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EDITORIAL

Substance Use Disorders in Schizophrenia—Clinical Implications of Comorbidity

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Nearly half of the people suffering from schizophrenia also present with a lifetime history of substance use disorders (SUD), a rate that is much higher than the one seen among unaffected individuals. This phenomenon suggests that the factors influencing SUD risk in schizophrenia may be more numerous and/or complex than those modulating SUD risk in the general population. It is critically important to address this comorbidity because SUD in schizophrenic patients is associated with poorer clinical outcomes and contributes significantly to their morbidity and mortality.

Key words: schizophrenia/substance use disorders/comorbidity

Nearly half of the people suffering from schizophrenia also present with a lifetime history of substance use disorders (SUDs).[1,2] This rate is much higher than the one seen in the general US population (table 1 provides prevalence estimates for the most frequently abused substances in schizophrenia patients compared with the general population),[11,12] which suggests that in addition to factors driving SUD in the general population, other factors are increasing the risk in schizophrenia. Addressing comorbidity is clinically relevant because SUD in schizophrenic patients is associated with poorer clinical outcomes[18] and contributes significantly to their morbidity and mortality.[19]

The mechanisms underlying the high comorbidity between SUD and schizophrenia are poorly understood but are likely to include both common (across all drugs) as well as drug-specific (eg, nicotine and marijuana) factors. The involvement of brain dopaminergic pathways is likely to be a shared feature in this comorbidity that is common to all drugs of abuse. To start with, the mesolimbic dopamine (DA) pathway has been implicated not only in the rewarding mechanism for all drugs of abuse (via DA increases in nucleus accumbens or NAcc) but also in the occurrence of positive symptoms in schizophrenia (via excess striatal DA). Thus, it is not surprising that drug intoxication (from cocaine, methamphetamine, or marijuana use) can trigger acute psychotic episodes and that some drugs (amphetamines) have been used to create surrogate animal models of schizophrenia. On the other hand, the mesocortical DA pathway has been implicated in the neuroadaptations that result from repeated drug exposures (via DA deficits in prefrontal regions)[20] and as a contributor to the negative symptoms of schizophrenia (via decreased DA in prefrontal cortex). Most antipsychotic medications block DA D2 receptors (D2Rs), thus interfering with DA neurotransmission. Therefore, it is conceivable that schizophrenia patients may resort to drugs of abuse to temporarily compensate for the anhedonia induced by D2R blockade in brain regions involved with reward (NAcc and ventral pallidum) and/or counteract the cognitive deficits (eg, impaired attention, working memory) that result from prefrontal D2R blockade. However, because chronic drug use is associated with reduced DA neurotransmission, this behavior could actually backfire and exacerbate negative symptoms and cognitive deficits (eg, attention, executive function, saliency) and interfere with functional recovery.[21]

The comorbidity of SUD and schizophrenia may also be a direct consequence of the underlying neuropathology of schizophrenia, which may contribute to enhanced addiction vulnerability by disrupting the neural substrates that mediate positive reinforcement.[22] One proposal is that an imbalance of hippocampal-prefrontal regulation of DA release in NAcc may contribute to both psychosis and the vulnerability to drug abuse in schizophrenia. Non-DA pathways have been implicated too. For example, the cognitive impairments associated with prefrontal circuits also involve dysregulated glutamatergic neurotransmission, and for both disorders, medications that affect glutamatergic neurotransmission are being evaluated as potential treatments.[23]

Nicotine is by far the most prevalent drug abused by schizophrenia patients. While this may be partly due to its legal status and easy access, it may also reflect nicotine's specific effects on brain nicotinic acetylcholine receptors (nAChRs). The "self-medication hypothesis" suggests that smoking may alleviate some of the cognitive

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Table 1. Schizophrenia Patients Report Consistently Higher Rates of Substance Abuse Than the General Population, Notably With Respect to 4 Licit (Nicotine and Alcohol) and Illicit (Cannabis and Cocaine) Substances

	Schizophrenia Patients		General Adult Population	
Abused Substance	Reported Rate of Use (Range From Various Studies)	Reported *DSM-IV* Abuse or Dependence (Range From Various Studies)	Rate of Use (Past month for ages 18 or older) (NSUDH) (SAMHSA 2008)	*DSM-IV* Dependence in Past Year
Nicotine	60%–90%[3–5a]	28.5%[6b]	25.9%	12.8%[7]
Cannabis	17%–80.3%[8–10c]	50.8%[8]	5.8%–16.4%	0.5%[11,12]
Alcohol	21%–86%[8,13–15d]	43.1%–65%[8,16]	2.9%–17.9%[e]	5.1%[11,12]
Cocaine	—	23%[16]	0.7%–1.7%	0.09%[11,12f]

Note: Prevalence ranges are merely intended to illustrate the consistency of the trend in this population because they represent diverse sampling methods among studies done with different adult populations and measures of abuse. The average rates of use and abuse or dependence in the general adult population were derived from the 2007 National Survey on Drug Use and Health[17] and secondary analyses of the 2000–2002 National Epidemiologic Survey on Alcohol and Related Conditions[11,12] and are not intended to provide control baselines but as expedient markers for general comparison. *DSM-IV*, *Diagnostic and Statistical Manual of Mental Disorders* (Fourth Edition); NSUDH, National Survey on Drug Use & health; SAMHSA, Substance Abuse and Mental Health Services Administration.
[a]Current daily smokers.
[b]Based on a calculated odds ratio of 2.8 higher than in controls.
[c]Past month.
[d]Alcohol misuse, abuse, or disorder.
[e]Heavy use.
[f]Stimulants.

deficits commonly observed in schizophrenia. There may be a neural basis for this hypothesis: specifically, it has been reported that individuals with schizophrenia have fewer and less functional, low-affinity and high-affinity nicotine receptors. This might explain how smoking by schizophrenia patients could improve some of the cognitive deficits seen in this disorder.[24] Postmortem studies have also reported that the brains of schizophrenia patients have deficits in inhibitory neurons. Thus, the recent findings showing that nicotine upregulated the expression of the glutamic acid decarboxylase gene, increasing γ-aminobutyric acid synthesis in the brain, could be another pharmacological effect that contributes to comorbidity.

Cannabis is also frequently abused by schizophrenic patients, and it is associated with worse clinical outcomes. For example, a recent magnetic resonance imaging study concluded that the loss of gray matter, commonly seen in the brains of schizophrenic patients, proceeds nearly twice as fast in patients who also used cannabis over a 5-year follow-up. Because the difference could not be explained by outcome or baseline characteristics, this result adds to the evidence in favor of a detrimental effect of cannabis in schizophrenia. Just as for other drugs, it is possible that schizophrenic patients abuse marijuana not only for its hedonic properties but also for other pharmacological effects of cannabinoids. Specifically, because a basic function of the endocannabinoid system in the brain is to control emotional responses to stress,[25] it is plausible that some schizophrenic patients may abuse marijuana to help them cope with stress. Though there is evidence of alterations in cannabinoid signaling in the brain of schizophrenic patients,[26] their role in the neuropathology of schizophrenia is still poorly understood. It is also still unclear if marijuana abuse constitutes a risk factor for schizophrenia that by itself has a causative role and/or if it just serves to trigger the disease in those who are vulnerable. In this respect, the role of marijuana on schizophrenia is a good example of the importance of gene/environment interactions in psychiatric diseases.

Genetic and gene/environment factors that contribute to schizophrenia may also contribute to addiction. Both schizophrenia and addiction are highly heritable and genetically complex disorders, and, even though studies are still struggling with small effect sizes and inconsistencies, the field appears to be coalescing around a select, albeit by no means controversy-free set of candidate genes. These include convergent findings, from genetic risk data, which suggest that individual differences in the *quality* and *quantity* of brain connections, during development and/or in adulthood, contribute to individual differences in vulnerability to addictions and to related brain disorders like schizophrenia.[27] Other findings point to overlaps between the genes identified in schizophrenia and some of the genes identified in addiction. These include genes involved in neuroplasticity and brain development, such as Neuregulin 1 (*NRG1*) and members of the neurexin family (*NRXN 1* and *3*) genes that code for molecular targets of drugs such as the a7nAChRs, and genes that modulate the activity of DA and other catecholamines, such as catechol-*O*-methyltransferase,

V-akt murine thymoma viral oncogene homolog 1 (*AKT1*), and Monoamine oxidase A (*MAOA*).

Common psychosocial factors (eg, limited education, poverty, unemployment, peer influence, and the structure of the mental health treatment system) may account for a portion of the increased comorbidity. Both disorders are associated with a greater exposure to stressors, which on one hand increase drug taking and on the other exacerbate psychotic symptoms in schizophrenia patients.[28] Thus, prevention interventions that mitigate the adverse effects of social stress on individuals at risk for schizophrenia may also help curb drug use in this population.

Finally, concurrent drug abuse is recognized to significantly contribute to the morbidity and mortality in schizophrenia patients. This includes the devastating consequences from heavy smoking in this patient population, as well as deaths from overdose and poisoning from other drugs of abuse.[19] Moreover, because some drugs of abuse target mechanisms implicated in the metabolic syndrome (ie, marijuana targeting the cannabinoid receptor), one could speculate that they may also exacerbate this side effect of antipsychotic medications.

Despite its importance, research on the treatment of comorbidity has been very limited. Nonetheless, some promising findings have been reported. This includes a recent study that focuses on the known disturbances in the endocannabinoid system of schizophrenics and points to anandamide as a promising target for medications to reduce substance abuse in schizophrenia patients. Similarly, some studies suggest that some second-generation antipsychotics may be effective for comorbid SUD in schizophrenia, particularly clozapine and nicotine dependence. Of the behavioral interventions that have been evaluated, assertive community treatments, which integrate the behavioral treatment of severe mental disorders, such as schizophrenia, and co-occurring SUD, is a promising example. There is also a need for services research that focuses on the special treatment challenges in patients with comorbid schizophrenia and SUD, such as the implementation of therapeutic interventions in criminal justice settings, where persons suffering from severe mental illness and SUDs are markedly overrepresented.

In summary, addressing comorbidity of SUD in schizophrenia has important clinical implications for both the prevention and treatment of these 2 disorders and also for decreasing morbidity and mortality. Moreover, research shows that treatment of patients with comorbidity should include interventions for both disorders because lack of adequate treatment of one of the disorders interferes with recovery.[29] These reasons highlight the urgency of addressing the need for integrated treatment interventions for SUD in patients with schizophrenia and for training psychiatrists in the proper screening and treatment of SUD in patients with schizophrenia and other mental illnesses.

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