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Editorial

Marijuana not ready for prime time as an analgesic

Eighteen states and the District of Columbia have legalized possession and use of medical marijuana. Registries from these state-approved programs suggest that up to 94% of participating patients are registered for severe or chronic pain [1]. The idea of physicians prescribing marijuana as an analgesic to treat chronic pain is currently fraught with a number of concerns including the uncharacterized chemical constituents unique to the plant and the wide variation in their concentration between marijuana specimens; the possible perturbation of the endocannabinoid system, one of the most widespread modulatory systems in the brain; marijuana's known deleterious effects on cognition; potential exacerbation of other psychiatric disorders common in patients with chronic pain; the risks of cannabis addiction including tolerance and withdrawal; smoked marijuana's possible physical health harms; and the lack of large, well-controlled studies to examine the efficacy and safety of smoked marijuana as a treatment for chronic pain. Each of these points will be discussed in turn to show that far more scientific research on the potential benefits and detriments of marijuana must be conducted before it could ever be wisely and safely prescribed as an intervention for chronic pain.

1. Chemical constituents of marijuana

Marijuana, derived from the plant *Cannabis sativa*, contains over 100 described cannabinoid compounds and over 500 noncannabinoid constituents [2]. Biological and pharmacological activity of most of these chemicals has not been characterized. The main psychoactive ingredient, Δ-9 tetrahydrocannabinol (THC), varies considerably in concentration from specimen to specimen, and, acting as a partial agonist at cannabinoid type 1 (CB1) and cannabinoid type 2 (CB2) receptors, when given acutely, variably causes euphoria and/or dysphoria, delays reaction time, impedes mental concentration, impairs memory and increases heart rate [3–7]. Another somewhat studied cannabinoid, cannabidiol, appears to act as a weak antagonist at CB1 and CB2 receptors, thus potentially opposing the effects of THC [8]. Somewhat paradoxically, cannabidiol may also inhibit the degradation of anandamide, the primary endogenous cannabinoid, thus increasing endogenous cannabinoid effects [9]. In addition, cannabidiol enhances adenosine signaling, may bind to some subtypes of serotonin receptors and may have antipsychotic properties [8,9]. Cannabidiol concentration also varies among marijuana specimens, and some strains, recently bred with the intention of enhancing the effects of THC, have very low cannabidiol concentrations [10].

2. The endocannabinoid system

The endocannabinoid system consists of CB1 and CB2 receptors and endogenous ligands for these receptors, primarily anandamide but also others that have not been thoroughly studied [11,12]. CB1 receptors are among the most abundant G-protein-coupled receptors found in the brain with localization in the basal ganglia, substantia nigra, globus pallidus, cerebellum, cingulate and prefrontal cortex, amygdala, hypothalamus and hippocampus [13]. CB1 receptor activation appears to regulate release of other key neurotransmitters including gamma-amino butyric acid, glutamate, serotonin, dopamine and endogenous opioids [11]. CB2 receptors are expressed on cells of the peripheral immune system and also primarily on microglia in the brain [12]. Their precise function is being investigated. The localization and neurophysiologic effects of cannabinoids suggest that they are likely to have substantial effects on mood and emotion, a concept supported by preclinical studies [11,14]. Given the widespread actions of cannabinoids and the varying concentrations of cannabinoids in marijuana, the actual impact on mood and anxiety in any individual at any given time could be unpredictable and may depend upon dose and setting. With smoked or even edible marijuana, the dose is difficult to measure or control.

3. Marijuana effects on cognition

In addition to its unpredictable effects on mood and anxiety, marijuana has confirmed deleterious effects on cognition. As noted, acute administration of marijuana or THC in the human laboratory delays reaction time, impedes mental concentration and impairs memory [3–7]. Chronic marijuana use has also been linked to difficulties with memory encoding, storage and retrieval in both adults and adolescents [15,16]. Among patients with multiple sclerosis, marijuana users performed more poorly on tests of executive functioning, information processing, working memory and visuospatial perception than did nonusers [17]. Heavy marijuana users continue to exhibit such cognitive deficits even after 28 days of abstinence from the drug [18]. Marijuana use by impairing the ability to judge distance as well as concentration, reaction time to signals and sounds, alertness and coordination negatively affects the skills needed to operate a motor vehicle safely [19]. Overall, the combination of cognitive impairments seen in regular marijuana users can impact judgement and decision making and may impair one's ability to learn new things and/or complete tasks that require focus and concentration [20].

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4. Impact of marijuana on psychiatric disorders

When considering the use of marijuana as an analgesic, it is important to point out that the majority of patients who suffer from chronic pain have co-occurring psychiatric disorders [21]. Several studies show an association between marijuana use and onset of mood disorders and psychosis [22,23]. Regular marijuana use is also associated with increasing symptoms of depression [24]. Marijuana use among individuals with psychotic disorder, though seeming to improve their mood, does worsen their psychotic symptoms [25,26]. Marijuana use also worsens the course of bipolar disorder [27,28]. Regular cannabis use leads to an increased risk for suicidal ideation in males [29] and possibly increased suicide attempts [30].

5. Risks of cannabis use disorder with marijuana

In both animal and human studies, THC administration induces release of dopamine in the striatum [31,32], the neurobiological signature of addictive substances. Not surprisingly then about 1 in 10 individuals newly exposed to marijuana will go on to develop a cannabis use disorder [33] with potential for all the concomitant psychosocial and physiological consequences as detailed in Diagnostic and Statistical Manual of Mental Disorders (DSM-5) including tolerance and a withdrawal syndrome, the hallmarks of which are sleep disturbance, anxiety, depressed mood and irritability.

6. Adverse health effects of marijuana

When smoked, marijuana also has potential adverse physical health effects. Although infrequent marijuana smoking may not cause functional pulmonary impairment [34], forced expiratory volume in the first second of expiration (FEV1) can be reduced at high levels of exposure [34,35], and regular marijuana smoking produces other pathologic lung conditions including chronic cough and sputum, widespread airway inflammation and injury and immunohistochemical evidence of dysregulated growth of respiratory epithelial cells [36]. Numerous case reports describe myocardial infarction and other cardiovascular events associated with marijuana smoking [37], which elevates the risk for myocardial infarction 4.8 times in the immediate hour postconsumption [38]. Acute cardiovascular deaths have also occurred after marijuana ingestion in young adults [39].

7. State of research on marijuana for pain

Numerous small controlled studies have repeatedly demonstrated that certain cannabinoids do reduce acute and chronic pain when compared to placebo in double-blind designs [40,41]. Most of these trials have use pharmaceutical forms of cannabinoids, either dranabinol (oral THC), nabilone (an oral, synthetic THC analog) or an extract of plant cannabis containing nearly equal proportions of THC and cannabidiol delivered as an oral mucosal spray, although a few have used smoked or vaporized marijuana. Most of the trials have relatively small samples sizes and used crossover designs over brief periods. One study of oral mucosal spray did have an open-label extension to 52 weeks with reported continuing benefits [42]. In all the studies, the cannabinoids had a worse side effect profile than placebo that sometimes included measurable cognitive adverse events. In one study, nabilone was less efficacious than dihydrocodeine but had more problematic side effects [43].

8. Conclusion

In summary, marijuana undoubtedly has analgesic effects under some circumstances but is a complex botanical with varying concentrations of many potentially psychoactive ingredients most of which remain unstudied. Marijuana consumption leads to perturbation of a very widespread modulatory system in the brain that can have unpredictable acute and chronic effects on mood and emotional state depending upon the individual, the dosage and the setting. In contrast, its effects on cognition quite predictably create impairments that make some everyday tasks such as driving unsafe. Marijuana has quite apparent addiction potential, such that some individuals exposed to it will end up using it in clearly unhealthy quantities and will experience tolerance and withdrawal. When smoked, marijuana may cause pulmonary or cardiac injury. In spite of these concerns, cannabinoids, some already available in pharmaceutically pure forms, certainly do show some promise as medications for chronic pain and possibly other conditions and definitely deserve considerably more investigation. However, in view of the several tangible harms detailed here, now is not the time for psychiatrists or other physicians to be prescribing or recommending nonpharmaceutical smoked marijuana for management of chronic pain.

Andrew J. Saxon, M.D.
Center of Excellence in Substance Abuse Treatment and Education
VA Puget Sound Health Care System
Seattle, WA 98108, USA
Department of Psychiatry & Behavioral Sciences
University of Washington
Seattle, WA, USA
E-mail addresses: Andrew.Saxon@va.gov asaxon@uw.edu

Kendall C. Browne, M.S.
San Diego State University/University of California
San Diego Joint Doctoral Program in Clinical Psychology
San Diego, CA, USA
Psychology Service, VA Puget Sound Health Care System
Seattle WA 98108, USA

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