Journal of Medical Clinical Case Reports

Project Twenty21 Australia: A Case Study of the Treatment of Chronic Pelvic Pain Due To Endometriosis with Cannabidiol Oil

Kylie O'Brien[1, 2, 3*], Sandy Fieldhouse[4], Justin Beilby[2], Michael Lynskey[5], Michael Barnes[6] and David Nutt[5,7]

[1]*NICM Health Research Institute, Western Sydney University, New South Wales, Australia.*

[2]*Torrens University, Adelaide, South Australia.*

[3]*Cann Compounding Group, Adelaide, South Australia.*

[4]*Releaf Clinic, Melbourne, Victoria, Australia.*

[5]*Drug Science, London, United Kingdom.*

[6]*University of Newcastle, Newcastle upon Tyne, United Kingdom.*

[7]*Imperial College, London, United Kingdom.*

***Corresponding Authors**

Kylie O'Brien PhD,
NICM Health Research Institute, Western Sydney University, New South Wales, Australia.
Torrens University, Adelaide, South Australia.
Cann Compounding Group, Adelaide, South Australia.

Submitted : 19 Jun 2025 ; Published : 11 Jul 2025

Citation: O'Brien, K. et al., (2025). Project Twenty21 Australia: A Case Study of the Treatment of Chronic Pelvic Pain Due To Endometriosis with Cannabidiol Oil. *J Medical Case Repo* 7(3):1-8. DOI : https://doi.org/10.47485/2767-5416.1119

Abstract

Project Twenty21 Australia was an open label, prospective observational cohort study investigating the effectiveness of medicinal cannabis in alleviating chronic pain, anxiety, PTSD and multiple sclerosis. Participants completed validated questionnaires at baseline then three-monthly (up to 12 months) to assess pain, sleep, mood, quality of life and perceived impression of change. This case study describes a 23-year-old woman who was a participant in Project Twenty21 Australia who presented with chronic pelvic pain due to endometriosis, with comorbidities of anxiety, depression and insomnia. She was prescribed a full spectrum cannabidiol (CBD) oil with a very low amount of tetrahydrocannabinol (THC). At three months follow-up, her pelvic pain had substantially improved. CBD was also able to alleviate some of her other comorbidities including poor sleep and depression and was not associated with any adverse effects. CBD oil, with low THC, may represent a therapeutic option for women with chronic pelvic pain associated with endometriosis, where other therapies have failed.

Introduction

Endometriosis is an estrogen-dependent, inflammatory condition in which endometrial-like tissue is found outside the uterus, often involving the bladder, bowel, pelvic wall and retroperitoneal structures (Crump et al., 2024; Lingegowda et al., 2022; Macer & Taylor, 2012; WHO, 2023). It typically occurs in women of reproductive age and is associated with pain during periods, sexual intercourse, bowel movements and/or urination, as well as chronic pelvic pain, abdominal bloating, fatigue, nausea and in some cases anxiety, depression and infertility(WHO, 2023). The pain is commonly accompanied by psychological distress and fatigue which can amplify the pain (Bouaziz et al., 2017). Sleep disturbance is also a comorbidity of endometriosis, something often overlooked in the clinic (Sumbodo et al., 2024). The global prevalence of endometriosis has been estimated to be somewhere between 10-18% (Al-Lami et al., 2024; Moradi et al., 2021; Szypłowska et al., 2023) and prevalence has been found to differ across continents (Moradi et al., 2021). In Australia the national cumulative prevalence of endometriosis is estimated at 6.0% (95% CI 5.8-6.2%) for clinically confirmed endometriosis by age 40-44 years, increasing to 11.4% (95% CI 11.1-11.7%) if diagnoses of clinically suspected endometriosis were included (Rowlands et al., 2021).

There is no current cure for endometriosis. Treatment options include pharmaceuticals (eg. analgesics, hormone therapy, antidepressants) and surgery, however a significant percentage (20-50%) of women experience a recurrence five years after surgery or medical treatment (Hickey et al., 2014). Painkillers such as opioids continue to be prescribed by some practitioners, often with benzodiazepines (Farooqi et al., 2023), both of which have side effects including cognitive impairment, severe withdrawal effects and addiction (Farooqi et al., 2023). There is a need for other treatment options for many women.

There is evidence that women with endometriosis are using medicinal cannabis (MC) to manage their symptoms. Several cross-sectional surveys have assessed the effects of MC on endometriosis symptoms (Armour et al., 2019; Armour et al., 2022; Jasinski et al., 2024; Sinclair et al., 2020), though some surveys have also included other diseases or conditions (Armour et al., 2021; Carrubba et al., 2021). For example,

a cross-sectional survey of Australian women aged 18-45 years with endometriosis (n= 484) found that 76% used self-management strategies in the last 6 months and of those using self-management, 13% used cannabis to manage symptoms, reporting high effectiveness in reducing pain (56% were able to reduce pharmaceuticals by at least 50%). Greatest improvements for cannabis users were for sleep and nausea/vomiting (Sinclair et al., 2020). Overall, results from cross-sectional surveys indicate that MC is efficacious for alleviating pelvic pain, improving sleep, reducing anxiety and depression, and reducing nausea and vomiting (Calleson Cummings et al., 2024). However, surveys are open to forms of bias.

Project Twenty21 Australia was an open label, prospective observational cohort study investigating the effectiveness of MC in alleviating chronic pain, anxiety, post-traumatic stress disorder and multiple sclerosis, described elsewhere (O'Brien et al., 2023). This case study describes the treatment and outcomes of one participant in Project Twenty21 Australia who presented with chronic pelvic pain due to endometriosis. It exemplifies some of the multiple benefits of MC in helping alleviate not only the primary complaint but also some comorbidities.

Case Study

A 23 year-old woman presented to the Releaf Clinic, a medical clinic specialising in MC, in the state of Victoria, Australia in August 2022. Her primary complaint was chronic pelvic pain due to endometriosis. She was interested in discussing whether MC may be suitable to manage her chronic pelvic pain, as well as anxiety, depression and insomnia.

She reported having had pelvic pain since the age of 15 years. She explained that the pain can be severe and last right through her period/cycle but is worse during her period and during ovulation. The pain interrupts daily functioning for up to 10 days each month, and she is often bedridden on those days.

She had a laparoscopy in mid-2020. Lesions were removed from the uterosacral ligament and Pouch of Douglas. However, the pain remained and persisted.

She also reported suffering from anxiety, depression and poor sleep. Specifically, she reported having trouble getting to sleep and waking often during the night, something that had been happening for years. She also had a history of migraine headaches.

Current medications included propranolol, sertraline (50mg) and valium prn (which she has not taken yet) plus panadol and nurofen. She was also taking valdoxan and panadeine.

She had no history of cardiovascular disease, liver disease, renal disease, or overweight/obesity. She had no personal or family history of schizophrenia or psychosis. She was not planning on becoming pregnant. She had no history of at-risk behaviours: she had not previously used cannabis or illicit drugs and had no history of alcohol or nicotine dependence. Her regular exercise was walking.

The patient was interested in participating in Project Twenty21 Australia. After screening by the Study Coordinator and completing the informed consent process, the patient was enrolled into the study. In addition to providing informed consent at Releaf Clinics to have MC prescribed and completing the informed consent process to participate in Project Twenty21, the patient also provided written informed consent for her medical information to be written up as a de-identified case study.

Treatment

Medicinal Cannabis Product

The Releaf Clinic doctor prescribed a full spectrum CBD dominant oil containing 100mg/ml CBD and ≤ 1mg/ml THC in a medium chain triglyceride carrier oil. It contained the following key terpenes: α-bisabolol (29%), caryophyllene/caryophyllene oxide (22%), guaiol (18%), terpineol (9%), linalool (8%), humulene (7%), and others (7%).

The starting dosage was 0.1 ml BD (ie. 10mg CBD and ≤ 0.1mg THCBD) and she was instructed to titrate up (by 0.1 ml every 3-4 days) to the therapeutic dosage that alleviated her symptoms which was 0.4 ml BD (equating to 40mg CBD and ≤ 0.4mg THC BD).

Project Twenty21 Outcome Variables Measured

In Project Twenty21 Australia participants completed a set of structured questionnaires at baseline then every three months, up to a maximum of 12 months (the study methodology is described elsewhere, see O'Brien et al. 2023). Briefly, chronic pain severity and interference are measured using the Brief Pain Inventory Short Form (Cleeland, 1991; Cleeland, 2009; Keller et al., 2004). Secondary outcome variables include mood/depression (measured using the Patient Health Questionnaire, PHQ-9) (Rancans et al., 2018), quality of life (measured using the Euro Quality of Life 5 Dimensions [EQ-5D-5L] (Euroqual.org, 2023), sleep (questionnaire adapted from the Pittsburg Sleep Quality Index (Buysse et al., 1989) and patient's perceived impression of change (Patient's Global of Change Questionnaire [PGIC]). A Cannabis Based Medicines Questionnaire (CBMQ) was used to assess potential problems related to dependence on prescribed MC products and a Symptoms Questionnaire was used to record positive and negative side effects (O'Brien et al., 2023).

Three-Month Follow-Up

Clinician Visit

At the three-month follow-up visit, the patient reported that her pelvic pain had substantially improved: it had all but resolved. She now had only 1-2 days of pain a month, during her period only. She reported that her sleep had also improved substantially and her anxiety was also slightly better. She was very happy with the result. The patient intended to continue on the CBD oil (0.4 ml BD), with further review scheduled in another 3 months' time.

Project Twenty21 Australia Outcome Variables

As part of Project Twenty21 Australia, patients must nominate a primary condition and any secondary conditions. The primary

condition nominated was chronic pain due to endometriosis. Secondary conditions nominated were: migraine, generalised anxiety disorder and major depressive disorder.

Scores from the BPI (chronic pain), PHQ-9 (mood/depression), sleep questionnaire, EQ5D5L (quality of life) questionnaires at baseline and three months are included in Table 1. Results demonstrate improvements in aspects of pain, including ratings of pain severity and pain interference, quality of life, mood and sleep. The EQ5D5L quality of life visual analogue scale indicates improvement in perceived overall health.

The Patient's Global Impression of Change (PGIC) questionnaire asks the patient to circle a number from 0 to 10 that matches the degree of change since beginning care at the clinic, with 0 equating to 'much better' and 10 equating to 'much worse', and 5 being 'no change'. The baseline PGIC value was rated as 5 (no change) and at 3 months follow-up it was rated as 0 indicating 'much better'.

The Cannabis Based Medicines Questionnaire (CBMQ) was developed to assess potential problems related to dependence on prescribed MC products. The very low score of 2 on this measure indicates that the patient was not experiencing problems related to dependence.

In relation to the Symptoms Questionnaire, the following positive effects were reported: pain reduction, reduced headache/migraine and reduced nausea. No adverse effects were reported.

Table 1: Change in Outcome Variables Over Three Months

Outcome Variables	Baseline t=0	t= 3 months
BPI Score Least Pain Rating (range 0-10, higher number indicates greater pain)	5	0
BPI Score Average Pain Rating (range 0-10, higher number indicates greater pain)	5	2
BPI Worst Pain Rating (range 0-10, higher number indicates greater pain)	9	1
BPI Current Pain Rating (range 0-10, higher number indicates greater pain)	7	0
BPI Pain Severity Score (mean of rating across 4 items; range 0-10, higher number indicates greater severity)	6.5	0.75
BPI Pain Interference (mean rating across 7 items; range 0-10, higher number indicates greater interference)	7.29	0.43
PHQ-9 score (mood/depression; range 0-27; higher numbers represent worse depression)	9	6
EQ5D5L score (VAS; range 0-100; 100 represents best possible perceived overall health)	40	75
EQ-5D-5L Summary Index weighted score (range -0.285 to 1, with higher score indicating better quality of life)	0.457	0.922
Sleep Questionnaire (total maximum score is 20, higher score indicates worse sleep quality)	14	11
Patient's Impression of Global Change	5	0
Cannabis-Based Medicines Questionnaire	NA	2

Doctor's Perspective

'As a general practitioner it is particularly pleasing to review this patient's experience. At the age of 23 she had already experienced 8 years of chronic pain due to endometriosis. She had daily pain regularly requiring bed rest and interrupting her daily functioning. She had had surgery with only limited benefit. Regular therapeutics had failed to give her relief. She came to see me in desperation to have reduced pain and recover an ability to live more fully. After three and a half months on CBD oil she was markedly improved with her daily pain resolved and pain on day 1-2 of her period only.

She experienced no side effects from the CBD oil. Typically, an overwhelming number of patients have no or very mild side effects to CBD oil, that settle within 1-2 weeks at most. In my experience there are a number of patients with this diagnosis who don't respond to traditional therapeutics. I am encouraged by the use of CBD oil in this patient and in others I have also treated with the same diagnosis. Additionally, the patient's other comorbidities of anxiety and insomnia were also improved by the use of CBD oil. I am encouraged by this experience and that of other patients of mine that CBD can be a life-changing medication'.

Patient Feedback

The patient gave the following feedback: 'My experience with using medicinal cannabis has been extremely positive. The chronic pain that I had been experiencing for the past several years had reached a point where my quality of life was severely impacted. Since starting to take daily medicinal cannabis, I have seen a significant reduction in my pain as well as an improvement in my mood and ability to live life to the fullest!'

Discussion

This case study of a woman with debilitating pelvic pain due to endometriosis demonstrates that for this individual, full spectrum CBD oil containing a small amount of THC plus several terpenes was efficacious. To date there has been little clinical research focused on MC for the treatment of endometriosis, despite the surveys indicating that women are reporting that use of cannabis is associated with improvement in pain from various gynaecological conditions, including endometriosis (Liang et al., 2022; Sinclair et al., 2020). In Australia, chronic pain is the top condition for which medicinal cannabis (MC) is prescribed under the Special Access Scheme B (MacPhail et al., 2022). The weight of evidence from systematic reviews suggests that MC is efficacious in treating

chronic pain (Aggarwal, 2013; Boychuk et al., 2015; Hill, 2015; Lynch & Campbell, 2011; Lynch & Ware, 2015; Martin-Sanchez et al., 2009; McDonagh et al., 2022; Mücke et al., 2018; TGA, 2017; Wang et al., 2021; Whiting et al., 2015), though at least one review concluded that evidence for the use of MC for chronic non-cancer pain was limited (Stockings et al., 2018).

There is a physiological basis for why MC might be useful in alleviating chronic pelvic pain associated with endometriosis. Components of cannabis interact with the body's endocannabinoid system (ECS), a neuro- and immune-regulatory cell-signalling system, involved in homeostasis of most bodily systems(O'Brien & Blair, 2021), and the components of the ECS are distributed throughout the female reproductive tract (Tanaka et al., 2022). CB1 receptors are highly expressed in the uterus, with levels of CB1 and CB2 receptors varying during the menstrual cycle. Endocannabinoids are abundantly expressed in the endometrium, influencing endometrial cellular function (Tanaka et al., 2022). AEA is found in female reproductive tract fluids and ovaries, playing an important role in folliculogenesis, pre-ovulatory follicle maturation, oocyte maturation and ovulation (Bouaziz et al., 2017). In fact, the uterus has the highest concentration of AEA within the reproductive tract (Tanaka et al., 2020). The ECS helps regulate pain and analgesia, inflammation, the gut, emotions, stress, sleep, and many other functions that are relevant to endometriosis (O'Brien & Blair, 2021).

Endometriosis is characterised by chronic local and general inflammatory environment (Lingegowda et al., 2022). The types of pain associated with endometriosis is heterogenous, involving nociceptive, neuropathic, nociplastic pain/central sensitisation, and inflammatory pain and the ECS is involved in modulation of these types of pain (Lingegowda et al., 2022; Whitaker et al., 2024). Endometriotic lesions can cause mechanical nerve compression and infiltration, and activate nociceptors (Bouaziz et al., 2017; Chen & Li, 2025). There are changes in peritoneal fluid including increased cytokines, growth factors and chemokines which activate peripheral nociceptors and sensitize peripheral nerves (Bouaziz et al., 2017). Inflammatory mediators interact with neurons to produce hypersensitivity and modify the perception of pain (Bouaziz et al., 2017). The ECS is known to be involved in the pathophysiological state of chronic pain and inflammation (Campos et al., 2021; Liang et al., 2022). There is evidence that the ECS is dysregulated in endometriosis, however many studies indicate an association of ECS dysregulation with disease or inflammatory state, but not necessarily a causal relationship (Lingegowda et al., 2022).

Thus, it is not unreasonable to expect that the ECS could be a useful therapeutic target for the treatment of chronic pain and endometriosis-associated pain; phytocannabinoids can act via several targets to modulate the ECS (Campos et al., 2021).

CBD was the predominant phytocannabinoid in the MC product that was prescribed to this patient. How CBD addresses chronic pain is likely to be multifaceted. CBD has very low affinity for cannabinoid receptors though its effects rely on the integrity of cannabinoid receptors (Ney et al., 2019). Instead, it is thought to act predominantly via activating the ECS indirectly and through many other receptor targets (Ney et al., 2019; S. Pisanti et al., 2017). Rodent experiments indicate that CBD can stimulate descending pathways of antinociception and cause analgesia by interacting with several target proteins involved in nociceptive control (Maione et al., 2011). CBD can act on serotonergic and glycinergic receptors in neurons involved in pain processing (Campos et al., 2021). CBD has been found to be a positive allosteric modulator at α1 and α1β glycine receptors in low concentrations and directly activate them at higher concentrations(Ahrens et al., 2009; Kicman & Toczek, 2020). As explained by Ahrens and colleagues, the loss of inhibitory synaptic transmission in the dorsal horn of the spinal cord plays a major role in chronic pain development after nerve injury or inflammation and in humans, glycine acts as the main inhibitory postsynaptic neurotransmitter in dorsal horn of spinal cord) (Ahrens et al., 2009). CBD can inhibit fatty acid amide hydrolase (FAAH, the main enzyme metabolising AEA) leading to an increase in AEA levels(Kicman & Toczek, 2020). It is also a TRPV1 agonist, similar to capsaicin (which can reduce the pain transmitter Substance P) (Baron, 2018; Campos et al., 2021). Other actions of CBD relevant to its analgesic and anti-inflammatory actions include being a TRPA1 agonist and TRPM8 antagonist (Baron, 2018). Being anxiolytic, CBD may also positively impact on how pain is experienced since pain is also an affect, that is, it has both physical/sensory and emotional dimensions (Simona Pisanti et al., 2017)(Pisanti et al., 2017).

There was a very small amount of THC in the MC product formulation, and this may have also contributed to the analgesic effect. THC has a range of mechanisms of action relevant to its analgesic effects including being a partial agonist at the cannabinoid receptors, affecting the glutaminergic system involved in neuropathic pain, affecting the serotonergic system (eg. decreasing 5-HT release from platelets, decreasing 5-HT re-uptake and increasing cerebral 5-HT production), blocking dopamine, stimulating beta-endorphin production, increasing proenkephalin mRNA levels in brainstem regions involved in pain processing, reducing NMDA responses with associated neuroprotective effects and blocking capsaicin-induced hyperalgesia (Substance P) (Baron, 2018; Russo, 2008). Its anti-inflammatory actions are also relevant to analgesia and include inhibiting PGE-2 synthesis, decreasing platelet aggregation and inhibiting lipoxygenase (a rate-limiting enzyme in the process of metabolism of arachidonic acid into leukotrienes that mediates inflammation) (Russo, 2008; Takeda et al., 2011). As explained by Campos and colleagues, THC may inhibit neuropathic pain by inhibiting COX-2, leading to increased levels of AEA and reduced prostaglandins and this may then reduce pro-inflammatory signalling and possibly decrease the glial and immunological response (Campos et al., 2021).

This patient also experienced anxiety, depression and poor sleep which appeared to be improved with MC treatment. There is preclinical and clinical evidence that CBD is anxiolytic and in animals it can also reduce depression-like behaviours (though there is less evidence in humans) (Bergamaschi et al., 2011; Masataka, 2019; O'Brien & Blair, 2021). There is also some clinical evidence that CBD may assist in addressing poor sleep, including case reports (Shannon & Opila-Lehman, 2015), case series (Shannon et al., 2019) and randomized controlled trials (RCTs) (Carlini & Cunha, 1981; Zuardi et al., 1993), including some more recent RCTs investigating combinations of CBD/THC in insomniacs (Ried et al., 2023; Walsh et al., 2021). However, more research is needed in relation to sleep as results have been somewhat mixed, with some research showing CBD to be sedative and others alerting (O'Brien & Blair, 2021). These different findings may be dose-related and results might differ between CBD isolate and full-spectrum CBD products.

The key terpenes in this product may also have contributed to the analgesia via the 'entourage effect', as well as addressing some of her comorbidities. For example, linalool has been shown to have anxiolytic actions in animal and human studies, as well as antidepressant, sedative, analgesic and anti-hyperalgesic effects, among many others (Baron, 2018; Liktor-Busa et al., 2021; Weston-Green et al., 2021). α-bisabolol has anti-anxiety properties as well as analgesic, antibiotic and anticancer activities (Kamatou & Viljoen, 2009; Tabari & Tehrani, 2017). β-caryophyllene, a selective CB2 receptor agonist, has many properties including being analgesic in inflammatory and neuropathic pain, and has potent anti-inflammatory actions (Baron, 2018; Fidyt et al., 2016). Caryophyllene oxide has analgesic and anti-inflammatory actions comparable to aspirin (Baron, 2018). α- caryophyllene is analgesic and anti-nociceptive, with anti-inflammatory properties comparable to dexamethasone (Baron, 2018). Terpineol has anti-inflammatory and analgesic, antioxidant and anti-cancer effects, whilst Guaiol has anti-bacterial and anti-cancer effects (Yang et al., 2023).

Importantly, the patient did not experience any negative side effects of using the MC product. Side effects of cannabis medicines can be related to THC and CBD content, as well as the carrier oil in the some products (if an oil). An audit of 397 patients prescribed CBD in a New Zealand Clinic found that CBD was found to be well tolerated with mild adverse events, most commonly related to sedation (2% of the sample who completed follow-up) (Gulbransen et al., 2020). CBD and to a lesser extent THC can also interact with certain pharmaceuticals (Brown & Winterstein, 2019).

Conclusion

This case study demonstrated that the use of full spectrum CBD oil over three months was associated with a clinically significant reduction in chronic pelvic pain due to endometriosis in a 23-year-old woman. CBD was also able to alleviate some of her other comorbidities including poor sleep and depression. Use of CBD was associated with improvements in sleep and mood/depression and was not associated with any adverse effects. There is sufficient evidence in the literature that MC may be useful in the alleviation of chronic pain and the potential mechanisms of action of phytocannabinoids and terpenes in alleviating pain and various comorbidities associated with chronic pain such as anxiety, depression and poor sleep are known to some extent. However, there is little clinical research investigating the efficacy of MC in alleviating symptoms associated with endometriosis. This case study contributes to a growing evidence-base associated with MC and endometriosis. MC products differ in relation to amounts and relative proportions of key phytocannabinoids as well as minor phytocannabinoids and terpenes, all of which will help determine therapeutic effect. Judicious choice of MC product, taking these factors into account, is a more nuanced approach to prescribing of MC.

Declarations and Acknowledgements

This case study was conducted as part of Project Twenty21 Australia, an observational study investigating medicinal cannabis for chronic pain, anxiety, PTSD and multiple sclerosis. Kylie O'Brien was one of the Chief Investigators for Project Twenty21 Australia and was previously the Chief Scientific Officer for Releaf Group Ltd. The case study was that of Dr Sandy Fieldhouse, a general practitioner who works for Releaf Clinic in St Kilda, Victoria, Australia.

Project Twenty21 Australia was conducted by the Australasian College of Cannabinoid Medicine (ACCM) which is a subsidiary of Releaf Group Ltd, with study participants recruited from Releaf Clinics (part of Releaf Group Ltd) in Victoria and Queensland, Australia. Patients were prescribed from a Project Formulary of medicinal cannabis products from supporting companies and dispensed primarily through Releaf Dispensaries (part of Releaf Group Ltd). Project Twenty21 Australia was supported by the following Australian medicinal cannabis companies: Cann Compounding Group, Beacon Medical Australia Pty Ltd, Cann Global Pty Ltd, and Levin Health Ltd. The study ceased recruiting in May 2023.

References

1. Crump, J., Suker, A., & White, L. (2024). Endometriosis: A review of recent evidence and guidelines. *Australian Journal for General Practitioners, 53*(1-2), 11-18. DOI: https://doi.org/10.31128/ajgp/04-23-6805
2. Lingegowda, H., Williams, B. J., Spiess, K. G., Sisnett, D. J., Lomax, A. E., Koti, M., & Tayade, C. (2022). Role of the endocannabinoid system in the pathophysiology of endometriosis and therapeutic implications. *J Cannabis Res, 4*(1), 54. DOI: https://doi.org/10.1186/s42238-022-00163-8
3. Macer, M. L., & Taylor, H. S. (2012). Endometriosis and infertility: a review of the pathogenesis and treatment of endometriosis-associated infertility. *Obstet Gynecol Clin North Am, 39*(4), 535-549. DOI: https://doi.org/10.1016/j.ogc.2012.10.002
4. WHO. (24 March 2023). Endometriosis. www.who.int/news-room/fact-sheets/detail/endometriosis

5. Bouaziz, J., Bar On, A., Seidman, D. S., & Soriano, D. (2017). The Clinical Significance of Endocannabinoids in Endometriosis Pain Management. *Cannabis Cannabinoid Res, 2*(1), 72-80. DOI: https://doi.org/10.1089/can.2016.0035
6. Sumbodo, C. D., Tyson, K., Mooney, S., Lamont, J., McMahon, M., & Holdsworth-Carson, S. J. (2024). The relationship between sleep disturbances and endometriosis: A systematic review. *European Journal of Obstetrics and Gynecology and Reproductive Biology*, 293, 1-8. DOI: https://doi.org/10.1016/j.ejogrb.2023.12.010
7. Al-Lami, R. A., Taha, S. A., Jalloul, R. J., & Taylor, H. S. (2024). Women with endometriosis in the United States: National Survey of Family Growth, 2011–2019. *Journal of Endometriosis and Uterine Disorders*, 8, 100081. DOI:https://doi.org/https://doi.org/10.1016/j.jeud.2024.100081
8. Moradi, Y., Shams-Beyranvand, M., Khateri, S., Gharahjeh, S., Tehrani, S., Varse, F., Tiyuri, A., & Najmi, Z. (2021). A systematic review on the prevalence of endometriosis in women. *Indian J Med Res, 154*(3), 446-454. DOI: https://doi.org/10.4103/ijmr.IJMR_817_18
9. Szypłowska, M., Tarkowski, R., & Kułak, K. (2023). The impact of endometriosis on depressive and anxiety symptoms and quality of life: a systematic review. *Front Public Health*, 11, 1230303. DOI: https://doi.org/10.3389/fpubh.2023.1230303
10. Rowlands, I. J., Abbott, J. A., Montgomery, G. W., Hockey, R., Rogers, P., & Mishra, G. D. (2021). Prevalence and incidence of endometriosis in Australian women: a data linkage cohort study. *Bjog, 128*(4), 657-665. DOI: https://doi.org/10.1111/1471-0528.16447
11. Hickey, M., Ballard, K., & Farquhar, C. (2014). Endometriosis. *BMJ : British Medical Journal*, 348, g1752. DOI: https://doi.org/10.1136/bmj.g1752
12. Farooqi, T., Bhuyan, D. J., Low, M., Sinclair, J., Leonardi, M., & Armour, M. (2023). Cannabis and Endometriosis: The Roles of the Gut Microbiota and the Endocannabinoid System. *Journal of Clinical Medicine, 12*(22), 7071. DOI: https://doi.org/10.3390/jcm12227071
13. Armour, M., Sinclair, J., Chalmers, K. J., & Smith, C. A. (2019). Self-management strategies amongst Australian women with endometriosis: a national online survey. *BMC Complementary and Alternative Medicine, 19*(1), 17. DOI: https://doi.org/10.1186/s12906-019-2431-x
14. Armour, M., Sinclair, J., Cheng, J., Davis, P., Hameed, A., Meegahapola, H., Rajashekar, K., Suresh, S., Proudfoot, A., & Leonardi, M. (2022). Endometriosis and Cannabis Consumption During the COVID-19 Pandemic: An International Cross-Sectional *Survey. Cannabis Cannabinoid Res, 7*(4), 473-481. DOI: https://doi.org/10.1089/can.2021.0162
15. Jasinski, V., Voltolini Velho, R., Sehouli, J., & Mechsner, S. (2024). Cannabis use in endometriosis: the patients have their say-an online survey for German-speaking countries. *Arch Gynecol Obstet, 310*(5), 2673-2680. DOI: https://doi.org/10.1007/s00404-024-07652-6
16. Sinclair, J., Smith, C. A., Abbott, J., Chalmers, K. J., Pate, D. W., & Armour, M. (2020). Cannabis Use, a Self-Management Strategy Among Australian Women With Endometriosis: Results From a National Online Survey. *J Obstet Gynaecol Can, 42*(3), 256-261. DOI: https://doi.org/10.1016/j.jogc.2019.08.033
17. Armour, M., Sinclair, J., Noller, G., Girling, J., Larcombe, M., Al-Dabbas, M. A., Hollow, E., Bush, D., & Johnson, N. (2021). Illicit Cannabis Usage as a Management Strategy in New Zealand Women with Endometriosis: An Online Survey. *J Womens Health (Larchmt), 30*(10), 1485-1492. DOI: https://doi.org/10.1089/jwh.2020.8668
18. Carrubba, A. R., Ebbert, J. O., Spaulding, A. C., DeStephano, D., & DeStephano, C. C. (2021). Use of Cannabis for Self-Management of Chronic Pelvic Pain. *J Womens Health (Larchmt), 30*(9), 1344-1351. DOI: https://doi.org/10.1089/jwh.2020.8737
19. Calleson Cummings, S., Ennis, N., Kloss, K., & Rosasco, R. (2024). Evaluating the Current Evidence for the Efficacy of Cannabis in Symptom Management of Endometriosis-Associated Pain. *Integr Med Rep, 3*(1), 111-117. https://doi.org/10.1089/imr.2024.0017
20. O'Brien, K., Beilby, J., Frans, M., Lynskey, M., Barnes, M., Jayasuriya, M., Athanasiou-Fragkouli, A., Blair, P., & Nutt, D. (2023). Preliminary findings from project Twenty21 Australia: An observational study of patients prescribed medicinal Cannabis for chronic pain, anxiety, posttraumatic stress disorder and multiple sclerosis. Drug Science, Policy and Law, 9, 20503245231164718. https://doi.org/10.1177/20503245231164718
21. Cleeland, C. (1991). Brief Pain Inventory. Handbook of Pain Assessment. The Guilford Press.
22. Cleeland, C. S. (2009). The Brief Pain Inventory. User Guide. https://www.mdanderson.org/documents/Departments-and-Divisions/Symptom-Research/BPI_UserGuide.pdf
23. Keller, S., Bann, C. M., Dodd, S. L., Schein, J., Mendoza, T. R., & Cleeland, C. S. (2004). Validity of the brief pain inventory for use in documenting the outcomes of patients with noncancer pain. *Clin J Pain, 20*(5), 309-318. DOI:https://doi.org/10.1097/00002508-200409000-00005
24. Rancans, E., Trapencieris, M., Ivanovs, R., & Vrublevska, J. (2018). Validity of the PHQ-9 and PHQ-2 to screen for depression in nationwide primary care population in Latvia. *Ann Gen Psychiatry*, 17, 33. DOI: https://doi.org/10.1186/s12991-018-0203-5
25. Euroqual.org. (2023). EQ-5D User Guides https://euroqol.org/publications/user-guides/
26. Buysse, D. J., Reynolds, C. F., 3rd, Monk, T. H., Berman, S. R., & Kupfer, D. J. (1989). The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. *Psychiatry Res, 28*(2), 193-213. DOI:https://doi.org/10.1016/0165-1781(89)90047-4
27. Liang, A. L., Gingher, E. L., & Coleman, J. S. (2022). Medical Cannabis for Gynecologic Pain Conditions: A Systematic Review. *Obstet Gynecol, 139*(2), 287-296. DOI: https://doi.org/10.1097/aog.0000000000004656

28. MacPhail, S. L., Bedoya-Pérez, M. A., Cohen, R., Kotsirilos, V., McGregor, I. S., & Cairns, E. A. (2022). Medicinal Cannabis Prescribing in Australia: An Analysis of Trends Over the First Five Years. Front Pharmacol, 13, 885655. DOI: https://doi.org/10.3389/fphar.2022.885655
29. Aggarwal, S. K. (2013). Cannabinergic pain medicine: a concise clinical primer and survey of randomized controlled trial results. *Clin J Pain*, 29, 162-171. DOI: https://doi.org/10.1097/ajp.0b013e31824c5e4c
30. Boychuk, D. G., Goddard, G., Mauro, G., & Orellana, M. F. (2015). The effectiveness of cannabinoids in the management of chronic nonmalignant neuropathic pain: a systematic review. *J Oral Facial Pain Headache, 29*(1), 7-14. DOI: https://doi.org/10.11607/ofph.1274
31. Hill, K. P. (2015). Medical marijuana for treatment of chronic pain and other medical and psychiatric problems: A clinical review. *JAMA., 313*(24), 2474-2483. DOI: https://doi.org/10.1001/jama.2015.6199
32. Lynch, M. E., & Campbell, F. (2011). Cannabinoids for treatment of chronic non-cancer pain; a systematic review of randomized trials. *Br J Clin Pharmacol, 72*(5), 735-744. DOI: https://doi.org/10.1111/j.1365-2125.2011.03970.x
33. Lynch, M. E., & Ware, M. A. (2015). Cannabinoids for the treatment of chronic non-cancer pain: An updated systematic review of randomized controlled trials. *J Neuroimmune Pharmacol*, 10, 293-301. DOI: https://doi.org/10.1007/s11481-015-9600-6
34. Martin-Sanchez, E., Furukawa, T. A., Taylor, J., & Martin, J. L. (2009). Systematic review and meta-analysis of cannabis treatment for chronic pain. *Pain Med, 10*(8), 1353-1368. DOI: https://doi.org/10.1111/j.1526-4637.2009.00703.x
35. McDonagh, M. S., Morasco, B. J., Wagner, J., Ahmed, A. Y., Fu, R., Kansagara, D., & Chou, R. (2022). Cannabis-Based Products for Chronic Pain : A Systematic Review. *Ann Intern Med, 175*(8), 1143-1153. DOI: https://doi.org/10.7326/m21-4520
36. Mücke, M., Phillips, T., Radbruch, L., Petzke, F., & Häuser, W. (2018). Cannabis-based medicines for chronic neuropathic pain in adults. *Cochrane Database Syst Rev, 3*(3), Cd012182. DOI: https://doi.org/10.1002/14651858.CD012182.pub2
37. TGA. (2017). Canberra, ACT: Therapeutic Goods Administration.
38. Wang, L., Hong, P. J., & May, C., Rehman, Y., Oparin, Y., Hong, C. J., Hong, B. Y., AminiLari, M., Gallo, L., Kaushal, A., Craigie, S., Couban, R. J., Kum, E., Shanthanna. H., Price, I., Upadhye, S., Ware, M. A., Campbell, F., Buchbinder, R., Agoritsas, T., & Busse, J. W. (2021). Medical cannabis or cannabinoids for chronic non-cancer and cancer related pain: a systematic review and meta-analysis of randomised clinical trials. Bmj, 8, 374. DOI: https://doi.org/10.1136/bmj.n1034
39. Whiting, P. F., Wolff, R. F., Deshpande, S., Di Nisio, M., Duffy, S., Hernandez, A. V., Keurentjes, J. C., Lang, S., Misso, K., Ryder, S., Schmidlkofer, S., Westwood, M., & Kleijnen, J. (2015). Cannabinoids for Medical Use: A Systematic Review and Meta-analysis. *Jama, 313*(24), 2456-2473. DOI: https://doi.org/10.1001/jama.2015.6358
40. Stockings, E., Campbell, G., Hall, W. D., Nielson, S., Zagic, D., Rahman, R., Murnion, B., Farrell, M., Weier, M., Degenhardt, L. (2018). Cannabis and cannabinoids for the treatment of people with chronic noncancer pain conditions: a systematic review and meta-analysis of controlled and observational studies. Pain, 159(10), 1932-1954. DOI: https://doi.org/10.1097/j.pain.0000000000001293
41. O'Brien, K., & Blair, P. (2021). Medicinal Cannabis and CBD in Mental Healthcare. Springer. DOI:https://psycnet.apa.org/doi/10.1007/978-3-030-78559-8
42. Tanaka, K., Amoako, A. A., Mortlock, S., Rogers, P. A. W., Holdsworth-Carson, S. J., Donoghue, J. F., Teh, W. T., Montgomery, G. W., & McKinnon, B. (2022). Gene expression of the endocannabinoid system in endometrium through menstrual cycle. *Sci Rep, 12*(1), 9400. DOI: https://doi.org/10.1038/s41598-022-13488-4
43. Tanaka, K., Mayne, L., Khalil, A., Baartz, D., Eriksson, L., Mortlock, S.-A., Montgomery, G., McKinnon, B., & Amoako, A. A. (2020). The role of the endocannabinoid system in aetiopathogenesis of endometriosis: A potential therapeutic target. European *Journal of Obstetrics & Gynecology and Reproductive Biology*, 244, 87-94. DOI: https://doi.org/https://doi.org/10.1016/j.ejogrb.2019.11.012
44. Whitaker, L. H. R., Page, C., Morgan, C., Horne, A. W., & Saunders, P. T. K. (2024). Endometriosis: cannabidiol therapy for symptom relief. *Trends in Pharmacological Sciences, 45*(12), 1150-1161. DOI: https://doi.org/10.1016/j.tips.2024.10.014
45. Chen, Y., & Li, T. (2025). Unveiling the Mechanisms of Pain in Endometriosis: Comprehensive Analysis of Inflammatory Sensitization and Therapeutic Potential. *Int J Mol Sci, 26*(4). 1770. DOI: https://doi.org/10.3390/ijms26041770
46. Campos, R. M. P., Aguiar, A. F. L., Paes-Colli, Y., Trindade, P. M. P., Ferreira, B. K., de Melo Reis, R. A., & Sampaio, L. S. (2021). Cannabinoid Therapeutics in Chronic Neuropathic Pain: From *Animal Research to Human Treatment. Front Physiol*, 12, 785176. DOI: https://doi.org/10.3389/fphys.2021.785176
47. Ney, L. J., Matthews, A., Bruno, R., & Felmingham, K. L. (2019). Cannabinoid interventions for PTSD: Where to next? Prog Neuropsychopharmacol Biol Psychiatry, 93, 124-140. DOI: https://doi.org/10.1016/j.pnpbp.2019.03.017
48. Pisanti, S., Malfitano, A. M., Ciaglia, E., Lamberti, A., Ranieri, R., Cuomo, G., Abate, M., Faggiana, G., Proto, M. C., Fiore, D., Laezza, C., & Bifulco, M. (2017). Cannabidiol: State of the art and new challenges for therapeutic applications. *Pharmacology & Therapeutics*, 175, 133-150.DOI: https://doi.org/https://doi.org/10.1016/j.pharmthera.2017.02.041
49. Maione, S., Piscitelli, F., Gatta, L., Vita, D., De Petrocellis, L., Palazzo, E., de Novellis, V., & Di Marzo, V. (2011). Non-psychoactive cannabinoids modulate the descending pathway of antinociception in anaesthetized rats through

several mechanisms of action. *Br J Pharmacol, 162(*3), 584-596.
DOI: https://doi.org/10.1111/j.1476-5381.2010.01063.x
50. Ahrens, J., Demir, R., Leuwer, M., de la Roche, J., Krampfl, K., Foadi, N., Karst, M., & Haeseler, G. (2009). The nonpsychotropic cannabinoid cannabidiol modulates and directly activates alpha-1 and alpha-1-Beta glycine receptor function. *Pharmacology, 83*(4), 217-222. DOI: https://doi.org/10.1159/000201556
51. Kicman, A., & Toczek, M. (2020). The Effects of Cannabidiol, a Non-Intoxicating Compound of Cannabis, on the Cardiovascular System in Health and Disease. *Int J Mol Sci, 21*(18). 6740. DOI: https://doi.org/10.3390/ijms21186740
52. Baron, E. P. (2018). Medicinal Properties of Cannabinoids, Terpenes, and Flavonoids in Cannabis, and Benefits in Migraine, Headache, and Pain: An Update on Current Evidence and Cannabis Science. Headache: *The Journal of Head and Face Pain, 58*(7), 1139-1186. DOI: https://doi.org/https://doi.org/10.1111/head.13345
53. Russo, E. B. (2008). Cannabinoids in the management of difficult to treat pain. *Ther Clin Risk Manag, 4*(1), 245-259. DOI: https://doi.org/10.2147/tcrm.s1928
54. Takeda, S., Jiang, R., Aramaki, H., Imoto, M., Toda, A., Eyanagi, R., Amamoto, T., Yamamoto, I., & Watanabe, K. (2011). Δ9-Tetrahydrocannabinol and Its Major Metabolite Δ9-Tetrahydrocannabinol-11-oic Acid as 15-Lipoxygenase Inhibitors. *Journal of Pharmaceutical Sciences, 100*(3), 1206-1211. DOI: https://doi.org/https://doi.org/10.1002/jps.22354
55. Bergamaschi, M. M., Queiroz, R. H., Chagas, M. H., de Oliveira, D. C., De Martinis, B. S., Kapczinski, F., Quevedo, J., Roesler, R., Schröder, N., Nardi, A. E., Martín-Santos, R., Hallak, J. E., Zuardi, A. W., & Crippa, J. A. (2011). Cannabidiol reduces the anxiety induced by simulated public speaking in treatment-naïve social phobia patients. *Neuropsychopharmacology, 36*(6), 1219-1226. DOI: https://doi.org/10.1038/npp.2011.6
56. Masataka, N. (2019). Anxiolytic Effects of Repeated Cannabidiol Treatment in Teenagers With Social Anxiety Disorders. *Front Psychol*, 10, 2466. DOI: https://doi.org/10.3389/fpsyg.2019.02466
57. Shannon, S., & Opila-Lehman, J. (2015). Cannabidiol Oil for Decreasing Addictive Use of Marijuana: A Case Report. *Integr Med (Encinitas), 14*(6), 31-35. https://pubmed.ncbi.nlm.nih.gov/26807069/
58. Shannon, S., Lewis, N., Lee, H., & Hughes, S. (2019). Cannabidiol in Anxiety and Sleep: *A Large Case Series. Perm J*, 23, 18-041. DOI: https://doi.org/10.7812/tpp/18-041
59. Carlini, E. A., & Cunha, J. M. (1981). Hypnotic and antiepileptic effects of cannabidiol. *J Clin Pharmacol, 21*(S1), 417s-427s. DOI: https://doi.org/10.1002/j.1552-4604.1981.tb02622.x
60. Zuardi, A. W., Cosme, R. A., Graeff, F. G., & Guimarães, F. S. (1993). Effects of ipsapirone and cannabidiol on human experimental anxiety. *J Psychopharmacol, 7*(1 Suppl), 82-88. DOI: https://doi.org/10.1177/026988119300700112
61. Ried, K., Tamanna, T., Matthews, S., & Sali, A. (2023). Medicinal cannabis improves sleep in adults with insomnia: a randomised double-blind placebo-controlled crossover study. *J Sleep Res, 32*(3), e13793. DOI: https://doi.org/10.1111/jsr.13793
62. Walsh, J. H., Maddison, K. J., Rankin, T., Murray, K., McArdle, N., Ree, M. J., Hillman, D. R., & Eastwood, P. R. (2021). Treating insomnia symptoms with medicinal cannabis: a randomized, crossover trial of the efficacy of a cannabinoid medicine compared with placebo. *Sleep, 44*(11). DOI: https://doi.org/10.1093/sleep/zsab149
63. Liktor-Busa, E., Keresztes, A., LaVigne, J., Streicher, J. M., & Largent-Milnes, T. M. (2021). Analgesic Potential of Terpenes Derived from Cannabis sativa. *Pharmacol Rev, 73*(4), 98-126. DOI: https://doi.org/10.1124/pharmrev.120.000046
64. Weston-Green, K., Clunas, H., & Jimenez Naranjo, C. (2021). A Review of the Potential Use of Pinene and Linalool as Terpene-Based Medicines for Brain Health: Discovering Novel Therapeutics in the Flavours and Fragrances of Cannabis. *Front Psychiatry*, 12, 583211. DOI: https://doi.org/10.3389/fpsyt.2021.583211
65. Kamatou, G. P., & Viljoen, A. (2009). A Review of the Application and Pharmacological Properties of α-Bisabolol and α-Bisabolol-Rich Oils. *J. Am. Oil Chem. Soc.,* 87, 1-7. DOI: https://doi.org/10.1007/s11746-009-1483-3
66. Tabari, M. A., & Tehrani, M. A. B. (2017). Evidence for the involvement of the GABAergic, but not serotonergic transmission in the anxiolytic-like effect of bisabolol in the mouse elevated plus maze. *Naunyn Schmiedebergs Arch Pharmacol, 390*(10), 1041-1046. DOI: https://doi.org/10.1007/s00210-017-1405-0
67. Fidyt, K., Fiedorowicz, A., Strządała, L., & Szumny, A. (2016). β-caryophyllene and β-caryophyllene oxide-natural compounds of anticancer and analgesic properties. *Cancer Med, 5*(10), 3007-3017. DOI: https://doi.org/10.1002/cam4.816
68. Yang, X., Yang, J., Gu, X., Tao, Y., Ji, H., Miao, X., Shen, S., & Zang, H. (2023). (-)-Guaiol triggers immunogenic cell death and inhibits tumor growth in non-small cell lung cancer. *Mol Cell Biochem, 478*(7), 1611-1620. DOI: https://doi.org/10.1007/s11010-022-04613-y
69. Gulbransen, G., Xu, W., & Arroll, B. (2020). Cannabidiol prescription in clinical practice: an audit on the first 400 patients in New Zealand. *BJGP Open, 4*(1). DOI: https://doi.org/10.3399/bjgpopen20X101010
70. Brown, J. D., & Winterstein, A. G. (2019). Potential Adverse Drug Events and Drug-Drug Interactions with Medical and Consumer Cannabidiol (CBD) Use. *J Clin Med, 8*(7). 989. DOI: https://doi.org/10.3390/jcm8070989