

THERAPEUTIC USE OF CANNABIDIOL IN ENDOMETRIOSIS: LITERATURE REVIEW

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Abstract: **Objective:** Expose existing therapies for the treatment and monitoring of endometriosis, delving into the use of cannabidiol as a new therapeutic form. **Methods:** A narrative review of the literature was carried out based on 37 articles that ranged between 2004 and 2022 between March and May 2023. The bibliography included the Portuguese and English languages, preferably from the last 5 years, and were taken from the SciELO databases, PubMed, Web of Science and Scopus. **Results:** The clinical picture of endometriosis is variable. Symptoms are associated with dysmenorrhea, dyspareunia, infertility, chronic pelvic pain, chronic fatigue, ovulatory pain, urinary or intestinal complaints. In patients in whom the clinical condition of endometriosis is minimal, initial treatment can be with progestogens or combined oral contraceptives (OC). There is evidence that cannabis acts to improve pain, quality of life and decrease complications. The vast majority report improvement in sleep quality, decrease in symptoms of nausea and vomiting. Added to this, they were able to completely discontinue medication use, with opioids being the most common class of discontinued analgesics. Current treatment options for endometriosis often affect fertility and can cause undesirable side effects that preclude long-term management of this condition. **Conclusion:** The main treatments are based on NSAIDs and opioids and, if used chronically, they can cause harm. Therefore, cannabis-based drugs are alternatives to conventional therapies, as they improve pain symptoms, enabling quality of life and reducing complications.

Keywords: endometriosis, cannabidiol, therapeutic uses.

METHOD

A narrative review of the literature was carried out based on 37 articles that ranged

between 2004 and 2022 between March and May 2023. The bibliography included Portuguese and English, preferably from the last 5 years, and were taken from the SciElo, PubMed, Web of Science and Scopus. The descriptors used were “endometriosis”, “cannabidiol” and “therapeutic uses”.

INTRODUCTION

Endometriosis is a common gynecological disorder, with a prevalence of 6 to 10% in women worldwide¹. The endometrium, tissue affected in this pathology, is the innermost layer of the uterus and responsible for the implantation of the embryo and its nutrition in the first weeks of pregnancy. However, in this disorder, the proliferation of this layer occurs in a disorderly way to places beyond the uterine cavity, such as abdominal organs or pelvic structures². The main manifestations are dysmenorrhea, non-menstrual pelvic pain and dyspareunia that affect well-being³.

This disease can have a significant impact on women's quality of life, either because of the pain, which can become chronic, or because of complications related to fertility and sexual dysfunction, in addition to the impact on social and professional life^{3,4}. There are several therapies available for the treatment of endometriosis, such as hormone therapy, analgesics, anti-inflammatories and surgical procedures. All this bearing in mind that the type of intervention will be in accordance with the need and severity of each patient's case.⁵ This way, the emotional impacts can be as significant as the physical ones, which makes it necessary to include measures to address the psychological concerns of these women^{6,7}.

Nonsteroidal anti-inflammatory drugs (NSAIDs) are the most commonly used analgesics. However, its prolonged use causes side effects, especially in the gastrointestinal tract, which may lead to ulcers, lesions and diarrhea⁸. Therefore, opioids are being used to

avoid these repercussions of endometriosis⁹. However, the availability and frequent use can generate dependence and indirectly encourage individuals to obtain them illegally¹⁰.

The endocannabinoid (ES) system is formed by a high number of receptors. Medicinal substances based on cannabis bind to cannabinoid receptors, promoting an improvement in pain symptoms related to endometriosis. Through this association, the use of cannabinoids constitutes a therapeutic alternative to the conventional treatment of endometriosis¹¹. The complex interactions between these substances and SE have not been fully elucidated, and it is necessary to improve studies about treatment targets for pain control. Through this improvement, it would be possible to spread the use of cannabinoids in clinical practice¹².

It is a pathology that has its peak in the interval between 25 and 35 years, and an annual incidence among women aged 15 to 49 years estimated at 0.1%, consequently generating significant costs to public health^{13,14}. At the same time, patients end up with high costs in different areas of life, whether direct costs such as hospitalizations, treatments and surgeries, and indirect costs such as absence from work, sex life and social relationships¹⁵.

The present study aims to expose the existing therapies for the treatment and monitoring of endometriosis, delving into the use of cannabidiol as a new therapeutic form.

RESULTS

PATHOPHYSIOLOGY

Endometriosis is a chronic inflammatory pathology characterized by the presence of stroma in its extrauterine endometrial glandular epithelial tissue, which can be located on the peritoneal surface, uterosacral ligaments, retrocervical region, ovaries, rectovaginal septum, appendix, bladder, terminal ileum, ureters, sigmoid colon and

rectum¹⁴.

The pathophysiology of the disease is still not well defined. However, there are two main currents, being the theory of coelomic metaplasia and retrograde menstruation. The first consists of changing the mesothelium into endometrial tissue, which undergoes metaplasia and forms endometriotic lesions. The second, in implants of endometrial cells that occur by menstrual blood reflux in the tubes going to the abdominal cavity, settling in the uterine cavity and by the influence of a favorable hormonal environment, in addition to immunological factors, are not eliminated¹⁵. There is evidence that genetic, hormonal and immunological factors contribute to the formation of ectopic foci of endometriosis¹⁵.

CLINICAL CONDITION

The clinical picture is variable. In most cases they are associated with symptoms such as dysmenorrhea, dyspareunia, infertility, chronic pelvic pain, chronic fatigue, ovulatory pain, urinary or intestinal complaints. Other manifestations may occur depending on the installation of the implant. In addition, it is believed that the disease is responsible for causing psychological and social harm¹⁶.

Most diagnosed cases are characterized by dysmenorrhea as the main complaint, corresponding to 62.2% of patients. Furthermore, chronic pelvic pain was the most prevalent symptom, followed by deep dyspareunia, reported by 56.8% and 54.7%, respectively¹⁷.

DIAGNOSIS

Although most of these women were diagnosed through magnetic resonance imaging, this is more indicated when there are ovarian masses with doubtful hypothesis. This occurs because it has high sensitivity and specificity, in addition to being an accurate method for detecting deep endometriosis¹⁶.

Still, when talking about the first exam in case of suspicion, the most indicated are transvaginal ultrasonography or magnetic resonance imaging, but in these cases the absence of findings in the exams does not exclude the possibility of the disease¹⁸. Furthermore, it is known that the gold standard method for this diagnosis is surgical means through laparoscopy, as it is more reliable¹⁶.

Some cytokines have been studied as non-surgical markers for the disease, such as interleukin-6 (IL-6), which seems to have played a better role in discriminating patients with this pathology. However, even with altered test results, investigations by imaging methods are still required for the final diagnosis. Still, it is important to highlight that the delay in the correct diagnosis, with an average time of 5 years since the appearance of the first symptoms, added to the lack of investigation, profoundly impacts the daily lives of patients¹⁶.

TYPES OF TREATMENT FOR ENDOMETRIOSIS

Endometriosis consists of a chronic disease in which it has several possibilities of treatments, whether medication and/or surgery. Its approach must be individualized and consider, in therapy, the main complaints of the patient, clinical condition, desire to get pregnant and socioeconomic factor¹⁹. Furthermore, associating drug therapy with the practice of physical exercises is characterized as a relevant improvement factor, as it collaborates with the excretion of clots present by strengthening the immune system²⁰.

In patients with pelvic pain or in whom the clinical condition of endometriosis is minimal, initial treatment can be performed with progestogens or combined oral contraceptives (OC), which are equally effective¹⁹. These drugs act by inhibiting the growth of

disease foci, generating decidualization and endometrial atrophy or by inducing a state of hypoestrogenism, with the aim of stabilizing the occurrence and increase of lesions, in addition to attenuating symptoms²⁰. Therefore, the most prescribed combined oral contraceptives are those containing progestogens with androgenic action, that is, 19-nortestosterone derivatives¹⁹.

In addition to hormone therapy, non-opioid and opioid anti-inflammatories and analgesics are prescribed for pain relief^{6, 29}. Regarding the use of opioids, which can be used in chronic endometriosis pain, there is an increased risk for use of opioids (TUO), increasing the chance of causing overdose and death⁹.

The recommended therapeutic resource for cases of deep infiltrating endometriosis corresponds to the use of gonadotropin-releasing hormone (GnRH) analogues associated with combined oral contraceptives as a control. In cases where there is suspicion of adhesions, presence of endometriomas larger than 3 cm or recurrence of pain, surgery must be recommended. Along with this, there are low-complexity surgical procedures that consist of cauterization of superficial foci of endometriosis implantation, release of pelvic or intestinal adhesions. High-complexity procedures include complex interventions in the ovaries, cul-de-sac of Douglas, bowel, bladder and ureters, depending on the size of the involvement¹⁹.

TREATMENT OF ENDOMETRIOSIS WITH CANNABIDIOL AND ITS ADVERSE EFFECTS

The cannabis plant, despite its natural origin, contains hundreds of chemical substances²². It was discovered that the Endocannabinoid System (ES) is associated with fundamental mechanisms for pain in the treatment of endometriosis, being involved in

inflammation, proliferation and cell survival²³. SE is defined as a group of endogenous cannabinoid receptors, neurotransmitters and enzymes required for neurotransmitter synthesis and breakdown. Thus, being extremely connected to physiological processes of pain, appetite, mood, memory, among others²⁴.

The female reproductive system has one of the highest concentrations of cannabinoid receptors in the human body. More specifically in the uterus, CB1 receptors are the most expressed, as well as in other non-reproductive tissues¹³.

Human oocytes express CB1 and CB2 receptors, and their location varies during the oocyte maturation phase²⁶. Added to this, there is the presence of anandamide (AEA) in the female reproductive system, being important in folliculogenesis, preovulatory follicle maturation, oocyte maturation and ovulation. Furthermore, some change in endocannabinoid signaling can promote spontaneous abortion in early pregnancy²⁷.

There is evidence that cannabis works to improve pain, improve quality of life and reduce complications that endometriosis can cause²⁸. In an Australian study, participants with a mean age of 32 years and approximately 80% being current marijuana users, the vast majority reported pain relief and improved sleep quality, decreased symptoms of nausea and vomiting. Added to this, more than half of the participants were able to completely discontinue the use of medications, with opioids being the most common class²⁹.

In order to evaluate the effectiveness of the treatment, a sample composed of women between 18 and 89 years old diagnosed with pelvic and perineal pain, presenting with dyspareunia or endometriosis, was used. 240 patients were approached, in which 113 responses were obtained (rate of 47.1%). These were asked to select which symptoms

improved with the use of cannabis, with 96% selecting one or more of the following responses: muscle spasms, pain, cramps, libido, anxiety, depression, sleep disturbances and irritability. Also, the prevalence of cannabis use in patients with chronic pelvic pain who seek gynecological care was highlighted³⁰.

The application of cannabis as a medicinal treatment, mainly for the treatment of chronic pain syndromes, has been growing significantly, also highlighting a cross-sectional study of Australian women with endometriosis that showed that 76% used rest, meditation, breathing exercises and dietary changes for control. adjunct to pain and 13% of these reported the use of cannabis to control symptoms. In addition, it is noteworthy that the use of medicinal cannabis can be administered orally³¹.

The 13% of users reported a reduction in pain scores of 7.6 on a numeric scale from 0 to 10, with 10 being the most effective. With this, it was noticed that 56% of the patients were able to reduce the use of pharmaceutical drugs by at least half. In contrast to the adverse events associated with the use of cannabis reported, 10% had effects such as drowsiness, increased anxiety or tachycardia, these being the most common. However, it was concluded that the potential benefits of cannabis may outweigh the harms and that long-term data are lacking³¹.

Gastrointestinal side effects include nausea, vomiting, abdominal pain, dry mouth, constipation or diarrhea. Already in the central nervous system we have memory alteration, mental confusion, paranoia, hallucinations, dizziness and drowsiness. It is necessary to emphasize that 84% of the complications reported regarding the use included drowsiness, dizziness and dry mouth³⁰.

PROGNOSIS AND BIOSTATISTICS OF TREATMENT

Current treatment options for endometriosis often affect fertility and can cause undesirable side effects that preclude long-term management of this condition. This finding is an alert for the need for a new therapeutic agent capable of ceasing the symptoms, eliminating the disease and preventing recurrence, without impairing fertility³¹. In addition, a therapeutic attempt in evidence is the use of endocannabinoids that can act in the regulation of actions in the female reproductive organs. In humans, CB1 and CB2 receptors have been identified in ovarian follicular tissue, and it has been observed that plasma concentrations of AEA increase at the time of ovulation³¹.

The role of cannabidiol (CBD) in the upregulation of reactive oxygen species (ROS) scavenging enzymes and endogenous antioxidant systems (GSH) was observed, as well as in the downregulation of ROS-producing enzymes (Nox). These regulators are related to anti-inflammatory, anti-proliferative effects, lesion size and peritoneal fluids. In addition, administration also reduced neurogenic inflammation by decreasing mast cell infiltration and degranulation in the spinal cord, as well as the expression of related neurosensitizing mediators, leading to reduced activation of astrocytes and microglia. Thus, all these effects help to reduce pain behavior and visceral sensitization³².

AEA, D9-tetrahydrocannabinol (D9-THC) and N-arachidonoyl glycine (NAGly) were found to induce migration of HEC-1B cells through CB1 cannabinoid receptor-independent mechanisms. This way, an understanding of the function and regulation of GPR18 and its interactions with endogenous ligands is allowed, as well as how phytocannabinoids play a role in GPR18 signaling, which are of vital importance

to comprehensively assess the function of the cannabinoid signaling system in endometriosis³³.

Work in vitro and in animal models has been conducted examining the effect of synthetic cannabinoids on endometriotic tissue. In these analyses, reduced levels of CB1 and CB2 receptors were observed in endometriotic and adenomyotic tissues compared to controls and demonstrated a dose-dependent CB1 and CB2 agonist-mediated pro-apoptotic and antiproliferative effect on endometriotic cells. Whereas the effect of different synthetic cannabinoids, such as WIN 55212-2, induced cell death through the CB1 receptor in endometrial stromal cells³⁴.

ACCESS TO CANNABIDIOL TREATMENT IN BRAZIL

In Brazil, for substances to be used as medicines, studies are needed to prove their effectiveness and proper registration. Law No. 6,360/1976 made medication registration mandatory. In addition, for medicines to be used in the Unified Health System (SUS), they must be reviewed and included in the National List of Essential Medicines (RENAME)³⁵.

Brazilian legislation exerts a negative influence on the medical use of Cannabis, with decrees that sometimes facilitate access to medication and sometimes make its use more difficult. Also, the newest bill in the Chamber of Deputies is PL 89/2023, which aims to ensure the right to cannabis-based medicines and its components, including tetrahydrocannabinol, in public health units and those associated with the SUS³⁶.

Despite efforts, there is still difficulty in accessibility for studies and production of drugs for therapeutic purposes. Moreover, its import is bureaucratic and with high import rates, increasing prices³⁷.

CONCLUSION

Endometriosis is a worldwide prevalent gynecological pathology with psychic and physical repercussions such as dysmenorrhea, dyspareunia, infertility and chronic fatigue. The main treatments are based on NSAIDs and opioids and, if used chronically, can cause harm. Therefore, cannabis-based drugs are alternatives to conventional therapies, as they improve pain symptoms, allowing quality of life and reducing complications.

However, accessibility to the medicinal plant is still difficult in Brazil, preventing studies. Thus, the approach to the patient must consider several treatment possibilities and be individualized based on her symptoms, desire to get pregnant and socioeconomic reality.

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