

## **Medical Marijuana - Evidence, Accepted Indications and Current use**

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### **Introduction**

The use of marijuana (cannabis) for medical indications remains controversial due to limitations in scientific evidence, state and federal restrictions, and legal status of marijuana. As of October 1, 2014, twenty three states and D.C. have enacted laws legalizing medical use of marijuana despite DEA classification of cannabis as a Schedule I drug with no currently accepted medical use and high potential for abuse. Three additional states have pending legislation or ballot measures to legalize medical marijuana. Physicians are caught between growing medical research indicating medical potential for  $\Delta(9)$ -tetrahydrocannabinol (THC) and cannabidiol (CBD) and federal regulations limiting legal prescribing.

In North Carolina, House Bill 1161, introduced on May 20, 2014, if passed would have placed on the Nov. 4, 2014 statewide election ballot, a constitutional amendment to allow the medical use of cannabis. The bill died when the legislature adjourned May 22, 2014, rendering medical marijuana currently illegal in North Carolina. However, a bill was signed and approved by the Governor in June 2014 legalizing the use of CBD oil, an extract from the popular strain of cannabis known as Charlotte's Web for intractable epilepsy in North Carolina.

### **Position Statements of National Medical Associations**

The American Medical Association (AMA) stated in June 2001: "The AMA calls for further adequate and well-controlled studies of marijuana and related cannabinoids in patients who have serious conditions for which preclinical, anecdotal, or controlled evidence suggests possible efficacy and the application of such results to the understanding and treatment of disease..." In November 2013, the AMA reaffirmed its opposition to marijuana legalization, but also called the current federal approach to reducing the drug's use "ineffective" and endorsed a review of the "risks and benefits" of new legal markets in Colorado and Washington. The 2011 position statement by American Society of Addiction Medicine (ASAM) asserts that "cannabis, cannabis-based products and cannabis delivery devices should be subject to the same standards

that are applicable to other prescription medications and medical devices, and that these products should not be distributed to patients unless such products or devices have received marketing approval from the Food and Drug Administration (FDA). ASAM rejects smoking as a means of drug delivery since it is not safe.” In 2013, the American Psychiatric Association (APA) announced its position statement on marijuana clarifying that “there is no current scientific evidence that marijuana is in any way beneficial for the treatment of any psychiatric disorder. In contrast, current evidence supports, at minimum, a strong association of cannabis use with the onset of psychiatric disorders. Further research on the use of cannabis-derived substances as medicine should be encouraged and facilitated by the federal government. If scientific evidence supports the use of cannabis derived substances to treat specific conditions, the medication should be subject to the approval process of the FDA.” A 2004 FDA testimony before the U.S. House of Representatives stated “Simply having access, without having safety, efficacy, and adequate use information does not help patients,” and “FDA will continue to be receptive to sound, scientifically based research into the medicinal uses of botanical marijuana and other cannabinoids.”

## **Synthetic Cannabinoids and Medical Uses**

Preparations of the marijuana plant *Cannabis sativa* has been used for centuries in the treatment of rheumatism, convulsions, pain and other medical indications throughout the world. Of the approximately 60 phytocannabinoids found in cannabis, the two most medically relevant are THC and Cannabidiol (CBD), a cannabinoid extract of botanical cannabis. CBD has been shown to have anti-convulsive, sedative, hypnotic, anti-psychotic, anti-nausea and anti-inflammatory effects.<sup>1</sup>

### Chemotherapy induced nausea and vomiting and AIDS-relating wasting syndromes

Synthetic cannabinoids approved by the FDA since 1985 include the Cannabinoid (CB1) receptor agonists dronabinol (Marinol®) and nabilone (Cesamet®). Dronabinol, a Schedule III controlled substance, is indicated for chemotherapy induced nausea and vomiting and AIDS-related anorexia and wasting, with therapeutic effects lasting up to six hours and onset of action 30 to 60 minutes. Nabilone has therapeutic effects that last up to twelve hours and onset is 60 to 90 minutes. Though synthetic, both THC analogs cause unwanted side effects similar to botanical cannabis, which is associated with euphoria, dysphoria, cognitive slowing and paranoia. Also, the long onset of action and oral preparation is argued to be less favorable to patients as opposed to immediate

onset with inhaled marijuana. A placebo-controlled randomized controlled clinical trial (RCT) found that in HIV-positive marijuana smokers, both dronabinol (at doses 8 times current recommendations) and marijuana [3.9% THC] were well tolerated and produced substantial and comparable increases in food intake."<sup>2</sup>

### Pain syndromes

Several molecular, biochemical and pharmacological studies support the existence of reciprocal interactions between the opioid and endocannabinoid systems, suggesting a common underlying mechanism.<sup>3</sup> Furthermore, these systems are thought to work synergistically to enhance analgesia. Recent reviews have indicated a likely future indication for the use of cannabinoids and opioids in tandem for pain and palliative care as a mode of minimizing adverse effects and tolerance associated with the use of opioids alone for analgesia; however no formal controlled trials support this indication at this time.<sup>4</sup>

The U.S. FDA have expedited a review of *Sativex*®, a medical marijuana spray for the treatment of pain in patients with advanced cancer that is currently in Phase III trials. *Sativex*®, generic name *nabiximols*, is composed of CBD and THC in a mucosal spray that is approved in Canada, Mexico and Europe for the treatment of muscle spasticity caused by multiple sclerosis. Canada also allows the use of *Sativex*® for relief of neuropathic and advanced cancer pain.

Medical marijuana is being used to treat pain associated with a multitude of medical conditions. A recent open-label study found that THC/CBD spray was effective for peripheral neuropathic pain associated with diabetes and allodynia, with half of the patients experiencing at least 30% improvement in pain, in addition to improvement in sleep quality.<sup>5</sup> A controlled trial found smoked marijuana was well tolerated and effectively relieved chronic neuropathic pain associated with HIV concluding its effects were as effective as conventional pain medications.<sup>6</sup> The safety evidence for medical marijuana as a treatment for HIV-associated neuropathic pain and weight loss is mixed, mainly due to concerns that inhaled marijuana may decrease immunity and contribute to opportunistic infections. There is limited evidence for cannabis as treatment for migraines.<sup>7</sup>

### Glaucoma

Cannabinoids in smoked marijuana have been shown to reduce intraocular pressure in humans and suggested a therapeutic role in glaucoma.<sup>8</sup> One limitation of smoked marijuana is that it reduces intraocular pressure for only 3-4 hours, necessitating

smoking 6-8 times a day and increasing risk of adverse effects. Based on available scientific evidence, the American Academy of Ophthalmology Complementary Therapy Task Force found no scientific evidence demonstrating increased benefit and/or diminished risk of marijuana use in the treatment of glaucoma compared with the wide variety of pharmaceutical agents available.<sup>9</sup> The National Institute on Drug Abuse (NIDA) approved the use of botanical cannabis for glaucoma in 1976, which led to a group of patients receiving treatment until 1992 when the FDA's Compassionate Investigational New Drug Study (CIND) program was suspended.<sup>10</sup> The CIND currently supports the treatment of approximately four patients with federally grown medical cannabis for diagnoses including glaucoma, multiple sclerosis, nail patella syndrome and a rare bone disorder.

### Neurological Disorders

Evidence supporting the use of medical cannabis for other neurological disorders is mixed. A recent systematic review concluded that oral cannabis extract, THC and nabiximols were possibly effective for Multiple Sclerosis related spasticity and central pain as well as spasms. Nabiximols was probably effective for bladder spasms, though THC and oral cannabis extract was probably not effective. THC and oral cannabis extract were probably ineffective and nabiximols was possibly ineffective for tremor, and oral cannabinoid extract was probably ineffective for levodopa-induced dyskinesias in Parkinson's disease. The review also concluded Oral cannabinoids are of unknown efficacy in non-chorea-related symptoms of Huntington disease, Tourette syndrome, cervical dystonia, and epilepsy and warned of the serious adverse psychological effects with the use of these medications.<sup>11</sup>

A high concentration CBD: THC strain of cannabis, popularly known as Charlotte's Web, is currently approved for refractory cases of epilepsy in eleven states. This strain gained prominence due to the case study of Charlotte, a 5 year old girl in Colorado with Dravet syndrome, a debilitating gene mutation that contributes to a form of epilepsy which caused her to have over 50 grand mal seizures daily, refractory to conventional anti-epileptic medications. After administering CBD oil in a dose of 4mg CBD/pound per day, Charlotte's seizures decreased to 3 seizures per month.<sup>12</sup> Its popularity and touted efficacy has thousands of patients on waiting lists to obtain the oil, traveling across Colorado state lines to obtain the medicine due to its limited availability and high demand. Although there are no available randomized controlled trials of botanical cannabis in epilepsy, anecdotal and survey evidence suggests that it may benefit patients with epilepsy.<sup>13</sup>

Epidiolex® is a highly purified CBD containing medication containing no THC extracted from botanical cannabis. Epidiolex® has been granted Orphan Drug Designation by the FDA in the treatment of Dravet and Lennox-Gastaut syndromes since November 2013, each of which are severe childhood-onset drug-resistant epilepsy syndromes. It is manufactured by the UK's GW Pharmaceuticals, and is composed of highly purified CBD containing no THC extracted from botanical cannabis. As of October 30, 2014, a worldwide phase 2/3 clinical trial is underway testing the safety and efficacy of Epidiolex® in children and adolescents with Dravet syndrome. Epidiolex® is considered a schedule 1 substance by the FDA and is closely monitored and restricted by both the FDA and U.S. Drug Enforcement Agency.<sup>14,15</sup>

### Psychiatric disorders

There is strong evidence to suggest that frequent cannabis use is an independent risk factor for emergence of psychosis and those with established vulnerability are particularly sensitive to its effects, leading to poor outcome.<sup>16,17</sup> A causal relationship between cannabis and schizophrenia has not been firmly established. Given the association between cannabis use and psychosis, individuals at risk for or suffering from schizophrenia or bipolar disorder should be discouraged from marijuana use.<sup>18</sup> However, GW Pharmaceuticals is currently enrolling patients in the UK and Poland in a phase 2a trial to investigate possible antipsychotic properties of a high potency CBD and low potency THC compound GWP42003 in patients with schizophrenia, noting on their web site "GWP42003 has shown notable anti psychotic effects in accepted pre clinical models of schizophrenia and importantly has also demonstrated the ability to reduce the characteristic movement disorders induced by currently available anti psychotic agents."<sup>19</sup>

Limited evidence from small studies suggests THC may reduce tics and behavioral problems in patients with Tourette syndrome.<sup>20</sup> There is minimal evidence to support use of medical marijuana for symptoms major depressive disorder, bipolar affective disorder, anxiety disorders and PTSD, with some evidence suggesting adverse effects of cannabis on these conditions in adolescents.<sup>21,22,23,24</sup>

While biochemically it is believed that the endocannabinoid system, specifically anandamide, may have implications in the extinction of fear, experts are hesitant to claim botanical cannabinoids in their current medicinal form may be useful as treatment for PTSD.<sup>25</sup> Current research indicates only temporary relief may be obtained for individuals with PTSD using currently available cannabinoids as treatment.<sup>26</sup>

There is insufficient evidence indicating positive effects of medical cannabis on symptoms of depression, however studies indicate significant daily use of marijuana is likely to contribute or exacerbate symptoms of depression.<sup>27</sup> Prospective and retrospective studies have found that marijuana use did not correlate with increased or decreased suicide.<sup>28,29</sup>

There is some pilot data that nabilone may reduce symptoms of marijuana withdrawal, however current evidence to support use of medical marijuana in marijuana, opioid or other substance dependence remains insufficient.<sup>30</sup>

### **Conclusions and Future Directions**

Medicinal use of marijuana may benefit selected cases of refractory chemotherapy-induced nausea and vomiting and AIDS-related wasting syndromes and intractable seizures. There is emerging evidence that medical marijuana may also have a role in specific pain syndromes and neurological disorders. However, in all these conditions, there is a clear need for more efficacy and safety research. Pharmacological studies investigating synthetic cannabinoid compounds that can selectively modulate the endocannabinoid system in humans have increased substantially. This may permit better understanding of the effects of THC and CBD on the individual CB1 and CB2 receptors and can clarify the potential medicinal effects of these chemicals.

The health risks posed by smoking marijuana, challenges of dose administration by smoking, and the negative psychological effects associated with ingesting and smoking botanical cannabis, limit acceptability and safe prescribing by the medical profession. Clinical research in medicinal use of marijuana can improve our understanding of potential positive effects as well as the the risk and safety of the product. Such research can help clinicians, patients, policy makers and the public to make informed decisions regarding the role of medical marijuana.

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