Cannabinoids and the Brain

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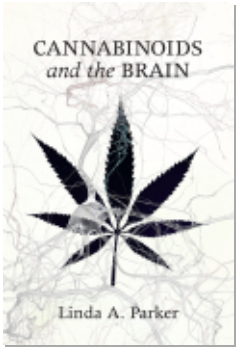

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Cannabinoids and Pain

The most common medical use of cannabis today and throughout human history is for the treatment of chronic pain, which is usually accompanied by some other disability or mood disorder. Estimates indicate that approximately 20 percent of the world's population suffers from chronic pain (Vos et al. 2012). Chronic pain is defined as pain that persists for more than three months. Current pharmacotherapies for chronic pain are ineffective in many patients; approximately 40 percent of patients with chronic pain are not satisfied with their treatment (Corcoran, Roche, and Finn 2015). In the past twenty years, the effectiveness of cannabis in reducing chronic pain has provided increasing evidence that the endocannabinoid system regulates the processing of pain.

Chronic pain can be broadly categorized as consisting of nociceptive pain and neuropathic pain (Beal and Wallace 2016). Nociceptive pain is produced by stimulation of specialized free nerve endings (nociceptors, or "pain receptors") that respond to tissue damage caused by intense chemical (e.g., chili peppers), mechanical (e.g., pinching), or thermal stimulation. Nociceptive pain is pain resulting from actual tissue damage or potential tissue damage; examples include post-operative pain, osteoarthritis-related pain, and mechanical low back pain. Once stimulated, the nociceptor sends a signal to the brain via the spinal cord, triggering a variety of autonomic responses that result in the subjective experience of pain. Neuropathic pain is pain that results from damage to the nervous system itself—examples include diabetic peripheral neuropathy, post-stroke pain and post-therapeutic neuralgia such as chemotherapy-induced neuropathy (Beal and Wallace 2016). Historically, opiates have been the primary class of medications used to treat patients with both acute and chronic pain. Acute pain is well controlled by available therapies, but chronic pain is often resistant to conventional pharmacotherapies. In addition, multiple studies have revealed the

adverse consequences of chronic opiate therapy in people without cancer (Rosenblum, Marsch, Joseph, and Portenoy 2008). Therefore, there is an interest in alternative medications for the management of chronic pain. Cannabinoids may have a role in such treatment of chronic pathological pain, including neuropathic pain.

Pre-Clinical Evidence of Analgesic Effects

There is very good pre-clinical evidence that cannabinoids are highly effective in reducing pain in animal models. The tests used to determine the analgesic properties of cannabinoids include tests that model both acute and chronic pain. The simplest tests measure the effect of drugs on acute pain, with analgesic drugs increasing the threshold to detect painful stimuli. In the tail-flick test, a beam of light is focused on a small segment of a rodent's tail; the initial low intensity of the light beam is increased incrementally until the normal pain threshold is reached and the tail is reflexively flicked out of the beam. The hot plate test is equally reliable as an assessment for analgesic drugs using thermal heat. A metal plate at the base of a cylinder is maintained at a temperature between 52° C and 58° C. When a rodent is placed on the hot plate, the latency to respond (by licking a paw or jumping) is measured.

The especially imperative need for new treatments for chronic pain requires the use of pre-clinical models of inflammatory and neuropathic pain to evaluate the potential effectiveness of cannabinoids in relieving distress. Models of chronic pain include models of inflammatory pain and models of neuropathic pain. One model of inflammatory pain is the plantar test, in which an irritant (carrageen, capsaicin, formalin, or lypopolysaccharide) is injected into a rodent's paw and results in a slowly developing inflammation. The paw becomes hypersensitive, and mechanical, thermal, and cold stimuli that normally would not provoke pain become painful (called allodynia); the latency to withdraw the paw from the stimulus is then measured. Analgesic drugs increase the latency for paw movement, and anti-inflammatory drugs reduce edema in the paw. Neuropathic pain models include chemotherapy-induced neuropathy (which produces allodynia) and constriction of the sciatic nerve; analgesic drugs reduce allodynia, as is evidenced by increased latency to respond. Pre-clinical evidence suggests that use of phytocannabinoids may be one of the most promising therapies for chronic neuropathic pain. Not only is THC effective in treatment of chronic pain; pre-clinical evidence

suggests that CBD, and perhaps other constituents of cannabis, may also be effective.

THC

Pre-clinical animal models have demonstrated that THC is effective in reducing pain in animal models (Costa and Comelli 2014). Indeed, hyperalgesia is one of the classical "mouse tetrad symptoms" used to classify a drug as acting like THC (Martin et al. 1991). THC has been tested in a wide range of anti-nociceptive assays and has been found to be effective in both acute (e.g., hotplate, tail flick) and chronic (e.g., inflammation, neuropathic pain) models. THC is effective when administered orally, systemically, or directly into the brain or the spinal cord (Costa and Comelli 2014). However, the psychoactive side effects of THC limit its usefulness in treating pain. One approach to overcoming that obstacle is the addition of CBD to THC. CBD has anti-nociceptive effects. Since THC is a mixed CB_1/CB_2-receptor agonist, another approach is the development of CB_2 agonists that only act on the non-psychoactive CB_2 receptors that are primarily located in the peripheral nervous system. Evaluation of THC in pathological pain (such as chronic inflammatory pain, in which the CB_2 receptor plays a pivotal role) has shown it to be an effective anti-nociceptive agent. For instance, in a rat model of chronic arthritic pain, THC was equally potent and effective in non-arthritic rats and arthritic ones. However, in arthritic rats the anti-nociceptive effects of THC were produced via activation of both the CB_1 receptor and the CB_2 receptor, whereas in non-arthritic rats the anti-nociceptive effect was mediated only by its action on the CB_1 receptors (Cox et al. 2007). These data suggest that chronic pain experienced by arthritics involves both peripheral CB_2 receptors and central CB_1 receptors. Therefore, treatments aimed at stimulating peripheral CB_2 receptors may reduce chronic arthritic pain. Another way to reduce the psychoactive side effects of central stimulation of CB_1 receptors is to develop peripherally restricted cannabinoid-receptor agonists that do not cross the blood-brain barrier. Ajulemic acid, a peripherally restrictive analogue of a metabolite of THC, binds to CB_1 receptors and to CB_2 receptors and reduces pain in chronic neuropathic and inflammatory animal models mediated by action at CB_1 receptors only (Dyson et al. 2005; Costa and Comelli 2014).

Because of interactions between the endocannabinoid system and the opiate system, synergistic effects have been reported between THC and opiates in the regulation of pain. Low doses of THC have been found to significantly enhance morphine-induced analgesia when THC and

opiates are co-administered systemically into the spinal cord or directly into the ventricles of the brain in animal models. In results from studies in which they are co-administered systemically by injection or orally, a clear synergy has been reported: THC enhanced the anti-nociceptive effects of both morphine and codeine. Therefore, pre-clinical findings suggest that combined treatment with cannabinoids and opioids may be able to produce long-term anti-nociceptive effects at doses that do not produce side effects, without tolerance to each effect (Costa and Comelli 2014).

CBD

Initial investigations of the analgesic effects of CBD in several animal models of acute pain (e.g., hot plate) revealed no evidence for an effect of CBD on pain (Sofia, Vassar, and Knobloch 1975). On the other hand, CBD was subsequently found to be effective in a model of chronic pain when given orally (Formukong, Evans, and Evans 1988). These conflicting results suggested that CBD was not effective against acute pain but was effective against chronic pain. Subsequently, the analgesic properties of CBD were tested specifically in models of persistent and inflammatory pain. Costa et al. (2004) have since found that giving very low oral doses of CBD (15 mg/kg) one hour before carrageenan reduced paw edema within three hours. Even lower doses of CBD (5–7.5 mg/kg, oral) administered two hours after carrageenan-induced inflammation reduced the pain behavior, and higher doses (10–40 mg/kg) eliminated pain behavior and edema. These effects were found to be mediated by the action of TRPV1 receptors as the TRPV1-receptor antagonist (capsazepine) reversed CBD's attenuation of pain (Costa, Giagnoni, Franke, Trovato, and Colleoni 2004). In addition, CBD has been shown to be effective in relieving neuropathic chemotherapy-induced pain in rats, and in diabetic mice (Ward et al. 2014), without the development of tolerance. An additional benefit of CBD is that it has been shown to block the progression of arthritis in a mouse model of collagen-type-II-induced arthritis (Malfait et al. 2000); the synovial (joint) cells from mice treated with an optimal dose of CBD (5 mg/kg, ip, for ten days) released significantly less TNFα, which suggested that the therapeutic effect of CBD on arthritis may be suppression of TNFα, a pro-inflammatory cytokine known to be a major mediator of arthritis.

The molecular targets of CBD that could be responsible for the analgesic effects are numerous, including not only TRPV1 agonism but also agonism of 5-HT_{1A}, antagonism of GPR55 receptors, weak antagonism at

CB_1 and CB_2 receptors, and positive allosteric modulation of glycine receptors. (See Pertwee 2009.) There is evidence for a role of each of these mechanisms in the analgesic effects of CBD. For instance, a recent report suggests that CBD suppresses neuropathic pain in rats with ligation of the spinal nerve by targeting the α3 glycine receptor (Xiong et al. 2012)—mice lacking the α3 glycine receptor, but not CB_1 or CB_2 receptors, were resistant to the analgesic effect of CBD. More recently, the CBD-induced antagonism of the GPR55 receptor has been shown to play a role in nociceptive signaling. That receptor is highly expressed by mouse primary sensory neurons, and GPR55 knockout mice do not develop hyperalgesia in response to inflammatory or neuropathic stimuli. CBD may also desensitize TRPA1, TRPV1, and TRPV2 channels, resulting in a reduction in hypersensitivity to thermal, chemical, and mechanical stimuli associated with neuropathies (Costa and Comelli 2014). Clearly, there is pre-clinical evidence that CBD attenuates chronic pain through several mechanisms. Because CBD is not psychotropic, it is a strong candidate for treatment of chronic inflammatory and neuropathic pain.

Other cannabis constituents

In addition to THC and CBD, other cannabinoids extracted from cannabis have been shown to have promise as potential analgesic treatments. For example, THCV behaves as a CB_2 partial receptor agonist *in vitro* and as an antagonist of the CB_1 receptor *in vitro* and *in vivo* (Pertwee 2008). The profile is of interest to pain researchers because there is evidence that CB_1 antagonists can reduce pain hypersensitivity by blocking the constitutive activity of the CB_1 receptor that maintains sensitized TRVP1 receptors and because CB_2 agonists are analgesics without psychoactive effects. Cannabigerol, which has not been well studied, may reduce pain by acting as a α_2-adrenergic agonist. And there is evidence that cannabichromene may potentiate the analgesic effect of THC, perhaps by inhibiting re-uptake of AEA. (See Costa and Comelli 2014 for a review.) There have been no clinical studies of the use of CBD alone to treat pain in humans.

GW Pharmaceuticals pioneered the development of nabiximols (whole extracts of cannabis) for therapeutic purposes, most notably for pain in patients with multiple sclerosis. They developed Sativex, which contains THC/CBD ins a ratio of approximately 1 to 1. Recent clinical trials revealed that Sativex is effective (with few side effects at low to moderate doses) in treating pain associated with multiple sclerosis, advanced cancer pain in opiate-resistant patients (Portenoy et al. 2012), and peripheral

neuropathic pain accompanied with alloynia (Serpell et al. 2014). Indeed, in Canada Sativex is approved for prescription for pain in MS and cancer and for spasticity in MS.

Such whole-plant extracts contain a mixture of natural cannabinoids and other non-cannabinoid compounds that may interact synergistically to reduce pain. Recent evidence that a high dose of CBD potentiated the ability of a sub-threshold dose of THC to reduce acute pain in the mouse tail-flick test (Varvel et al. 2006) suggests a synergistic effect of CBD and THC in pain reduction. More recently, Comelli et al. (2008) reported that a CBD and THC extract produced a greater analgesic effect than equivalent respective doses of each compound separately in an animal model of neuropathic pain. To determine whether the improved effect was due entirely to THC and CBD or whether it may have been modulated by the other compounds in the extracts, the effectiveness of a combination of the pure compounds was compared against that of the extracts. The pure compounds produced a weaker effect than the plant extracts at the same doses of THC and CBD (Comelli, Giagnoni, Bettoni, Colleoni, and Costa 2008). Therefore, it is necessary to characterize these constituents more fully. Indeed, there is recent evidence that terpenoids present in the plant may facilitate the analgesic effects of the extracts. The terpenoid β-caryophyllene, the most common terpenoid in cannabis, displays anti-inflammatory and analgesic effects by acting as a CB_2 agonist (Gertsch et al. 2008).

Manipulations of the Endocannabinoid System: Pre-Clinical Evidence

Systemic administration of THC and synthetic CB_1-receptor agonists is well known to produce analgesia in animal models of acute and chronic pain. However, concerns about dependence, tolerance, and the cognitive side effects produced by global agonism of the CB_1 receptor and medicinal marijuana remain. Therefore, pre-clinical research has focused on potential manipulations of the endocannabinoid system that do not produce the side effects produced by CB_1 activation. These potential treatments include CB_1 allosteric modulators, FAAH inhibitors, MAGL inhibitors, and CB_2 agonists.

CB_1 allosteric modulators

Endocannabinoids inhibit pain transmission by acting on CB_1 receptors at central, spinal, and peripheral synapses. The use of THC and other CB_1 agonists as analgesics is limited by the psychoactive side effects

produced by their action on the orthosteric pocket on the CB_1 receptors throughout the brain. Although endocannabinoids also bind to the orthosteric sites of the CB_1 receptor, both AEA and 2-AG are released on demand where and when they are needed and are quickly metabolized. Therefore, their action is more transient and selective with highly specific temporal and spatial regulation. Allosteric modulators of the CB_1 receptor bind to a distinct site apart from the orthosteric site and produce conformational changes in the receptor, thereby altering the potency of the ligand when it binds to the receptor (Kenakin 2013). However, allosteric modulators have no physiological effect in the absence of ligand binding. Therefore, CB_1-positive allosteric modulators would be expected to enhance the pain-relieving effects of endocannabinoids, but with limited side effects. Indeed, a recent study found that the CB_1 positive allosteric modulator ZCZO11 reduced neuropathic pain and inflammatory pain in pre-clinical animal models without development of tolerance or occurrence of psychoactive side effects (Ignatowska-Jankowska et al. 2015).

FAAH and MAGL inhibitors

Exogenous administration of AEA or 2-AG systemically is unsuitable as a treatment for pain because they are rapidly degraded. However, treatment with inhibitors of the enzymes that degrade these endocannabinoids—MAGL (which degrades 2-AG) and FAAH (which degrades AEA and other fatty acids)—is promising. Because of their "on-demand" production and release, endocannabinoids are specifically generated at sites of nociceptive activity, which prevents unwanted effects of global CB_1-receptor agonism. This strategy also has the potential to improve our current understanding of the functional roles of endogenous AEA and 2-AG in regulating pathological pain. The beneficial effects of activating the endocannabinoid system in different neuropathic pain models were reviewed by Guindon and Hohmann (2009).

Animals genetically engineered to lack FAAH have abnormally high levels of AEA. Although FAAH knockout mice act relatively normal, they are less responsive to pain (Lichtman, Shelton, Advani, and Cravatt 2004). Systemic administration of MAGL inhibitors (Ignatowska-Jankowska et al. 2014; Kinsey et al. 2009; Kinsey et al. 2013; Long, Li, et al. 2009) or of FAAH inhibitors (Fegley et al. 2005; Jayamanne et al. 2006; Kathuria et al. 2003; Lichtman et al. 2004) has been shown to be anti-nociceptive in models of acute and chronic pain, including inflammatory pain and neuropathic pain. Both FAAH inhibition and MAGL

inhibition prevent chemotherapy-induced mechanical and cold allodynia (Guindon, Lai, Takacs, Bradshaw, and Hohmann 2013). Both a CB_1 antagonist and a CB_2 antagonist blocked the effects of elevated AEA and 2-AG, but a TRPV1 antagonist blocked only the effect of elevated AEA. In addition, local peripheral (intra-plantar) injection of MAGL inhibitors into the paw of a rat increased local 2-AG levels and blocked pain behavior produced by intra-plantar injections of capsaicin or formalin by a CB_1 and CB_2 mechanism of action of 2-AG (Desroches, Guindon, Lambert, and Beaulieu 2008; Guindon, Guijarro, Piomelli, and Hohmann 2011).

Although FAAH and MAGL inhibitors consistently attenuate neuropathic and inflammatory pain in pre-clinical models, they often lack full efficacy in such models, and thus their clinical development is limited. On the other hand, the dual FAAH-MAGL inhibitor JZL195 produced enhanced anti-nociceptive effects in several pre-clinical pain models (Anderson, Gould, Torres, Mitchell, Vaughn, et al. 2014; Long, Li, et al. 2009); however, JZL195 also produced hypomotility, catalepsy, and THC-like subjective effects in a drug-discrimination assay, and impaired spatial memory in the Morris water-maze task in mice (Anderson et al. 2014; Long, Li, et al. 2009; Wise et al. 2012). Although these THC-like psychoactive effects present limitations in the use of dual inhibitors for the treatment of pain, JZL195 was about three times as potent in reducing pain behaviors as it was in producing the psychoactive effects (Anderson et al. 2014). In addition, tolerance is a concern in the development of new analgesics. Tolerance to the analgesic effects of sustained complete FAAH inhibition did not occur (Schlosburg et al. 2010), but tolerance (and physical dependence) did develop to the analgesic effects of sustained complete MAGL inhibition (Ignatowska-Jankowska et al. 2014; Schlosburg et al. 2010). However, full inhibition of FAAH (with a high dose of the FAAH inhibitor PF3845) and partial inhibition of MAGL (with a low dose of the MAGL inhibitor JZL184—4 mg/kg) were recently reported to produce sustained reduction of pain in models of inflammatory and neuropathic pain, with minimal cannabimimetic side effects and no tolerance (Ghosh et al. 2015). Therefore, full FAAH inhibition combined with partial MAGL inhibition may be a preferred treatment for neuropathic and/or inflammatory pain.

URB937, a new peripherally restrictive FAAH inhibitor that does not cross the blood-brain-barrier and therefore cannot produce unwanted psychoactive side effects, has been shown to block neuropathic and inflammatory pain via action of AEA on peripheral CB_1 receptors;

however, unlike actions of 2-AG, peripheral effects of AEA may not involve CB_2 receptors (Clapper et al. 2010). Both brain-penetrant FAAH inhibitors (Naidu, Booker, Cravatt, and Lichtman 2009) and non-brain-penetrant FAAH inhibitors (Sasso et al. 2012) act in a synergistic manner with COX inhibitors (non-steroidal anti-inflammatory drugs) to attenuate inflammatory pain in mice. Therefore, treatments that boost the activity of either AEA or 2-AG when and where they are needed have potential as therapeutic agents for pain relief.

CB_2 agonists

There is evidence that the analgesic effects of THC and synthetic cannabinoids (including the full agonist CP55,940) are mediated not only by their action at the CB_1 receptor but also by their action at the CB_2 receptor (Deng, Cornett, Mackie, and Hohmann 2015). Since CB_2 agonism does not produce the psychoactive side effects of CB_1 agonism, considerable recent research is focused on the potential of selective CB_2 agonists to reduce pain.

CB_2-receptor expression may be confined to immune cells such as macrophages, lymphocytes, and mast cells in the periphery and astrocytes and microglia in the CNS. However, recent studies have demonstrated CB_2-receptor activity on neurons, but whether such activity is present in the absence of inflammation is controversial. Activation of CB_2 receptors mediates the anti-inflammatory effects of endocannabinoids as well as having a role in the anti-hyperalgesia in inflammatory pain states (Pacher and Mechoulam 2011). The CB_2 receptor plays an important role in pain signaling and may be of particular importance in the development of chronic pain states. It is not involved in acute pain, such as that measured in hotplate tests and tail-flick tests; instead CB_2 mechanisms are detected in animal models of persistent or chronic pain (Guindon and Hohmann 2009). Since activation of CB_2 receptors does not produce the psychoactive side effects of activation of CB_1 receptors, recent findings that CB_2-receptor agonists are effective analgesic treatments have great promise for the development of novel treatments for chronic pain. Indeed, recent evidence indicates that chronic CB_2 activation reversed neuropathic pain without the development of tolerance (Deng et al. 2015). Repeated systemic administration of the selective CB_2 agonist AM1710 suppressed peripheral neuropathy produced by administration of the chemotherapeutic agent paclitaxel in a mouse model by reducing the pro-inflammatory cytokine tumor necrosis factor α. Since tolerance develops after prolonged chronic dosing with CB_1 agonists

(Bass and Martin 2000), it is noteworthy that tolerance to the analgesic effects of the CB_2 agonist does not develop. There is considerable preclinical evidence that targeting CB_2 receptors to bypass unwanted central effects associated with CB_1-receptor activation is promising as a therapy for neuropathic pain in which the development of effectiveness-reducing tolerance might not occur.

Endocannabinoid Regulation of Pain in the Central Nervous System

Since cannabis and manipulations of the endocannabinoid system reduce acute and chronic pain, it is clear that the endocannabinoid system regulates pain signaling in the central nervous system. The dorsal horn of the spinal cord plays a major role in the processing of pain. It receives and encodes sensory input from the periphery and integrates the descending signals from the brain. When administered into the spinal cord intrathecally (that is, into the spinal theca), cannabinoids reduce acute pain, an effect mediated by CB_1 receptors. However, in sustained painful stimulation, spinal 2-AG levels gradually increase. The increase corresponds to an increase in activation of glial cells and an upregulation of CB_1 receptors, which accompany resolution of a pain state (Alkaitis et al. 2010). Therefore, it is believed that spinal 2-AG signaling initiated by excessive nociceptive activity negatively modulates the acute pain signal, inhibiting the release of pro-nociceptive neurotransmitters (Woodhams, Sagar, and Chapman 2015).

In chronic pain, such as neuropathic pain resulting from peripheral nerve damage, the spinal nociceptive circuitry becomes sensitized, which results in hyperalgesia (excessive pain after a nociceptive stimulus) and allodynia (perception of a normally innocuous stimulus as painful). Treatments that boost the endocannabinoid system have great potential for alleviating these chronic pain states, whereas current analgesics are ineffective (Woodhams et al. 2015). In animal models of neuropathic pain, both CB_1 receptors and CB_2 receptors are upregulated, as are levels of AEA and 2-AG in the spinal cord. However, in view of the role of 2-AG signaling at CB_2 receptors in resolving pain (Alkaitis et al. 2010), a novel area of ongoing research involves intrathecal injections of CB_2-receptor agonists to treat chronic pain states (Burston et al. 2013). Spinal CB_2 expression is elevated and CB_2 agonism alters spinal nociceptive activity in a model of osteoarthritic pain, without effect on control animals. The CB_2 receptor is primarily expressed on glial cells of the CNS; therefore these cells are most likely to mediate the effects of CB_2 agonists in models

of persistent pain. Activation of CB_2 receptors can reduce the release of pro-inflammatory cytokines from glial cells, which is important in the analgesic mechanism.

In the brain, the endocannabinoid system influences ascending pain signals in the thalamus, influences descending modulatory signals in the brainstem, and influences the affective/emotional aspects of pain sensation through actions in the higher cortico-limbic circuits. Direct infusion of cannabinoid agonists into the brainstem regions of the peri-aqueductal gray (PAG) and the rostral ventromedial medulla produces anti-nociceptive effects that can be blocked by CB_1 antagonists. The involvement of endocannabinoids at these sites is mediated by the release of AEA after electrical stimulation of the PAG or after peripheral inflammatory insult. PAG levels of AEA and 2-AG are also elevated in animal models of neuropathic pain. FAAH inhibition in the PAG is anti-nociceptive in acute pain tests, but at very high levels AEA produces pro-nociceptive effects by action at TRPV1 receptors. The PAG is also the site of action of endocannabinoids mediating stress-induced analgesia in rodents (Hohmann et al. 2005). In the region of the rostral ventromedial medulla of the brainstem, "on" cells facilitate nociceptive activity, whereas "off" cells inhibit nociceptive activity; the action of endocannabinoids in that region inhibits the "on" cells and promotes the firing of the "off" cells (Woodhams et al. 2015).

Higher brain regions in the limbic system (in particular the amygdala) and cortical regions mediate the emotional components of pain. Indeed, pre-clinical studies demonstrate that lesions of the amygdala (which regulates emotional behavior) reduce the analgesia produced by THC. A recent fMRI study of healthy humans (Lee et al. 2013) investigated the effects of THC on brain activity produced by ongoing cutaneous burning pain induced by topical administration of capsaicin (an alkaloid derived from chili peppers). Lee et al. (ibid.) found that THC reduced the reported unpleasantness, but not the intensity, of pain. The reduced unpleasantness of pain was accompanied by reduced activity in the anterior cingulate cortex (a cortical region involved in the perception of pain) and by reduced functional connectivity between the amygdala and primary sensorimotor areas during the pain state. Interestingly, the reduction in connectivity was positively correlated with the reductions in ratings of unpleasantness of pain. These findings suggest that the amygdala activity may be related to inter-individual differences in response to cannabinoid analgesia.

Clinical Trials in Humans

There are few effective therapeutic options for patients living with chronic pain. It has been reported that only 40–60 percent of patients obtain even partial relief of their pain with current medications (Wilsey et al. 2008). There is very good evidence that cannabinoids, including marijuana, can be effective in relieving pain as assessed on a visual analog scale, even at low doses (1.29 percent THC) that do not produce psychoactive or cognitive side effects (Wilsey et al. 2013). There have been no clinical trials with humans of the efficacy of CBD alone for chronic pain.

Mary Lynch and colleagues (Lynch and Campbell 2011; Lynch and Ware 2015) conducted systematic reviews of randomized controlled trials conducted since 2003 examining cannabinoids in the treatment of chronic non-cancer pain. The cannabinoids included in the reviews were smoked cannabis, oromucosal extracts of cannabis-based medicines, nabiximols, nabilone, dronabinol, and a novel THC analogue of the metabolite THC-11-oic acid (ajulemic acid). The chronic pain conditions included neuropathic pain, fibromyalgia, rheumatoid arthritis, and mixed chronic pain. Among the 29 trials included in the reviews, 22 found significant analgesic effects of the cannabinoid as compared with either placebos or active control compounds, and several reported significant improvements in sleep. No serious adverse effects were reported; the adverse effects that were reported were mild to moderate and led to only a few participants withdrawing from the studies. The reviews concluded that there is evidence that cannabinoids are safe and moderately effective in treating neuropathic pain, and that there is some evidence of efficacy in fibromyalgia and rheumatoid arthritis. Of particular importance, two of the trials examining smoked cannabis (Abrams et al. 2007; Ellis et al. 2009) demonstrated a significant analgesic effect in HIV neuropathy, a type of pain highly resistant to any available treatment for neuropathic pain. In addition, Abrams et al. (2011) have shown that vaporized cannabis can augment the analgesic effects of opioids, an effect also demonstrated in the pre-clinical animal literature; it will be interesting to determine if this important finding can be replicated using a double-blind placebo control procedure. It was noteworthy that in a trial of the effect of Sativex in the treatment of rheumatoid arthritis a significant reduction in disease activity was also noted (Blake et al. 2006), which is consistent with pre-clinical work showing that cannabinoids are anti-inflammatory.

High doses of THC may not be necessary to control neuropathic pain. A recent double-blind, placebo-controlled crossover study (Wilsey et al. 2013) evaluated the potential of vaporized cannabis (placebo, medium-dose THC [3.53 percent], or low-dose THC [1.29 percent]) to reduce neuropathic pain in humans who were resistant to traditional treatment. Both the high and the low dose were equally effective in reducing pain, yet the psychoactive effects of the low dose were minimal and were well tolerated.

The first cohort study of the long-term safety of medical cannabis use was recently reported by Mark Ware and colleagues; it involved patients being treated for non-cancer chronic pain in seven clinics in Canada over the course of a year (Ware, Wang, Shapiro, Collet, et al. 2015). The primary outcome measures were severe adverse events and non-severe adverse events as defined by the International Conference on Harmonization (http://www.ich.org/cache/compo/276-254-1.html). The comparison groups included 215 individuals with chronic pain who were given cannabis (12.5 percent THC) and 216 individuals with chronic pain who were not given cannabis. The cannabis users were advised to use the delivery method with which they were most comfortable and to titrate their dose to the level they tolerated best. The median intake was 2.5 grams per day, and no relationship was found between increasing the daily dose and the development of adverse effects. This suggests that the patients titrated their dose to control adverse effects. Over the year of treatment the cannabis group, but not the control group, showed a significant reduction in pain intensity. In addition, there was no difference among the groups in the risk of severe adverse events (cannabis group 13 percent, non-cannabis group 19 percent). Most patients in the cannabis group (88.4 percent) and most in the control group (85.2 percent) reported at least one non-severe adverse event, with a mean of three events per participant in the cannabis group and a mean of two events per participant in the control group. The overall incidence of non-severe adverse events in the cannabis group (818) was significantly higher than that in the control group (581). The specific events associated with cannabis included headache, dizziness, nausea, and somnolence.

As a secondary measure, Ware et al. (2015) administered neurocognitive tests at the start of the study, at 6 months, and at 12 months, using two sub-tests of the third edition of the Wechsler Memory Scale (Verbal Paired Associates I, including recall, and Verbal Paired Associates II, including recall and recognition) and two sub-tests of the third edition of the Wechsler Adult Intelligence Scale (Digit Symbol-Coding and Picture

Arrangement). Significant improvements were observed in all neurocognitive sub-tests after 6 months and after 12 months in both the cannabis group and the controls. No differences in neurocognitive function were seen between the two groups. Measures of pulmonary function did not differ between the groups after adjusting for tobacco smoking. The cannabis users did not show changes in liver, kidney, or endocrine functioning as assessed by blood tests. Therefore, this first follow-up study of medical cannabis users suggests that its adverse effects are small and are comparable both quantitatively and qualitatively to those of prescription cannabinoids, such as naboline. The average dose of 2.5 g/day of 12.5 percent THC cannabis may be safe as a part of a carefully monitored pain-management program (Ware et al. 2015).

Using a conservative criterion of risk of bias of results, Whiting et al. (2015) conducted an extensive systematic review of 79 randomized controlled trials that examined the benefits and adverse effects associated with medical cannabis across a broad range of conditions, the majority of the trials evaluating nausea and vomiting due to chemotherapy or chronic pain and spasticity due to MS and paraplegia. In determining the quality of a trial, Whiting et al. used the Cochrane Collaboration's tool for assessing risk of bias in randomized trials, which covers six domains of bias: selection bias, performance bias, detection bias, attrition bias, reporting bias, and other bias. If at least one domain was rated high, a trial was considered at high risk of bias. The review concluded that most studies suggested that cannabinoids were associated with improvements in symptoms. The evidence was strongest that smoked cannabis and oromucosal THC:CBD mixtures may be beneficial for the treatment of chronic neuropathic or cancer pain and that nabiximols, naboline, THC/CBD capsules, and dronabinol may be beneficial for the treatment of spasticity due to multiple sclerosis, with moderate risk of bias for most of these studies. Although the cannabinoids also were effective for chemotherapy-induced nausea and vomiting, the risk of bias among these studies was high. Interestingly there was no clear evidence for a difference in effectiveness or in adverse effects based on the type of cannabinoid or the mode of administration.

Although the use of FAAH and MAGL inhibitors in pre-clinical studies has clearly supported the use of endocannabinoid-targeted compounds in clinical pain trials with humans, there has been only one published report of such a trial, and it was a failure. The pharmaceutical corporation Pfizer developed a highly selective FAAH inhibitor, PF-04457845, to produce analgesia in an osteoarthritic patient population (Huggins,

Smart, Langman, Taylor, and Young 2012). That compound reduced FAAH activity by 96 percent and increased AEA levels substantially, but was not differentiated from placebo in reduction of pain. However, it was well tolerated, with no evidence of cannabinoid-type adverse events.

The pain targeted in the Pfizer clinical trial, osteoarthritis pain, may differ qualitatively from the pain typically measured in many pre-clinical models that have demonstrated analgesic effects of FAAH inhibition. Most pre-clinical models measure reflex responses to a mechanical or thermal stimulus, whereas the predominant symptom in neuropathic pain evident in osteoarthritis is not evoked pain but instead spontaneous pain, which is more difficult to model pre-clinically (Fowler 2015). In an attempt to model osteoarthritic pain in animals more closely, Bryden et al. (2106) injected monosodium iodoacetate into rats' knees, producing histological changes representative of those seen in human osteoarthritic patients. The measure of pain was the likelihood that a rat would spontaneously burrow into bedding (an innate rodent behavior indicative of well-being). Bryden et al. (2016) demonstrated deficits in burrowing in this model that were reversed by COX inhibitors (ibuprofen and celecoxib), but were not reversed by the Pfizer FAAH inhibitor, PF-04457845, which was also ineffective in human osteoarthritis patients (Bryden et al. 2015). The pre-clinical data thus mirror the human clinical data for this indication. In view of the considerable pre-clinical evidence of the potential of FAAH inhibitors and MAGL inhibitors to reduce pain in a variety of models, there is a clear need to continue to evaluate the potential benefits of these treatments in other human models of chronic pain.

Conclusion

A majority of the patients who use medical marijuana are prescribed marijuana for pain—particularly chronic neuropathic pain, which is resistant to current treatments. Since opiates are the most common treatment for pain, it is interesting that considerable pre-clinical animal research demonstrates a clear interaction between cannabinoids and opiates at a number of levels within the cell, including direct receptor associations, alterations in endogenous opiate release, and post-receptor interactions via shared signal transduction pathways. Various studies have demonstrated cross-tolerance, mutual potentiation, and receptor cross-talk between the μ-opiate receptor and the CB_1 receptor. Drugs that target the cannabinoid system often affect the opioid system in tandem.

Considerable evidence indicates a synergistic effect of cannabinoid-opiate drugs (Scavone et al. 2013). For instance, sub-threshold combined doses of cannabinoids and morphine reduce pain in animals and in humans. These findings suggest that the combined use of THC and opiates may provide an opportunity for better pain relief from lower doses of each drug. In addition, the use of nabiximols (Sativex) for chronic pain associated with multiple sclerosis and cancer has shown promise, with the additional benefit that CBD tempers the intoxicating effects of THC.

Although the first clinical trial of a FAAH inhibitor to produce analgesia in an osteoarthritic population failed, the pre-clinical evidence suggests that continued investigation of both FAAH and MAGL inhibitors is warranted, especially for non-osteoarthritic chronic pain. Pre-clinical evidence points to future development of effective CB_2 agonists, devoid of the psychoactive side effects of CB_1 agonists, to produce pain-relieving anti-inflammatory effects.