Medical Marijuana: What Do We Know?

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HISTORY

There is evidence that smoke from the plant Cannabis sativa has been inhaled for at least 3,000 years.[1,2] It is generally accepted that the plant was used medicinally by the Chinese about 700 BCE, and Queen Victoria is said to have used cannabis for her menstrual cramps. Starting at the turn of the 20th Century, governments have attempted to place restrictions on the use of cannabis with varying success. In 2004, the United Nations stated that cannabis was the most widely used illicit substance in the world and that approximately 5% of the world's population used the drug regularly with 0.6% (22.5 million) using the drug on a daily basis.[3] The United States Drug Enforcement Agency has designated marijuana a Schedule 1 drug—"the most dangerous class of drugs with a high potential for abuse and potentially severe psychological and/or physical dependence."

PHARMACOLOGY

Almost 300 cannabinoids have been found in *Cannabis Sativa,* of which the most psychoactive is tetrahydrocannabinol (THC). Many synthetic cannabinoids have been produced as well. The existence of specific cannabinoid receptors in the human body was first proposed in the 1940's and was proven conclusively in the 1980's. Although cannabinoids are often thought of in regard to their neuro- and psychoactive effects, cannabinoid receptors are actually widespread throughout the body on cells of the joints, bone, skin, and immune system, as well as on neurons. There are two main receptors: CB_1, found mostly in CNS tissues, and CB_2, in non-CNS locations.

The discovery of receptors was followed by the finding of endogenous cannabinoids in mammalian tissues. Together, the cannabinoid receptors and endogenous cannabinoids constitute what is now called the endocannabinoid system,[4] which is thought to be involved in maintaining homeostasis, particularly in regard to stress, sleep, and modulation of pain.

Upregulation of the endocannabinoid system may cause a reduction in the severity of symptoms or a slowing of the disease's progression in multiple sclerosis, certain types of pain, cancer, schizophrenia, post-traumatic stress disorder, some intestinal and cardiovascular diseases, and traumatic head injury. In contrast, upregulation may also produce undesirable effects in disorders such as impaired fertility in women, obesity, cerebral injury from stroke, endotoxemic shock, cystitis, ileitis and paralytic ileus.

This difference in effect suggests that the specific pathophysiology of the endocannabinoid system might be exploited, which has prompted a search for clinical strategies that would, on the one hand, mimic or augment endocannabinoid-mediated 'auto-protection' and, on the other hand, prevent endocannabinoid-mediated 'auto-impairment.' Solid evidence that this can be done has not yet emerged, but this idea has fueled both scientific and political interest in "medical marijuana."[5]

MEDICALLY USEFUL CANNABINOIDS

THC AND CBD

Attempts to use cannabis for medical purposes have focused on THC and cannabidiol (CBD). The latter is a non-euphoriant, anti-inflammatory analgesic with effects as a CB_1 receptor antagonist and endocannabinoid modulator.[6]

TOXICITY AND SAFETY

THC has very low toxicity, with death from overdose being exceedingly rare, usually after intravenous use of hash oil. However, adverse effects on the liver, lungs, cardiovascular system, and immune system have been reported.[7] Since marijuana smoke contains many of the same carcinogens as tobacco smoke, many studies have examined the possible carcinogenic effects of smoking cannabis. Unfortunately, studies of its adverse effects have necessarily involved its *illicit* use, and suffer from confounding factors in the users' lifestyles that add to its overall risk, including heavy use of alcohol and cigarettes.

ADMINISTRATION

Because of the uncontrolled production of medical cannabis in various preparations (dried for smoking, or in oils to be applied, eaten, or drunk), there can be vastly different concentrations of the cannabinoid compounds in different products, which makes it difficult to predict the response to a particular product. Although smoking remains the most common mode of ingestion for medical cannabis, vaporization via "e-cigarettes" is becoming increasingly popular among medical and recreational users who perceive it to be relatively safe due to the release of a significantly lower percentage of potentially harmful chemicals. The volatility of cannabinoids allows it to vaporize at a much lower temperature than needed for the combustion of plant matter. As a result, when heated air is drawn through cannabis, the active components will aerosolize and can be inhaled without the generation of smoke.

Systemic bioavailability of inhaled THC is 10%–35%, with plasma concentrations peaking within 3–10 minutes, followed by a rapid fall while levels of intoxication are still rising. In contrast, THC absorption after oral ingestion is slow and erratic with serum levels peaking in 45–120 minutes or more. Systemic bioavailability is also quite low due to rapid first-pass hepatic metabolism to 11-hydroxy-THC.[8]

Many patients have a strong preference for smoked marijuana over the synthetic cannabinoids delivered orally.[9] Several reasons for this preference have been suggested: a) the advantages of self-titration with smoked marijuana; b) the difficulty of swallowing pills while experiencing emesis; c) faster speed of onset for inhaled or injected THC compared with oral delivery; d) a combination of the action of other unmeasured cannabinoids that are found in marijuana smoke.

CANNABINOIDS FOR NAUSEA

Considerable evidence demonstrates that manipulation of the endocannabinoid system regulates nausea and vomiting in humans and other animals. CB_1 agonism suppresses vomiting, and animal experiments suggest that cannabinoids may be especially useful for symptoms of nausea and anticipatory nausea in chemotherapy patients who have demonstrated resistance to conventional pharmaceutical agents. A 2011 review of cannabinoids for nausea states, "Although many marijuana users have claimed that smoked marijuana is a more effective anti-emetic than oral THC, no controlled studies have yet been published that evaluate this possibility."[10] Dronabinol and Nabilone are approved in the US for treatment of nausea secondary to cancer chemotherapy (see below). CBD (cannabidiol) has a distinct anti-emetic effect without the intoxicating effects of THC. No controlled clinical trials of CBD have been carried out in humans.

CANNABINOIDS FOR PAIN

Four available oral formulations have been studied for use in pain, especially in patients with multiple sclerosis. The studies have been mostly uncontrolled, with small patient populations Results have been mixed, with MS patients possibly experiencing the greatest efficacy.

AVAILABLE MEDICAL FORMULATIONS

1. Dronabinol: Marketed as Marinol® (Solvay Pharmaceuticals), this drug comes in pill form and was approved by the FDA in 1985 for nausea associated with chemotherapy and in 1992 for appetite stimulation in HIV/AIDS. Dronabinol did demonstrate some effectiveness in at least one study for relief of neuropathic pain in MS.[11] Otherwise, though there are numerous case reports, there have been no well-done studies of dronabinol for pain relief.
2. Nabilone (Cesamet): A synthetic dimethylheptyl analogue of THC that displays greater potency and prolonged half-life, this drug was reapproved by the FDA in 2007 as an anti-emetic in chemotherapy. There have been few studies of Nabilone for pain relief, with one RCT[12] showing a *worsening* of pain when it was used post-operatively. A small study of 9 patients looked at its efficacy for electrically induced pain, axon reflex flare, and psychometric variables. Five of the participants withdrew due to adverse side effects. Although THC had no effect on axon reflex flare, patients' daily recorded pain was significantly reduced.[13]
3. Cannador® (IKF-Berlin) is a cannabis extract that is not available in the U.S. It is administered in oral capsules, with differing figures as to THC:CBD ratios (generally about 2:1). A single RCT in MS patients showed no benefit in spasticity but a small improvement in spasticity-related pain.[14] This drug showed little or no benefit in post-operative pain or post-herpetic neuralgia and showed prominent psychoactive sequelae.[15]
4. Sativex® (GW Pharmaceuticals), approved in Canada and the UK but not in the US, is an

oromucosal whole cannabis-based spray indicated for MS pain and spasticity. It combines a CB1 partial agonist (THC) with a cannabinoid system modulator (CBD), minor cannabinoids and terpenoids, plus ethanol and propylene glycol excipients and peppermint flavoring. In all RCTs, Sativex® was adjunctively added to optimal drug regimens in subjects with intractable symptoms, those often termed "untreatable." A 2007 review of this drug cited 9 studies (largest patient cohort 125) of various kinds of pain with 8 of these showing at least some efficacy.[16] In a study of 58 rheumatoid arthritis patients over 5 weeks, Sativex was associated with significant decreases in the visual analog scale for both pain and anxiety. There were no significant improvements in the placebo group.[17]

SMOKED OR VAPORIZED CANNABIS SATIVA

Very few randomized controlled trials (RCTs) have been conducted using smoked cannabis despite many anecdotal claims of efficacy for a wide range of conditions. Studies of inhaled marijuana are fraught with peril, as self-administration often plays a large role, with the result that study participants may be biased toward a favorable outcome. Smoked cannabis was studied in 168 fibromyalgia patients with a statistically significant reduction in pain and stiffness.[18] Among 457 patients with fibromyalgia, 13% were already using cannabinoids, of whom 80% were using herbal cannabis (marijuana). The investigators concluded, "Although cannabinoids may offer some therapeutic effect, caution regarding any recommendation should be exercised pending clarification of general health and psychosocial problems, especially for those self-medicating."[19]

CANNABIS AND PSYCHOMOTOR IMPAIRMENT

As in nearly all scientific inquiry into cannabis, evidence to support or refute the need for a warning against driving or operating machinery after use of medical cannabis is fraught with political overtones. There is ample evidence that cannabis impairs psychomotor skills, but, unlike data for alcohol, evidence that use of THC significantly impairs driving is not as strong. In experimental conditions cannabis users tend to reduce their driving speed and are less likely to attempt to overtake and pass another vehicle, whereas drunk drivers tend to drive faster and more aggressively.[20] Furthermore, cannabis users tend to overestimate their impairment whereas people who use alcohol underestimate theirs.[21,22] The best evidence about cannabis and motor vehicle crashes comes from modern "culpability studies" in Australia[23] and France,[24] which found that crashed drivers who used cannabis were more likely to have caused the crash than drug- and alcohol-free drivers. However, this risk was relatively small—comparable to that associated with alcohol levels around 0.05%.

SUMMARY

The evidence that cannabis in any form is superior to existing treatments for pain, nausea and vomiting, or spasticity is spotty at best. Evidence for other alleged benefits (seizures, psychiatric disease, etc.) is largely non-existent except for sporadic case-reports. High patient drop-out rates, an inherent tendency for studies to maintain participation of those who find the CNS effects of cannabis to be pleasant, uncontrolled and unknown amounts of compounds in smoked cannabis preparations, and various political agendas both for and against legalization of marijuana, have made conclusive research difficult. It may be a long while before any truly evidence-based conclusions can be drawn.

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Breaking Light
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