Received: 31 May 2023 | Revised: 29 August 2023 | Accepted: 4 September 2023

DOI: 10.1111/jnc.15964

Journal of Neurochemistry JNC The Official Journal of the International Society for Neurochemistry WILEY

REVIEW

Cannabis constituents for chronic neuropathic pain; reconciling the clinical and animal evidence

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Abstract

Chronic neuropathic pain is a debilitating pain syndrome caused by damage to the nervous system that is poorly served by current medications. Given these problems, clinical studies have pursued extracts of the plant Cannabis sativa as alternative treatments for this condition. The vast majority of these studies have examined cannabinoids which contain the psychoactive constituent delta-9-tetrahydrocannabinol (THC). While there have been some positive findings, meta-analyses of this clinical work indicates that this effectiveness is limited and hampered by side-effects. This review focuses on how recent preclinical studies have predicted the clinical limitations of THC-containing cannabis extracts, and importantly, point to how they might be improved. This work highlights the importance of targeting channels and receptors other than cannabinoid CB1 receptors which mediate many of the side-effects of cannabis.

KEYWORDS
cannabidiol, cannabis, delta-9-tetrahydrocannibinol, ion channel, neuropathic pain, receptor

1 | INTRODUCTION

Nociceptive or acute pain is an adaptive, neuroprotective and short-lived sensation that promotes the survival of an organism by producing behavioural adaptations that act to prevent potential or ongoing injury (Woolf et al., 2004). Chronic pain, often viewed as a maladaptive response, is identified as pain that lasts beyond the expected time required for normal tissue healing, typically 3–6 months. It affects up to 40% of US adults and is estimated to cost $560 billion per annum in lost productivity and medical treatment (Dahlhamer et al., 2018).

Neuropathic pain is a form of chronic pain that arises from lesions or damage to the somatosensory nervous system and surprisingly has only recently been added to the 11th edition of the International Classification of Diseases (Raja et al., 2020; Scholz et al., 2019). Approximately 25% of individuals diagnosed with chronic pain suffer from neuropathic pain (Torrance et al., 2006). Neuropathic pain can be caused by diseases such as diabetes and multiple sclerosis, physical trauma resulting from injury and surgery, viruses such as Herpes and HIV and chemotherapy medications such as paclitaxel which affect the peripheral and/or central nervous system (Colloca et al., 2017). This condition is associated with a highly abnormal pain syndrome

Abbreviations: 2-AG, 2-arachidonoyl-glycerol; 5-HT1A, Serotonin 1A receptor; AM281, 1-(2,4-Dichlorophenyl)-5-(4-iodophenyl)-4-methyl-N-4-morpholinyl-1H-pyrazole-3-carboxamide; Anandamide, N-arachidonoyl-ethanolamine; CB1/2, cannabinoid receptor 1/2; CBD, cannabidiol; CBM, cannabis-based medicine; ED50, median effective dose; FAAH, fatty acid amide hydrolase; GABA, gamma-aminobutyric acid; GlyR, glycine receptor; GPCR, G-protein coupled receptor; JZL195, 4-[(3-Phenoxyphenyl)methyl]-1-piperazinecarboxylic acid 4-nitrophenyl ester; MAGL, monoacylglycerol lipase; PAM, positive allosteric modulators; PPARs, peroxisome proliferator-activated receptors; THC, delta-9-tetrahydrocannabinol; TRP, transient receptor potential; TRPV1/2, transient receptor potential vanilloid 1/2; VGCC, voltage gated calcium channel; VGCS, voltage gated sodium channel.

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This article is part of the special issue "Pain".

that includes spontaneous pain (pain in the absence of a stimulus), allodynia (pain caused by a non-painful stimulus such as cool and light touch) and hyperalgesia (exaggerated responses to painful stimuli).

Chronic pain treatment is symptomatic and difficult given its complex and widespread profile. Indeed, a polypharmacy approach is often used for this condition. Current pharmacological treatments are associated with numerous acute adverse effects including dizziness, sedation and sleep disorders, which can limit their clinical value. Importantly, there are also substantial long-term problems including issues such as drug dependence and abuse. Thus, issues with the pain-relieving efficacy and adverse effects of all current drugs mean that they are effective in less than half of chronic pain sufferers (Finnerup et al., 2015). As such, there is a significant need to develop new therapies for chronic neuropathic pain which could act as first-line therapies or second-line agents to augment current therapies. While this review is focused on pharmacological treatments, it is important to note that neuropathic pain is associated with debilitating psychological comorbidities, such as depression, anxiety and sleep disorders and that psychological interventions are highly beneficial, especially given their lack of drug-linked side effects (Cohen et al., 2021; Williams et al., 2020).

2 | CANNABIS AND THE ENDOGENOUS CANNABINOID SYSTEM

Extracts of the *Cannabis sativa* plant have long been utilised for not only its recreational effects but also its medicinal qualities such as pain relief (Notcutt et al., 2004; Ware et al., 2005). Recreational use and widespread abuse, however, have posed a major barrier to exploiting the potential of cannabis-based medicines (CBMs).

2.1 | Cannabis sativa and its constituents

Over the past 50 years, unfolding evidence has revealed potentially powerful therapeutic properties of CBMs, including plant extracts (phytocannabinoids) and their synthetic derivatives. While *Cannabis sativa* contains hundreds of distinct chemical constituents, this review will focus on only two of these. The major psychoactive cannabis constituent is delta-9-tetrahydrocannabinol (THC) which has been shown to have analgesic, anti-inflammatory and anti-emetic properties in animal studies (Borgelt et al., 2013; Robson, 2014). The primary non-psychoactive cannabis constituent is cannabidiol (CBD), which has therapeutic potential in managing chronic pain, anxiety, epilepsy and neuroprotection (De Gregorio et al., 2019; Robson, 2014). CBD is the first and only non-psychoactive phytocannabinoid approved in the US for medical use, for treating seizures in infants (Devinsky et al., 2019). These advances in our understanding and shifts in perception about the therapeutic potential of cannabis have propelled the development of CBMs.

2.2 | The endogenous cannabinoid system

Over the past few decades, it has been shown that cannabis, including its extracts and associated synthetic compounds, produces its physiological effects by acting on an endogenous cannabinoid (endocannabinoid) system (Winters & Vaughan, 2021). The endocannabinoid system is a lipid signalling system composed of endogenous cannabinoids, target proteins such as cannabinoid receptors and the enzymes involved in their production and degradation (Lu & Mackie, 2021). N-arachidonoyl-ethanolamine (anandamide) and 2-arachidonoyl-glycerol (2-AG) are two of the most common endocannabinoids found throughout the human body and brain. These compounds are involved in various functions including controlling mood, memory, anxiety and pain (Wolf et al., 2020).

It has long been known that synthetic cannabinoids and endocannabinoids modulate activity within the nervous system by presynaptically inhibiting synaptic transmission. In the early 2000s, it was demonstrated that endocannabinoids achieve this by a mechanism fundamentally different to other neurotransmitters, a phenomenon known as retrograde signalling. In this form of signalling, endocannabinoids are synthesised 'on-demand' within the postsynaptic neuronal cell body and travel "backwards" to activate pre-synaptic receptors, thereby inhibiting the release of neurotransmitters, such as glutamate and GABA, onto the postsynaptic neuron (Castillo et al., 2012; Kano et al., 2009). Their activity is terminated by their uptake into neurons and glia, possibly via a transporter and subsequent enzymatic degradation (Giuffrida et al., 2001; Lu & Mackie, 2021). In this regard, the actions of anandamide and 2-AG are terminated by their hydrolysis via the enzymes fatty acid amide hydrolase (FAAH) and monoacylglycerol lipase (MAGL), respectively (Blankman & Cravatt, 2013; Fowler, 2015).

It is important to note that (endo)cannabinoids produce not only short-term changes in synaptic strength that reverse upon their washout/elimination but also long-term changes in synaptic transmission (Winters & Vaughan, 2021). This long-term plasticity underlies many vital functions such as learning, memory and fear and also pathological maladaptations in brain function (de Melo Reis et al., 2021; Lu & Mackie, 2016; Riedel & Davies, 2005).

Synthetic cannabinoids, cannabis constituents, such as THC and CBD, and endocannabinoids produce their effects by acting on a range of target proteins. While many of the well-known effects of cannabinoids are mediated by a class of Gi/o-coupled cannabinoid G-protein coupled receptors (GPCRs), they also act via a range of other GPCRs, ligand-gated ion channels, voltage-gated ion channels and enzymes involved in endocannabinoid degradation (Howlett, 2002; Pertwee, 2005). A description of the major targets is provided later in the review, focusing on those implicated in preclinical neuropathic pain studies (Section 4.6).

3 | CLINICAL EFFICACY AND SAFETY OF CANNABINOIDS FOR NEUROPATHIC PAIN

As permissive cannabis policies become more prevalent globally, it is critical to identify optimal strategies that promote the benefits of CBMs whilst reducing their adverse effects. Here we first focus on peer-reviewed clinical studies that have examined CBMs for non-cancer chronic neuropathic pain, and then the meta-analysis of chronic pain studies. It is important to note that most of these studies have investigated the effects of whole cannabis, THC and its synthetic analogues nabilone and dronabinol and THC:CBD combinations which are known as nabiximols.

3.1 | Clinical studies: Whole cannabis

There have been a number of studies that have examined the effectiveness of whole cannabis on different types of neuropathic pain. Smoked cannabis has been shown to reduce pain intensity scores to a greater extent than placebo cigarettes in individuals suffering from HIV-associated, diabetic, post-surgery/traumatic and other unspecified forms of neuropathic pain (Abrams et al., 2007; Corey-Bloom et al., 2012; Ellis et al., 2009; Finnerup et al., 2015; Ware et al., 2005, 2010; Wilsey et al., 2008). Vapourised cannabis has also been reported to significantly improve symptoms in various forms of neuropathic pain (Eisenberg et al., 2014; Wilsey et al., 2013, 2016). In addition, sublingual THC-enriched cannabis oil has been reported to improve the pain associated with fibromyalgia (Chaves et al., 2020). Interestingly, in some of these studies, low-dose cannabis was reported as having a beneficial pain-relieving effect that approached that of higher-dose cannabis, but with fewer psychoactive side effects. However, it is important to note that not all of these studies have been randomised, double-blinded and placebo-controlled.

3.2 | Clinical studies: THC

A number of randomised, double-blind, placebo-controlled clinical trials have examined the effects of THC on a range of neuropathic pain states. In a number of studies, oral dronabinol, nabilone or THC produced greater pain relief than placebo in patients with diabetes, multiple sclerosis and fibromyalgia (Skrabek et al., 2008; Toth et al., 2012; Zajicek et al., 2012). Similarly, oromucosal THC produced greater pain relief than placebo in various forms of neuropathic pain (Wade et al., 2003; Weizman et al., 2018). By contrast, oral THC and dronabinol did not have a significantly greater effect than placebo in patients with cervical dystonia and patients with polyneuropathy, post-herpetic neuralgia and peripheral nerve injury and post-surgery patients (Buggy et al., 2003; Zadikoff et al., 2011; Zubcevic et al., 2023). While not placebo-controlled, a recent large cohort study found that oral dronabinol provided effective pain relief in a range of treatment-resistant neuropathic pain conditions (Ueberall et al., 2022). Interestingly, another study has shown that oral dronabinol did not produce a significant reduction in multiple sclerosis-related pain until 10 weeks after commencing treatment (Schimrigk et al., 2017). In all of these studies, adverse effects were generally reported as being predictable and well tolerated, although these led to some participant dropouts. These studies indicate that THC has potential as a treatment for neuropathic pain, including treatment-resistant conditions. However, this is generally associated with non-serious cannabis-like adverse effects that will lead to patient dropouts.

3.3 | Clinical studies: CBD

Compared to THC, there are few clinical trials on CBD. In one study, oromucosal CBD produced greater pain relief than placebo in patients with chronic radicular neuropathic pain (Wade et al., 2003). By contrast, oral CBD did not have a significantly greater effect than placebo in patients with peripheral neuropathic pain (Zubcevic et al., 2023). Recently, it has been shown that topical CBD reduces the focal pain associated with peripheral neuropathy (Xu et al., 2020). Thus, evidence supporting the therapeutic benefits of CBD remains to be established.

3.4 | Clinical studies: Nabiximols

Nabiximols such as Sativex, which is a 1:1 THC:CBD formulation, have been examined in a number of clinical studies. The rationale for examining combination THC:CBD is based on the long-held hypothesis that it provides a powerful synergistic analgesic interaction whilst quelling the THC-induced psychoactive side effects (Russo, 2011). To this end, it has been shown that combined THC:CBD has fewer adverse effects than THC alone in both neuropathic pain and pain-free people (Morgan et al., 2010; Ueberall et al., 2022). However, a more recent randomised controlled trial has shown that CBD does not protect against THC-induced adverse effects, at a range of THC:CBD dose ratios, including standard 1:1 ratios and other combinations with a higher CBD content (Englund et al., 2023).

In some studies, oromucosal Sativex has been shown to reduce pain intensity in people with multiple sclerosis and various forms of peripheral neuropathic pain (Nurmikko et al., 2007; Rog et al., 2005; Serpell et al., 2014; Wade et al., 2003). Furthermore, oromucosal nabiximols provided superior pain relief and fewer adverse effects compared to oral dronabinol alone in patient populations resistant to standard neuropathic pain treatments (Ueberall et al., 2022). By contrast, other studies have provided negative data on nabiximols. Oromucosal Sativex failed to produce a significant pain improvement compared to placebo in patients with brachial plexus avulsion and diabetic neuropathy (Berman et al., 2004; Selvarajah et al., 2010). Similarly, oral nabiximol did not have a significantly greater effect on pain scores than placebo in patients with various forms of peripheral neuropathic pain (Zubcevic et al., 2023). These studies indicate that nabiximols have potential as a treatment for neuropathic pain, although it is unclear whether they have superior efficacy and safety compared to THC alone.

3.5 | Clinical meta-analyses

To gain a better understanding of the overall efficacy and safety of the cannabinoids, there have been a number of meta-analyses examining the impact of these CBMs on chronic pain. Some of these meta-analyses have reported that CBMs have a beneficial pain-relieving impact on chronic neuropathic and non-cancer pain (Bialas et al., 2022; Dykukha et al., 2021; Johal et al., 2020). By contrast, others have reported that they have only a modest effect, or no pain-relieving impact, especially when compared to placebo (Canavan et al., 2022; Gedin et al., 2022; Meng et al., 2017; Mucke et al., 2018; Sainsbury et al., 2021; Stockings et al., 2018; Tyree et al., 2019; Walitt et al., 2016; Wang et al., 2021; Whiting et al., 2015; Wong et al., 2020). Furthermore, these studies indicate that CBMs produce adverse effects, which lead to dropouts, although these are mostly reported as non-serious (Meng et al., 2017; Mucke et al., 2018; Whiting et al., 2015; Wong et al., 2020).

The overall implication of the meta-analyses is that the future of CBMs for chronic neuropathic pain is not promising. However, there are a number of questions that highlight important gaps in our knowledge. Some of these issues relate to the specific types of CBM, their dosage and route of delivery and potential interactions with other medications. For example, while there is little precise data on comparisons between the different cannabinoids, there are some suggestions that THC (and its analogues) alone provides better pain relief, although others have reported no differences between CBMs (Johal et al., 2020; Whiting et al., 2015). In addition, there are conflicting reports as to whether oral, smoked or oromucosal routes of administration provide superior pain relief (Aviram & Samuelly-Leichtag, 2017; Johal et al., 2020; Tyree et al., 2019; Wang et al., 2021). A potential problem in these comparisons is the conflation of drug type and route of administration, for example, in a recent study it was suggested that oromucosal nabiximols are superior to oral dronabinol (Ueberall et al., 2022).

Finally, there is reasonably clear clinical evidence that CBMs are more effective when administered long-term (Giossi et al., 2022; Johal et al., 2020). However, it is unclear whether specific types of neuropathic pain might be better treated by CBMs. While most meta-analyses have examined their utility for a variety of chronic pain syndromes, only a few have examined specific forms of neuropathic pain or treatment-resistant neuropathic pain. The mixed conclusions between these systemic reviews and meta-analyses only emphasise the need for a more nuanced approach to clinical research for CBMs and neuropathic pain.

4 | PRE-CLINICAL ANIMAL STUDIES

There is overwhelming evidence from pre-clinical animal studies that synthetic cannabinoid receptor agonists are highly effective in relieving neuropathic pain (Rahn & Hohmann, 2009). This is interesting given the above inconclusive evidence for cannabinoids in the clinical setting. However, unlike clinical studies, most animal studies of neuropathic pain are devoted to investigating the effects of synthetic compounds, such as agonists and degradation inhibitors. Below, we focus on studies that have examined THC, CBD and nabiximols in animal models of neuropathic pain. Given its prevalence in clinical studies, the emphasis will be on systemic delivery.

4.1 | Pre-clinical studies: THC

A number of rodent studies have shown that systemic THC administration reduces mechanical and thermal allodynia in nerve-injury, diabetic and chemotherapy drug models of neuropathic pain (Casey et al., 2017; De Vry et al., 2004; Harris et al., 2016; King et al., 2017; Linher-Melville et al., 2020; Mitchell et al., 2021; Williams et al., 2008). It is important to note that, unlike the clinical data, THC has high efficacy in rodents, virtually abolishing allodynia at high doses. However, THC also produces prototypical cannabinoid-like side effects, including catalepsy, disrupted motor coordination, sedation and hypothermia (Boggs et al., 2018; Hayakawa et al., 2008; Taffe et al., 2015; Varvel et al., 2006).

The apparent disparity in the reported efficacy of THC between pre-clinical and clinical studies could be because of a number of factors. Besides mixed patient populations, one such factor is the wide range of doses used in different studies. Recent studies have addressed this by examining the dose–response profile of THC to assess the therapeutic window between beneficial pain-relieving effects and side effects; this can be quantified by the therapeutic index which is the ratio of the ED_{50} for side effects versus anti-allodynia. In doing so, it has been demonstrated that subcutaneously injected THC has a relatively modest therapeutic index of approximately 5 (Casey et al., 2017). Consequently, significant side effects including sedation, motor incoordination and catalepsy were observed at THC doses which produce sub-maximal reductions in allodynia. Nonetheless, it might be noted that the therapeutic window of THC is better than that of subcutaneously injected synthetic non-selective cannabinoid receptor 1/2 (CB 1/2) agonists, such as WIN55212, CP55950 and HU210, which display no window between analgesia and side effects (therapeutic index approximately1; Fox et al., 2001; Kazantzis et al., 2016; Scott et al., 2004). Additionally, orally administered THC has a poor therapeutic index (between 1 and2; Mitchell et al., 2021). The reason for this difference is unclear but may be related to the relatively lower efficacy of THC at CB1 receptors compared to synthetic agonists (Adamson Barnes et al., 2016).

Overall, these pre-clinical findings provide a basis for the relatively poor effectiveness of THC observed in clinical studies. The animal studies indicate that while THC is highly effective in reducing neuropathic pain symptoms such as allodynia, this only occurs at doses where substantial side effects are observed. Indeed, this would equate to relatively high doses in clinical studies where intolerable cannabis-like adverse effects have been reported.

4.2 | Pre-clinical studies: CBD

More recently, there has been an increasing interest in the actions of CBD in neuropathic pain models. Delivery of CBD via various

routes of administration alleviates the mechanical and cold allodynia associated with rodent neuropathic pain models induced by nerve and spinal cord injury, chemotherapy drugs and diabetes (Casey et al., 2017, 2022; Costa et al., 2007; Harris et al., 2016; King et al., 2017; Li et al., 2018; Linher-Melville et al., 2020; Mitchell et al., 2021; Toth et al., 2010; Ward et al., 2011, 2014). Importantly, maximally effective doses of CBD produce this 'pain-relief' without any of the cannabis-like side effects observed with THC and combination THC:CBD (Casey et al., 2017; Mitchell et al., 2021). Thus, CBD has a therapeutic index in excess of 10–50.

It is important to note that in some studies, CBD has been reported as having less than half the maximal anti-allodynic efficacy of THC (Casey et al., 2017; Mitchell et al., 2021). This could be partially because of its poor oral bioavailability and/or rapid and variable degradation (Hlozek et al., 2017; Lucas et al., 2018). To overcome this, there have been some attempts to improve its bioavailability and stability, such as unique delivery techniques and metabolically stable analogues (Matarazzo et al., 2021; Nutt et al., 2022; Pertwee et al., 2018).

4.3 | Pre-clinical studies: Combination THC:CBD (nabiximols)

As with clinical studies, there has been substantial pre-clinical interest in the effects of THC:CBD combinations in animal neuropathic pain models. Intraperitoneal administration of a 1:1 ratio of THC:CBD has been shown to reduce the development of paclitaxel and nerve-injury-induced mechanical allodynia when given prior to or just after induction of the neuropathic pain model (King et al., 2017; Linher-Melville et al., 2020). In addition, CBD combined with a homologue of THC, tetrahydrocannabivarin, has similar effectiveness in the paclitaxel model (Kumar Kalvala et al., 2022). In a nerve-injury model of neuropathic pain, it has been demonstrated that subcutaneous injection of combination THC:CBD after the development of neuropathic pain reduces mechanical and cold allodynia (Casey et al., 2017). Thus, nabiximols are effective in neuropathic pain models when administered as prophylactic and therapeutic treatment regimens.

Isobolographic analysis of the dose–response analysis in these studies, however, reveals some important features of nabiximols (Casey et al., 2017; King et al., 2017). There is a highly synergistic analgesic interaction, with a 1:1 combination of THC:CBD displaying a 10–200-fold greater potency than that predicted for a simple additive interaction. Consequently, doses of THC and CBD which are ineffective when administered individually, produce significant reductions in allodynia when given together. While interesting, this analgesic synergy would mean nothing if there was an equal synergistic THC:CBD interaction in the production of side effects. Remarkably, it was observed that there was only an additive side effect interaction between THC and CBD when injected subcutaneously (Casey et al., 2017). While this lack of side effect synergy needs confirmation in other neuropathic pain models, it indicates that nabiximols can provide substantial relief from neuropathic pain in the absence of cannabis-like side effects.

It would appear difficult to reconcile this pre-clinical pain-relieving nabiximol synergy with the clinical observations. The isobolographic analysis indicates there are distinct low and high-dose actions of combination THC:CBD in the animal preclinical work (Casey et al., 2017). Low-dose combination THC:CBD is devoid of side effects but its anti-allodynic efficacy is relatively low. At high doses, combination THC:CBD is indistinguishable from THC, producing a near abolition of allodynia and significant cannabis-like side effects. This indicates that, like THC, nabiximols will only have low pain-relieving efficacy at the low doses where side effects are observed.

4.4 | Pre-clinical studies: Route of administration

While most of the above pre-clinical studies use more direct routes of administration, such as intraperitoneal and subcutaneous injection, a number of clinical trials have focussed on oral administration. Recently, it has been shown that oral delivery of THC, CBD and combination THC:CBD reduces nerve-injury-induced allodynia (Dumbraveanu et al., 2023; Linher-Melville et al., 2020; Mitchell et al., 2021). Unlike more direct injection routes of administration, oral THC:CBD only has a moderately synergistic interaction in reducing allodynia and producing side effects. Interestingly, THC:CBD combinations with a higher CBD content (1:8 and 1:80 THC:CBD) had an additive anti-allodynic interaction, and surprisingly, a mildly synergistic side effect interaction (Mitchell et al., 2021). Rather than a pharmacodynamic mechanism, this is likely to be because of pharmacokinetic interactions in the metabolism of THC and CBD. It has been shown that CBD undergoes rapid metabolism (to inactive forms) which reduces the breakdown of THC (Hayakawa et al., 2008; Hlozek et al., 2017; Lucas et al., 2018; Varvel et al., 2006), such that the CNS exposure to THC is likely to be higher in these THC:CBS combinations. Overall, this poor therapeutic profile provides a basis for the modest clinical efficacy and associated adverse effects of orally delivered THC-containing CBMs observed in clinical studies.

Issues with centrally mediated side effects can be circumvented by other approaches, such as site-specific delivery. It is known that while the cannabis-like side effects of cannabinoids are mediated by the brain, its analgesic effects are also mediated by the spine and even the periphery (Clapper et al., 2010; Jhaveri et al., 2006; Martin et al., 1999; Smith & Martin, 1992). Accordingly, intrathecal delivery of synthetic non-selective cannabinoid receptor agonists reduces allodynia in a range of neuropathic pain models (Fox et al., 2001; Hama & Sagen, 2011; Lim et al., 2003; Rahn et al., 2007; Vuong et al., 2008; Zhu et al., 2009). It is therefore not surprising that intrathecal delivery of THC and combination THC:CBD also produces efficacious reductions in allodynia (Casey et al., 2022; Xiong et al., 2012). Interestingly, intrathecal CBD also reduces allodynia in neuropathic pain models (Casey et al., 2022; Dos Santos et al., 2023; Jesus et al., 2019; Xiong et al., 2012). The pain-relieving effects of THC, CBD and

combination THC:CBD are not associated with any cannabis-like side effects, even at doses 10–20 times greater than those at which a substantial reduction in nerve-injury-induced anti-allodynia is observed. Furthermore, intrathecal combination THC:CBD displayed a mildly synergistic two-fold increase in analgesic potency, compared to its predicted additive effect (Casey et al., 2022). In addition to the spinal route, there may also be promise in targeting peripheral cannabinoid receptors using drugs that do not pass the blood–brain barrier (Guindon & Hohmann, 2009).

4.5 | Pre-clinical studies: Chronic drug delivery

While the majority of the above studies have examined the acute actions of the phytocannabinoids THC and CBD, some studies have examined their effectiveness during chronic administration. Prolonged administration of THC, CBD and combination THC:CBD reduces the allodynia associated with animal neuropathic pain models (Costa et al., 2007; King et al., 2017; Linher-Melville et al., 2020; Silva-Cardoso et al., 2021; Ward et al., 2011, 2014). Interestingly, CBD-induced analgesia is observed even at low doses which are ineffective when administered acutely (King et al., 2017). These studies indicate that chronic CBD treatment might provide an alternative therapeutic approach for chronic neuropathic pain that has seldom been explored in the clinical setting.

4.6 | Pre-clinical studies: Pharmacology and mechanisms

The mechanisms of cannabinoid actions in neuropathic pain states have been examined exclusively in animal models. Numerous studies have shown that THC and CBD act via not only cannabinoid GPCRs but also a range of other targets (Figure 1). It is important to note that the in vivo actions of cannabinoids in neuropathic pain models are not easily predicted by the targets identified in in vitro studies (McPartland et al., 2015). Thus, the following mechanistic discussion focuses on targets which have been linked to cannabinoid actions in neuropathic pain states, starting with the individual actions of THC and CBD in neuropathic pain states, followed by THC:CBD combinations. For more detailed general information on cannabinoid targets and mechanisms, the reader is referred to more detailed reviews (Castillo-Arellano et al., 2023; De Petrocellis et al., 2017; Howlett, 2005; Muller et al., 2018; Pertwee, 2008; Starowicz & Finn, 2017).

4.6.1 | Cannabinoid GPCRs

A major target of cannabinoids is a class of Gi/o-coupled CB1 and CB2 GPCRs which inhibit intracellular signalling cascades, such as adenylyl cyclase, and voltage-gated calcium channels, as well as activating inward rectifying potassium channels and various protein kinases (Howlett, 2005). CB1 receptors are expressed at very high levels throughout the nervous system, particularly in brain regions involved in memory, anxiety and pain. While CB2 receptors are mainly expressed in immune-related cells such as microglia, they are present within the central nervous system and are known to be upregulated in chronic pain states (Jordan & Xi, 2019).

While cannabinoid CB1 and CB2 receptor agonists have been shown to reduce neuropathic pain signs such as allodynia and hyperalgesia in rodents. However, the relative roles of these receptors in the actions of THC and CBD are likely to differ because of their differing affinity and efficacy (Lu & Mackie, 2021; Pertwee, 2008; Rahn & Hohmann, 2009). While THC has moderate-high affinity and efficacy at both CB1 and CB2 receptors, CBD has only modest affinity and efficacy for these receptors and is therefore likely to act via other mechanisms (McPartland et al., 2015). Thus, antagonist neuropathic pain studies have demonstrated that the anti-allodynic effects of THC are reduced by cannabinoid CB1 antagonists, while CB2 receptor antagonists have a lesser effect which differs between cold and mechanical allodynia (Casey et al., 2017, 2022; Mitchell et al., 2021). By contrast, cannabinoid CB2 receptor antagonists have a modest effect and CB1 receptors have no effect on

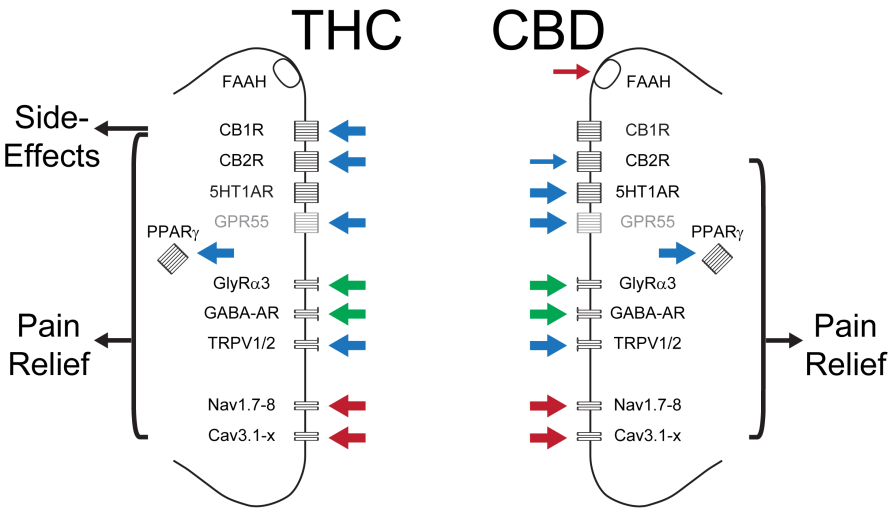

FIGURE 1 Schematic of identified targets of THC and CBD which have been associated with animal neuropathic pain models. Targets at which THC and CBD act as agonists, positive allosteric modulators or antagonists/inverse agonists are shown by blue, green and red arrows; while those which are unaffected by THC/CBD, or only with low potency have no or smaller arrows. Targets which have little to no effect in neuropathic pain models or have been disputed are depicted in grey.

the anti-allodynic actions of CBD, suggesting the involvement of other targets (Casey et al., 2017; Jesus et al., 2019; Kumar Kalvala et al., 2022; Malvestio et al., 2021; Mitchell et al., 2021; Silva-Cardoso et al., 2021; Ward et al., 2011, 2014).

The common side effects produced by THC (e.g., sedation, motor incoordination and catalepsy) in animals that have undergone neuropathic pain models are largely CB1-receptor-mediated, although CB2 and GRP55 receptors have also been implicated (Casey et al., 2017; Mitchell et al., 2021; Wang et al., 2020). The absence of cannabis-like side effects with CBD in neuropathic pain models is consistent with the lack of involvement of cannabinoid CB1 receptors in its anti-allodynic profile (Casey et al., 2017; Mitchell et al., 2021; Wang et al., 2020). Thus, while both cannabinoid CB1 and CB2 receptors make important contributions to neuropathic pain relief, cannabis-based treatments that do not target CB1 receptors are likely to provide safer options (Figure 1).

4.6.2 | Voltage-gated ion channels

Cannabinoids, including cannabis constituents and synthetic ligands, are known to inhibit voltage-gated sodium and calcium channels, VGCSs and VGCCs (Howlett, 2005; Pertwee, 2005). These cannabinoids non-selectively inhibit most VGCs subtypes, $Na_v1.1$–1.8 (Ghovanloo et al., 2018; Watkins, 2019). The recently described high-affinity cannabinoid inhibition of the $Na_v1.7$–1.8 subtypes (Huang et al., 2023; Zhang & Bean, 2021) is of particular interest because of the role of these Na_v subtypes in neuropathic pain and the current lack of selective drugs (Hameed, 2019; Xue et al., 2021).

Various cannabinoids have also been shown to inhibit voltage-gated calcium channels, including high-voltage activated N- and P/Q-type channels ($Ca_v2.1$–2) via CB1-mediated and more direct mechanisms (Harding et al., 2023; Mackie & Hille, 1992). Interestingly, cannabinoids including THC and CBD inhibit the transient T-type channel subtypes ($Ca_v3.1$–3) with varying potency and efficacy via a direct CB1-independent mechanism (Mirlohi et al., 2022; Ross et al., 2008). These T-type channels are particularly interesting because of their expression in pain pathways, role in neuropathic pain and the lack of selective drugs (Cai et al., 2021; Choi et al., 2007; Dogrul et al., 2003; Jagodic et al., 2008; Na et al., 2008).

4.6.3 | Ligand-gated ion channels

Cannabinoids act on a range of ligand-gated ion channels (Castillo-Arellano et al., 2023; Howlett, 2005). It is well known that cannabinoid ligands, including THC and CBD, activate a number of ion channels with the transient receptor potential (TRP) family, including the thermal nociception transducers TRPV1 and TRPV2 (De Petrocellis et al., 2017). In this regard, both TRPV1 agonists and antagonists have been examined as analgesic targets for a range of chronic pain models (Wong & Gavva, 2009). The recent evidence that TRPV1 agonists ablate TPRV-containing nociceptor terminals is of particular interest given that it is associated with long-lasting analgesia (Arora et al., 2022). Cannabinoids such as THC and CBD are also known to act as positive allosteric modulators (PAMs) of specific subtypes of glycine (GlyR) and GABA-A ligand-gated ion channels (Bakas et al., 2017; Xiong et al., 2012; Yevenes & Zeilhofer, 2011). In particular, THC and CBD produce GlyRα3-mediated analgesia at the spinal level in neuropathic pain models (Xiong et al., 2012).

4.6.4 | Other GPCRs and receptors

Besides cannabinoid receptors, other GPCRs have been identified as cannabinoid targets in neuropathic pain states (Figure 1). Antagonist studies have demonstrated that 5-HT1A receptors have a major role in the anti-allodynic effects of acutely and chronically administered CBD in diabetic and paclitaxel models of neuropathic pain (Jesus et al., 2019; Ward et al., 2014). This is consistent with observations that CBD but not THC acts as an agonist at 5-HT1A receptors (Pertwee et al., 2018; Russo et al., 2005). Another GPCR of interest is GPR55, which has been shown to be modulated by not only THC, CBD and synthetic cannabinoid receptor agonists, but also by selective CB1/2 antagonists (Anavi-Goffer et al., 2012; Ryberg et al., 2007). However, these results are complicated by conflicting reports on the effect of GPR55 knockout on the induction and maintenance of nerve injury and chemotherapy drug models of neuropathic pain (Carey et al., 2017; Staton et al., 2008).

In addition to GPCRs, nuclear receptors which regulate gene expression, such as peroxisome proliferator-activated receptors (PPARs), have also been implicated in neuropathic pain (Okine et al., 2019; Starowicz & Finn, 2017). Thus, PPAR-γ has been identified as a target of cannabinoids, such as CBD and THC, and has been shown to mediate their anti-allodynic effects in neuropathic pain models (Hind et al., 2016; Jhaveri et al., 2008; O'Sullivan, 2007, 2016; Silva et al., 2022).

4.6.5 | Endocannabinoid degradation enzymes

It has long been proposed that drugs that block endocannabinoid degradation enzymes have the potential to produce more subtle effects on many conditions, including chronic pain, than globally acting receptor agonists (Maione et al., 2013). Interest in these drugs progressed following the development of highly selective ligands that block FAAH, MAGL or both enzymes, such as PF3845, JZL184 and JZL195, respectively (Ahn et al., 2009; Long, Li, et al., 2009; Long, Nomura, et al., 2009). By blocking their degradation, these drugs specifically elevate the levels of endocannabinoids where they are being released. Thus, both FAAH and MAGL inhibitors reduce allodynia in animal models of neuropathic pain and have a good therapeutic window (Adamson Barnes

et al., 2016; Ignatowska-Jankowska et al., 2014; Jayamanne et al., 2006; Kinsey et al., 2009, 2010, 2013; Russo et al., 2007). While it has been shown that CBD but not THC inhibits FAAH (De Petrocellis et al., 2011), its role in the effects of CBD in neuropathic pain models has not been explored.

4.6.6 | Targets of THC:CBD Combinations

The above evidence suggests that THC and CBD can act via multiple targets to produce pain relief in animal pre-clinical models of neuropathic pain. It might therefore be speculated that the targets of THC:CBD combinations are extremely diverse (Castillo-Arellano et al., 2023). Unfortunately, few studies have examined the targets that mediate the actions of THC:CBD combinations in neuropathic pain models. In a nerve-injury neuropathic pain model, the anti-allodynic effects of low-dose THC:CBD combinations are not mediated by either cannabinoid CB1 or CB2 receptors, while the analgesia and side effects at high doses are largely CB1 receptor-mediated (Casey et al., 2017; Mitchell et al., 2021). In parallel with these anti-allodynic effects, low but not higher doses of the THC:CBD combination were devoid of CB1 receptor-mediated side effects. Thus, unlike their individual actions, the targets at which THC:CBD combinations produce their effect in most neuropathic pain models remain to be determined, particularly at low doses which lack cannabis-like side effects.

5 | CONCLUSIONS

The current meta-analysis evidence for the clinical use of cannabis extracts in the treatment of chronic neuropathic pain is not encouraging and is difficult to reconcile with the large body of positive evidence from pre-clinical animal neuropathic pain models. When assessing clinical effectiveness, there is little data on comparisons between the different types of cannabis extracts (THC, CBD and nabiximols), dosing regimens (dose level and duration of treatment and route of administration) and targets. These factors are important because there are emerging signals from the pre-clinical animal studies that provide a rational basis for the poor clinical effectiveness observed for CBMs and potential clues as to how they might be refined.

Clinical evaluation has largely been restricted to THC-containing medicines, either cannabis, THC alone (or its synthetic derivatives) or nabiximols (THC:CBD combinations, such as Sativex). The clinical issue is that these THC-containing extracts do not provide a more effective treatment option for chronic neuropathic pain than placebo and that they are generally associated with the typical cannabis-like side effects. This is reflected in the pre-clinical animal work where direct injection of THC reduces allodynia in many neuropathic pain models with high effectiveness, but only at doses where substantial cannabinoid-like side effects are observed. Injected nabiximols only produce modest reductions in allodynia at low side effect-free doses but are indistinguishable from THC at higher doses. Furthermore, oral nabiximols display little to no analgesic synergy and therefore have no advantage over THC. These issues arise because higher doses of THC-containing medicines (THC alone and THC:CBD combinations) produce pain relief and side effects via a common target, cannabinoid CB1 receptors (Figure 1). These issues reflect many of the problems observed in clinical studies on THC-containing CBMs. Thus, it is essential to distinguish between different THC-containing formulations, including their dosing and routes of administration, in terms of their activation of cannabinoid CB1 receptors.

On the contrary, CBD alone appears to provide a potentially safer alternative because it reduces the allodynia associated with many neuropathic pain models without the cannabis-like side effects associated with THC. Importantly, its effectiveness increases with chronic treatment. This greater safety is likely because of the lack of involvement of cannabinoid CB1 receptors. The current animal literature therefore highlights the potential importance of CBD as a therapeutic tool against neuropathic pain, particularly with long-term treatment, either alone or as an adjuvant to current drugs. However, CBD has lower effectiveness than THC-containing drugs. It also undergoes rapid and variable metabolism making it more difficult to assess, particularly with oral administration. To determine the optimal approach, pre-animal research on CBD is needed, particularly on its non-cannabinoid CB1 receptor-related mechanisms of action. This is crucial in determining the direction of future clinical research into these CBMs, particularly the potential of CBD as an alternative treatment option.

AUTHOR CONTRIBUTIONS

The authors contributed by writing different sections of the review article. All authors checked and edited the full manuscript until a final manuscript was collectively agreed upon.

ACKNOWLEDGEMENTS

This work was supported by the National Health & Medical Research Council of Australia Ideas Grant (APP2002877). E Sokolaj was in receipt of an Australian Government Research Training scholarships.

CONFLICT OF INTEREST STATEMENT

Christopher W. Vaughan is an Editor for the Journal of Neurochemistry and edited this special issue. There are no further potential conflicts of interest to declare.

PEER REVIEW

The peer review history for this article is available at https://www.webofscience.com/api/gateway/wos/peer-review/10.1111/jnc.15964.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study. This article is a review

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How to cite this article: Sokolaj, E., Assareh, N., Anderson, K., Aubrey, K. R., & Vaughan, C. W. (2023). Cannabis constituents for chronic neuropathic pain; reconciling the clinical and animal evidence. *Journal of Neurochemistry*, *00*, 1–14. https://doi.org/10.1111/jnc.15964