

Editorial

Is it the Ideal Time to Start Prescribing Cannabis Derivatives to Treat Endometriosis-associated Pain?

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Endometriosis affects ~5%-10% of women of reproductive age and is often associated with painful symptoms like dysmenorrhea, dyschezia, dyspareunia, and even non cyclical pain.¹ The disease is diagnosed in at least 20% of women with dysmenorrhea and/or non-menstrual pelvic pain, reaching a prevalence of 50% among adolescents.² There is an alignment among international societies^{3,4} that the presumed diagnosis of this disease is enough to start clinical treatment. Moreover, there seems to be a consensus that first-line treatment should be hormonal contraceptives since the efficacy is similar to that of surgery but with lower complication rates and costs.⁵ However, these drugs are effective in only approximately two-thirds of patients,⁶ have limited long-term efficacy,⁷ and may occasionally lead to undesirable side effects. Additionally, there are serious limitations in the interpretation of clinical trials.⁸ Accordingly, evidence on the best therapeutic regimens has not yet been established.⁹ Other clinical options exist, but the cost, side effects, and similarity of results compared with hormonal contraceptives give them limited utility.¹⁰ Thus, due to the persistence of pain, a significant portion of women undergo surgery, which is obviously capable of eliminating visible endometriotic lesions, but not curing the disease.¹¹ Despite short-term clinical improvement, postoperative recurrence is common, especially if hormone therapy was not initiated.¹²

Thus, the clear clinical demand for more effective or lasting options for symptomatic relief, together with an increasing recognition of the participation of the central nervous system in the genesis and/or modulation of chronic endometriosis-associated pain,¹³ has aroused growing interest in novel therapeutic modalities.¹⁴ Among these treatments, drugs derived from the *Cannabis sativa* plant, which

we will call cannabinoids in the following text, currently seem to be the main topic. In fact, increasing attention has been directed to the potential beneficial effects of these medicines in controlling the symptoms of patients with chronic pain.¹⁵ *Cannabis* contains over a hundred chemical compounds that act on the endocannabinoid system, yet two are rather distinct, delta-9-tetrahydrocannabinol (THC), which is responsible for the psychoactive effects associated with the use of this plant, and cannabidiol (CBD), which does not produce psychomimetic symptoms.¹⁶ Overall, unlike THC, CBD is not addictive or tolerant and has a very favorable safety and adverse effect profiles. At first, it was believed that cannabinoids produced their analgesic effects by the direct activation of specific receptors (CB1 and CB2). However, it is now known that they can reduce pain by interacting with a wide range of cannabinoid, opioid, vanilloid, serotonergic, and anti-inflammatory receptors.¹⁷ Furthermore, preclinical studies have shown that CBD can interfere with the levels of cytokines potentially involved in the pathophysiology of endometriosis-associated pain¹⁸; CBD has been shown to decrease the secretion of pro-inflammatory cytokines, including IL-6 and TNF- α , and increase levels of anti-inflammatory cytokines, including IL-10.¹⁹ In addition to these broad potential pain-related mechanisms of action, there is a vast evidence on its anxiolytic, antidepressant, neuroprotective, mood-stabilizing, sleep-modulating effects of cannabinoids, along with many other benefits,²⁰ which may be useful in the concomitant treatment of non-painful symptoms as the aforementioned comorbidities are also frequent among patients with endometriosis. This makes cannabinoids potentially useful in treating patients with pelvic pain secondary to endometriosis.

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A recent Australian national survey found that 13% of women with surgically confirmed endometriosis reported significant positive effects of using *cannabis in natura* both on relieving pain and reducing the use of pharmaceutical drugs as a form of self-medication. However, as the study was not controlled and the investigational products did not have a pharmaceutical grade as a standardized formulation, the conclusions and the reproducibility of findings are limited.²¹ Nevertheless, similar findings have been reported in other longitudinal studies.²² However, at least two meta-analyses focusing on different types of pain^{23,24} clarified the limitation of the methodological designs available thus far. Furthermore, they raised a legitimate concern about the significantly higher prevalence of the adverse effects on the nervous system and psychiatric disorders associated with THC use,²⁴ particularly including psychosis, depressive episodes, and cognitive alterations commonly. More specifically, regarding the treatment of endometriosis-associated pain, two clinical trials registered on the clinicaltrials.gov platform (NCT03875261 and NCT04527003) were retrospectively proposed by researchers from Barcelona and Pennsylvania to assess the effect of cannabinoids on hyperalgesia in women with deep endometriosis, yet both are currently "not yet recruiting." To the best of our knowledge, in Brazil, we already have a clinical trial in progress and another that will soon start recruiting and is under our responsibility.

Considering the popular saying that "not everything that glitters is gold" there has been a growing concern in the specialized scientific community regarding the increasingly frequent use of *cannabis* or its derivatives for pain relief, despite the potential adverse effects, the lack of robust evidence on benefits and, consequently, the absence of clear recommendations on doses and/or composition to be used. In 2021 the International Association for the Study of Pain (IASP) published a statement position²⁵ recognizing the legitimacy of the life experience of people who report an improvement in pain following the use of *cannabis* and cannabinoids. Nevertheless, the association made it explicit that it does not endorse the use of cannabinoids until rigorous investigations and robust results clearly show the benefits and harms of its use in humans. The PAIN journal has even allocated an entire collection of 13 scientific articles representing the IASP's Presidential Task Force on *Cannabis* and Cannabinoid Analgesia and calling for high-quality clinical trials to be initiated. Some of the concerns regarding the use of cannabinoids are potential reductions in neurocognitive performance, macrostructural and microstructural brain development, and alterations in brain function secondary to heavy use by adolescents,²⁶ who have a higher risk of early onset psychosis,²⁷ and addiction.²⁸

In Brazil, cannabinoid-based medications are officially approved for use only in patients with refractory epilepsy with a THC concentration <0.2%. These drugs have a very high cost and any use outside the approved indication is off-label. In any case, we have seen a growing supply of *cannabis*-derived products on the market linked to the promise of pain relief. Many serious groups and companies have devoted efforts to drug development, but international quality standards are not followed by all, which poses a health risk as it is

impossible to guarantee a high level of quality, adequate pharmacovigilance, and extensive monitoring of adverse reactions. This can also lead to abusive and illegal use.

Nevertheless, the prospect of good results is an encouragement to women with persistent symptoms and professionals who assist them to use cannabinoids, but it is necessary to be aware of the temptation of the premature clinical use of medication. Unfortunately, from a strictly medical and scientific point of view, it is currently impossible to guarantee the efficacy, safety and tolerability of *cannabis* or its derivatives in the treatment of pain symptoms in women with endometriosis. Incentives have been made to disseminate the need for large clinical trials in this domain. To finish, I will restate a part of a text written by Michael Eisenstein²⁹ which seems to me to be very lucid, sensible and relevant for the situation that we are currently living in: "Unfortunately, if studies such as these are not done—or not done properly—then consumers will be left to fend for themselves in a poorly monitored marketplace. In that scenario, the signal of true clinical benefit would almost certainly be drowned out by the noise from personal anecdotes and the placebo effect, which could jeopardize the future of a potentially valuable medicine."²⁹

Conflicts to Interest

None to declare.

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