Systematic Review

Medical Cannabis for Gynecologic Pain Conditions

A Systematic Review

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OBJECTIVE: The endocannabinoid system is involved in pain perception and inflammation. Cannabis contains delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD), which are cannabinoids that bind to endocannabinoid system receptors. A fatty acid amide called palmitoylethanolamide (PEA) enhances endogenous cannabinoids. Given that use of medical cannabis is increasing, we sought to characterize patterns of cannabis use for gynecologic pain and its effectiveness as an analgesic.

DATA SOURCES: We searched PubMed, EMBASE, Scopus, Cochrane, and ClinicalTrials.gov using terms for "woman," "cannabis," and "pain" or "pelvic pain" or "endometriosis" or "bladder pain" or "cancer." The search was restricted to English-language articles published between January 1990 and April 2021 and excluded animal studies.

METHODS OF STUDY SELECTION: The initial search yielded 5,189 articles with 3,822 unique citations. Studies were included if they evaluated nonpregnant adult women who used cannabinoids for gynecologic pain conditions (eg, chronic pelvic pain, vulvodynia, endometriosis, interstitial cystitis, malignancy). Study types included were randomized controlled trials (RCTs), cohort studies, and cross-sectional studies. Covidence systematic review software was used.

TABULATION, INTEGRATION, AND RESULTS: Fifty-nine studies were considered for full review, and 16 met inclusion criteria. Prevalence of cannabis use ranged from 13% to 27%. Most women ingested or inhaled cannabis and used cannabis multiple times per week, with dosages of THC and CBD up to 70 mg and 2,000 mg, respectively. Sixty-one to 95.5% reported pain relief. All six prospective cohort studies and one RCT of PEA-combination medications reported significant pain relief, and the average decrease in pain after 3 months of treatment was 3.35±1.39 on the 10-point visual analog scale. However, one fatty acid amide enzyme inhibitor RCT did not show pain reduction.

CONCLUSION: Survey data showed that most women reported that cannabis improved pain from numerous gynecologic conditions. Cohort studies and an RCT using PEA-combination medications reported pain reduction. However, interpretation of the studies is limited due to varying cannabis formulations, delivery methods, and dosages that preclude a definitive statement about cannabis for gynecologic pain relief.

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Chronic pelvic pain is estimated to affect 26% of women worldwide.[1] In the United States, it accounts for 10% of gynecologic office visits, 40% of laparoscopies, and 12% of hysterectomies each year.[1] Similarly, endometriosis can not only cause severe pelvic pain but also decrease physical activity, mental health, social relationships, and financial stability.[2] Other gynecologic conditions associated with pain include vulvodynia, dysmenorrhea, gynecologic malignancy, and interstitial cystitis or bladder pain syndrome. These conditions can be challenging to treat, as there are different types of pain involved,

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including neuropathic and nociceptive pain. Neuropathic pain occurs with nerve injury or entrapment and is often described as shooting pain. Nociceptive pain occurs as a response to noxious stimuli by sensory receptors of the peripheral nervous system.[3] Current treatments include hormonal suppression, analgesics, neuromodulators, and surgery. However, hormonal suppression limits fertility; traditional analgesics and neuromodulators have limited effectiveness; and recurrence rates of pain after endometriosis surgery can be as high as 40–50%.[4] New treatments for gynecologic pain conditions are clearly warranted.

The endocannabinoid system is a complex network of cannabinoid receptors with endogenous ligands that is involved in pain perception and inflammation. The endocannabinoid system has recently emerged as a pharmaceutical target and is the system stimulated by medical cannabis.[5] Cannabis, which includes the species *Cannabis sativa* and *Cannabis indica,* contains 61 cannabinoids and hundreds of secondary metabolites. Two main phytocannabinoids found in cannabis that affect the endocannabinoid system in humans are delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD). Delta-9-tetrahydrocannabinol is responsible for the psychoactive effects (eg, feeling "high"), whereas CBD is nonpsychoactive and recognized for many therapeutic effects, including antiinflammatory activity.[6] These cannabinoids bind to cannabinoid receptor-1 and 2, which are part of the seven-transmembrane G protein-coupled receptor superfamily.[7] Cannabinoid receptor-1 receptors are mostly found in the central and peripheral nervous system but also found in the uterus and ovaries. Cannabinoid receptor-2 receptors are mainly found in the immune system but also found in the gastrointestinal tract, uterus, and skin.[8] Endogenous cannabinoids include derivatives of arachidonic acid called anandamide and 2-arachidonoylglycerol. These endogenous cannabinoids can be enhanced by other endogenous compounds, one of which is a fatty acid amide called palmitoylethanolamide (PEA). Palmitoylethanolamide has affinity for the cannabinoid receptor-2 receptor with resulting antiinflammatory and analgesic effects.[9] A membrane enzyme called fatty acid amide hydrolase metabolizes endocannabinoids such as anandamide,[10] and inhibitors of fatty acid amide hydrolase have been found to induce analgesia.[11] Various dietary supplements have targeted the endocannabinoid system and have been manufactured with antioxidants. The antioxidants polydatin and alpha-lipoic acid have been combined with PEA and are being studied for their potential application in pain management. Oxidative stress, which is an imbalance between antioxidants and reactive oxygen species, can lead to tissue injury and inflammation and has been implicated in several pain conditions, including gynecologic conditions.[12]

Historically, cannabis has been used as medicine for thousands of years dating back to 2900 BC. U.S. physicians regularly prescribed cannabis until the Marihuana Tax Act of 1937 that regulated the importation, cultivation, possession, and distribution of marijuana,[13] followed by the removal of cannabis from the U.S. Pharmacopeia in 1942.[14] The Federal Narcotics Control Act in 1956 led to strict penalties for cannabis possession, and, in 1970, cannabis was classified as a schedule I drug, meaning that there were no acceptable medical uses and it had a high potential for abuse.[15] Several attempts to overturn federal legislation have been unsuccessful, leading states to pass their own laws. As of June 2021, 15 states have decriminalized possession of small amounts of cannabis beginning with Oregon in 1973, 36 states have legalized medical cannabis beginning with California in 1996, and 17 states have legalized recreational cannabis.[16] The Farm Bill of 2018 allowed cultivation and commercialization of hemp, which is a strain of *Cannabis* that has less than 0.3% of THC,[17] and has led to an increase in available CBD products on the U.S. market.

The majority of Americans believe that cannabis should be legalized for medical purposes.[18] Cannabis use has doubled from 6.7% in 2004–2005–12.9% in 2014–2015,[19] and adults with medical conditions are more likely to report current cannabis use than those without medical conditions.[20] This increase remains significant in subset analyses of women and adults age 50 and older.[19] For clinicians in states with legalized medical cannabis, it remains federally illegal to prescribe the drug. However, it is legal to recommend marijuana for conditions that the state's law specifically covers.[21] The purpose of this systematic review is to characterize patterns of cannabis use for gynecologic pain and its effectiveness as an analgesic.

SOURCES

A medical librarian conducted a systematic literature search of PubMed (includes MEDLINE), EMBASE, Scopus, Cochrane, and ClinicalTrials.gov to find original research that studied the use of cannabinoids for pain from gynecologic conditions. The search was restricted to English-language articles published between January 1990 and April 2021 and excluded animal studies. Search terms were used to capture the

concepts of "woman" AND "cannabis" AND "pain" or "pelvic pain" or "endometriosis" or "bladder pain" or "cancer." A detailed search strategy is provided in Appendix 1, available online at http://links.lww.com/AOG/C550. All results were imported into an EndNote X9 library (Clarivate, London, United Kingdom) to remove duplicates and then transferred into Covidence systematic review software (Veritas Health Innovation, Melbourne, Australia) to ensure rigorous methodology and reporting. Reference lists of relevant articles and reviews were manually searched for additional reports.

STUDY SELECTION

This study was conducted in accordance with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions. The protocol for this review was prospectively registered in PROSPERO (registration number: CRD42021248057).

Studies were included in this systematic review if they evaluated nonpregnant adult women (age 18 and older) who used cannabinoids for managing pain from gynecologic conditions. Study types included were randomized controlled trials (RCTs), cohort studies, cross-sectional studies, and case series. Systematic reviews, case reports, commentaries, letters to the editor, conference proceedings, and study protocols were excluded.

Titles and abstracts of retrieved articles were independently reviewed by two authors (A.L.L., E.L.G.), and any discrepancies were resolved by consensus with a third author (J.S.C.). Studies that were included after the title and abstract screening were then obtained for full-text screening. These were independently reviewed by the same two authors (A.L.L., E.L.G.), and any discrepancies were resolved by consensus with a third author (J.S.C).

Two authors (A.L.L., E.L.G.) collaborated for data extraction. A standardized data form was used to extract data regarding study characteristics; participant characteristics; the cannabinoid product used, including type, dosage, frequency, and route of administration; the gynecologic condition managed with cannabis; and results regarding pain management.

Two authors (A.L.L., E.L.G.) assessed the risk of bias for each study. Risk of bias in randomized trials was assessed by the Cochrane Collaboration tool. Risk of bias in nonrandomized trials was assessed by the Newcastle-Ottawa Scale (scored 0–9), which assesses the domains of selection, comparison, and outcome. Studies were considered to have a low risk of bias with a score of 7–9, medium risk with a score of 4–6, and high risk with a score of 0–3.

RESULTS

The initial search yielded a total of 5,189 articles with 1,614 citations in PubMed, 2,822 in EMBASE, 81 in Scope, 602 in Cochrane, and 59 in ClinicalTrials.gov. A total of 1,367 duplicates were removed, leaving 3,822 unique citations. Of these, 59 were considered for full review, and 16 met complete inclusion criteria (Fig. 1). There were 13 discrepancies out of 3,822 studies at the initial screening stage, and three discrepancies out of 59 studies at the full-text screening stage.

Eight of the 16 studies were cross-sectional studies that evaluated cannabis use (Tables 1 and 2). Two studies examined chronic pelvic pain, one vulvodynia, four endometriosis, and two gynecologic malignancy; some studies assessed multiple gynecologic pain conditions. Participants were recruited through social media or clinic, and sample sizes ranged from 36 to 3,426. Four studies were conducted in the United States, one in Canada, two in Australia, and one in New Zealand.

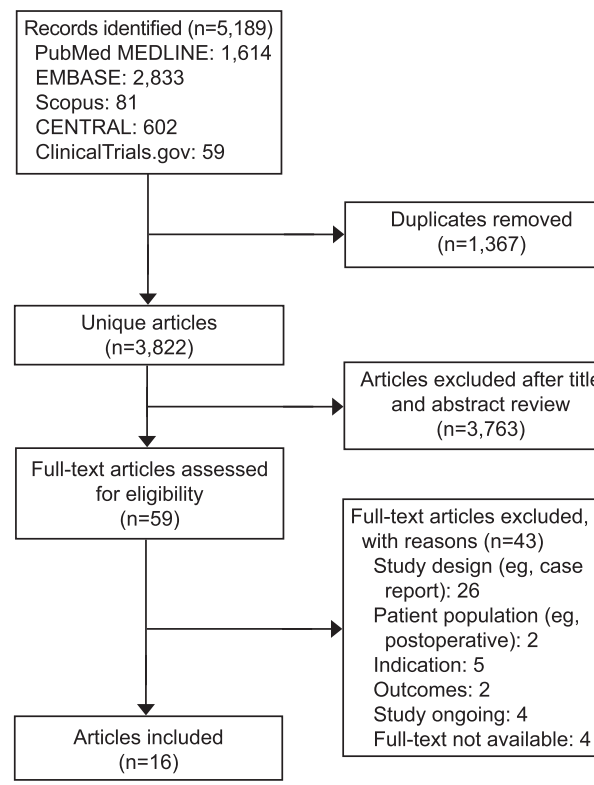

Fig. 1. Flow diagram of included studies.
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The other 8 of the 16 studies included six prospective cohort studies and two RCTs that evaluated the efficacy of PEA medications or an fatty acid amide hydrolase inhibitor (Table 3). Five studies focused on endometriosis-associated chronic pelvic pain, two focused on interstitial cystitis and bladder pain syndrome, and one focused on primary dysmenorrhea. Five studies investigated the efficacy of combined PEA plus polydatin, two studied the efficacy of combined PEA plus alpha-lipoic acid, and one assessed the efficacy of an fatty acid amide hydrolase inhibitor. The dosages for PEA ranged from 300 to 600 mg, for alpha-lipoic acid ranged from 300 to 400 mg, and for polydatin was consistently 40 mg. Treatment included twice daily dosing ranging from 3 to 9 months. Houbiers et al[10] registered their trial in EudraCT (the European Union Drug Regulating Authorities Clinical Trials Database): number 2011-004555-39.

All the studies were rated to have a low risk of bias. However, all the cross-sectional studies may have been influenced by selection and response biases due to recruitment through clinic and social media. Of the four studies that recruited from clinic, response rates ranged from 41% to 94%. In terms of the prospective cohort studies, the rates of complete follow-up ranged from 73.3% to 100%. However, these studies did not include a control group, so it is not possible to compare the effects of the interventions to placebo or standard of care. The rates of complete follow-up for the RCTs were 93% and 100%.

Four cross-sectional studies reported on prevalence of cannabis use (Table 1). In Canada and Colorado, where recreational cannabis is legal, prevalence was similar at 21.5% and 27%.[22,23] Meanwhile, in regions where only medical cannabis is legal, Carrubba et al found a prevalence of 23% in Florida and Armour et al found a rate of 13% in Australia.[24,25]

The four studies that included frequency of cannabis use found that most women used cannabis multiple times per week (Table 1). Approximately one third of participants used cannabis daily.[23,24,26] Barach et al[27] calculated that mean (±SD) usage was 17.3±11.6 days per month.

Four studies surveyed patients about the cannabis formulation (eg, delivery method, cannabis type, and dosage). Although many patients have used multiple delivery methods, Table 1 shows that all four studies found that the most common methods were ingestion (ranging from 25% to 77%) and inhalation (ranging from 32% to 80%).[23,24,26,28] Use of topical methods was lower at 25–43.7%. Carrubba et al[24] also noted that most (60%) patients used CBD plus THC, though some used CBD alone (24%) or THC alone (12%). Daily dosages of CBD and THC used ranged widely, from 1 mg to 2,000 mg per day of CBD and from 1 mg to 70 mg per day of THC.

Six studies asked patients about pain relief from cannabis use. Although each study used a different instrument to assess pain relief, all studies reported that most patients who used cannabis experienced pain relief (Table 2). The rate of pain relief ranged from 61 to 95.5%.[24,26,28] In the survey by Armour et al,[25] patients with endometriosis were asked to rate numerous self-management strategies, such as heat, diet, and exercise, and cannabis was reported as the

Table 1. Characterization of Cannabis Use

	Ref.
Characteristic	
23% cannabis use	Carrubba et al[24]
24% CBD, 12% THC, 60% CBD+THC	
13% cannabis use before legalization of cannabis	Geoffrion et al[22]
22% cannabis use after legalization of cannabis	
13% cannabis use	Armour et al[25]
3% hemp oil or CBD oil use	
27% cannabis use after cancer diagnosis	Blake et al[23]
Frequency	
35% daily use	Blake et al[23]
72% weekly use	Carrubba et al[24]
32% used 6–7 d/wk	Webster et al[26]
32% used 3–5 d/wk	
17.26±11.62 (mean±SD) days of cannabis use/month	Barach et al[27]
Delivery method	
Oral	
66% eaten as a cooked recipe	Armour et al[28]
77% ingested CBD or THC	Carrubba et al[24]
52% oral CBD	Blake et al[23]
47% edible marijuana	
25% edible cannabis	Webster et al[26]
41% tincture, oil, or sublingual cannabis	
Inhaled	
80% smoked as a cigarette	Armour et al[28]
62% inhaled CBD/THC	Carrubba et al[24]
38% inhaled marijuana	Blake et al[23]
32% smoked cannabis	Webster et al[26]
32% vaporized cannabis	
Topical	
44% used as a balm	Armour et al[28]
31% topical CBD or THC	Carrubba et al[24]
38% topical CBD	Blake et al[23]
25% topical, salve, or balm cannabis	Webster et al[26]
Dosage	
1–2,000 mg CBD/d	Carrubba et al[24]
1–70 mg THC/d	

CBD, cannabidiol; THC, delta-9-tetrahydrocannabinol.

Table 2. Cross-Sectional Studies of Cannabis Effectiveness on Gynecologic Pain Conditions

Reference	Year	Location	Condition	Recruitment	N*	Effectiveness	Adverse Events	RoB	Reported Limitations†
Carrubba et al [24]	2020	United States	Chronic pelvic pain	Clinic	26	84% reported improved pain, cramping, and muscle spasms 31% reported decreased opioid use	84% reported side effects, especially dry mouth, sleepiness, "high"	Low	Limited generalizability; response bias due to less than 50% response rate
Geoffrion et al [22]	2021	Canada	Chronic pelvic pain	Clinic	509	After legalization, cannabis users were less likely to use other painkillers, including opioids	Not mentioned	Low	Observed increase in cannabis use may be due to increased willingness to admit use
Barach et al [27]	2020	United States	Vulvodynia	Online	38	Women expected cannabis to have moderate to large effects on vulvodynia symptoms with greater relief for burning or stabbing pain and dyspareunia	No correlation between cannabis-related problems and expected relief	Low	Small sample size; potential self-report bias
Armour et al [25]; Sinclair et al [29]‡	2019	Australia	Endometriosis	Online	484	Cannabis was most effective self-management strategy 7.6±2.0 pain relief on 0–10 scale 77% reported decreased use of endometriosis-related medication by more than 25%	10% reported side effects, including drowsiness, anxiety, tachycardia	Low; low	Limited generalizability (unable to calculate response rate); potential self-report bias
Armour et al [28]	2020	New Zealand	Endometriosis and/or PCOS	Online	213	95.5% used cannabis for pain relief 81% reported pain "much better" 81.4% reported decreased use of other painkillers, including opioids	Not mentioned	Low	Did not distinguish between patients with endometriosis vs PCOS; potential self-report bias
Blake et al [23]	2019	United States	Gyn malignancy	Clinic	225	68.3% used cannabis for pain relief 45% reported decreased narcotic use	Not mentioned	Low	Descriptive survey design; potential selection bias

(*continued*)

Table 2. Cross-Sectional Studies of Cannabis Effectiveness on Gynecologic Pain Conditions (*continued*)

Reference	Year	Location	Condition	Recruitment	N*	Effectiveness	Adverse Events	RoB	Reported Limitations†
Webster et al [26]	2020	United States	Gyn malignancy	Clinic	31	83% reported symptom relief (eg, appetite, insomnia, neuropathy) 61% used cannabis for pain relief, of whom 63% reported decreased opioid use	36% reported side effects, including dry mouth (22%), GI irritation (16%), constipation (16%), and lethargy (16%)	Low	Small sample size; no validated survey; no standardized form of cannabis evaluated

RoB, risk of bias; PCOS, polycystic ovarian syndrome; GI, gastrointestinal.
* Number of study participants who were cannabis users, not total number of study participants, which may include noncannabis users.
† Limitations as reported by reference authors.
‡ Armour et al[25] and Sinclair et al[29] present data from the same survey of the same population.

most effective in reducing pelvic pain (7.6±2.0 on a scale of 0–10). Carruba et al found that significantly more CBD plus THC users reported improvement in pelvic pain, cramping, and muscle spasms (100%, 15/15) than CBD alone users (50%, 3/6) and THC alone users (67%, 2/3) (P=.01).[24] In addition, most

Table 3. Prospective Cohort Studies and Randomized Controlled Trials on Effectiveness of Palmitoylethanolamide-Combination Medications and Fatty Acid Amide Hydrolase Inhibitor on Gynecologic Pain Conditions

Reference	Year	Location	Condition	n	Treatment
Prospective cohort studies					
Caruso et al [30]	2015	Italy	CPP or endometriosis	56	300 mg PEA + 300 mg LA
De Leo et al [31]	2019	Italy	CPP or endometriosis	60	300 mg PEA + 400 mg LA + 100 mg myrrh
Indraccolo and Barbieri [32]	2010	Italy	CPP or endometriosis	4	400 mg PEA + 40 mg PLD
Loi et al [33]	2019	Italy	CPP or endometriosis	30	600 mg PEA then 400 mg PEA + 40 mg PLD
Giugliano et al [34]	2013	Italy	Endometriosis	47	400 mg PEA + 40 mg PLD
Cervigni et al [9]	2019	Italy	Interstitial cystitis or bladder pain syndrome	32	400 mg PEA + 40 mg PLD
Randomized controlled trials					
Tartaglia et al [35]	2015	Italy	Primary dysmenorrhea	220	440 PEA + 40 mg PLD (n=110)
Houbiers et al [10]	2020	12 European countries	Interstitial cystitis or bladder pain syndrome	287	50, 150, or 300 mg FAAH inhibitor (ASP3652)

RoB, risk of bias; CPP, chronic pelvic pain; PEA, palmitoylethanolamide; LA, alpha-lipoic acid; VAS, visual analog scale; NSAIDs, nonsteroidal antiinflammatory drugs; PLD, polydatin; FAAH, fatty acid amide hydrolase.

participants of the Armour et al[28] study (67.8%) found that inhaled forms of cannabis were more effective for pain relief than topical or oral forms. Multiple studies noted that some cannabis users were able to decrease their consumption of other pain relief medications, including opioids, with rates ranging from 31 to 81%.[22–24]

Three studies reported on the adverse effects of cannabis use. The rates of adverse effects ranged from 10% (5/50) to 84% (21/25).[24,26,29] The most common side effects included dry mouth, sleepiness, increased appetite, and palpitations. In addition, feeling "high" was more likely with THC use (100%, 3/3) compared with CBD use (0%, 0/6) (P=.001).[24]

Five prospective cohort studies and one RCT evaluated the efficacy of PEA, polydatin, and alpha-lipoic acid for chronic pelvic pain, endometriosis, and primary dysmenorrhea, asking participants to indicate their pain on a visual analog scale (VAS) where 0 = "no pain" and 10 = "the most painful sensation imaginable." All studies reported significant decreases in chronic pelvic pain and dyspareunia; all but one study also reported significant decreases in dysmenorrhea (Table 3).[9,30–35] Figure 2 presents the VAS scores for chronic pelvic pain at baseline and follow-up across studies. Averaged across the four studies with these data, the decrease in VAS score from baseline to 3 months after treatment was 3.35 ± 1.39.[31–34] In the RCT by Tartaglia et al,[35] 98.2% of patients who received treatment reported improvement in pelvic pain compared with 56.4% of those who received placebo. Caruso et al and Indraccolo et al further reported significant decreases in use of other pain medications.[30,32]

One prospective cohort study and one RCT focused on interstitial cystitis and bladder pain syndrome (Table 3 and Fig. 2). A combination of PEA and polydatin was associated with a significant decrease in pain in the prospective cohort study by Cervigni et al[9] However, an fatty acid amide hydrolase inhibitor did not decrease pain compared with placebo in the RCT by Houbiers et al[10]

Of the cohort studies and RCTs, two studies noted adverse events (Table 3). In the Indraccolo et el.

Control	Frequency, Duration	Effectiveness	Adverse Effects (n)	RoB	Rate of Follow-up
None	Twice daily, 9 mo	CPP, dysmenorrhea, and dyspareunia decreased by 6 mo per VAS; 78% stopped NSAIDs by 9 mo	Not mentioned	Low	91% at 3 mo 82% at 6 mo 73% at 9 mo
None	Twice daily, 6 mo	CPP, dysmenorrhea, and dyspareunia decreased by 3 mo per VAS	None	Low	100%
None	Twice daily, 3 mo	CPP and dyspareunia decreased by 1 mo per VAS; no decrease in dysmenorrhea; all reported decreased analgesic use by 1 mo	Nausea (1) Spotting (1)	Low	100%
None	Twice daily, 10 d then twice daily, 80 d	CPP, dysmenorrhea, and dyspareunia decreased by 3 mo per VAS	None	Low	93%
None	Twice daily, 3 mo	CPP, dysmenorrhea, and dyspareunia decreased by 1 mo per VAS in both rectovaginal septum and ovary groups	Not mentioned	Low	100%
None	Twice daily, 3 mo then once daily, 3 mo	Pain intensity decreased by 6 mo per VAS	None	Low	84%
Placebo (n=110)	Once daily, 10 d	Greater percentage with improvement in CPP with treatment (98.2%) vs placebo (56.4%); greater improvement in VAS with treatment (4 points) vs placebo (1 point)	None	Low	100%
Placebo	Twice daily, 3 mo	No significant difference for FAAH inhibitor vs placebo in improving mean daily pain	29% reported side effects	Low	Study stopped due to lack of effect

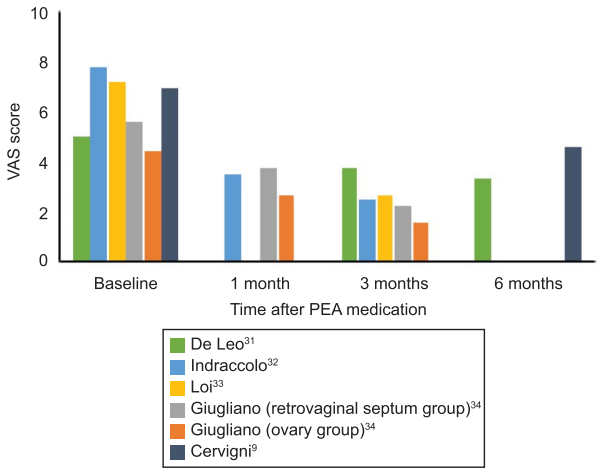

Fig. 2. Effect of palmitoylethanolamide (PEA)-combination medications on visual analog scale (VAS) pain score over time. In the study by Giugliano et al,[34] patients were grouped based on endometriosis site: rectovaginal septum or ovary.

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study of PEA and polydatin in four women, one woman reported nausea and another reported spotting.[32] Four of the studies noted an absence of adverse events from the PEA medication, and two did not mention whether there were adverse events.

DISCUSSION

This systematic review revealed that many women use cannabis products, such as THC, CBD, or a combination of both, to manage pain from gynecologic conditions, including chronic pelvic pain, vulvodynia, endometriosis, and gynecologic malignancy. Most patients used cannabis multiple times per week, and they used a variety of delivery methods and a wide range of doses. One of the most common reasons for cannabis use was pain management, and all the cross-sectional studies found that most women reported pain relief with cannabis use, especially among women who used a combination of CBD plus THC compared with either cannabinoid alone. Overall, side effects were minimal; the most common included dry mouth and sleepiness, as well as a "high" associated with THC. In analyzing cohort studies and RCTs of compounds with endocannabinoid products, this review further found that PEA, combined with the antioxidants polydatin or alpha-lipoic acid, significantly decreased pain from primary dysmenorrhea, pelvic pain, and interstitial cystitis. The PEA-combination medications were well tolerated by study participants, with only one small study noting nausea and spotting as potential side effects. Conversely, fatty acid amide hydrolase inhibitor failed to decrease pain from interstitial cystitis.

Our review of survey data is consistent with other survey-based studies of general pain conditions, where most respondents indicated improved pain from cannabis use.[36] However, due to their methodology, these studies had several limitations, including the possibility of selection and response biases. Additionally, it was not possible to compare the effect of cannabis relative to placebo or another analgesic. One systematic review of 13 RCTs that evaluated the efficacy of cannabis for general chronic pain in a mixed population reported more mixed results, where five trials demonstrated moderate analgesic effects and eight trials showed no significant analgesic effects.[37]

Similar to studies included in this review, studies of PEA for other nongynecologic pain conditions also demonstrated efficacy. RCTs of PEA for knee osteoarthritis and for temporomandibular joint inflammatory pain both found that PEA decreased pain significantly more than placebo and ibuprofen.[38,39] Another RCT also reported that PEA and polydatin decreased abdominal pain significantly more than placebo in patients with irritable bowel syndrome.[40]

The findings that the fatty acid amide hydrolase inhibitor ASP3652 did not significantly improve pain more than placebo was consistent with other trials of fatty acid amide hydrolase inhibitors. Although animal studies have shown that fatty acid amide hydrolase inhibition increases concentrations of endocannabinoids with analgesic effects, fatty acid amide hydrolase inhibitors have achieved limited success in human trials.[41] In a phase II trial, a fatty acid amide hydrolase inhibitor was found to be ineffective as an analgesia in patients with osteoarthritis pain.[42]

The strengths of this review include the broad scope of the literature search, which included studies from around the world, allowing for insights from countries with varying cannabis legislation. The search also included a variety of cannabis and cannabinoid products to reflect patient usage. Any gynecologic condition associated with pain was included as well to capture the breadth of female patients' experiences. Lastly, given limited data regarding cannabis use, this review included numerous types of studies, including cross-sectional studies, prospective cohort studies, and RCTs, to gather multiple perspectives.

There are multiple limitations to this review. First, the variation across studies precluded rigorous meta-analyses. For example, the cross-sectional studies used different survey instruments, and the prospective

cohort studies and the RCTs used different treatment regimens. There is also a wide array of cannabis strains, dosages, and delivery methods, and most of the cross-sectional studies included in this review did not include these specifications. Second, cross-sectional and prospective cohort studies did not include control groups, making it difficult to account for any placebo effect. Third, the sample size for some of the cross-sectional and prospective cohort studies were small ($n<30$), and multiple studies shared single-institution experiences, which may limit the generalizability of their results. Fourth, the results may have been affected by publication bias, as all the studies reported positive results without serious adverse events. Lastly, because non–English-language publications were excluded from the literature search, the studies may not be fully representative of non–English-speaking cultures. Different cultures may have unique perspectives on whether and how cannabis should be used, which affects the prevalence and frequency of use as well as the preferred delivery method and dosage.

Although much controversy surrounds cannabis and its potential medicinal applications, increasingly permissive legislation has made it more easily accessible. Without risk for overdose and minor negative side effects, many of which can be avoided with CBD-predominant strains that lack psychoactive properties, cannabis has potential to serve as a safe and effective therapy. This review suggests that cannabinoids, such as THC and CBD, and endocannabinoid-enhancing compounds, such as PEA, may be effective in alleviating pain from numerous gynecologic conditions, including chronic pelvic pain, vulvodynia, endometriosis, interstitial cystitis, and gynecologic malignancy. Although PEA alone is commercially available for purchase without a prescription, mostly through online distributors, combinations with antioxidants, such as polydatin and alpha-lipoic acid, to our knowledge, are only available in research settings. As the federal government permits more cannabis research, it is critical that various strains, delivery methods, and dosages are standardized and studied. The potential synergistic effect of the many bioactive compounds (eg, terpenes) found in whole plant cannabis should also be evaluated to establish efficacy and safety. As health care professionals and their patients look for alternatives to opioids and other pharmaceutical analgesics, cannabis and compounds that affect the endocannabinoid system may become potential options. Allowing and funding future human studies in the United States with appropriate controls would enable health care professionals to better counsel patients on whether medical cannabis is effective for pain relief.

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