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# Medical Marijuana: The Pitfalls and the Pendulum

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## Introduction

Marijuana (both *Cannabis indica* and *Cannabis sativa*) was criminalized in the U.S. in 1937, and has been classified as a Schedule I medical plant, meaning it has no currently accepted medical use and a high potential for abuse, since 1970 [1]. Various medical organizations including the AMA, American Academy of Pediatrics and the American Society of Addiction Medicine, have taken positions opposing the use of marijuana for medical purposes. However, the pendulum of public opinion has clearly begun to swing the other direction. At the present time, 23 states and the district of Columbia have approved the use of marijuana to treat various medical conditions, notwithstanding the continuing Federal ban [2]. The conditions for which medical marijuana use has been approved vary from state to state, and in most cases do not meet the standards that would be required for FDA approval for a new medication [3]. In part, this reflects the current paradoxical position of marijuana in the field of medicine where use for specific conditions is being approved on an ad hoc basis by state legislatures, while Federal law prevents the type of large-scale randomized placebo controlled trials that would normally be required for FDA approval.

Recent reviews have addressed the risks/ benefits of the use of marijuana for specific medical conditions [1,4,5] as well as potential adverse effects associated with its use [6]. Here, I present briefly evidence for some of these proposed medical uses as well as special considerations related to use of medical marijuana in patients with major psychiatric illness.

### Evidence supporting medical marijuana for specific indications

**Chronic pain:** Medical marijuana is currently approved for treating chronic pain in 19 states [5]. The review by Hill et al [5], which included 6 trials involving patients with chronic pain (total n=325) and an additional 6 trials related to neuropathic pain (total n=396), concluded that there was high-quality evidence favoring use of medical marijuana for chronic or neuropathic pain. While the review by Whiting et al [4], which included 28 studies (total n=2454) regarding use of cannabinoids for chronic pain (including both neuropathic pain and pain related to cancer), found that the evidence favoring use of medical marijuana was only moderate. Of the 28 studies included, 2 studies were felt to be at low risk for bias, 9 at unclear risk, and the remainder had high risk for bias. Overall, the number of patients who reported a reduction in pain of at least 30% was greater with cannabinoids than with placebo (OR, 1.41 [95% CI, 0.99-2.00]).

**Spasticity related to multiple sclerosis (MS):** Medical marijuana is currently approved for the treatment of spasticity and/or MS in the District of Columbia and all of the states that have authorized the use of medical marijuana [5]. The review by Hill et al. [5], which included 12 trials (n=1600) of cannabinoids in patients with MS found that there was high qualify evidence supporting the use of medical marijuana in this patient group. The review by Whiting et al [4], which included 14 trials of spasticity related to MS (11 studies, total n=2138) or paraplegia caused by spinal cord injury (3 studies, total n=142) found that there was moderate evidence supporting use of cannabinoids.

**Nausea/vomiting related to chemotherapy:** Medical marijuana is currently approved for treating nausea in 19 states, and is approved in the District of Columbia for patients undergoing chemotherapy or radiotherapy [5]. Whiting et al. [4] analyzed 28 studies (total n=1772) that have examined the use of cannabinoids (not marijuana) for the treatment of nausea/vomiting related to chemotherapy. These studies were consistent in finding a greater benefit for cannabinoids over either placebo or active comparators such as prochlorperazine or chlorpromazine. However, the overall quality of the evidence supporting medical marijuana for this indication was felt to be low since the majority of studies (23/28) had a high risk for bias, and only 8 included a placebo control.

**Glaucoma:** Medical marijuana is currently approved for treating glaucoma in 19 states and the District of Columbia [5]. Experiments in animals indicate that both synthetic and natural cannabinoids (THC, cannabinol, and nabilone) are able to decrease intra-ocular pressure in rabbits [7]. Older studies of intra-ocular pressure in human subjects suggest that smoking marijuana may have similar effects [8-10]. The recent review by Whiting [4], identified only a single controlled study involving 6 subjects, and found no difference between placebo and cannabinoids on measures of intraocular pressure.

Other indications for which medical marijuana has been approved include: hepatitis C (9 states), Crohn's disease (13 states), Parkinson's disease (5 states), and Tourette's syndrome (2 states), and epilepsy (16 states), and amyotrophic lateral sclerosis (10 states). None of these indications was found by either Whiting et al. [4] or Hill et al. [5] to have high or even moderate quality evidence supporting them.

### Effects in individuals with specific psychiatric disorders:

**Schizophrenia (Or Prodrome):** Cannabis use, especially in adolescents, greatly increases the risk for later development of psychotic disorders, and appears to play a causal role in individuals with high risk genotypes [11]. The psychosis-inducing effects of cannabis are strongest in those with both high-risk genotypes and a history of childhood abuse [12, 13]. Cannabis use also appears to mediate the effect of genetic risk scores (based on a large number of risk alleles for Schizophrenia identified from GWAS studies) on decreased cortical thickness (higher scores were associated with lower thickness only in males who used cannabis) [14].

Studies have also found that cannabis exacerbates psychotic symptoms including positive symptoms, negative symptoms and cognitive deficits in subjects with an established diagnosis of schizophrenia or related disorders [11].

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**Bipolar disorder:** Cannabis use has been associated with more time in affective episodes and increased risk of rapid cycling following first hospitalization for mania [15], and continued cannabis use was associated with increased manic symptoms and lower global functioning in patients with bipolar I disorder 1 year after diagnosis [16]. Cannabis use has also been found to decrease long-term remission rates in patients with both bipolar and schizoaffective disorder [17].

**Post-traumatic stress disorder (PTSD):** medical marijuana is currently approved as a treatment for PTSD in 5 states, however it remains unclear whether cannabis use ameliorates or exacerbates the core symptoms of PTSD. Some evidence of benefit of cannabis use for PTSD symptoms was provided by case reports [18] and from retrospective chart review of patients evaluated for the New Mexico Medical Cannabis Program [19]. However, longitudinal prospective studies of military veterans with PTSD have found that continued cannabis use during treatment is associated with less improvement in core PTSD symptoms of avoidance/numbing and hyper-arousal [20] and conversely, PTSD symptom severity is associated with severity of cannabis withdrawal, and experiences of craving related to compulsive use [21]. Moreover, data presented at the recent American Academy of Addiction Psychiatry (AAAP) Annual Meeting found that cannabis use among veterans was significantly associated with worse outcomes in PTSD symptom severity, violent behavior, and measures of alcohol and drug use [22].

**Substance dependence:** While many patients report that they use cannabis in order to relieve stress or "self-medicate", use of cannabis as a strategy for coping with stress is associated with a higher risk of addiction [23]. The possible role of cannabis as a "gateway drug" increasing the likelihood of abuse/addiction to other substances has been debated for decades. A twin study conducted by Ken Kendler and colleagues [24] found that the majority of the relationship between cannabis and other substance use was due to "correlated genetic and environmental influences with some persisting evidence for some causal influences". More recently, analysis of data from the National Epidemiological Survey on Alcohol and Related Conditions (NESARC) found that 44.7% of individuals with lifetime cannabis use progressed to other illicit drug use at some time in their lives [25]. Risk was highest among subjects with a co-morbid psychiatric disorder.

## Conclusions

The pendulum is of public opinion is clearly swinging away from long-standing prohibitions regarding marijuana use either recreationally or for specific medical indications. For proponents of marijuana legalization, medical marijuana has provided a convenient back door approach to legalization generally. Among some, marijuana use is being embraced as a panacea for a variety of unrelated illnesses, both medical and psychiatric. However, as medical practioners, we owe it to our patients to provide a more balanced view that includes both the limitations and potential risks of medical marijuana. Indications for medical marijuana with moderate to strong evidence from include chronic pain, spasticity related to MS, and nausea/ vomiting related to chemotherapy. Evidence for other indications is much less strong. Current recommendations include trials of standard therapies for these conditions, as well as FDA approved cannabinoids (Dronabinol (Marinol) ($\Delta^9$-THC); FDA approved for nausea/vomiting related to chemotherapy and AIDS associated-anorexia/ weight loss; and Nabilone (Cesamet), a synthetic cannabinoid, FDA approved for nausea/vomiting related to chemotherapy) before initiating treatment with medical marijuana. In addition, prescribers should rule out co-morbid psychiatric and substance use disorders, as marijuana use is associated with worse outcomes for these patients. Finally, as with any medical prescription, prescribers should follow-up with their patients and assess the risks/ benefits of medical marijuana for the condition being treated in an ongoing collaborative way.

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