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Review Article

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

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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, it is essential that anecdotal data and the high level of interest in this treatment 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 the herbaceous plant with versatile uses and effects. Marijuana comes from the cannabis flower; the terms "cannabis" and "marijuana" are often

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used 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 nonpsychoactive 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] demonstrated that schizophrenia was not triggered more frequently by adolescent compared with later-onset cannabis use, and that the characteristic white matter abnormalities in the corpora callosa of schizophrenics were not correlated with age of onset of cannabis use. Therefore the schizophrenia-like psychotic disorders associated with heavy cannabis use are likely distinct from schizophrenia.

Another consideration is that cannabis use may precipitate psychosis in susceptible individuals. A study of 410 patients with first-episode psychosis found that those with a history of cannabis use presented with psychosis at a younger age than those who never used cannabis. In addition, those using high-potency cannabis (skunk-type) every day had the earliest onset compared with never users.[21] The findings in a study of more than 1000 patients with psychotic disorders, their unaffected siblings, parents, and control subjects suggest that gene–cannabis interactions may influence vulnerability to adverse mental health effects of cannabis use.[9,22] However, the possibility that individuals with emerging mental illness might seek out psychoactive substances limits the ability to establish a clear cause–effect relationship between cannabinoid use and psychiatric disease based on retrospective studies.

Cannabis use and cognitive impairment

Meta-analysis data show that heavy cannabis using adults exhibit significant deficits in learning, working memory, and attention, but with abstinence, these problems may resolve.[23] In contrast, adolescence is a critical period of neurodevelopment during which synaptic modulation and myelination are highly active and therefore could be disrupted by exogenous exposures to drugs and toxins.[23] In this regard, concerns have been raised about chronic heavy cannabis use and cognitive decline in adolescents. To help address this question, a birth cohort of 1037 individuals was followed from birth (1972/1973) to age 38 years in Dunedin, New Zealand. Cannabis use was ascertained at ages 18, 21, 26, 32, and 38 years, and neuropsychologic testing was performed on all subjects at ages 13 and 38 years. This study found that persistent cannabis use was associated with broad neuropsychologic declines across multiple domains of functioning, even after controlling for years of education. Persistent users reported more cognitive problems. Cognitive impairment was mainly associated with cannabis use from adolescence, and more persistent use led to greater declines in cognitive function. The gravity of these problems is highlighted by the finding that cessation of cannabis use did not fully restore neuropsychologic function in adolescent-onset cannabis users.[24]

Cannabis use worsens neuropsychologic function in people with multiple sclerosis

As a partial answer to the question about potential contributions of cannabis use to neurobehavioral dysfunction, one study evaluated effects of cannabis on cognition in patients with multiple sclerosis (MS). Twenty subjects with MS who smoked cannabis and 19 with MS who abstained from cannabis were subjected to integrated psychometric tests of verbal and visual memory, information processing speed, and attention when undergoing functional MRI (magnetic resonance imaging) studies. The subjects were matched on demographic and neurological variables. Cannabis users had more diffuse cerebral activation across all trials, and they made more errors in working memory tasks relative to nonusers. Working memory task errors were associated with increased activity in parietal and anterior cingulate regions, which are known to be involved with working memory. In contrast, there were no intergroup differences in resting-state network activity or structural MRI variables.[25]

Cannabis-associated subcortical nuclear gray matter structural changes—neuroimaging

Besides its adverse effects on cognitive, behavioral, and psychiatric functions, cannabinoid use has been linked to structural changes in the brain. High-resolution MRI with morphometric analysis of gray matter density, volume, and shape was performed on 20 individuals, aged 18 to 25 years, who either had self-report histories of least weekly cannabis use or were abstinent control subjects.[26,27] None of the cannabis users met DSM-IV criteria for drug dependence or any current or lifetime Axis I disorder, and all tested negative for alcohol use disorder. The study found a statistical trend effect of higher gray matter densities in the left nucleus accumbens among cannabis users compared with control subjects. In addition, there were statistically significant shape differences in the left nucleus accumbens and right amygdala among cannabis users. Gilman et al.[26] concluded that in adolescent humans, the cannabis exposure-dependent alterations of the neural matrix of core reward structures are reminiscent of the dendritic arborization changes observed in experimental animal studies.

Safety concerns

In several small human studies designed to assess adverse effects of CBD, significant adverse effects on the central nervous system, mood, or vital signs could not be demonstrated. In addition to the lack of statistical power, a broader array of potential pathophysiologic effects should be considered in the analysis because, for example, *in vitro* experiments showed that CBD can suppress interleukin 8 and 10 production and induce lymphocyte apoptosis, suggesting that CBD exposures carry at least a theoretical risk of immunosuppression. Large-scale systematic clinical studies are needed to examine the safety of CBD use in adults. Adding to these safety concerns are the findings of a report from the Potency Monitoring program, a program of the National Institute on Drug Abuse, which provided data on 46,211 cannabis samples seized by law enforcement agents and analyzed from 1993 to 2008. The data showed an upward trend in the mean Δ9-THC content of all confiscated cannabis preparations, which increased from 3.4% in 1993 to 8.8% in 2008. The study found that the increase in cannabis preparation potency was mainly because of the increase in the potency of nondomestic versus domestic samples.[28]

Despite the great interest in the use of CBD to treat pediatric epilepsy, little is known about the pharmacokinetics and toxicity of CBD in children. In an open label,

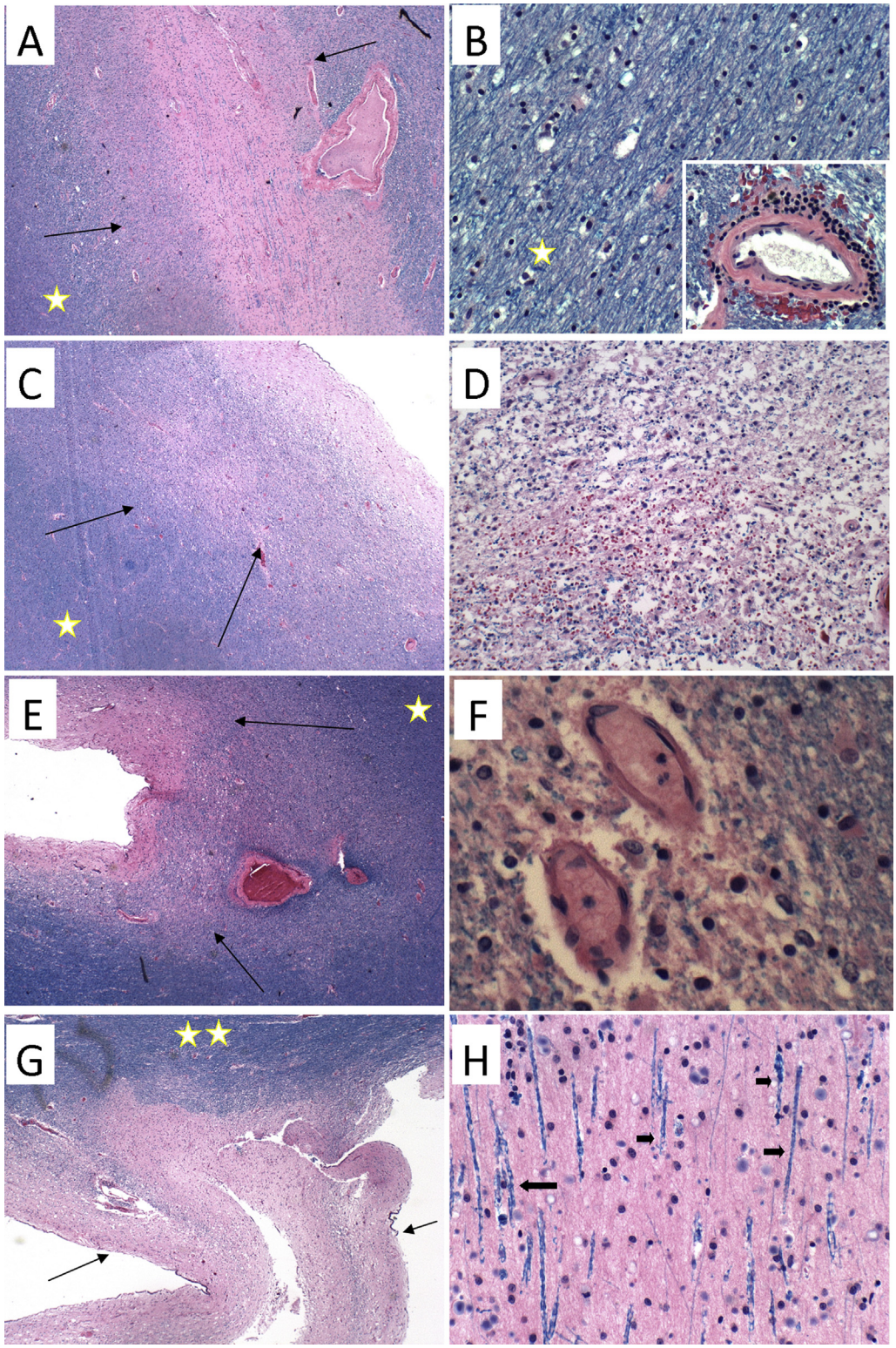

FIGURE 1.
Cannabis-associated cerebral white matter degeneration and demyelination. Histologic sections including white matter from the (A and B) frontal lobe, (C and D) periventricular parietal area, (E and F) periventricular occipital region, and (G and H) fornix with corpus callosum were stained with luxol fast blue and hematoxylin and eosin. Myelin stains blue, and loss of myelin appears eosinophilic (pink). Note the defined regions of white matter demyelination or degeneration (arrows) in (A), (C), (E), and the fornix (G), and relative preservation of myelin in adjacent white matter (*), including the corpus callosum (G, **). (B) An area of intact frontal white matter with the inset showing perivenular lymphocytic inflammation. (D) Abundant macrophages infiltrating the subacute region of demyelination in (C). (F) Perivascular macrophages corresponding to a higher magnification image of (D). (H) Severe established loss of myelin with gliosis. The paucity of myelinated fibers (arrowheads) corresponds to axonal loss (see Fig 2). (The color version of this figure is available in the online edition.)

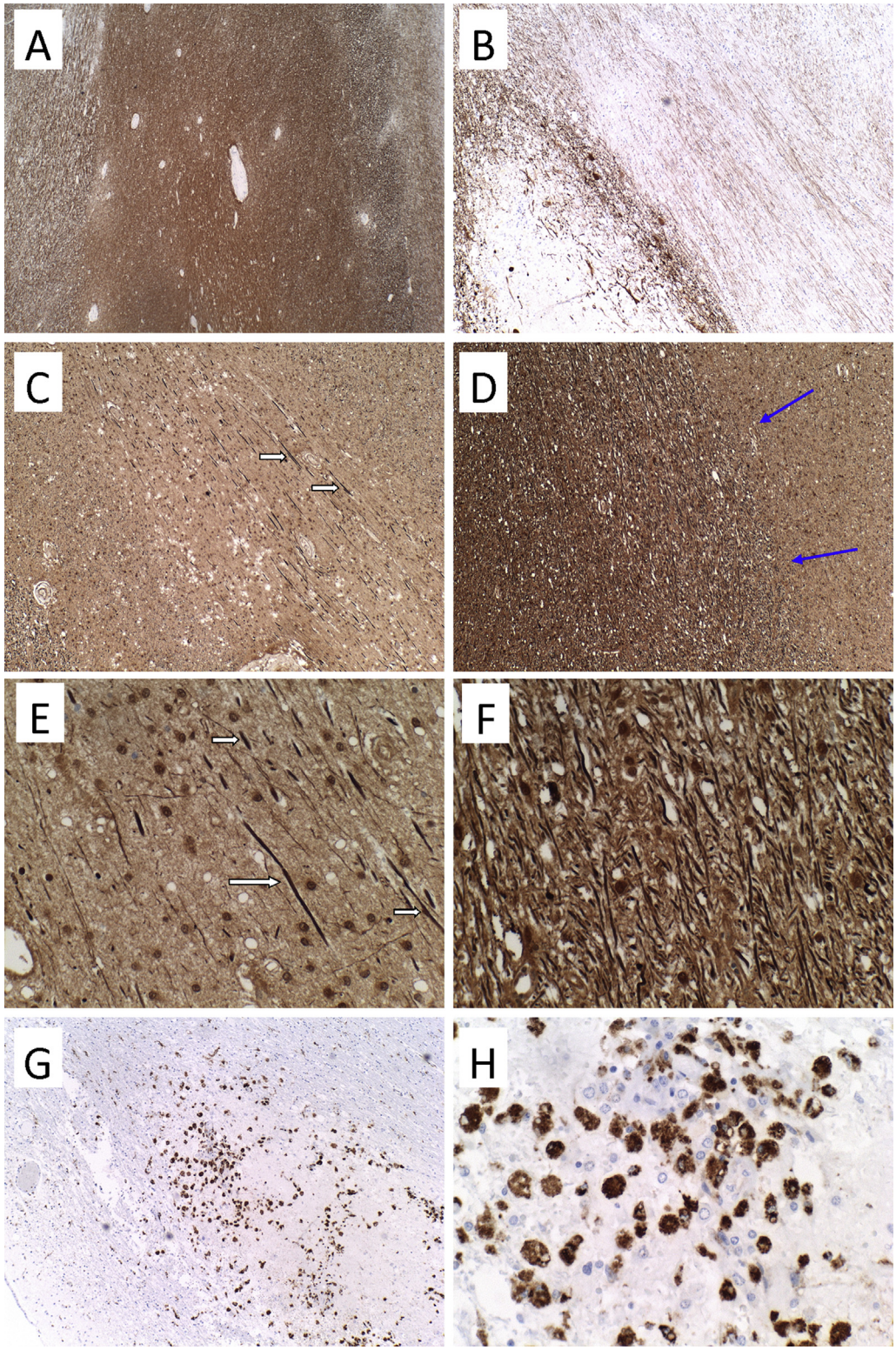

FIGURE 2.
Immunohistochemical staining to demonstrate (A and B) gliosis, (C and F) axonal loss, and (G and H) macrophage infiltrates in white matter lesions. Gliosis was detected by immunostaining for glial fibrillary acidic protein. Note the dense area of immunoreactivity (brown staining) in (A), which corresponds to the lesion highlighted with arrows in Fig 1A. In contrast, panel (B) shows less severe gliosis, corresponding to Fig 1B and illustrates low-level injury despite relative preservation of myelin staining (luxol fast blue and hematoxylin and eosin). Neurofilament immunostaining was used to detect axonal loss. Panels (C) and (E) show severe axonal loss in the same region depicted in Figs 1A and 2A (axons are highlighted with arrowheads). In contrast, panels (D) and (F) correspond to the regions shown in Figs 1B and 2B, and illustrate relative preservation of axons. In panel (D), the arrows point to central white matter containing abundant axons. (G and H) Macrophages were detected by immunohistochemical staining for CD68. The panels depict (G) low and (H) high magnification images of macrophage infiltrates into subacute lesions shown in Fig 1C and D. (The color version of this figure is available in the online edition.)

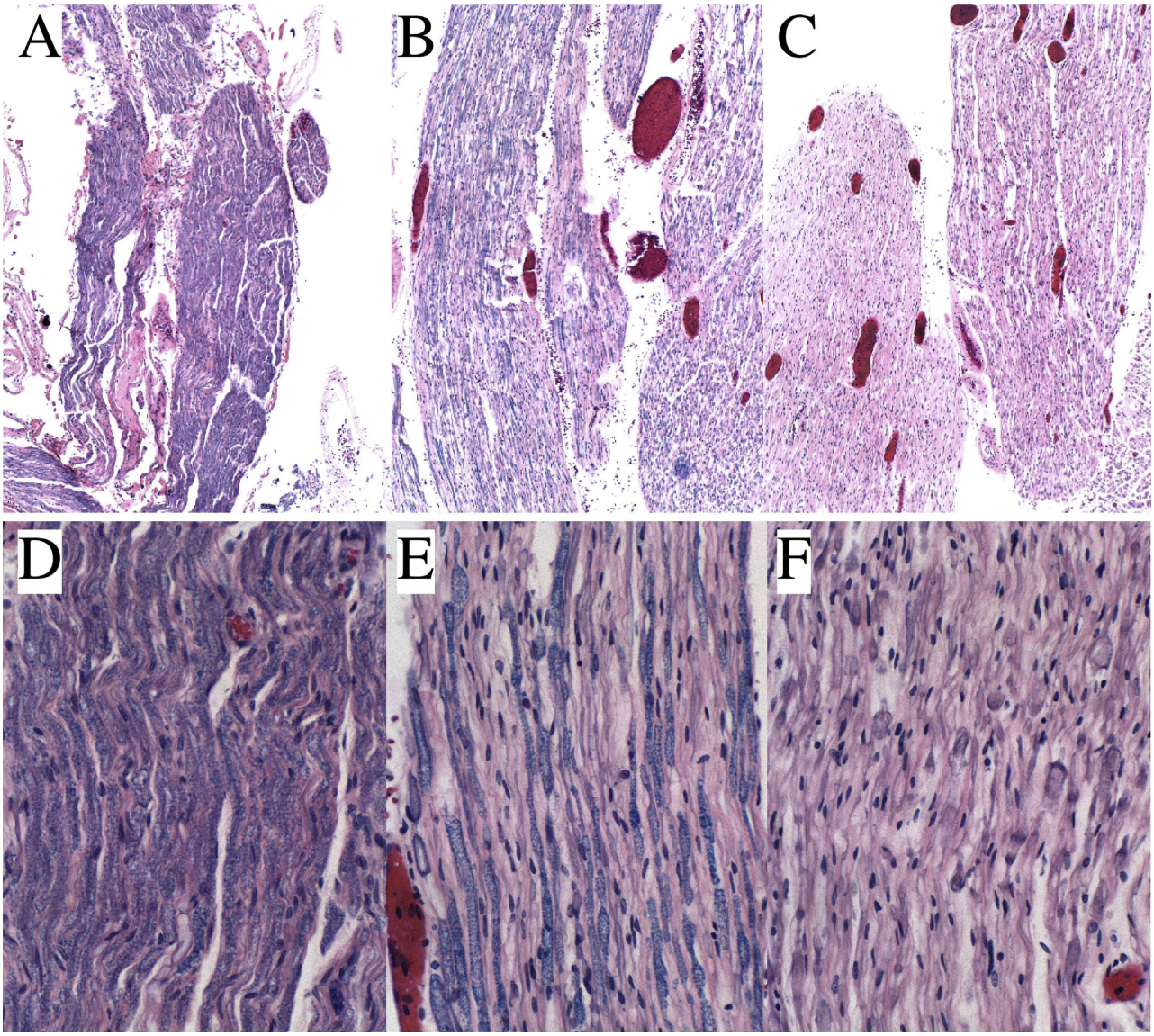

FIGURE 3.
Spinal radiculopathy. Histologic sections of nerve roots from the cauda equina were stained with luxol fast blue and hematoxylin and eosin. (A and D) Intact well-myelinated nerve roots. (B and E) Patchy regions of myelin and myelinated fiber loss. Some axonal swellings are evident in (E). (C and F) Severe nerve root degeneration with loss of myelin and axons, and associated with axonal swellings and Schwann cell proliferation. There was no evidence of inflammation associated with these chronic degenerative lesions in the nerve roots. (The color version of this figure is available in the online edition.)

uncontrolled study of CBD in children with refractory epilepsy, adverse events were reported in 128 of 162 (79%) of the enrolled subjects.[29] The most common adverse effects were somnolence (25%), decreased appetite (19%), diarrhea (19%), fatigue (13%), and convulsions (11%). Serious adverse events, including one death, occurred in 30% of patients, and in 12%, the adverse effects were directly attributed to CBD. The most common serious adverse effect was status epilepticus (6%). Mechanistically, some adverse effects such as somnolence and fatigue may have been caused by CBD-induced increases in serum clobazam levels.[29]

Despite these concerns, it is important to note that the subject populations in the studies by Devinsky et al.[29] and Tzadok et al.[13] had refractory epilepsy and failed to respond to conventional medicines. In that regard, the outcomes could be interpreted as a basis for some optimism, in that many subjects did have positive therapeutic responses to the CBD treatments with, as noted previously, the caveat that the responses may, at least in part, have been attributable to a rise in clobazam levels. Furthermore, the study design did not permit ascertainment of whether the serious adverse events, including death, could be directly attributed to the effects of CBD versus the underlying refractory nature of their seizure disorders. Clearly more clinical and translational research is needed to define the subset of epilepsy patients and other disease states that will likely benefit from CBD with high degrees of safety and efficacy. It will be especially important to examine responses and therapeutic effects in randomized controlled, double-blind clinical trials, with concomitant clobazam use eliminated as

confounding factor, as the results of the Devinsky et al. study were not conclusive.[14,15] Our main concern is that the current level of enthusiasm for the use of CBD is not justified by the available data and therefore should be tempered given that dangers and complications of these treatments exist and their mechanisms are not fully understood, as illustrated by the following case presentation.

Patient Description

This 52-year-old man had a long (many years) history of depression, anxiety, and at least a two-decade long history of heavy marijuana smoking. It is not known whether heavy marijuana use preceded or followed the onset of depression and anxiety. He was not under regular psychiatric care or taking prescribed medications to manage his symptoms. There was no history of other licit or illicit substance uses or abuse, or family history of psychosis or chronic depression. The man lived independently with relatives; his employment status was unknown. He had experienced several episodes of acute psychotic-type behavior that occurred while intoxicated with marijuana only. On at least two occasions, he walked directly into on-coming traffic and sustained motor vehicle trauma. His final admission to the hospital followed a similar episode. His blood toxicology screen demonstrated high levels (not quantified) of THC and no other drugs or metabolites. The general autopsy demonstrated an incompletely healed scalp wound, bronchopneumonia, and sepsis.

Postmortem examination of the brain revealed multifocal regions of subacute or chronic demyelination involving the periventricular and central cerebral white matter, the fornix, and corpus callosum (Fig 1). The zones of demyelination were minimally inflammatory, contained only scant collections of lipid-laden macrophages, and were not consistently perivenous. White matter in the frontal, parietal, temporal, and occipital lobes were affected. The boundaries of demyelination were feather-like and ill-defined, in contrast to the discrete plaques of MS. Immunohistochemical staining for glial fibrillary acidic protein demonstrated white matter gliosis in regions of demyelination (Fig 2). Immunostains for CD68 confirmed the presence of macrophages in foci of subacute white matter injury. Neurofilament immunohistochemistry highlighted axonal degeneration in subacute and chronic white matter lesions (Fig 2). In addition, severe, noninflammatory, predominantly demyelinating, but focally axonal, radiculopathy was present at multiple spinal cord levels (Fig 3). Fiber loss and degeneration in spinal nerve roots were confirmed by neurofilament Immunohistochemical staining (not shown). Gray matter structures exhibited terminal acute terminal hypoxic-ischemic encephalopathy.

Discussion

Studies have shown that the rates of marijuana use in the general population are higher in states where medical marijuana use has been legalized. The net result has been to increase marijuana abuse and dependence.[30] Adolescence is a critical period of neuromaturation including progressive myelination and a stage of development when cannabinoid receptors are highly abundant in white matter. Cannabis can damage white matter connections and integrity. Mechanistically, endocannabinoid receptors modulate synaptic plasticity and impact cortical connectivity throughout life. Therefore, in addition to assessing volumetric changes, functional abnormalities must be considered to appreciate the full impact of cannabis use on global network efficiency and organization. In this regard, the structural changes that are associated with cannabis-altered networks, manifested by reduced efficiency, integration, regional connectivity, correlate with schizoid and impulsive personality characteristics.[31]

Cannabis-associated neuropathology

Previous neuroimaging studies demonstrated that the major targets of cannabis-mediated neurodegeneration include white matter in the frontal lobes, fornix, fimbria of the hippocampus, frontal-limbic connections, corpus callosum, and commissural fibers.[32,33] In addition, cannabis targets the cerebellar structure and function such that cerebellar white matter atrophy can be significant and associated with neurobehavioral deficits and psychotic symptoms.[33] Conceptually, cannabis-induced white matter destruction impairs conductivity.[32-34] In the present case, direct neuropathologic studies revealed prominent demyelination and axonal damage within fornix, corpus callosum, and central cerebral white matter, corresponding to neuroimaging data obtained from heavy marijuana users. The finding of similar abnormalities in spinal nerve roots is novel and suggests that individuals exposed to cannabis may develop motor or sensory peripheral nerve root dysfunction. Although some of the subacute foci of white matter injury with axonal spheroids could have been caused by traumatic sheer and rotational forces two weeks before death, the extensive, chronic cerebral white matter demyelination, and mixed demyelinating and axonal radiculopathy cannot be attributed to trauma.

The neuropathologic findings that we describe may be at the extreme end of the severity spectrum. Nonetheless, the nature and regional distributions of lesions detected in white matter, including loss of myelin and axonal integrity, correspond to published data obtained by neuroimaging. We posit that the severity and extent of cannabis-induced neuropathologic changes vary with the dose, frequency, duration of exposure, and age when the exposure began, with adolescence being a highly vulnerable period. Another point is that one might predict that lower levels of similar neuropathology, although not sufficient to cause overt neurobehavioral deficits, may additively or synergistically contribute to the development of other disease processes such as psychosis and schizophrenia, particularly in adolescents.[35]

Correlates of cannabis-associated microstructural white matter pathology

Diffusion tensor imaging (DTI) provides a microstructural, quantitative assessment of white matter. Fractional anisotropy (FA) measures the degree of directionality and coherence of white matter fiber and has been used as an index of white matter tracts; the high degree of directionality of white matter tissue reflects axonal direction. Apparent diffusion coefficient or “Trace” averages diffusion over multiple directions and measures the magnitude of molecular motion; this has been used to identify ischemia. In a study designed to correlate white matter structural alterations with behavioral effects of marijuana exposure, DTI was performed on six brain regions of 15 chronic marijuana smokers and 15 control subjects. The subjects were also administered clinical rating scale of impulsivity. Chronic marijuana use was found to be associated with significantly higher impulsivity scores, reductions in left frontal FA, and increased apparent diffusion coefficients in the right genu of the corpus callosum.[36] In addition,

impulsivity was positively correlated with left frontal FA values. However, one limitation of this study is that one cannot assess cause versus effect, i.e., whether the increased impulsivity and white matter changes cause or are consequences of marijuana use.

DTI mapping of the brain after long-term cannabis use revealed microstructural alterations reflecting significantly impaired axonal connectivity in the right fimbria of the hippocampus (fornix), splenium of the corpus callosum, and commissural fibers. Radial and axial diffusivity in these pathways correlated with age of exposure onset and duration of cannabis use.[32,37] Furthermore, executive function deficits and DTI abnormalities in brain structure, brain volume, and white matter integrity can be detected after one or two years of heavy marijuana use.[23] Beyond structural defects detected by neuroimaging, functional MRI studies have demonstrated that heavy cannabis use among adolescents can alter prefrontal cortex activity in the direction of reduced processing efficiency during performance of novel working memory tasks.[23]

Is the exuberance for cannabis irrational?

The rapid spread of cannabis use across the nation and the desire for further liberalization of policies pertaining to its access stem from the widespread perception that the drug is safe and its beneficial properties outweigh its dangers. Such perceptions are reinforced by reports suggesting that marijuana is safer to use than either tobacco or alcohol and that previous studies may have exaggerated the harmful effects of marijuana. Independent of the societal issues regarding the criminalization of marijuana use, the concern of the medical community should be whether the chronic use of a substance that can damage brain structure and function is a sensible and responsible risk.

Here the concerns are mainly focused on adolescents, whose brains are not fully mature, yet they are clearly willing and able to participate in use and abuse of cannabis. The downward shifting age of initiating cannabis use raises concerns about increased susceptibility of the adolescent brain to long-term structural damage. In a 1.5-year study of adolescents, aged between 16 and 19 years, cannabis use was associated with poorer integrity of frontolimbic white matter (fornix, superior corona radiata, superior longitudinal fasciculus, and superior fronto-occipital fasciculus), greater propensity for risk taking behavior, and early initiation of heavy substance abuse.[38] Moreover, after a three-year follow-up, the adolescent cannabis users had significant declines in white matter integrity along with poor global neurocognitive performance.[39,40] Other studies also showed that adolescent heavy cannabis users developed structural abnormalities in white matter characterized by reduced FA, increased radial diffusion, and increased trace in the contralateral hemisphere.[41] Cannabis-induced altered microstructure and reductions in FA in frontal white matter have been correlated with increased rate and extents of impulsivity.[42] These findings indicate that the adolescent brain is susceptible to significant white matter damage and lasting impairments in neuropsychologic and cognitive function after heavy cannabis use. The finding that, even after marijuana use during adolescence, abstinence spared the adolescent brains of microstructural pathology[39,40] may be reassuring.

Despite objective data pointing to concerns about the therapeutic responses to CBD, subjective impressions continue to fuel debate and frustration about its use as an accepted medicinal compound, including in adolescents. For example, a recent study of parental impressions about the efficacy of oral cannabis extracts for the treatment of epilepsy reported high rates of improved of seizure control (57%), including reduced rates of seizures, gains in behavior, language, motor skills, and energy level; yet in the few individuals who underwent an EEG, no changes were observed.[43] Although the study provided some evidence that oral cannabis is well tolerated by children and adolescents with seizures, it has been acknowledged that open-label trials are challenged by a number of confounders. However, additional well-controlled human clinical research is needed to assess the effects of age, cannabis dose, and exposure duration in relation to occurrence and reversibility of brain damage, cognitive dysfunction, and neuropsychiatric disorders. In addition, further understanding about the neurobehavioral and brain effects of specific forms of cannabis exposure will aid in delineating and predicting therapeutic responses. For example, CBD may have protective effects against some of the adverse effects that THC has on frontotemporal neurocognitive networks.[23]

To assess the potential medicinal effects of medical marijuana, studies must be conducted with purified, dose-regulated, pharmaceutical compounds that enable investigator to separate responses to CBD and THC and examine their interactive effects. Furthermore, state-sponsored marijuana plants should be independently categorized with respect to their THC and CBD compositions to classify the plants as suitable for medicinal purposes versus recreational consumption. Alternatively, medicinal marijuana that contains optimized compositions of cannabinoids could be made available as a pharmaceutical.

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