Cannabinoid Analgesia as a Potential New Therapeutic Option in the Treatment of Chronic Pain

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OBJECTIVE: To review the literature concerning the physiology of the endocannabinoid system, current drug development of cannabinoid agonists, and current clinical research on the use of cannabinoid agonists for analgesia.

DATA SOURCES: Articles were identified through a search of MEDLINE (1966–August 2005) using the key words cannabis, cannabinoid, cannabi*, cannabidiol, nabilone, THC, pain, and analgesia. No search limits were included. Additional references were located through review of the bibliographies of the articles identified.

STUDY SELECTION AND DATA EXTRACTION: Studies of cannabinoid agonists for treatment of pain were selected and were not limited by pain type or etiology. Studies or reviews using animal models of pain were also included. Articles that related to the physiology and pharmacology of the endocannabinoid system were evaluated.

DATA SYNTHESIS: The discovery of cannabinoid receptors and endogenous ligands for these receptors has led to increased drug development of cannabinoid agonists. New cannabimimetic agents have been associated with fewer systemic adverse effects than delta-9-tetrahydrocannabinol, including recent development of cannabis medicinal extracts for sublingual use (approved in Canada), and have had promising results for analgesia in initial human trials. Several synthetic cannabinoids have also been studied in humans, including 2 cannabinoid agonists available on the international market.

CONCLUSIONS: Cannabinoids provide a potential approach to pain management with a novel therapeutic target and mechanism. Chronic pain often requires a polypharmaceutical approach to management, and cannabinoids are a potential addition to the arsenal of treatment options.

KEY WORDS: analgesia, cannabinoids, chronic pain.

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It has been estimated that chronic pain affects 86 million Americans and costs about $90 billion annually in reduced employment, medication expenses, and medical care.[1] Just over one-half of patients who report chronic pain feel that their pain is under control.[2] There is a need for additional treatment options for these people, as many suffer from intractable pain that is not relieved by current treatment modalities. Many other people are unable to tolerate current treatment options, such as opioids and nonsteroidal antiinflammatory drugs (NSAIDs). This is a review of recent information regarding an approach to pain management using novel pharmacologic targets and mechanisms.

Cannabis-based medicines have recently been studied for a variety of uses including treatment of the pain and spasticity associated with multiple sclerosis, control of nausea and vomiting, appetite stimulation, and analgesia.[3-6] Interest in cannabinoid agonists has increased since the isolation of specific cannabinoid receptors and endogenous ligands for these receptors. Cannabis has had a long history of use both recreationally and medicinally, but has faced increasing opposition as a medicinal agent.[7] Drug development has recently focused on synthetic cannabinoid agonists that have more favorable adverse effect profiles than cannabis.[8]

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History of Cannabis-Based Medicine

Cannabis has been used anecdotally for more than 5000 years to treat a variety of conditions including hysteria, delirium, insomnia, nausea, anorexia, glaucoma, and pain.[7,8] At the turn of the 20th century, cannabis was being prescribed in the US and Europe to treat pain, pertussis, asthma, gastrointestinal disorders, Grave's disease, anorexia, diarrhea, and malaria, and as a sedative.[7] By the mid-20th century, however, pharmaceutical products to treat most of these conditions replaced the use of cannabis. The Controlled Substances Act of 1970 classified cannabis as a Schedule I drug, which classified marijuana as a drug with no medicinal value.[9]

In recent years, there has been renewed interest in the use of cannabis for medicinal purposes, including passage of referenda in California, Arizona, Oregon, Nevada, Maine, Hawaii, Montana, Vermont, Colorado, Alaska, and Washington, to allow the use of marijuana for medicinal purposes.[10] Although recent legislation has allowed prescription of marijuana for select patients, many practitioners are reluctant to recommend its use due to intense scrutiny by the federal government. The state referenda, such as Proposition 215 in California, prevent patients from being prosecuted for possession or use of marijuana as treatment for a serious medical illness. Proposition 215 also protects physicians who recommend medical use of marijuana from punishment or loss of privileges.[11]

Identification of the active component of marijuana and specific cannabinoid receptors in humans has sparked a flurry of research and drug development. The primary active component of marijuana, delta-9-tetrahydrocannibinol (THC), is responsible for most of its common effects, including its psychoactive effects. THC was identified in 1964.[12] Cannibidiol (CBD), another major cannabanoid component of marijuana that is thought to have antioxidant and antiinflammatory properties without the psychoactive effects of THC, was identified in 1934.[13] Today, a total of 483 natural components of marijuana have been identified, including 66 cannabinoids.[7] Cannabigerol, cannabichromene, delta-8-tetrahydrocannabinol, cannabinol, and cannabinodiol are the other major cannabinoids identified in marijuana; however, their activity profiles have not yet been clarified.[7]

Cannabis-based medicines are a particularly attractive prospect because of the favorable safety profile of cannabis and cannabinoids. The dose to produce lethal effects in 50% of recipients of oral THC in rats has been found to be 800–1900 mg/kg.[14] Researchers reported no deaths with oral doses up to 3000 mg/kg in dogs and 9000 mg/kg in monkeys.[14] Additionally, there have been no reported deaths directly attributed to cannabis overdose.[8]

Development of an appropriate dosage form to deliver THC has not been an easy process. THC is very lipophilic and can easily cross the blood–brain barrier, which allows interactions with receptors within the central nervous system that elicit psychoactive side effects. Cannabinoid receptors within the central nervous system are also important for the therapeutic effects of THC making it very difficult to create a form of THC that does not have unwanted psychoactive side effects.[15] This high lipophilicity lends itself to a large first-pass effect and low oral bioavailability.[16] The development of a useful dosage form has also been complicated by the gum-like, noncrystalline nature of THC.[12] Smoking cannabis is an efficient delivery method, but this is an unacceptable medical practice due to the additional dangers associated with the act of smoking and problems with dose standardization.[17]

The adverse effect profile of cannabis and THC has made clinical use of these compounds very complicated, as both natural THC and its synthetic analogs have shown similar adverse effects in human and animal trials.[18,19] Both cannabis and THC cause significant psychoactive adverse effects, such as hallucinations, dissociation, euphoria, or dysphoria, in the majority of patients who use them. This has spurred development of other cannabinoid agonists that may have more favorable adverse effect profiles.

Physiology and Pharmacology of the Endocannabinoid System

CANNABINOID RECEPTORS

For many years, there were misconceptions about the pharmacologic actions of THC and marijuana.[15] It was long thought that THC worked by disrupting cellular membranes without interacting with a specific receptor, and specific cannabinoid receptors were not discovered until the 1990s.[20-23] Since discovery of the receptors, interest in the development of drugs that can specifically interact with cannabinoid receptors has increased.

The first cannabinoid receptor identified was CB1. It was discovered in the rat cortex in 1990, nearly 30 years after identification of the active ingredient in cannabis.[20] CB1 is ubiquitous and is found in the central nervous system, peripheral nervous system, and other peripheral tissues (Table 1).[24-26] CB1 is a G-protein–coupled receptor that inhibits adenylyl cyclase and subsequently leads to decreased cyclic adenosine monophosphate levels.[15,27] CB1 is thought to affect the actions of neurotransmitters such as acetylcholine, norepinephrine, dopamine, 5-hydroxytriptamine, γ-aminobutyric acid, glutamate, and D-aspartate.[7] CB1 receptors are thought to be coupled with N-, L-, and P/Q-type calcium channels, as well as A- and M-type potassium channels.[7,28-31] The density of CB1 receptors is greatest in the central nervous system, located in high concentrations in the basal ganglia, cerebellum, hippocampus, and cerebral cortex (Table 1).[32] The high concentrations of

CB1 receptors in the central nervous system may account for the ability of CB1 receptor agonists to impair cognition and memory and alter motor function, as well as reflect many of the medicinal effects associated with the use of cannabinoids such as analgesia, muscle relaxation, appetite enhancement, and hormonal activity.[8,32] The analgesic effect of cannabinoid agonists may be related to their activity on CB1 receptors located on the terminals of primary peripheral afferent neurons, as well as in the central nervous system.[6,7,24]

A second cannabinoid receptor, CB2, was identified in 1993 and has been found mainly in peripheral tissues (Table 1).[21] CB2 inhibits adenylyl cyclase similarly to CB1; however, it has not been shown to affect ion channels as does CB1.[15,32] The distribution of CB2 is localized to the immune system, and it is thought to have immunosuppressive and antiinflammatory activities.[8,15,33] The physiological roles of CB2 receptors have not yet been clearly elucidated.[7]

KNOWN ENDOCANNABINOIDS

Since the discovery of cannabinoid receptors, several endogenous ligands for these receptors, termed endocannabinoids, have been identified. The first ligands identified were *N*-arachidonyl ethanolamide (anandamide), 2-arachidonyl-glycerol (2-AG), homo-γ-linolenylethanolamide, and 7,10,13,16-docosatetranylethanolamide.[34-36] All of these endocannabinoids have been found to be CB1 agonists in mice, and both anandamide and 2-AG also have activity at the CB2 receptor.[8,15] Anandamide has been found in the human brain at concentrations as high as 100 pmol/g, as well as in the periphery at lower concentrations.[37] The concentration of 2-AG in the brain may be up to 170 times higher than that of anandamide.[38] It is thought that anandamide and 2-AG are synthesized within the cell membranes but are not stored in vesicles. It is currently believed that anandamide and 2-AG are produced and released by neurons upon depolarization.[15,39]

Table 1. Distribution of Cannabinoid Receptors[15,21]

Receptor	Central Distribution	Peripheral Distribution
CB1	basal ganglia	adrenal glands
	cerebellum	bone marrow
	cerebral cortex	endothelium
	entopeduncular nucleus	heart
	globus pallidus	kidneys
	hippocampus	lungs
	periaqueductal gray	lymphocytes
	putamen	peripheral neurons
	rostral ventrolateral medulla	phagocytes
	spinal dorsal horn	prostate
	substantia nigra pars reticulata	smooth muscle
		sperm
		spleen
		testes
		thymus
		tonsils
		uterus
CB2		leukocytes
		B lymphocytes
		monocytes
		natural killer cells
		PMNs
		T4 lymphocytes
		T8 lymphocytes

PMNs = polymorphonuclear leukocytes.

ENDOCANNABINOID METABOLISM

Inactivation of anandamide occurs intracellularly by enzymatic degradation after reuptake by a selective transporter into neurons or astrocytes. The exact transport molecules have not been identified.[40,41] Fatty acid amide hydrolase (FAAH), also known as anandamide amidase, shows significant specificity for anandamide and is the primary enzyme responsible for anandamide metabolism. The inactivation pathway for 2-AG is not entirely clear.[39,42] No transport molecule has been identified for 2-AG, and 2-AG may enter cells by diffusion rather than active transport.[39]

Cannabinoids and Analgesia

There are several potential mechanisms of analgesia for endocannabinoids. CB1 receptors are present in areas that modulate pain transmission, and cannabinoids appear to act at both spinal and supraspinal levels to produce analgesia.[24,43] Furthermore, endocannabinoids may have analgesic activities by modulation of pain signals in both ascending and descending pathways, by direct spinal action, or by actions on peripheral nerves.[44-46] In contrast, low levels of CB1 in brain stem respiratory centers may lead to a low risk of respiratory depression and a high therapeutic index of marijuana.[8] This finding presents several potential targets for drug development.

CANNABINOID DRUG DEVELOPMENT

Several cannabimimetic agents have been developed; however, few have been studied in humans. Ajulemic acid (CT-3) is an analog of one metabolite of THC and has shown promise as an analgesic without psychoactive effects.[47,48] CT-3 has been studied in humans and, in those studies, had a more tolerable side effect profile compared with THC. Preliminary studies of CT-3 suggest that it may have antiinflammatory activity similar to that of NSAIDs.[49,50] Experimental dosing at supratherapeutic doses in rats did not produce gastrointestinal adverse effects as NSAIDs do, which may prove to be a therapeutic advantage over traditional antiinflammatory agents such as NSAIDs or corticosteroids.[51] CT-3 has low binding affinity

for CB1 and CB2; hence, its primary therapeutic actions appear to be due to interactions at other sites yet unknown.[48,50]

Other cannabinoids have been developed for use as analgesics. Levonantradol, a synthetic cannabinoid developed by Pfizer, was found to be approximately equivalent in efficacy to codeine 60–120 mg, but was not approved for use due to its adverse effect profile.[7,52] Levonantradol was found to produce dysphoria, somnolence, hallucinations, "weird dreams," confusion, nervousness, and apprehension in early trials assessing its efficacy as an analgesic and antiemetic.[52,53]

HU-210 and HU-211 (also called dexanabinol) are THC analogs that differ from each other only in their enantiomeric configuration.[7] This difference in conformation makes HU-210 an effective, but extremely psychoactive analgesic, while HU-211 is completely devoid of psychoactive properties. HU-211 does not bind to cannabinoid receptors and has been found to produce *N*-methyl-D-aspartate receptor antagonism in animal models.[54] HU-211 substantially lowers tumor necrosis factor-alpha levels both in vivo[55] and in vitro[56] and is being studied for potential use in traumatic head injury and neurodegenerative diseases.[57,58] In rat and gerbil models of ischemia and closed head injury, HU-211 has been shown to improve neurologic status and recovery of motor and memory functions, as well as protect the blood–brain barrier and attenuate the development of cerebral edema.[59,60] HU-211 reduced mortality and hypotension in a mouse model of septic shock primarily by reducing tumor necrosis factor-alpha and nitric oxide levels.[56]

There has been some preclinical drug development targeting endocannabinoid metabolism. Reuptake inhibitors of endocannabinoids have been developed, some of which also bind to the CB1 receptor. Reuptake inhibition prevents intracellular metabolism and allows for the endocannabinoid to remain active extracellularly. Binding to the CB1 receptor may also block receptor activity, thus potentially blocking the response of CB1 agonism. For example, AM 404 is a synthetic fatty acid in development that inhibits the anandamide transporter and has very low affinity for CB1 receptors.[61] Other potential targets for interference with endocannabinoid metabolism would act through FAAH inhibition. Arachidonyl trifluoromethyl ketone (Arach-CF3) is an amidase inhibitor that is relatively selective and potent and does not bind to CB1 receptors with high affinity.[62] Methyl-arachidonyl fluorophosphonate is approximately 1000 times more potent than Arach-CF3 as an amidase inhibitor, but also binds irreversibly to the CB1 receptor, making it less useful as an analgesic agent.[63]

ANIMAL MODELS OF CANNABINOID ANALGESIA

Cannabinoids have been shown to influence a myriad of organ systems in rodents, including the central nervous, immune, cardiovascular, reproductive, visual, respiratory, and gastrointestinal systems.[15] Additionally, there has been a wealth of research in animal models supporting cannabinoid analgesia.[6,8,15,19] Animal evidence has suggested that cannabinoids may be effective for both acute and chronic pain.[6,46,64] Some promising studies using rodent models have demonstrated some analgesic potential of metabolic enzyme inhibitors, such as AM 374, and transporter inhibitors, such as AM 404.[15,65,66] To our knowledge, as of August 2005, there have been no studies in humans using FAAH inhibitors or anandamide transporter inhibitors.

Two other agents in development have had promising results in animal models of pain. WIN-55,212-2 is a mixed CB1/CB2 agonist that preferentially agonizes the CB2 receptor. WIN-55,212-2 has shown promise as an effective analgesic in rodent models of pain both topically and systemically.[67,68] AM 1241 has been studied as a potential agent for the treatment of peripherally mediated neuropathic pain.[69,70] AM 1241 is a CB2 selective agonist that has demonstrated antinociceptive effects without central nervous system adverse effects in rats and mice.

Human Studies of Cannabinoid Agonists

A review of the efficacy of cannabinoid agonists for pain evaluated 9 trials involving 222 humans and concluded that these agents are not ready for widespread clinical use for analgesia.[18] Most of the investigations were single-dose studies, and several different cannabinoid agonists were represented (Table 2). Findings also showed that oral THC in doses of 5–20 mg and intramuscular levonantradol in doses of 0.5–3 mg were approximately equivalent to codeine 60–120 mg. Additionally, adverse effects of mild to moderate severity were noted in almost all patients who used cannabinoid agonists for analgesia, including feelings of euphoria/dysphoria, dry mouth, and drowsiness (Table 3).

COMMERCIALLY AVAILABLE CANNABINOIDS

As of this writing, there are 3 cannabinoid agonists currently available on the international market: dronabinol, nabilone, and a cannabis medicinal extract (CME). Dronabinol is synthetically manufactured THC and is available in the US as a Schedule III controlled substance indicated for use as an appetite stimulant in patients with HIV or for chemotherapy-induced nausea and vomiting. Nabilone is a THC analog and is available in Switzerland, the UK, and Canada. Nabilone is indicated only for chemotherapy-induced nausea and vomiting, but there have been case reports of its successful use for pain and spasticity associated with multiple sclerosis.[71] CME was approved in Canada in April 2005 with the indication of adjunctive treatment for symptomatic relief of neuropathic pain in adults with multiple sclerosis. It is a sublingual whole-plant extract that contains a 1:1 ratio of THC and CBD.

Dronabinol

Dronabinol has been studied for use as an analgesic, but results have been disappointing due to the incidence of adverse effects at therapeutic doses (Table 3).[72,73] In one clinical trial, THC 5 mg was found to be about as effective as codeine 60 mg.[74] Other studies have found THC to be more effective than placebo for analgesia, but less effective than morphine.[72,73]

One study compared oral THC with morphine in experimentally induced pain and found that THC did not have significant analgesic effects in any of the pain conditions tested.[73] The pain tests that were conducted were pressure (induced on the fingers by an electronic pressure algometer), heat applied to the forearm, 2-minute cold immersion test, and transcutaneous electrical stimulation. In this study, morphine was only marginally better than placebo or no different from placebo in most of the tests, and adverse effect profiles were similar between morphine and THC. Adding morphine to THC did seem to decrease the euphoria associated with THC. These results may not translate to clinical practice, as experimentally induced pain in healthy volunteers may not adequately measure the analgesic efficacy of THC in patients with acute or chronic pain.

In another study of THC for use in postoperative pain, THC 5 mg was no better than placebo as an analgesic.[72] This was a single-dose trial in 40 women who underwent elective abdominal hysterectomy. The primary outcome was sum of the pain intensity differences over a 6-hour period and time to rescue analgesia. In this study, patients reported an increased awareness of their surroundings with THC, but there were no other differences in adverse effects. A single dose of 5 mg is lower than that used in several other studies, and the lack of effect may indicate that this dose is too low for use in postoperative pain.[73-75] The lack of adverse effects, however, suggests that THC may have an acceptable adverse effect profile at lower doses.

A 6-week, single-patient, double-blind, placebo-controlled, crossover study using an extract containing THC, CBD, and cannabinol in a patient with familial Mediterranean fever showed a significant morphine-sparing effect in favor of the THC extract.[75] Capsules containing an extract of cannabis, standardized to contain 10 mg of THC per capsule, were administered 5 times per day during each active treatment phase (2 wk of active treatment, 2 wk of placebo). Pain scores as reported on a visual analog scale (VAS) were 4.8–6.2 cm during active treatment and 5.5–6.1 cm during placebo treatment ($p = 0.3$); however, the patient consumed 170 mg of morphine as escape analgesia during the active treatment periods compared with 410 mg of morphine during the placebo periods ($p < 0.001$). Assessment of adverse effects was complicated by nausea and vomiting that occurred throughout the study.

Interpretation of the results of this report is difficult because the patient had self-administered cannabis prior to the study to relieve his pain. It was also noted that the patient was able to determine which treatment he was receiving during the first 4 weeks of the trial. The significant decrease in the use of escape analgesia during treatment with THC suggests that the cannabis extract did produce analgesia.[75]

Whole-Plant Cannabis Extracts

In 1999, CMEs became available in Germany, Switzerland, the UK, and Canada for research.[76] These extracts are available from GW Pharmaceuticals Ltd. in England as

Table 2. Clinical Trials with Cannabinoid Agonists

Drug	N	Outcomes	Comments
THC[74]	36	high dose: THC 20 mg or codeine 120 mg pain reduction > placebo ($p < 0.05$) low dose: THC 10 mg or codeine 60 mg not significantly better than placebo no statistically significant differences in pain reduction between codeine and THC	THC 20 mg highly sedating, associated with dose-limiting effects
THC[73]	12	THC 20 mg not significantly better than placebo in any test THC/morphine sulfate better than placebo in TENS and cold tests morphine sulfate better than placebo in pressure, cold, and TENS tests	experimentally induced pain model
THC[72]	40	no differences in mean SPID at 6 h or time to rescue analgesia between THC 5 mg and placebo groups	postoperative pain
CME[78]	24	pain relief associated with both THC 2.5–120 mg/day and CBD superior to placebo THC and THC:CBD better than placebo for spasm on VAS	intoxication highest with THC
CME[79]	34	THC and THC:CBD better than placebo for 2 main symptoms all CME improved quality of sleep	median THC daily dose during treatment: 18–20 mg
CME[80]	48	mean pain severity and sleep measures significantly improved with CME	NNT of 3 to reduce pain by 1 box[a] NNT of 9 for 30% pain reduction with THC:CBD CME
CT-3[47]	21	CT-3 40 and 80 mg/day significantly reduced VAS and VRS ratings vs placebo	80 mg did not increase analgesia or adverse effects

CBD = cannabidiol; CME = cannabis medicinal extract; CT-3 = ajulemic acid; NNT = number needed to treat; SPID = summed pain intensity difference; TENS = transcutaneous electrical nerve stimulation; THC = delta-9-tetrahydrocannabinol; VAS = visual analog scale; VRS = verbal rating scale.
[a]Using an 11-point ordinal pain severity scale.

high-THC, high-CBD, or 1:1 THC:CBD sublingual formulations.[76] The THC:CBD combination extract was recently approved for use in Canada and is under consideration in the UK for approval for commercial use.[77]

Three recent studies have compared sublingual CME with placebo for treatment of pain.[78-80] These studies used high-THC, high-CBD, 1:1 THC:CBD, and placebo sublingual sprays. Standardized extracts contained THC 2.5 mg, CBD 2.5 mg, or THC 2.7 mg/CBD 2.5 mg (1:1 THC: CBD). The sublingual dosage form allows for dose titration to analgesic effect balanced with avoidance of adverse effects associated with fixed-dose oral forms. The studies found significant improvements in pain and sleep scores for CME compared with placebo, but there were some variations in symptom relief and adverse effect profiles between the different CME formulations. When patients were taking THC containing CME, drowsiness and euphoria/dysphoria were more common.[79] These were very small studies with other limitations in design, such as variability in dosing of CME; however, they provide promising preliminary results for a delivery method of cannabinoids that may be both tolerable and efficacious.

Table 3. Adverse Effects Occurring More Frequently with Cannabinoids than with Placebo

Drug	Adverse Effect	Frequency vs placebo (%)
THC[74,a]	ataxia	29 and 44 vs 9
	blurred vision	41 and 65 vs 9
	dizziness	59 and 97 vs 26
	dry mouth	74 and 76 vs 35
	increased appetite	26 and 21 vs 9
	mental clouding	32 and 53 vs 18
	sedation	71 and 94 vs 29
THC[73]	anxiety	33 vs 0
	dry mouth	100 vs 42
	euphoria	75 vs 8
	hallucinations	50 vs 0
	vertigo	92 vs 25
THC:CBD CME[78]	cough	5 vs 0
	impaired balance	5 vs 0
	sleepiness	10 vs 5
THC:CBD CME[79]	drowsiness	58 vs 33
	dry mouth	83 vs 46
	dysphoria/euphoria	50 vs 4
THC:CBD CME[80]	dizziness	19 vs 8
	dysgeusia	21 vs 2
	feeling drunk	8 vs 0
	somnolence	15 vs 10
CT-3[47,b]	dizziness	NR
	dry mouth	
	increased pain	
	sweating	
	tiredness	
	trouble concentrating	

CT-3 = ajulemic acid; THC = delta-9-tetrahydrocannabinol; THC:CBD CME = tetrahydrocannabinol:cannabidiol cannabis medicinal extract.
[a]10- and 20-mg doses, respectively; statistical significance not reported.
[b]Frequency not reported; occurred more frequently with CT-3 than with placebo.

An exploratory, randomized, double-blind, placebo-controlled, crossover trial using 24 patients with chronic neurologic diagnoses evaluated the effect of CME on patient-identified target symptoms.[78] In this trial, patients received high-THC, high-CBD, 1:1 THC:CBD, or placebo CME for 2-week treatment periods. Patients were asked to identify 5 troublesome symptoms and rate them on a VAS daily during the treatment periods. The VAS scores ranged from 0 to 100, with 0 representing worst possible and 100 representing best possible for each target symptom. Each subject was allowed to titrate the CME dose to optimal effect without intolerable adverse effects, thus complicating interpretation of the efficacy of the CME. CBD and THC significantly improved ratings of pain compared with placebo (VAS scores 54.8, 54.6, and 44.5, respectively; $p < 0.05$). THC and THC:CBD also improved ratings of spasm compared with placebo (VAS scores 58.4, 55.8, and 47.3, respectively). These results are difficult to interpret, as patients were able to select symptoms to rate, as well as titrate their doses.

A similarly designed study evaluated CME in 34 patients with chronic, stable pain who were poorly responsive to other treatments.[79] This randomized, double-blind, placebo-controlled, crossover trial used high-THC, high-CBD, 1:1 THC:CBD, and placebo CME. Patients selected their 2 worst symptoms on which to record daily VAS ratings. Patients also titrated their CME doses, resulting in a range of 1–8 sprays per dose. There were significant improvements in the ratings of the 2 self-selected symptoms with THC and THC:CBD. Again, interpretation of these results is complicated by the lack of standardization of dosing regimen and symptom ratings.

Efficacy of high-THC and THC:CBD CME was evaluated in 48 patients with pain resulting from brachial plexus injury.[80] This randomized, double-blind, placebo-controlled, crossover study consisted of three 14-day treatment periods. The primary measure of efficacy in this trial was a standard, 11 point, ordinal pain severity scale ranging from zero (best imaginable) to 10 (worst imaginable), recorded by marking one of a row of boxes labeled 0–10. Clinical significance was established as a reduction of pain score of 2 boxes compared with placebo. Neither the THC: CBD nor high-THC CME reached the a priori assumed level for clinical significance. THC:CBD CME compared with placebo reduced the pain rating by 0.58 boxes, while high-THC CME reduced the pain rating by 0.64 boxes ($p = 0.005$ and 0.002, respectively). Based on these results, the authors calculated a number needed to treat (NNT) of 3 to reduce pain ratings by 1 box and an NNT of 9 to reduce pain ratings by 30% with THC:CBD CME. No serious adverse events occurred during this study, although more adverse events were reported during the active treatment periods (Table 3).

CANNABINOIDS IN DEVELOPMENT

A recent, double-blind, placebo-controlled, crossover trial in 21 patients with chronic neuropathic pain found CT-3 to be more effective than placebo for pain.[47] The study design included two 1-week treatment periods (CT-3 or placebo) separated by a 1-week washout period. During the active treatment week, a 40 mg daily dose was taken for the first 4 days, followed by 80 mg/day during the following 3 days. The 80 mg dose did not provide any more analgesia than the 40 mg dose in this study, but also did not increase the incidence of adverse effects. Patients reported significantly more adverse events during the CT-3 treatment period ($p = 0.02$), although frequencies of specific adverse effects were not reported. The most common adverse effects were tiredness and dry mouth, but also included trouble concentrating, dizziness, sweating, and increased pain. Only 2 patients dropped out of the trial: one during active treatment and one during placebo treatment. The duration of treatment during this study was very short; therefore, long-term efficacy could not be assessed. Future clinical studies with this drug are warranted to confirm these results and further investigate appropriate dosing for optimal effect.

Clinical Impact of Recent Trial Evidence

Initial studies using the currently available cannabinoid agonists have shown promise for additional analgesic options. The growing body of research regarding the use of cannabinoid agonists suggests that these agents may become important additions to medical practice. At this time, there are not sufficient data to support widespread use of the currently available agents for analgesia. The cannabinoids that have at this time undergone human trials (dronabinol, nabilone, CT-3, CME) may eventually be useful as adjunctive agents for the treatment of pain as their physiological roles are more clearly identified. Studies have shown that dronabinol and CMEs may have dose-limiting adverse effects at the potential analgesic doses. CT-3 may prove to be tolerable at analgesic doses; however, further studies are needed with this agent.

Cannabinoids as novel therapeutic targets have the potential to be additional therapeutic options for the treatment of chronic pain for some patients. Additionally, there are several potential targets for future cannabinoid drug development: (1) specific spinal or peripherally acting cannabinoids,[81] (2) FAAH or transporter inhibitors,[61,62] (3) development of alternative delivery methods such as inhaled or intranasal dosage forms, and (4) identification of any additional cannabinoid receptors and associated receptor activity.

The primary drawback to the use of cannabinoid agonists in clinical practice is the unfavorable adverse effect profile seen in most trials to date. The most troubling adverse effects have been euphoria/dysphoria, sedation, and mental clouding (Table 3). A large proportion of patients experience adverse effects when using cannabinoid agonists. CT-3 has shown the most favorable adverse effect profile thus far and may prove to be the first cannabimimetic agent whose therapeutic efficacy outweighs the adverse effect profile, although larger studies are necessary to confirm the results of the initial human study conducted with this agent. Some of the cannabinoids in development, such as HU-211 and AM 1241, may prove to have more desirable adverse effect profiles as results of human studies become available.

Summary

There is a need for more effective treatments of chronic and neuropathic pain conditions because current treatments are ineffective or intolerable for a large number of patients with these conditions. Cannabinoids have shown promise for use in chronic pain conditions, especially with the newer synthetic agents that have shown more favorable adverse effect profiles in preliminary studies.

Pain is a multidimensional phenomenon involving sensory, emotional, and physical components. There is no single pharmaceutical target for pain control. Pain management often requires a polypharmaceutical approach to treatment, and cannabinoid agonists could provide additional options. The older agents, dronabinol and nabilone, have considerable drawbacks associated with their use, and further drug development is warranted. CT-3 and CMEs have shown efficacy in preliminary findings and comparatively may have a more tolerable adverse effect profile. As human studies become available, other cannabinoid agonists, such as WIN-55,212-2, HU-211, and AM 1241, may prove to be effective analgesics without the significant dose-limiting adverse effects associated with dronabinol and nabilone. New drugs that could inhibit degradation or block reuptake of endocannabinoids could potentially become effective analgesic agents.

There has been tremendous progress in our understanding of the physiology and pharmacology of the endocannabinoid system in recent years. Currently, the clinical application of cannabinoids for management of chronic pain is not clear. The available agents do not provide a clear distinction of analgesic benefit given their adverse effect profiles. Research into the development of potential cannabinoid agents with better analgesia to adverse effect profiles may provide future therapeutic options for the treatment of pain. Additionally, a better understanding of which patient populations may receive the most benefit from cannabinoid agonists is needed to help determine the potential effectiveness of these medications and their clinical application.

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EXTRACTO

OBJETIVO: Revisar la literatura concerniente a la fisiología del sistema endógeno de cannabinoides, el desarrollo actual de agonistas de cannabis como agentes farmacológicos, y la investigación clínica sobre el uso de agonistas de cannabis en el manejo del dolor.

FUENTE DE DATOS: Se identificaron artículos a través del MEDLINE (1966–agosto de 2005) usando las palabras clave cannabis, cannabinoide, cannabi*, canabidiol, nabilone, THC, dolor, y analgesia. No se establecieron límites a las condiciones de búsqueda. Se obtuvieron referencias adicionales de las bibliografías de los artículos seleccionados.

SELECCIÓN DE ESTUDIOS Y EXTRACCIÓN DE DATOS: Se seleccionaron estudios sobre los agonistas de cannabis en el manejo del dolor. Los estudios no fueron limitados por el tipo de dolor o la etiología. Se incluyeron estudios y artículos de revisión usando modelos de animales y artículos sobre la fisiología y farmacología del sistema endógeno de cannabinoides.

SÍNTESIS DE DATOS: El descubrimiento de receptores de cannabis y sustratos endógenos para estos receptores ha llevado a un aumento en el desarrollo de agonistas de cannabis como agentes farmacológicos. Recientemente, se han desarrollado agentes que imitan el cannabis y que han sido asociados a menos efectos sistémicos que el delta-9-tetrahidrocanabinol. Esto incluye el desarrollo de extractos de cannabis para propósitos medicinales mediante administración sublingual (aprobado en Canadá) y que ha demostrado resultados positivos en el manejo del dolor en humanos. Además, ha habido varios cannabinoides sintéticos estudiados en humanos, incluyendo 2 agonistas comercialmente disponibles en el mercado internacional.

CONCLUSIONES: Los cannabinoides proveen una alternativa potencial para el manejo del dolor mediante un mecanismo novel. El manejo del dolor crónico frecuentemente requiere del uso de múltiples agentes farmacológicos, y los cannabinoides representan una adición potencial al arsenal de opciones terapéuticas.

Mitchell Nazario

RÉSUMÉ

OBJECTIF: Réviser la littérature portent sur la physiologie du système des endocannabinoïdes, l'état du développement des agonistes des récepteurs cannabinoïdes et l'état de la recherche sur ces agonistes cannabinoïdes comme analgésiques.

SOURCE DE L'INFORMATION: Les articles pertinents ont été identifiés par une recherche sur MEDLINE (1966–août 2005) à l'aide des mots clés suivants: cannabis, cannabinoid, cannabi*, cannabidiol, nabilone, THC, pain, et analgesia. Aucune autre borne de recherche a été utilisée. Des références additionnelles ont été identifiées dans les bibliographies des articles cités.

SÉLECTION DES ÉTUDES ET EXTRACTION DE L'INFORMATION: Les études portant sur l'utilisation des agonistes cannabinoïdes dans le traitement de la douleur ont été sélectionnées. Les études n'étaient pas sélectionnées selon le type de douleur ou son étiologie. Les publications de données

animales ont aussi été retenues. Enfin, les auteurs ont aussi révisé les études de physiologie ou de pharmacologie du système des endocannabinoïdes.

SYNTHÈSE DE L'INFORMATION: La découverte de récepteurs cannabinoïdes et de ligands endogènes pour ces récepteurs a conduit au développement d'agonistes pharmacologiques. Les récents développements d'agent cannabimimétique ont permis une réduction des effets indésirables systémiques par rapport au delta-9-tetrahydrocannabinol, comme par exemple l'extrait de cannabis utilisé à des fins médicales par voie sublinguale (approuvé dans Canada) qui semble un analgésique prometteur. Plusieurs autres cannabinoïdes synthétiques ont été étudiés chez l'humain, et 2 de ces agonistes sont disponibles sur le marché international.

CONCLUSIONS: Les cannabinoïdes constituent une nouvelle modalité analgésique dotée d'un mécanisme d'action nouveau et distinct. La douleur chronique nécessite souvent une approche pharmacologique multiple, et les cannabinoïdes constituent une addition potentielle à l'arsenal thérapeutique.

Marc Parent