown that more hospitalizations associated with the higher polygenic score for schizophrenia. And also in relation to treatment outcomes, polygenic score for schizophrenia has also been associated with less response to the mainstay treatment lithium, that is the pharmacological medication most commonly used in bipolar. I think I would expect that we should see a higher polygenic score for schizophrenia associated with this type of outcomes. But I think it's still interesting that we see that this also is true or that we also find this for the occupational dysfunction outcomes.

Aaron van Dorn (06:21):

Even with the best available treatment, many bipolar patients remain impaired and the impacts can last long after they've recovered from the initial symptoms. The differences between polygenic risk scores in your samples suggest that there are different ways that bipolar disorder might present itself in patients. What does this mean for the clinical work of treating bipolar disorder?

Dr. Lina Jonsson (06:37):

I think it's important to start by mentioning that polygenic scores cannot currently be used clinically as they explained very little on an individual level. We find these differences when we compare groups, but it's still too early to use or to consider using polygenic scores for diagnostics or to predict disease outcome in psychiatry at the moment.

Aaron van Dorn (07:01):

Mm-hmm.

Dr. Lina Jonsson (07:02):

But the future hope is of course that this could be used together with clinical information for better predictions of disease outcome and also to understand the differences in both different disease outcomes in bipolar disorder. But I think that our study, if we think about possible clinical implications that our study could have, I think that our findings suggest that clinicians may need to use other interventions to mitigate occupational dysfunction compared to those who use to prevent mood episodes.

Aaron van Dorn (07:32):

Mm-hmm.

Dr. Lina Jonsson (07:33):

But these occupational dysfunctions, it could be that you need to address comorbid disorders such as ADHD in the clinical care as well.

Aaron van Dorn (07:44):

What were the limitations of your research?

Dr. Lina Jonsson (07:46):

As with all studies, our study also has limitations. We do have quite a large sample, but we are working with the Swedish National Register data. One limitation in using national register data science in Sweden is that we do not catch the reason for different events.

Aaron van Dorn (08:05):

Mm-hmm.

Dr. Lina Jonsson (08:06):

For example, the reason for being without employment, it could of course be factors that are other than the bipolar disorder.

Aaron van Dorn (08:14):

Mm-hmm.

Dr. Lina Jonsson (08:15):

And that could also include university studies, for example. That is mean that they are not in employment because they are studying and we try to avoid this factor by limiting our analysis to only include those older than 25 years of age when most people have finished their university studies. And also when working with registered data, so we included registered data from the 1970s and 1990s. And some of these measures have been subject to differences in definitions over time or for example, different changes in clinical practices over time. And these type changes over time is sometimes difficult to fully capture when you do these type of analysis.

Aaron van Dorn (09:01):

What's next for your research?

Dr. Lina Jonsson (09:03):

This study was conducted in the first wave of the Svebyg cohort. We are now very excited that the second wave of Svebyg has been finalized, which will include 5,000 bipolar disorder cases in addition to the first 5,000 bipolar. In total, the Svebyg cohort will now include approximately 10,000 subjects. We are very excited to start following up the results from this study as well. And also I want to mention Mikael Landen who has done a lot of work on the data collection in the Svebyg cohort and his API for the Svebyg cohort. You should also mention that ours and other findings on disease outcome are important when we now initiate studies of pharmacological treatment response as it is important to interpret treatment outcome in relation to disease outcome.

Aaron van Dorn (09:56):

Mm-hmm.

Dr. Lina Jonsson (09:57):

We are also working within the European Commission funded Psychstrata projects that started in 2022 to study treatment resistance across the disorders, bipolar disorder, depression, and schizophrenia. We're excited to continue that work as well.

Aaron van Dorn (10:11):

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

Dr. Lina Jonsson (10:13):

Thank you.

Aaron van Dorn (10:14):

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

Dr. Ned Kalin (10:19):

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

Aaron van Dorn (10:21):

Earlier I spoke with Dr. Lina Jonsson about their paper looking at the occupational dysfunction in hospital admissions in people with bipolar disorder and how those are associated with different polygenic profiles. What can you tell us about it?

Dr. Ned Kalin (10:31):

This is a really interesting paper that attempts to get at the genetic underpinnings of different presentations of bipolar disorder. And what these authors focus on are heterogeneity and how severe the illness is and also how functionally disabled individuals are that have bipolar disorder.

Aaron van Dorn (10:49):

Mm-hmm.

Dr. Ned Kalin (10:49):

They drew on patients that were in the Swedish registries and had a very large sample, about 4,700 bipolar patients that had at least 10 years of follow-up compared to around approximately 3,000 control individuals. And what they did is they looked at the number of hospitalizations per year as the major indicator of how severe an individual's illness was, and they also looked at the amount of sick leave and unemployment time to be a proxy for occupational function. And what they found was, first of all, not surprisingly, they found that the bipolar patients were unemployed for 40% of the years that were assessed as compared to the 15% of the control. We know that bipolar disorder is a disorder that not only is a disorder of severe mood regulation but also is has long-term functional consequences. And this once again establishes that. But they also looked at the genetic underpinnings of individuals that had severe illness, as well as individuals that were quite disabled. And what they found was is that in general there appears to be different genetic underpinnings that underlie the propensity to have severity versus the propensity to be disabled and functionally.

(12:07):

And you might think that these would have the same genetic underpinnings because you might think, well, if you have more severe illness, well then you'll have more disability. But it turns out while those two things may go together, that they have different maybe genetic make-ups. The way they did this is they calculated polygenic risk scores for a variety of different psychiatric illnesses. And so these are again using the genome-wide association of studies using them to predict schizophrenia for example, or major depression or alcohol abuse.

Aaron van Dorn (12:38):

Mm-hmm.

Dr. Ned Kalin (12:38):

But using those scores then in these patients, using the genetic findings from these patients to try to understand which of these types of scores were most associated with either severity of illness or disability. And what they found was, for example, that the relationship between polygenic risk scores and illness severity, for example, the schizophrenia polygenic risk score was associated with an increase in the number of hospitalizations per year. However, when they looked at the occupational disability, the functional problems, the polygenic risk scores for major depression, schizophrenia, ADHD, and educational achievement were associated with increased risk to be more disabled. They're beginning to show that different types of genetic make-ups may be associated with different outcomes. This is a very early beginning that sheds light on the genetic underpinnings of bipolar disorder suggesting that they may differ from illness severity compared to long-term occupational disability.

Aaron van Dorn (13:37):

Up next, we have an overview by Bauman colleagues looking at pharmacogenetic clinical support tools in the treatment of depression.

Dr. Ned Kalin (13:43):

This has been a very hot area over the last decade or so trying to come up with genetic markers that will predict outcome or more importantly, that will predict responses to different types of antidepressants.

And there have been a number of studies that have been done. And what these authors did along with other authors from the APA Research Council was to take a look now at where we are in the field by pulling together all of the papers that are meeting certain criteria and trying to come up with some recommendations about the use of these tools. And the bottom line is what they conclude is that we are still not at a point where we can reliably use pharmacogenetic tools to make predictions about the treatment of depression and the use of antidepressants. And that's despite marketing that is out there for a lot of these tools. And a lot of institutions that use these tools actually believe that they are useful. However, again, I would go with the conclusion of this paper in relation to really feeling that we cannot confidently use these tools at this point. Now, hopefully in the future we'll be able to, but they're really not ready for prime time yet in relation to clinical care.

Aaron van Dorn (14:55):

Kang and colleagues have a paper looking at the shared biology and metabolic traits in treatment-resistant depression in a GWAS.

Dr. Ned Kalin (15:00):

Yeah. This is an attempt to understand more of the genetic underpinnings of treatment-resistant depression, and there are a lot of different definitions for treatment-resistant depression. But in general, one of the most common used definitions is the failure to respond to at least two anti-adequate, and I underline adequate antidepressant trials. It's not just exposure to two antidepressants, but having adequate doses for at least four to six weeks, two trials. And if you fail those, then you're considered to be treatment-resistant. Now, what's unique about this paper is that it was based on trying to understand this in large electronic medical record databases in which also genetic data was collected. But to do this, it's very difficult from these large electronic medical databases to really be sure of the fact that someone has treatment-resistant depression. The way that these authors went about it is that they used a database first from individuals.

(15:56):

In this case it was about 460 individuals that had received ECT for depression. And they made this assumption that if you've received ECT, well then you have treatment-resistant depression. And I think that's a very reasonable assumption. They used those individuals to develop a model of what would predict the factors that would predict getting ECT, and they used artificial intelligence to do that or machine learning. And then they used that model further in a large electronic medical database that was comprised of over 150,000 individuals to predict within that database who would have treatment-resistant depression. They're using the prediction for ECT, which they're sure of, to then use in a larger sample where there's lots of data and use that model to pull out the individuals or to gauge the likelihood of those individuals having ECT or in this case as a proxy for treatment-resistant depression.

(16:57):

That's a little complicated, but that's how it works. And when they did that, they had then had access to a much larger database of individuals that were predicted to be treatment-resistant, okay. And I used the word predicted. And what they found them was by looking at the GWAS data from all of these patients, and this was a meta-analysis, that they basically found that there were two significant genetic loci that they could identify. And the two genes were interesting. One was called melanin-concentrating hormone receptor one, that's been implicated in eating behavior. And another one was related to body mass index. What they concluded was that this is a reasonable way to look at large samples in electronic medical records to pull out treatment-resistant depression, and also by using this machine learning

model and also some hints that there may be some genes that are involved with metabolic processes that may be related to treatment-resistant depression.

Aaron van Dorn (18:02):

Following that, there's an article from Rodin colleagues looking at antidepressant-induced mania in patients with bipolar disorder in a registry-based trial emulation from Denmark.

Dr. Ned Kalin (18:10):

This has been an ongoing long-term issue in clinical psychiatry about whether or not to use antidepressants to treat individuals that have bipolar depression. Bipolar depression frequently is very difficult to treat and also probably has a different biology than just simple major, what we used to call unipolar depression. There have been lots of anecdotal observations that the addition of antidepressants, especially tricyclic antidepressants, may trigger hypomania or a manic episode in someone that is bipolar. And so many people have veered away from using antidepressants to treat bipolar depression, have treated them more with just simply mood stabilizers or now with atypical antipsychotic medication shown to be helpful. This was an attempt to use a database with a relatively large sample of individuals who have bipolar depression to try to answer this question about whether or not the use of antidepressants facilitates hypomania or... And what they did here was something called a trial emulation study.

(19:18):

This is not a typical controlled randomized clinical trial that we think of as being the gold standard for testing these types of questions, but rather going into a database trying to match individuals, those that have bipolar depression that were treated with antidepressants and those that have bipolar depression that were not treated with antidepressants and match them. And also to try to control for a variety of other variables across these two samples and to use that as if it's a clinical trial. That's really important to keep in mind that this is not a prospective designed randomized clinical trial, okay. But having done that, they identified two comparison groups, 358 individuals that were taking antidepressants who had bipolar depression, and about twice that number, 621 individuals that were not taking antidepressants. What they concluded by following these individuals for one year, and again, one year is not a long time. By following these individuals for one year that there was not a difference that was significant between the two groups for hospitalizations for hypomania or mania as their primary outcome.

(20:29):

Now what's also interesting is that they also found that these individuals that were on antidepressants did not have a better outcome for the standpoint of depression relapse, which is something that would be surprising. That is to say if antidepressants were actually helping or making a difference, you would expect that. It looks like from this study that there is no greater risk with using antidepressants in treating bipolar depression. However, we have a really nice editorial that accompanies this paper by doctors Nowli Gottlieb and Alan Young from Pinks College London. And I would really encourage the readers that are interested in this paper to read the editorial as well because this is a counterpoint and talks about some of the issues in this analysis that could be questionable or some of the limitations and really stresses that there's a lot of data out there also that does suggest that antidepressants, especially tricyclics, can trigger hypomania and mania.

(21:24):

And the conclusion of the editorial is that this data that is presented in the paper is not sufficient to change treatment guidelines about not using antidepressants at this point. The answer to the question is

really not resolved, but it's a really nice study. It's well done. The conclusions are real, but also the editorial points out some of the limitations of the study and why we need to be cautious when we do use antidepressants in treating patients with bipolar depression. And from a personal experience, I would say that if used judiciously, antidepressants can be helpful and safe in patients that have "refractory bipolar depression." But again, we need to be very careful about the induction of hypomania and mania as well.

Aaron van Dorn (22:06):

Next we have a paper from Ironside and colleagues looking at the association of anterior cingulate GABA plus and dysregulated cortisol stress response in young adults with depression. What did they find?

Dr. Ned Kalin (22:15):

This is a study that's somewhat complicated. It uses multiple biological measures to really help us understand how alterations and how one responds to stress may relate to the pathophysiology of depression. It's a relatively small study sample in general, but when you look at all the measures that were used, it's not so small because it's hard to get that many measures in large populations. We would call this a deeply phenotyped sample. They used 44 patients who had major depression. They had 42 patients who had major depression, but were well, that is to say they're symptom remitted, and they had 44 control subjects. And what they did is they looked at fMRI data when participants were exposed to a stressful paradigm. They also sampled cortisol levels, a stress hormone, when the individuals were exposed to the stressful paradigm. And also when the individuals are at rest, they used a method called magnetic resonance spectroscopy, which allows one to actually look at the chemistry of what's going on in the brain.

(23:20):

And in this case, they set the parameters to estimate GABA levels, GABA the major inhibitory neurotransmitter of the brain, and they particularly focused on the rostral anterior cingulate cortex because this is a region that is involved with mood regulation, involved with depression, we believe, and also can be a target from the standpoint of thinking about some of the neuromodulation treatments that we might be using. By looking all these measures, they then try to use all these measures as conglomerate measures to say more about stress responsivity in depressed patients. What is also associated with that and they found a number of things. First they found, which is somewhat interesting, that the patients who had current major depression had a blunted cortisol response. Now, this is not always consistent with other literature because other literature would actually suggest that a subset of patients with major depression actually have an elevated cortisol response.

(24:13):

It's not clear to me exactly what was different in the patient population that they have, but nonetheless, in their paradigm that they used, they found that the depressed patients had somewhat of a blunted cortisol response. They also found that when they looked at the stress-related activity of the brain, that patients who had major depression, whether they had the current symptoms or not, that is were remitted, had alterations and decreased activity in some of the frontal and parietal networks in the brain, which are thought to be involved in mood regulation and have increased activity usually in relation to salient and stress-related types of things. Decreased activity in some of those regions across both depressed and remitted depressed patients compared to controls. They also found that in both of the clinical groups, that there were decreases in GABA levels in the rostral anterior cingulate cortexes compared to controls.

(25:10):

And then finally they found that the individual differences in cortisol reactivity distress had different associations with brain activity in one direction with depressed patients and in another direction with normal patients. What does all this say? It really supports the idea that in depressed patients, there is aberrant top-down regulation from frontal parietal networks related to stress responses and also different types of associations with brain activity in relation to cortisol in patients with depression. This all points to the understanding that patients with depression have alterations in the way they process stress responses, and that may be or may give us some hints into how stress relates to getting depressed and what some of the systems are that may be modulated or mediated. A complicated study, but really interesting. Again, there's a really nice article from a group from Baylor headed up by the senior author Dr. Chatty Abdallah that talks about some of the limitations of the study, particularly the sample size, but also talks about the value of the study from the standpoint of these multiple measures and bringing them together.

Aaron van Dorn (26:21):

And finally, we have a paper from Chen and colleagues, a forty-year long longitudinal study looking at potential links between mental health conditions in youth and cardio metabolic complications in midlife.

Dr. Ned Kalin (26:30):

This is a really interesting study, and we've known for years that patients with psychiatric illnesses tend to have metabolic problems. They tend to have an increase in weight, they tend to die younger from heart disease and a whole host of types of other things. And this can be attributed sometimes to the medications that we use to treat individuals, but also can be attributed to the disease processes themselves and perhaps the idea that these are individuals that not only have psychiatric illnesses but are chronically having more stress, which relates to cortisol. And cortisol has some of these types of effects as well when it's chronically elevated. This particular study, again, is quite interesting because it uses a very, very large sample. It uses data from over 670,000 individuals that were born in between the mid-1950s and the early 1960s, and looks at their psychiatric data when they were young between the ages of 18 and 25 years of age, and then follows them for many, many years to understand whether they develop cardio metabolic problems, and also whether certain types of illnesses, psychiatric illnesses, are more or less associated with the development of those illnesses.

(27:45):

As well as looking at what we call a general psychopathology factor, which is something that runs across all illnesses. And so they try to understand are there specific relationships between one type of illness, for example, schizophrenia or depression with the development of these problems, or is this a general type of thing that runs across all psychopathology? Cardio metabolic problems are related to what we call metabolic syndrome and what was originally called term syndrome X. and the original description of syndrome X many years ago was thought to be due to insulin resistance as a primary problem. Metabolic syndrome was defined as having at least three of the following types of things. One, increased waist circumference, another increased triglycerides in the blood, decreased HDL cholesterol, which is thought to be the good cholesterol, increased blood sugar or glucose, and elevated blood pressure. Having three of those components were thought to constitute the diagnostic criteria for metabolic syndrome.

(28:43):

What the researchers found was that when they followed these individuals psychiatric illnesses for many, many years, they found that all of the psychiatric categories including a history of committing a crime, and the reason they put that in there was because psychiatric patients have a tendency to be

more involved with some of these types of crimes. All of these were associated with an increased risk to develop cardiovascular disorders and elevated indices of metabolic syndrome. Some of the things that I talked about. Alcohol abuse had the highest odds ratio for the development of cardiovascular disease, and it was about 2.44 likelihood of developing cardiovascular disease if you had alcohol abuse as compared to normals. Schizophrenia had the highest odds ratio, in this case, 3.49 for the development of type two diabetes. Alcohol abuse also had the highest odds ratio, in this case, about 2.67 for the development of obesity.

(29:40):

Depression had an odds ratio of 2.46 for the development of Rode BC. But interestingly enough, when they looked at the general psychopathology factor basically controlled for these different diagnoses in their analysis, they found that the general psychopathology factor itself could account for these types of alterations or increased risks. The conclusion is yes, there's a marked increased risk in individuals that have psychiatric diagnosis over a many year period for developing cardio metabolic problem, but that it does not appear to be specific to any one illness. It tends to run across all psychiatric illnesses. This is really important and speaks to the need, I think, at a clinical level for psychiatrists and clinicians to not only be thinking about treating the symptoms of psychiatric illnesses, but to be aware of and mindful of, and even either referring or treating themselves, some of the metabolic problems that arise as patients are treated over a long period of time, help reduce the mortality and morbidity that may be associated with the metabolic problems in the patients that we treat.

Aaron van Dorn (30:46):

Well, Dr. Kalin, thank you once again for joining us.

Dr. Ned Kalin (30:49):

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

Aaron van Dorn (30:51):

That's all for this month's AJP Audio, but I hope you'll check out the other podcasts on author from the APA at psychiatryonline.org/podcasts or wherever you get podcasts. The views and opinions expressed in this podcast are those of the individual speakers only and do not necessarily represent those of the American Psychiatric Association. The content of this podcast is provided for general information purposes only and does not offer medical or any other type of professional advice. If you're having a medical emergency, please contact your local emergency response number.