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# Cannabinoids for Neuropathic Pain

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**Abstract** Treatment options for neuropathic pain have limited efficacy and use is fraught with dose-limiting adverse effects. The endocannabinoid system has been elucidated over the last several years, demonstrating a significant interface with pain homeostasis. Exogenous cannabinoids have been demonstrated to be effective in a range of experimental neuropathic pain models, and there is mounting evidence for therapeutic use in human neuropathic pain conditions. This article reviews the history, pharmacologic development, clinical trials results, and the future potential of nonsmoked, orally bioavailable, nonpsychoactive cannabinoids in the management of neuropathic pain.

**Keywords** Cannabinoids · Endocannabinoid system · Neuropathic pain

## Introduction

Forty-five years ago, commenting on the inadequate state of understanding of potentially therapeutic vs adverse health effects of cannabinoids, Raphael Mechoulam, a pioneer in cannabinoid pharmacology, said: "It is a sad truth, however, that in spite of the voluminous literature on the subject, critical scientific evaluation of the different aspects of the problem are few"[1]. PubMed indexed publications referencing cannabis and cannabinoids ran at a rather steady rate of about 200 per year for several decades, until about 10 years ago. Since then, there has been more than an 8-fold increase in such citations. Nevertheless, were Mechoulam's words of almost one-half a century ago uttered today, they would be as accurate in describing our depth of applied pharmacologic understanding , largely because of social and regulatory constraints that have trumped both knowledge and potential welfare of innumerable patients living with intractable conditions for which cannabinoids may have therapeutic benefit.

The more recent explosion of literature does signal both a rapidly growing interest in and understanding of the endocannabinoid system, cannabinoids, and the relationship between cannabinoids and potential medical applications. This foray into cannabinoid science coupled with a rapidly evolving re-evaluation of prohibitions surrounding use of cannabis can now complement a vast anecdotally-based oral and written history, derived from millennia of cannabis use for recreational and health-related purposes [2]. Although this article's focus is on current pharmacologic and clinical science related to cannabinoids and the medical indication of neuropathic pain, it is useful to provide a brief overview of the historical context undergirding our current understanding of the endocannabinoid system and cannabinoids.

## Early History of Cannabis for Pain

Historical accounts of cannabis use as an analgesic are inconsistent. Egyptian relics dating to the 16th century BC appear to ascribe medicinal benefit to cannabis. In India, the medical and religious use of cannabis probably began together around 3000 years ago. The plant was used for many pain-related purposes, including neuralgia, headache, and toothache. Evidence from a 4th century BC tomb near Jerusalem suggests use of cannabis to ease the pain of childbirth. Intoxicating effects were recognized and memorialized in Sanskrit, Hindu, and Chinese writings starting about 2000 years ago. In 2nd century China, cannabis resin, mixed with wine, was used with apparent success as an anesthetic in

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order to perform major surgical procedures. The first comprehensive writings in western society are found in the "material medica" written by the Greek physician Dioscorides in the 1st century CE who was accompanying the Roman army. Cannabis is listed as an herbal remedy, especially useful for ear aches. Later, in the 2nd century CE, Galen described the analgesic effects of cannabis. Although hemp was cultivated widely throughout many geographic areas, there is little medical documentation until centuries later.

In Europe, during the early 19th century, science-minded soldiers in Napoleon Bonaparte's army published papers extolling the virtues of cannabis for pain and other virtues. George Washington is reported to have used cannabis for tooth pain. The mid-1800s saw a great surge of interest in potential medical benefits of cannabis resin and extracts, administered in a variety of forms to treat acute and chronic pain and alcohol withdrawal, among other conditions. Cannabis was accepted into the U.S. Pharmacopoeia in 1850 and was included in many compounds marketed by major mainstream pharmaceutical companies of the era.

During the temperance movement of the late 19th century and early 20th century, along with fears related to racial and ethnic prejudices, the term cannabis became conflated with the Spanish term marihuana, which was used to describe recreational use. Eventually, and in the absence of any scientific understanding of cannabinoid pharmacology, concerns about medical benefits vs adverse side effects and abuse liability dominated policy around cannabis use. This led to the 1937 Marihuana Tax Act that imposed untenable regulatory barriers to medical use or research. The 1970 Controlled Substances Act, listing any and all cannabinoids as Schedule 1 substances, effectively closed the door on therapeutic investigation for many years [2–6]. Extraordinary efforts are required to obtain authorization for cannabinoid research in the United States, under the aegis of the National Institute on Drug Abuse (NIDA). As a direct result, almost all reports of cannabinoid use for pain in the modern era have come from very limited trials or anecdotal reports [7]. Notwithstanding these severe shortcomings, there appears to be compelling evidence that some cannabinoids may fill an important treatment gap in the management of neuropathic pain [8, 9].

## Present Day Cannabinoid Science

The endogenous cannabinoid system has been described as "an ancient lipid signaling network, which in mammals modulates neuronal functions, inflammatory processes, and is involved in the etiology of certain human lifestyle diseases, such as Crohn's disease, atherosclerosis, and osteoarthritis. The system is able to downregulate stress-related signals that lead to chronic inflammation and certain types of pain, but it is also involved in causing inflammation-associated symptoms, depending on the physiological context [10]." Within this system, 2 distinct receptor types have been identified, that serve as binding sites for endogenous and exogenous cannabinoids.

### $CB_1$ Receptors

The $CB_1$ receptor has been cloned from humans [11]. Activation of $CB_1$ receptors leads to dose-dependent and stereo-selective inhibition of adenylate cyclase activity, with effects on memory, perception, and movement. The $CB_1$ receptor appears to be responsible for the mood enhancing effects of cannabis as well as negative psychotomimetic effects, including anxiety, paranoia, and dysphoria, in susceptible individuals.

$CB_1$ receptor distribution has been well-characterized in the human brain [12]. The receptors are expressed in high abundance in the hippocampus and associational cortical regions, the cerebellum, and the basal ganglia. This widespread distribution in the brain matches well with the known pharmacodynamic effects of cannabinoids. In contrast, binding is sparse or absent from the brain stem, medulla, and thalamus. The paucity of $CB_1$ receptors in these areas helps explain the absence of life-threatening effects on vital physiological functions associated with extremely high doses of cannabinoids.

Outside of the brain, $CB_1$ receptors occur in the testis, and on presynaptic sympathetic nerve terminals [13]. $CB_1$ receptor mRNA has been identified in the adrenal gland, heart, lung, prostate, bone marrow, thymus, and tonsils [14, 15].

### $CB_2$ Receptors

Although $CB_1$ and $CB_2$ receptors share considerable structural similarities, their distribution and activity diverge. Among other actions, including pain modulation, $CB_2$ receptors are thought to serve an important role in immune function and inflammation [16•]. There is ample evidence that $CB_2$ receptor activation reduces nociception in a variety of preclinical models, including those involving tactile and thermal allodynia, mechanical, and thermal hyperalgesia, and writhing [17]. With regard to their role in modulating neuropathic pain, the presence of $CB_2$ receptors on microglia within the nervous system may explain the putative benefits of cannabinoids in reducing cytokine-mediated neuroinflammation.

$CB_1$ and $CB_2$ receptors inhibit adenylate cyclase via interactions at the G-protein complex. However, their activation and consequent inhibition of various ion channels differs [18]. The key point is that differential binding of $CB_1$ or $CB_2$ receptors, either separately or in combination by their respective endogenous or exogenous ligands, leads to varied physiological effects, mediated via several neurotransmitters, including acetylcholine, glutamate, and dopamine.

## Endogenous Cannabinoids and Pain Signal Processing

The first compound to be identified as an endogenous cannabinoid receptor ligand was given the name anandamide, after the Sanskrit word for bliss. Anandamide bears no chemical resemblance to the aromatic phytocannabinoids such as THC and CBD, but rather is an arachidonic acid derivative [19]. Several other endogenously generated moieties (endocannabinoids) have been identified that bind to cannabinoid receptors, but their roles in homeostatic functions and in disease states remain poorly defined. The physiologic role of anandamide continues to be actively explored, having been identified in central and peripheral tissues of man [20].

It appears that the endocannabinoid system is intimately involved in tissue healing in the face of inflammatory conditions, correlating clinically with prevention and treatment of inflammation-mediated pain [21]. With regard to potential pain-modulating activity, anandamide has been shown to be a full agonist at vanilloid ($TRPV_1$) receptors, and may play a modulating role at other transient receptor potential (TRP) receptor types [22]. Anandamide is reported to produce effects similar to THC at $CB_1$ receptors, via G-protein coupled inhibition of adenylate cyclase. These effects include antinociception, hypomotility, and reduced memory [23].

There are distinct differences between anandamide and other cannabinoids with respect to their antinociceptive properties and other physiological effects, which vary as a function of route of administration. It is not known whether anandamide acts at the same sites as phytocannabinoids to produce antinociception. The behavioral effects of THC and anandamide after administration suggest that they act, at least in part, in the brain and/or spinal cord. These studies suggest that anandamide is less potent and has a shorter duration of action than THC [24].

Studies have demonstrated that antinociceptive effects of cannabinoids are mediated through mechanisms distinct from those responsible for other behavioral effects. For instance, THC has additive analgesic efficacy with kappa opioid receptor agonists. This effect is blocked by kappa antagonism but opioid receptor antagonism does not alter psychoactive effects of THC [25]. Investigations into the endogenous cannabinoids and their effector sites (including $CB_1$ and $CB_2$ along with other noncannabinoid receptors) have exploded in recent years and insights reveal this area of pharmacology to be highly complex and dynamic. For instance, there is mounting evidence that endogenous and exogenous cannabinoids exert some influence on opioid, $5HT_3$, N-methyl-d-aspartate, and most recently, α3 glycine receptors. These interactions suggest a role for endocannabinoids in homeostatic pain modulation (antinociception), thus, their use as exogenous agents in pain management [26].

Evidence now suggests that by binding effects at $CB_1$ and $CB_2$ receptors, respectively, the cannabinoid agonists anandamide and N-palmitoyl-ethanolamine (PEA) induce peripheral antinociception through activation of the central endogenous noradrenergic pathway and peripheral adrenoreceptors [27•]. Other studies have demonstrated the expression of functional $CB_2$ receptors in areas of human dorsal root ganglion (DRG) sensory neurons. $CB_2$ receptor expression also has been demonstrated in the spinal cord as well as in other brain regions particularly relevant for nociceptive integration [28–30].

These findings implicate $CB_2$ receptors in the analgesic effects produced by $CB_2$ agonists [31, 32]. Other evidence for the involvement of the endocannabinoid system in peripherally-mediated pain control includes the finding that $CB_2$ receptor agonists can evoke analgesia by triggering the release of beta-endorphin in response to the stimulation of $CB_2$ receptors expressed in human keratinocytes [33]. Many other studies have linked cannabinoid and opioid effects through primary receptor interactivity as well as downstream second messenger effects. From a clinical standpoint, this may provide an opportunity for therapeutic synergy [34].

The role of $CB_2$ receptors in antinociception has been demonstrated in inflammatory and neuropathic pain models. Investigations involving carrageenan-induced inflammatory pain in rodents demonstrate that activation of $CB_2$ receptors by $CB_2$ selective agonists suppresses neuronal activity in the dorsal horn via reduction in C-fiber activity and wind-up involving wide dynamic range (WDR) neurons [35, 36]. The involvement of cannabinoid receptors in modulating pain has been supported further by findings that there are increases in peripheral $CB_2$ receptor protein or mRNA in inflamed tissues and in the dorsal root ganglion in neuropathic states [37–39]. Data from studies investigating viscerally-induced pain due to colorectal distention indicate that peripheral $CB_1$ receptors mediate the analgesic effects of cannabinoids on visceral pain from the gastrointestinal tract [40].

Not all of the pain-relieving effects of cannabinoids can be explained by interactions at $CB_1$ and $CB_2$ receptors. Xiong et al [41••] have shown that both systemic and intrathecal administration of CBD suppress chronic inflammatory and neuropathic pain without the development of tolerance in a rodent model. The mechanism of pain relieve appears to be through significant potentiation of glycine currents in dorsal horn neurons, and this analgesic effect does not correspond to $CB_1$ and $CB_2$ binding affinity. Corroborating this extra-CB-receptor phenomenon is the observation that analgesic efficacy of CBD is diminished in mice lacking the α3 glycine receptor.

Several additional animal models have established a strong basis for cannabinoid attenuation of neuropathic pain. Neuropathic pain models evaluating the role of cannabinoids as analgesics include chronic constriction injury, partial sciatic nerve ligation, and spinal nerve ligation, among others. Similarly, disease-related animal models have also demonstrated

reduction or elimination of mechanical allodynia and/or hyperalgesia, common and unifying phenomena underlying neuropathic pain. Efficacy of cannabinoids in reducing these signs and symptoms has been shown in streptozotocin-induced diabetic neuropathy, chemotherapy-induced neuropathy (vincristine, cisplatin, and paclitaxel), HIV-associated neuropathy, demyelination-induced neuropathy, and in postherpetic neuralgia (PHN) [42].

The sum of these data strongly suggest that cannabinoids play a pivotal role in homeostatic modulation of nociception, and that exogenous cannabinoids may offer an important therapeutic opportunity as nontraditional analgesics in various pain states [43]. With this foundation to build upon, the proceeding section will explore the role of cannabinoids in clinical pain relief in humans. Much has been learned since a decade ago when there was significant doubt about translating research findings linking cannabinoids to antinociception with pain relief in actual patients [44]. But there are now methodically sound studies that may lead to important therapeutic advances for people living with neuropathic pain.

## Cannabinoids and the Management of Pain

Evidence continues to accumulate suggesting that cannabinoids can impact normal inhibitory pathways and pathophysiological processes influencing nociception in humans [37, 45]. When cannabinoids do have an analgesic effect, it is more likely to occur in hyperalgesic and inflammatory states [46]. Clinical trials lasting from days to months, involving more than 1000 patients, have shown efficacy in different categories of chronic pain conditions but the vast majority of controlled trials have involved patients with chronic neuropathic pain (Table 1).

When cannabinoids lead to a reported reduction in pain, it remains unclear where the effects are triggered, or which aspect of the pain experience is most affected and under what circumstances. As well, different cannabinoids may lead to mechanistically different pain relieving effects. For instance, a recent study of functional brain imaging in human volunteers investigated the means by which THC may influence pain resulting from capsaicin-induced hyperalgesia. The study results suggest that "peripheral mechanisms alone cannot account for the dissociative effects of THC on the pain that was observed. Instead, the data reveal that amygdala activity contributes to inter-individual response to cannabinoid analgesia, and suggest that dissociative effects of THC in the brain are relevant to pain relief in humans" [47]. In other words, cannabinoids, and THC in particular, may have differential effects on the sensory (eg, intensity; quality) vs affective (eg, unpleasantness; suffering) components of pain.

The 2 best studied cannabinoids implicated as having potential analgesic properties are THC and cannabidiol (CBD) (Fig. 3). THC was first isolated from cannabis by Raphael Mechoulam and colleagues in 1964 at the Hebrew University of Jerusalem, identifying it as the major psychoactive component of cannabis, with preferential binding at $CB_1$ receptors [48]. Synthetic forms of THC, like dronabinol and nabilone, are commercially available in several countries, and are considered controlled substances. These have indications for treating anorexia in AIDS patients and as a therapy for intractable nausea and vomiting during cancer chemotherapy. In a wide range of oral doses, dronabinol, which is chemically identical to the THC extracted from plants, has not demonstrated significant pain relief in several naturally occurring and experimental pain conditions [49–51]. In contrast, nabilone, which is chemically similar to THC but not identical [52] has demonstrated modest efficacy in fibromyalgia [53] but with dose-limiting adverse effects. Its use has led to paradoxical increases in pain in the postoperative setting [54].

Cannabidiol is a major constituent of cannabis. It has virtually no psychoactivity compared against THC [55]. Cannabidiol has low affinity for both cannabinoid $CB_1$ and $CB_2$ receptors. Limited pharmacodynamic effects due to relatively weak receptor binding (low affinity) may be overcome with higher doses of agonist. Whereas the dose-limiting factor with THC resides in the highly variable propensity among individuals to experience and tolerate negative affective, cognitive and psychotomimetic effects, the ability of cannabidiol to behave as a $CB_1$ receptor inverse agonist may contribute to its documented mitigating action on THC psychotomimetic effects. More recently it has been postulated that cannabidiol may exert its effects via inhibition of anandamide deactivation or otherwise enhancing anandamide signaling [56].

Cannabidiol agonist activity at $CB_2$ receptors seems to account for its anti-inflammatory properties and both primary and secondary influences on pain [57, 58]. As well, memory impairments associated with THC are not apparent with CBD, and when combined, CBD reduces the negative impact of THC on memory. This mitigating effect also has been attributed to the inverse agonist effect at $CB_1$ receptors by CBD. Anxiolytic effects of CBD may also be attributed to its agonist effect at the $5\text{-}HT_{1A}$ receptor [59].

A pharmaceutical combination product of THC and CBD now exists as an oral spray consisting of 27 mg Δ9-tetrahydrocannabinol and 25 mg cannabidiol per ml (100 microliters per administered dose; ie, 2.7 mg THC and 2.5 mg CBD), extracted from Cannabis sativa L. This formulation is approved in Canada, New Zealand, Israel, and several European countries for the management of central pain and spasticity in multiple sclerosis (MS). There are several ongoing trials on its efficacy in treating MS-related pain [60]. The therapeutic value of THC and THC-CBD via oral mucosal delivery in the treatment of various other neuropathic pain conditions show promising, albeit, modest results [61, 62]. The limited efficacy is likely due to the relative low dose of

**Table 1** Clinical trials: cannabinoid and NP pain

| NP type | Number of subjects | Cannabinoid type, preparation | Dosage and route | Treatment duration | Study design | Results | Author, reference |
|---|---|---|---|---|---|---|---|
| HIV | 50 | Marijuana | 3.56 % THC, smoked 3 times per d | 5 d | RCT | Significant pain reduction in active treatment group. | Abrams et al [78] |
| Chronic NP pain | 34 | THC+CBD 1:1 | Oral mucosal, variable dose | 12 wk | RCT | Positive pain relieve (not otherwise specified). | Notcutt et al [79] |
| Chronic NP pain | 21 | CT-3 (THC analog) | Oral, 20 mg twice daily× 4 d, then 40 mg twice daily×3 d | 7 d | RCT cross-over | Significant decrease in hyperalgesia, allodynia and VAS pain intensity scores. | Karst et al [80] |
| MS | 630 | THC cannabis extract | Oral, variable dose | 15 wk, with 52 wk continuation | RCT | Statistically significant reduction in pain scores and clinically meaningful sense of improvement. | Zajicek et al [81] |
| MS | 24 | Dronabinol | Oral 10 mg | 3 wk | RCT cross-over | Significant pain reduction with active treatment. | Svenden et al [82] |
| MS | 137 | THC+CBD 1:1 (Sativex) | Oral mucosal, variable dose | 10 wk controlled trial followed by 52 wk open label | RCT and open label | Significant pain reduction with active treatment; continued pain relieve in about half of long-term use patients. | Wade et al [83] |
| MS | 66 | THC+CBD 1:1 (Sativex) | Oral mucosal, variable dose | 4 wk | RCT | Significant pain reduction with active treatment. | Rog et al [84] |
| Chronic NP pain conditions | 24 | THC+CBD 1:1 | Oral mucosal, variable dose | 2 wk | RCT cross-over | Significant pain reduction with active treatment. | Wade et al [85] |
| Brachial plexus injury | 48 | THC+CBD 1:1 (Sativex) vs THC vs placebo spray | Oral mucosal, variable dose | Three 2-wk treatment period | RCT cross-over | Significant pain reduction with both active treatments | Berman et al [86] |
| Peripheral NP pain | 125 | THC+CBD 1:1 (Sativex) | Oral mucosal, variable dose | 5 wk controlled trial followed by 52 wk extension | RCT | Significant pain reduction with active treatment | Nurmikko et al [87] |

*MS* multiple sclerosis, *NP* neuropathic pain

this combination of cannabinoids. It is important to note that the dose-limiting factor is how much THC may be tolerated. With higher doses via smoking marijuana or inhaling vaporized cannabis, hyperalgesic, and cognitive effects become more pronounced and problematic, especially in cannabis-naïve individuals [63–67]. Beyond these trials involving CBD and THC, comparative or head-to-head studies of individual cannabinoids or various cannabinoid combinations and routes of administration evaluating clinical outcomes are lacking.

## Combining Phytocannabinoids and Terpenes: the Entourage Effect

The entourage effect is the term used to describe enhancement of efficacy, with related improvement in overall therapeutic effectiveness, derived from combining phytocannabinoids and other plant-derived molecules [68]. Besides CBD, phytocannabinoids that have been identified as exerting clinically-useful effects without psychoactivity include tetrahydrocannabivarin, cannabigerol, and cannabichromene. Innovative conventional plant breeding has been yielding Cannabis chemotypes expressing high titres of each component for future study.

A chemical class known as the terpenes share a precursor molecule with phytocannabinoids, and are all flavor and fragrance components common to human diets. Terpenes have been designated Generally Recognized as Safe (GRAS) by the US Food and Drug Administration and other regulatory agencies. Cannabis-derived terpenes include limonene, myrcene, α-pinene, linalool, β-caryophyllene, caryophyllene oxide, nerolidol, and phytol. These terpenes are also found in other plants [69].

Terpenes are quite potent, and affect animal and even human behavior when inhaled in very low concentrations. They display unique therapeutic effects that may contribute meaningfully to the entourage effects of cannabis-based medicinal extracts. Of particular interest are the phytocannabinoid-terpene interactions that could produce synergy with respect to treatment of pain and inflammation. Phytocannabinoid-terpene synergy increases the likelihood that an extensive pipeline of new therapeutic products is possible from this age-old plant.

The synergistic contributions of cannabidiol to Cannabis pharmacology—and specifically analgesia—have been scientifically demonstrated. Preclinical and clinical data indicates that cannabinoids administered together are more effective at ameliorating neuropathic pain than the use of a single agent [68].

The terpene β-caryophyllene is found in a number of commonly available plants, including black pepper, cinnamon, clove and other spices. It selectively binds to the $CB_2$ receptor at nanomolar concentrations and acts as a full agonist. β-caryophyllene and cannabidiol abundantly occur in Cannabis sativa [70]. So, this plant species produces at least 2 entirely different chemical substances able to differentially target $CB_2$ receptors. Although studies on the pharmacokinetics of β-caryophyllene are still ongoing, it is already clear that this terpene is readily bioavailable. Unlike many polyphenolic natural products, it is not metabolized immediately but shows a Tmax >1 hour after 1 single oral administration. Orally administered β-caryophyllene (<5 mg·kg-1) produces strong anti-inflammatory and analgesic effects in wild type mice but not in $CB_2$ receptor knockout mice, which is a clear indication that it may be a functional $CB_2$ ligand [71].

Ongoing studies show that β-caryophyllene is effective at reducing neuropathic pain in a $CB_2$ receptor-dependent manner [72]. Like other $CB_2$ ligands β-caryophyllene inhibits the pathways triggered by activation of the toll-like receptor complex CD14/TLR4/MD2, which typically lead to the expression of pro-inflammatory cytokines (eg, IL-1 beta, IL-6; IL-8, and TNF alpha), is synergistic with opioid analgesic effects, and promotes a Th1 immune response that plays a critical role in neuroinflammation, sensitization, and pain [73]. Therefore, the FDA approved food additive β-caryophyllene seems an attractive candidate for clinical trials targeting the $CB_2$ receptor. Indeed, in cases of intractable or difficult-to-control pain, combination therapy with small doses of opioid and nonpsychoactive cannabinoid receptor agonists may be an alternative way to circumvent the undesirable side effects of opioids alone, yet obtain far greater analgesic efficacy than achieved with cannabinoids alone [74–77].

## Conclusions

Great progress has been made in understanding the pharmacology of the endocannabinoid system and elucidating the structures of several phytocannabinoids and many of their physiological effects. These steps have provided a rational foundation upon which to test the efficacy of high therapeutic index cannabinoids such as cannabidiol in experimental neuropathic pain models, as well as in several difficult-to-control human neuropathic pain conditions. These early trials suggest that cannabidiol may offer a safe and effective alternative or adjunct to currently used pharmacotherapies (eg, tricyclic antidepressants, anticonvulsants, opioids, and local anesthetics). With a rapidly-emerging shift toward a less stringent regulatory environment, there is a widening window of opportunity for methodologically sound research to explore the role of phytocannabinoids—especially nonpsychoactive and orally bioavailable formulations—in the treatment of neuropathic pain.

**Compliance with Ethics Guidelines**

**Conflict of Interest** Perry G. Fine and Mark J. Rosenfeld serve on the Board of Directors of ISA Scientific, Inc., a medicinal cannabinoid research and development company.

**Human and Animal Rights and Informed Consent** This article does not contain any studies with human or animal subjects performed by any of the authors.

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- • Of importance
- •• Of major importance


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