“Correlation does not Imply Causation”, while Psychotropic Drugs do cause Neurochemical Imbalances and Dysfunction of Neurotransmission

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Abstract

Mental health professionals often prescribe psychotropic drug to patients diagnosed with mental health illnesses under the premise that neurochemical imbalance is a cause of mental health disorders. In this paper we discuss reasons to believe that there is no scientific research which provides evidence that neurochemical imbalances or problems with neurotransmission in the brain are causative factors in the etiology of mental health illnesses. Behavioral and neurochemical research studies in animals show an **association** between mental health states and alteration of neurotransmitter signaling. However, correlation does not imply causation. To the contrary, stress paradigms in rodents show a diminishing of the activity of the mesolimbic dopaminergic reward pathway *as a result of* long-term stressful stimuli. Furthermore, studies in human cases of mental health disorders show that psychotropic drugs cause disturbances in neurotransmission or neurochemical homeostasis as seen in biochemical research studies, and this is manifest by the behavioral consequences experienced during withdrawal in humans and animals.

Significance: This paper presents reasons to question the safety and efficacy of the common use of psychotropic drugs in the mental health industry.

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Introduction

Introduction to Psychotropic Drugs

Mental health disorders are commonly believed to involve pathophysiological processes in the brain. Of note, many doctors and researchers have come to believe that imbalances and impairment of neurotransmitter signaling in the brain is the underlying cause of disorders such as depression, insomnia, somnolence, ADHD, PTSD, Bipolar disorder, and schizophrenia. Under this premise, the use of psychotropic drugs has greatly increased in the past several decades, and i*t* is reported recently that over 24% of Americans are taking prescription mental health medication (Vinzant, 2022). Psychotropic drugs have several mechanisms: they either mimic the effects, block the function, or in some form change the storage, release, and uptake of neurotransmitters (Vaughan, 2024). Thus neurotransmitter signaling is the target of psychotropic drugs. The following are the neurotransmitters that are commonly targeted: **dopamine, GABA, Serotonin, acetylcholine, glutamate, adrenaline** (*epinephrine*), and **oxytocin**.

As of 2017, there were 108 psychotropic drugs available according to Neuroscience-based Nomenclature (Sathyanarayana, 2016). Psychotropic drugs fall into these categories: antidepressants, anti-anxiety medication, stimulants, antipsychotics, and mood stabilizers. However, these drugs often have multiple effects on neurotransmitter signaling. For example, *quetiapine*, a drug taken for schizophrenia and major depressive order, is a dopamine, serotonin, as well as an alpha-2 noradrenergic receptor antagonist. The drug *clozapine* also has multiple targets of action. (Sathyanarayana. 2016). Furthermore, with all the psychotropic drugs, there are 1 or more of 10 modes of action: 1) *receptor agonist, 2) receptor partial agonist, 3) receptor antagonist, 4) reuptake inhibitor, 5) reuptake inhibitor and releaser, 6) reuptake inhibitor and receptor antagonist, 7) an enzyme inhibitor, 8) ion channel blocker, 9) positive allosteric modulator, 10) enzyme modulator* (Sathyanarayana, 2016).

Proposed Cause of Mental Health Illnesses

Many research scientists and doctors believe that mental illnesses are a result of "*problems*" in communication within the brain. This is an inference based on research studies which reveal neurochemical abnormalities in individuals with mental health disorders. For example, in individuals with depression, a low level of serotonin is a common finding (NIH, 2007). This finding led to the use of *SSRIs* (selective serotonin reuptake inhibitors), which reduce the amount of serotonin taken back into the presynaptic neuron leaving more serotonin in the synaptic space nearby the postsynaptic neuron. This in turn increases serotonin levels and signaling. However, it is important to note that mental health disorders are diagnosed based on symptoms rather than with blood tests, pathogen culture, urinalysis, x-ray, etc. Family doctors and pediatricians

will often refer suspect individuals to mental health professionals (psychiatrists, psychologists) who will closely examine the mental health symptoms in conjunction with general health status, and prescribe psychotropic drugs accordingly (NIH, 2007). Thus, this leaves the diagnosis of mental health disorders highly subjective.

Of interest, the neurotransmitter dopamine, and its signaling pathways are implicated in the pathophysiology of many mental health disorders. Dopamine neurotransmitter signaling occurs in three common pathways. The **nigrostriatal pathway** involves dopaminergic neurons in the *substantia nigra pars compacta* that project to the dorsal striatum. This pathway is involved in *locomotion* and *movement*. The *mesocorticolimbic pathway* involves dopaminergic neurons in the *ventral tegmental area* that project to the *nucleus accumbens* and *limbic systems* (**mesolimbic pathway**), which is also called the *dopaminergic reward pathway*, and the *prefrontal cortex* (**mesocortical pathway**) (Luo, 2016). The **tuberoinfundular pathway** projects from the *arcuate nucleus* of the *hypothalamus* to the *median eminence* and regulates the secretion of *prolactin* in the anterior pituitary gland.

Researchers have for decades been looking at the **mesolimbic dopaminergic pathway** as relates to the etiology of major depressive disorders and other mental health disorders. They believe that dysfunction of the dopaminergic system is "*hallmark*" in the pathology of Parkinson's disease, drug addiction, depression, and schizophrenia (Baik, 2020). The dopaminergic mesolimbic pathway is also known as the **dopaminergic reward system** because of many behavioral studies in rodents which have examined the effects of both reward and stress on neurotransmission within this pathway which extends from the *Ventral Tegmental Area* (VTA) to the *Nucleus accumbens* and *amygdala*. Of interest, it is observed that both reward and short-term stress excite the mesolimbic dopaminergic pathway (Baik, 2020). Whereas long term stressful aversive events can depress the dopaminergic reward system by decreasing sensitivity to reward while subjects are in the state of *anhedonia*. The effects of stress on the mesolimbic dopaminergic system as observed in rodents shows an increase in dopaminergic activity in the VTA following short term stressful events, such as chronic restraint for 1 hour a day for 10 consecutive days, or chronic social defeat stress (*CSDS*) which involves introducing a single male intruder for 5-10 minutes a day, leaving sensory exposure for the remainder of the day for 10 consecutive days. In the case of CSDS, two categories of rodents were observed to respond differently (*resilent* and *susceptible* rodents). Whereas another stress paradigm in which rodents are subjected to a variety of stressful events administered randomly over the course of 4-6 weeks called Chronic Mild Stress (*CUMS*) showed a decrease in activity in the dopaminergic nerurons of the VTA and in D2 receptor binding in the *nucleus accumbens* (Baik, 2020). Thus, researchers hypothesize that repeated exposure to stressful stimuli over the course of a prolonged period of time may lead to impairment of neurotransmission as well as behavioral phenotypes of depression and anhedonia (lack of responsiveness to reward or failure to fight to survive). However, the discrepancies of results in various studies and circumstances have left scientists uncertain how exactly this stress and reward system works and how directly applicable it is to human cases of major depressive disorder. What is important to consider in light of these studies is that regardless of the differing effects based on the time scale and the manner of experimentation, stressful stimuli were *upstream* to any observed changes in dopamine signaling in the dopaminergic mesolimbic pathway.

Discussion

Flaws in the Theory of Neurochemical Imbalance/Problems with Neurotransmission as the Cause of Mental Health Illness

The above research is a primary example of behavioral studies that are often performed in which abnormal neurotransmission is observed in the brain in conjunction with the behavioral phenotype of major depressive disorder or another mental health illness. In rodent studies, stress paradigms are employed. Whereas in human studies which examine neurotransmission through measuring levels of neurotransmitters and their signaling, the subjects are already indicated for mental health illness. For example, it is observed that GABA and glutamate levels as well as dopamine, serotonin, and norepinephrine homeostasis are altered in individuals with Autism Spectrum Disorder (Teleanu, 2022). Similarly, depression in humans is associated with atrophy of neurons in the cortical and limbic brain regions and general decrease in concentration of dopamine, serotonin, and norepinephrine (Teleanu, 2022). Furthermore, therapeutic strategies to offset these abnormalities ("*finetuning brain NT homeostasis*") through administration of psychotropic drugs has proven to mitigate symptoms in affected individuals both in animal and clinical studies. Nevertheless, the entire premise that mental health illnesses are *caused by* or *a result of* problems in neurotransmission is based on flawed science. All young and upcoming research scientists are taught the fundamental principle of science theory and research practice: "*Correlation does not imply causation*!" To the contrary, as we discussed, rodent studies of the dopaminergic reward pathway from the *VTA* to the *nucleus accumbens* shows that prolonged states of "*stress*" resulted in perturbations in dopamine signaling, and not the other way around! Furthermore, the term "*stress*" is ambiguous as in some studies there were both resilient and susceptible types of rodents, all of which were subjected to stressful stimuli. In fact, even within mental health research it is reported: "*Indeed, the term stress has been used to indicate both a response (or a set of responses) and the stimuli that promote the response*" (Cabib, 2012).

Doctors are treating the associated abnormalities in neurotransmitter signaling without ever determining the true cause of mental health disorders. The major health associations of the United States can only hypothesize what are the causes of these disorders, and often note the difficulty of biochemical assessment of diagnosed individuals due to the presence of the blood brain barrier. Genetics (*due to the fact that mental health illnesses tend to run in families with similar behavioral and neurochemical manifestations*), environmental factors such as traumatic events and "*stress*", as well as "*chemical imbalances*" in the brain are proposed as likely causes of mental health illnesses. Yet there are tremendous differences among the human population observed in the coexistence of these potential causes and mental health disorders, and no clear research-based evidence that chemical imbalances in the brain (*abnormalities in neurotransmission*) is a **causative factor**. Thus, mental health professionals are subjectively diagnosing a condition with no objective means of testing by biochemical assay, and then treating these conditions which have no clear biochemical *causes*. They are seeking to correct a supposed perturbation of neurotransmitter homeostasis with a seemingly effective therapeutic approach, albeit, a dangerous one! What is the result? Withdrawal symptoms, dependence, and addiction!

Results

A Dangerous Therapeutic Approach!

Withdrawal symptoms in discontinuing, switching, or attenuating psychotropic drug medication are the most dreaded aspect of patients and mental health professionals who treat these patients. A recent review article which examined conventional and new withdrawal symptoms (related to the drug use), rebound symptoms (related to original mental health illness), and persistent withdrawal effects found that all of the following drugs may induce withdrawal symptoms, and rebound effects, even with a slow tapering off of use: *benzodiazepines, nonbenzodiazepine benzodiazepine receptor agonists, antidepressants, ketamine, antipsychotics, lithium, mood stabilizers* (Flammetta, 2020). The authors of the study gave warning about the introduction of new psychotropic drugs into the market, while the long-term persistent withdrawal effects have not yet been catalogued and taken into account.

If we are going to speak about problems in brain neurotransmission, we need to speak about problems in brain transmission that occur as a result of the introduction of new psychoactive substances into the brain. The brain is known to consistently, and often quickly and dramatically, respond to the primary effects of any psychoactive substance. This can occur through impaired neurotransmitter receptor function or sensitivity, decrease in the number of receptors, decreased neurotransmitter production, impaired neurogenesis, increased stress hormones, decreased stress response, and brain cell death (*neurotoxicity*) (Renoir, 2012). For example, SSRIs, which are administered in hopes of increasing the amount of serotonin available to the postsynaptic cell, cause the brain to respond with biochemical mechanisms which reduce or even completely reverse the effect of the drug (Breggin, 2012). Similarly, the potency of anti-anxiety drugs which increase GABA signaling can be weakened and reversed through compensatory mechanisms in the brain. Withdrawal and dependence in the case of psychoactive drugs are shown to occur through decrease of activity of the mesocorticolimbic dopaminergic system and decreased activity in the nucleus accumbens and amygdala (Lerner, 2019). Thus, when patients decrease or discontinue use of drugs, withdrawal symptoms often appear with devastating effects. A recent study of 585 users of anti-psychotic drugs who stopped taking their drugs found that 72% of users reported experiencing classic withdrawal symptoms associated with other types of psychotropic drugs (Read, 2022). Of these, 52% categorized the symptoms as severe. Psychosis was reported by 18% of the participants. While we do not have evidence to say that neurochemical imbalances cause mental health illnesses, we do have substantial evidence through behavioral and neurochemical research studies of withdrawal that psychotropic drugs themselves cause neurochemical imbalances and impairment. And when individuals have been on psychotropic drugs for months at a time, withdrawal can feature immediate as well as prolonged serious effects not only on the brain, but on body weight (promoting obesity), metabolism, cardiovascular function, sleep, menstruation, alertness, bowel health, and many others (Mazareel, 2020. Furthermore, a study found that from 1999 to 2019, 51,446 psychotropic-drug-implicated deaths occurred with a dramatic increase over time due to the rise in prevalence of these drugs among the US population (Vuolo, 2021).

The real effectiveness of psychotropic drugs for improving the symptoms of psychotropic drugs also needs to be closely examined. Dr. Peter Gøtzsche explains that most studies looking at the efficacy of psychotropic drugs are looking at a

short time scale, and the effectiveness often drops within days beyond the latter end of the study duration, while adverse effects increase. He also points out that many of the study participants in notable studies were originally taking a psychotropic drug and are experiencing severe withdrawal symptoms upon starting the placebo course, thus leading to an overly optimistic view of the efficacy of the drug tested. He also notes that studies looking at withdrawal effects and suicide are also flawed because of too short of a timespan of observation. For example, he reports based on his research that there were 14 suicides among 9956 patients in study trials of fluoxetine and paroxetine, whereas the FDA only reports 5 suicides among 52 960 patients. He attributes this to the 24-hr time span of observation by the FDA for suicide after discontinuing the drug (Gøtzsche, 2015).

> *"Psychiatric drugs are responsible for the deaths of more than half a million people aged 65 and older each year in the Western world, as I show below.[1] Their benefits would need to be colossal to justify this, but they are minimal... Given their lack of benefit, I estimate we could stop almost all psychotropic drugs without causing harm —by dropping all antidepressants, ADHD drugs, and dementia drugs (as the small effects are probably the result of unblinding bias)[1 24] and using only a fraction of the antipsychotics and benzodiazepines we currently use[1]. This would lead to healthier and more long lived populations…..[1 22]" (Dr. Peter Gøtzsche)*

Conclusion

In summary, there is no scientific research which provides evidence that neurochemical imbalances or problems with neurotransmission in the brain are causative factors in the etiology of mental health illnesses. Behavioral and neurochemical research studies in animals show an **association** between mental health states and alteration of neurotransmitter signaling. However, correlation does not imply causation. To the contrary, stress paradigms in rodents show a diminishing of the activity of the mesolimbic dopaminergic reward pathway *as a result of* long-term stressful stimuli. Furthermore, studies in human cases of mental health disorders show that psychotropic drugs cause disturbances in neurotransmission or neurochemical homeostasis as seen in biochemical research studies, and this is manifest by the behavioral consequences experienced during withdrawal in humans and animals.

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