Aaron van Dorn (00:07):

Welcome to AJP Audio for June 2024. I'm Aaron van Dorn. This month on the podcast I spoke with Sara Tramazzo, a graduate student in psychiatry at Hofstra University and formerly of Stony Brook University. Ms. Tramazzo and colleagues have a paper in the June issue of AJP, looking at the long-term course of remission and recovery in patients with schizophrenia spectrum disorder and other psychotic disorders over the course of 25 years in one county in New York State. Afterwards we'll once again hear from Dr. Ned Kalin, AJP Editor-in-Chief, on the rest of the June issue of the American Journal of Psychiatry.

(00:35):

Ms. Tramazzo, understanding the course of a disorder is vital for understanding the implications and expectations for treatment and recovery. Your study looked at the long-term course of psychotic disorders over a 25-year period in a longitudinal cohort of patients with a diagnosis of psychotic disorders, including schizophrenia. What did you find?

Ms. Sara Tramazzo (00:50):

So we found in general that the rates of remission and recovery are declining across the waves that we have in the study. And, to explain, we have different waves which were different follow-ups where we had our participants come back in, we interviewed them, assessed them. They were done at six months, two years, 10 years, 20 years, 25 years so they're all at various points. And, for people with schizophrenia, the rates of remission and recovery were declining across each of those waves. People with schizophrenia had a lower odd of being in remission and recovery at each of those time points that we followed up with them. Unfortunately, the rates declined with people with schizophrenia.

Aaron van Dorn (01:32):

Mm-hmm.

Ms. Sara Tramazzo (01:33):

People with other psychotic disorder, they tend to have an intermittent pattern of recovery and remission. So at each time point they were either in recovery and remission or not in recovery and remission. So it seems like they were going in and out.

Aaron van Dorn (01:47):

As you just mentioned, your study found lower levels of recovery and remission than many other long-term studies of psychotic disorders. What do you think accounts for this discrepancy?

Ms. Sara Tramazzo (01:55):

Yeah, so it seems like we have lower rates of remission and recovery than other studies, but that depends on what study you're looking at. So there is a study that's similar to ours in their methodology. It's a study out of Denmark that is a countywide sampling study and their rates of remission and recovery were actually similar to ours. Other studies that we wrote about or compared ourselves to, they might have been from one hospital, or outpatient studies. So our study really stands out because it's an epidemiological sample. It's from every available hospital in the county, so it's a representative sample of the area, and so it's giving a big picture, or a more accurate picture, of what it looks like for the average person who is diagnosed with schizophrenia, what do they look like? It's not just from one hospital or an outpatient sample, it's a countywide epidemiological sample.

Aaron van Dorn (02:51):

It must be very difficult to follow the same cohort of people over 25 years. So what can you tell us about the baseline cohort your study looked at and how did that cohort differ from the ones that you were evaluating at 25 years?

Ms. Sara Tramazzo (03:01):

The people after 25 years are from the baseline cohort-

Aaron van Dorn (03:05):

Of course.

Ms. Sara Tramazzo (03:05):

... that we were able to follow for 25 years. When we were writing this paper we wanted to look at it two different ways and consider what a clinician might look at. Given that a person has just been admitted to a hospital, what is their trajectory likely to look like? And that's what the baseline cohort is. So we looked at those people, the baseline cohort, and we wanted to see what is the outcome that we can predict for them. And then there's more of an epidemiological question. So if we could follow these people for 25 years, so the people that we have complete data for that we are able to follow for this long, what do their patterns look like?

(03:49):

So they answer two different questions. "Given that one person's admitted and this is their diagnosis, how can I predict what their outcome is going to be? Can we make some baseline predictions?" And then, "What are the actual patterns that we see if we are able to follow people for 25 years?" And it turns out it's pretty similar. So the data that we actually do have, the complete data, where we were able to follow people for 25 years, looks like the predicted data. So if someone is hospitalized and they're diagnosed with schizophrenia, our data shows that you can predict what their future might look like.

Aaron van Dorn (04:25):

There was a major distinction in your findings between recovery and remission for people diagnosed with schizophrenia and spectrum disorders versus other psychotic disorders. What were the outcomes between these two groups and what differentiates the two?

Ms. Sara Tramazzo (04:35):

So I think the biggest thing that differentiates them is the diagnosis and the nature of both disorders. So people with schizophrenia spectrum disorder, it's characterized by negative symptoms. So it's characterized by having trouble in their social life, holding jobs, being able to go out and have a productive day, things like that. So when we're looking at recovery and remission, a lot of that is measured by their functioning, their job, their social life, as well as lack of symptoms, the decrease in symptoms.

(05:14):

People with schizophrenia, they're going to have more negative symptoms, which makes it hard for them to do these things that meet the recovery criteria. Even being engaged in school or having intense volunteer commitments that can count as the criteria to be recovered, but people with negative symptoms, it makes it really hard. So I think it is just the nature, and, again, as we saw, people with

other psychotic disorder they are in and out of remission and recovery. So they have periods where they are remitted and recovered and they are able to maybe work and hold jobs and have more periods where they have less symptoms and are able to do these things.

Aaron van Dorn (05:54):

What are the clinical implications of your findings? Do they differ for clinicians who might be looking at someone newly diagnosed with a psychotic disorder or versus someone who might be dealing with one who has been dealing with it for decades?

Ms. Sara Tramazzo (06:03):

I think it's really important to look at people with other psychotic disorders who do come in and out of remission and recovery, that we found. So at some point they're in a place where maybe they're functioning well and they don't have a lot of symptoms, and that's great, that's great news that they have these periods.

Aaron van Dorn (06:24):

Mm-hmm.

Ms. Sara Tramazzo (06:25):

But it's also important, and important for you if you're diagnosed, that there's someone to understand your disorder. You might have a period, or you're likely to have a period, where you're symptomatic again, maybe you're not functioning as well, the illness symptoms come back. So in periods where somebody is feeling good, they're functioning well, they're not as symptomatic, they have to be alert and their doctors have to be alert, that it is likely that these symptoms will come back.

(06:55):

And then in people with schizophrenia who most commonly had a course of no recovery and no remission, I think it is very clear that we need to provide long-term care for this population. There is a lot of research and a lot of emphasis for first episode treatment, and there's a lot of programs where they treat people pretty intensely for a couple of years, but then it doesn't really matter, then, these older adults are still sick or getting more sick as they age. So I think it is clear that we need a treatment that helps people in the long run, helps these older adults, there's consistent chronic care for this population because clearly it is a chronic illness. So, I don't know, I think those are the clinical implications just for both groups, consistent care.

Aaron van Dorn (07:48):

What were the limitations of your study?

Ms. Sara Tramazzo (07:49):

So, like I mentioned before, we had these different follow-up waves and they happened regularly in the beginning. They were pretty close, maybe just six months apart. And then there's a 10-year gap and then a five-year gap, and then a two-and-a-half-year gap. So the follow-ups are pretty irregular. It's not really useful in maybe understanding someone with other psychotic disorder who, like I said, we see them coming in and out of remission and recovery. That might be tricky in really fully understanding them if maybe we only saw them during a brief period where they weren't doing well and maybe at all other time points they were doing great, but just the couple of moments we saw them, they weren't doing

well and they were symptomatic. So it takes a step back and gives you a big picture. But the regular time points make it difficult to really fully understand how people or an individual could be doing. These are averages at random follow-up points so people could have really extremely different experiences that we're just not fully capturing.

(08:54):

And, then, also too with a long follow-up study like this, for 25 years, and now they are actually doing their 35-year follow-up, but this data was just for the 25-year follow-up, but over that long it is really hard to get people to come in and want to do it. I was the study coordinator for the 25-year follow-up and the 27-and-a-half-year follow-up, and it is my full-time job to just get people to come in. So attrition is hard. We did do a good job and we do have the best retention rate of other first episode studies. But yeah, people over time, they don't want to talk about their illness anymore. They don't want to come in, they move, or people are just missing or hard to find if they are someone who's really sick. Their family loses contact with them and we can't find them.

(09:44):

So, yeah, those are the limitations, but we do work really hard to maintain relationships with people over this long. We send holiday cards and birthday cards and check in and follow up with people even when we're not running the study, and try to maintain good relationships.

Aaron van Dorn (09:59):

When you're looking at long-term longitudinal cohorts like this, maybe you're looking at something the study wasn't originally designed for so there aren't super regular intervention points, but what would, do you think, would be a good, regular, periodic check-in with people? Because you don't want to have it too close together because you're getting basically the same snapshot and you don't want to have it too far apart because you might be missing some things. So what kind of periodicity do you want to see?

Ms. Sara Tramazzo (10:21):

Yeah, that's interesting. That is interesting. I mean, unfortunately, with research you have to depend on writing grants and when you get funding and stuff like that. I do feel like 10 years is a huge gap.

Aaron van Dorn (10:35):

Sure, a lot of life in that time.

Ms. Sara Tramazzo (10:37):

Six months is too short. I feel like maybe one or two years. One or two years, you can get a pretty good picture of how someone was doing over a year when they come in and they tell you how they're doing. We also interview people's family members to get an idea of how our participants were doing and compare with what our participants were saying. We get medical records. It is difficult to sort through all that information when there is a five or a 10-year gap, but I think one or two years, it's easier to get a better snapshot of how somebody's doing with all the other records we get, aside from the participant interview.

Aaron van Dorn (11:13):

And since we're talking about how the best to design research going forward, what's next for your research?

Ms. Sara Tramazzo (11:17):

Well, like I said, I am no longer with Stony Brook. I love Stony Brook. I did undergrad there. I was an undergraduate research assistant for this project, and then when I graduated they hired me as a full-time coordinator and interviewer so I was there for another four years. So I absolutely loved this project and I loved my time there, but I got into a graduate program at Hofstra University. I'm just finishing up my first year there so it's very course-heavy and I am not starting any research yet. I am working under Dr. Serper who does do research on psychosis and schizophrenia, so it is aligned with my interest. I do want to continue working with this population, very passionate about working with psychotic disorders so my research will be in that field. I just don't know exactly what it is yet, and I have some time to think about it.

(12:11):

And, going back to Stony Brook, I do want to give a shout-out to my mentor at Stony Brook who really, really helped me with this project. She held my hand through it and she taught me how to write a paper and she taught me how to do lit reviews. She really held my hand through this process. Dr. Katherine Jonas, she was a big help and a great mentor, and I just wanted to thank her for helping me.

Aaron van Dorn (12:35):

Well, Ms. Tramazzo, thank you for taking the time to speak with us today.

Ms. Sara Tramazzo (12:37):

Of course. Thank you so much.

Aaron van Dorn (12:39):

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

Dr. Ned Kalin (12:44):

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

Aaron van Dorn (12:45):

This month on the podcast I spoke with Ms. Sara Tramazzo about their paper on the long-term effects of remission and recovery in psychotic disorders. What can you tell us about it?

Dr. Ned Kalin (12:53):

Yeah, this is a really interesting paper and, I think, provides important data about how we think about long-term outcomes in our patients, especially those with psychotic disorders. I should say that this issue has a number of papers relevant to schizophrenia and psychotic disorders, as well as other neurodevelopmental disorders, which we'll talk about as we get into the podcast.

(13:16):

This particular paper really provides results that in some ways are not surprising, but in other ways are really important to note. It's a study of patients that were hospitalized for their first psychotic episode in New York and Suffolk County between 1989 and 1995. Of those patients that were enrolled, 311 of those individuals completed follow-ups in the study over a 25-year period. So very long outcome data, which is important, and I think this will be clear as we get into the data.

(13:50):

The authors compared the outcomes in individuals that had schizophrenia spectrum disorders to those that had other psychosis, for example, someone that might have bipolar disorder or mania with a psychosis. And what they show is that, overall, when you look longitudinally over this period, that there are low levels of recovery and remission at the 25-year follow-up assessment. But these outcomes, and this is what's not unexpected, were considerably worse in individuals that had schizophrenia or schizophrenia spectrum disorders.

(14:18):

So, for example, at the 25-year outcome point, when they looked at who was recovered and who wasn't at that time point, only 14 percent of individuals with schizophrenia disorder were recovered and about twice as many, or 28 percent, with other psychoses were recovered. So, low for both groups, but twice as high for those that had non-schizophrenia spectrum disorder related psychosis.

(14:42):

Even more importantly, when they looked at all the different time points, they found that, for example, that individuals that had schizophrenia, only 0.6 percent of those individuals had a recovery pattern over the 25 years that was stable across all the time points. So very, very few people were well, fully well, and this was considerably higher, again, in the individuals that had other psychoses, it was around 20, 21 percent. So basically showing that not good outcomes overall, we need to do much better with our treatments over time. This is an area where we need improvement for sure, but worse outcomes in individuals with schizophrenia spectrum disorders.

(15:22):

And also when they looked at race within this group they found that being white was an advantage. And, again, I guess this is not surprising given what we know about the effects of structural racism and other types of discrimination from a stress standpoint. But there was about an eightfold greater likelihood of having a pattern of stable recovery in individuals that were white as compared to non-white individuals.

Aaron van Dorn (15:46):

Next, we have a paper from Erwin and colleagues looking at perturbed striatal gene expression dynamics in donor brains.

Dr. Ned Kalin (15:51):

So this is, I think, a really important paper. And this is basically cutting edge developmental neuroscience that's then translated to psychiatry. And it really shows, I think, the best of how we can bring our science together with clinical work and also hope related to the development of new treatments. This builds on, or adds to, a review that we have in the journal as well that is written by Dr. Rebecca Birnbaum and Dr. Daniel Weinberger. And the review is a outstanding review that focuses on how we think of the genesis of schizophrenia as a very early neurodevelopmental disorder where genetic patterns are already set that are risk patterns in environmental events or early in life, perhaps even in utero, come together to affect brain development and the development of certain circuits in the brain that then proceed to go on to facilitate the development of symptoms in someone that has the risk to involve schizophrenia.

(16:51):

So getting back to this paper, this is a paper by one of those authors that wrote the overview. Dr. Weinberger is also a co-author in this paper. And what's really exciting about this paper is that this is a paper where postmortem tissue was used from schizophrenia and non-schizophrenia subjects to create what we call organoids. Organoids are derived from stem cells. And, in this particular case, what was

particularly creative was that the brains have been collected in a postmortem brain bank. And what the authors used were actually tissue from the dura, which is the tissue that covers the surface of the brain, to create stem cells from that, from the subjects.

(17:32):

What they found was, and then what they were attempting to do was to create stem cells that look like a part of the brain that we know is important in schizophrenia, and this is the striatum. And so they were able to accomplish this. They developed these organoids that are rudimentary in brain structure that are derived from stem cells from each individual. And then were able to go on and characterize what was different in the organoids between the brains for normal individuals versus the brains for the schizophrenia individuals.

(17:56):

And what they were able to find, using a variety of techniques, is that there are a number of genes, many, many genes, that have altered expression patterns. That is, they're operating differently in these cells as compared to in the normals. It suggested that many of the issues are in fact neurodevelopmental in nature. And also one of the findings was that there may be alterations in some of the cells that are more inhibitory or GABAergic types of cells. And then, finally, I think one of the really important contributions of this study was that they were able to show that what they found in the brain organoids at a molecular level was also similar to what we know about and what they found in postmortem brain tissue, suggesting that the organoids can serve as a really good in vitro test tube, if you will, model where we can now create brain cells from individuals that already have passed away who we know had a certain illness, and then try to use that information to think about how we can develop and test new drugs.

(18:53):

So quite exciting, and I think it's going to be a paper that will, over time, become more and more important.

Aaron van Dorn (18:59):

Following that, there's a paper from van der Pluijm and colleagues looking at neuromelanin-sensitive MRIs as a potential candidate marker for treatment in first episode schizophrenia.

Dr. Ned Kalin (19:07):

This is another really interesting, novel approach. And I think what I like about this issue is that we have some fairly novel and cutting edge types of things. This study is looking at, as you mentioned, neuromelanin MRI. Now, neuromelanin is a substance that's deposited in cells in certain parts of the brain, especially in cells that contain dopamine. And it turns out that neuromelanin is actually a metabolite or a byproduct of dopamine and norepinephrine. Medical physicists over time have learned how to image neuromelanin in the brain, and that now is being used by a number of clinical research teams to serve as a proxy for dopamine availability and dopamine, perhaps, dopamine turnover.

(19:49):

And what the authors did is that they looked at neuromelanin levels in a region of the brain, the substantia nigra, which is a region of the brain also that has dopamine and is very involved with mediating, we think, some of the symptoms of schizophrenia as well as a target for the medications that we use, the antipsychotic medications. And what they found was that individuals that had higher levels of this neuromelanin, likely meaning higher levels of dopamine in this region, were more likely to have better responses to treatment when they were treated naturalistically for their first episode of

schizophrenia. So this is beginning to get at a biomarker that we can use with imaging that's novel, that allows us to think about, when we treat individuals, what the likelihood of the response may be. Again, very early, but, I think, quite promising and new methods that we're highlighting.

Aaron van Dorn (20:40):

Next we have a paper by Vita and colleagues looking at the impacts of cognitive remediation on cognition and psychosocial function in patients with schizophrenia.

Dr. Ned Kalin (20:47):

Again, just to highlight the schizophrenia issue, we've moved from a study of long-term outcomes, a naturalistic observational, longitudinal study to a very basic molecular study creating brain organoids from brains from schizophrenia subjects to now looking at treatment, and in this case, using a non-pharmacological treatment, which is cognitive remediation therapy, which is an attempt to get at the cognitive alterations that are part and parcel of having schizophrenia. And we now know that these cognitive alterations may be the most significant from the standpoint of impairing people's function over time. Cognitive remediation therapy is a therapy that is actually focused on improving some of these types of alterations, and it's focused on improving functional outcomes based on enhancing people's ability to problem solve and to be in situations that are stressful. And in this particular study, this is a study that is a meta-analysis looking across many, many studies, it comprised over 67 different studies with over 5,000 different individuals, and they followed them and looked at the data to see how effective cognitive remediation therapy was and how durable it was over time.

(22:02):

And what they found was is that the numbers of studies that they studied followed people on average for about 15 weeks. Well, excuse me, I should correct myself. The average length of time was, it was 14, 15 weeks, but it varied quite a bit across studies. And they found that there was a durable effect, but, not surprisingly, the studies that used more intensive therapy did it for longer periods of time and when it was combined with other types of therapies aimed at psychosocial functioning the patients did better than those that didn't have, if you will, as high a dose or other therapies added in. So this makes a lot of sense. Most importantly it reifies the concept that cognitive remediation therapy ought to be available to all individuals that suffer from schizophrenia. And we ought to be thinking about how to really get that out, in a public health kind of way, to all of our patients.

Aaron van Dorn (22:59):

Moving away from schizophrenia and on to ADHD and autism spectrum disorder, we have a paper by Tamon and colleagues looking at the neural correlates of ADHD and autism spectrum disorder.

Dr. Ned Kalin (23:08):

Well, this is another meta-analytic approach which, again, uses data across many, many studies. In this case, they're actually, all the studies added up to around 12,000 individuals. Roughly half of those were patients, half were controls. And the patients and controls were constituted of individuals that had autism spectrum disorder and ADHD. And the question that was asked was, "To what extent are functional brain alterations as detected by task-based fMRI common across these two disorders, and what might be different?"

(23:41):

And the reason that's of interest is because both of these disorders are neurodevelopmental in nature. They start early in life and we think they have to do with alterations and neurodevelopmental processes. And there are many symptoms that are common to individuals that have these types of problems. And also there's a high level of comorbidity across these types of problems. Now, having said that, these are very distinct illnesses and in no way should we imply that they're overly similar as well.

(24:11):

Nevertheless, what the authors found after looking at these brain scans, and these were activation scans using a task to activate their brain, they found that there were quite a few alterations that appear to be shared across these illnesses. But more importantly, and I think not surprisingly given what we know about their clinical presentation and the other factors related to these illnesses, is that there were more differences between the illnesses than what were shared as far as alterations of brain circuitry go. And I'm not going to go into all of the detail now, allow our readership to look at the paper, but some of the alterations that were different were related to the temporal gyrus and the right hippocampus in ASD subjects, and in ADHD subjects increased activation in the insula and the amygdala and the singular cortex.

Aaron van Dorn (25:01):

Finally, we have a paper from Norman and colleagues also looking at ADHD. What can you tell us about that?

Dr. Ned Kalin (25:06):

So this now focuses specifically on ADHD. It doesn't use what we call task-based brain activity. It uses what we call resting functional connectivity. So this is looking now at the brain in individuals with fMRI functionally when they're at rest. So not stimulating the brain, but in a sense looking at the idling of the brain. And we've learned a lot from studies that look at the resting state of the brain and we think that this may relate to a lot of trait like qualities of individuals. So in this particular paper what the authors did was what we call a mega-analytic approach, which is different than a meta-analytic approach. A meta-analytic approach looks at various studies and tries to pull the conclusions of the different studies. A mega-analytic approach actually takes the individuals from the different studies that have already been published and reanalyzes it as one individualized analysis.

(26:01):

So what they did is here they gathered enough data from over 6,000 youth. Most of these individuals came from the Adolescent Brain Cognitive Development Study that has been funded by the National Institute of Health and has been a tremendous resource in the field. And this is a public database that has phenotypic data ranging from psychiatric types of symptoms to substance use to other normative cognitive factors, and also has structural and functional brain imaging.

(26:30):

And what they found was that, overall, youth with ADHD had increased functional connectivity or coupling in their brains compared to individuals that were normal, youth that were normal. And these were particularly interesting because they were between striatal regions and the caudate and the putamen with a variety of cortical regions including the frontal and parietal cortices. They also found increased connectivity between one of the brain's regions that is subcortical that has a lot to do with emotion processing, which is the amygdala, and again, a region of the cingulate cortex, the dorsal cingulate cortex.

(27:08):

They also looked at this dimensionally. So this is categorical, they look to see if you have the illness versus if you don't have the illness. But we also know that individuals that do not meet full criteria also have symptoms of ADHD. And so they look to see whether or not the same types of brain alterations were found in a dimensional way, that is, that people that had more symptoms had more of these alterations, people that had less symptoms had less of them, people in the middle had a middle level, and, in fact, they found that. So this suggests that the findings are strong, but also that we can think of some of these symptoms as being dimensional and not simply yes or no or categorical.

(27:47):

I should mention, however, that the effect size, or the strength of the findings, is low, so that these are relatively small differences, but in such a large sample they're significant. This also highlights why we need very large samples because some of these differences that we're detecting are subtle. Now, whether or not that subtlety means they're not going to be particularly important, we don't know. It doesn't mean that for sure. It could be that some of these subtle differences have bigger effects downstream in ways that we don't fully understand at this point.

(28:19):

But just to wrap things up, I think this is a really exciting issue. It's focused mostly on what we think of as neurodevelopmental problems. Schizophrenia is a highlight. It's not typically called a neurodevelopmental disorder in DSM, however, I think most of us in the field think of it as a neurodevelopmental disorder. So I'm looking forward to having our readership take a more in-depth look at the issue.

Aaron van Dorn (28:43):

Dr. Kalin, thank you once again for walking us through the issue.

Dr. Ned Kalin (28:45):

You're welcome. It's a pleasure.

Aaron van Dorn (28:46):

That's all for this month's AJP Audio, but be sure to check out the other podcasts from the APA, including the Medical Mind Podcast which continues its series on Women Psychiatrists Caucus Chats with Dr. Gia Merlo of the NYU Grossman School of Medicine. That and much more can be found at psychiatryonline.org/podcasts or wherever you get podcasts.

(29:03):

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