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Review

Cannabinoids and chronic pelvic pain in women: Focus on endometriosis

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Abstract

Chronic pelvic pain in women is common and frequently difficult to treat. Chronic pelvic pain often develops in the setting of endometriosis, interstitial cystitis/bladder pain syndrome, and vulvodynia. Cannabinoids are a promising treatment modality for non-cancer chronic pain, but have not been studied in women with chronic pelvic pain nor in specific chronic pelvic pain conditions. This review focuses on the interaction of the endocannabinoid system with the menstrual cycles, with endometriotic lesions, and within the bladder. Furthermore, it provides a brief overview of existing literature of the effects of endocannabinoids on chronic pain generally, with a focus on neuropathic pain. Finally, it discusses limited data available regarding the use of cannabinoids in women with chronic pelvic pain conditions. In the opinion of the authors, cannabinoids are a reasonable treatment modality for refractory chronic pelvic pain, especially if a neuropathic component is suspected. Practitioners should expect a modest effect on pain levels with an acceptable safety profile.

Keywords

Cannabinoids, marijuana, THC, CBD, pelvic pain, endometriosis, interstitial cystitis, bladder pain syndrome, vulvodynia

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Introduction

Over the last few decades there has been a shift toward legalization of marijuana for medicinal use; marijuana has been increasingly legalized or decriminalized in many states for recreational and medical purposes. There is accumulating data supporting the use of cannabinoids for chronic pain, especially neuropathic pain, although not as first line therapy. Chronic pelvic pain in general and endometriosis specifically can be difficult to medically manage, even with multimodal therapy.[1] However, no randomized studies exist regarding cannabinoids for chronic pelvic pain nor for chronic pain syndromes such as endometriosis or interstitial cystitis/bladder pain syndrome (IC/BPS).

The therapeutic potential of cannabinoids for gynecologic or genitourinary chronic pelvic pain depends on a thorough understanding of the analgesic mechanisms of cannabinoids as well as their interactions with the gynecologic organs and the menstrual cycle. Therefore, we provide a review of the complex physiologic role of the endocannabinoid system (ECS) in the menstrual cycle followed by a review of the existing literature of cannabinoids for chronic pain. As part of our review, we focus on neuropathic pain, chronic pelvic pain, and gynecologic pain specifically.

The clinician can infer possible roles for cannabinoids for the treatment of chronic pelvic pain from relevant trials in which cannabinoids are used to treat other types of chronic pain. While our understanding of the role of cannabinoids in the treatment of chronic pelvic pain is limited, the parallels from domains of studies do suggest multiple avenues for further research.

Cannabinoid background

The first biologically active component of cannabis was identified in the 1960s as Delta-9-tetrahydrocannabinol

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(THC), a potent drug classified as a sedative-hypnotic. This was followed by the discovery of two cannabinoid receptors, cannabinoid receptor 1 (CB1R) and cannabinoid receptor 2 (CB2R), in the early 1990s. Both CB1R and CB2R are G-protein-coupled receptors and serve as the primary sites of action for THC. Together, they are involved in the major neuromodulatory ECS, whose primary goal is to promote homeostasis. The predominant components of the ECS are the CB1R and CB2R, their endogenous ligands, anandamide (AEA) and 2-arachidonoylglycerol (2-AG), and the enzymes that modulate their breakdown (fatty acid amide hydrolase and monoacylglycerol lipase). They are synthesized by fatty-acid metabolism and located in neurons, where they are released on demand by simple diffusion.

The ECS is widespread and found primarily in the central nervous system, the peripheral nervous system, in the immunologic system, and in peripheral organs (Figure 1). The cannabinoid receptors differ in their anatomic distribution. CB1Rs are found throughout the central nervous system and some peripheral tissues. CB2Rs are primarily found in peripheral tissues and immune cells. Centrally, these receptors are more densely expressed in the neurons of thalamus, hypothalamus, hippocampus periaqueductal grey matter, amygdala, cerebral cortex, parts of the basal ganglia, and cerebellum and as such are present in central nociceptive centers.[2] They are also expressed on the dorsal horn, which is involved in the processing of pain signals.[3–5] Furthermore, they are expressed on a small proportion of peripheral C-fibers and more so on myelinated A-delta fibers.[6] Peripherally, cannabinoid receptors are found in organs responsible for producing sex hormones, such as the adrenals, which provide a source of androgens, and the ovaries, which provide a source of estrogen, progesterone, and androgens.[7,8] Furthermore, receptors have been noted on the oocytes themselves as well as the uterus.[7,8]

Cannabinoids act on receptors other than CB1R and CB1R. Both endocannabinoids as well as exogenous cannabinoids modulate transient receptor potential (TRP) channels, including TRP vanilloid (TRPV) channels, which are involved in the sensation of temperature, pressure, pH, and neuropathic pain signals.[9] Moreover, cannabinoids have been shown to activate peroxisome proliferator-activated receptors (PPARs), proteins which regulate gene expression.[10]

There is a broad range of mechanisms by which cannabinoids modulate pain, which reflects their broad distribution. Modulation of pain signals in the CNS is the primary mechanism of analgesia, mostly mediated through the CB1R.[2] Therefore, CB1R-mediated activation of the ECS leads to sedation, euphoria, and adverse memory effects.

However, CB1R-mediated analgesia is not limited to nervous system modulation: CB1R also results in analgesia because it potentiates an anti-inflammatory effect on mast cells.[11,12]

Activation of CB2R also leads to analgesia, but through different mechanisms: CB2R activation inhibits proinflammatory signals that would otherwise be released near nociceptive nerves.[2] CB2 activation also leads to downstream release of endogenous opioids.[13]

Other antinociceptive effects of cannabinoids that may pertain to the pathophysiology of endometriosis are the antiangiogenic and antiproliferative effects of cannabinoids.[14,15] Cannabinoids also have an immune modulating effect that may lead to decreased pain in autoimmune disorders.[16]

There is evidence for the pathologic connection between the ECS and pain in animal studies; mice treated with an cannabinoid agonist were found to have an anti-hyperalgesic effect secondary to the cannabinoid agonist's effect on TRPA1, a nociceptive channel.[53] Moreover, the ECS seems to follow sexual dichotomy. Female rats in proestrus had a more pronounced antinociceptive response to intracerebroventricular Delta-9 THC than males of females in estrus.[54] By the same token, female rats also developed greater and faster tolerance to THC antinociceptive effects than male rats.[55] Female rats self-administer CB1R agonists at higher rates than males. 20 Cannabinoids have also been noted to have more pronounced effects human females compared to males, with women being more likely to experience severe withdrawal from cannabinoids.[21]

Cannabinoids and the menstrual cycle

A sound understanding of cannabinoid's interaction with the menstrual cycle is necessary in order to understand how cannabinoids affect gynecologic and urogynecologic-related chronic pelvic pain. The ECS has a regulatory role in the menstrual cycles. Cannabinoid receptors have been found centrally in the hypothalamus, in the uterus, ovary, and oocyte.[7,8,17] While the CB1Rs found in the hypothalamus are at relatively low levels compared to other areas in the CNS, they are highly active receptors.[17] CB1R mRNA is secreted by cells in close proximity to cells secreting gonadotropin-releasing hormone (GnRH).[18]

Moreover, the density of CB1Rs follows sexual dichotomy in rat brains, which echoes the refrain of sexual dichotomy of cannabinoid effect as well.[3,19] Delta-9 THC increases CNS release of pregnenolone via the CB1R, which then affects a negative feedback loop that dampens the effect of THC on CNS CB1R.[22] Moreover, treatment of ovariectomized rats who had been exposed to delta-9 THC with physiologic doses of estrogen improved accuracy in memory and learning tasks, again enforcing that female sex hormones attenuate CNS response to THC.[23]

In terms of the putative mechanism of ECS on hypothalamus, pituitary, and ovary (HPO) axis regulation, cannabinoids have been found to decrease fertility by modulating release of hypothalamic GnRH via effect on gamma-aminobutyric acid (GABA) input.[18] Not only does it appear that the ECS impacts release of GnRH, but it

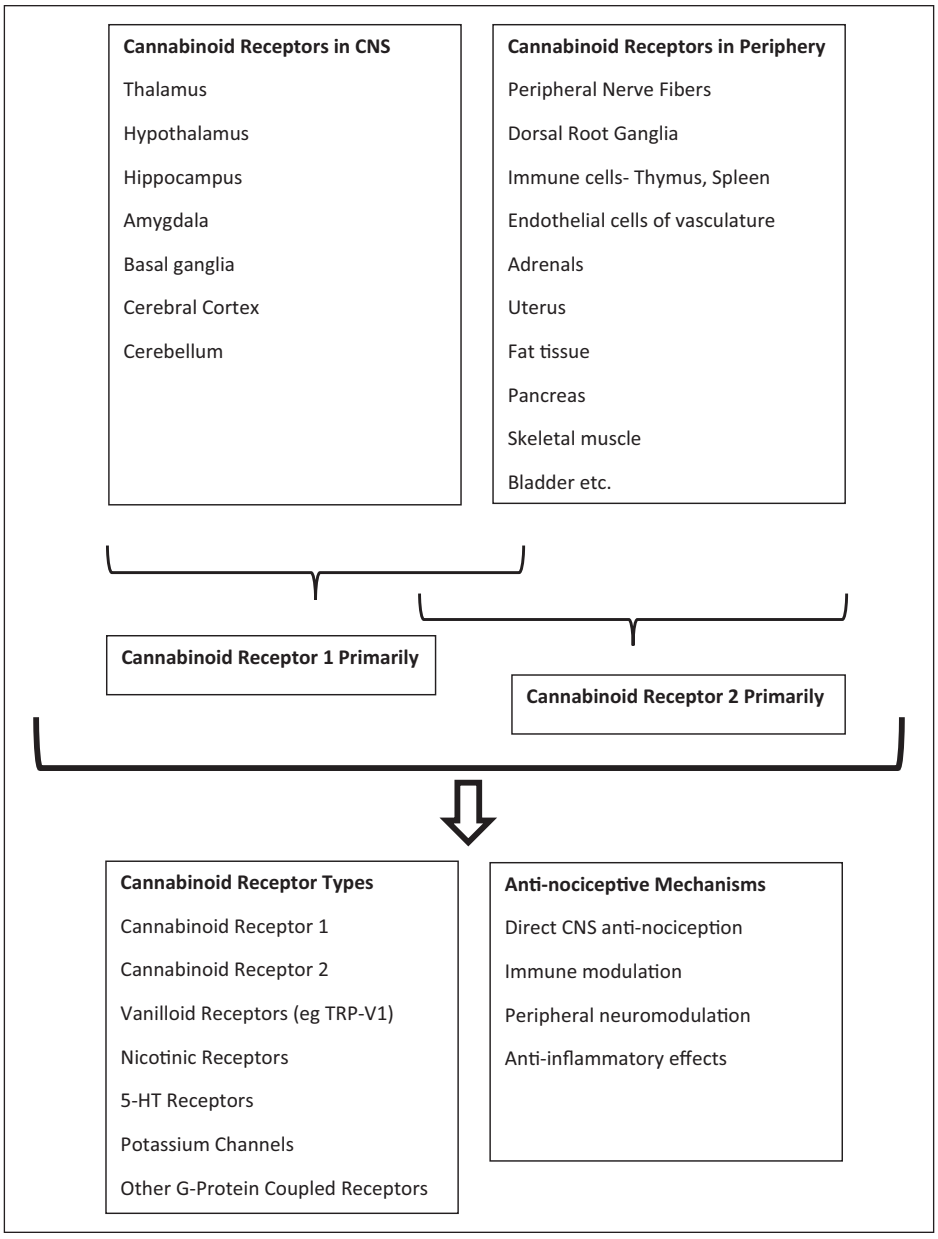

Figure 1. Overview of the endocannabinoid system. This figure highlights the breadth of cannabinoid receptors in the central nervous system (CNS) in the periphery. Listing of cannabinoid receptors in the periphery is not an exhaustive list. Cannabinoid receptor types are listed to provide understanding of the breadth of cannabinoid receptors, again without being exhaustive. Common anti-nociceptive mechanisms of cannabinoids are also listed.

appears that sex steroid levels impact the effect of the ECS on the HPO axis. AEA leads to an increase of luteinizing hormone releasing hormone (LHRH) release only in the presence of circulating estrogen in a rat model, with no increase in LHRH in ovariectomized rats.[24] THC was also shown to decrease release of luteinizing hormone (LH) and follicle-stimulating hormone (FSH) in intact female mice as well as decreasing LH in ovariectomized rats; this effect was altered in ovariectomized mice.[25,26] The effect of the ECS has been shown to be at the level of the hypothalamus on multiple animal models, including rhesus monkeys, the animal model with a menstrual cycle most analogous to that of humans.[27]

In regards to findings in rhesus monkeys, THC administration during the follicular phase led to anovulatory cycles.[27] However, THC administration to rhesus monkeys during the luteal phase did not result in changes in progesterone level or duration of luteal phase.[28] Another study on rhesus monkeys, however, showed that THC administration the luteal phase led to luteal phase disruption with less progesterone secretion noted.[29] Prolonged exposure of THC in rhesus monkeys leads to tolerance after several months.[30]

The ECS has varying effects in human females, depending on the phase of the menstrual cycle. Some but not all of the effects in human studies are in disagreement with findings in rhesus monkey models. During the human luteal phase, there is decreased tone of the ECS secondary to the presence of oxidative enzymes.[31] Marijuana use is associated with a longer follicular phase in humans, with a dose dependent relationship, with ovulation timing based on surrogate chemical markers.[32] Marijuana use in women was associated with shorter luteal phase in a study which assessed follicular and luteal phases with urinary LH detection kits.[33,34] Inhaled THC during the luteal phase suppressed LH in humans, in line with some, but in opposition to other findings in rhesus monkeys.[35] Some of the differences in these studies may be accounted for by decreased ability to control confounders in human studies, the self-reported nature of human studies, the possibility of tolerance—which is as of yet not well characterized in humans—or dose-dependent effects, or possibly by genuine interspecies differences in ECS control of menstrual cycles.

It appears, moreover, that marijuana use does not vary by phase of menstrual cycle nor does there appear to be a difference in CNS-related effects, such as pulse rate or intoxication, on the basis of menstrual phase.[36,37]

The ECS has also been linked to the menstrual dysregulation of polycystic ovarian syndrome (PCOS).[38] Endocanabinoids, 2-AG and AEA as well as CB1Rs and CB2Rs are upregulated in women with PCOS.[39,40] Moreover, CB2Rs is expressed at higher levels in the adipose tissue of women with PCOS versus controls, with possible implications for the metabolic implications of the ECS in women with PCOS.[39]

Chronic pelvic pain and cannabinoids

The prevalence of chronic pelvic pain in women ranges between 5.7% and 26.6% and is often difficult to treat, due to the multiple etiologies that synergistically cause and worsen pain.[41,42] The health care utilization of women with CPP is significantly amplified compared to women without CPP, with patients being four times as likely to undergo gynecologic surgery and five times as likely have undergone hysterectomy.[43–46] Chronic pelvic pain has a significant detrimental impact on quality of life, and often is associated with the development of psychiatric comorbidities such as depression and anxiety.[47] Women with chronic pelvic pain frequently have a neuropathic component to their pain as well as frequently have endometriosis, irritable bowel syndrome, and interstitial cystitis/painful bladder syndrome (IC/BPS), as well as musculoskeletal pain, often making appropriate treatment of pain challenging. As such, appropriate non-surgical treatment of chronic pelvic pain, including the potential use of cannabinoids, is a subject of interest.

No prospective studies have been performed to assess the benefit of cannabinoids in chronic pelvic pain. A 2020 survey based study of 122 female respondents with pelvic/perineal pain, dyspareunia, or endometriosis found that 26 (23%) reported using cannabis.[48] Of these 26, 24 (92.3%) reported improvement in symptoms such as pain, cramping, muscle spasm, sleep problems as well as depression and anxiety.[49] Subsequent sections of this review will discuss the existing data regarding cannabinoids and chronic pain.

When discussing chronic pain syndrome, it is important for the clinician to recognize the role of sleep quality. Poor sleep is a common finding in women with chronic pelvic pain and exacerbates pain.[50,51] Cannabinoids and endocannabinoids appear to have an effect on sleep-wake cycles, with THC alone appearing to be more sedating with higher incidence of memory impairment, and THC-CBD modulating sleep phases and with improved recall test scores compared to placebo.[52] Improvement in sleep was noted in a systematic review assessing the effect of cannabinoids on chronic non-cancer pain.[53]

Chronic pain and cannabinoids

Clinical data regarding treatment of chronic pain with cannabinoids indicates that cannabinoids result in a moderate improvment in pain scores. The studies, however, are heterogeneous, a fact which reflects the multiple cannabinoid formulations as well as multiple types of chronic pain etiologies. Given this, evaluation of existing reviews of cannabinoid use in patients with chronic pain provides are valuable.

At the broadest level, as of 2017, National Academies of Sciences, Engineering, and Medicine provided an overview of the five systematic reviews of chronic pain and cannabinoids, concluding that all of the reviews noted modest improvement in pain scores secondary to cannabis.[58]

A recent systematic review by Whiting *et al*.[59] of the medical uses of marijuana assessed 79 trials. The review concluded that while most studies showed improvement in symptom scores, whether assessing for pain or nausea, many did not demonstrate statistical difference. The majority of pain conditions assessed were neuropathic, although chemotherapy-related pain, musculoskeletal pain, rheumatologic pain, cancer pain, and multiple sclerosis were also represented. Twenty-eight randomized trials were included in the final review, the majority of which included cannabinoids derived from plant sources. Twenty-seven of 28 trials compared cannabinoids to placebo. Cannabinoids were associated with a reduction in pain of at least 30%, with an odds ratio 1.41, but with 95% CI 0.99–2.00 in the review of eight trials which assessed this end point. Of these eight trials, one assessed inhaled THC and the others oromucosal nabiximols.[59] The greatest effect noted was a trial assessing the effect of inhaled THC on HIV-associated pain, with an OR of 3.43 in the reduction of pain by 30%,

with a wide 95% CI 1.03–11.48 with reduction in pain of 34% versus 17% for placebo ($p = 0.03$).[59,60]

A 2017 review of cannabinoids for chronic pain also echoed that inhaled cannabis demonstrated reproducible effects in decreasing non-cancer pain. It also reported that while oral cannabinoids did not have as strong of an impact on pain as inhaled formulation, that oral formulations resulted in a positive impact on sleep.[61] The difference in patient response may be secondary to the more favorable pharmacokinetics of inhaled cannabinoids. Lynch and Campbell also support the use of cannabinoids for chronic non-cancer pain in a 2011 systematic review, noting that 15 of 18 studies showed significant pain reduction of cannabinoids compared to placebo.[53] A further review from 2020 supported cannabinoids in the treatment of non-cancer chronic pain, showing that there was a reduction of 64%–75% in opiate usage when patients were treated with medical cannabis compared to opiates alone.[62]

Cannabinoids have also been studied in the setting of chronic visceral pain, which may be pertinent to certain etiologies of chronic pelvic pain. A systematic review in 2016 that sought to examine the effect of medical marijuana in visceral pain caused by gastroenterological conditions identified only one high quality study to include in the review.[70] Medical marijuana significantly decreased abdominal pain and improved appetite in patients with Crohn's disease in a randomized control study.[71] However, a subsequent phase 2 placebo-controlled study in 2017 did not show an improvement in chronic abdominal pain in patients with chronic pancreatitis after taking THC.[72]

It must also be noted that studies regarding the analgesic potential of cannabinoids study cannabinoid agonists, whether synthetic or naturally occurring. The modulation of the ECS itself has promise in regards to analgesic effects, with a wider therapeutic widow than cannabinoid agonists.[63,64]

Moreover, while many studies address plant-derived cannabinoids, which contain a combination of THC and CBD as well as combined THC/CBD synthetic derivatives, there appears to be a difference between the antinociceptive effects of CBD and THC. THC has psychoactive effects and antinociceptive effects. CBD has anti-anxiety and pain-relieving effects.[87] CBD has been shown to have anti-inflammatory effects on rats with induced osteoarthritis, through a mechanism that appears to involve the nociceptive channel TRPV1, and further work is needed to assess the impact of varying cannabinoid formulations on pain.[57,88]

Chronic neuropathic pain and cannabinoids

Chronic pelvic pain has a significant neuropathic component, up to 50% of CPP being neuropathic.[47] While many studies assessing the effect of cannabinoids on chronic pain include patients with chronic neuropathic pain, the analgesic effect of cannabinoids in patients with only neuropathic pain conditions appears to be somewhat more robust. A meta-analysis that assessed the effect of inhaled cannabis on neuropathic pain concluded that inhaled cannabinoids improve pain by 30% in one of every five to six patients; the odds ratio for a 30% reduction in pain is 3.2 (Bayesian credible interval 1.59–7.24).[65] This odds ratio is somewhat higher than the ratio found in Whiting *et al*.'s review.

Another systematic review of cannabinoids for palliative medicine or pain management, reviewed 750 publications, with only 11 meeting inclusion criteria, concluded that THC/CBD spray may help with neuropathic pain, although in the setting of limited data.[66] A 2018 Cochrane review included 16 studies and assessed both plant based and synthetic cannabinoids against placebo (15 studies) and dihydrocodeine (one study).[67] They concluded that cannabinoids may lead to a greater proportion having a significant remission of pain, defined as 50% or greater pain relief, 21% versus 17% (95% CI 0.00–0.09). They cited a number needed to benefit of 20. Of note, this percentage of pain relief in this study was 50% or greater, whereas most of the literature uses a cut-off of 30% pain relief.

In a longitudinal study assessing the long-term effects of THC/CBD spray on neuropathic pain, pain scores decreased over time from 6.9 of 10 to 4.2 points, up to 9 months' time.[68] The long-term improvement in pain may reflect long term anti-inflammatory effects of cannabinoids. As a result of this body of data, a 2014 consensus statement of the Canadian Pain Society now lists cannabinoids at third line for treatment of chronic neuropathic pain, behind first line neuromodulators and second line analgesics.[69]

In the setting of sparse studies regarding cannabinoids for CPP, clinicians may consider data about effectiveness of cannabinoids for fibromyalgia, given that the mechanisms for the development of CPP and fibromyalgia may have significant overlap.[73] A 2016 Cochrane review identified only two moderate quality studies of nabilone, a synthetic cannabinoid, as compared to amitriptyline or to placebo, for fibromyalgia-related pain.[74] Only a modest, low-quality level of pain improvement was reported. Since that review, Van De Donk *et al*.[75] performed a randomized, placebo-controlled crossover trial of inhaled cannabis with varying THC: CBD ratios. They found that THC-containing varieties resulted in an increased pain threshold but that combinations of THC and CBD, while increasing plasma levels of THC, led to decreased analgesia, highlighting the complex interaction of both CBD and THC with the ECS.

Although the neuropathic chronic pain that has been the subject of significant research on cannabinoids has some physiologic plausibility for applicability to CPP, it does

not entirely translate to the setting of multifactorial causes of pain, as are seen in chronic pelvic pain, because often, neuropathic pain is accompanied by visceral and musculoskeletal pain.

Clinical endocannabinoid deficiency

It has been proposed that certain pain conditions may be the manifestation of what has been termed Clinical Endocannabinoid Deficiency (CED), a condition in which patients have abnormally low endocannabinoid levels, in an analogous manner in which depression is associated with decreased serotonin.[76] There is greatest evidence for CED in regards to fibromyalgia, migraine, and IBS. While these conditions are not chronic pelvic pain conditions, they likely have shared etiology with CPP. They are, moreover, considered 'overlapping chronic pain conditions' along with endometriosis and IC/BPS.[77]

Adverse events and dosage curves of cannabinoids

In regards to adverse events, a systematic review of the safety of cannabinoids on neuropathic pain which demonstrated a marginal benefit in cannabinoids treatment over placebo found a number needed to harm of 19, with no statistically increased rates of adverse effects over placebo.[66,78] Andrea *et al*.'s[65] review of cannabinoids for treatment of neuropathic pain, which included five randomized control trials, reported rare study withdrawal due to adverse events. In Whiting *et al*.'s[59] broader systematic review of medical uses for cannabinoids, they report that cannabinoids are associated with a higher risk of any adverse events as well as serious adverse events. It should be noted, however, that the confidence interval of multiple studies in systematic review crosses 1, the odds ratio of no effect. Adverse events include dizziness, dry mouth, somnolence, drowsiness, anxiety, diarrhea, negative memory, psychomotor, and concentration effects, dry eyes, headache, numbness, increased heart rate, and euphoria.[59,65]

The therapeutic window for cannabinoids is narrow, meaning that there is a small range of dosages that lead to analgesic effects without leading to adverse effects.[79,80] However, the addition of other pain modulating medications, such as gabapentin, may increase the therapeutic window of cannabinoids.[81,82] Opioids and cannabinoids may have a synergistic antinociceptive effect through shared GABA modulation.[2] However, there is limited data overall to support synergistic effects between cannabinoids and other medications.

Of note, there is evidence that at high doses of cannabis use, hyperalgesia may result. Nabiximols have been found to decrease cancer-related chronic pain at low and medium doses, but no nociceptive effect was noted at high doses.[83] A randomized, double-blinded, crossover trial also showed dose dependent response with increased capsaicin- induced nociception with higher doses of THC and decreased nociception with medium doses of THC.[84]

This same U-shaped, dose-dependent curve was noted in a survey-based study of 989 participants with chronic pain as well as in regards to the antianxiety-effects of CBD.[85] That being said, CBD shows promise of pain control without tolerance, as was demonstrated by Xiong *et al*.[86] in a study of intrathecal CBD in a mouse model.

The non-linear dose-response curve of cannabinoids on pain reflects the complex role that cannabinoids play in nociception. Activation of the CB1R found on the spinal dorsal horn may lead to increased pain sensitization, through complex local interactions leading to decrease of GABA, and opioid release.[4,5]

Endometriosis and cannabinoids

Given the high impact of endometriosis on women's quality of life in conjunction with the high prevalence of endometriosis, cannabinoid-mediated effects on endometriosis-related pain has become a subject of inquiry. Endometriosis will affect between 10% and 15% of reproductive age women and is far more common, in women with chronic pelvic pain, with higher ranges of 70%–80%.[89–91] Surgically, patients can have small superficial lesions or significant distortion of anatomy. Endometriosis is diagnosed in tissue pathology in 15% of uterine specimens after hysterectomy.[92]

Causes of endometriosis pain can be categorized nociceptive, inflammatory, and neuropathic, all of which may be modulated by cannabinoids and higher levels of oxidative stress markers.[93,94] The intraperitoneal fluid of women with endometriosis has a higher level of cytokines and there is a higher expression of nociceptive TRPV1 on peritoneal endometriosis.[95,96] Central nervous system changes have also been noted in women with chronic pelvic pain in general and endometriosis in specific.[97]

There is evidence that a disruption of the normal endocannabinoid system potentiates pain in women with endometriosis. Endocannabinoids in women without endometriosis have an anti-inflammatory effect at the level of the uterus; the CB2R is upregulated preferentially on the mast cells of women with endometritis, therefore potentiating the anti-inflammatory effects.[98] There also may be a cyclical variation in CB1R in women with endometriosis, with more receptor expressed during the secretory phase, although not all studies support this finding.[7,99] However, it appears that the anti-inflammatory, progesterone-mediated regulation of endometrial cannabinoid receptors is disrupted in women with endometriosis.[7] In women with endometriosis, decreased CB1R expression compared to controls and increased AEA and 2-AG expression are consistent with a negative feedback loop that is permissive of inflammation.[99,100]

Exogenous cannabinoids appear to correct this dysregulation in *in vitro* studies. When endometrial cells were treated with cannabinoid agonist WIN 5512-2, the result was decreased cell proliferation, decreased reactive oxygen species production, and reduction in alpha-smooth muscle actin expression, lending supporting evidence to the anti-inflammatory effects of cannabinoids.[15] This is supported by the findings of Bilgic *et al*.[101] who found that CB1R and CB2R expression is decreased in endometriosis tissue compared to control tissue, with concurrent decreased apoptosis indexes. The same study found that exposure of endometriosis tissue to CB1R and CB2 agonists resulted in pro-apoptotic effects. A nude mouse model of transplanted human deep infiltrating endometriosis confirmed the antiproliferative effects of cannabinoids on the growth of deep infiltrating lesions.[15] The above in vitro study and the deep infiltrating endometriosis mouse model findings are in contrast to findings that activation of the CB1R in a mouse model with a mouse analog of early-stage endometriosis resulted in increased disease burden.[99] The complexity of the ECS superimposed on the two different mouse models used may account for the different results.[38]

The ECS may have a role in other aspects of the development of endometriosis. Endocannabinoids have been shown to trigger endometrial cell migration.[102] Moreover, CB1Rs have been found on the sensory and sympathetic neurons innervating endometriosis lesions, which suggests that endocannabinoids may contribute to the innervation of endometriosis lesions.[103]

Given the above role of the ECS in the modulation of endometriosis, cannabinoids have been proposed as putative therapy for endometriosis. And in fact, patients with endometriosis have found relief in self-therapy with cannabis. An Australian cross-sectional survey showed that self-management strategies were very common in women with endometriosis, and that Cannabis and cannabis products were among the most effective at pain reduction.[104] While animal-model and survey-based data is promising, prospective studies on treatment of endometriosis-related pain wtih cannabinoids are lacking.

Vulvodynia and cannabinoids

Vulvodynia is a chronic overlapping pain syndrome that affects between 8% and 16% of women.[105] Therapeutic options for vulvodynia are wide-ranging and reflect the likely multifactorial etiologies for the disorder.[106] There are no studies in humans regarding cannabinoid use for vulvodynia. A retrospective study reports that 7% of women with vulvodynia self-medicated with marijuana, but notes that this may be an underestimate of true values.[107] However, a mouse model of chemically-induced vulvodynia showed that treatment with topical THC led to decreased pain sensitivity and decrease in mast cell density in affected tissue.[108] Studies regarding the effect of cannabinoids on chronic neuropathic pain may be of particular relevance to the treatment of vulvodynia, as the disorder has a significant neuropathic component. On the same note, the finding that oromucosal sativex, a THC:CBD combined medication decreased allodynia and pain in patients with peripheral neuropathic pain, is of clinical relevance to practitioners treating vulvodynia, given that allodynia is a frequent finding in women with vulvodynia.[109]

Interstitial cystitis/bladder pain syndrome and cannabinoids

Women with chronic pelvic pain frequently also suffer from IC/BPS. Although there are few studies on the role of cannabinoids for treatment of IC/BPS, what is known is that cannabinoid receptors are present in the bladder (Tyagi *et al*.[110] provides a good overview). CB1R have been found in rodent bladders, and CB1R agonists were found to decrease afferent nerve signals from the bladder.[111] Moreover, intravesical instillation of CB2R agonists can protect against the nociceptive effects of bladder irritants in rats.[112] Given the presence of both CB1R and CB2R in the bladder, and the ability to minimize systemic effects through intravesical instillation, intravesical cannabinoid treatments may prove to be a helpful modality for pain control in IC/BPS.

Conclusions

On the basis of multiple review articles, it is reasonable to offer cannabinoids as treatment of chronic pain. However, the role of cannabinoids in the treatment of chronic pelvic pain uncertain, given that no studies have addressed this clinical question. It may be reasonable to treat chronic pelvic pain refractory to other treatment with cannabinoids, with the expectation of a modest improvment in pain, with the understanding that this is still a field requiring active study. From both human and animal studies, it is clear that the role of the ECS on the menstrual cycle is complex, with modulation both on the level of the CNS as well as the local level. The intricacy of the ECS system can account for the sometimes-contradictory results obtained from studies. The therapeutic window for cannabinoids is narrow and may have a U-shaped pharmacokinetic dose-response curve, resulting in a heterogeneous group of studies. Given the complexity of the ECS system in regards to the menstrual cycle and pelvic signaling, combined with the multifactorial and individualized causes of chronic pelvic pain ranging from nociceptive, neuropathic, and visceral pelvic pain, the homology between other chronic pain conditions and chronic pelvic pain weakens.

While the pervasive effects of the ECS system in pain as well as menstrual modulation complicate the role of cannabinoids as analgesics, this also results in multiple possible therapeutic targets, at different levels. The different etiologies of CPP permit the possibility of topical cannabinoid use for vulvodynia or dyspareunia or intravesical instillations for IC/BPS.

Certainly, the role of cannabinoids in the management of chronic pelvic pain demands for further study, given the promise of an additional therapy for patients with refractory pain, who otherwise would have high medical utilization rates and low quality of life.

Author contributions

Ioana Marcu: conception of idea, data collection, manuscript writing, editing of manuscript. Amy Gee: data collection, manuscript writing. Becky Lynn: conception of idea, manuscript writing, editing of manuscript.

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