Cannabinergic Pain Medicine

A Concise Clinical Primer and Survey of Randomized-controlled Trial Results

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Objectives: This article attempts to cover pragmatic clinical considerations involved in the use of cannabinergic medicines in pain practice, including geographical and historical considerations, pharmacokinetics, pharmacodynamics, adverse effects, drug interactions, indications, and contraindications. Topics include molecular considerations such as the 10-fold greater abundance of cannabinoid type 1 receptors compared to μ-opioid receptors in the central nervous system and anatomic distributions of cannabinoid receptors in pain circuits.

Methods: The article uses a narrative review methodology drawing from authoritative textbooks and journals of cannabinoid medicine, Food and Drug Administration-approved cannabinoid drug labels, and current and historical pain medicine literature to address core clinical considerations. To survey the current evidence base for pain management with cannabinergic medicines, a targeted PubMed search was performed to survey the percentage of positive and negative published randomized-controlled trial (RCT) results with this class of pain medicines, using appropriate search limit parameters and the keyword search string "cannabinoid OR cannabis-based AND pain."

Results: Of the 56 hits generated, 38 published RCTs met the survey criteria. Of these, 71% (27) concluded that cannabinoids had empirically demonstrable and statistically significant pain-relieving effects, whereas 29% (11) did not.

Discussion: Cannabis and other cannabinergic medicines' efficacies for relieving pain have been studied in RCTs, most of which have demonstrated a beneficial effect for this indication, although most trials are short-term. Adverse effects are generally nonserious and well tolerated. Incorporating cannabinergic medicine topics into pain medicine education seems warranted and continuing clinical research and empiric treatment trials are appropriate.

Key Words: cannabis, cannabinoid, endocannabinoid, medical marijuana, descending pain pathways

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The utility of cannabinergic or cannabinoid-based medicines in clinical pain practice is gaining increasing recognition as physicians, other health care practitioners, and drug regulators familiarize themselves with the endocannabinoid signaling system and the safety and efficacy of drugs that target it. *Cannabinioids* are a class of drugs that take their name from the cannabinoid botanical *Cannabis sativa* from which they were first isolated and include herbal preparations of cannabis as well as synthetic, semisynthetic, and extracted cannabinoid preparations. In addition to their millennia-long role in spiritual practice and inebriation, cannabis-based preparations have had an extensive history in pain management,[1] as documented in the *materia medica* of ancient civilizations, including those of India, Egypt, China, the Middle East, and elsewhere.[2] Cannabis-based preparations were produced and sold by numerous major pharmaceutical houses such as Eli Lilly from the mid-1850s to the early 1940s and were significantly utilized during that time in Western medical practice for their analgesic and antispasmodic properties with reported success.[3,4] This is evidenced, for example, by Sir William Osler, MD's recommendation of "*Cannabis indica*" as "probably the most satisfactory remedy" in the treatment of migraine in the first modern textbook of internal medicine in 1892 (the most recent edition of this textbook was published in 2001)[5] and by a nuanced 1887 description of the unique analgesic effects of cannabinoid-based extractions on pain perception published by Penn Clinical Professor Dr Hobart Amory Hare who conducted clinical, animal, and self-experiments: "During the time that this remarkable drug is relieving pain a very curious psychical condition sometimes manifests itself; namely, that the diminution of the pain seems to be due to its fading away in the distance, so that the pain becomes less and less, just as the pain in a delicate ear would grow less and less as a beaten drum was carried farther and farther out of the range of hearing."[6]

For complex political reasons, lack of understanding, and concern over its believed risk of inducing "homicidal mania,"[7–10] cannabis was removed from the United States Pharmacopoeia in 1942[11] and later placed in Schedule I by Congress in 1970,[12] only to be reintroduced into medical practice in the mid-1990s by popular vote and legislative acts, starting in California and gradually over 16 years in 16 states (Alaska, Arizona, California, Colorado, Delaware, Hawaii, Maine, Michigan, Montana, Nevada, New Jersey, New Mexico, Oregon, Rhode Island, Vermont, and Washington) and the District of Columbia, paralleling practices in several other countries. Although contrary to federal law, these state programs have been bolstered by official federal statements of cooperative noninterference by the Veteran's Health Administration (VA)[13] and the US Department of Justice,[14] and all, with the exception of New Jersey, where pain malingering was an overriding political concern, explicitly cite pain relief as an accepted application for which health providers may authorize their patients'

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medicinal use of in-state–produced or in-district–produced cannabinoid botanicals. Although the thousands of practitioners who professionally participate in-state medical cannabis programs[15] are legally protected[16] and maintain DEA registrations in good standing,[17] it must be noted that cannabis and many natural cannabinoids continue to be listed under (the slang term) *marijuana* in the federal Schedule I classification, which substantially restricts research, impedes development of a pharmacy-stocking system needed for in-patient and out-patient empiric treatment trials, and places cannabinoid botanical-using patients at risk for criminal sanction. Professional medical associations and expert study groups such as the Institute of Medicine (IOM), the American Medical Association, and the American College of Physicians, among others,[12] have called for a review of this classification.

Four patients receive cannabinoid botanicals by prescription on an ongoing basis supplied by the federal government as part of a now-closed empiric treatment program involving a federally contracted Mississippi farm and local pharmacies, with 75% of participating patients using the drug for chronic pain.[18] In addition, 2 Food and Drug Administration (FDA)-approved cannabinoids available since 1985, dronabinol (Marinol, Unimed Pharmaceuticals, Marietta, GA)[19] in Schedule III, the naturally occurring (-)trans isomer of delta-9-tetrahydrocannabinol (THC) dissolved in a sesame seed oil soft-gel cap, and nabilone (Cesamet, Valeant Pharmaceuticals North America, Aliso Viejo, CA)[20] in Schedule II, a THC analog, are used off-label by prescription for analgesia in routine clinical practice and research in many countries. Finally, nabiximols (Sativex, GW Pharmaceuticals, Salisbury, England, UK),[21] an oromucoal cannabis-based medicinal extract produced by mixing liquid carbon dioxide extractions of 2 types of herbal cannabis,[22] is currently undergoing FDA-approved phase III clinical trials in the United States for cancer pain refractory to maximal opioid management and has been approved for select pain indications internationally. Some drugs currently in early development seek to prolong or enhance endocannabinoid activity for pain relief.[23]

MATERIALS AND METHODS

By using a narrative review methodology that draws from authoritative textbooks and journals of cannabinoid medicine, FDA-approved cannabinoid drug labels, and current and historical pain medicine literature, the objectives of this article are to cover pragmatic clinical considerations involved in the use of cannabinergic medicines in pain practice, including geographical and historical considerations, pharmacokinetics, pharmacodynamics, adverse effects, drug interactions, indications, and contraindications. Close attention is paid to the oldest and most widespread "signature" cannabinoid botanical medicine, cannabis, and the interaction of its constituents with the endocannabinoid system. In addition, the adverse effects section is covered in greater depth to address clinical safety concerns.

In the latter section of the article, a targeted PubMed search is performed to survey the totality of published randomized-controlled trial (RCT) results for this class of pain medicines. To investigate the current RCT evidence database for cannabinoids in the management of pain, a PubMed search with the keywords "cannabinoid OR cannabis-based AND pain" and the Limits, Type of Article: Randomized Controlled Trial and Species: Human, was performed on December 13, 2010. Trials that investigated other variables, which may have stood as proxies for pain but did not specifically investigate pain, were excluded. Articles were reviewed for significant pain-relieving outcomes with investigated cannabinergic pain medicines.

RESULTS

Pharmacokinetics

Essentially a herbal cannabinoid drug, the resin-secreting flowers of select varietals of the female cannabis plant contain approximately 6 dozen of different *phytocannabinoids* or plant-derived cannabinoids; these compounds are generally classified structurally as terpenophenolics with a 21-carbon molecular scaffold.[24] Other compounds, such as terpenoids, flavonoids, and phytosterols, which are common to many other botanicals, are also produced by cannabis and have some demonstrated pharmacologic properties.[25,26] The best known naturally produced analgesic cannabinoids generally found in highest concentrations are THC and cannabidiol. They occur in their acid forms in herbal cannabis and must be decarboxylated to become activated. Five minutes of heating at 200 to 210°C has been determined as the optimal conditions for maximal decarboxylation; with a flame, where temperatures of 600°C are achieved, only a few seconds are needed.[27]

Cannabis is mainly administered by 3 routes: through the lungs by inhalation of vaporized or smoked organic plant material; through the gut with ingestion of lipophilic, alcoholic, or supercritical fluidic extracts of plant material, or through the skin by topical application of plant extracts.[28] Each of these routes has a distinct absorption and activity time course. Lung administration is akin to an IV (intravenous) bolus, with passive diffusion into alveolar capillaries and rapid onset in seconds to minutes, achieving maximal effect after 30 minutes, and lasting 2 to 3 hours in total. With oral administration of cannabinoid medicines, including cannabis-based medicinal extracts and single cannabinoid pills, the absorption is somewhat more variable, depending on gastric contents, with a slower onset of action of 30 minutes to 2 hours, and a longer, more constant, duration of action, over 5 to 8 hours in total. Little data are available on the pharmacokinetics of topically administered cannabinoids.[29]

THC and its metabolites are lipophilic compounds and their tissue distribution is governed by their physiochemical properties. In the plasma, about 95% to 99% of THC is bound to plasma proteins, primarily lipoproteins. Metabolism of THC occurs quickly, mainly in the liver by hydroxylation, oxidation, and conjugation through the cytochrome P-450 complex, specifically CYP2C9 and CYP3A.[30] The majority is rapidly cleared from the plasma, with 70% taken up by tissues, especially highly vascularized ones, and 30% converted by metabolism. First-pass liver metabolism occurs in oral administration, and a greater proportion of 11-OH-THC, a key active metabolite, is produced compared with that which occurs in pulmonary administration. As far as complete elimination is concerned, it occurs over several days given the slow rediffusion of THC from body fat and other tissues, with body fat being the major long-term storage site of THC and its biometabolites. In the perinatal setting, cannabinoids distribute into the breastmilk of lactating mothers (where endocannabinoids are also found in appreciable quantities[31]) and diffuse across the placenta (Pregnancy Category C). Excretion of THC occurs within days and weeks, mainly as metabolites, with approximately 20% to

35% found in urine and 65% to 80% found in feces, and < 5% as unchanged drug, when administered per os.[29]

Pharmacodynamics

The majority of the effects of THC are mediated through its partial agonism of cannabinoid receptors. Of relevance for pain management, in addition to analgesia, the following dose-dependent pharmacologic actions of THC have been observed in studies: muscle relaxation, anti-inflammatory effects, neuroprotection in ischemia and hypoxia, enhanced well-being, and anxiolysis.[32] To understand how this range of effects is possible, an understanding of cannabinoid molecular biology is needed.

Cannabinoids produce analgesia through supraspinal, spinal, and peripheral modes of action, acting on both ascending and descending pain pathways. Their mechanism of action was only recently understood with the discovery of the endogenous cannabinoid (or endocannabinoid) system, a 600 million-year-old signaling system in evolution,[33,34] which regulates neuronal excitability and inflammation[35] in well-described pain circuits and cascades.[36–39] The endocannabinoid system helps regulate the function of other systems in the body, making it an integral part of the central homeostatic modulatory system. It has been shown to play a regulatory role in movement, appetite, aversive memory extinction, hypothalamic-pituitary-adrenal axis modulation, immunomodulation, mood, blood pressure, bone density, tumor surveillance, neuroprotection, reproduction, inflammation, among other actions.[23,40] Studies in animals and humans that have assessed preexposure and postexposure endocannabinoid levels have suggested that the "runner's high,"[41] the effects of osteopathic manipulative treatment,[42,43] and the effects of electroacupuncture[44] are mediated by the endocannabinoid system.

The endocannabinoid system consists of receptors, their endogenous ligands, and ancillary proteins.[45] Cannabinoid receptors, CB_1 and CB_2, and likely others, are transmembrane G-protein–coupled receptors whose activation is negatively coupled to adenylyl cyclase and positively coupled to mitogen-activated protein kinase. In neural tissue, their activation suppresses neuronal Ca^{2+} conductance, activates inward rectifying K^+ conductance, and thus modulates neuronal excitability.[46] An adjective for anything that drives or stimulates this system is "cannabinergic."

The CB_1 receptor is the most highly expressed G-protein–coupled receptor in the brain and is 10 times more prevalent in the central nervous system as compared to the other well-studied receptor involved in pain: the μ-opioid receptor.[47] Among many other tissues, cannabinoid receptors have been found in abundance on cells in areas relevant to pain: the periaqueductal gray, basal ganglia, cerebellum, cortex, amygdala, hippocampus, dorsal primary afferent spinal cord regions, including peripheral nociceptors, spinal interneurons, and finally inflammatory cytokine-releasing immune cells.[46,47] In the brainstem, cannabinoid receptor expression is low, accounting for the lack of respiratory depression and absence of fatal overdose with cannabinoid drugs.[48]

Endocannabinoids such as arachidonylethanolamide (anandamide) and 2-arachidonylglycerol, and others, serve as tonically active retrograde synaptic neurotransmitters, meaning that they travel "backwards" across the synaptic cleft from postsynaptic to presynaptic neurons, thereby providing feedback that, in turn, directly upregulates or downregulates the release of other presynaptic neurotransmitters, such as gamma-aminobutyric acid, dopamine, norepinephrine, glutamate, and others.[32] This feedback has physiological implications for a host who may have succumb to insult or injury leading to pain.[49] Experiments have also shown that the endocannabinoid system is upregulated in animal models of nerve damage [50] and intestinal inflammation.[51] Ultimately, while there is much that is still poorly understood, the known pharmacodynamics of cannabinergic analgesic effects have been established through carefully designed experiments observing the physiological or radiologic effects of natural and synthetic exogenously administered cannabinoids in clinical and laboratory animal models and the blockade of those effects by genetic or pharmacological means.

Adverse Effects

The main adverse effects of cannabinoids to focus on presently are those that may arise with use of these drugs in a medical context rather than in a nonmedical setting; however, since there are far less data on the use of the drugs in the former setting, the latter, though less ideal, must be relied upon as well. Given cannabinergic drugs' psychoactive properties, adverse effects to consider would include overdose, abuse, dependence, psychomotor effects, cognitive effects, and adverse medical and psychiatric effects, both short and long term. Generally, as analgesics, cannabinoids have minimal toxicity and present no risk of lethal overdose.[48] End-organ failure secondary to medication effect has not been described and no routine laboratory monitoring is required in patients taking these medications. With regard to cannabinoid botanicals, the IOM concluded after a comprehensive government-commissioned review published in 1999 that "except for the harms associated with smoking, the adverse effects of marijuana [cannabinoid botanicals] use are within the range of effects tolerated for other medications."[52]

The FDA-approved product insert for dronabinol, the THC pill, reports the following adverse effects from overdose:

Signs and symptoms following MILD MARINOL Capsules intoxication include drowsiness, euphoria, heightened sensory awareness, altered time perception, reddened conjunctiva, dry mouth and tachycardia; following MODERATE intoxication include memory impairment, depersonalization, mood alteration, urinary retention, and reduced bowel motility; and following SEVERE intoxication include decreased motor coordination, lethargy, slurred speech, and postural hypotension. Apprehensive patients may experience panic reactions and seizures may occur in patients with existing seizure disorders.[19]

Regarding the dependence potential of THC and cannabinoid drugs, the IOM concluded that "Although few marijuana [cannabinoid botanicals] users develop dependence, some do. Risk factors…are similar to those for other forms of substance abuse. In particular, antisocial personality and conduct disorders…" With regard to withdrawal, although still a matter of dispute, the IOM concluded: "A distinctive marijuana [cannabinoid botanicals] withdrawal syndrome has been identified, but it is mild and short-lived. The syndrome includes restlessness, irritability, mild agitation, insomnia, sleep EEG disturbance, nausea, and cramping."[52]

The IOM report also discussed the adverse effects of cognitive and psychomotor impairment associated with acutely administered cannabinoid botanicals, although it did not take into consideration the possibility of tolerance

or preparation variability in modifying these effects. "The types of psychomotor functions that have been shown to be disrupted by the acute administration of marijuana [cannabinoid botanicals] include body sway, hand steadiness, rotary pursuit, driving and flying simulation, divided attention, sustained attention, and the digit-symbol substitution test." Given the concern for occurrence these adverse effects and that of cognitive impairment, which has been characterized as transient short-term memory interruption (see above MARINOL product insert), the panel recommended that "no one under the influence of marijuana [cannabinoid botanicals] or THC should drive a vehicle or operate potentially dangerous equipment."[52]

Another important source of adverse effects data is cannabinoid clinical trials; 2 reviews are summarized below. A 2008 review of reported adverse effects of medical cannabinoids[53] examined 31 clinical trials (23 RCTs and 8 observational studies) of cannabinoid single-molecule agents and cannabis-based medicinal extracts but not cannabinoid botanicals (due to the fact that such studies did not report adverse events in the standardized format investigators sought) in various patient populations and showed that the vast majority of adverse events with cannabinoid medications in clinical trials were nonserious (96.6%). In the 23 RCTs, the median duration of cannabinoid exposure was 2 weeks (range, 8 h to 12 mo). With respect to the "164 serious adverse events" that occurred, the most common were relapse of multiple sclerosis (21 events [12.8%]), vomiting (16 events [9.8%]), and urinary tract infection (15 events [9.1%]). However, investigators reported that "there was no evidence of a higher incidence of serious adverse events" in the groups assigned to cannabinoids "compared with control [drugs] (rate ratio [RR] 1.04, 95% confidence interval [CI], 0.78-1.39)."[53] In addition, serious adverse events were not evenly reported in the literature, with 99% coming from only 2 trials. The most commonly reported nonserious adverse events were dizziness (714 events [15.5%]), followed by somnolence (377 events [8.2%]), muscle spasm (289 events [6.3%]), other gastrointestinal tract disorder (285 events [6.2%]), pain (278 events [6.0%]), dry mouth (239 events [5.2%]), and bladder disorder (222 events [4.8%]). Unlike the serious adverse events, the rate of nonserious adverse events was nearly 2 times higher among participants assigned to cannabinoids than among controls (rate ratio [RR] 1.86, 95% CI, 1.57–2.21).

A more recent 2011 systematic review of RCTs of cannabinergic medicines specifically for the treatment of pain which pooled 18 trials of inhaled cannabinoid botanicals, oromucosal cannabis-based medicinal extracts, and cannabinoid single-molecule agents involving 766 patients in total found no occurrence of serious adverse events, with the most serious treatment-related event in the entire sample being a subject's fractured leg related to a fall that was thought to be related to dizziness in a treatment trial with nabilone. Nonserious adverse events most frequently reported included "sedation, dizziness, dry mouth, nausea and disturbances in concentration" and less commonly reported adverse events included "poor coordination, ataxia, headache, paranoid thinking, agitation, dissociation, euphoria and dysphoria." Investigators noted: "Adverse effects were generally described as well tolerated, transient or mild to moderate and not leading to withdrawal from the study. This is a significant difference from the withdrawal rates seen in studies of other analgesics such as opioids where the rates of abandoning treatment are in the range of 33%."[54]

With regard to severe psychiatric sequalae such as psychosis, if a very large dose of cannabinoid botanicals is consumed, which typically occurs through oral ingestion of a concentrated preparation, agitation and confusion, progressing to sedation, generally results.[55] This is self-limited and generally disappears entirely once the psychoactive components are fully metabolized and excreted. Some have called this an "acute cannabis psychosis," and this generates concern that cannabinoid use, in the long term, might lead to schizotypy such as chronic, debilitating psychosis. There is some documentation of a syndrome of acute schizophreniform reactions to cannabinoid botanicals that may occur in young adults who are under stress and have other vulnerabilities to schizophreniform illness. Furthermore, there is an association between cannabinoid botanicals use history and schizophrenia, but the causal direction of this link has not been established[56,57] and schizophrenia prevalence rates have not changed over the last 50 years despite increasing use rates of cannabis in the general population.[58]

Recent preliminary work has examined gene-environment interactions to identify the genetic background of populations at-risk for this cannabinoid-associated psychosis with retrospective, population-based studies, and empiric cannabinoid drug exposure studies, with candidate genes including a commonly studied functional polymorphism in the catechol-O-methyltransferase gene (COMT Val(158)Met)[59] and a brain-derived neurotrophic factor gene polymorphism (BDNF Val(66)Met),[60] among others. Given these risks, cannabinoid medical use should be closely monitored or potentially avoided in early teens or preteens who have preexisting symptoms of mental illness or patients with significant family or personal history of mental illness.

For physiological and pharmacological reasons,[61] smoking cannabinoid herbals does not seem to have a similar health hazard profile as tobacco smoking, aside from the potential for bronchial irritation and bronchitis. Smoking cannabis was not associated with an increased risk of developing chronic obstructive pulmonary disease (COPD) in a random sample of 878 people aged 40 years or older living in Vancouver, Canada who were surveyed about their respiratory history and lifetime cannabis and tobacco use exposure and subjected to spirometric testing before and after administration of 200 μg of salbutamol, a short-acting β2-receptor agonist. Investigators concluded that smoking both tobacco and cannabis synergistically increased the risk of respiratory symptoms and COPD but that smoking only cannabis was not associated with an increased risk of respiratory symptoms or COPD.[62] This finding was also confirmed in a recently published longitudinal study involving spriometric testing over a period of 20 years. Researchers followed more than 5000 people in several major American cities over 2 decades and found that the exposure equivalent of moderate inhalation of cannabinoid botanical smoke daily for 7 years did not impair spirometric-testing performance.[63]

With regard to the question of lung cancer risk, a variety of opinions and conflicting results are found in the literature, likely related to study sizes, designs, and confounding factors in existing research. However, the results of 2 well-designed, large studies conducted by senior investigators in this field are worth noting. A recent large, population-based retrospective case-control study involving

1212 incident cases of lung and upper aerodigestive tract cancer and 1040 cancer-free age-matched and gender-matched controls in the Los Angeles area demonstrated significant, positive associations with tobacco-smoking history and the incidence such cancers but failed to demonstrate any significant positive associations or dose dependence with cannabis-smoking history and the incidence of such cancers. In fact, a significant, albeit small, protective effect was demonstrated in 1 group of smoked cannabis consumers.[64] A second population-based case-control study involving smoked cannabis use and head and neck squamous cell carcinoma with 434 cases and 547 age-matched, gender-matched, and geographically matched controls in the greater Boston area similarly concluded that moderate cannabis use is associated with reduced risk of head and neck squamous cell carcinoma.[65] These 2 studies, while large and sensitive to confounders, need replication. Certainly, although hundreds of citations can now be found in the National Library of Medicine of studies demonstrating antitumor properties of cannabinoids in numerous tissue types in mostly lab settings, some of which are also reviewed on an online clinical knowledge database maintained by the National Cancer Institute,[66] the inhalation of fumes, combustion byproduct particulate matter, and polycyclic aromatic hydrocarbons attendant with inhaled cannabinoid botanical smoke can nevertheless be noxious for some patients and the use of vaporizers for lung administration should be encouraged. Heated air can be drawn through cannabinoid herbal matter and, due to the volatility of cannabinoids, which allows them to vaporize at a temperature much lower than actual combustion of plant matter, active compounds will vaporize into a fine mist which can then be dosed and inhaled without the generation of smoke.[67]

As to questions of overall adverse effects of long-term cannabinoid treatment in medical settings, there are essentially no long-term controlled longitudinal studies in such populations, with the exception of one 3-decade old, prospective, federally funded inhaled cannabinoid botanical clinical study mentioned previously in the Introduction section. Administered by the National Institute on Drug Abuse and FDA and now involving only 4 chronically ill patients, this study, now closed to new enrollment, has never systematically collected or disseminated clinical response data. One independent comprehensive health assessment in 2001 of 4 of the then 7 enrolled patients showed "mild changes in pulmonary function" in 2 patients and no other demonstrable adverse outcomes or "functionally significant attributable sequelae" based on a battery of tests, which included: magnrtic resonance imaging scans of the brain, pulmonary function tests, chest x-ray, neuropsychological tests, hormone and immunological assays, electroencephalography, P300 testing, history, and neurological clinical examination.[68]

Drug Interactions

Research suggests that when THC is coadministered with cannabidiol, as can occur with the usage of some strains of herbal cannabinoid medicines and certain cannabis-based extractions, the anxiogenic, dysphoric, and possibly short-term memory interrupting effects of THC are mitigated.[69,70] In addition, noncannabinoid components in cannabinoid botanicals such as terpenoids can also help to mitigate THC side effects.[71] There is increasing evidence suggesting that cannabinoid drugs can enhance the analgesic activity of opioids,[72,73] and thereby their concomitant use may reduce the dosages of opioids that chronic pain patients take.[74,75]

With the large number of individuals who have used cannabinoid botanicals concomitantly with numerous prescription medicines, no unwanted side effects of clinical relevance have been described in the literature to date. Nevertheless, cannabinoid medicines should be used with caution in patients taking other sedating psychotropic substances such as alcohol and benzodiazepines. Again, from the FDA-approved dronabinol product insert:

In studies…MARINOL Capsules has [sic] been co-administered with a variety of medications (e.g., cytotoxic agents, anti-infective agents, sedatives, or opioid analgesics) without resulting in any clinically significant drug/drug interactions…cannabinoids may interact with other medications through both metabolic and pharmacodynamic mechanisms. Dronabinol is highly protein bound to plasma proteins, and therefore, might displace other protein bound drugs. Although this displacement has not been confirmed in vivo…[19]

Indications

Indications mentioned below are bolded. A 2010 review counted at least 110 controlled clinical studies of cannabis or cannabinoids conducted around the world, mostly outside the United States, involving over 6100 patients investigating a wide range of conditions.[76] With regard to pain indications, cannabinoids are best researched clinically for their role in the management of **neuropathic pain**, but **malignant pain**, **other chronic pain syndromes**, especially those involving **hyperalgesia** and **allodynia**, as well as **acute pain** applications have also been described.[77]

Two recent systematic reviews of cannabinergic medicines for pain are worth mentioning. A 2011 systematic review of cannabinoids for treatment of chronic noncancer pain[54] analyzed studies of neuropathic pain, fibromyalgia, rheumatoid arthritis, and mixed chronic pain syndromes. In all, 18 cannabinoid RCTs, 4 of which tested inhaled cannabinoid botanicals, conducted from 2003 to 2010, involving 766 participants in total, with a mean duration of treatment of 2.8 weeks (range, 6 h to 6 wk), were reviewed. Investigators noted that "overall the quality of trials was excellent," with mean score of 6.1 on the 7-point modified Oxford scale [scores randomization (0-2), concealment of allocation (0-1), double blinding (0-2), and flow of patients (0-2)] and that "15 of the 18 trials that met inclusion criteria demonstrated a significant analgesic effect of cannabinoid as compared with placebo" with 4 also reporting "significant improvements in sleep." They concluded: "overall there is evidence that cannabinoids are safe and modestly effective in **neuropathic pain** with preliminary evidence of efficacy in **fibromyalgia** and **rheumatoid arthritis** [emphasis added]". Investigators also observed that in the trials involving cannabinergic medicines in rheumatoid arthritis, "a significant reduction in disease activity was also noted, [and] this is consistent with preclinical work demonstrating that cannabinoids are anti-inflammatory." In addition, authors made special mention of the fact that 2 of the trial examining smoked cannabinoid botanicals demonstrated a significant analgesic effect in **HIV neuropathy**, "a type of pain that has been notoriously resistant to other treatments normally used for neuropathic pain."

A 2009 systematic review and meta-analysis counted 229 studies that had used cannabinoids on people with pain from 1975 to February 2008, with 18 of these having a

double-blind, randomized-controlled design. A meta-analysis with 7 of these trials, which included 6 with cross-over and 1 with parallel design and included a total of 142 pooled patients with **malignant pain**, **multiple sclerosis**, and **chronic upper motor neuron syndromes**, concluded that a statistically significant standardized mean difference favoring cannabinoids over placebo existed, −0.61 (−0.84 to −0.37), measured in terms of the change from the baseline (0) intensity of pain, with all studies yielding results in the same direction and with no statistical heterogeneity.[78]

Chart reviews can also suggest potential indications for cannabinergic pain medicines. An uncontrolled retrospective chart review conducted by this author and colleagues of 139 patients at a pain sub-specialty clinic who were authorized to use cannabinoid botanicals medicinally for a total of 236.4 patient-years found a variety of chronic pain syndromes, in accord with existing cannabinoid literature, being managed in this population (Table 1). Eighty-eight percent of the patients in the study had more than 1 type of chronic pain syndrome.[74]

To investigate the current published, randomized-controlled clinical trial (RCT) evidence database indexed in the National Library of Medicine for cannabinoids in the management of pain, a PubMed search was performed as described in the Materials and Methods section. Fifty-six hits were generated, and of these, 38 were actual RCTs of various cannabinoid medicines such as dronabinol, nabilone, cannabinoid herbals, cannabinoid-based medicinal extracts, and other synthetic cannabinoids versus placebos or other drugs in which pain efficacy was specifically assessed, either in patients with pain or healthy subjects with experimentally induced pain. Eighteen studies were excluded because they did not explicitly examine pain outcomes and instead examined spasticity, cramps, or a nonspecific global measure of benefit. Perusing abstracts and in case of ambiguity, full articles, of the 38 RCTs that met inclusion criteria, 27 (71%) concluded that cannabinoids had empirically demonstrable pain-relieving effects,[73,79–104] whereas 11 (29%) did not.[105–115] Of the 11 negative studies, 3 investigated postoperative pain, 3 experimentally induced pain in healthy volunteers, 1 neuropathic pain in spinal cord injury, 2 pain in multiple sclerosis, 1 central neuropathic pain in brachial plexus avulsion, and 1 painful diabetic peripheral neuropathy. The 27 positive RCTs, the largest of which enrolled 630 subjects,[103] investigated a variety of pain syndromes (Table 2), all of which could be considered as potential pain indications for this class of drugs.

TABLE 1. Diagnosed Chronic Pain Syndromes Documented in Cannabinoid Botanical Use-authorized Patient Series (n = 139)[74]

Chronic Pain Syndrome	Frequency of Occurrence* (%)
Myofascial pain	82
Neuropathic pain	64
Discogenic back pain	51.7
Osteoarthritic pain	26.6
Central pain syndrome	23
Fibromyalgia	14
Visceral pain	10
Spinal cord injury	6
Rheumatoid arthritis	4
Diabetic neuropathy	4
Malignant pain	4
Phantom pain	1
HIV neuropathic pain	1

*Eighty-eight percent of the patients in the study had more than one type of chronic pain syndrome.
HIV indicates human immunodeficiency syndrome.

Contraindications

Cannabinoids are absolutely contraindicated in patients who have a rare hypersensitivity to THC or allergies to any of the inert materials with which cannabinoid medicines may be formulated. There is some concern in the basic science literature that cannabinoid's immunomodulatory properties through CB_2 activity can cause a shift from T_h1 to T_h2 type activity and that this might have severe consequences for a patient who is fighting an infection (such as *Legionella*) that requires T_h1 immunity activity for inhibition.[116,117] In these settings, cannabinoids should be used with caution. Early concern in the 1990s regarding the use of cannabinoids in HIV patients given possible immunomodulatory effects in already-immunosuppressed patients was addressed by Abrams et al's[118] randomized-controlled inpatient clinical trial with inhaled cannabinoid botanicals which showed no reduction in viral load or CD4 cell count in HIV patients. This conclusion was also recently bolstered in a primate study showing that SIV (simian immunodeficiency virus) viral loads in a cohort of rhesus macaques were not adversely affected by daily THC administration over a 6-month period, and in fact were associated with decreased early mortality, reductions in SIV viral load, and improvements in the ratio of CD4 to CD8 cells.[119] Finally, as mentioned previously, cannabinoids should be used cautiously in patients with a personal or family history of psychosis, with particular attention paid to adolescent patient populations under psychosocial stress who may be at increased risk for developing psychosis.

DISCUSSION

Cannabinergic pain medicine is an emerging field of pain practice that incorporates new and old cannabinoid pharmacotherapies with a clinically relevant physiological understanding of endocannabinoid signaling. By drawing from current and authoritative sources, this review concisely addressed relevant clinical considerations, including historical and geographical context, pharmacokinetics, pharmacodynamics, adverse effects, drug interactions, indications, and contraindications for utilization of this class of pain medicines. A focused PubMed literature survey, which was meant to be easily reproducible and to serve as a guide to evidence-based clinical practice queries, showed that there are over 30

TABLE 2. Descriptors of Pain Syndromes Investigated in Positive Outcome Randomized-controlled Trials of Cannabinoids[73,79–104]

Experimentally induced pain in healthy volunteers	Chronic pain in rheumatoid arthritis
Unspecified chronic noncancer pain	Chronic pain in multiple sclerosis
Chronic pain secondary to chronic upper motor neuron syndrome	Chronic neuropathic pain with hyperalgesia and allodynia
Cancer-related pain	Chronic neuropathic pain related to HIV, trauma, surgery, and CRPS
Chronic pain in fibromyalgia	

CRPS indicates complex regional pain syndrome; HIV, human immunodeficiency syndrome.

published RCTs indexed in the National Library of Medicine that have evaluated specific cannabinoid medications for strict pain indications, and nearly 3-quarters of these studies are positive and statistically significant.

An overall review of adverse effects from reviews of cannabinoid clinical trials and other sources does show that short-term use of existing cannabinoid medicines seems to increase the risk of nonserious adverse events, but in general these events are modest and well tolerated. Little data are available on the risks associated with long-term medical use in published clinical trials. Overall, based on the existing clinical trials database, cannabinergic pain medicines have been shown to be modestly effective and safe treatments in patients with a variety of chronic pain conditions, with more data for analgesia in noncancer pain than cancer-related pain available. Neuropathic pain is an indication for which cannabinoid botanicals seem to have a stronger evidence base. However, most studies are of short trial duration and enrolled small sample sizes. High-quality trials of cannabinergic pain medicines with large sample sizes, long-term exposure, including head-to-head trials with other analgesics, focused on pain relief and functional outcomes, are needed to further characterize safety issues and efficacy with this class of medications.

Nevertheless, for notoriously difficult to treat conditions such as HIV neuropathy, which significantly affects approximately 40% of HIV-infected individuals treated with antiretroviral therapies,[120] cannabinergic pain medicines, particularly inhaled cannabinoid botanicals, are one of the only treatments that have been shown to be safe and effective with the highest level of evidence. This was shown in a 2011 systematic review and meta-analysis of prospective, double-blinded RCTs investigating the pharmacological treatment of painful HIV sensory neuropathy. When analyzing he 14 trials which fulfilled the inclusion criteria, investigators found that the only interventions demonstrating greater efficacy than placebo were smoked cannabis, number needed to treat (NNT) 3.38, 95% CI (1.38-4.10); topical capsaicin 8% with a presumed NNT of 6.46, 95% CI (3.86-19.69); and recombinant human nerve growth factor, with no NNT calculable. No superiority over placebo was reported in RCTs that examined amitriptyline (100 mg/d), gabapentin (2.4 g/d), pregabalin (1200 mg/d), prosaptide (16 mg/d), peptide-T (6 mg/d), acetyl-L-carnitine (1 g/d), mexilitine (600 mg/d), lamotrigine (600 mg/d), and topical capsaicin (0.075% q.s.).[121]

CONCLUSIONS

The positive clinical evidence base for cannabinergic pain medicine is explained by extrapolating from an understanding of the properties and mechanism of action of these drugs derived from extensive basic science research. Cannabinoids have been shown to inhibit pain in "virtually every experimental pain paradigm" in supraspinal, spinal, and peripheral regions.[37] That cannabinergic therapeutics are of great interest in the field of pain medicine currently is evidenced in large part by the numerous review articles that have been published recently on this topic in pain and therapeutics journals and the recent convening of a "Cannabinoids and Pain" Satellite Symposium of the 13th World Congress on Pain held in Montreal, Canada in July 2010.

The limitations of this review article are that it did not exhaustively cover the cannabinoids and pain literature or all clinical details such as those regarding cannabinoid dosing, nor did it address the ongoing controversies regarding the implementation of medical marijuana programs in the United States or the necessary policy debates involved in the rescheduling of cannabis for general prescription use as an FDA-unapproved drug. In addition, the focused PubMed search was only targeted at determining the percentage of RCTs indexed in the National Library of Medicine showing efficacy for cannabinergic medications for pain and did not fully evaluate the pros and cons of each study. Nevertheless, by focusing on practical clinical considerations and drawing on established literature, including published systematic reviews and meta-analyses, attempts were made to compensate for these limitations. The implications of this study are that, with proper clinical education, the use of cannabinergic medicines could become one more needed tool in the pain physician's toolbox, with further research, clinical experience, and empiric treatment trials needed to better develop, improve, and expand these therapies.

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