Understanding the Neurobiological Basis of Drug Abuse: Comorbidity in Schizophrenia

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It is clear that the prognosis for schizophrenia is much better when patients achieve drug abstinence, including in the domains of depression, quality of life, and community integration.

Schizophrenia is a severe psychiatric disorder that affects approximately 1% of the general population. The 12-month prevalence of substance use disorders (SUDs) among the general US population is approximately 12% for alcohol and 2% to 3% for illicit drugs. It is interesting to note that nearly 50% of people with schizophrenia also suffer from a comorbid substance-related illness during their lifetime. There are complex interactions between substance use and psychiatric disorders, including schizophrenia.

Patients who receive a dual diagnosis—a psychiatric disorder and an SUD—are faced with serious challenges related to treatment and prognosis. Many clinicians focus solely on treating either the psychiatric illness or the SUD. This lack of integration of psychiatric and addiction treatment is a significant issue for dual-diagnosis patients; growing evidence suggests a poorer prognosis with nonintegrated treatment. Psychiatric illness appears to be a vulnerability factor for substance abuse, and because substance abuse can lead to an exacerbation of psychiatric symptoms, there is a critical need to understand the factors that influence both the onset and duration of substance abuse and psychiatric illness, particularly how they interact to influence prognosis.

The pathophysiology of schizophrenia
Schizophrenia is characterized by the disturbance of cognition and sometimes behavioral and emotional processes. Positive symptoms of schizophrenia can include hallucinations, paranoia, and delusions, while negative symptoms can include blunted affect, cognitive deficits, social avoidance, and anhedonia. Reductions in brain volume typically occur in patients with schizophrenia (as a function of the illness, medications, or both), primarily in the prefrontal cortex (PFC) and temporal lobes, which may contribute to the cognitive deficits commonly seen in patients.

There are 4 central dopamine (DA) systems: mesolimbic, tuberoinfundibular, mesocortical, and nigrostriatal. The mesolimbic pathway projects from the ventral tegmental area and substantia nigra of the midbrain to the nucleus accumbens (NAc), olfactory tubercle, and amygdala. The DA hypothesis may be insufficient to explain the complexity of schizophrenia. However, there is mounting evidence to support DA dysfunction in schizophrenia. In particular, schizophrenia appears to be associated with hyperactive subcortical mesolimbic DA pathways in the brain and deficient DA function in the PFC. Moreover, all effective antipsychotic medications are antagonists of the DA D\textsubscript{2} receptor.

Mesocortical DA modulates working memory and executive function, and dysregulation of this pathway may underlie some of the positive and negative symptoms associated with schizophrenia. The nigrostriatal pathway extends from the substantia nigra to the dorsal striatum via the median forebrain bundle, and overactivity of striatal DA release may be a key factor in the development of schizophrenia (Figure). DA influences motor activity and attention in humans and plays a critical role in stress. In animals that are subjected to stress, DA is released in the cortical and limbic areas of the brain and may exacerbate symptoms associated with schizophrenia that could be a result of too many demands on the already diminished population of dopamine neurons. The DA system also plays a large role in the reward- and pleasure-seeking system, particularly the D\textsubscript{1} and D\textsubscript{2} receptors. Many drugs of abuse block the function of the DA transporter, resulting in a large increase of DA in the synapse and increased D\textsubscript{1} and D\textsubscript{2} receptor signaling that mediates the reward pathway, usually in the NAc.
Thompson and colleagues\textsuperscript{14} recently reported that striatal DA release is increased in patients with schizophrenia, primarily in the precommissural caudate, and reduced in the ventral striatum in individuals with addiction. They measured the change in amphetamine-induced D\textscript{2/3} receptor availability in both dual-diagnosis schizophrenia patients and in schizophrenia-only patients using positron emission tomography. Dual-diagnosis patients reported greater increases in happiness and energy following drug administration, but amphetamine reduced D\textscript{2/3} receptor availability across both groups.

**Schizophrenia and SUD**

Many hypotheses have been put forth to explain the link between substance abuse and schizophrenia. The two hypotheses that we discuss are the self-medication hypothesis (SMH) and the addiction vulnerability hypothesis (AVH).\textsuperscript{15,16} The SMH posits that drugs of abuse relieve psychological suffering and that a person’s preference for a particular drug involves some degree of psychopharmacological specificity.\textsuperscript{17} By contrast, the AVH suggests that the of schizophrenia may increase vulnerability to drug reward and reinforcement, thus promoting concurrent expression of these disorders.\textsuperscript{16}

The SMH entails relief of negative symptoms, such as anhedonia, depression, blunted affect, and neurocognitive deficits.\textsuperscript{15} This hypothesis claims that drug addiction is a secondary process, or a reaction, to schizophrenia; the dysfunctional leads to aversive symptoms and to self-medication. Khantzian\textsuperscript{17} suggested that “it is not so much a psychiatric condition that one self-medicates, but a wide range of subjective symptoms and states of distress that may or may not be associated with a psychiatric disorder.”

People with schizophrenia may be targeting the negative symptoms and/or motor adverse effects of antipsychotic medications. The SMH explains comorbid drug addiction through a negative reinforcement model, in which drugs may serve to reduce aversive symptoms associated with the psychiatric disorder.\textsuperscript{17}

Over the past few decades, the SMH has drawn criticism. Since support for the SMH has focused on subjective, self-report measures, many researchers question the validity of this hypothesis. Amelioration of negative symptoms and adverse effects of medication is among the reasons Khantzian provides for individuals with schizophrenia who use drugs.\textsuperscript{17} Tobacco use is common in patients with schizophrenia, and nicotine may alter nicotinic acetylcholine receptor abnormalities in schizophrenia.\textsuperscript{18}

The effects of smoking abstinence on visuospatial working memory (VSWM; a cognitive process dependent in part on prefrontal DA) were examined in smokers with schizophrenia and smokers without schizophrenia (controls).\textsuperscript{19} Smoking abstinence in the schizophrenia group was associated with a decreased VSWM; in the control quitters, VSWM improved. The findings indicate that nicotine may have beneficial effects on cognition in smokers with schizophrenia. Although these data appear to support the SMH, it is important to note that cognition is subconscious and an individual with schizophrenia is unlikely to describe the effects of smoking on such unconscious processes. Another shortcoming of the SMH is that when dual-diagnosis patients stop using their drug of choice, their psychiatric symptoms improve or remain unchanged rather than worsen after drug withdrawal is complete.\textsuperscript{4,20} Moreover, findings from prospective clinical trials suggest that patients with schizophrenia who quit smoking have no significant changes in positive and negative symptoms.\textsuperscript{21} Results from a retrospective study show that smokers with schizophrenia significantly decreased their reported daily cigarette use when they switched from neuroleptics to the atypical antipsychotic clozapine.\textsuperscript{22} If the SMH were supported, it would be expected that smokers would not decrease their daily smoking in response to medication (and may in fact increase smoking), since the SMH suggests that individuals use drugs to relieve medication adverse effects.

The AVH differs from the SMH in that it does not assume there are any beneficial (or detrimental) reasons for comorbid drug addiction. While the SMH posits that dual-diagnosis patients become addicted to relieve deficits, such as mood and anxiety symptoms, the AVH claims that dual-diagnosis patients become addicted to drugs despite the negative consequences of the drug.\textsuperscript{23}

With its focus on the common pathophysiology of addiction and schizophrenia, the AVH does not rely on the positive aspects of a drug as mediating the addictive process. The AVH suggests that addiction and schizophrenia are primary disease symptoms with common abnormalities. In addition, environmental influences can have a strong effect on the development of either one of the comorbid diseases. The combination of environmental and genetic influences may predispose an individual to a comorbid drug addiction, often before prodromal psychotic symptoms appear.\textsuperscript{24}

Animal studies provide some of the best data with respect to modeling the comorbidity process; neo-natal ventral hippocampal lesions (NVHLs) in rats mimic symptoms similar to those of
Rats with NVHLs responded more actively to an initial cocaine injection than did controls, and they had greater patterns of behavioral sensitivity after 7 days of injections. Such altered patterns of behavioral sensitization may result from abnormal present in schizophrenia, which promotes greater vulnerability to addiction.

In the brains of individuals addicted to drugs, the NAc is in an activated state, whereby DA inputs to the NAc are increased. DA inhibits hippocampal and PFC glutamatergic input and decreases NAc GABAergic outflow to the ventral pallidum and thalamus. In this disinhibited state, the reward circuitry is dysfunctional, and DA levels continue to rise, producing increased drug reinforcement. Developmental abnormalities in both the hippocampal and PFC circuitry in schizophrenia may impair projections to the NAc. This results in hyperresponsiveness to basal and drug-stimulated DA release. Therefore, the abnormal underlying schizophrenia can result in dysfunctional basal DA and GABA resting states similar to those of an addicted individual. This process increases the vulnerability of patients with schizophrenia to drug addiction. Furthermore, the individual with schizophrenia may be more sensitive to the rewarding and reinforcing properties of addictive drugs because of excessive mesolimbic functioning.

One observation that supports the AVH is that generally the onset of drug abuse occurs before the onset of psychiatric symptoms, consistent with a common in schizophrenia and addictions. A study of 45,570 Swedish conscripts supports the AVH—the risk of schizophrenia among cannabis users was elevated 6-fold compared with non-users. It is possible that cannabis may induce schizophrenia per se, but a more likely explanation is that individuals with a predisposition to schizophrenia are more likely to use cannabis, as a function of the common underlying both disorders.

**Conclusions**
Identifying reasons for comorbid drug addiction in schizophrenia has been difficult. Many theories have been proposed to try to explain the root cause of drug addiction in patients with schizophrenia, but no one theory has been put forth that encompasses all aspects of drug addiction in these patients. The SMH falls short by assuming that drug addiction in schizophrenia operates on a negative reinforcement model. Nonetheless, it is clear that the prognosis for schizophrenia is much better when patients achieve drug abstinence, including in the domains of depression, quality of life, and community integration.

Clearly, more research on the interrelationships between substance use disorders and schizophrenia is needed to support or refute the SMH or the AVH—and to establish the sequence of onset of the comorbid disorders. In other words, which came first, the chicken or egg? The answer to this question may have important implications for how we assess and treat people with drug addiction and schizophrenia.

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