Substance abuse in patients with schizophrenia

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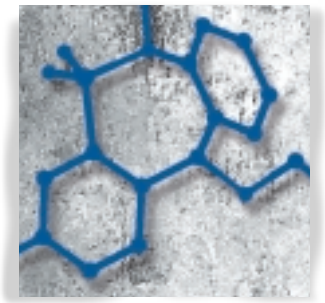

The comorbidity of schizophrenia and substance abuse has attracted increasing attention in the past years, with multiple potential links, including genetic vulnerability, neurobiological aspects, side effects of medications, and psychosocial factors being under discussion. The link between the use of substances and the development of psychoses is demonstrated by the high prevalence of substance abuse in schizophrenia. Apart from alcohol misuse, substances commonly abused in this patient group include nicotine, cocaine, and cannabis. In particular, heavy cannabis abuse has been reported to be a stressor eliciting relapse in schizophrenic patients. In general, substance use in psychosis is associated with poorer outcomes, including increased psychotic symptoms and poorer treatment compliance. Since both disorders have been observed to be closely interdependent, a particular treatment for schizophrenic patients with comorbidity of substance abuse is needed in order to provide more effective care. In this article, we discuss various potential modes of interaction and interdependence, and the possibility of embarking on new therapeutic paths for treating this particular population.

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The high frequency of co-occurring substance use disorder in schizophrenia is linked to an increased risk of illness and injury.[1] Apart from impaired cognitive functioning during intoxication, substance misuse is associated with poorer outcomes in psychosis and higher rates of presentation to inpatient and emergency services.[2] Another problem relates to the high occurrence of incarceration, predominately among persons with a diagnosis from the schizophrenia spectrum, who are actively abusing substances.[3] It is primarily these individuals, with comorbidity of schizophrenia and drug addiction and who lack stable housing, who run a high risk of being incarcerated. Thus, comorbid substance abuse disorders in schizophrenic patients have been shown to be a considerable obstacle to carrying out effective treatment. The development of effective intervention programs demands a global understanding of the risk factors for developing a comorbid substance disorder, as well as the consequences of substance abuse in schizophrenia.

Epidemiology

Epidemiological research in this field focuses on the identification of risk factors, the temporal relationship of the onsets of the disorders, and on specific symptoms. The proportion of schizophrenic patients with comorbidity of substance abuse varies in published studies from 10% to 70%, depending on how patients are diagnosed with schizophrenia, the types of populations studied, and the different ways of defining drug and alcohol disorders.[4] However, an increasing number of publications demon-

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strate a high prevalence of substance abuse in schizophrenia.[2,5-7] Up to 50% of patients with schizophrenia exhibit either alcohol or illicit drug dependence, and more than 70% are nicotine-dependent.[8] In particular, heavy cannabis abuse has been reported to be a stressor, eliciting relapse in patients with schizophrenia and related disorders.[9]

Consistent findings concerning demographic characteristics and gender aspects suggest that male persons of younger age and lower educational level are associated with a greater risk for substance abuse.[4] However, it seems important to mention that substance abuse difficulties among women with schizophrenia are often insufficiently identified, and that women with comorbidity of substance abuse are less likely to obtain substance abuse treatment.[10]

The Epidemiologic Catchment Area (ECA) Study[5] investigated a sample of 20 291 subjects from community and institutional settings with regard to prevalence and comorbidity, using a standardized diagnostic interview schedule according to the third edition of the *Diagnostic and Statistical Manual of Mental Disorders (DSM-III)*.[11] In the results of this study, 47% of the subjects with a lifetime diagnosis of schizophrenia met the criteria for some form of substance abuse. In comparison with the general population, the odds of having a substance abuse diagnosis were found to be 4.6 times higher for subjects with schizophrenia.

Increased occurrence of substance use in schizophrenia: what are the links?

Comorbidity of schizophrenia and substance abuse has provoked controversy for decades. Multiple potential links, including genetic vulnerability, side effects of medications, and psychosocial factors, have been discussed. However, explanations of the increased incidence of substance use in schizophrenia have been dominated by the self-medication hypothesis.[2] Thus, self-medication is primarily used in order to deal with negative symptoms, such as social withdrawal and apathy, dysphoria, and sleeping problems, as well as drug use, in an attempt to decrease discomfort from the side effects of antipsychotic medication. Levin et al[12] found that nicotine could reverse haloperidol-induced deficits in memory and complex reaction time in patients with schizophrenia. However, the effective treatment dose of antypsychotic medications is increased in smokers, in part because of a smoking-induced increase in neuroleptic metabolism.[13] Nicotine cessation is very highly supported in health prevention programs worldwide. However, according to careful interpretation of the results reported by Adler et al,[14] nicotine improves cognitive performance in schizophrenic patients. The role of substance abuse in regard to schizophrenia has also been discussed in terms of psychopathology.[15] Overall, positive symptoms were found to be more prominent among substance-abusing schizophrenic subjects. In particular, auditory hallucinations and paranoid delusions occur more often among alcohol abusers.

Vulnerability

Various genetic and environmental vulnerability factors, including family and social influences, specific personality traits, early life trauma, and poor frontal lobe functioning, contribute to the development of psychiatric distress and drug abuse.[8] Overall, chronic stress plays an important role in both the severity of psychiatric symptoms associated with schizophrenia and in substance use. Epidemiological studies indicate that the first psychotic episode, as well as experimentation with addictive drugs and onset of addictive disorders, occurs in adolescence or early adulthood. During that period environmental stressors, interacting with changes in the brain and its functioning, are described as being risk factors for the onset of psychiatric disorders.[16] Chambers et al[17] emphasize adolescence as a critical period for the neurodevelopment of brain regions associated with impulsivity, motivation, and addiction.

Neurobiological aspects

In general, common neurobiological pathways and abnormalities seem to be involved in addiction and various psychiatric disorders.[8] It is hypothesized that, on one hand, addiction and other psychiatric disorders are different symptomatic expressions of similar preexisting neurobiological abnormalities, and that on the other hand, repeated drug administration leads to biological changes that have elements in common with the abnormalities mediating certain psychiatric disorders.[18] Schizophrenia has been suggested to affect the neural circuitry mediating drug reward, leading to an increased vulnerability to addiction. Chambers et al[19] hypothesized that abnormalities in the hippocampal formation and

frontal cortex associated with schizophrenia affect the reinforcing effects of drug reward and reduce inhibitory control over drug-seeking behavior. Several neurotransmitters, such as the glutamatergic and the dopaminergic systems, are involved in the onset and course of psychosis and addiction. Dysregulated neural integration of dopamine and glutamate in the nucleus accumbens could lead to neural and motivational changes similar to those seen in long-term substance abuse.

Using functional magnetic resonance imaging (fMRI), Juckel et al[20] found decreased activation of the left ventral striatum, one of the central areas of the brain reward system, to be correlated with the severity of negative symptoms in medication-free schizophrenic patients. In addition, dysfunction in the ventral striatum was detected in patients with alcohol craving.[21] These findings point to a specific neuronal correlation in the brain reward system, which may be prominent in schizophrenic patients with substance-abuse behavior.

Mathalon et al[22] compared magnetic resonance images in groups of subjects with schizophrenia, schizophrenic patients with comorbidity of alcohol dependence, and alcohol-dependent patients with those from a matched control group. Although found in all three patient groups, gray matter deficits were greatest in the group with comorbidity, with most prominent deficits in the prefrontal and anterior superior temporal regions. Thus, as a result of an interactive effect, comorbidity might compound the prefrontal cortical deficits independently present in schizophrenia, as well as in alcohol dependence.

Nicotine and schizophrenia

Nicotine interacts with several central pathways involved in schizophrenia, such as the dopaminergic and the glutamatergic pathways in the mesolimbic areas. More than 70% of patients with chronic schizophrenia are nicotine-dependent.[7] Goff et al[13] compared cigarette-smoking versus nonsmoking schizophrenic patients with regard to gender and age factors, as well as neuroleptic dose. As a result, smokers were significantly more likely to be men, and to have had an earlier age of onset and a greater number of previous hospitalizations. Furthermore, smokers received significantly higher doses of neuroleptics than nonsmokers. In a recent study, Weiser et al[23] investigated a sample of more than 14 000 adolescents followed over a period of 4 to 16 years, and found that adolescents who smoked more than 10 cigarettes per day at initial evaluation were significantly more likely to be hospitalized for schizophrenia during the follow-up period. Thus, either smoking might be used as self-medication of symptoms, or abnormalities in nicotinic transmission might be involved in the pathophysiology of schizophrenia. Careful interpretation is recommended, as further investigation in this area will be necessary in order to determine the role of nicotine dependence in schizophrenic patients.

Cannabis and schizophrenia

During recent years, controversial discussions have resumed regarding whether cannabis consumption might increase the risk of developing schizophrenic symptoms. Andreasson et al[24] referred to the first evidence that cannabis may be a causal risk factor for later schizophrenia. Several recent studies have investigated the risk factor of cannabis use for future psychotic symptoms, and research in this field has provided a growing body of evidence that the use of cannabis may be associated with increased risks of psychosis and psychotic symptoms.[25,26] According to Arsenault et al,[27] cannabis use in adolescence appears to confer a twofold risk for schizophrenia or schizophreniform disorder in adulthood, whereas an earlier age of onset of cannabis use is associated with a greater risk for psychotic outcomes. In particular, heavy cannabis use may accelerate or exacerbate psychotic symptoms in vulnerable individuals.

In recent years, advances in the understanding of brain cannabinoid receptor function and the association between cannabinoid compounds and psychosis have been made. Data from a double-blind, randomized, and counterbalanced study indicate that intravenously administered delta-9-tetrahydrocannabinol (delta 9-THC) produces a wide range of transient symptoms, behaviors, and cognitive impairments in healthy individuals, resembling several aspects of endogenous psychoses.[28]

A longitudinal study from New Zealand[25] was based on a birth cohort of 1073 people born in 1972 and 1973. At the age of 11 psychotic symptoms were assessed from self reports. Following the same procedure at 15 to 18 years, the subjects were examined with regard to their cannabis use. At the age of 26, psychiatric symptoms were evaluated using a standardized interview schedule to obtain diagnostic criteria according to the *Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-*

IV).[29] The results from a total of 759 study members indicate that cannabis users by age 15 and 18 exhibited more schizophrenic symptoms at age 26 than controls. Another New Zealand longitudinal study[26] investigated a cohort of 1265 people born in mid-1977. At ages 18, 21, and 25 years, sample members were administered a comprehensive mental health interview designed to assess a number of aspects of mental health and psychosocial adjustment. In addition, at each assessment subjects were questioned about their cannabis use. The findings of this study, based on a sample of 1055 participants, suggest that daily users of cannabis had rates of psychotic symptoms that were between 1.6 and 1.8 times higher than in nonusers of cannabis.

However, critical comments do not support these results, but emphasize that the findings of Fergusson et al,[26] based on just 10 items from the Symptom Checklist-90, would raise more questions than they would be able to answer.[30] It remains to be considered whether an item that is an indicator for psychosis on one hand could also be a normal reaction in people using marijuana. Marijuana smokers may have beliefs that are different from the mainstream, and thus could be suspicious of others. An important limitation, however, includes the fact that prospective studies are based on self-reported measurements of cannabis use.

Overall, cannabis does not seem to represent a sufficient cause for the development of schizophrenia. However, even though the majority of young people who use cannabis in adolescence do so without experiencing a harmful outcome, there are consistent findings that cannabis use does indeed increase the risk for schizophrenia and other psychotic disorders in vulnerable people.[27,31]

Cocaine and schizophrenia

It is emphasized that schizophrenic patients who abuse cocaine have an increased risk of suicide, are less compliant with treatment, and have a higher hospitalization rate than patients without cocaine abuse.[32] Concerning the increased risk of cocaine abuse in schizophrenia, underlying dopamine-dependent mechanisms have been hypothesized in both disorders. Cocaine yields to a blockade of presynaptic dopamine reuptake, producing a large increase in synaptic dopamine. This effect is blocked through dopamine receptor antagonists, and should discourage abuse. However, this may be counterbalanced through other factors, including negative symptoms and depressed mood. Based on the self-medication hypothesis, schizophrenic patients may use cocaine to counteract extrapyramidal side effects occurring as a result of antipsychotic drug treatment. Furthermore, cocaine may be used in order to overcome a defect in dopamine-mediated reward circuits.[33]

It has been suggested that atypical antipsychotics may have enhanced efficacy in the treatment of schizophrenic patients with comorbid cocaine abuse compared with the traditional antipsychotic agents, such as haloperidol.[34] A double-blind, prospective, randomized, parallel-group study comparing olanzapine with haloperidol in patients with comorbid diagnosis of schizophrenia and cocaine addiction did not find significant differences in regard to cocaine negative urinalyses or retention, although haloperidol resulted in significantly reduced cocaine craving compared with olanzapine.[32] Finally, a poor overall response rate of schizophrenic symptoms in both groups was determined, with no significant differences concerning positive, negative, or depressive symptoms. An important limitation, however, involves the small sample size of 24 patients. A recent pilot study, however, provided some evidence that treatment with aripiprazole, a partial dopamine agonist with high affinity for both dopamine D_2 and D_3 receptors, might possibly lower both the desire for and the use of cocaine in these patients.[35] As a result, significant decreases in craving for cocaine, strikingly fewer positive urine screens, and significant decreases in psychotic symptoms suggest that aripiprazole may be of benefit. Anyway, these findings need a cautious interpretation with respect to the small sample size of 10 subjects, and should be reassessed anyway using a double-blind, randomized comparison study design.

Intervention and aim of treatment

Since schizophrenia and substance misuse have been determined to be closely interdependent, a dual diagnosis—treatment of schizophrenia and drug abuse is needed. Currently, research is focusing on a range of psychological strategies such as family intervention, skills training, cognitive therapy, or development of substance refusal.[36,37] Most of these psychological interventions are based on cognitive behavioral procedures. To date, there is a growing body of evidence that motivational enhancement interventions, which tend to alter drug use and refine skills, may be a feasible first-line intervention for

substance abuse in early psychosis.[38] Kavanagh et al[2] recommend a division into at least three groups: schizophrenic patients with mild substance-related problems, who benefit from brief, motivational interventions; those patients who profit from social support and more extensive skills training; and finally those patients with severe cognitive deficits who need ongoing environmental structure and social support for an indefinite period.

However, the main focus of treatment for these patients consists in stabilization of psychotic symptoms, hostility, and agitation. Several new antipsychotic medications, such as risperidone, clozapine, or olanzapine, have been introduced, and appear to be at least as effective as the typical antipychotics. Furthermore, strong evidence have been provided that these "atypical" neuroleptics produce fewer extrapyramidal side effects (EPS) and a lower risk of tardive dyskinesia.[39] As already discussed, patients who develop EPS or neuroleptic dysphoria may use substances in order to alleviate these side effects. Therefore some atypical antipsychotics may be of benefit.[40] Currently, most of the data on comorbidity are based on clozapine, which has been found to be approximately equally effective in treatment-resistant patients with and without substance abuse. Patients treated with newer agents also tend to perform better on neurocognitive measures than patients who receive traditional antipsychotic medications.[41,42] Thus, improvements in neurocognitive performance may help these patients to plan more effective strategies to prevent substance misuse. However, it should be noted that newer antipsychotics also produce some adverse effects.

Although data from atypical interventions in this field are limited to those from small, mostly uncontrolled studies, atypical antipsychotics are associated with a decrease in substance abuse in schizophrenic patients.[8] These findings, however, may be explained by the feasibility of new antipsychotics having a normalizing effect on the signal detection capabilities of the mesocorticolimbic reward circuitry. Finally, neuroleptic medication may contribute to dysphoria and anhedonia, which might be a consequence of impaired dopamine function in the nucleus accumbens and play an important role in regard to comorbidity with substance abuse disorders.[16] As a consequence, it is important to optimize neuroleptic medication with regard to the subjective experience of the patient. Preliminary results[43] suggest a window of D_2 receptor occupancy between 60% and 70% to be optimal for the subjective experience of patients, which is clinically relevant concerning medication compliance and quality of life. However, careful interpretation is recommended, as further research is needed in order to investigate the effects of antipsychotics on subjective well-being, as well as on craving for drugs.

Overall integrated treatment models that address both disorders have been found to increase retention and participation in treatment, reducing symptoms and substance use.[4] Therefore, it will be necessary to provide care assessment methodologies in both systems, addiction clinics, and mental health clinics, which simultaneously address both schizophrenia and substance abuse disorders.

Conclusion and future directions

It has been determined that schizophrenic patients with co-occurring substance misuse disorders are vulnerable to an increased risk of illness and injury, poorer outcomes in psychosis, and higher rates of presentation to inpatient and emergency services. Another tremendous problem involves the high occurrence of incarceration among persons with a diagnosis of schizophrenia, who abuse substances and lack stable housing. Even though the vulnerability of persons with schizophrenia to substance abuse has been emphasized, the degree of risk and adverse consequences diversify across various studies.

Gender-specific approaches stress that young male patients are associated with a greater risk for substance abuse. However, substance use difficulties among women with schizophrenia are often insufficiently identified. Thus, it represents a great challenge that women with comorbidity of substance abuse in many cases do not obtain adequate substance-abuse treatment, and gender-specific approaches should be incorporated into treatment strategies.

Overall, substantial contributions to the understanding of the relationship between substance abuse and schizophrenia have been made, but there is still a lack of consequences in terms of appropriate intervention programs. Thus, it appears that the issue of comorbidity is twofold, since schizophrenic patients using drugs show specific problems that demand special intervention as well as compliance with treatment; on the other hand, community facilities are often inexperienced in treating double diagnoses. Moreover, clinics for addiction disorders might underdiagnose psychotic disorders, just as mental health clinics may overlook co-occurring substance abuse disorders. Care assessment methodologies in both systems

address only one type of disorder. The consequences of the inability to provide adequate treatment for these patients leads to poor outcomes and hence higher costs. However, the problem of comorbidity has obtained increasing attention in the past years, and integrated treatment models that address both disorders have been found to be most promising. Further research will be required in order to establish optimal psychological and antipsychotic therapy for schizophrenic patients with comorbid substance abuse. Finally, we urgently need changes in our public policies in order to develop treatment systems that meet the requirements to implement these results, and subsequently provide adequate treatment for this particular patient group. ❑

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El abuso de sustancias en pacientes con esquizofrenia

La comorbilidad de la esquizofrenia con el abuso de sustancias ha captado gran atención en los últimos años, con múltiples potenciales conexiones, que incluyen vulnerabilidad genética, aspectos neurobiológicos, efectos secundarios de los medicamentos y factores psicosociales, temas que están en discusión. La vinculación entre el uso de sustancias y el desarrollo de psicosis está demostrada por la alta prevalencia del abuso de sustancias en la esquizofrenia. Además del alcohol, en este grupo de pacientes las sustancias de las cuales comúnmente se abusa incluyen nicotina, cocaína y cannabis. En particular, se ha informado que el abuso grave de cannabis constituye un estresor que produce la recaída en pacientes esquizofrénicos. En general, el uso de sustancias en la psicosis se asocia con peores evoluciones, incluyendo aumento de los síntomas psicóticos y peor adherencia a los tratamientos. Dado que se ha observado que ambos trastornos son altamente interdependientes, se requiere de un tratamiento específico para pacientes esquizofrénicos con abuso de sustancias comórbido con el objetivo de proporcionar un cuidado más eficaz. En este artículo se discuten varios modos potenciales de interacción e interdependencia, y la posibilidad de aventurarse en nuevas alternativas terapéuticas para tratar esta población especial.

Consommation de drogues chez les patients schizophrènes

Ces dernières années, la comorbidité de la schizophrénie et de la consommation de drogues a focalisé l'intérêt en raison de leurs liens potentiels nombreux, dont la vulnérabilité génétique, les aspects neurobiologiques, les effets indésirables des traitements et les facteurs psychosociaux encore discutés. Le lien entre l'utilisation de drogues et le développement des psychoses est démontré par la forte prévalence de la consommation de drogues chez les schizophrènes. L'alcool mis à part, les drogues couramment consommées chez ce groupe de patients comprennent la nicotine, la cocaïne et le cannabis. La forte consommation de cannabis en particulier est connue pour être un facteur stressant de rechute chez les patients schizophrènes. En général, la consommation de drogues chez les psychotiques est associée à de mauvais résultats, voire à l'aggravation des symptômes et à une faible observance du traitement. Les deux troubles étant étroitement interdépendants, un traitement particulier pour les patients schizophrènes consommateurs de drogues est nécessaire pour les soigner plus efficacement. Dans cet article, nous discutons les éventuels différents modes d'interaction et d'interdépendance et la possibilité de nouvelles voies thérapeutiques pour traiter cette population particulière.

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