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Cannabinoids and the endocannabinoid system in fibromyalgia: A review of preclinical and clinical research

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ABSTRACT

Characterised by chronic widespread musculoskeletal pain, generalised hyperalgesia, and psychological distress, fibromyalgia (FM) is a significant unmet clinical need. The endogenous cannabinoid system plays an important role in modulating both pain and the stress response. Here, we appraise the evidence, from preclinical and clinical studies, for a role of the endocannabinoid system in FM and the therapeutic potential of targeting the endocannabinoid system. While many animal models have been used to study FM, the reserpine-induced myalgia model has emerged as perhaps the most translatable to the clinical phenotype. Inhibition of fatty acid amide hydrolase (FAAH) has shown promise in preclinical studies, ameliorating pain- and anxiety-related behaviour .

Clinically, there is evidence for alterations in the endocannabinoid system in patients with FM, including single nucleotide polymorphisms and increased levels of circulating endocannabinoids and related *N*-acylethanolamines. Single entity cannabinoids, cannabis, and cannabis-based medicines in patients with FM show promise therapeutically but limitations in methodology and lack of longitudinal studies to assess efficacy and tolerability preclude the current recommendation for their use in patients with FM. Gaps in the literature that warrant further investigation are discussed, particularly the need for further development of animal models with high validity for the multifaceted nature of FM, balanced studies to eliminate sex-bias in preclinical research, and ultimately, better translation between preclinical and clinical research.

Contents

Abbreviations: AEA, anandamide/ *N*-arachidonylethanolamine; AEs, adverse effects; ACR, American College of Rheumatology; BDNF, brain derived neurotrophic factor; CB_1, cannabinoid receptor type 1; CB_2, cannabinoid receptor type 2; CBD, cannabidiol; DAG, diacylglycerol; FAAH, fatty acid amid hydrolase; FIQ, Fibromyalgia Impact Questionnaire; FM, fibromyalgia; IBS, irritable bowel syndrome; MGL, monoaglycerol lipase; NAE, *N*-acylethanolamine; NAPE, *N*-acyl phosphatidyl ethanolamine; NGF, Nerve growth factor; NRS, numeric rating scale; ODI, Oswestry Disability Index; OEA, *N*-oleoylethanolamine; PEA, *N*-palmitoylethanolamine; PPAR, peroxisome proliferator-activated receptor; PSQI, Pittsburgh Sleep Quality Index; RCT, Randomised controlled trial; RIM, reserpine-induced myalgia; SEA, *N*-stearoylethanolamine; SF-12, 12-Item Short Form Survey; SF-36, 36-Item Short Form Health Survey; SIH, stress-induced hyperalgesia; SNP, single nucleotide polymorphism; THC, Δ^9-tetrahydrocannabinol; TRPV, transient receptor potential vanilloid; VAS, visual analogue scale; WPI, Widespread Pain Index; 2-AG, 2-arachadonoglycerol.

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1. Introduction to fibromyalgia

1.1. Epidemiology

Chronic pain affects approximately 20% of the adult population (Breivik, Ventafridda, & Gallacher, 2006; Yong & Bhattacharyya, 2022). Chronic pain conditions include fibromyalgia (FM), musculoskeletal pain and joint pain, chronic headache, cancer pain, neuropathic pain, post-surgical pain, and back and neck pain (Barke, Jakob, & Rief, 2022). Originally termed "fibrositis" in 1904 by the British neurologist Sir William Gowers, FM originally encompassed local or regional musculoskeletal pain. Subsequent descriptions of generalised pain by Smythe in 1972 lead to the term "fibromyalgia" being coined in 1976.

FM affects millions of people worldwide and has a significant impact on quality of life. Globally, there are variable epidemiological data for FM. For example, in the United States, one study (Brill, Goor-Aryeh, & Slefer, 2012) reported a prevalence of 6.4% of the overall population, while another study a year later (Wolfe, 2013) reported a prevalence of 2.1%. This high degree of variability is due to the lack of consistency in diagnosis, whereby different classification criteria were used. Moreover, some studies generalise estimates on the prevalence of FM based off a certain patient population which doesn't accurately represent the overall demographic. On average, the reported prevalence of FM in the general population is approximately 2–4%, afflicting women more than men (Stensson, Ernberg, Kosek, & Ghafouri, 2020) with the incidence increasing with age (Vincent, Wolfe, & Whipple, 2013).

1.2. Characteristics/symptomatology

FM is characterised by complex polysymptomatology, especially chronic widespread pain which includes generalised hyperalgesia and palpation-specific tender points, fatigue, stiffness, sleep disturbances, as well as somatic and cognitive dysfunction (Sarzi-Puttini, 2020). A major challenge for patients with FM is reaching a diagnosis, often remaining undiagnosed for many years or even misdiagnosed (Häuser & Fitzcharles, 2019). Diagnosis of FM, on average, takes 2.3 years and patients usually have to attend multiple medical specialists during that time (Alexander, DeVries, Kigerl, Dahlman, & Popovich, 2009; Choy, Leon, Petersel, & Kramer, 2010). Due to the complexity and multifaceted nature of FM, it constitutes a significant diagnostic challenge for clinicians.

Several classification, diagnostic and screening criteria have been developed, but there continues to be a need to further refine these criteria to reflect the current and evolving understanding of FM. Clinical diagnosis of FM is largely based on criteria endorsed by the American College of Rheumatology (ACR) which were first introduced in 1990 wherein pain pressure up to 4 kg/cm^2 was evaluated at 18 specified body points (Wolfe, Yunus, Bombardier, & Tugwell, 1990). For diagnosis, pain must be elicited in at least 11 of the 18 points. However, these criteria were widely denounced for a number of reasons, including; difficulties in using pressure algometry in the primary healthcare setting (Buskila, 1997; Fitzcharles, 2003) and limited predictive validity for clinical pain. Moreover, there was a narrow diagnostic window where there was very little space for variation of symptoms (and loss of FM diagnosis with moderate symptom improvement) which ultimately led to subsequent revisions of the ACR classification (Wolfe, Fitzcharles, Katz, & Russell, 2010). In 2010, the ACR revised the previous classification for FM diagnosis and introduced a new classification that was easier to apply and interpret. In particular, the new revised classification did not require tender point examination and was consistent and easy to apply by primary care physicians in all healthcare settings (Wolfe et al., 2010).

1.3. Pathophysiology

The aetiology and pathophysiology of FM remains unclear but is thought to involve a number of components stemming from a dysfunction in central processing, including central sensitisation and impaired processing in the descending inhibitory pain pathway. Central sensitisation is a phenomenon that manifests as enhanced function of neurons and circuits within the somatosensory system in response to activity, inflammation, and neural injury (Ji, Huh, & Maixner, 2018). It results from increased membrane excitability and synaptic efficacy, coupled with reduced inhibition of the somatosensory system resulting in plastic changes.

Dysfunction in neurotransmitter, neuroendocrine and autonomic nervous systems has been reported in patients with FM. Abnormalities have been detected in cerebrospinal fluid of patients with FM, including elevated levels of substance P (Russell, Littman, & Alboukrek, 1994), brain-derived neurotrophic factor (BDNF), nerve growth factor (NGF) (Sarchielli, Floridi, Rossi, Acciarresi, & Calabresi, 2007) and lower levels of serotonin metabolites (Russell, 1992). Conflicting reports of normative and elevated levels of BDNF and NGF have also been reported in serum and plasma samples of patients with FM (Nugraha & Gutenbrunner, 2013; Ranzolin, 2016). Serum levels of BDNF have been found to be age-dependent in healthy controls which could account for the conflicting reports if appropriate age-matched controls were not used (Nugraha & Gutenbrunner, 2013). For example, in a recent study, there was no evidence that peripheral growth factors, BDNF or NGF, were altered in patients with FM but the authors acknowledged that there was significant heterogeneity between the clinical and control groups in age, gender, medications and alcohol consumption ((Baumeister, Saft, & Hellweg, 2019). Nonetheless, alterations in NGF and BDNF could indicate a central mechanism by which central growth factors drive the development of sensitisation, particularly as BDNF readily crosses the blood-brain barrier (Pan, Fasold, & Kastin, 1998).

Lower levels of serotonin have also been reported in serum of patients with FM compared to healthy controls, which were also found to correlate with severity of the disease (Al-Nimer & Alsakeni, 2018; Cordero, 2010; Wolfe, Vipraio, & Anderson, 1997). This is an important finding, given the role of serotonin nociception.

Genetic factors, such as a single nucleotide polymorphism (SNP) in the serotonin transporter (SLC6A4) gene, have been detected in patients with FM (Cohen, 2002), and in comorbid somatic disorders such as irritable bowel syndrome (Yeo et al., 2004). A Catechol-*O*-methyltransferase gene polymorphism has also been detected in patients with FM, which influences anxiety, depression and disability (Fernández-de-Las-Peñas, Gil-Crujera, & Peñacoba-Puente, 2012).

Stress is also thought to contribute to the pathophysiology of FM. Many patients with FM have identified a stressful event that may have triggered the onset of their chronic pain, such as emotional, physical or sexual abuse (Häuser, Üceyler, & Sommer, 2011). Cortisol levels in patients with FM have demonstrated to be quite variable, but it is thought that lower levels of cortisol in patients with FM (Lin, Chow, Liu, & Chen, 2021; Riva, Westgaard, & Lundberg, 2010) could be due to a maladaptive response to stress resulting from a central abnormality of the hypothalamic-pituitary-adrenal axis.

Another hypothesis on the pathophysiology of FM is small fibre neuropathy. Small fibre neuropathy is a disorder of the peripheral nerves that primarily affects small myelinated Aδ fibres or unmyelinated C fibres, resulting in altered nociception and autonomic dysfunction. Small fibre neuropathy has been identified in 30–41% of patients with FM (Giannoccaro, Incensi, & Liguori, 2014; Kosmidis, Alexopoulos, Vlachoyiannopoulos, Moutsopoulos, & Dalakas, 2014) (Oaklander, 2013). Idiopathic small fibre neuropathy and severe FM have been associated with SCN9A gene-encoded Nav1.7 dorsal root ganglia sodium channel gain-of-function variant (Faber, Ahn, Han, Estacion, & Gerrits, 2012; Vargas-Alarcon, Fragoso, Martinez, & Martinez-Lavin, 2012). These channels are predominantly expressed in nociceptors in the dorsal root ganglia and sympathetic ganglia neurons (Djouhri & Levinson, 2003; Toledo-Aral, He, Whisenand, & Wolf, 1997). Hyperexcitability of C-fibres has been reported in patients with FM and SFN (Serra, Solà, & Torres, 2014). Therefore, it is plausible that small fibre neuropathy could be a peripheral nervous system contributor to the complex pathophysiology of pain associated with FM (Üçeyler, Kahn, Kittel-Schneider, Casanova-Molla, & Sommer, 2013).

FM is associated with the presence of soft tissue pain of the muscles, ligaments, and tendons. However, previous FM studies have not consistently shown evidence of peripheral abnormalities or tissue inflammation, unlike some other chronic pain conditions (Jahan, 2012). Therefore, despite chronic widespread pain often being debilitating, patients with FM do not develop tissue damage or life-threatening symptoms, suffer from any deformities, or experience disease progression.

It has been suggested that FM could be a "clinical endocannabinoid deficiency" syndrome (Russo, 2004), whereby levels of endocannabinoids are lower in patients with FM, which contributes to the manifestation of the clinical symptoms associated with the disease. However, there are few published studies supporting this. In fact, from the limited literature available, (Kaufmann et al., 2008; Stensson, Ernberg, Kosek, & Ghafouri, 2018) elevated levels of endocannabinoids and associated *N*-acylethanolamines are reported in patients with FM, rather than a deficiency. These and related studies will be discussed in more detail in section 6.2.

2. Fibromyalgia comorbidities

2.1. Psychiatric

The high prevalence of psychiatric comorbidities in FM has been well established. The most common comorbidities include depression, anxiety and personality disorders (e.g. obsessive-compulsive) (Galvez-Sánchez & Reyes Del Paso, 2019; Kayhan & Satan, 2016; Uguz, Salli, Albayrak, & Uğurlu, 2010). Concurrent psychiatric conditions in patients with FM are important indicators of treatment response for physicians, typically being associated with worse prognosis and clinical profile and reduced quality of life due to reduced functional abilities and increased pain perception (Giesecke, Harris, & Tian, 2003).

A recent systemic review revealed a high prevalence for current and lifetime depression, 43% and 63%, respectively, in patients with FM (Kleykamp, McNicol, Arnold, & Fillingim, 2021). It is not surprising that FM is frequently found comorbid with depression and anxiety as they share common neurochemical dysfunction such as a hypofunction within the serotonergic system and altered reactivity of the hypothalamic-pituitary-adrenal axis. The data available on the prevalence of lifetime and/or current anxiety disorders concurring with FM have been reported in numerous studies with a high degree of variability, ranging from 30 to 80% (Arnold & Keck, 2006; Consoli, Ciapparelli, Massimetti, Rossi, & Dell'Osso, 2012; Kleykamp et al., 2021). In addition to depression and anxiety, Kleykamp et al. (2021) also found that nearly one third of patients examined experienced current or lifetime bipolar disorder, panic disorder and post-traumatic stress disorder, as well as to a lesser degree, obsessive-compulsive disorder and specific phobias.

2.2. Non-psychiatric

FM is often accompanied by other somatic comorbidities such as irritable bowel syndrome, migraine and temporal mandibular disorder. Irritable Bowel Syndrome is a functional disorder of the gastrointestinal tract characterised by abdominal pain, spasms, and altered bowel movements. A recent case-control study found that the prevalence of FM in a cohort of patients with irritable bowel syndrome was 30% compared with 3% of healthy controls (Bayrak, 2020). The prevalence of FM in patients with irritable bowel syndrome ranges from 32 to 77% and the prevalence of irritable bowel syndrome in patients with FM ranges from 28 to 65%, demonstrating a bi-directional relationship (Whitehead & Jones, 2002). This bi-directional association is also observed in patients with migraine and FM and also in temporomandibular disorder and FM (Lim & Khan, 2011; Penn, Chuang, & Kao, 2019). The prevalence of migraine with FM ranges from 18 to 35.6% (Peres, Kaup, & Silberstein, 2001).

3. Cannabis, cannabinoids, and the endocannabinoid system

3.1. Receptors

To date, two cannabinoid receptors belonging to the G-protein-coupled receptor family have been discovered and validated as the main pharmacological targets of cannabinoids: the cannabinoid receptor type 1 (CB_1) (Devane, Johnson, & Howlett, 1988) and the cannabinoid receptor type 2 (CB_2) (Munro & Abu-Shaar, 1993). The CB_1 receptor is encoded by the gene *CNR1* and consists of 472 amino acids in humans (473 amino acids in rat and mouse, with 97–99% amino acid sequence identity among these species). The CB_2 receptor is encoded by the gene *CNR2*, which consists of 360 amino acids in humans (with an amino acid sequence homology of approximately 80% between humans and rodents) (Zou & Kumar, 2018).

The CB_1 receptor is the most abundant neuromodulatory receptor in the brain, but is also found in most tissues in the periphery. Cannabinoid receptors are expressed at peripheral, spinal and supraspinal sites involved of relevance to pain and its modulation. In supraspinal sites involved in the modulation of pain, the CB_1 receptor is ubiquitously expressed, particularly in the amygdala, thalamus, parabrachial nucleus, periaqueductal grey, and rostroventral medulla (Starowicz & Finn, 2017). At the level of the spinal cord, the CB_1 receptor is expressed in dorsolateral funiculus and the superficial dorsal horn. Both CB_1 and CB_2 are expressed peripherally in the dorsal root ganglia with CB_1 also being expressed in peripheral sensory nerve endings (Starowicz & Finn, 2017). The CB_2 receptor is expressed on microglia in the central nervous system and is predominantly found on the cells and tissues of the immune system, and is upregulated in times of need, suggesting a role for the endocannabinoid system as a modulator of the immune system.

Since the identification of CB_1 and CB_2 receptors, other putative cannabinoid receptors have been identified, including members of the orphan G-protein-coupled receptors; GPR18 (Console-Bram, Brailoiu, & Abood, 2014), GPR55 (Lauckner & Chen, 2008), GPR119 (Syed, Beavers, Ficorilli, & Kuo, 2012), transient receptor potential vanilloid (TRPV) channels (Muller & Reggio, 2019), and peroxisome proliferator-activated receptors (PPARs)(O'Sullivan, 2007), all of which have been shown to modulate nociception (Guerrero-Alba, González-Hernández, Granados-Soto, & Marichal-Cancino, 2019).

3.2. Ligands (phyto, synthetic and endogenous)

There are three classes of cannabinoid ligands: phyto- (plant derived), synthetic- and endogenous cannabinoids (endocannabinoids). *Cannabis sativa*, has been cultivated and used for recreational and medicinal purposes for at least 5000 years (Crocq, 2020). Cannabis contains more than a hundred phytocannabinoids that have been identified to

date (Hanuš, Muñoz, & Appendino, 2016; Morales & Reggio, 2017). Phytocannabinoids are a diverse class of naturally occurring chemical compounds, some of which interact with, and mediate their effects via, CB_1 and CB_2 receptors, both centrally and in the periphery.

The most prevalent and well-characterised phytocannabinoids are Δ^9-tetrahydrocannabinol (THC) and cannabidiol (CBD). THC is a partial agonist for CB_1 and CB_2 receptors and with high binding affinity for CB_1, which mediates its psychoactive effects. CBD's orthosteric binding to CB_1 receptors is weak, however, recent pharmacological studies have demonstrated that CBD is a negative allosteric modulator of CB_1 and an orthosteric partial agonist at CB_2 receptors (Laprairie, 2015; Tham & Alaverdashvili, 2019). Nabiximols, also known as Sativex®, is a Food and Drug Administration (FDA)- approved oromucosal spray containing CBD and THC extracts in a 1:1 ratio derived from the cannabis plant that is approved for treatment of spasticity associated with multiple sclerosis. Epidiolex® is pharmaceutical-grade and FDA-approved pure CBD used for the treatment of epilepsy.

Endocannabinoids are unsaturated fatty-acid ethanolamides, glycerol esters or arachidonoyl glycerol ethers. The endocannabinoid ligands, 2-arachidonogylcerol (2-AG) and anandamide/ *N*-arachidonylethanolamine (AEA), exert their effects through the cannabinoid receptors, with concentrations of 2-AG in the brain approximately 170 times higher than AEA (Stella & Piomelli, 1997). AEA and 2-AG have high and low-to-moderate affinity, respectively, for CB_1 receptors. AEA is thought to be a partial agonist for CB_1 (Steffens, 2005) and a weak partial agonist at CB_2 whereas 2-AG is a CB_1/CB_2 full agonist (Gonsiorek & Fan, 2000; Savinainen, 2001). *N*-oleoylethanolamine (OEA) and *N*-palmitoylethanolamine (PEA) are structurally-related *N*-acylethanolamines (NAEs), often called endocannabinoid-like compounds, and while they do not have affinity for CB_1 or CB_2, they can modulate endocannabinoid signalling indirectly via substrate competition at fatty acid amide hydrolase, a key degradatory enzyme for AEA (Cravatt et al., 1996).

Synthetic cannabinoids, many of which are cannabinoid receptor agonists, have been developed and investigated as potential therapeutic agents for over 50 years. Synthetic drugs based on THC, such as nabilone (Cesamet®) and dronabinol (Marinol®), have also been FDA-approved and are used clinically (including off-label) for the treatment of conditions like chemotherapy-induced nausea and vomiting, chronic pain conditions, multiple sclerosis, palliative care, and glaucoma (Gaisey, 2021; Harrison & Simpson, 2021; Krcevski-Skvarc & Häuser, 2018).

Both THC and CBD are highly lipophilic and readily cross the blood-brain barrier. THC's bioavailability is 20% and 6% when inhaled or administered orally, respectively. Inhaled THC peaks in plasma after 3–10 min, while oral THC is more variable and unpredictable in terms of the absorption with plasma concentrations peaking after 1–8 h (McGilveray, 2005). CBD's bioavailability after smoking is about 31% and with little published data on the bioavailability after oral administration, it is estimated to be approximately 6% (Millar & O'Sullivan, 2018; Perucca & Bialer, 2020). Similar to THC, nabilone and dronabinol undergo extensive distribution and first-pass hepatic metabolism. However, they are well absorbed and the pharmacokinetics, although variable, appear to be linear (Oh, Khurana, & Vetticaden, 2017; Rubin, Warrick, Sullivan, & Obermeyer, 1977).

Cannabinoid-induced antinociception is likely mediated in both the CNS and in the periphery. Cannabinoids modulate proalgesic and proinflammatory factors released by peripheral cells, therefore, peripherally restricted cannabinoids can reduce the production of these factors, mostly via CB_2. Moreover, peripheral CB_2 activation has been shown to stimulate the release of endogenous opioids, resulting in reduced nociceptive behaviour (Ibrahim et al., 2005).

3.3. Endocannabinoid enzymes

Endocannabinoid signalling is rather unique due to the fact endocannabinoids are lipid-based neuromodulators and synthesised on demand in the plasma membrane, unlike classical neurotransmitters which are stored in synaptic vesicles. Another noteworthy feature of endocannabinoid signalling is that endocannabinoids act in a retrograde manner to transiently inhibit neuronal firing and presynaptic neurotransmitter release through activation of presynaptic CB_1 receptors (Ohno-Shosaku & Kano, 2001).

There are a number of pathways suggested to contribute to the synthesis of AEA, PEA, and OEA from their precursor, *N*-acyl phosphatidyl ethanolamine (NAPE). The most widely studied biosynthetic pathway involves NAPE-phospholipase D catalysing the cleavage of membrane NAPEs, N-arachidonoyl phosphatidyl ethanolamine, N-oleoyl phosphatidyl ethanolamine or N-palmitoyl phosphatidyl ethanolamine, to generate AEA, OEA and PEA, respectively (Sagar, Okine, Wong, & Chapman, 2009). AEA and related NAEs are primarily catabolised by FAAH through the hydrolytic cleavage of the amide bond to form arachidonic acid and ethanolamine.

A number of biosynthetic pathways have also been suggested for the synthesis of 2-AG, of which, the phosphatidylinositol-phospholipase C and diacylglycerol (DAG) pathway is the best described. Briefly, arachidonate-containing inositol membrane phosphatidylinositols are hydrolysed by phospholipase C to generate 1, 2- DAG which is hydrolysed by DAG-lipase (DAGL) to 2-AG. Two DAG lipases (DAGLα and DAGLβ) catalyse the hydrolysis of DAG to bioactive 2-AG. Metabolism of 2-AG occurs by intracellular enzymatic degradation by monoaglycerol lipase (MGL) to generate arachidonic acid and glycerol (Dinh, Leslie, Katona, & Piomelli, 2002). While MGL is the main enzyme that hydrolyses 2-AG, three other serine hydrolases have also shown to catabolise 2-AG, including; FAAH, serine hydrolase α-β-hydrolase domain 6 (ABHD6) and serine hydrolase α-β-hydrolase domain (ABHD12) (Blankman, 2007). These enzymes also break down 2-AG to produce arachidonic acid and glycerol have an important function as rate-limiting enzymes in the production of free arachidonic acid.

4. Animal models of FM

Fibromyalgia is a differentiated pain syndrome as it is diagnosed by symptoms and not by pathological features. There is no single animal model of FM that encompasses all of the clinical manifestations. The lack of a well-established animal model for FM hampers investigation of the underlying aetiology and pathology of FM and the development of novel treatments. Despite the presence of soft tissue pain affecting the muscles, ligaments, and tendons, FM itself is not associated with evidence of tissue inflammation or damage, which represents a challenge when modelling the disease. Certain considerations must be employed when deciding on what model to use for such a heterogeneous condition and these will be discussed in this section.

Several animal models of FM have been established in an effort to better characterise and understand the mechanisms that underpin this chronic disease. Animal models of FM can be induced in a variety of ways, including stress-induced hyperalgesia (SIH) models, repeated muscle insult models and the biogenic amine depletion model, reserpine-induced myalgia. All of the models for FM produce the characteristic chronic widespread musculoskeletal pain, the cardinal symptom reported in the clinic and used for diagnosis.

4.1. Stress-induced hyperalgesia models (SIH)

It is well established that stress exacerbates existing pain associated with chronic pain disorders and that stress and anxiety are frequently found co-morbid with FM (Pérez, Medina, Ramírez, Monsalve, & Osorio, 2020). Animal models analogous to the clinical condition should ideally simulate the development of these symptoms. It is thought that animal models of SIH are suitable for modelling FM, particularly those devoid of a surgical or chemical intervention for model induction. SIH models range from physically or psychologically stress-inducing or a combination of both. SIH models have been comprehensively reviewed

(Brum, Becker, & Fialho, 2021; Jennings, 2014; Nagakura, 2015; Olango & Finn, 2014). Therefore, for the purpose of this article these are summarised briefly.

4.2. Cold stress

Originally termed the "specific alternation rhythm of temperature" model, this well-known FM model is more commonly referred to now as the intermittent cold stress or repeated cold stress model. The intermittent cold stress-induced experimental FM model has already been established in both mice and rats in numerous studies, with few protocol deviations between species and strains of rodents (Fujisawa, Naiki, Masuko, & Suematsu, 2008; Kawanishi, Tamura, & Ono, 1997; Nasu & Mizumura, 2010; Nishiyori & Ueda, 2008; Ohara & Namimatsu, 1991; Wakatsuki, Uchimura, & Mizumura, 2021). This model involves alternating between room temperature (24 °C) and a colder temperature (−3 °C or 4 °C) for 5–7 days and has demonstrated the ability to induce mechanical hypersensitivity as evident by decreased nociceptive thresholds in von Frey and Randall–Selitto tests (Nasu & Mizumura, 2010; Wakatsuki et al., 2021). In another study, intermittent cold stress induced thermal hypersensitivity but had no effect on anxiety or depressive-like behaviours in the elevated plus maze or tail suspension test. Treatment with a single intrathecal injection of antidepressants (milnacipran, amitriptyline, mianserin or paroxetine) had an acute analgesic effect on intermittent cold stress-induced thermal hypersensitivity at post-stress day 1. Moreover, following repeated daily antidepressant treatments during post-stress days 1–5, the reduction in thermal pain threshold was gradually reversed, an effect that was maintained for at least 7 days after the final treatment. This compliments the clinical data for the efficacy of antidepressants on reducing FM-associated pain (Üçeyler, Häuser, & Sommer, 2008).

4.3. Swim stress

Quintero and Avila (2000) first provided evidence that repeated forced swim stress could induce thermal hyperalgesia. The forced swim stress paradigm involves placing rats in a cylinder (30cmx50cm, diameter x height) filled with water to a height of 20 cm (water temperature 24–26 °C), for 10 min on the initial exposure and for 20 min on the two subsequent days. Hyperalgesia to thermal and chemical stimuli were still present 8 and 9 days after the last swim session, respectively. The forced swim stress model has also been shown to induce anxiety-like behaviour, a common comorbidity associated with FM (Nazeri & Pourzare, 2017). An important feature of this model is that it responds to some of the classic pharmacological treatments used clinically for patients with FM, including, tricyclic antidepressants, selective serotonin reuptake inhibitors and the precursor to serotonin, tryptophan (Quintero & Avila, 2000).

4.4. Sound stress

The sound stress paradigm involves exposing rats to sound stress over 4 days whereby, they are placed 3 per cage and the cage placed 25 cm from a speaker emitting 4 pure tones (5, 11, 15 and 19 kHz) of 5 or 10 s duration. The tones' amplitudes vary through time independently from 20 to 110 dB sound pressure level at random times each minute, lasting 5 or 10 s. Animals are exposed to the sound stressor on days 1, 3, and 4. This model has been found to exhibit musculoskeletal and cutaneous mechanical hyperalgesia and increased anxiety-related behaviour in the elevated plus maze (Dina & Green, 2011; Khasar, 2009).

4.5. Restraint/ immobilisation stress

The chronic restraint stress paradigm is also a possible model for FM. The experimental protocol involves placing the animal in a well ventilated tube or cage, which restricts movement (Gamaro, Denardin, Ely, & Dalmaz, 1998). Thermal hyperalgesia has been reported in this model in the tail flick test (da Silva Torres et al., 2003; Gamaro et al., 1998). This paradigm also induces long-lasting mechanical allodynia-like behaviour to von Frey, but not Randall–Selitto test, and thermal allodynia-like behaviour (see Table 1). It has also been shown to exacerbate formalin-evoked nociceptive behaviour (Bardin & Newman-Tancredi, 2009). Moreover, visceral hypersensitivity has been reported in this model, which is an important feature, given the comorbidity of FM and irritable bowel syndrome(Shen, Qian, & Hou, 2010).

4.6. Repeated muscle insult models

There are currently two models of FM that fall under the category of repeated muscle insult models: Acid saline-induced pain (Sluka & Moore, 2001) and fatigue-enhanced muscle pain (Gregory, 2013). Sluka and Moore (2001) developed and characterised an animal model of persistent mechanical hyperalgesia induced by repeated intramuscular injections of low pH saline. For this paradigm to produce long-lasting hyperalgesia, rats were anesthetized briefly and one gastrocnemius muscle was injected with 100 μl of pH 4.0 preservative-free sterile saline followed by a second injection into the same muscle 2 or 5 days later. This repeated injection of low pH saline into the gastrocnemius muscle produces a long-lasting, widespread mechanical hyperalgesia in the absence of motor deficits or any significant tissue damage (Sluka & Moore, 2001). Interestingly, Sluka and Moore (2001) and colleagues were the first to suggest a possible central nervous system mechanism underpinning the sustained hyperalgesia in this model. Further to this, widespread mechanical hyperalgesia was demonstrated in mice in the acid saline-induced pain model (Sluka & Breese, 2003).

The fatigue-enhanced muscle pain model combined localised muscle fatigue with a subthreshold muscle insult for induction of the model (Gregory, 2013). Muscle fatigue was induced by electrical stimulation through needle electrodes implanted in the gastrocnemius muscle followed by 2 x pH 5.0 saline intramuscular injections. It is noteworthy that neither localised muscle fatigue nor the subthreshold muscle insult produced muscle hyperalgesia when given alone. This contrasts with what was previously found by Sluka and Moore (2001), where hyperalgesia was apparent when injected with acidified saline (pH 4.0) 2 and 5 days apart. This difference highlights the importance of using an appropriate pH value (pH 4.0 vs pH 5.0), however, another reason for this observed difference could be the use of different rodent species. The induction and development of hyperalgesia in this model were also found to occur in a sex-dependant manner, with muscle hyperalgesia lasting significantly longer in female mice compared to males (Gregory, 2013).

4.7. Reserpine-induced myalgia (RIM)

The reserpine-induced myalgia (RIM) model, also known as the biogenic amine depletion model, was first developed by Nagakura (2009) and is currently the most recent and promising of animal models for FM. Induction of the RIM model involves daily subcutaneous administration of reserpine at 1 mg/kg for three consecutive days. This significantly reduced brain amine concentrations in all the tissues measured ($p < 0.001$) and demonstrated that the model induced a significant decrease in muscle pressure threshold as evident using Randall–Selitto test and tactile allodynia-related behaviour using von Frey testing. These pain-related behavioural changes associated with the model were long-lasting in both male and female Sprague–Dawley rats.

Numerous studies using the RIM model have reported increased immobility times in the forced swimming test and tail suspension test and decreased swimming times in the forced swimming test, indicative of depressive-like behaviour in both rats and mice (Kaur, Singh, & Bhatti, 2019; Nagakura, 2009; Xu, Shao, Wang, & Li, 2013). The RIM animals also displayed increased anxiety-like behaviour as revealed by

Table 1
Summary of animal models used in the literature to model FM.

References	Animal Model	Species, Sex and Strain	Pain Test	Pain-related behaviour	FM comorbidities assessed	Drugs tested	Drug effects
	SIH models						
(Fujisawa et al., 2008)	Intermittent Cold Stress	Male Wister rats	Randall–Selitto	Mechanical Hyperalgesia	n/a	n/a	n/a
(Nasu & Mizumura, 2010)		Male Sprague-Dawley rats	von Frey Randall–Selitto	Mechanical hyperalgesia	n/a	n/a	n/a
(Nishiyori et al., 2011)		Male C57BL/6J mice	Paw withdrawal threshold (thermal and mechanical)	Mechanical allodynia-related behaviour and thermal hyperalgesia	Elevated plus maze and tail-suspension test (no change)	Intrathecal antidepressants administration: milnacipran, amitriptyline, mianserin or paroxetine	Acute antinociceptive effect on thermal hyperalgesia at post-stress day 1 in a dose-dependent manner. Attenuated mechanical allodynia 9 days after drug treatment
(Wakatsuki et al., 2021)		Male Sprague-Dawley rats	von Frey Cold and heat stimulation	Mechanical Hyperalgesia	n/a	n/a	n/a
(Quintero & Avila, 2000)	Forced Swim Stress	Male Sprague-Dawley rats	Hot plate and formalin test	Thermal and inflammatory hyperalgesia	n/a	Clomipramine, fluoxetine, or tryptophan	Prevented the development of chemical and thermal hyperalgesia
(Nazeri & Pourzare, 2017)		Male Wistar rats	Eye wiping test and orofacial formalin test	Hyperalgesia	↑ Anxiety-related behaviour in the elevated plus maze	n/a	n/a
(Lomazzo et al., 2015)	Chronic unpredictable stress (with multiple injections of nerve growth factor	Male C57BL/6J mice	Hot plate test and Von Frey	Chronic widespread hypersensitivity	↑ Anxiety-related behaviour in the elevated plus maze	URB597 and JZL184	URB597 reversed development of mechanical hypersensitivity and ↓ anxiety-related behaviour
(Khasar, 2009)	Sound Stress	Male Sprague-Dawley rats	Paw withdrawal threshold	Enhanced inflammatory pain-like behaviour	↑ Anxiety-related behaviour in the elevated plus maze	n/a	n/a
(Gamaro et al., 1998)	Chronic Restraint Stress	Male and female Wistar rats	Tail flick	Thermal hyperalgesia	n/a	n/a	n/a
(Torres et al., 2003)		Male Wistar rats	Tail flick	Thermal hyperalgesia	n/a	Morphine	↓ Morphine response in stressed rats but not control
(Bardin & Newman-Tancredi, 2009)		Male Sprague–Dawley rats	von Frey, Randall–Selitto and tail immersion test, acetone drop test, formalin test	Mechanical (von Frey) and thermal (cold – acetone drop test) allodynia-related behaviour, and inflammatory hyperalgesia	n/a	n/a	n/a
(Shen et al., 2010)		Male Sprague–Dawley rats	Colorectal distension	Visceral hyperalgesia	n/a	CB_1 receptor agonist or antagonist	Agonist ↓ Visceromotor Reflex and antagonist ↑ reflex
(Scheich et al., 2017)		Male CD1 mice	Dynamic plantar aesthesiometry, Cold tolerance test, hotplate test	Mechanical and cold hypersensitivity	No effect on open-field and tail suspension test ↑ light preference in the light–dark box test	n/a	n/a
	Repeated muscle insult models						
(Sluka & Moore, 2001)	Acid-Saline	Male Sprague–Dawley rats	Paw withdrawal threshold to radiant heat and von Frey	Mechanical hypersensitivity	n/a	n/a	n/a

Table 1 (*continued*)

References	Animal Model	Species, Sex and Strain	Pain Test	Pain-related behaviour	FM comorbidities assessed	Drugs tested	Drug effects
(Da Silva et al., 2010)		Male Sprague–Dawley rats	von Frey and muscle withdrawal threshold on the gastrocnemius muscle	Cutaneous and muscle hypersensitivity	n/a	MK-801 (non-competitive NMDA receptor antagonist) intracerebral into the RVM	Reversed hypersensitivity
(Gregory, 2013)	Fatigue-enhanced muscle pain	Male and female C57BL6/J mice	Muscle withdrawal threshold on the gastrocnemius muscle	Mechanical hyperalgesia	n/a	n/a	n/a
	Biogenic-amine depletion model						
(Nagakura, 2009)	Reserpine-induced myalgia	Male and female Sprague–Dawley rats	von Frey and muscle pressure threshold	Decreased muscle pressure threshold and tactile allodynia-related behaviour	↑ Immobility in the forced swim test	n/a	n/a
(Xu et al., 2013)		Male ICR mice	Thermal tail withdrawal and von Frey	Thermal hyperalgesia and mechanical allodynia-related behaviour	↑ Immobility in the forced swim test and tail suspension test	Ferulic acid	↑ pain threshold and ameliorates depression-like behaviours
(Nagakura et al., 2019)		Male Sprague–Dawley rats	von Frey and rat grimace scale	mechanical hypersensitivity and ↑ spontaneous pain-associated facial expression	n/a	Gabapentin, duloxetine, diclofenac, buprenorphine and diazepam	Gabapentin and duloxetine ↑ paw withdrawal threshold to von Frey and ↓ rat grimace scale

increased time spent in closed arm of the elevated plus maze (Kaur et al., 2019). Furthermore, cognitive deficits were also reported in the Morris water maze and passive avoidance test where RIM animals displayed an increased latency to reach the platforms (Kaur et al., 2019). Recently, Nagakura, Yoshida, Tanei, and Takeda (2019) were the first to apply the rat grimace scale, a facial expression-dependent measure developed for quantifying spontaneous pain, to the RIM model in rats. A significant increase in the rat grimace scale score was reported in the RIM rats. This also appeared to be long-lasting and was sustained for at least 2 weeks.

The ability of the RIM model to elicit not only the cardinal symptomology of FM but also associated comorbidities of depression- and anxiety- related behaviour and cognitive dysfunction, lends credence to the RIM model as one of the most translational models for FM. Furthermore, most studies investigating pain-like behaviour in models of FM focus on evoked pain. However, patients with FM predominantly report spontaneous pain, a measure which has not been evaluated in most models to date, aside from the RIM model.

5. Alternations in the endocannabinoid system in animal models of FM

There is limited published data investigating role of the endocannabinoid system in animal models of FM. One group (Hong, Kemmerer, Evans, & Wiley, 2009; Hong & Wu, 2011) demonstrated a down-regulation of CB_1 receptor expression in the dorsal root ganglia in a rat model of water avoidance SIH. Moreover, levels of AEA and TRPV1 receptor mRNA expression were significantly elevated in the dorsal root ganglia. Although water avoidance would pertain more to a model of irritable bowel syndrome, it is relevant to this review, given the manifestation of somatic syndromes and comorbidities associated with FM.

The SIH model of repeated forced swim stress has been found to differentially affect formalin-evoked nociceptive behaviour and the endocannabinoid system in stress normo-responsive (Sprague Dawley) and stress hyper-responsive (Wistar-Kyoto) rats (Jennings, Olango, & Finn, 2016). In fact, 10 days of repeated swim stress increased levels of MGL mRNA expression in the ipsilateral side of the dorsal spinal cord of Sprague Dawley rats, an effect not observed in Wistar-Kyoto rats. Interestingly, in the amygdala, swim stress reduced AEA levels in the contralateral amygdala of Sprague Dawley rats, but not Wistar-Kyoto. Repeated swim stress did not significantly alter the levels of AEA or 2-AG in the spinal cord in either Sprague Dawley or Wistar-Kyoto rats compared with non-stressed, naive controls. This study provides evidence for altered endocannabinoid gene expression in a SIH model relevant to FM.

5.1. Cannabinoid-based drugs in animal models of FM

Few preclinical studies have investigated cannabinoid-based drugs in animal models of FM. Systemic administration of the synthetic CB_1 receptor full agonist, WIN 55,212–2, and the TRPV1 antagonist, capsazepine, prevented visceral hypersensitivity in the water avoidance SIH model (Hong et al., 2009). The mechanisms of action of WIN 55,212–2 were not investigated in this study but it has been reported that WIN 55,212–2 dephosphorylates and desensitises TRPV1.

The therapeutic effects of chronic administration of URB597, JZL184, and a combination of both drugs were investigated in a model of chronic widespread hyperalgesia (Lomazzo, Remmers, Schwitter, & Lutz, 2015). This study combined chronic unpredictable stress and multiple intramuscular nerve growth factor injections, which induced chronic widespread hypersensitivity and anxiety- and depression-related behaviour. Chronic inhibition of FAAH using URB597 (which increases AEA, PEA and OEA levels) reversed the development of mechanical hypersensitivity and decreased anxiety-like behaviour in the elevated plus maze (Lomazzo et al., 2015). Interestingly, administration of JZL184, a MGL inhibitor (will increase 2-AG levels), did not produce long-lasting anti-hypersensitivity effects. In fact, JZL184 appeared to induce anxiogenic effects in the elevated plus maze when used alone, and in combination with URB597 in control animals. Combining URB597 and JZL184 did not offer any additional therapeutic effect. These data

suggest that reductions in AEA, PEA and OEA signalling, which occur following chronic stress, may contribute to the development of hypersensitivity via CB_1 receptor- or PPAR-mediated mechanisms, or a combination of both (Lomazzo et al., 2015).

While the mechanism of action underlying the effects of URB597 was not investigated in this study (Lomazzo et al., 2015), and remains unclear, other studies using neuropathic pain and inflammatory pain models have investigated possible mechanisms using microinjections of CB_1, TRPV1 and PPARα antagonists prior to a microinjection of URB597 in the insular cortex, an important brain region involved in processing of pain and emotion (Kim & Kim, 2018; Kwilasz, Poklis, & Negus, 2014). Blockade of CB_1 and PPARα, but not TRPV1, reversed the anti-nociceptive effects of URB597. Antagonism of the CB_1 receptor was more efficacious in attenuating the antinociceptive effects of URB597 compared to PPARα. These results indicate that CB_1 may be more involved in the antinociceptive mechanism compared to PPARα in nerve-injured rats. However, mechanisms of URB597 need to be investigated in a model related to FM.

One group, Kiso and Sekizawa (2020), demonstrated that RIM rats had significantly lower muscle pressure threshold compared to the sham controls. Models of neuropathic pain (spinal nerve ligation and chronic constriction injury) were also assessed in this study to evaluate the antinociceptive effect in multiple chronic pain models. Following confirmation of the model induction, a single oral administration of ASP8477 (0.3, 1 and 3 mg/kg), a FAAH inhibitor, or vehicle, were administered to the RIM and neuropathic pain groups. For the RIM group, muscle pressure thresholds were restored by the 1 and 3 mg/kg doses but not 0.3 mg/kg. For the spinal nerve ligation model, 1 and 3 mg/kg significantly improved mechanical allodynia-like behaviour 2 h after administration, an effect that was not observed in the chronic constriction injury model. Interestingly, for the RIM model, the antinociceptive effect of the 3 mg/kg dose was sustained for at least 8 h but less than 24 h. In a study using the spinal nerve ligation model of neuropathic pain, the antinociceptive effect of ASP8477 is completely inhibited by the CB_1 receptor antagonist SR141716A, but not by the CB_2 receptor antagonist, SR144528 (Watabiki & Kiso, 2017). Spinal anti-nociceptive mechanisms of ASP8477 were also investigated in NMDA-, AMPA-, PGE2-, PGF2α-, and bicuculline-induced allodynia in mice (Kiso & Sekizawa, 2020). ASP8477 significantly improved AMPA-, NMDA-, PGE2-, and PGF2α-induced tactile allodynia but not bicuculline-induced allodynia.

A noteworthy finding of the aforementioned study was the effect of a single acute oral administration of ASP8477 on acute pain. At doses up to 10 mg/kg there was no effect observed on acute pain, as evident in the hot plate and tail pinch tests. Therefore, attenuation of acute pain-like behaviour is not possible with increased basal AEA, PEA and OEA concentrations through FAAH inhibition. These results suggest that ASP8477 may have efficacy against chronic pain but not acute pain. It is possible that CB_1 receptor expression or activation is reduced in the chronic pain models, which may contribute to the increase in pain-related hypersensitivity. Lastly, previous reports of seven-day repeated dosing of ASP8477 in a rat model of capsaicin-induced secondary hyperalgesia did not induce analgesic tolerance, unlike morphine. This is an important finding, given the epidemic with opioid use and the potential for cannabinoid-modulating drugs to be used therapeutically as a long-term alternative for chronic pain conditions.

In a model of visceral hypersensitivity induced by restraint SIH, intraperitoneal injection of ACEA, a CB_1 receptor agonist, abolished chronic stress-enhanced electromyogram to colorectal distension compared with vehicle. Furthermore, intraperitoneal injection of SR141716A, a CB_1 receptor antagonist, exacerbated the chronic stress-induced hypersensitivity compared to the vehicle-treated group (Shen et al., 2010).

In conclusion, the available data on cannabinoid-modulating drugs in animal models of FM provide insight into the therapeutic potential for drugs that enhance CB_1 receptor activation for treatment of FM symptomology.

5.2. Gaps in the literature and limitations

Despite the inherent difficulties in accurately and convincingly modelling FM in laboratory animals, animal models can play a critical role in informing our understanding of the underlying pathophysiology, identification of novel therapeutic targets, and assessment of the efficacy of potential therapies for FM. An important consideration to note is that the majority of studies utilising animal models for FM have only used male rodents (81% of the literature reviewed by Brum et al. (2021)). Moreover, of the studies reviewed in section 5.0–5.1, where cannabinoid-modulating drugs and endocannabinoids were investigated in animal models of FM, only male rodents were included (Häuser et al., 2011; Hong et al., 2009; Jennings et al., 2016; Kiso & Sekizawa, 2020; Lomazzo et al., 2015; Shen et al., 2010). It is well-established that there are sex differences in pain processing and inhibition (Mogil, 2012) but there are also distinct sex differences in the endocannabinoid system and the analgesic response to cannabinoids (Blanton & McHann, 2021). The influence of sex is evident from the gender-biased representation of FM and related or comorbid chronic pain disorders such as irritable bowel syndrome and migraine, all of which have a higher incidence in females than in males (Arout & Bastian, 2018; Finocchi, 2014; Kim & Kim, 2018). It is imperative to address the discrepancy in animal studies and models of FM to accurately translate results between preclinical and clinical studies and better understand their potential therapeutic implications for patients with FM. For example, sex differences have been demonstrated in the muscle alterations of male rats submitted to the ICS model of FM which was not observed in female rats (Bonaterra, Oezel, Ocker, Fazio, & Kinscherf, 2016).

Chronic widespread pain is a hallmark of FM, and spontaneous pain is a key characteristic of the pain experienced by patients with FM. Spontaneous pain has been not replicated or measured in many studies. Only recently has spontaneous pain been measured in the RIM model (Nagakura et al., 2019). Its evaluation is an important measure as most other tests are based only on reflex responses that do not reflect spontaneous pain observed in FM patients.

Finally, it is also extremely important that experimental FM models respond to the drugs used clinically to manage symptoms of FM (e.g., serotonin-norepinephrine reuptake inhibitors). Without this, it is difficult to validate a model as truly representative of the disease.

6. Alterations in the endocannabinoid system in patients with FM

6.1. Genetics

Genome-wide expression profiling of patients with FM did not report any alterations within the endocannabinoid system (Jones et al., 2016). One study (Smith, Fillingim, Gracely, Zaykin, & John, 2012) found that a *CNR1* SNP occurred in a cohort of patients with FM, but a replication study failed to reach significance. The *CNR1* SNP, rs6454674, is located on chromosome 6 and is an intronic variant (T > G) encoding the CB_1 cannabinoid receptor with many suggested associations including addiction (Zuo, Luo, & Gelernter, 2007), obesity (Benzinou et al., 2008), post-traumatic stress disorder and attention deficit hyperactivity disorder (Lu, Järvelin, Loo, McGough, & Peltonen, 2008) but overall its clinical significance remains unclear. In a recent genotyping study, there was no reported statistical difference or association in *CNR1* or related SNP expression between patients with FM and respective controls (Gerra et al., 2021). However, when the FM group were stratified into a subgroup characterised by clinical phenotypes including depression and sleep impairment, it was revealed that patients with FM developing or with depression displayed a strong association with the *CNR1* SNP, rs6454674, compared with FM patients without depression. However, the functional consequence of this SNP on function of the CB_1 receptor is yet to be determined. Revisiting the findings from Smith et al. (2012), it could be suggested that stratifying the

participants in a similar way to Gerra et al. (2021) and colleagues, may reveal a stronger and replicable association with the *CNR1* SNP, rs6454674. Interestingly, variants within the *CNR1* locus have been associated with other chronic conditions that are frequently found comorbid with FM, including migraine (Juhasz et al., 2009; DSmith, Foss, & McKernan, 2017), irritable bowel syndrome (Jiang, 2014; Park, Cho, Kim, & Chung, 2011), and posttraumatic stress disorder (Korem, Xu, & Pietrzak, 2021; Mota, Lowe, Uddin, & Wildman, 2015).

6.2. Endocannabinoid levels

Alterations in circulating endocannabinoids and related NAEs in patients with FM have also been reported (Kaufmann et al., 2008; Stensson et al., 2020; Stensson, Ghafouri, & Ghafouri, 2017). Kaufmann et al. (2008) determined plasma levels of catecholamines, cortisol and anandamide in 22 patients with primary FM and 22 age- and sex-matched healthy controls (17 female and 5 male). Inclusion criteria for all patients who participated in this 1-year-study was to meet the 1990 diagnostic criteria by the ACR for FM. Some of the exclusion criteria included inflammatory conditions, diabetes mellitus, endocrinologic disorders, muscle or joint diseases, major depressive disorder, addiction, general anxiety disorder and psychosis. Plasma concentrations of AEA and cortisol were significantly higher in patients with FM compared to healthy controls. Plasma AEA levels did not correlate with Fibromyalgia Impact Questionnaire (FIQ), visual analogue scales (VAS) and Post-Traumatic Stress Symptom 10-Questionnaire scores or disease duration. No other endocannabinoid or NAE levels were measured in this study. Given the presence of comorbid conditions such as anxiety and depression in patients with FM, the exclusion of patients with such conditions could confound the results and not appropriately capture the total disease state.

Further to the initial characterisation of plasma endocannabinoids in patients with FM, Stensson et al. (2017) investigated a number of NAEs and cytokines in 17 women with chronic widespread pain and 21 healthy controls. Chronic widespread pain is a hallmark pain symptom associated with FM. Plasma levels of OEA and PEA were significantly higher in patients with chronic widespread pain compared to healthy controls. No alterations in the levels of cytokines were observed and no correlation between levels of lipids and cytokines were found. Further to this, OEA, PEA, *N*-stearoylethanolamine (SEA), and 2- AG have also been reported to be significantly higher in patients with FM compared with controls (Stensson et al., 2018). However, when statistically controlling for body mass index and age, significance only remained for OEA and SEA.

The elevated circulating levels of these lipids suggests that there could be low-grade inflammation in FM, as SEA has been shown to have anti-inflammatory activity (Dalle Carbonare et al., 2008). Moreover, OEA has been shown to produce antinociceptive effects in animal models of visceral and inflammatory pain, independent of PPAR-α receptor activation (Suardíaz, Goicoechea, & de Fonseca, 2007).

In summary, the limited available data on circulating levels of endocannabinoids in patients with FM reveal elevated levels of AEA and other related ethanolamines. This is suggestive of a possible compensatory mechanism or that the circulating levels of these lipids have a role in the complex pathophysiology of FM.

6.3. Effects of cannabinoids on FM symptomology

Few clinical trials have investigated the effects of cannabis, cannabis extracts, synthetic cannabinoids, and endocannabinoid-modulating drugs for the treatment of FM. In the last 20 years, 15 published research articles have investigated the use of cannabis (including extracts, THC, and CBD, synthetic- and phyto-cannabinoids) for FM symptoms, with the majority of these being observational studies. Due to the disparity and inconsistency in methodology and study design, there is limited evidence for effectiveness, tolerability, and safety. Nevertheless, prospectively collected data of FM patients using a variety of cannabis-based medicinal products to treat their condition (primary and secondary) show promising results (Sagy, 2019). The available clinical trial literature is summarised in Table 2.

6.4. Randomised-controlled trials of whole plant cannabis

In a randomised placebo-controlled 4-way crossover trial the analgesic effects of inhaled pharmaceutical-grade cannabis in 20 patients with FM were investigated (van de Donk & Kowal, 2019). 25 participants were initially recruited to participate with 5 patients ending their participation after their first study visit for unknown reasons (1), AEs such as dizziness and nausea (3), and fear of needles (1). Primary outcome measures were assessed as relief of experimental pressure pain, electrical pain, and spontaneous pain. Secondary outcome measures were subjective and psychotropic effects. All participants rated their FM pain on an 11-point VAS at baseline and at 1, 2, and 3 h after cannabis inhalation. Four different cannabis varieties were tested, with detailed knowledge of their THC and CBD content: Bedrocan® (22.4-mg THC, <1-mg CBD), Bediol® (13.4-mg THC, 17.8-mg CBD) Bedrolite® (18.4-mg CBD, <1-mg THC), and a placebo variety without any THC or CBD. None of the treatments had an effect greater than placebo on spontaneous or electrical pain responses. Cannabis varieties containing high THC concentrations, Bedrocan® and Bediol®, did significantly increase pressure pain threshold compared to the placebo ($P < 0.01$). Cannabis with high CBD, Bedrolite®, did not display any analgesic activity in any of the pain tests investigated in this study. Finally, CBD increased plasma concentrations of THC but had an antagonistic effect on analgesia when combined with THC. All of the AEs in this study were reported as mild and include, coughing during inhalation (66%), sore throat and bad taste (33%) nausea without vomiting (33%). This study did not satisfy its primary outcome measures; a contributing factor could be the duration of the study, whereby a single acute administration of the cannabis product was not enough to produce an analgesic effect for spontaneous pain associated with FM. Studies that titrate the dose of cannabis over a number of weeks could be more effective. Also, tolerability may pose an additional challenge for the dosage and routes of administration used given the incidence of drop out from the study was 12% due to AEs.

6.5. Observational studies

A cross-sectional survey conducted by Fiz, Durán, Capellà, Carbonell, & Farré, (2011) recruited 56 patients with FM (28 non-cannabis users and 28 cannabis-users). There were varying routes of cannabinoid administration (smoking (54%), oral (46%) and combined (43%)), amount and frequency used and duration of life-long cannabis use. Due to different sources of cannabis, and the nature of the study, it should be noted that the THC and CBD concentration that each participant consumed varied. In this study patients used cannabis to alleviate pain and for almost all the symptoms associated with FM. No FM patients in this study reported worsening of symptoms following cannabis use. Most of the cannabis used was sourced by the patients from a non-regulated environment, rather than it being prescribed and dispensed by a physician. Almost 30% of the cannabis users had been using it recreationally prior to use for symptom management of FM. Cannabis significantly relieved pain and stiffness and improved relaxation, somnolence, and perception of well-being, evaluated by VAS before and 2 h after self-administration. The 36-item Short Form Health Survey (SF-36), FIQ and Pittsburgh Sleep Quality Index (PSQI) were used to assess quality of life. The mental health component summary score of the SF-36 was significantly higher in the cannabis group compared to the non-cannabis users. The physical component summary scores of the SF-36, FIQ and PSQI were not significantly different between cannabis and non-cannabis smokers. This is an interesting finding, given the statistically significant improvements observed pre vs post cannabis self-administration, suggesting cannabis was having primarily a

Table 2
Summary of published literature on the efficacy of cannabinoids for treatment of FM symptoms in chronological order. [1]Numeric Rating Scale (NRS), [2]Multidimensional Pain Inventory (MPI), [3]Pittsburgh Sleep Quality Index (PSQI), [4]Short Form 36 Health Survey Questionnaire (SF-36), [5]Pain Disability Index (PDI), [6] Fibromyalgia Impact Questionnaire (revised) (FIQ or revised FIQ), [7]Visual Analogue Scale (VAS), [8] Hospital Anxiety and Depression Scale (HADS), [9]Pain Related Quality of Life Impairment, [10]Short Form 12 Health Survey Questionnaire (SF-12), [11]Oswestry Disability Index (ODI), [12]Global Impression Of Change (PGIC) Scale, [13]Quality of Life Questionnaire (QOL), [14]Fibromyalgia Assessment Status (FAS), [15]Self-Administered Pain Scale (SAPS), [16]The Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue Scale, [17]The Zung Self-Rating Depression Scale (ZSR-D), [18]The Zung Self-Rating Anxiety Scale (ZSR-A), [19]Adverse effects (AEs), [20] Widespread Pain Index (WPI), [21]Patient Global Assessment (PtGA) Of Health Status, [22]Physician Global Assessment (PGA).

Reference	Type of Study	Duration of Study	Number of participants	Cannabinoid investigated	Primary Outcome	Secondary Outcome	Results	Most common AEs	Drop out % in treatment group	FM Diagnosis Criteria
(Schley et al., 2006)	Observational (Prospective)	3 months	9 (Sex not specified)	δ-9-THC/Dronabinol 2.5-15 mg/day (2.5 mg increase each week)	- Daily pain ratings using NRS[1] (1−10) - Experimentally induced pain -Axon reflex flare	MPI[2] PSQI[3] SF-36[4] PDI[5] FIQ[6]	- No effect on allodynia and hyperalgesia - Attenuated electrically induced pain ($p < 0.05$) at 10-15 mg/day - Daily recorded pain scores were significantly reduced ($p < 0.01$)	Sedation, daze, fatigue, and tiredness (continuous)	55.6% AEs[19]	ACR 1990
(Skrabek et al., 2008)	Randomised placebo-controlled trial	10 weeks	40 (Sex not specified)	Nabilone 0.5 mg/day for 1 week and doubled every week after	- Pain intensity at 2 and 4 week follow-up using VAS[7]	- Number of tender points - Average tender point pain threshold - FIQ[6]	VAS, FIQ and anxiety scores were significantly lower after 4 weeks of treatment	Drowsiness, Dry mouth Vertigo	5% AEs	ACR 1990
(Weber et al., 2009)	Observational	7 months	172 (62% female) Complete data for 124 patients (32 of whom are FM patients)	Dronabinol 7.5 mg/day	Pain intensity, Max pain and min pain using NRS[1]		Pain intensity improved ($P < 0.001$)	Tiredness Dizziness Increased appetite	~25% Lack of effect of total group – data not reported for FM only	ACR 1990
(Ware, Fitzcharles, Joseph, & Shir, 2010)	randomised, active-control, equivalency clinical trial using a 2-period crossover design	10 weeks	29 (90% female)	Nabilone 0.5 mg or amitriptyline 10 mg; the dose was doubled every week	Improved: - Quality of sleep - Self-reported insomnia	- Pain - Mood - Quality of life - Global satisfaction with the treatment - Adverse effects	- Nabilone was superior to amitriptyline at improving sleep and marginally better at improving restlessness - No effects on pain, mood or quality of life	Dizziness Nausea Dry mouth	0%	Not specified
(Fiz, Durán, Capellà, Carbonell, & Farré, 2011)	Observational (cross-sectional survey)	1 day (Data from baseline and 2 h after self-administration)	28 (93% female)	Arbitrary values "1–2 cigarettes when smoking and 1 spoonful eating" Smoking (54%) Oral (46%) Combined (43%)	- Perceived relief using 5 point Likert scale - Perceived benefits on: Pain, stiffness, relaxation, drowsiness, well-being using VAS[7]	PSQI[3] SF-36[4] FIQ[6]	All symptoms assessed by VAS significantly improved	Somnolence Dry mouth Sedation Dizziness High Tachycardia Conjunctival irritation Hypotension	n/a	ACR 1990
(Habib & Artul, 2018)	Observational (Retrospective)	2 months	26 (73% female)	26 ± 8.2 g/ month Smoked only 58% Vaporized only 23% Vaporized + smoked 14% Oral drops + smoked 8%	Revised FIQ[6]	n/a	All aspects of the revised FIQ significantly improved	Dry mouth Red eyes Hunger	n/a	ACR 2010
(Habib & Artul, 2018)	Observational (Retrospective)	n/a	383 (85% female)	Cannabis 31.4 ± 16.3 g/month	Pain relief Quality of sleep Depression	n/a	Significantly improved primary outcomes	Data not shown - eye or throat irritation was the only AEs	n/a	ACR 2010

				Smoking with cigarette 63% Smoking pure cannabis 17% Oil (sublingual) 5% Vaporizing 15%	Anxiety Daily activity			listed		
(Yassin, Oron, & Robinson, 2019)	Observational (Cross over)	9 months	31 (90% female)	First 3 months of SAT[24]: 2 × 5 mg/day of oxycodone hydrochloride (equivalent to 4.5 mg oxycodone and 2.5 mg naloxone hydrochloride) and duloxetine 30 mg/day Second 3 months: Cannabis 20 g/month Last 3 months: Option to increase to 30 g/month Cannabis administrated via smoking or vaporization	Pain intensity using VAS[7] ODI[11] Revised FIQ[6] PGIC[12] SF-12[10] Modified Schober test	Analgesic drug use	Significant improvement in all primary outcome measures at 3 months after initiation of cannabis treatment and the improvement was maintained at 6 months	SAT: Constipation (48%) Loss of appetite (26%) Zombie-like feeling (16%) Haemorrhoids (13%) Medicinal Cannabis: Red eyes (90%) Increased appetite (16%) Sore throat (10%)	19% from SAT due to AEs	Not specified
(Sagy, 2019)	Observational	6 months	367 (82% female) 211 completed	20 g or less of cannabis per month	Treatment response (defined as at least moderate or significant improvement in a patient's condition at six months follow-up without the cessation of treatment or serious AEs[19])	Pain intensity using NRS QOL[13] Perception of the general effect of cannabis using Likert scale	Treatment success was achieved in patients 81.1% Sleep problems improved in 73.4% and disappeared in 13.2% Depression-related symptoms 80.8% QOL to be good or very good in 61.9%	Dizziness Dry mouth Nausea Hyperactivity	17% AEs	ACR 2010
(van de Donk & Kowal, 2019)	Randomised Placebo-Controlled 4-Way Crossover Trial	~8 weeks (Participants visited every 2 weeks for a one dose treatment)	25 (All female)	4 varieties of cannabis: Bedrocan®: 22.4 mg THC/>1 mg CBD Bediol®: 13.4 mg THC /17,8 mg CBD. Bedrolite®: <1 mg THC / 18,4 mg CBD. Placebo One inhalation.	- experimental pressure pain - electrical pain - spontaneous pain	Subjective and psychotropic effects: - Bowdle questionnaire - Bond and Lader questionnaire	- No effect greater than placebo on spontaneous or electrical pain responses Compared to placebo: - Bediol displayed a 30% decrease in pain scores - Cannabis varieties containing THC increased pressure pain threshold	Drug high Dizziness Nausea During inhalation: sore throat, bad taste, coughing	12% AEs 8% other	ACR 2010
(Giorgi et al., 2020)	Observational (Prospective)	6 months	102 (91% female)	Oil-diluted cannabis extracts: Bedrocan: 22% THC, <1% CBD Bediol: 6.3% THC, 8% CBD	Revised FIQ[6] FAS[14] SAPS[15] FACIT[16] PSQI[3] ZSR-D[17] ZSR-A[18]	n/a	A significant improvement in: PSQI and revised FIQ In 44% and 33% of patients, respectively. 50% showed a moderate improvement in ZSR-D and	Dizziness Nausea Palpitations	5.9% AEs 18.6% other	ACR 2010

(continued on next page)

Table 2 (*continued*)

Reference	Type of Study	Duration of Study	Number of participants	Cannabinoid investigated	Primary Outcome	Secondary Outcome	Results	Most common AEs	Drop out % in treatment group	FM Diagnosis Criteria
(Chaves, Bittencourt, & Pelegrini, 2020)	Randomised, Double-Blind, Placebo-Controlled Clinical Trial	8 weeks	17 (All female)	Cannabis: (White Widow variety - 48:1 THC:CBD) or Placebo 1 drop/day sublingually	FIQ[6]	n/a	ZSR-A Cannabis group presented a significant decrease in FIQ score in comparison with the placebo group the cannabis groups baseline score	Somnolence Dizziness Dry Mouth	0%	ACR 2010
(Mazza, 2021)	Observational (Retrospective)	12 months	38 (95% female)	Cannabis: Starting dose of the milled flowers in the sachet was 50 or 100 mg twice per day Olive oil extract, gradually increase their dosage at small intervals, i.e., a single oil drop every 3–4 days until the therapeutic effect Various doses – Physician prescribed dose per participant	Pain relief - measured using a NRS[1]	AEs[19] ODI[11] HADS[8] WPI[20] SyS[21]	30, 18, and 12 patients continued therapy for 1, 3, and 12 months, respectively. Significant improvements were observed in: - NRS, ODI, WPI, and Severity Score at 1 month - NRS, ODI, and WPI at 3 months - NRS, ODI, and Severity Score at 12 months.	Mental confusion Dizziness Nausea Restlessness/irritation	14.3% AEs	ACR 2010
(Fitzcharles et al., 2021)	Observational	2 months	117 (91.5% female) Never used medicinal cannabis: 89 Have used medicinal cannabis: 28	Cannabis: Inhaled cannabis 0.5 to 2 g/day	Disease assessment: - Pain in the last 7 days using VAS[7] - PtGA[21] - PGA[22] Obtained medicinal cannabis use information	n/a	No differences in pain, PtGA or PGA between patients that used medicinal cannabis and those that didn't	Not listed	Of the ever cannabis users: 39.3% due to lack of effect 14% AEs	Not specified
(Boehnke, & Matallana, & Williams., 2021)	Observational (Survey)	2 month (April–May 2020)	$N = 2701$ 94.7% female 38.1% reported never using CBD, 29.4% reported past CBD use, 32.4% reported current CBD use.	CBD [note: one-third of participants also reported past-year medical cannabis use and 20.2% reported using CBD products with >0.3% THC, so benefits may be due to synergism between CBD, THC, and other cannabis plant components rather than CBD alone.	Only 28.3% of participants initiated CBD use based on the recommendation of a medical professional or physician	N/A	% reporting "much" or "very much" improvement for the following symptoms: 30.5% for pain, 40.1% for insomnia/sleep problems, 40.0% for anxiety, 20.0% for fatigue, 32.3% for depression, 21.9% for memory/clarity of thought, and 43.2% for other symptoms	No SAEs reported 51.7% reported sleepiness, 36% dry mouth, 12.8% dry eyes	Rationale for CBD discontinuation ($n = 795$): participants discontinued due to costs (46.7%), lack of effects (62.3%), negative side effects (8.6%)	2011 FM Survey Criteria and Complex Medical Symptom Inventory (CMSI)

psychological effect. Also, the findings of improved pain and stiffness in the 2 h post-cannabis could be due to a bias effect of the patient receiving a putatively effective drug that is known not to be a placebo. Moreover, the dosage could not be stratified from the data provided (e.g. 1 spoonful of edible). Patients with comorbid symptoms were included in this study but data were not stratified accordingly.

In an observational cross-over study, Yassin, Oron, & Robinson (2019) investigated the effect of adding medicinal cannabis to analgesic treatment in patients with severe low back pain related to FM. 31 patients were recruited (91% female) and underwent an initial 3 month period using standardised analgesic therapy (see Table 2). After this initial 3 months, patients had the option of initiating treatment with medicinal cannabis in combination with standard analgesic treatment, for at least 6 months. Primary outcomes for this study were assessed using the Revised FIQ, VAS, Oswestry Disability Index (ODI) and 12-Item Short Form Survey (SF-12) and lumbar range of motion using the modified Schober test. After 3 months of medicinal cannabis use all primary outcomes significantly improved, which was maintained after 6 months of treatment, with the exception of range of motion which continued to improve. Comparing the AEs from this study, AEs during the medicinal cannabis treatment were mild and included red eyes (90%), increased appetite (16%) and sore throat (10%). However, AES associated with standardised analgesic therapy treatment prior to medicinal cannabis were constipation (48%), loss of appetite (26%), zombie-like feeling (16%) and haemorrhoids (13%) with another 6 patients stopping standardised analgesic therapy due to AEs. This highlights a rather important advantage for cannabis-based medicines as an alternative to opioid therapy. Like other observational studies reported, this study lacked the standardisation of concentration of THC and CBD. Also, compliance wasn't tracked in this cohort via urine sampling for metabolites. This study was only carried out in patients with severe low back pain, so a comparison study would be useful against patients with FM without low back pain and should be carried out using a randomised controlled trial (RCT) to reduce bias. For patients to progress from standardised analgesic therapy to medicinal cannabis, they were aware that they needed to show insufficient efficacy to standardised analgesic therapy in order to obtain regulated medicinal cannabis which could bias the results. Nonetheless, more severe AEs presented in the standardised analgesic therapy group compared with the medicinal cannabis group that also reduced their opiate analgesics. Overall, this study shows that cannabis was well tolerated in a subset of patients with FM and that medicinal cannabis shows promise as a conjunct treatment.

A prospective study with a six months follow-up period was carried out by Sagy (2019). The primary outcome measure for this study was treatment response which was defined by the authors as moderate or significant improvement in a patient's condition at the six months follow-up without the cessation of treatment or serious AEs. Secondary outcomes were pain intensity, assessed using a numeric rating scale, quality of life and perception of the general effect of cannabis, both of which were assessed using a Likert scale. 367 patients with FM were recruited to take part in this study, of which 211 completed the six months follow-up. 49% of participants were 40–60 years old and 82% were female patients, consistent with the reported prevalence of FM. The median duration of FM symptoms was 7 years. 45% of patients had reported previous experience with recreational cannabis in the past. Route of administration were oil (20%), inflorescence (67%) and oil and inflorescence combined (12%) and unspecified (0.05%). The median cannabis approved dosage was 670 mg/day (dried weight) at the beginning of the study and 1000 mg/day at six months ($p = 0.01$). No serious AEs were observed; common AEs included dizziness (8%), dry mouth (7%), nausea/vomiting (5%), and hyperactivity (6%). The primary outcome measure of treatment success was reported by 81.1% of patients. Significant improvement in pain intensity, overall quality of life and FM-related symptoms were reported after six months of medical cannabis therapy. The large cohort of patients with FM taking part in this study and the relatively long follow-up analysing the effect and safety of medicinal cannabis on FM symptoms are of particular merit. However, no breakdown or comparison between cannabis routes of administration was provided, and it was not specified if inflorescence was smoking or vaping or if any products were consumed orally by an edible. These are important considerations due to the difference in pharmacokinetics from inhaled vs consumed cannabis. Results need to be interpreted cautiously here due to the risk of bias in this study with a high incidence of recreational use by patients prior to partaking in this study (45%). Evidence from the multivariate regression analysis showed that spasticity at initiation of treatment and previous use of cannabis were associated with treatment success. Moreover, concerns about cannabis treatment were associated with treatment failure. The highlights the need for RCTs to validate results obtained from observational studies.

Recently, a cross-sectional audit carried out in Canada investigated the use of medical cannabis by patients with FM following cannabis legalisation (Fitzcharles, Sampalis, Cohen, & Häuser, 2021). 117 patients with FM were recruited (91.5% female; mean age 57 ± 12 years). This study involved the completion of questionnaires. Physicians completed the Physician Global Assessment for each patient. Participants completed a questionnaire comprised of: pain in the past 7 days using a VAS, Patient Global Assessment of health status using a VAS, ever and current recreational cannabis use; ever and current medicinal cannabis use. 24% of patients with FM (including those with comorbid rheumatic conditions) had tried medicinal cannabis as a therapeutic intervention, with 57% of those patients reporting continued use (<14% of all patients in this study). No differences in Physician Global Assessment, Patient Global Assessment or pain were found between groups that used medicinal cannabis vs those that have never tried medicinal cannabis though the self-selected nature of the medical cannabis use limits conclusions.

A retrospective review was carried out and examined the effects of licensed medicinal cannabis on patients with FM in an Israeli population which included 26 patients, 19 of whom were female (73%) (Habib & Artul, 2018). The mean duration of FM was 4.3 ± 2.64 years and all the patients smoked or inhaled cannabis except for one patient who used a combination of smoking and oral oil drops. The mean dose of cannabis was 26 ± 8.3 g per month. Participants completed the Revised FIQ in the period before and after treatment with medicinal cannabis. Also, records on medications prescribed and consumed prior to and while using medicinal cannabis were recorded, as were adverse effects (AEs). Results from this study revealed that 13 patients (50%) were able to cease using other medications and 12 patients (~46%) reduced medications by at least 50% while using medicinal cannabis. AEs reported were dry mouth (27%), red eyes (27%), and hunger feeling (15%). Medicinal cannabis significantly improved ($p \leq 0.001$) all items of the Revised FIQ. Results from this study appear to show promise for medicinal cannabis as a treatment for FM symptoms. However, the results should be interpreted with caution for a number of reasons; Revised FIQ results were retrospective, meaning the score prior to starting medicinal cannabis was actually completed after the treatment had commenced, the small sample size and the lack of information on comorbid conditions.

A retrospective study examining the analgesic efficacy of medicinal cannabis and AEs was carried out with patients diagnosed with FM who were deemed resistant to conventional drugs (Mazza, 2021). The primary outcome measure of this study was pain relief, and was assessed using a numerical rating scale. The secondary outcome measures for this study were AEs, which were assessed at monthly follow-up visits by a physician. These include disability, mood disorders, and severity of FM, which were assessed using the ODI, Hospital Anxiety and Depression Scale, Widespread Pain Index, and Severity Score, respectively. Participants received licensed medicinal cannabis with various THC and CBD content, as powdered whole flowers (decoction or vaporization) or oil extracts. 35 patients with FM took part in this study with 30, 18, and 12 participants continuing therapy for 1, 3, and

12 months, respectively. Four patients vomited after intake of one sachet of cannabis (Bedrocan 100 mg, $n = 2$; FM2 100 mg, n = 2) and one other participant experienced several AEs after a single dose, in all 5 participants discontinued medicinal cannabis treatment before reaching the 1 month follow-up. Therefore, 30 patients completed one month of treatment with 67% of them reporting analgesic effects. 18 participants continued to use medicinal cannabis up until 3 months, with 12 discontinuing due to mild AEs or ineffectiveness. Of these participants, 12 completed the 12 month follow-up. The 6 participants that ceased treatment between the 3 month and 12 month follow-ups were not due to AEs, rather, due changes in personal circumstances such as relocation. At 1, 3, and 12 month follow-ups, pain was reduced by at least 30% and there was a significant improvement in both ODI and SyS. There were no significant improvements in the anxiety or depression components of the Hospital Anxiety and Depression Scale at any time point. Widespread Pain Index was significantly improved at 1 and 3 months but not at 12 months.

Of all the observational studies discussed thus far, this study provided the most comprehensive and thorough investigation into medicinal cannabis for patients with FM. One particular strength of the current study was evaluating the effects of long-term medical cannabis therapy (12 months) in a controlled and regulated environment. Another strength of the study was the inclusion of other relevant clinical data such as questionnaires pertaining to comorbid symptoms like anxiety and depression.

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6.6. Synthetic THC

One of the first published studies to investigate dronabinol, synthetic THC, as monotherapy for FM administered 2.5-15 mg/day (dosage was increased weekly by 2.5 mg if no severe side effects (e.g. sedation) were reported) (Schley, Skopp, Konrad, & Rukwied, 2006). Primary outcome measures were daily pain recordings by the patient, experimentally induced pain, and axon reflex flare recorded by a laser Doppler scanner. This study assessed touch-evoked allodynia, pinprick-induced hyperalgesia, and axon reflex flare, none of which were significantly affected by dronabinol administration at any dose. However, electrically induced pain was significantly attenuated and daily pain recordings were significantly reduced (Cohen's $d = 0.4$). This pilot study provides some evidence that dronabinol could be recommended for the treatment of FM, one of the main reasons for this being the small sample size which did not provide sufficient statistical power for conclusive investigation of the effects of dronabinol on symptoms of FM. Tolerability of dronabinol was also a factor, with five out of nine suitable patients with FM withdrawing due to adverse effects AEs (see Table 2).

The next available clinical data on dronabinol for FM came from Weber et al., (2009), which was a retrospective study assessing 32 patients with FM as part of a sub-analysis from a larger cohort including patients with chronic neuropathic pain. Participants received a daily dose of 7.5 mg. Pain intensity, maximum pain scores and minimum pain scores all reduced following treatment with dronabinol (Cohen's $d = 0.76$, 0.69 and 0.69, respectively). Pain intensity did not differ between the FM and neuropathic pain patients, therefore, clinical questionnaire data were not analysed separately. For the FM and neuropathic pain combined questionnaire data, dronabinol significantly improved Pain Disability Index, SF-12 and quality of life (assessed by the pain summary scale) (Cohen's $d = 0.53$, 0.53 and 0.74, respectively).

There are only two published research articles reporting the effect of nabilone for treatment of FM symptoms. Both studies are RCTs, however, pain associated with FM was only investigated in one of these two research articles (Skrabek, Galimova, & Ethans, 2008). In a double-blinded RCT the therapeutic potential of nabilone for pain management and quality of life improvement were assessed in 40 patients with FM (Skrabek et al., 2008). In this study, patients were recruited from the musculoskeletal practices of attending Psychiatrists and Rheumatologists at the Rehabilitation Hospital. Inclusion criteria included diagnosis by the ACR (1990) criteria, aged between 18 and 78 years, having continued pain despite the use of other oral medications, and no previous use of oral cannabinoids for pain management. Participants were randomly assigned into treatment and control groups ($n = 20$). Both groups of patients were seen at baseline, 2 weeks and 4 weeks post-treatment and after a 4-week washout period. The primary outcome measure for the 2- and 4-week follow-up visits, was pain score using VAS. Secondary outcome measures included, number of tender points, the average tender point pain threshold, and FIQ. Nabilone was self-administered in an oral capsule with subjects in the treatment group receiving 0.5 mg at bedtime for a 1-week period, with instructions to increase to 0.5 mg twice a day after 7 days. At the 2-week visit, dosage increased to 0.5 mg in the morning and 1 mg at bedtime, with instructions to increase to 1 mg twice a day after 7 days. Patients in the control group received a corresponding placebo. Pain scores, FIQ and anxiety scores were all significantly lower after 4 weeks of treatment with nabilone. The placebo-control group showed no significant improvements. AEs that were reported by the group receiving nabilone include drowsiness, dry mouth and vertigo (47%, 33%, and 27% at the 4-week follow-up, respectively). Authors concluded that nabilone appears to be a beneficial, well-tolerated treatment option for patients with FM. However, further research into nabilone as a potential treatment for managing FM pain and anxiety symptoms are warranted to further validate this finding.

Sleep disturbances affect patients with many chronic pain conditions, including FM. Ware, Fitzcharles, Joeseph, & Shir, (2010) carried out a randomised, active-control, equivalency clinical trial using a 2-period crossover design, investigating the effects of nabilone on sleep in FM. The primary outcome measure of this study was to determine whether nabilone is equivalent to amitriptyline, a commonly prescribed tricyclic antidepressant, in improving quality of sleep for patients with FM and self-reported insomnia. The secondary outcome measure were to assess the effect nabilone on the other clinical variables associated with FM including pain, mood, quality of life, global satisfaction with the treatment, and adverse effects. This study was carried out over the course of 10 weeks, with 2 weeks alternating between a washout period and treatment. The first, third, and fifth of the 2 week periods were washout phases. Recruitment was through the Pain Clinic at the McGill University Health Centre. Eligible inclusion criteria were males and females over the age of 18 with a diagnosis of FM and who had self-reported chronic insomnia. Study participants were randomly assigned their treatment and self-administered either nabilone or amitriptyline (0.5 mg or 10 mg, respectively) using an oral capsule received either nabilone 0.5 mg or amitriptyline 10 mg at the start of the treatment cycle of the study. A physician evaluated whether dosing should be increased after 1 week of each treatment cycle. After a 2 week washout period, subjects underwent the same protocol but with the other study drug. There were no differences between nabilone and amitriptyline on relief of fibromyalgia symptoms (pain, mood, and quality of life). These findings were reported but the data were not provided, therefore

it is difficult to interpret if the two drugs improved equally or did not change from baseline. Compared with amitriptyline, more people experienced mild to moderate AEs with nabilone. At the completion of the trial, 41% of participants reported preference for nabilone, 32% for amitriptyline and there was no report on preference for the remaining 17%.

Reviewing these studies investigating the efficacy of nabilone for FM, the evidence is not of sufficiently high quality to suggest that nabilone is more useful than traditionally prescribed medications as a treatment for FM syndrome. In a meta-analysis and systematic review of cannabinoid effects for rheumatoid diseases including FM, it was found that these studies also had a high risk of bias (Fitzcharles, 2016). The risk of bias was assessed across 5 domains including random sequence, allocation concealment, blinding outcome, incomplete data outcome and size. Given the small sample sizes, the statistically significant results reported may not accurately represent the true effect or potential of the drug for treatment of FM symptoms. Therefore, larger trials are warranted based on these proof of concept studies.

From the literature reviewed, particularly the controlled studies, THC-rich compounds show promise for pain associated with FM. These findings compliment preclinical data demonstrating that inhibition of FAAH, and consequent activation of CB_1, is antinociceptive.

6.7. Current clinical trials with cannabinoids for FM

Currently, there are two clinical trials scheduled to begin recruitment which aim to investigate the use of cannabinoids for treatment of FM symptoms. CBD and THC combined (KL16–012) is currently recruiting for phase 2 clinical trial for use in patients with FM (NCT04239469). This randomised double-blind, placebo-controlled study will recruit 44 patients which will receive a liquid standardised extract of cannabis containing 1 mg of THC and 0.45 mg of CBD or placebo. Administration will be sublingual, while dosing will begin at 3 drops per day and be increased to 15 drops per day by week 5. Primary outcome measure is an improvement in FIQ from baseline to week 12 and secondary outcomes are improved biweekly and monthly FIQ score, improvement in insomnia, improved pain score using VAS and changes in plasma cytokines. The duration of this study will be 12 weeks in total.

CBD is in phase 3 clinical trials for treatment of FM (NCT04729179). The primary outcome measure is pain intensity and secondary outcomes of the trial is to investigate if CBD can improve sleep and quality of life. The study will include 200 patients, who will receive either CBD (starting with 10 mg of CBD daily and the dose will be increased every third day until the maximum dosage of 50 mg is reached (after two weeks)) or placebo in a randomised, double-blind, placebo-controlled, parallel-group, single centre trial over a period of 24 weeks which is due to be completed in 2023.

There is no record of Nabiximols trials past or present for treatment of FM.

6.8. Effects of cannabinoids on co-morbid symptoms/ chronic overlapping conditions

To our knowledge, there are no RCTs investigating the effect of cannabinoids on symptoms of FM and chronic overlapping conditions such as anxiety, depression and IBS. Many anecdotal reports imply that cannabis is effective for treatment of depressive symptoms. However, to the best of our knowledge there are no RCTs for cannabinoid treatment of depression and it has been concluded that there is currently no high-quality evidence to support the use of cannabis in the treatment of mood symptoms or affective disorders (Black et al., 2019) . The biphasic effect of cannabis, particularly THC, whereby high doses are anxiogenic and low doses are anxiolytic, have been shown in both rodent and human studies (Karschner, McMahon, Wright, & Huestis, 2011; Rey & Viveros, 2012). A number of RCTs have investigated the use of CBD for treatment of anxiety. These studies have demonstrated CBD to be effective at reducing self-reported anxiety scores (Bergamaschi, 2011; Crippa et al., 2011), cortisol levels following the Trier Social Stress Test (Appiah-Kusi, Wilson, Bossong, & Mondelli, 2020) and social anxiety (Masataka, 2019).

A recent cross-sectional online survey of a population of medical marijuana users ($n = 367$) in Illinois, United States, found that almost 50% of the responders reported severe FM (Bruce & Shattell, 2021). Pain was the most frequently reported use for medicinal cannabis at 74.9%, followed by anxiety (65.7%), insomnia (56.4%) and depression (49.3%). Interestingly in terms of chronic-overlapping conditions, 75.5% of the participants reported two or more of these symptoms.

A small randomised, double blind, placebo controlled, cross-over trial assessed dronabinol in healthy volunteers and patients with irritable bowel syndrome (Klooker, Van Den Wijngaard, & Boeckxstaens, 2011). This study, and others, found that dronabinol did not reduce visceral perception to rectal distension in healthy volunteers or patients with IBS (Wong, Busciglio, Szarka, & Zinsmeister, 2011; Wong, Eckert, Ryks, & Zinsmeister, 2012). This evidence does not support the potential use of dronabinol in patients with concurring FM and irritable bowel syndrome. Moreover, in a recent retrospective cross-section study, patients with IBS and cannabis use disorder were at 40.7% higher odds for IBS-hospitalisations with a rising trend of cannabis use disorder and related psychiatric comorbidities. This is a significant finding given the psychiatric comorbidities associated with IBS and FM, which could exacerbate IBS symptoms and health-related quality of life. Nonetheless, there are studies targeting the endocannabinoid system that have shown promise, such as dietary supplementation with PEA and polydatin which has been reported to significantly improve abdominal pain (Cremon et al., 2017). Overall it can be concluded that there are few studies investigating the use of cannabis and cannabinoids for IBS and given the scarcity of data, more research is warranted.

6.9. Gaps in the literature and limitations

While evidence from the studies described show a possible implication of the endocannabinoid system in FM, it cannot be concluded that there is sufficient evidence for the proposed hypothesis of clinical endocannabinoid deficiency (Russo, 2004). Rather, from the limited studies available it appears that FM is more associated with elevated levels of endocannabinoids. The elevated levels of endocannabinoids and related NAEs reported in a number of studies (Kaufmann et al., 2008; Stensson et al., 2017; Stensson et al., 2020) are possibly a compensatory mechanism. However, further research is essential in order to validate this hypothesis and would require longitudinal studies, large patient cohorts and interventions such as FAAH inhibitors or CB_1 antagonists e.g. rimonabant to determine causality. Nonetheless, evidence of a *CNR1* polymorphism could indicate that there are indeed alterations in cannabinoid signalling at the level of the receptor, rather than (or in addition to), changes circulating endocannabinoid levels. In order to fully interpret this result, the full functional implications of the SNP needs to be investigated, including the relevance to subpopulations of patients. Given the overlap with other conditions, could it have the potential to be biomarker along with other genetic alterations within the serotonergic system and provide a more stringent diagnosis criteria? Currently, there are very few studies reporting levels of circulating endocannabinoids and related NAEs in patients with FM or chronic widespread pain. This represents a substantial gap in the literature that should be addressed.

Within the published clinical trial literature there several limitations. Overall, it can be concluded that the majority of clinical trials described are at least at a moderate risk of bias. Due to the nature of observational studies and the psychoactivity of cannabis/cannabinoids, patients can be aware that they are receiving an active drug and a significant portion of participants have used cannabis recreationally prior to receiving it for treatment of FM symptoms. It is difficult to recommend or interpret a specific dosage, cannabis product or route of administration that

would provide the most effective therapy for symptoms related to FM. It is also difficult to monitor compliance to the treatment which could result in findings that are misleading or difficult to interpret. Also, due to the heterogeneous nature of FM, distinct subpopulations with chronic over-lapping conditions are often excluded from studies therefore, cohorts of patients with FM studied do not truly reflect the variable clinical phenotype. There is also a lack of consistency in diagnosis of FM along with limitations to the ACR criteria such as imprecise language and definition, a lack of clarity regarding FM diagnosis when co-occurring with other diseases and reliability of diagnosis or exclusion of other pain syndromes (Wolfe, Fitzcharles, Häuser, & Mease, 2016). Finally, study duration is another limitation of many of the reviewed studies. Most studies only last for a number of weeks or months, therefore, no conclusions can be extrapolated regarding the long-term safety and efficacy. This is a particular limitation due to FM being a chronic disorder. Moreover, sample sizes at present remain small.

Currently, there is not enough high-quality evidence to indicate that cannabis or cannabinoids are at least as efficacious as other currently available treatments. More robust, high quality RCTs are required with increased sample sizes, rigorous dosing regimens, consistency with inclusion/exclusion criteria and clear outcome measures coupled with more high quality real world evidence studies.

7. Discussion and conclusion

FM is a complex, heterogeneous condition that is poorly understood and lacks effective treatments, partly due to the broad-spectrum polysymptomology. Reviewing the literature from preclinical and clinical data, has identified a number of gaps and limitations. Currently, face, construct and predictive validity have not been comprehensively established in a particular animal model for FM. This represents a major challenge in preclinical research into FM. The relatively new model, RIM, has emerged as the most translational model developed thus far. Not least because of its reproducibility in both male and female rodents, but also the induction of less ubiquitous symptoms, which is more representative of the diverse subgroups within patient populations of FM (Nagakura, 2009; Nagakura et al., 2019). Nonetheless, characterisation of the endocannabinoid system is yet to be carried out in this model. The use of a FAAH inhibitor restored muscle pressure thresholds in the RIM model, demonstrating the effectiveness of modulating the endocannabinoid system in alleviating pain in a model of FM (Kiso & Sekizawa, 2020). However, the effect of FAAH inhibition on spontaneous pain-like behaviour was not assessed, a cardinal feature of FM, therefore, it would be important to establish if inhibition of FAAH reduces this behaviour. Moreover, this model has its limitations and discordant symptoms, such as altered locomotor activity and hypokinesia (Blasco-Serra, González-Soler, Blasco-Ausina, & Cervera-Ferri, 2015), which occur upon induction of the model but cease 5 days after the last reserpine administration. This is not surprising, given reserpine is also used to induce models of Parkinson's disease by repetitive dosing (Leal, 2019).

SIH models are, to the best of our knowledge, the only models that have investigated components of the endocannabinoid system in a model related to FM. Therefore, overall, preclinical data from animal models have not demonstrated the involvement of the endocannabinoid system in FM. Not only is there a need to characterise the endocannabinoid system in models of FM but also to carry out studies involving cannabinoid-modulating drugs to determine their therapeutic potential. Presently, observational studies and RCTs show a high degree of variability which needs to be addressed and informed by preclinical research in FM models.

Given the small number of trials, it cannot be ruled out that synthetic THC or CBD may have therapeutic potential for treatment of FM. There are many advantages to using pharmaceutical-grade oral cannabinoids such as nabilone and dronabinol, including standardised concentrations or doses and easy route of administration. However, there are limitations to oral cannabinoids such as the low bioavailability of THC (6–20% (Wall, Brine, & Perez-Reyes, 1983)) and CBD (13–19% (Millar & O'Sullivan, 2018)), which is predominantly due to its lipophilic nature and extensive first pass metabolism. Furthermore, extracts and synthetic cannabinoids may lack the so-called 'entourage effect' hypothesised with whole cannabis plant that contains a plethora of phytocannabinoids and terpenes, although further research is required to test this hypothesis. Another route of administration that could be of benefit to patients with FM is transdermal skin patches for localised musculoskeletal pain. These could avoid first-pass metabolism and offer additional benefits such as reduced frequency of dosing, slow release over a prolonged period to minimise adverse effects, and less abuse potential.

Self-medication with unregulated cannabis such as the observational study conducted by Fiz et al., (2011) offers an additional challenge when interpreting data. This is due to the variable potency of cannabis which has shown to be increasing in THC concentration in both dispensaries and the illegal market. A recent systemic review has shown that between 1975 and 2017, THC concentrations from herbal cannabis and resin have increased yearly by 0.29% and 0.59%, respectively (Freeman, Wilson, ElSohly, & Lynskey, 2021). This is an important consideration, given the analgesic and anxiolytic effects of cannabinoids have shown to be dose-dependent in studies of chronic pain and anxiety (Patel & Hillard, 2006; Wallace, Marcotte, Umlauf, Gouaux, & Atkinson, 2015). Self-medication and opioid-sparring using CBD as an alternative has recently been reported in a large online survey in patients with FM. The over-prescription of some pain medications and the ongoing opioid epidemic highlights the need for alternative therapies and the potential role for CBD (Boehnke, 2021).

A possible mechanisms of action through which CBD may be beneficial for FM could be through enhancement of endogenous AEA levels through inhibition of intracellular fatty-acid binding proteins that are responsible for the transport of AEA to its catabolising enzyme FAAH (Elmes et al., 2015). Other possible mechanisms include modulation of serotonergic transmission (particularly positive allosteric modulation of 5-HT_{1A}) (Jesus et al., 2019), desensitisation of TRPV1 (Anand, Jones, Korchev, Pacchetti, & Sodergren, 2020) and antagonism of GPR55 (Ryberg, Sjögren, Hermansson, & Elebring, 2007). It is worth noting that there are multiple molecular targets for CBD (de Almeida & Devi, 2020), with some studies reporting more than 60 (Ibeas Bih, Chen, Bazelot, & Whalley, 2015). However, the precise mechanisms of action are yet to be elucidated.

Based on the reviewed literature, inhaled cannabis has been shown to be the most beneficial in terms of pain, quality of life and sleep. However, there are inherent limitations to inhaled cannabis, such as undefined long-term effects. Moreover, significant variations in methodological approach, herbal cannabis preparations, treatment duration, small sample sizes and narrow demographic of patients, preclude the recommendation of its immediate use for treatment of FM symptoms.

Cannabis (including extracts, synthetic and phytocannabinoids) with various THC/CBD concentrations have demonstrated to be efficacious for a spectrum of chronic conditions, some of which include epilepsy (Hausman-Kedem & Kramer, 2018), cancer pain and emesis (Blake, Malek, & Diaz, 2017; Tramèr & Campbell, 2001), human immunodeficiency virus and chronic pain (Wilsey & Deutsch, 2013). Based on the evidence from the available literature, it is difficult to draw any robust conclusions or make recommendations for the use of cannabis-based medicines from the treatment of FM. Currently, there is not enough high-quality evidence to indicate that cannabis is superior or at least as efficacious as other currently available treatments. Promising patient reported outcomes indicate the potential for cannabinoid-based drugs for the treatment of FM, particularly given the lack of serious AEs associated with their use. However, there is an overarching need to conduct more RCTs with increased sample sizes, rigorous dosing regimens, and consistency with the inclusion/exclusion criteria, more extensive

outcome measures, and inclusion of longitudinal studies to assess efficacy and tolerability.

Declaration of Competing Interest

DJN is Chair of the charity Drug Science and AKS is Head of Research of Drug Science. Drug Science receives an unrestricted educational grant from a consortium of medical cannabis companies. AKS is scientific advisor to the Primary Care Cannabis Network, and executive member of the Cannabis Industry Council. Both roles are unpaid and neither AKS nor DJN would stand to benefit from the wider prescription of medical cannabis in any form. SOS is VP of Translational Sciences at Artelo Biosciences, and an independent consultant to several pharmaceutical companies through CanPharmaConsulting. None of these businesses are working in fibromyalgia. DPF reports research grants in the area of cannabinoids or the endocannabinoid system and pain from Shionogi Ltd. (Shionogi Science Programme) and from B. Braun Ltd. jointly with Science Foundation Ireland.

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