RESEARCH UPDATE

Novel Insights on Cannabis and Psychosis

» Brian Miller, MD, PhD, MPH

Substance use comorbidity in schizophrenia has been described as "the rule rather than the exception."[1] The large Epidemiological Catchment Area study estimated that 47% of patients with schizophrenia also had a lifetime comorbid diagnosis of a substance use disorder.[2] Substance use comorbidity is also often deleterious to the course of schizophrenia, including potential contributions to medication non-adherence and illness relapse.[1] Cannabis (marijuana) is one of the most commonly used substances by patients with schizophrenia.

There is recent, renewed interest in the endocannabinoid system, which represents a novel potential treatment target in schizophrenia.[3] Modulation of this system by the main psychoactive component in marijuana, Δ^9-tetrahydro-cannabinol (THC), can induce acute psychosis and cognitive impairment. However, the non-psychotropic plant-derived agent cannabidiol (CBD) may decrease psychotic symptoms and improve cognitive function in schizophrenia.[4-6]

Presently, CBD oil is sold at numerous shops throughout the US, with purported benefits that include alleviation of symptoms such as depression, anxiety, insomnia, and pain. However, the purity and safety of CBD is not regulated by the US Food and Drug Administration. CBD may be "contaminated" with some amount of THC and/or other unknown ingredients. In the past decade, there have been a number of systematic reviews regarding associations between cannabis use and psychosis. Therefore, a review of systematic evidence for associations between cannabis use, risk of psychosis, and the clinical course of schizophrenia is of particular relevance to the practicing clinician.

Adverse effects of cannabis on psychosis and cognition

There is evidence from a quantitative review of 15 studies in healthy participants that a single administration of THC (intravenous, oral, or nasal) versus placebo induced positive, negative, and other psychopathology with large effect sizes (ESs).[7] Furthermore, evidence from 69 studies, comprising 2152 adolescents and young adults who used cannabis and 6575 controls with minimal cannabis exposure, showed that frequent or heavy use was associated with significantly reduced cognitive functioning with a small-to-medium ES = -0.25, although these effects were diminished with abstinence for more than 72 hours.[8]

Cannabis use and risk of psychosis

Moore and colleagues[9] performed a systematic review of 35 studies of cannabis use and risk of psychotic mental health outcomes. They found that individuals who had used cannabis had a significant, 1.4-fold increased risk of any psychotic outcomes, independent of potential confounding and transient intoxication effects. Findings also provided evidence for a dose-response effect, with even greater, 2.1-fold risk in individuals who used cannabis most frequently.

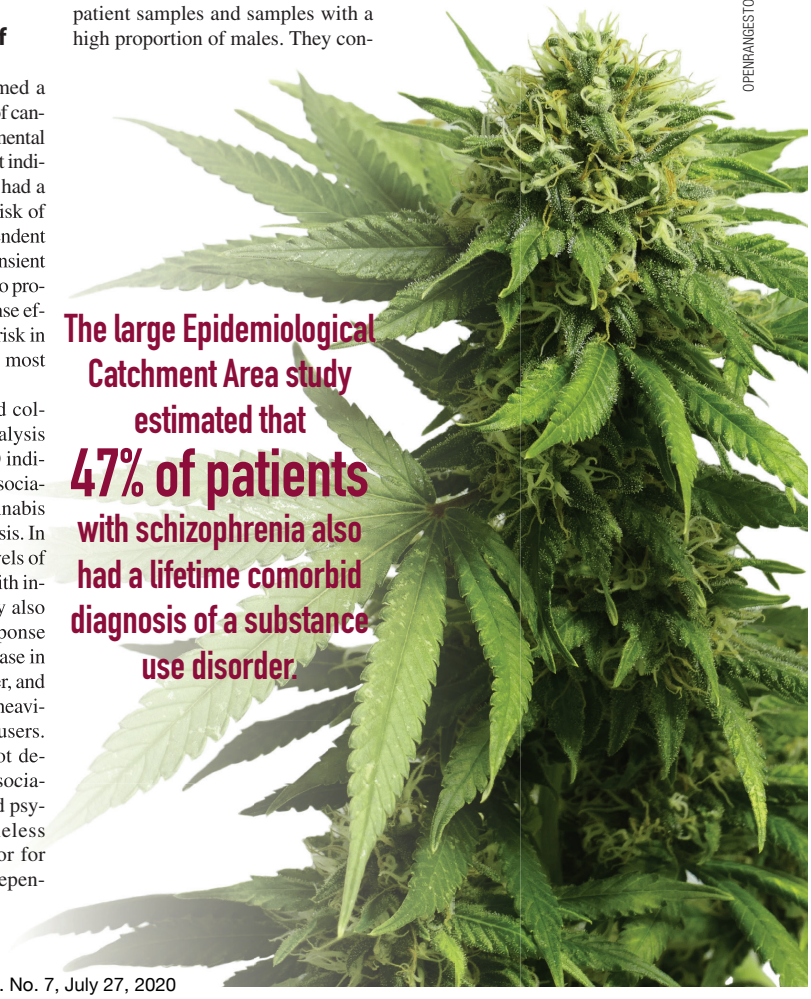
More recently, Marconi and colleagues[10] performed a meta-analysis of 10 studies, including 66,810 individuals, that investigated the association between the degree of cannabis consumption and risk of psychosis. In all individual studies, higher levels of cannabis use were associated with increased risk of psychosis. They also found evidence for a dose-response relationship, with a 2-fold increase in risk for the average cannabis user, and a 4-fold increase in risk for the heaviest users, compared with non-users. Although these findings do not definitively establish a causal association between marijuana use and psychotic disorders, it nevertheless remains a replicated risk factor for psychosis with a clear dose-dependent relationship.

Cannabis use in patients with psychotic disorders

Koskinen and colleagues[11] performed a quantitative review of the rates of cannabis use disorders (CUDs) in clinical samples of patients with schizophrenia. They identified 35 studies for inclusion in the meta-analysis. The median current rate of CUD was 16.0% (Interquartile Range [IQR] 8.6-28.6%), and the median lifetime rate of CUD was 27.1% (IQR=12.2-38.5). The rate of current/lifetime CUDs was markedly higher in first-episode (28.6%/44.4%) versus chronic schizophrenia (22.0%/12.2%), as well as in younger patient samples and samples with a high proportion of males. They concluded that approximately 1 in 4 patients with schizophrenia has a diagnosis of a comorbid CUD.

Hunt and colleagues[12] more recently performed a systematic review of the prevalence of comorbid substance use in patients with schizophrenia spectrum disorders. They identified 69 studies, and the pooled estimate for current or lifetime CUD was 26.2%. Consistent with the review by Koskinen and colleagues,[11] the prevalence was significantly higher in individuals with first-episode psychosis (35.6%) versus chronic schizophrenia (20.8%), but did not differ by study setting or patient clinical status.

The substantial prevalence of cannabis use also appears to extend to the psychosis prodrome. There is evidence from 30 studies, including 4205 individuals at ultra high risk



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(UHR) for psychosis, that there are high rates of current (26.7%) and lifetime (52.8%) cannabis use, and CUDs (12.8%).[13] Compared with non-users, UHR cannabis users also had higher rates of suspiciousness and unusual thought content.

Furthermore, research suggests that people with substance-induced psychoses will later transition to a diagnosis of schizophrenia. Murrie and colleagues[14] synthesized the results of longitudinal observations studies of transition from substance-induced psychosis to schizophrenia. Six studies with estimates of transition to schizophrenia among 3040 people with cannabis-induced psychosis were included. The risk of transition to schizophrenia in these individuals was 34% (95% CI 25-46%), which was the highest risk among all substances. They concluded that substance-induced psychoses are common reasons for seeking care, and these serious conditions are associated with substantial risk of transition to schizophrenia. Treatment of cannabis-induced psychoses should be considered in the same framework as that for other brief psychotic disorders (ie, engagement, assessment, and care); this also may help decrease rates of transition to schizophrenia.

Impact of cannabis on psychotic disorders

Large and colleagues[15] conducted a systematic review of the association between cannabis use and the age of onset of psychosis. They included 41 samples, finding that the age of onset of psychosis for those who used cannabis was 2.7 years younger than for non-users, corresponding to a small-to-medium effect size of 0.41. These findings are broadly consistent with a potential causal role for cannabis in the development of psychosis in some patients.

Bogaty and colleagues[16] performed a meta-analysis of 14 studies of neurocognition in lifetime cannabis users and never-users in young patients with psychotic disorders (aged 15 to 45 years). They found that lifetime cannabis users performed significantly worse than never-users on several cognitive domains, including premorbid and current IQ, verbal learning and working memory, and motor inhibition. Effect sizes were small to medium for most domains (0.17-0.40), except for verbal working memory, which showed a large effect size (0.76). Interestingly, patients who use cannabis performed better on tests of conceptual set-shifting. Increasing age exacerbated the between-group differences.

Schoeler and colleagues[17] conducted a systematic review and meta-analysis of the effect of continued versus discontinued cannabis use after the onset of psychosis. They identified 24 studies, including 16,565 patients with preexisting psychosis and at least a 6 month duration of follow-up. They found that continued cannabis use was associated with a significant: increase in risk of relapse of psychosis compared with non-users (ES=0.36) and discontinued users (ES=0.28); longer hospital admissions than non-users (ES=0.36); and more severe positive, but not negative, symptoms. Krause and colleagues[18] performed a meta-analysis of the efficacy, acceptability, and tolerability of antipsychotics in patients with schizophrenia and comorbid substance use. They included 8 randomized controlled trials in patients with cannabis use comorbidity. Clozapine was superior to other antipsychotics for reduction of substance use and negative symptoms in those who used cannabis. Risperidone was superior to olanzapine for reducing of drug cravings and weight gain.

Conclusions

Premorbid cannabis use is associated with a dose-dependent increased risk of developing a psychotic disorder. There is evidence in both patients with psychotic disorders and the general population that cannabis use is associated with adverse effects of psychopathology and cognition. Cannabis use and CUDs are highly prevalent throughout the clinical course of illness.

"Research suggests that people with substance-induced psychoses will later transition to a diagnosis of schizophrenia."

Cannabis use is associated with an earlier age of onset of psychosis and more severe impairments in neurocognition. Continued cannabis use after the onset of psychosis is associated with increased risk of illness relapse, longer hospitalizations, and more severe positive psychopathology. There is also evidence for superior efficacy of clozapine for reduction of substance use and negative symptoms in patients with schizophrenia and comorbid cannabis use. Targeted interventions for improved prevention, detection, and treatment are warranted to improve outcomes in this population.

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