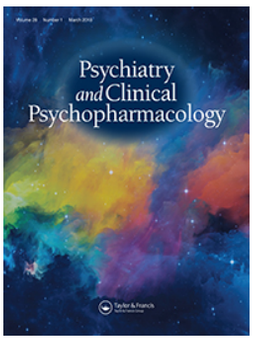

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EDITORIAL

Cannabis-associated psychotic symptoms and neurocognitive effects at high risk psychosis patients

Since ancient times, various forms of the plant cannabis sativa have been used and more recently for therapeutic purposes including (but not limited to) antiemetic, anticonvulsant, anti-inflammatory, analgesic, antispasmodic, antitussive, appetite stimulant, and aphrodisiac effects. For decades, the relationship of cannabis and psychiatric disorders has been particularly linked to psychotic disorders. In recent years, the potency of the street cannabis has increased to mean tetrahydrocannabinol (THC) levels to 16% and 20%. Novel ways of extracting THC from the plant have produced a range of new products from edibles to resin oil with up to 75% THC content. Since 2008, the recreational use of synthetic cannabinoids, sometimes termed Spice or K2, has increased dramatically. While THC is a partial agonist with weak affinity for the CB1 receptor, synthetic cannabinoids are full agonists and generally have higher affinity for the receptor. Not surprisingly, they pose a greater mental health risk compared to plant cannabis in traditional forms. A case-controlled study showed that people using high-potency cannabis on a daily basis were five times more likely than non-users to suffer from a psychotic disorder [1].

The current literature concerning whether use of cannabis increases the risk of schizophrenia-like psychoses is all-encompassing. Regarding the acute and long-term effects of cannabis, Murray et al. [2] provided a comprehensive point of view on the status of the endogenous cannabinoid system in psychotic disorders to highlight factors important for psychosis vulnerability. Other researchers found that cannabis use was associated with a significantly increased risk of the subsequent development of psychotic symptoms or psychotic disorder [3,4]. In a meta-analysis, Marconi et al. [5] attempted to quantify the magnitude of this effect. A dose–response relationship with the risk was reported increasing with the more cannabis consumed; meaning the odds ratio for risk of psychosis-related outcomes reached almost four times in the heaviest users compared to the non-users. Large et al. [6] reported that psychotic patients who use cannabis had an earlier psychotic illness onset than those who do not. Those individuals were also reported to have higher premorbid IQ, better premorbid social function, and less likely to show neurological soft signs than non-using patients. A possible explanation ofthis finding might be that many non-drug-using psychotic patients already show neurodevelopmental impairment with poor premorbid cognitive and social function. On the other hand, the cannabis users are often are reported to be adequately socially adept to be able to conceal their drug habit. However, among psychotic patients, continued use of cannabis would harbour a bad outcome. Despite these divergent findings, a meta-analysis demonstrated that those who continue cannabis use have higher relapse rates, longer hospital admissions, and more severe positive symptoms than non-users [7].

Several imaging studies have reported that regular cannabis use is associated with lower grey matter volumes in regions that have also been implicated in psychotic disorders, such as the hippocampus, amygdala, putamen, and prefrontal cortex [8–10]. It was also shown that reduction in hippocampal volume was correlated with cumulative exposure and with subclinical psychotic symptoms. Rigucci et al. [11] examined corpus callosal microstructure in patients with their first onset of psychotic disorders and users of high potency cannabis had higher total mean diffusivity and axial diffusivity in the corpus callosum than both low potency users and non-users. Bhattacharyya et al. [12] assessed the effects of THC on 15 healthy males during a verbal paired associative memory task. THC altered medial temporal activation during encoding such that the normal linear task response and the correlation with recall scores were lost. THC also attenuated striatal activation during recall, and this was correlated with the level of positive psychotic symptoms the cannabis induced.

The epidemiological evidence clearly demonstrates that heavy cannabis use, particularly of high potency types, or of synthetic cannabinoids, increases the risk of psychotic disorders, especially in those who start their use in their early teen years [13]. Genetic predisposition to schizophrenia does not explain the proportion of cannabis use in the general population or in patients; this undermines the argument that those individuals who develop psychotic dosorders following cannabis use were destined to develop schizophrenia anyway and their cannabis use was simply an epiphenomenon of this predisposition. Preliminary evidence from candidate gene studies also suggested that certain individuals were especially vulnerable to cannabis-induced psychosis due to the fact that they

possess risk alleles in DRD2 and AKT1 genes. These genes are involved in postsynapic dopamine signalling. Therefore, these findings are compatible with the notion that chronic cannabis use induces postsynaptic supersensitivity in the striatum; this supersensitivity might explain the occurrence of psychosis symptoms in cannabis users with low striatal dopamine [14]. Cannabinoid receptors are some of the most densely expressed G protein-coupled receptors the brain. Functional imaging studies have produced interesting findings. THC can reduce ability to regulate inhibitory control over impulses, thoughts, emotions, and behaviours as exemplified by its ability to attenuatuate inferior frontal activation during response inhibition tasks. THC's well-known effects on learning are reflected in altered medial temporal activation during encoding. THC also attenuates striatal activation during recall though to a smaller extent than, for example, amphetamine and this has been correlated with the level of positive psychotic symptoms it induced. THC also appears to modulate the neural substrate of salience processing, providing another mechanism by which cannabis could induce or exacerbate psychotic symptoms [15]. Chronic cannabis users show decreased striatal dopamine synthesis, which contrasts with the usual findings in acutely psychotic patients.

In laboratory studies, administration of cannabis or its primary psychoactive component (THC) may acutely produce psychotic-like and neurocognitive effects, with its most robust effects in participants with psychotic disorders [16]. More recently, Vadhan et al. examined the acute psychological and physiological effects of smoked marijuana (5.5% THC) in cannabis users at clinical high-risk (they had previously experienced certain changes in thoughts, behaviour, or perception, and may have had a family history of psychosis or recent declines in social function) ($n = 6$) to develop a psychotic disorder and those not at risk ($n = 6$) under controlled laboratory conditions. All participants at least weekly users of marijuana who were physically healthy, had minimal use of other illicit substances. In this double-blind controlled study, each participant made subjective measures of their mood and perceptions prior to smoking and also completed neurocognitive and cardiovascular tests. All 12 participants smoked both active and placebo cannabis (on different days). Following the active cannabis, participants in both groups experienced increased heart rates and reported feeling high, relative to the placebo cannabis. In the high-risk group, active cannabis (relative to placebo) increased subjective ratings of paranoid ideation, anxiety, slowed time perception, visual illusions, feelings of strangeness and inattention, and poor performance on tasks related to working memory and response inhibition. This small study demonstrated the feasibility of studying effects of cannabis in people at clinical high-risk for psychotic disorders in a controlled environment, and suggests that cannabis might affect individuals at high risk for psychotic disorders differently than cannabis users without such risk. The results of this preliminary study are the first demonstration of cannabis producing some psychotic symptoms and neurocognitive effects under controlled conditions selectively in the high-risk individuals. The clinical relevance of the psychotic-like effects is demonstrated by a larger study [17] that found that those CHR patients who endorsed experiencing cannabis-induced psychotic symptoms were almost five times more likely to develop a subsequent psychotic disorder than those who did not. The neurocognitive functions affected by cannabis in this study were relatively higher order functions that are considered uniquely relevant to psychosis development.

In sum, these results indicate the feasibility of cannabis administration research in the CHR population and the possibility that the psychotic-like effects of cannabis might be related to an individual's preexisting level of risk for psychotic disorders. Such insights are an essential foundation for the rational development of pharmacologic interventions. It is uncertain that how psychotic-like effects of cannabis would affect the legalization attempts of cannabis in the US. Growing understanding of the impact of exogenous cannabioids on the endocannabinoid system would provide plausible molecular explanations for the association between cannabis and psychotic disorders/ associated neurocognitive impairments. While the precise mechanisms by which cannabinoids induce psychosis in humans remains elusive, understanding these mechanisms is important not just for cannabis-associated psychosis but also our understanding of psychosis in general. Replication research on focusing on preclinical mechanisms and human neuroimaging in cannabis users which would highlight the fundamental role of dopaminergic pathways in the brain, modulated via cannabinoid receptor signalling in regulating psychotic disorders and associated neurocognitive impairments, is warranted.

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