



The problem of substance abuse in people with schizophrenia

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Each year we compile reviews focusing on the most timely topics that are being addressed about schizophrenia over the previous year and into the future. This year we have included several topics related to diagnosis, treatment and outcome, but one that has remained an issue over the years and is not reviewed this year is that of illegal substance abuse co-occurring with schizophrenia, as well as prior to its onset. Many substances have been linked to schizophrenia for decades, such as amphetamines, hallucinogens and phencyclidine. This year, it is timely to discuss specifically the relationship of cannabis (marijuana) with schizophrenia now that it has become legalized in some states in the USA as well as other parts of the world. This is pertinent both with respect to individuals who are at high risk for developing schizophrenia as well as for those who already have been diagnosed with the disorder. The problems in assessing its risks are many, as the use of marijuana is often accompanied by use of several other drugs (alcohol, hallucinogens, opiates, etc.); the composition of cannabinoids in the marijuana sold on the street varies considerably; there are over 400 known compounds in the cannabis plant, Δ 9-tetrahydrocannabinol being considered the major active component, but at least 84 other cannabinoids, including cannabidiol, cannabinol, and others, exist [1]. Δ 9-Tetrahydrocannabinol is thought to account for most of marijuana's psychotropic and medical effects, such as sometimes benefiting chronic pain, anxiety and insomnia, whereas sometimes having adverse effects, such as increased heart rate, arrhythmias, fluctuations in blood pressure, myocardial infarcts, decreased pulmonary function, and even increased cancer risk as well as obviously abuse and addiction [2,3]. There is extensive literature showing that patients with schizophrenia who were heavy marijuana users prior to developing schizophrenia have an earlier age of illness onset [4] and an association of the age at onset of cannabis use with the age at onset of psychosis [5,6]. When users continue to abuse marijuana after onset of a psychotic illness, they have a worsened outcome (e.g., more relapses, more symptoms) [7–9]. In addition, epidemiological studies have suggested that marijuana by itself when used in adolescence can increase one's risk of later

developing schizophrenia in a dose-dependent fashion [10] (reviewed in [11]), thus suggesting that in some individuals, it is actually causative. It remains controversial as to whether this increased risk is associated with a genetic risk of schizophrenia or a gene–environment interaction [12]. More data are needed to clarify this putative causative factor for schizophrenia.

The hypothesis is that marijuana may specifically have an effect on adolescent brain development and thus create an abnormal trajectory of higher cortical structural differentiation, particularly in the frontal and limbic cortices that could lead to an increased risk of schizophrenia. Although the majority of earlier brain imaging studies have not supported this (reviewed in [13]), very recent studies suggest that marijuana may have subtle effects on hippocampus, amygdala, both anterior and posterior cingulate volume, nucleus accumbens and frontal–temporal white matter connectivity (reviewed by [14], and the data keep accumulating [15–18]). On the other hand, Malchow *et al.* [19] in a review of studies of high risk of schizophrenia and first-episode individuals found weak evidence that cannabis had an effect on producing the brain abnormalities characteristic of schizophrenia. In patients continuing to use marijuana after a schizophrenia diagnosis, it could produce further changes, but it remains unclear which of those had been present prior to the onset of the psychotic illness. More longitudinal studies need to be performed, controlling for genetic risk, to assess the direct effects of marijuana on the brains of people who eventually develop schizophrenia.

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On the contrary, there is some tentative indication that marijuana may be beneficial to people with schizophrenia and that specific cannabinoids, such as cannabidiol, may be novel therapeutic agents for some symptoms of schizophrenia [20,21], although to date, there is little overall evidence for a true antipsychotic effect of cannabinoids [22]. In an age when exciting new research findings have not yet translated into novel approaches to treatment, this provides a potentially promising path for further exploration.

Nevertheless, there is much that remains unknown. Future studies need to clearly examine the content of marijuana patients use and also how each component interacts with genetic risk factors to produce a psychotic illness. With the widespread legalization of marijuana, this should serve as a natural experiment, which will allow for evaluating large-scale population-derived findings of cannabinoid use in both the general and the at-risk populations. Given that it is now being sold within candies and chocolates, it is also likely that use in prepubertal children will be increasingly common. This is a matter of considerable concern that will also need to be scrupulously studied. What effect this early intake of marijuana will have on active brain growth and differentiation remains to be seen.

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