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Topical Review

Adverse Structural and Functional Effects of Marijuana on the Brain: Evidence Reviewed

David E. Mandelbaum MD, PhD [a], **Suzanne M. de la Monte MD, MPH** [b,*]

[a] *Departments of Neurology and Pediatrics, Hasbro Children's Hospital and Rhode Island Hospital, and the Alpert Medical School of Brown University, Providence, Rhode Island*
[b] *Departments of Neuropathology and Neurosurgery, Hasbro Children's Hospital and Rhode Island Hospital, and the Alpert Medical School of Brown University, Providence, Rhode Island*

ABSTRACT

The growing use and legalization of cannabis are leading to increased exposures across all age groups, including in adolescence. The touting of its medicinal values stems from anecdotal reports related to treatment of a broad range of illnesses including epilepsy, multiple sclerosis, muscle spasms, arthritis, obesity, cancer, Alzheimer disease, Parkinson disease, post-traumatic stress, inflammatory bowel disease, and anxiety. However, anecdotal data and the high level of interest in this treatment must not obscure objective assessments of any potential and realized short- and long-term adverse effects of cannabis, particularly with respect to age of onset and chronicity of exposure. This critical review focuses on evidence-based research designed to assess both therapeutic benefits and harmful effects of cannabis exposure and is combined with an illustration of the neuropathologic findings in a fatal case of cannabis-induced psychosis. The literature and reported case provide strong evidence that chronic cannabis abuse causes cognitive impairment and damages the brain, particularly white matter, where cannabinoid 1 receptors abound. Contrary to popular perception, there are few objective data supporting preferential use of cannabis over conventional therapy for restoration of central nervous system structure and function in disease states such as multiple sclerosis, epilepsy, or schizophrenia. Additional research is needed to determine if subsets of individuals with various neurological and psychiatric diseases derive therapeutic benefits from cannabis.

Keywords: marijuana, cannabis, white matter, human brain, treatment, epilepsy, psychosis, multiple sclerosis

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Narrative review

Historical perspective

Cannabis sativa has been used for nearly 5000 years. The Chinese and Indian cultures were the first to recognize the properties of this drug. After the fifth century AD, travelers, traders, and adventurers brought the drug to Persia and Arabia. On the return of Napoleon's army from Egypt, cannabis became widely accepted by Western medical practitioners for its pain relieving and sedative effects. As eloquently stated by Mikuriya, "To the agriculturist cannabis is a fiber crop; to the physician of a century ago it was a valuable medicine; to the physician of today it is an enigma; to the user, a euphoriant; to the police, a menace; to the traffickers, a source of profitable danger; to the convict or parolee and his family, a source of sorrow."[1]

Terminology

Cannabis sativa is a herbaceous plant with versatile uses and effects. Marijuana comes from the cannabis flower; the terms "cannabis" and "marijuana" are often used

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* Communications should be addressed to: Dr. de la Monte; Rhode Island Hospital; Pierre Galletti Research Building; 55 Claverick Street; Room 419; Providence, RI 02903.
E-mail address: Suzanne_DeLaMonte_MD@Brown.edu

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interchangeably. However, the leaves and resinous extracts of the plant can also be consumed by smoking, eating, or inhaling vapors. In addition, cannabis hempseeds are used to produce oil for cooking, lighting, and wood surface coatings. Today, the main interest in this plant is that it is a rich source of cannabinoids. Cannabinoids are chemical substances consumed largely for recreational and spiritual purposes, but also for their medicinal effects. Differences in the chemical structures of cannabinoids account for their differential psychoactive and medicinal effects. The two cannabinoids of greatest interest today are cannabidiol (CBD) and (delta)9-tetrahydrocannabinol (Δ9- or D9-tetrahydrocannabinol; THC). CBD is one of the major non-psychoactive phytocannabinoids present in cannabis such that nearly 40% of cannabis extracts comprise CBD. CBD is a substance in cannabis that is thought to have potential medicinal applications,[2,3] lack psychoactivity, and not interfere with psychomotor learning or neuropsychologic functions. In contrast, THC, the other main active component in cannabis, is responsible for the mood altering effects, and unlike CBD, THC has potent adverse psychoactive effects, inducing anxiety and paranoia.[4] Of growing interest is the possibility that CBD may be capable of counteracting adverse psychoactive effects of THC in humans.[5,6]

Cellular drug actions

THC is the major psychoactive ingredient in cannabis, with agonist properties at the cannabinoid 1 (CB1) receptors, which are located primarily in the brain. This seven transmembrane G protein–coupled receptor mediates neuronal inhibition by decreasing calcium influx and increasing potassium efflux across the cell membrane. CB1 receptors are found in inhibitory (GABAergic) and excitatory (glutamatergic) neurons. THC is a partial agonist of CB2 receptors, which are located primarily in immune and hematopoietic cells.[7]

CBD is the major nonpsychoactive component of cannabis, acting as an agonist at the 5-HT1a, α3 and α1 glycine receptors. CBD binds very weakly to CB1 receptors[8] and, in fact, diminishes the effects of CB1 activation. CBD has antiapoptotic, neuroprotective, and anti-inflammatory effects.[7] CBD modulates intracellular Ca^{2+} concentration by inhibiting T-type calcium channels inside the cell.[9]

Disputed antiepileptic effects

A review of the literature on the antiepileptic effects of cannabinoids concluded, "No reliable conclusions can be drawn at present regarding the efficacy of cannabinoids as a treatment for epilepsy."[10] The review found that studies were not adequately powered (between nine and 15 patients) and were of "low quality." The review concluded, "In addition to the inconclusive evidence of efficacy, other evidence has suggested marijuana and low-dose THC can represent a possible seizure precipitant."[10] For the most part, these studies involved the use of cannabinoid products with variable potency and combinations of THC and CBD and not pharmaceutical grade products, limiting the conclusions that can be made from these reviews; as it has been said, "Absence of evidence is not evidence of absence." However, even the findings in a recent open-label clinical trial using pharmaceutical grade CBD were compromised by the failure to control for the interaction between CBD and clobazam; among the children treated with CBD, those also taking clobazam had a notably higher response rate than those who were not.[10] CBD has been shown to raise serum clobazam levels considerably.[11,12] A retrospective, unblinded study of 74 children with refractory epilepsy treated with CBD that was carefully analyzed for CBD and THC contents found a response rate (greater than 50% seizure reduction) in 51% of patients and aggravation of seizures in 18%. No information was provided regarding other medications the children were taking in conjunction with CBD; hence, the role of a rise in clobazam levels, or other drug interactions, in seizure reduction is not known.[13] Thus even with carefully prepared CBD products, concerns remain regarding efficacy and adverse events.[14,15]

Causal agent in psychosis

A retrospective, cohort study of Swedish conscripts reviewed data on 50,087 individuals regarding self-reported use of cannabis and other drugs, and on several social and psychological characteristics. The study found that cannabis was associated with an increased risk of developing schizophrenia in a dose-dependent fashion both for subjects who had ever used cannabis (adjusted odds ratio [OR], 1.2; 95% confidence interval [CI], 1.1 to 1.4; $P < 0.001$) and for subjects who had used only cannabis and no other drugs (adjusted OR, 1.3; 95% CI, 1.1 to 1.5; $P < 0.015$). The adjusted OR for using cannabis more than 50 times was 6.7 (95% CI, 2.1 to 21.7) in the cannabis only group. Similar results were obtained when analysis was restricted to subjects developing schizophrenia 5 years after conscription, in an effort to exclude prodromal cases.[16]

A literature review on the risk of mental health disorders associated with cannabis use included 35 studies from 4804 references. Studies included were population-based, longitudinal, or case–control nested within longitudinal designs. This literature review found an increased risk of any psychotic outcome in individuals who had ever used cannabis (pooled adjusted OR, 1.41; 95% CI, 1.20 to 1.65), with evidence of a dose–response effect, and greater risk in people who used cannabis most frequently (OR, 2.09; 95% CI, 1.54 to 2.84).[17]

Neuropsychiatric effects of cannabis vary in severity and can be associated with neuropsychologic deficits, reduced motivation and activity, hallucinations, or symptoms of schizophrenia-like psychotic disorders.[18] Heavy regular cannabis use, especially in adolescents (before age 15 years), is associated with higher rates of persistent negative outcomes in adulthood, including increased rates of mental illness and cognitive impairment.[19] Because schizophrenic psychosis and cannabis use share a number of similarities and both begin in late adolescence, a major concern is whether adolescent cannabis use causes or triggers chronic psychosis or schizophrenia and whether the neuroanatomic substrates of cannabis neurodegeneration and schizophrenia are shared.[18] For example, both heavy cannabis users and schizophrenics have diminished regional gray and white matter volumes, and close relatives of schizophrenics have high cannabis use.[20] However, in a well-controlled study, Dekker et al.[18]