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### The Neurobiology of Childhood Depression

#### Male Speaker:

You are listening to ReachMD, the channel for medical professionals. This segment is made possible by an educational grant from Shire Pharmaceuticals. Welcome to Updates from the Mayo Clinic, focusing on primary care pediatrics and child mental health. Here's your host, Dr. Peter S. Jensen, a childhood and adolescent psychiatrist and professor of psychiatry at Mayo Clinic in Rochester, Minnesota.

#### Dr. Peter S. Jensen:

Welcome to this Mayo Clinic series on primary care child mental health. I am your host, Peter Jensen, a child psychiatrist here at Mayo Clinic, and I am delighted today to have one of my colleagues, Dr. Paul Croarkin, assistant professor of psychiatry here at Mayo Clinic and an expert in the area of depression. Paul, welcome.

#### Dr. Paul Croarkin:

Thanks, Peter. Thanks for having me.

#### Dr. Peter S. Jensen:

Well, it's a great pleasure, and I'm particularly pleased because you are part of a team that has been focusing on primary care depression, and Paul is going to take us into the future today as we talk about...both the current as well as the future as we talk about the biology of youth depression. So Paul, I guess the first thing, you know, I've been aware from the large, federally funded treatment of adolescent depression studies as well as other depression studies that not every kid gets better with some of our medication treatments, and even when they're combined with a therapy. So I'm wondering if you can tell us, maybe take a step back down to the level of the neuron, what do we know about depression and what's actually going on at the level of the neuron?

#### Dr. Paul Croarkin:

Well that's very, very well said, Peter. As you suggested, you know, traditional treatments involve psychotherapy and usually medicines that act on the monoamine systems, things like serotonin, reuptake inhibitors, and we've done some very, you know, as a field we have some very impressive results from years of studies and well-designed studies have looked at SSRIs in children and adolescents with severe to moderate depression, and we know 50 percent or more of the time these options are often suboptimal, and you know, the bulk of prior neurobiologic research has focused on the serotonin system with the idea that there's a deficit in this brain chemical, either an up regulation or a down regulation in one or more of various serotonin receptors. Probably in reality it's much more complex than this and there are some more emerging theories looking at different neurotransmitter systems, GABA and glutamate in particular.

#### Dr. Peter S. Jensen:

I know you've been doing work in that area with GABA and glutamate and I know you're quite knowledgeable, obviously, about the serotonin system. Would you say that these are our two most promising areas or just how many neurotransmitters do you think might be involved in depression?

#### Dr. Paul Croarkin:

There potentially are multiple or dozens involved and probably the safest bet with respect to the GABA and the glutamate system is that it more than likely is a key player just because they're both so ubiquitous in the central nervous system in the brain, but more than likely it is as you've suggested, very complex with you know, probably depressions, you know, different individuals have different symptomatology, different dysfunctions, and different neurocircuitry pathways, and neurochemicals. There has been much recent interest in both GABA and glutamate in that they are thought of as kind of the ying and the yang of the central nervous system in that

GABA primarily serves an inhibitory function and glutamate is an excitatory function, and there is well documented evidence from basic science studies that for instance there is kind of GABA-serotonin cross talk in the raphe nuclei and in areas like the nucleus accumbens. There is much more work to be done, however, initial studies are very, very interesting and this theory has been looked at time and time again.

Dr. Peter S. Jensen:

Well you know, one of the puzzles that I've often thought was quite extraordinary, interesting, is that you can treat a child for ADHD and you'll get an immediate response. Why does it take so darn long for the brain and the person to respond to some of these other treatments? What's going on in the underlying circuits, do you think?

Dr. Paul Croarkin:

And that's an excellent question and the traditional, you know, I think probably what you may have been taught in training somewhere along the way and that I was taught, that we think that that may be involved to the idea that certain receptors have to down regulate on neurons, be it serotonin or beta-adrenergic. That by and large though, if you look at the literature closely, is largely theoretically.

Truth be told, I don't think we really know why these standard antidepressants take so long to enact an effect on a suffering child or parent or family, which points to some very interesting, somewhat preliminary and controversial work that's looked in adults at the ketamine story which is along the lines of what I've been talking about with the glutamate, that there's been some very preliminary but impressive research studies that have looked at the idea of administering ketamine to severely treatment-resistant depressed adults or suicidal adults with some pretty profoundly impressive results almost immediately, that patients are able to articulate that they see color and feel much better for a short time.

There's, you know, obviously a lot to be excited about in that regard, but there's also a lot to be skeptical about in that, you know, it's difficult to have proper controls for these studies, and there's really a lot of uncertainty about the safety of doing this, and the long term durability, and then thinking about an adolescent or a child in that regard, we would need much more, you know, much more granularity on the mechanism and would this be something that would be safe and effective for a developing brain.

But it does kind of throw the spotlight on one of the neurotransmitter systems I mentioned, the glutamatergic neurotransmitter system, in that ketamine is an NMDA antagonist which to me is...you know, I have kind of an idiosyncratic interest in this because some of the recent research we've done with transcranial magnetic stimulation, you know, is sort of tangentially interesting in this regard in that we recently looked at a group of depressed adolescents compared to some healthy age and sex matched controls. We did this, we recruited these...these were children anywhere from ages seven to 18 years of age that were really we thought clinically sick enough after a real detailed interview with family and the patient to warrant treatment with an SSRI. So we looked at what are called TMS, transcranial magnetic stimulation, measures of cortical inhibition, cortical excitability, and this is...I think you've had Dr. Wall on the program already, and when I talk about TMS this is a much different kind of TMS in that we're not providing treatment, this is a way to look at neurophysiologic paradigms that we think index the synaptic activity of certain chemicals such as GABA and glutamate.

Dr. Peter S. Jensen:

In a way...I mean, you talk about glutamine and glutamate, you're talking about systems in balance, I mean, very complex systems it seems like, and I guess all living creatures like to stay in balance, keep the same temperature, keep, you know, fed, watered, and you know, appropriate sleep. Is that part of what you're talking about, is systems in balance or out of balance?

Dr. Paul Croarkin:

I believe you're right. The results of the study I had mentioned actually suggested that depressed children and adolescents have an excess of cortical NMDA mediated glutamatergic neurotransmission. So this would suggest that maybe early onset depression is associated with an imbalance in this inhibitory-excitatory system. We know from other work that too much of a good thing, too much glutamate, is a bad thing through what's called neurotoxicity, and that this can have a pernicious kind of toxic effect on other neurons, and theoretically that's one model for how, you know, lifelong history of depressive systems and poorly treated illness could lead to much more severe recalcitrant illness later in life.

Dr. Peter S. Jensen:

We're talking today with Dr. Paul Croarkin, a national expert in the treatment and understanding the neurobiology as well as the treatment of youth depression. Paul, I'm wondering, you think about these systems that are in balance or sometimes not, seem to be maybe tipped the wrong way on the scale, one way or the other, is that because of genes or environment? How does that happen?

Dr. Paul Croarkin:

Well, it's probably a mixture of both is a short, easy answer. You know, we know that there are, from clinical practice, there are many individuals that have a, you know, tremendous family burden, genetic loading for depression. We see those patients in clinic. We also

see depression almost present spontaneously within a family tree. Studies have suggested that it's probably a gene-environment interaction or a stress diathesis model that certain individuals have a genetic predilection to develop these symptoms, and life stressors also bring these out. Another kind of interesting, you know, basic science field that's looking at this in a much more sophisticated manner is the field of epigenetics with the idea that we think that these really sophisticated studies have demonstrated that life events, good and bad, can actually alter the structure and function of DNA beyond standard mutations, for example, control the amount of acetylation of certain proteins within the DNA that affects how they're ultimately transcribed and read. So this is an interesting theory in that would provide kind of really tangible evidence for what you and I are talking about, that early life stressful experiences or trauma could lead to dysfunctional neurocircuitry through genetic material, and on a more positive note, really good psychotherapeutic interventions at a really critical time, for example, could have an actual effect on a patient's genetics and thereby neurocircuitry.

Dr. Peter S. Jensen:

You know, that's so interesting. It really becomes quite compelling, that we toss around this phrase gene-environment interaction, but you're really talking that the environments, both good and bad, can actually change how genes work. Would that be an overstatement?

Dr. Paul Croarkin:

No. That's exciting to think about.

Dr. Peter S. Jensen:

Well you know, that would kind of suggest that we have a kind of a brave new world future in front of us with all kinds of interesting discoveries to be made. You know, this has got to be complex and I think of just these balancing systems that you tweak one and then there's some adjustment, it may not want to move too far. As you think about the future what do you think the big breakthroughs and the kinds of areas we'll be looking at and finding things about in the next ten years?

Dr. Paul Croarkin:

Well I'm hopeful that in the next ten years and God willing in my lifetime that we'll have...you know, I'm very passionate about the idea of biomarkers, that we will better personalize psychotherapy and chemical treatments. We just don't...we do very careful, careful interviews and we have, you know, well-designed studies that have demonstrated that, you know, there are certain children that benefit from SSRIs for example. I'm, as a clinician, still very concerned that we feel that we could do better with matching the appropriate treatment, be it what kind of psychotherapy does the child need, what type of medication, hopefully we'll have additional medications to balance these neurochemical systems you and I have been talking about, and improve outcomes so patients don't have to wait six months to get the correct treatment and to figure out what's going to work, and this is maybe a bit of a reach, but I feel like our lack of definitive understanding of the neurophysiology of our illnesses in some respects drives the stigma associated with mental illness and I feel like a greater depth to that will help our patients and our practice.

Dr. Peter S. Jensen:

You know, we have many primary care providers who probably kind of wonder, worry about whether they should get their hands dirty so to speak, intervening and finding kids who might be depressed and learning how to intervene and assist these children. What would you tell them in terms of the difference they can or can't make and the importance of age in the diagnosis and management of depression?

Dr. Paul Croarkin:

Oh, I'm so glad you brought that up. Primary care I think is...you know, you and I have been kind of talking about chemicals and interesting ideas, I think I love what I do, but I feel like child psychiatry, our field, it's a bit of a mess, which is frustrating and inspiring, but we definitely need, on our end, we need to do better, and assist our primary care colleagues, and get them comfortable and involved because they have an immense potential to improve the lives of children. It's critical that we do a better job of recognizing these illnesses. Even where we're at right now with current diagnostic systems and treatment, it's critical that we get a higher level of identification and treatment because more than likely the more we can do that on a larger scale we're going to prevent morbidity for individuals, family systems, and society on a large level.

Dr. Peter S. Jensen:

And for the primary care doctor, is there any evidence if they could actually find, identify, and assist these kids early it'll actually make a difference in outcomes or are their fates sealed and there's nothing really the primary care doc can do?

Dr. Paul Croarkin:

No. No. Their fates are not sealed. I mean, there's good evidence to suggest that their involvement will optimize their outcomes.

Dr. Peter S. Jensen:

We have been talking today with Dr. Paul Croarkin, a professor of psychiatry here at the Mayo Clinic, national expert in the neurobiology of depression and its treatment. Paul, thank you so much.

Dr. Paul Croarkin:

Thanks, Peter.

Dr. Peter S. Jensen:

We'd like to thank our listeners and you can tune in to ReachMD, [www.reachmd](http://www.reachmd), and download this and other podcasts concerning depression, ADHD, bipolar disorder, conduct problems and aggression, part of the Mayo Clinic series on primary care child mental health. This is your host, Dr. Peter Jensen, thank you for joining us and tune in again.

Male Speaker:

Thank you for listening to Updates from the Mayo Clinic and thank you to Shire Pharmaceuticals, whose educational grant makes this program possible. For more details on the interviews and conversations in this week's show and many others or to download this segment go to [ReachMD.com/MayoClinic](http://ReachMD.com/MayoClinic).