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From Monoamines to Neurocircuits: Our Evolving Understanding of Depression

Announcer:
Welcome to ReachMD.

This medical industry feature, titled "From Monoamines to Neurocircuits: Our Evolving Understanding of Depression," is sponsored by Otsuka Pharmaceutical Development & Commercialization, Incorporated.

Here's your host, Dr. Charles Turck.

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Dr. Turck:
Our understanding of depression has evolved over the past several decades, leading us to some potentially exciting new treatment options that aren't focused on chemical imbalance and negative cognitive biases, but rather, neuroplasticity.

This is ReachMD, and I'm Dr. Charles Turck. Joining me to discuss the history of depression treatment approaches and the emerging concept of neuroplasticity is Dr. Joseph Goldberg, who's the Clinical Professor of Psychiatry at the Icahn School of Medicine at Mount Sinai in New York City.

Dr. Goldberg, welcome to the program.

Dr. Goldberg:
Thank you for having me.

Dr. Turck:
So why don't we start off with a brief history about our knowledge of the pathophysiology of depression. Dr. Goldberg, what can you tell us here?

Dr. Goldberg:
Well, our understanding of the pathophysiology of depression has certainly evolved from the monoamine hypothesis, which states that depression is caused by a deficit in the production or the uptake of neurotransmitters, such as serotonin, norepinephrine, and dopamine —basically, the idea of a chemical imbalance.[1-3] For decades, the driving concept was that if you could increase the availability of synaptic monoamines with antidepressant therapy, that would, in turn, increase postsynaptic binding, meaning there would be more neurotransmitter signaling.[4]

But there are some problems with this concept. First, increased postsynaptic binding can take a while, sometimes weeks, to actually see an effect on symptoms.[5] Second, if increased neurotransmission was the surefire way to treat depression, then we'd expect to see higher response rates. As it is, a number of patients don't respond to antidepressant therapy.[6]

And then let's not forget about Aaron Beck's cognitive theory of depression from the 1970s. Aaron Beck observed that our thoughts influence our feelings, and we can have biases in our thinking that influence the ways we feel. So for example, if I have a negative cognitive bias or expectancy that things are bad and aren't going to get better, that can feed on itself and trigger the signs and symptoms of depression.[7]

For this to happen, though, patients would have to be susceptible to it either from environmental conditions, and/or they'd need to have some biological susceptibility that increases their genetic risk for depression.[7,8]

Dr. Turck:
Thank you, Dr. Goldberg. And if we stay with Beck's cognitive theory for another moment, how did it influence treatment of depression?

Dr. Goldberg:
Yes, so Aaron Beck is considered the father of cognitive behavioral therapy, or CBT.[9]

The idea is that if we modulate our thoughts and our behaviors, we might be able to modulate our feelings.[10] For example, with CBT, we learn that expecting failure is not helpful. It can distort our thinking, make it harder for us to find solutions.[10] If I'm playing chess, I automatically assume that my opponent will call checkmate, I may not see the next move even if it's right in front of me.[11]

So, once patients are aware that they may have negative cognitive biases that are causing problems, they can learn how to change them.[10] They can learn how to think through problems more clearly and realistically, and how to unbias their thinking, and move from "glass is half empty" to "glass half full" so they might be able to prevent or overcome the symptoms of depression.[11]

Dr. Turck:
So how can we take what's not working to help change the way we think about depression and to create additional treatment options?

Dr. Goldberg:
So, antidepressant therapy and psychotherapy, including CBT, have been the standard of treatment for depression.[12] And I've been asked whether we should think of depression as a disease of both chemical imbalance and negative cognitive biases. But I think we need to move forward and think about depression more as a disease of faulty wiring in the brain.[13]

And by wiring, I'm talking about neurocircuits that act like information highways to allow areas of the brain to communicate with other areas. Strong neural connections and greater synaptic density create a solid, well-paved highway, but poor connectivity and decreased density leads to a highway that's filled with potholes.[13]

So, in depression, we don't so much have a deficiency of neurotransmitters—or the cars in this scenario—per se, but our highway is filled with disruptions to traffic flow. Neurotransmitters have to avoid the potholes, so they move slowly and traffic backs up. Information isn't moving efficiently from point A to point B.[14]

So how does antidepressant therapy play a role in the wiring of the brain? Well, contrary to historical thinking, we now believe that effective pharmacotherapies that modulate monoamines turn on genes that protect nerve cells from damage.[15] They protect the highways and keep it whole.

And psychotherapy involves learning, and learning creates new synaptic connections and greater connectivity in the brain to repair the highway.[16-18] So, like antidepressant therapy, psychotherapy makes the nerve cell connections stronger and more viable, and this is how we believe both types of treatment exert their therapeutic effect.[15-18]

Dr. Turck:
For those just tuning in, you're listening to ReachMD.

I'm Dr. Charles Turck, and today I'm speaking with Dr. Joseph Goldberg about our evolving understanding about the underlying pathways of depression.

Now, Dr. Goldberg, you just mentioned a new system for how we can potentially treat depression, so let's explore this further. What else can you tell us?

Dr. Goldberg:
So this is where we get into the concept of neuroplasticity, which is the ability of the brain to reorganize its structure and functions in response to internal or external stimuli.[19]

Neuroplasticity is kind of like your lawn. Drought, cold weather, the absence of nutrients can all interfere with growth and make your lawn look sparse. And it's the same with synaptic density. If you take a rodent and put it in an adverse environment where there's stress and no enrichment or positive stimulation, at autopsy you'll see that the synaptic connections in the brain are relatively sparse.[20,21]

So going back to cognitive theory, I talked about how adversity can lead to negative cognitive biases, and that occurs via impaired

neuroplasticity.[22]

So there are things we can do to make your lawn look more lush. Sunlight, water, fertilizer will all help make your grass grow. And in depression, whether it's pharmacotherapy, psychotherapy, neurostimulation, or exercise, we should aim to increase synaptic density and strengthen the nerve cell connections.[15-18,23,24]

Dr. Turck:
And where in the brain does neuroplasticity come into play?

Dr. Goldberg:
So, there are two key brain areas that are at odds with one another in someone with depression—the prefrontal cortex and the limbic system, a deeper subcortical structure in the brain.[25]

As you know, the prefrontal cortex drives executive functioning and attentional processing—logical things like planning, organizing, problem-solving, weighing consequences. We call this cold cognition.[25]

And then there's the limbic system. That's involved with emotional processing. So this area we refer to as "hot cognition". It drives the impulsive fight-or-flight response.[25]

We think in depression, there's dysfunction in emotional processing and regulation.[26] So for example, the limbic system may be overactive and exert control over the prefrontal cortex.[26] This person could be impulsive and emotional, and not thinking about consequences. They leap without looking.[25] We call this bottom-up processing because the deeper limbic structure's override the higher brain structures and function of the prefrontal cortex.[25]

An overactive limbic system is analogous to a car alarm going off every time the wind blows—so, it goes off with far too much sensitivity when there's no real threat.[27] We need the prefrontal cortex to come in and say, "Oh, that's a false alarm. Calm down, nobody's breaking into your car."[28] There's not a real threat present.

So clearly, we need to restore the balance between bottom-up emotional processing and top-down emotional regulation.[28] And we can do that by strengthening the nerve cell connections between the prefrontal cortex and the limbic system so that neurotransmission flows more smoothly between these two brain areas.[28]

Dr. Turck:
Thanks, Dr. Goldberg. So then how do we strengthen the connections between the prefrontal cortex and the limbic system?

Dr. Goldberg:
So in the 1940s, there's a psychologist named Donald Hebb and he said, "neurons that fire together wire together."[29] Meaning, if you can fire neurons in the prefrontal cortex and the limbic system at the same time, you can strengthen synaptic connections.[28,29] If you think about dialectical behavior therapy, it's about using what we call the wise mind.[30] The reasonable mind is driven by logic, or the prefrontal cortex, while the emotional mind is driven by feelings, or the limbic system, and the wise mind is somewhere in between.[25,30] So in this kind of psychotherapy, a patient learns and practices skills to use the wise mind and activate this synchrony between these two areas of the brain.[30]

But there could be other ways to fire these neurons together. Maybe it's a task or a learning activity that engages a patient's emotions and cognitions at the same time.[28]

So if we focus on this as a target, I think we may be able to develop novel treatments for depression that go beyond the mechanisms of action that we currently have. We're going from chemical imbalances to the cognitive theory of depression to neuroplasticity, and now we're targeting specific neurocircuits.[1,7,22,28]

There are multiple ways we can deliver these novel treatments. As we've seen, especially during the pandemic, treatment doesn't always have to be face-to-face. It can be delivered virtually with telehealth,[31] or digitally, where software provides the treatment. We've seen this with psychotherapy apps, for example, which may be one way to increase access to treatment, especially if there's clinical evidence showing that they can improve patient outcomes.[32]

Dr. Turck:
These all sound like great developments. Now as we come to a close, is there anything you'd like to leave with our audience today?

Dr. Goldberg:
Cognitive theory has taught us that our thoughts can influence our emotions. And cognitive exercises for depression strive to correct faulty thinking patterns that reinforce negative emotions.[7,22]

But effective pharmacotherapies or psychotherapies for depression are also thought to result in enhanced neuronal signaling in brain circuits that are involved in emotional processing.[12]

And now with modern theories about the treatment of depression involving strategies that can enhance neuroplasticity, or the viability and strength of nerve cell connections in brain regions involved in processing emotional information,[19] I think we have exciting possibilities for how we treat depression and how to deliver the treatment. It'll be very interesting to see how these things continue to evolve.

Dr. Turck:
Those are some great comments for us to think on as we come to the end of today's program.

And I want to thank my guest, Dr. Joseph Goldberg, for his insights into how our understanding of depression has evolved.

Dr. Goldberg, it was great speaking with you today.

Dr. Goldberg:
Pleasure was mine. Thank you again for having me.

Announcer:
This program was sponsored by Otsuka Pharmaceutical Development and Commercialization, Incorporated. If you missed any part of this discussion, visit ReachMD.com/industryfeature. This is ReachMD. Be Part of the Knowledge.

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