Marijuana and Psychosis

Diana O. Perkins, MD MPH, Professor, Department of Psychiatry, University of North Carolina at Chapel Hill; Medical Director, Outreach and Support Intervention Services

Marijuana use, especially a pattern of use that begins during early adolescence, or heavy use in late adolescence or early adulthood, has emerged as an environmental risk factor for the development of psychosis, increasing risk about 4-fold (1-5). This means that about 4% of heavy or early marijuana users will develop schizophrenia, compared to about 1% of the general population. Thus marijuana may increase risk of schizophrenia, but only in persons who have a biological vulnerability. These studies also suggest that, given current rates of marijuana use, marijuana likely plays a causal role in about 10-14% of all cases of schizophrenia (6).

Interestingly, at the first episode of psychosis the “kind” of schizophrenia associated with marijuana use is characterized by less severe negative symptoms and cognitive impairments (7, 8) as well as an earlier age of onset (9). It is currently unclear if these differences in presentation are due to marijuana, is exerting some therapeutic benefit, that the type of schizophrenia where marijuana is a risk factor is a more benign disorder than the type of schizophrenia that develops for other reasons, that obtaining marijuana use requires intact social skills, or some other confounding factor. However, once schizophrenia develops continued use of marijuana is associated with relapse, re-hospitalization, and worse functional outcomes (10, 11). For this reason substance abuse treatment is a critical component of the care of persons with schizophrenia who use marijuana.

The brain’s own cannabinoid system, termed the endocannabinoid system, is a key regulator of neurotransmitter release (including dopamine, GABA, and glutamate) and neuronal plasticity (12). The endocannabinoid system is now known to regulate recovery of the endocrine and autonomic nervous system from stress, immune system function, and energy balance. The endocannabinoid system also plays key roles in neurodevelopment. Marijuana contains multiple cannabinoids, with the main cannabinoid delta-9-tetrahydrocannabinol (THC). THC is a “partial agonist” at cannabinoid receptors in the brain, and thus activates these receptors. THC is a prime suspect to explain the impact of marijuana on psychosis, based on evidence that THC administration induces a transient psychosis in healthy persons as well as persons with schizophrenia (10). This idea has led to trials of cannabinoid receptor antagonists, such as rimonabant, in schizophrenia, that unfortunately have failed thus far to show clinical benefits (13).

Cannabis also contains cannabidiol (CBD), which is reported to have anti-anxiety and antipsychotic effects, and to protect against the psychosis-inducing effects of THC (14). CBD appears to have very weak effects on cannabinoid receptors, but has been shown to influence the metabolism of the body’s own cannabinoid, anandamide, increasing anandamide levels. A recent 4-week double-blind clinical trial in 42 patients with acute psychosis compared CBD to amisulpiride (an antipsychotic available in Europe) (15). In this study CBD was comparable to amisulpiride in reduction of total, positive, and negative symptoms, and was not associated with extrapyramidal side effects, weight gain, or prolactin elevation. CBD treatment was also
associated with elevations in blood levels of anandamide, and change in anandamide levels were highly and significantly correlated with symptom change. The authors advance the intriguing theory that anandamide is protective against psychosis, and that cannabidiol mechanism of action is to interfere with anandamide metabolism and thus boost anandamide levels.

In summary, marijuana contains a complex mixture of potential active compounds, with THC and CBD seeming to have opposing effects relative to psychosis. Use of marijuana in childhood or adolescence, or heavy use in young adulthood appears to increase risk of schizophrenia by about 4-fold, with THC the likely culprit. The impact of increasing use of marijuana in adolescents together with the increasing concentrations of THC relative to CBD in strains of marijuana raise concerns that the relative contribution of marijuana to development of schizophrenia could increase in the future. The endocannabinoid system is emerging as an intriguing treatment target in persons with schizophrenia, with CBD in particular showing early promise as an effective drug.

References


