Is Depression a Chemical Imbalance?

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Dr. Michael Cummings and Dr. David Puder who were in the audio of this interview have no conflicts of interest.

On July 20, 2022, Nature published a meta-analysis, "The Serotonin Theory of Depression: A Systematic Umbrella Review," that concluded serotonin levels are not decreased in people with depression.

In the weeks since, there has been a flurry of articles sensationalizing this news and calling to question the efficacy of antidepressants given this "new" information. We will address some of the questions that these articles pose.

For decades the public has been led to believe that depression is due to a chemical imbalance in the brain. Is this true?

It is important to recognize where this belief originated. When the first antidepressants–known as tricyclic antidepressants–were developed in the 1950s, researchers knew the drugs increased serotonin so they outlined a model that explained depression as a serotonin deficiency based on this simplistic deduction. In the 1990s and early 2000s, after the invention of dozens of SSRIs, pharmaceutical companies used this incomplete model of depression in their advertising and educational materials for physicians. The pharmaceutical companies marketed their drugs to physicians with explanations such as, "These drugs give patients more serotonin which cures their depression, so therefore we conclude that depression is due to a serotonin deficiency."

In some ways, this line of thinking was helpful to the adoption of SSRIs. Mental illness had long been stigmatized and equating depression to faulty brain chemistry made it more acceptable in society. This chemical theory of depression removed blame from the individual and increased acceptance of medication therapy for depression.

Why doesn't the public know about this?

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After the establishment of new information and guidelines for a medical practice, it can take up to ten years to become the new norm. This inherent delay, plus the power of pharmaceutical ad campaigns, has made this myth a difficult one to bust. The reductionist explanation for depression is enticing. Blaming depression on something as nebulous as brain chemistry that a pill can cure is easy to conceptualize and has stuck in the public's mind for decades.

What causes depression, then?

Current research points to primary pathology in the limbic system, the circuitry in the brain responsible for memory, motivation, and behavior. In a 2012 paper in *Science,* by Ronald Duman and George Aghajanian, it was concluded that one of the chief characteristics of major depression is a loss of synaptic connectivity, particularly atrophy of dendritic spines that is associated with a decrease in neurotrophic factors like BDNF, as well as a decrease in overall metabolic neuronal activity in the limbic system. Depression is also associated with reduced size of prefrontal cortex and hippocampus, with decreased neuronal synapses in these areas. The paper, "Synaptic Dysfunction in Depression: Potential Therapeutic Targets," had a few important takeaway points:

A. Chronic unpredictable stress decreases neurogenesis, dendrite complexity, and spine density in the prefrontal cortex.
B. Chronic stress leads to hypertrophy in the nucleus accumbens and the amygdala. The nucleus accumbens is responsible for motivation and reward, and the amygdala is responsible for fear.
C. In mice, seven days of 20-30 minute restraint stress lead to atrophy of prefrontal cortex pyramidal neurons.
D. Glucocorticoids and/or stress decrease BDNF in the prefrontal cortex and hippocampus.
    a. Autopsy of people with depression shows lower BDNF.
    b. Decreased BDNF leads to involution of neuronal processes, dendrite shrinkage, and synaptic terminal atrophy.
    c. Depressed people have lower counter regulatory neuro-steroids like allopregnanolone & dehydroepiandrosterone. Allopregnanolone is associated with abortion of depression and is infused postpartum to prevent postpartum depression.
E. Prior studies have shown that antidepressants, exercise, and enriched environments increase dendrite complexity and synaptic density.

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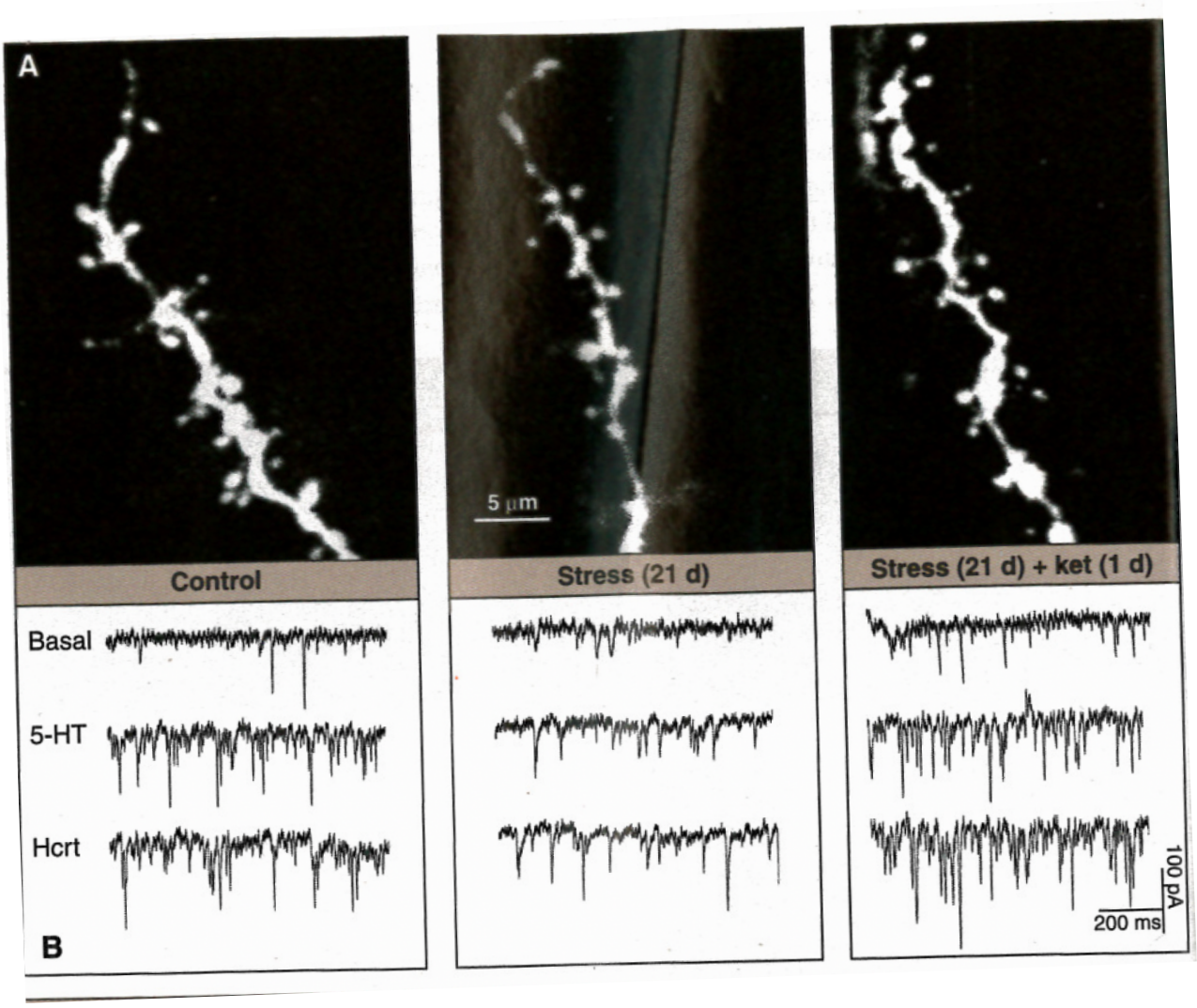

Caption: Control (non-depressed state) vs. stress (depressed) vs. stress treated with ketamine. The neurons regenerate!

Why does increasing serotonin help, if it's not due to a deficiency of serotonin?

The limbic system changes in response to the increased serotonin, modulating itself to work with the new flood of hormones. These changes are beneficial to depression, but as we know, it does not cure the primary cause or prevent depression from reoccurring. Antidepressants produce a 50% reduction in symptoms in about two-thirds of cases of major depression, but produce remission in only about one-third. SSRIs aren't a perfect solution, but they are certainly a good one for some people.

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Just knowing the brain areas associated with depression does not mean medications will be the only solution. It is well-established that therapy changes the brain, as well. Often people do not realize that it takes a significant amount of therapy to produce changes in the brain:

- A study of over 10,000 therapy clients, assessed session-to-session with a validated outcome instrument, found that it took 21 sessions, or about six months of weekly therapy, to see clinically significant changes in 50% of patients. Only after 40 sessions, or almost a year of weekly therapy, did researchers see significant changes in 75% of patients (Lambert, 2001).
- An Emory University survey of 270 experienced psychotherapists found that their last completed therapies "in which patient and therapist agreed that the outcome was reasonably successful" required a median of 52 to 75 sessions (Morrison, Bradley & Westen, 2003).

Changes are made in the brain with therapy that are similar to changes produced by medications. Psychotherapies tend to have more permanent changes post-treatment. Well-done psychotherapy does not end with the last session.

Why do SSRIs take so long to work?

As with psychotherapy, the changes in the brain that occur with SSRIs require chronic exposure to the therapy. When medications work, they tend to work faster than psychotherapy. However, psychotherapy tends to have more lasting effects. To illustrate this point, Dr. Hyman in the *American Journal of Psychiatry* emphasized in his paper, "Initiation and Adaptation: A Paradigm for Understanding Psychotropic Drug Action"(1996), that neurotransmitter turnover is not the accurate picture, rather "chronic drug administration drives the production of adaptations in postreceptor signaling pathways, including regulation of neural gene expression." Initiation of the therapy, either through medication or psychotherapy, repeatedly perturbs the neuronetwork and leads to adaptation.

Do we have anything faster and/or more effective?

Ketamine is known to be faster and ECT is typically more effective. Duman and Aghajanian (2012) found that prefrontal cortex and hippocampal damage reversed with ketamine. Ketamine and ECT seem to be more able to stimulate synaptic genesis and turn on rapid-response genes that activate structural genes in the limbic system neurons. It is important to note, however, that even though their focus was on ketamine and its rapid response, other things like

antidepressants, exercise, and environmental changes also effectively reverse this damage, albeit more slowly.

Does depression cause changes in the brain itself?

Yes, which is why the chemical hypothesis is inadequate. From Duman and Aghajanian, we have evidence that neuronal and structural deterioration is associated with depression. Furthermore, a 2011 paper in *Dialogues in Clinical Neuroscience*, "Of Sound Mind and Body: Depression, Disease, and Accelerated Aging," Owen Wolkowitz and colleagues discussed how depression is associated with accelerated aging–yet more evidence that depression has a strong biological component. Major depression is associated with increased incidence of atherosclerosis, heart disease, hypertension, stroke, cognitive decline, dementia, and osteoporosis.

Additionally, "Depressive symptoms in neurodegenerative diseases," published in 2015 by Baquero and Martin, showed impressive links between the two pathologies. The following list of facts from the paper further illustrates this point:

A. Depression is found in 40% of patients with frontotemporal degeneration.
B. Up to 73% of patients diagnosed with corticobasal degeneration have been found to have comorbid depressive symptoms.
C. Suicide rates in patients with Huntington's disease have been reported to be four times that of the general population.
D. Depressive symptomatology is seen in up to 50% of patients with Parkinson's disease.
E. Patients with middle cerebral artery lesions were found to have higher rates of depression than patients with lesions affecting posterior circulation.
F. Importantly, in Lewy body disease, which is caused by deposits of alpha-synuclein in the limbic, paralimbic, and neocortical regions of the brain, depressive symptoms are more severe than in other neurodegenerative diseases. This further highlights evidence that the limbic system plays a major role in depression.

Underlying diseases that adversely affect frontotemporal neural circuits, such as schizophrenia, can produce symptoms fulfilling multiple DSM diagnoses, including depression. Upthegrove and colleagues published "Depression and Schizophrenia: Cause, Consequence, or Trans-diagnostic Issue" in 2016, showing an elevated rate of depression in patients with schizophrenia. In acute episodes, up to 60% of schizophrenic patients suffer from depressive symptoms. Longitudinal studies indicate that up to 80% of schizophrenic patients experience at least one episode of major depression. Evidence has shown that schizophrenic patients who exhibit depressive symptoms have poorer outcomes than others, with risk of suicidality greatly increased in these patients.

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The pathophysiology of schizophrenia and depression have many similarities, including hippocampal gray matter volume loss, high rates of childhood trauma, and elevated inflammatory markers such as IL-4, IL-6, IL-10, and TNFα. Blunted affect and withdrawal in depression have been shown to be inversely proportional to gray matter volume in the bilateral cerebellum. Social withdrawal, anhedonia, and loss of motivation are shown to be the most consistent similarities seen between major depression and schizophrenia spectrum disorders. The overlap in symptoms can be explained by alterations in common circuitry, blurring the lines between diagnoses and further illuminating the biological basis of depression.

Why do some people get depressed, while others don't?

From Wolkowitz et al., the moderating effects of depression are coping styles, genetic predispositions, and epigenetic modifications like childhood adversity. Some of the mediating effects are the limbic, hypothalamic-pituitary-adrenal axis alterations, reduced glucocorticoid receptor function, altered glucose tolerance and insulin sensitivity, excitotoxicity, increased intracellular calcium, oxidative stress, plus proinflammatory milieu. These physiologic changes that occur in the depressed brain are in addition to the major changes described by Duman and Aghajanian.

Chronic stress plays a major role in the epigenetic modifications that can contribute to depression. Exposure to excessive chronic cortisol seems to be associated not only with promoting depression, but with producing resistance to antidepressant treatments. Each person's stress tolerance is different, with resilience and mature coping mechanisms acting as protective factors. As people learn and adapt to ways of dealing with distressing events or circumstances, those events or circumstances can become inherently less stressful for them. This does not necessarily include adverse childhood experiences or complex traumas, which can themselves create chronic stress on the body and mind. However, the objective of psychiatric treatment with medication and therapy is to increase resilience, therefore decreasing perceived stress.

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How should depression be treated?

Ideally, any mental illness will be treated holistically. There is strong evidence that multimodal treatment, meaning medication plus therapy plus exercise, can produce more robust results than any modality by itself. Medication can help the patient start their therapeutic process and enable them to re-engage with their life. Patients should be encouraged to take further steps to regain control of their lives and take ownership of their healing. Adding exercise and psychotherapy to one's daily life can provide lasting relief from a depressive episode. However, it is important to weigh the risks and benefits of discontinuing medication therapy, especially if the risk of relapse is high.

Psychiatric medications are typically not curative. They could be better characterized as tools, which may then help make the person more available to participate in things like therapy and exercise and life changes. In treating someone medically, Dr. Cummings recommends a medication trial up to at least minimum therapeutic dose plasma concentration (when blood levels can be measured). If the person doesn't respond, keep titrating upward until either they reach a point where they're having unmanageable side effects or the drug's point of futility is reached.

Hopefully, through this podcast we have shown how complex the treatment of depression is and how many factors need to be both considered and addressed when treating it. Here are some highlights:

1) SSRI and SNRI deep dives:
    a) Duloxetine efficacy goes up with more severe depression (Episode 112).
2) In regards to therapy:
    a) Cognitive distortions (faulty ways of thinking and feeling) impact mood and can be targeted (Episode 003).
    b) Emotional detachment can be overcome by finding congruence with safe people (Episode 021).
    c) Trauma can change our nervous system (Episode 023).
    d) Connection is important in both treatment and in training (Episode 149).
    e) There are multiple effective treatments of borderline personality disorder (Episode 140).
    f) Meaning impacts mental health (Episode 082).
    g) Great books have information that can guide some of our most pressing questions (Episode 120).
3) In regards to sensorium:
    a) Patients can look depressed when really it is a sensorium issue (Episode 006).
    b) Patients can have medications which can impact their sensorium making them look depressed (Episode 011).

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    c) Anticholinergic medications may make someone look depressed (Episode 102).
4) In regards to exercise:
    a) Strength training can clearly reduce depression (Episode 018).
    b) Strength training in recent studies continues to have a strong, and maybe stronger impact, on depression compared to cardio (Episode 096).
    c) Steady state exercise has value, and most endurance athletes spend the majority of their training in lower heart rate zones (Episode 142).
5) In regards to diet:
    a) New studies continue to come out showing the mental health benefits of certain foods (Episode 131).
6) In regards to non-SSRI pharmacotherapy treatments:
    a) Ketamine is a powerful tool for treatment resistant depression (Episode 137).
    b) Blood levels can be helpful for tracking medications (Episode 127).
    c) Psilocybin combined with therapy could be an up and coming treatment (Episode 106).
7) In regards to interventional treatments:
    a) ECT is a powerful treatment for severe depression, catatonia and more (Episode 152).
8) Other things that might be present with depression and complicate it:
    a) BPD is commonly comorbid with depression and has a unique impact on treatment (Episode 115).
    b) Sometimes severe bodily anxiety is akathisia (Episode 111).
    c) Neuroticism, one of the Big 5 personality traits, can be the underlying issue in someone presenting with depression, and may need a longer course of therapy (Episode 092).
    d) Disorganized attachment can impact mental health and present as depression (Episode 087).

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