Drugs (2018) 78:1665–1703
https://doi.org/10.1007/s40265-018-0996-1

REVIEW ARTICLE

Medical Use of Cannabinoids

Ana Isabel Fraguas-Sánchez[1] · Ana Isabel Torres-Suárez[1,2]

Published online: 29 October 2018

Abstract
Cannabinoid receptors, endocannabinoids and the enzymes responsible for their biosynthesis and degradation constitute the endocannabinoid system. In recent decades, the endocannabinoid system has attracted considerable interest as a potential therapeutic target in numerous pathological conditions. Its involvement in several physiological processes is well known, such as in energy balance, appetite stimulation, blood pressure, pain modulation, embryogenesis, nausea and vomiting control, memory, learning and immune response, among others, as well as in pathological conditions where it exerts a protective role in the development of certain disorders. As a result, it has been reported that changes in endocannabinoid levels may be related to neurological diseases such as Parkinson's disease, Huntington's disease, Alzheimer's disease and multiple sclerosis, as well as anorexia and irritable bowel syndrome. Alterations in the endocannabinoid system have also been associated with cancer, affecting the growth, migration and invasion of some tumours. Cannabinoids have been tested in several cancer types, including brain, breast and prostate cancers. Cannabinoids have shown promise as analgesics for the treatment of both inflammatory and neuropathic pain. There is also evidence for a role of the endocannabinoid system in the control of emotional states, and cannabinoids could prove useful in decreasing and palliating post-traumatic stress disorder symptoms and anxiolytic disorders. The role of the endocannabinoid system in addictions has also been examined, and cannabinoids have been postulated as alternative and co-adjuvant treatments in some abuse syndromes, mainly in ethanol and opioid abuses. The expression of the endocannabinoid system in the eye suggests that it could be a potential therapeutic target for eye diseases. Considering the importance of the endocannabinoid system and the therapeutic potential of cannabinoids in this vast number of medical conditions, several clinical studies with cannabinoid-based medications are ongoing. In addition, some cannabinoid-based medications have already been approved in various countries, including nabilone and dronabinol capsules for the treatment of nausea and vomiting associated with chemotherapy, dronabinol capsules for anorexia, an oral solution of dronabinol for both vomiting associated with chemotherapy and anorexia, a Δ^9-tetrahydrocannabinol/cannabidiol oromucosal spray for pain related to cancer and for spasticity and pain associated with multiple sclerosis, and an oral solution of cannabidiol for Dravet and Lennox–Gastaut syndromes. Here, we review the available efficacy, safety and tolerability data for cannabinoids in a range of medical conditions.

1 Introduction

Initially, the term 'cannabinoids' was used to designate a group of specific compounds present in the *Cannabis sativa* plant, which is known for its psychoactive effects and which has been used in medicine since ancient times [1, 2]. For example, in traditional Chinese medicine, cannabis was used for the treatment of asthma, malaria and gout, and in India for neuralgias, convulsions and migraines [3, 4]. In the nineteenth century, the use of cannabis became very popular in Europe and USA, where ethanolic extracts of cannabis (known as cannabis tincture) were also utilised to treat various disorders such as convulsions in infants, tetanus, cholera and rabies, among others. However, these disappeared from therapeutic use in the first half of the twentieth century owing to an inability to prepare standardised cannabis preparations, which resulted in the risk of producing over- or under-dosed formulations [4–7].

The most relevant cannabinoids are Δ^9-tetrahydrocannabinol (Δ^9-THC), the most abundant cannabinoid and the one mainly responsible for the psychoactive properties of cannabis, and cannabidiol (CBD), the second

✉ Ana Isabel Torres-Suárez
galaaaa@ucm.es

[1] Department of Pharmaceutics and Food Technology, Faculty of Pharmacy, Plaza Ramón y Cajal s/n, 28040 Madrid, Spain

[2] Institute of Industrial Pharmacy, Complutense University of Madrid, 28040 Madrid, Spain

Key Points

The expression of the endocannabinoid system, and especially of cannabinoid receptors, has been found to be altered in a great number of disorders, making it a potential therapeutic target.

Cannabinoids, particularly Δ^9-tetrahydrocannabinol, have demonstrated efficacy as analgesics, antiemetic agents and antispastic agents.

Δ^9-Tetrahydrocannabinol has shown beneficial effects as an add-on therapy for the treatment of neuropathic pain in combination with opioids, and might enable the required dosage of opioids to be lowered.

Cannabidiol has demonstrated its effectiveness as an anticonvulsant agent, being especially helpful in the treatment of Lennox–Gastaut and Dravet syndromes.

most abundant and lacking psychoactive activity. However, the discovery of specific receptors for these compounds in the 1990s demonstrated that membrane receptors mediated cannabinoid effects. This discovery led to the search for endogenous ligands that activate them, which are called endogenous cannabinoids or endocannabinoids. Today, the term cannabinoids not only includes plant cannabinoids, also known as phytocannabinoids, but also endocannabinoids and the synthetic analogues of both groups. The major cannabinoids of each group are shown in Fig. 1.

To date, two cannabinoid receptors have been studied: CB_1 and CB_2 [8, 9]. CB_1 receptors have a ubiquitous distribution, being found predominantly in the central nervous system (CNS) [in nerve cells], but also in peripheral nerve terminals and non-neuronal tissues including the uterus, prostate, testis, stomach, vascular endothelium and skeletal system, among others. CB_2 receptors have a more limited distribution and are mainly located in the immune system, in both cells and tissues [10, 11]. However, it has been demonstrated that CB_2 receptors are also present in the CNS (but only in glial cells, not in nerve cells), especially under certain circumstances, such as in inflammation [12, 13]. It has to be taken into account that some effects of cannabinoids, including endocannabinoids, are mediated by non-cannabinoid receptors such as other G-protein-coupled receptors GPR55 and GPR19, transient receptor potential vanilloid channels and peroxisome proliferator-activated receptors [14]. In fact, the GPR55 receptor has been postulated to be part of the endocannabinoid system (ECS).

With respect to endocannabinoids, the most relevant compounds are *N*-arachidonoylethanolamine, commonly known as anandamide (AEA), and 2-arachydonoilglycerol (2-AG). Both are synthesised on demand. The mechanisms responsible for their synthesis and degradation are summarised in Fig. 2 [15–20].

Cannabinoid receptors, endocannabinoids and the enzymes responsible for their biosynthesis and degradation constitute the ECS. In recent decades, the ECS has attracted considerable interest as a potential therapeutic target in numerous pathological conditions. Its involvement in several physiological processes is well known, such as in energy balance, appetite stimulation, blood pressure, pain relief, embryogenesis, nausea and vomiting control, memory, learning and immune response, among others [21–24], as well as in pathological conditions where it exerts a protective role in the development of certain disorders. As a result, it has been reported that changes in endocannabinoid levels

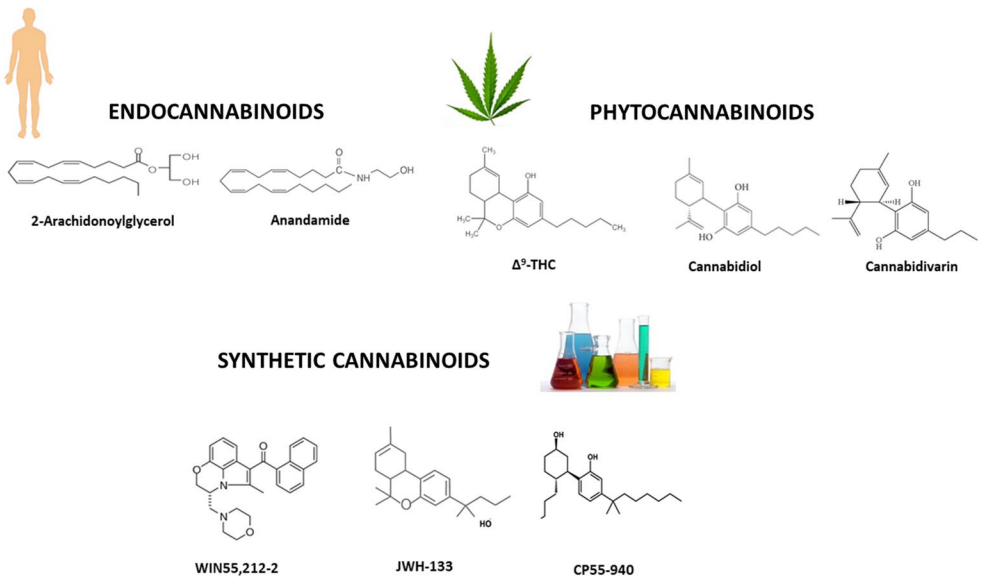

Fig. 1 Chemical structures of the main representative endo-, phyto- and synthetic cannabinoids. *THC* tetrahydrocannabinol

may be related to neurological diseases such as Parkinson's disease (PD), Huntington's disease (HD) or multiple sclerosis (MS), as well as anorexia and irritable bowel syndrome [25–29]. Alterations in the ECS have also been associated with cancer, affecting the growth, migration and invasion of some tumours [30–33] (Fig. 3).

Considering the importance of the ECS and the therapeutic potential of cannabinoids in a vast number of medical conditions, several clinical studies with cannabinoid-based medications are ongoing. Specifically, some cannabinoid-based medications have already been approved for the treatment of nausea and vomiting associated with chemotherapy, anorexia, pain related to cancer, and spasticity and pain associated with MS (shown in Table 1). This work provides a review of the preclinical and clinical data of cannabinoid use in therapeutics, especially of indications with high evidence.

2 Cannabinoids and Neurological Disorders

2.1 Multiple Sclerosis

2.1.1 Preclinical Studies

Some authors have described altered expression of the ECS in MS, which mediates disease progression. For example, a study undertaken post-mortem in the brain of MS donors evidenced that the expression of CB_1 and CB_2 receptors was increased [34]. Interestingly, in plasma samples obtained from patients with MS with different clinical subtypes of the disease (relapsing-remitting, secondary-progressive and primary-progressive), an increase in messenger RNA levels of both CB_1 and CB_2 receptors was only found in patients with primary-progressive MS. However, the levels of several endocannabinoids (AEA, palmitoylethanolamide

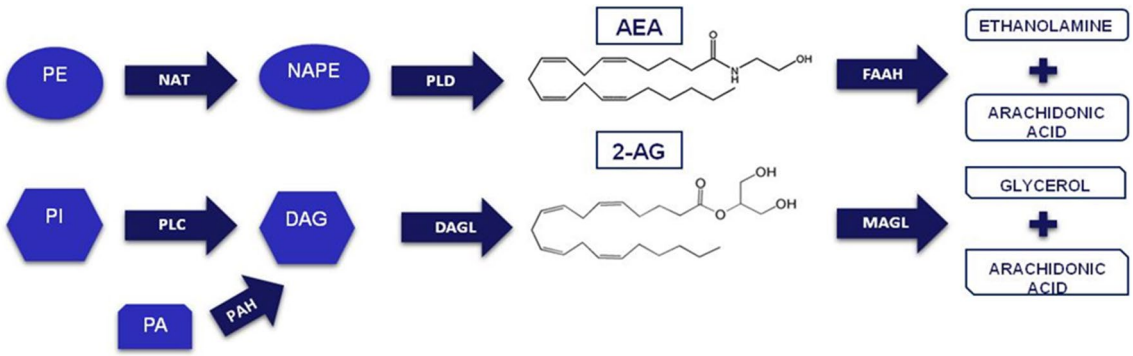

Fig. 2 Scheme showing principal anandamide (AEA) and 2-arachydonoilglycerol (20AG) synthesis and degradation pathways. AEA is obtained from *N*-arachidonoyl phosphatidylethanolamine (NAPE) via NAPE-phospholipase D (PLD). NAPE is synthesised by the translation of an arachidonoyl group to phosphatidylethanolamine (PE) through the action of *N*-acetyltransferase (NAT). 2-AG is mainly obtained through the action of a diacylglycerol lipase (DAGL) from diacylglycerol (DAG), formed from phosphatidylinositol (PI) via phospholipase-C (PLC) or by an alternative route, in which a phosphatidic acid hydrolase (PAH) hydrolyses phosphatidic acid (PA) generating DAG. Finally, the fatty acid amide hydrolase (FAAH) and monoacylglycerol lipase (MAGL) are the principal enzymes responsible for AEA and 2-AG degradation respectively

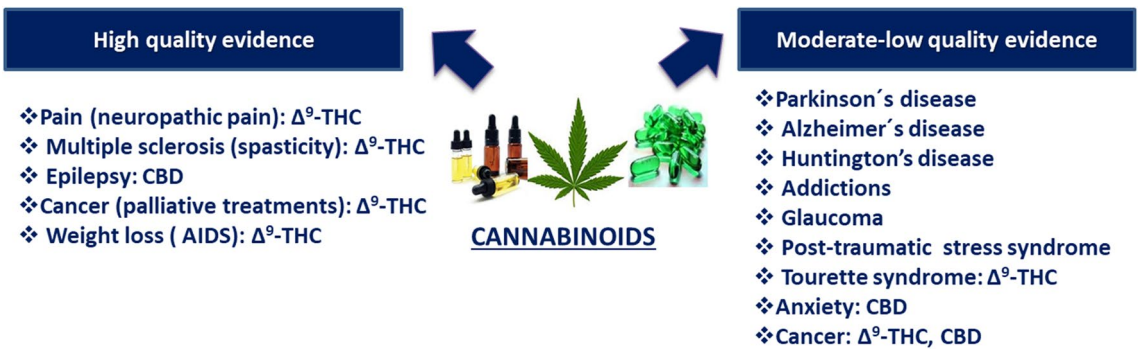

Fig. 3 Potential therapeutic applications of cannabinoids. *AIDS* acquired immunodeficiency disease, *CBD* cannabidiol, *THC* tetrahydrocannabinol

and oleoylethanolamide) were elevated in all MS subtypes. The levels of AEA were especially high in secondary-progressive disease, probably owing to the decline of fatty acid amide hydrolase (FAAH) expression (its major metabolising enzyme) [35]. Similar results were noted in peripheral lymphocytes and the cerebrospinal fluid of patients with MS, with a rise of AEA levels. In relapsing-remitting MS samples, an increase of *N*-arachidonoyl phosphatidylethanolamine (NAPE) activity and a decrease of FAAH action were also detected, although no differences in 2-AG levels were reported [36, 37]. Studies in mouse models of MS also noted elevated AEA in brain and spinal cord samples, being specially marked in the spinal cord (≈200%). Even though no differences in 2-AG levels were found in human samples, it was higher in the spinal cord of mice [38].

Table 1 Formulations based on cannabinoids

Brand name	Cannabinoid component	Administration route	Dosage form	Indications	Countries
Sativex®	Nabiximols (*Cannabis sativa* extracts including mainly Δ^9-THC and CBD at a ratio of 1:1)	Oromucosal	Spray	MS spasticity, symptomatic relief of neuropathic pain in MS[a] Pain in patients with advanced cancer[a]	Canada, Mexico and several European countries, among others[b]
Cesamet®	Nabilone (Δ^9-THC analogue)	Oral	Capsules	Nausea and vomiting induced by chemotherapy[c]	UK, Ireland, USA, Canada
Canemes®	Nabilone (Δ^9-THC analogue)	Oral	Capsules	Nausea and vomiting induced by chemotherapy	Germany, Austria
Marinol®	Dronabinol ((-)-trans-Δ^9-THC)	Oral	Capsules	Anorexia related to weight loss in patients with AIDS Nausea and vomiting induced by chemotherapy[c]	UK, Ireland, USA, Canada
Syndros®	Dronabinol ((-)-trans-Δ^9-THC)	Oral	Solution	Anorexia related to weight loss in patients with AIDS Nausea and vomiting induced by chemotherapy[c]	USA
Epidiolex®	Pure plant-derived CBD	Oral	Solution	Resistant epileptic syndromes[d]	USA
GWP42006 ®	CBDV (plant extracts)	Oral	–	Epilepsy, autism	Not approved
Acomplia ®	Rimonabant (SR141716)	Oral	Tablets	Obesity	Withdrawn[e]
Cannabis extracts (e.g. Tilray)	Δ^9-THC and CBD at different ratios	Oral	Solution and capsules	Various[g]	Canada, South America, Australia, New Zealand and Europe
Dried flowers (Bedrocan®)	Δ^9-THC and CBD at different ratios	Oral	Plant material	Various[g]	Europe

AIDS acquired immune deficiency syndrome, *CBD* cannabidiol, CBDV cannabidivarin, *MS* multiple sclerosis, *THC* tetrahydrocannabinol

[a]Approval indicated in Canada

[b]It is approved in more than 20 countries worldwide and, within Europe, in Austria, the Czech Republic, Denmark, Finland, France, Germany, Ireland, Island, Israel, Luxembourg, the Netherlands, Norway, Italy, Poland, Slovakia, Spain, Switzerland, Sweden and the UK

[c]In patients who did not respond properly to conventional antiemetic treatments

[d]It is approved for the treatment of Dravet syndrome and Lennox–Gastaut syndrome. It is being evaluated for tuberous sclerosis complex

[e]Withdrawn from the global market because of its psychological side effects, including depression and suicidal impulses

[f]In several states in USA, cannabis extracts are approved for post-traumatic stress disorder

[g]Including pain, insomnia, stress, MS and depression

The administration of several cannabinoid receptor agonists (K_i values are listed in Table 2) including Δ^9-THC, WIN 55,212-2, JWH-133 (a more selective CB_2 agonist) and methanandamide (AEA analogue) was shown to lessen tremor and spasticity associated with this pathology in mouse models of MS. This action appeared to involve cannabinoid receptors because the use of specific antagonists of these receptors produced an exacerbation of symptoms that was more marked with CB_1 blockage [39]. Other authors have also identified the CB_1 receptor as primarily responsible for cannabinoid anti-spastic action because the spasticity reduction of CB_2 agonists was absent in CB_1-deficient mice [40]. Finally, the inhibition of endocannabinoid metabolising enzymes has also been studied, and FAAH inhibitors reduced spasticity [41]. This inhibition led to an increase in AEA levels, suggesting a potential role of AEA in MS pathology.

Interestingly, monoacylglycerol lipase (MAGL) inhibitors lowered neuronal excitotoxicity and avoided demyelisation [42], delaying disease progression in these models of MS [43]. Feliú and co-workers have also recently examined the relationship between 2-AG and demyelisation in a progressive model of MS, where the inhibition of MAGL, with the consequent increase of 2-AG, modulated neuroinflammation and diminished the deposit of chondroitin sulphate proteoglycans, which impair axon regeneration and remyelination around demyelinated lesions [44].

Recently, in a mouse model of MS, Elliott and co-workers described that CBD (20 mg/kg intraperitoneally administered) attenuated experimental autoimmune encephalomyelitis with the triggering of different anti-inflammatory pathways, including a decline of proinflammatory cytokines, the induction of anti-inflammatory cytokines and the gain of myeloid-derived suppressor cells [45].

2.1.2 Clinical Studies

Having clearly established the role of the ECS in MS disease and the therapeutic potential of cannabinoids in ameliorating disease progression and in treating motor symptoms and disability, several clinical studies have been conducted in patients with MS to evaluate the efficacy of cannabinoids, and these have produced contradictory results (Tables 3 and 4). Killestein et al. recorded that neither *C. sativa* extracts nor Δ^9-THC (orally administered) were efficient in improving muscle spasticity [46]. However, the dosage of Δ^9-THC used by this group (2.5 or 5 mg) was too low. Ungerleider et al. discovered that dosages of 7.5 mg of Δ^9-THC were necessary to achieve a significant improvement in spasticity [47].

The CAMS study also indicated that oral administration of both cannabis extracts and Δ^9-THC at doses of 2.5–25 mg for 15 weeks resulted in no significant differences compared with the placebo group in the treatment of spasticity when evaluated with the Ashworth Scale. However, a slight improvement of mobility and pain was appreciated in the cannabinoid-treated group [48], as well as a slight improvement in spasticity after 12 months of treatment with Δ^9-THC. This was also indicated, but not objectively confirmed, by the patients treated with cannabis extracts [49]. Arguably, the Ashworth Scale is not the best option to measure spasticity, and the absence of a significant difference could be attributed to this issue.

In another study (MUSEC), patients treated with the same cannabis extracts exhibited a nearly two-fold improvement in muscle stiffness compared with the placebo group [50]. The efficacy of a Δ^9-THC/CBD oromucosal spray (nabiximols [Sativex]®) was also tested, producing a reduction in spasticity not greater than the oral administration of Δ^9-THC or the cannabis extracts mentioned previously [51–53] (Table 1). Moreover, the maintenance of Δ^9-THC/CBD oromucosal spray efficacy in spasticity relief was confirmed by a long-term trial (with a mean of 3.4 years of treatment) [54]. Interestingly, a 19-week follow-up trial revealed that the Δ^9-THC/CBD oromucosal spray as an add-on treatment also significantly reduced MS spasticity compared with placebo. An improvement of spasm frequency, sleep disturbances and global clinical profile in the cannabinoid-treated group was perceived as well [55]. In addition, this preparation has been proven useful as an analgesic for central neuropathic pain associated with MS, lowering pain intensity, and improving sleep disorders after 4 weeks of treatment [56] and this study was extended for up to 2 years as an open-label study, duplicating the same results [57]. However, some adverse effects were evident in a high number of cannabis-treated patients, although most of them were judged to be mild to moderate in severity, including somnolence, dizziness and dry mouth [57].

The efficacy of cannabinoids in the management of urinary incontinence associated with MS has also been considered. On this point, Brady and co-workers reported that the oral-mucosal administration of a Δ^9-THC/CBD spray

Table 2 K_i values of different cannabinoid receptor agonists

Agonists	CB_1 (nM)	CB_2 (nM)
CP 55,940	0.6	0.7
HU-210	0.061	0.52
JWH-015	383	13.8
JWH-133	677	3.4
Methanandamide	28.3	868
Nabilone	1.84	2.19
WIN 55,212-2	62.3	3.3
Δ^9-THC	53.3	75

THC tetrahydrocannabinol

Table 3 Clinical studies undertaken in patients with multiple sclerosis (MS): oral administration of cannabinoids

Cannabinoid-based treatments	Study type	Daily dose/dosage form	Patients/major aspect evaluated	Tolerability/efficacy	References
Two formulations: (1) Cannabis extract (standardized Δ^9-THC content) (2) Dronabinol (Marinol®)	Interventional (placebo controlled)	Δ^9-THC 2.5/5 mg for 4 week/ capsules	Primary ($n=6$) and secondary ($n=10$) progressive MS/ evaluation of muscle spasticity, disability	Cannabinoids were well tolerated with no serious adverse effects (e.g. dry mouth, somnolence, dizziness, headache). Adverse effects were more common in cannabis extract treatment. No significant differences were detected in muscle tone and disability	[46]
Δ^9-THC	Interventional (placebo controlled)	Δ^9-THC 2.5–15 mg	Patients with MS and significant spasticity/spasticity	Δ^9-THC at doses higher than 7.5 mg showed an improvement in spasticity (significant results) compared with placebo. Some adverse effects were detected in Δ^9-THC treated patients, including dry mouth, weakness and dizziness. No intolerable events were found at doses of 7.5 mg of Δ^9-THC	[47]
Two formulations: (1) Cannabis extract (containing Δ^9-THC/CBD at a ratio of 2:1 and minor cannabinoids < 5%) (Cannador) (2) Dronabinol (Marinol®)	Interventional (placebo controlled) [CAMS study]	Δ^9-THC 2.5–25 mg for 15 week/ capsules	Patients with stable MS ($n=630$)/ evaluation of: spasticity, mobility and pain	In the cannabinoid treated group, an improvement in spasticity was not found using AS. However, an objective improvement in mobility and an analgesic perception was detected by cannabinoid-treated patients	[48]
Two formulations: (1) Cannabis extracts (containing Δ^9-THC/CBD at a ratio of 2:1 and minor cannabinoids < 5%) (Cannador) (2) Dronabinol (Marinol®)	Interventional (placebo controlled) [CAMS study 12-mo follow-up)	Δ^9-THC 2.5–25 mg for 12 month/ capsules	Patients with stable MS ($n=630$)/ evaluation of spasticity	No major safety concerns were found An improvement in spasticity was detected in the Δ^9-THC-treated group measured with AS A mild improvement was also found in cannabis extract-treated patients but not objectively confirmed In general, patients perceived both cannabinoid treatments as helpful in disease palliation	[49]

Table 3 (continued)

Cannabinoid-based treatments	Study type	Daily dose/dosage form	Patients/major aspect evaluated	Tolerability/efficacy	References
Cannabis extracts (standardized Δ^9-THC content)	Interventional (placebo controlled) [MUSEC study]	Δ^9-THC 5–25 mg for 12 week/capsules	Patients with stable MS ($n=144$)/evaluation of muscle stiffness, spasticity	More adverse effects were detected in the cannabis extract-treated group (e.g. dizziness, headache, dry mouth). Almost two-fold improved muscle stiffness relief was found in the cannabis extract-treated patients compared with the placebo group	[50]
Two formulations: (1) Δ^9-THC (2) Cannabis extracts Δ^9-THC/CBD at a ratio of 2:1	Interventional (placebo controlled) [CAMS-LUTS]	Δ^9-THC 2.5–25 mg and CBD 1.25–12.5 mg/capsules	Patients with MS from CAMS study. ($n=528$)/evaluation of bladder dysfunction	A significant reduction in incontinence episodes was recorded in both cannabis extract- (38%) and Δ^9-THC-treated patients (33%) compared with the placebo group (18%)	[59]
Two formulations: (1) Cannabis extract (containing Δ^9-THC (2.5 mg) CBD (20–30%) and minor cannabinoids (<5%) (2) Dronabinol (Marinol®)	Interventional (crossover)	Δ^9-THC 2.5–20 mg/capsules	Patients with MS ($n=16$)/evaluation of immunomodulatory effects	In patients receiving cannabis extracts, a slight increase in TNF-α in LPS-stimulated samples was found. However, other cytokine (IL-12p40, IL-12p70 and IL-10) levels remained unchanged. Interestingly, an increase of IL-12p40 was noted in cannabis extract-treated patients, with high adverse effects	[63]
Dronabinol (supplied by *Insys* Therapeutics)	Interventional (placebo controlled)	Δ^9-THC 7–28 mg/capsules	Patients with either a primary progressive or a secondary progressive disease course of MS ($n=498$)/evaluation of disease progression	No major safety concerns were apparent in the dronabinol-treated group. However, these patients exhibited more adverse effects compared with the placebo group. No influence on the progression of this disease was displayed in the progressive phase	[64]

AS Ashworth Score, *CBD* cannabidiol, *CE* cannabis extracts, *IL* interleukin, *LPS* Lipopolysaccharide, *THC* tetrahydrocannabinol, *TNF* tumour necrosis factor

Table 4 Clinical studies undertaken in patients with multiple sclerosis (MS): oromucosal administration of cannabinoids

Cannabinoid-based treatments	Study type	Daily dose/dosage form	Patients/major evaluated aspect	Tolerability/efficacy	References
Nabiximols (Δ^9-THC/CBD at a ratio of 1:1) [Sativex®]	Interventional (placebo controlled)	Δ^9-THC 2.5–120 mg and CBD for 6 week/oromucosal spray	Patients with any type of MS ($n=160$)/evaluation of spasticity	Spasticity, measured with VAS, was significantly reduced in cannabis-treated patients compared with the placebo group	[51]
Nabiximols (Δ^9-THC/CBD at a ratio of 1:1) [Sativex®]	Interventional (placebo controlled)	Oromucosal spray	Patients with stable MS ($n=187$)/evaluation of spasticity	An improvement of spasticity relief was detected in the Sativex®-treated group. ITT analysis showed a significant anti-spastic efficacy in the NRS score. However, using AS, no statistical significant results were found	[52]
Nabiximols (Δ^9-THC/CBD at a ratio of 1:1) [Sativex®]	Interventional (placebo controlled)	Δ^9-THC 2.5–64.8 mg and CBD/oromucosal spray	Patients with any type of disease of at least 6 months duration ($n=337$)/evaluation of spasticity	In the cannabis-treated group, ITT analysis did not demonstrate significant improvement in the NRS score. However, significant improvement in responder analysis (> 30%) was reported	[53]
Nabiximols (Δ^9-THC/CBD at a ratio of 1:1) [Sativex®]	Interventional (placebo controlled)	A mean of 8.64 sprays per day ($\approx$23.32 mg of Δ^9-THC/CBD)/oromucosal spray	MS patients receiving Sativex® for at least 12 week prior to screening (36 patients)/evaluation of spasticity	Treatment failure was lower in the cannabis-treated patients (44%) compared with the placebo group (94%) Significant changes in the Carer and Subject Global Impression of Change scales were also found in favour of cannabinoids	[54]
Nabiximols (Δ^9-THC/CBD at a ratio of 1:1) [Sativex®] as add-on-therapy	Interventional (placebo controlled)	Δ^9-THC 2.5–32.4 mg and CBD/oromucosal spray	Patients with any subtype of MS ($n=572$)/evaluation of spasticity and sleep disorders	ITT analysis reported a greater difference in favour of the cannabinoid-treated group. The Spasm Frequency Score, Sleep Disturbance NRS Patient, Carer and Clinician Global Impression of Change were all significant in this group	[55]
Nabiximols (Δ^9-THC/CBD at a ratio of 1:1) [Sativex®] as add-on-therapy	Interventional (placebo controlled)	Δ^9-THC 2.5–129.6 mg and CBD/oromucosal spray	Patients with MS and central pain states ($n=66$)/evaluation of neuropathic pain and sleep disorders	Cannabinoid treatment was well tolerated, but showing higher episodes of dizziness. An improvement of pain and sleep disorders was noted in the cannabis-treated group	[56]

Table 4 (continued)

Cannabinoid-based treatments	Study type	Daily dose/dosage form	Patients/major evaluated aspect	Tolerability/efficacy	References
Nabiximols (Δ^9-THC/CBD at a ratio of 1:1) [Sativex®]	Interventional (open label)	Δ^9-THC 2.5–129.6 mg and CBD/oromucosal spray	Patients with central neuropathic pain associated with MS/evaluation of neuropathic pain	In 92% of cannabinoid-treated patients, more than one adverse effect related to treatment was detected (e.g. dizziness, nausea and feeling intoxicated) and classified as mild to moderate. A reduction in pain (evaluated using NRS) was found in patients receiving cannabinoids (3.8) compared with the placebo group (5.0)	[57]
Two formulations: (1) Δ^9-THC (2) Cannabis extract Δ^9-THC/CBD at a ratio of 1:1	Interventional (open label, pilot)	Δ^9-THC 2.5–120 mg and CBD (8 week) followed by Δ^9-THC 2.5–120 mg (8 week)/oromucosal spray	Patients with advanced MS and lower urinary tract symptoms ($n=21$)/evaluation of bladder dysfunction	An improvement of urinary incontinence was appreciated in the cannabinoid-treated group, with a reduction in urinary urgency, the number and volume of incontinence episodes, frequency and nocturia Patients also noticed an improvement in pain, spasticity and sleep disorders	[58]
Nabiximols (Δ^9-THC/CBD at a ratio of 1:1) [Sativex®]	Interventional (placebo controlled)	Δ^9-THC 2.5–129.6 mg and CBD/oromucosal spray	Patients with MS and overactive bladder/evaluation of bladder dysfunction	Patients receiving cannabinoids displayed a slight reduction in the number of incontinence episodes compared with the placebo group. However, the incidence of nocturia, overall bladder condition and number of voids/day was significantly improved in favour of cannabis. An improvement of urinary incontinence and quality of life was also perceived in this group	[60]

CBD cannabidiol, *ITT* intention to treat, *NRS* Numeric Rating Scale, *THC* tetrahydrocannabinol, *VAS* Visual Analogue Scale

for 8 weeks and Δ^9-THC for a further 8 weeks resulted in an improvement of bladder incontinence, decreasing the volume and number of episodes and nocturia, among others [58]. Similar effects were found in a sub-study of the CAMS trial, where the administration of cannabis extracts (Δ^9-THC and CBD at a 2:1 ratio) also reduced incontinence episodes [59]. Finally, Kavia et al. also noted that the administration of a Δ^9-THC/CBD oromucosal spray for 10 weeks improved bladder dysfunction without statistical significance [60].

Although several studies undertaken in murine models of MS have reported that cannabinoids (including WIN 55,212-2 and JWH-015) produced an anti-inflammatory effect (with the moderation of interferon-γ production and the inhibition of proinflammatory cytokine expression) [61, 62], a small clinical study with patients receiving oral cannabis extracts (with standardised levels of Δ^9-THC, CBD and minor cannabinoids) demonstrated significant proinflammatory activity that was not observed in patients treated with dronabinol. This effect could be attributed to non-Δ^9-THC cannabinoids, but this may be unreliable and further studies are necessary [63]. Finally, a more recent study has evaluated the effect of Δ^9-THC in disease advancement in patients in the progressive phase of MS, and it was judged ineffective [64].

Even though some clinical trials have not achieved significant improvement in the symptoms associated with MS, including spasticity, muscle stiffness, disability and pain, most studies mention a subjective amelioration perceived by the cannabinoid-treated patients compared with the control group. The differences in results could be attributed to the different doses employed, the different design of each study and to a placebo response. Adverse effects, in general, were classified as mild to moderate (e.g. dizziness, somnolence, headache and dry mouth).

In conclusion, the Δ^9-THC/CBD oromucosal spray might be a beneficial tool in the treatment of MS, especially for spasticity relief, with no severe adverse effects. In fact, this medication is already approved in some countries for the treatment of spasticity and neuropathic pain related to MS (Table 1).

2.2 Epilepsy

2.2.1 Preclinical Studies

The role of the ECS in endogenous protection against excitotoxicity has been observed, signalling it as a potential target for the treatment of neurodegenerative disorders that have excitotoxic events as their main characteristic. In this context, Marsicano and co-workers have reported that CB_1 receptors in mice models participate in protecting against kainic acid-induced excitotoxicity, with CB_1-negative mice having many more severe seizures than CB_1-positive mice. They have also pointed to an increase in AEA levels in the hippocampus, while 2-AG levels remained unaltered [65], suggesting a possible protective role of AEA. However, other authors have noted significantly higher levels of 2-AG in the hippocampal region in the rat pilocarpine model of epilepsy [66]. The inhibition of FAAH and MAGL enzymes, with the consequent increase of AEA and 2-AG levels, also exerts a protecting role in seizures induced by kainic acid in a rat convulsion model [67, 68]. The involvement of the endocannabinoid system in anticonvulsant effects has also been recently described. Shirzadian et al. showed that the blockage of CB_1 receptors (using AM251) in mice models that employed pentylenetetrazole to induce seizures avoided the anticonvulsant action of acute foot-shock stress at doses of 1 pg/kg to 100 µg/kg, which also suggested a CB_1 connection [69].

Wallace et al. also showed that Δ^9-THC administration considerably decreased the seizures induced by kainic acid in the rat model and that this also involved CB_1 receptors [66]. Cannabidivarin (CBDV), another phytocannabinoid, has also been proven to lessen seizures in a broad range of rodent models, such as maximal electroshock and audiogenic seizures in mice and pentylenetetrazole-induced seizures in rats, without affecting normal motor function. This cannabinoid also significantly attenuated seizures in the pilocarpine-induced seizure model in combination with valproate [70, 71]. Amada and co-workers demonstrated a reduction in seizure severity in the pentylenetetrazole-induced seizure model, suppressing the expression of several genes (Fos, Egr1, Arc, Ccl4 and Bdnf) related to seizure induction in the CBDV responder group [71]. Unlike Δ^9-THC, the anticonvulsant action of CBDV seemed to be mediated by non-cannabinoid receptors, specifically by transient receptor potential vanilloid-1 channels [72, 73].

2.2.2 Clinical Studies

Considering the potential participation of the ECS in seizure management and the ability of some cannabinoids to control this, several studies have been performed with patients (Table 5). Several non-interventional studies have reported that smoking marijuana may have a beneficial action on controlling seizures in conjunction with antiepileptic drugs [74–76]. However, another non-interventional study produced contrary results, namely that cannabis use did not affect seizures in patients with epilepsy [77].

The effect of oral cannabis extracts has also been evaluated in several cases of child epilepsy. In this respect, Porter and Jacobson found that the oral administration of CBD-enriched cannabis extracts as add-on therapy lowered seizure frequency in 84% of patients, achieving a seizure reduction higher than 80% in 42% of responding patients. An improvement of behaviour, sleep and alertness were also detected

[78]. Other authors have supported these findings [79]. The administration of cannabis extracts containing CBD and Δ^9-THC at a ratio of 20:1 also exhibited anticonvulsant efficacy of around 89% and an improvement in sleep, mood and motor skills [80].

Press et al. evidenced that cannabis extracts were very effective in treating Lennox–Gastaut Syndrome, decreasing seizure frequency in 88.9% of patients, although some adverse effects (including seizure worsening) were evident in some cases, which limited cannabis therapeutic use [81]. Another study also highlighted great benefit in Dravet syndrome [82]. Maa and Figi provided an account of a girl with Dravet syndrome, where treatment with oral cannabis extracts containing Δ^9-THC and CBD markedly altered her nocturnal seizure frequency from 50 per day to two to three per month [83]. The administration of CBD oral solution (Epidiolex®) has also proven to ameliorate the frequency and duration of seizures in six of seven patients with febrile infection-related epilepsy syndrome [84].

A study in children and young adults with Dravet syndrome also described that the administration of CBD oral solution as an adjuvant with standard antiepileptic drugs produced an improvement in seizure frequency greater than 50% in 43% of patients [85]. In a study undertaken with more than 200 patients, the same authors also documented the anticonvulsant efficacy of CBD, with a median decline in motor seizures of 36.5%. Although, in general, CBD had an adequate safety profile, some adverse effects were detected, limiting its therapeutic use. Most of them were mild to moderate in severity (e.g. somnolence, loss of appetite and diarrhoea) but some patients showed severe side effects such as status epilepticus [86].

Recently, a study involving the use of cannabis to treat epilepsy in children reported more severe seizures in those using cannabis compared with non-users. However, high variability was evident in cannabis preparations, most of them with a high content of Δ^9-THC and low levels of CBD. This could explain the inefficacy of these extracts. Therefore, CBD is probably the most promising cannabinoid for treating seizures [87]. In particular, Dravet and Lennox–Gastaut syndromes appeared to exhibit high response rates. In fact, an oral solution based on pure plant-derived CBD (Epidiolex®) (NCT02397863) has been recently approved in USA for the treatment of both epileptic syndromes in patients 2 years of age and older. It is also being evaluated in tuberous sclerosis complex (NCT02544763) [88, 89] and as a promising pharmacotherapy in adults for disorders related to cannabis use (NCT03102918).

Another CBD oral solution is under study for epilepsy (NCT03355300, NCT03336242). Finally, a compound based on CBDV is under clinical study (NCT02365610) to evaluate its potential antiepileptic activity as add-on therapy in patients with inadequately controlled focal seizures.

In conclusion, CBD has displayed clear effectiveness as an anticonvulsant drug, especially for children with epileptic syndromes. The absence of Δ^9-THC psychoactive activity and its good safety profile make CBD a good therapeutic option in these disorders. In fact, an oral solution containing CBD has been recently approved for these purposes (Table 1).

2.3 Parkinson's Disease

2.3.1 Preclinical Studies

As a result of the high expression of the ECS in the basal ganglia, its role in movement control has been examined and its activation identified as being related to motor inhibition [90, 91]. Regarding ECS expression in PD, an analysis performed in post-mortem brain samples from patients with this disorder described lowered expression of CB_1 receptors in some areas of the basal ganglia (caudate nucleus, anterior dorsal putamen and external segment of the globus pallidus). However, they remained unaltered in other brain areas (nucleus accumbens, anterior and posterior ventral putamen, and substantia nigra) [92]. Cerebrospinal fluid samples from patients at different stages of PD were also tested and indicated more than a two-fold rise in the levels of AEA. This AEA up-regulation was disease-stage independent [93]. Finally, higher levels of AEA have also been detected in animal models of PD. Gubellini and co-workers noted higher striatal levels of AEA and lower activity of the AEA membrane transporter and FAAH enzyme in several rat models. Nevertheless, 2-AG levels remained unchanged [94].

The role of FAAH and MAGL inhibitors has also been investigated. On the one hand, the inhibition of MAGL prevented induced motor impairment in the chronic methyl-4-phenyl-1,2,3,6-tetrahydropyridine mouse model and increased the number and the density of dopaminergic neurons, suggesting the neuroprotective role of 2-AG [95]. On the other hand, FAAH inhibition also prevented motor deficits in both chronic methyl-4-phenyl-1,2,3,6-tetrahydropyridine and haloperidol-induced catalepsy mouse models. However, with respect to its neuroprotective effect, opposing results have been presented. While Celorrio et al. stated that the FAAH inhibitor URB597 did not reduce dopamine cell death, Viveros-Paredes and co-workers reported that it gave rise to a protecting effect because it inhibited dopaminergic neuronal death [96, 97].

The blockage of CB_1 also produced antiparkinsonian activity in rat models of PD. In this respect, El-Banoua and co-workers demonstrated that the administration of a CB_1 antagonist (SR141716A, also known as rimonabant) into the striatum, globus pallidus and subthalamic nucleus reduced motor asymmetry in parkinsonian rats (using a unilateral 6-hydroxydopamine-induced nigra lesion model). While

Table 5 Studies undertaken in patients with epileptic syndromes

Cannabinoid-based treatments	Study type	Administration route/dosage form	Daily dose/duration	Type of epilepsy	Tolerability/efficacy	References
CBD-enriched cannabis extracts	Report of parental surveys	Oral	–	Children with treatment-resistant epilepsy [Dravet syndrome, Doose syndrome, Lennox–Gastaut syndrome and idiophatic epilepsy][1] ($n=19$)	A reduction in seizure frequency was reported in 84% of the cannabis-treated patients. Of these, 11% experienced complete seizure freedom An improvement of mood and sleep disorders was also described	[78]
CBD-enriched cannabis extracts	Interventional (placebo controlled)	Oral	4.3 mg of CBD/kg (median dose)/6.8 months (median duration)	Patients with infantile epilepsies [Lennox–Gastaut syndrome and infantile spasms] ($n=117$)	A reduction in seizure frequency and complete seizure freedom were described in 54% and 14% of the patients, respectively. An improvement in mood and sleep disorders was also observed No side effects were evident, except an increase in appetite	[79]
CBD-enriched cannabis extracts (CBD/Δ^9-THC at a ratio of 20:1) [supplied by licensed growers: Better and Tikun Olam, Tel-Aviv, Israel]	Retrospective	Oral	1–20 mg of CBD/kg/at least 3 months (median duration of 6 months)	Children and adolescents with intractable epilepsy resistant to > 7 anti-epileptic drugs ($n=74$)	89% of patients exhibited a decrease of seizure frequency. Of these, 13 patients (18%) reported a reduction above 75% and 25 patients (34%) reported a 50–75% reduction An improvement in motor skills, alertness, mood and sleep disorders was also detected Some adverse effects (e.g. somnolence, fatigue, gastrointestinal disturbances and irritability) were present, which led to the withdrawal of 5 patients	[80]
Cannabis extracts: (1) Only CBD (2) CBD + other phytocannabinoids (3) Only THCA (4) Other	Retrospective	Oral	–	Children and adolescents with Dravet syndrome or Lennox–Gastaut syndrome ($n=75$)[1]	43 (57%) of patients showed an improvement in seizure frequency. Of these, 23 patients described a reduction above 50%. Only two patients (0.3%) experienced complete seizure freedom. Interestingly, responder rate depended on the epilepsy syndrome: Dravet syndrome 23% and Lennox–Gastaut syndrome 89%. Patients with Doose syndrome did not respond to the treatment An improvement of alertness, sleep disorders, motor and language skills was also evident No statistical differences between cannabis extracts were recorded In 33 patients (44%), adverse effects were present (e.g. seizure worsening, somnolence and gastrointestinal symptoms)	[81]

Table 5 (continued)

Cannabinoid-based treatments	Study type	Administration route/dosage form	Daily dose/duration	Type of epilepsy	Tolerability/efficacy	References
Cannabis extracts	Retrospective	Oral	0.3–57 months	Children and adolescents with Dravet syndrome, Doose syndrome or Lennox–Gastaut syndrome ($n=117$)	24% of the patients reported a > 50% seizure reduction. However, response rate depended on the epilepsy syndrome, and patients with Lennox–Gastaut syndrome were the only group that demonstrated statistically significant values Adverse effects related to cannabis treatments were noted in 19% of the patients	[82]
Cannabidiol (Epidiolex®)	Interventional (open-label case series)	Oral/solution	Maximum dose of 20 mg of CBD/kg	Children with febrile infection-related epilepsy syndrome resistant to antiepileptic drugs ($n=7$)	An improvement of seizure frequency and duration was described in 6 patients (85%)	[84]
Cannabidiol (Epidiolex®) as add-on therapy	Interventional (placebo controlled)	Oral/solution	20 mg of CBD/kg/14 weeks	Children and young adults with Dravet syndrome ($n=120$)	The frequency of seizures decreased in the cannabidiol-treated patients compared with the placebo group. 43% of the patients showed a > 50% reduction A higher rate of adverse effects (e.g. somnolence, fatigue and gastrointestinal symptoms) was recorded in cannabidiol-treated patients	[85]
Cannabidiol (Epidiolex®)	Interventional (open label)	Oral/solution	2–5 mg of CBD/kg with a maximum dose of 25 mg of CBD/kg 12 weeks	Patients with conventional drug-resistant epilepsy including Dravet syndrome and Lennox–Gastaut syndrome ($n=214$)	A reduction in the monthly seizure frequency occurred in the cannabidiol-treated group, with a median value of 36.5%. 79% of the patients experienced adverse effects associated with cannabidiol (e.g. somnolence, loss of appetite, gastrointestinal symptoms, fatigue, convulsions and status epilepticus), and 3% discontinued the treatment	[86]

CBD cannabidiol, *THCA* Tetrahydrocannabinolic acid

at the dorsal striatum level, the effect was associated with the modulation of dopaminergic receptor function, with an increase of D_1 receptor function and a decrease of D_2 receptor function, at the pallidus and subthalamic nucleus that relationship was not appreciated [98]. However, González et al. stated that it was not related to dopaminergic, GABAergic, or glutamatergic transmission changes at the striatal level [99]. Interestingly, Kelsey et al. showed that SR141716A also enhanced the effect of moderate doses of L-DOPA, proposing its use as add-on therapy [100]. The potential antiparkinsonian activity of Δ^9-THCV has also been evaluated in a 6-hydroxydopamine-induced nigra lesion model, ameliorating parkinsonism and delaying disease progression (with preservation of tyrosine hydroxylase-positive neurons), with the involvement of CB_2 receptors [101].

Despite its potential in rodents, SR141716A did not exhibit antiparkinsonian activity in primates (probably a more suitable model for predicting its therapeutic utility) [102]. A study in patients with PD also recorded the failure of this compound to improve parkinsonian motor disability [103].

2.3.2 Clinical Studies

Cannabis extracts orally administered for 4 weeks achieved neither an objective nor subjective improvement in dyskinesia and parkinsonism. However, an improvement in Mini-Mental State Examination results implied a possible rapid pro-cognitive action of cannabis [104]. In contrast, CBD, after daily oral administration (controlled study) at doses of 75 or 300 mg/day, has ameliorated motor symptoms and the quality of life in patients with PD with no psychiatric co-morbidities [105]. As add-on therapy, it has also helped with psychosis, and rapid eye movement sleep behaviour disorders in patients with PD [106, 107]. However, these last two studies were open-label and case reports, respectively, and more controlled research is probably required. In conclusion, CBD can improve the quality of life of patients with PD, although further studies are needed.

2.4 Alzheimer's Disease

The expression of ECS components has been investigated in brain samples of patients with AD. Studies involving brain areas with a high density of Aβ plaques (hippocampus and entorhinal and parahippocampal cortices) have detected an up-regulated expression of FAAH and CB_2 in glial cells associated with senile plaques, with FAAH activity also elevated while CB_1 density remained unchanged in the vicinity of these structures [108]. Nevertheless, Ramirez et al. found that CB_1 expression was lowered in AD brains [109]. Some years later, Solas et al. noted similar results and described higher expression of CB_2 in patients with AD, using cortical brain tissues (Brodmann area 10). This over-expression was correlated with amyloid-β-42 (Aβ-42) levels. Lower levels of CB_1 were also reported [110]. Finally, an experiment in a mouse model of AD also revealed the involvement of CB_2 receptors in the neuropathology of this disorder, indicating that CB_2-deleted mice had higher levels of Aβ-42 and augmented plaque deposition [111].

All the previous studies suggest CB_2 targeting for new therapeutic approaches and, in fact, several cannabinoid receptor agonists have been examined. For example, JWH-015 (a selective CB_2 agonist) in vitro induced the removal of Aβ plaques from human AD tissues, and also from THP-1 macrophages even at a very low concentration (1 nM), achieving a plaque decrease of around 39% [112]. Research with transgenic amyloid precursor-protein mice has also demonstrated that the oral administration of both JWH-015 and WIN 55,212-2 at doses of 0.2 mg/kg/day for 4 months was able to moderate inflammation and cortical Aβ levels, probably owing to an increase in Aβ clearance. JWH-015, but not WIN 55,212-2, also improved cognitive deficit in mice, implying the involvement of CB_2 [113].

Other authors have shown that the intracerebroventricular administration of WIN55,212-2 in rats prevented microglial activation induced by Aβ, cognitive impairment and loss of neuronal markers [109]. Fakhfouri et al.'s study supported these data. In a mouse model of AD, WIN55,212-2 exerted neuroprotective and anti-inflammatory activity opposing the damage induced by Aβ in a mechanism that not only involved CB_1 and CB_2, but also peroxisome proliferator-activated receptor-γ [114].

MDA-7 (a CB_2 selective agonist) intraperitoneally administered for 14 days to rats also promoted Aβ clearance and reverted cognitive deficiency. Interestingly, it decreased up-regulated CB_2 levels, indicating the potential involvement of these receptors in the neuropathology of AD [115].

JWH-133 intraperitoneally administered at doses of 0.2 mg/kg/day for 5 weeks, has also been reported to ameliorate memory impairment in mice in the pre-symptomatic and early symptomatic stages of the disease. This effect was attributed to a decline in inflammation, stress oxidative responses to Aβ and tau hyperphosphorylation around Aβ plaques [116].

In addition to cannabinoid receptor agonists, CBD, which binds to these receptors with low affinity, has been cited as having beneficial effects in AD. In this respect, CBD intraperitoneally administered at doses of 2.5 or 10 mg/kg/day for 7 days reduced neuroinflammation induced by Aβ [117]. Using higher doses (20 mg/kg/day intraperitoneally administered for 3 weeks) also reversed cognitive deficits in AD mouse models [118] and after long-term exposition (20 mg/kg/day orally administered for 8 months) prevented social recognition deficits in AD mouse models [119]. Finally, Aso and co-workers confirmed that the combination of Δ^9-THC

and CBD was more therapeutically beneficial than the compounds administered alone, and that they lowered Aβ-42 levels and changed plaque composition, as well as manifesting anti-inflammatory properties [120].

Considering all these findings, it could be concluded that the ECS, and especially CB_2 receptors, are involved in AD neuropathology and that targeting these receptors may be useful in ameliorating disease symptoms. However, the utility of cannabinoids in this disorder is not yet confirmed and further studies are necessary.

2.5 Huntington's Disease

2.5.1 Preclinical Studies

Numerous studies have described altered ECS expression in the areas involved in HD, suggesting a role in disease progression. Post-mortem studies of the brains of patients with HD have revealed a significant loss of CB_1 (nearly 97.5%) in basal ganglia structures, especially in the globus pallidus [121, 122]. Experiments with rodent models of HD have shown similar results, with lower expression of CB_1 receptors in the lateral striatum, cortex and hippocampus in initial phases of the disease [123–125], which is associated with disease progression [126]. With regard to CB_2 receptors, higher levels have been evidenced in striatal microglia, exerting a preventive role in disease progression as a result of the attenuation of microglial activation [127].

Endocannabinoid levels have also been found to be altered in HD mice models, but providing conflicting results. Bisogno and co-workers reported a decrease of 2-AG (between 30 and 60%), AEA and palmitoylethanolamidein striatum, an increase of AEA (around 50%) and a reduction of 2-AG (close to 28%) in the cortex and similar values in the hippocampus, compared with healthy mice [128]. Dave et al. found much higher levels (around 147%) of 2-AG in the cortex and lower levels (nearly 67%) of AEA in the hippocampus [125]. The expression of the enzymes responsible for endocannabinoid synthesis and degradation has also been shown to be diminished, and lower levels of diacylglycerol lipase and *N*-arachidonoyl phosphatidylethanolamine-phospholipase D have been detected in the striatum [129].

Studies in animal models of HD have indicated that Δ^9-THC augments the neurotoxicity induced by malonate [130], but exerts a neuroprotective effect against neurotoxicity induced by 3-nitropropionic acid, via CB_1. This implies the participation of these receptors in disease pathogenesis [131]. Cannabidiol (in a CB_1-independent manner) and WIN-55-212 also attenuated 3-nitropropionic acid-induced neurotoxicity. The mechanisms responsible for WIN-55-212 activity appeared to be related to endocannabinoid-signalling induction and *N*-methyl-D-aspartate receptor hypofunction [132, 133].

2.5.2 Clinical Studies

Some clinical studies have also been completed, showing that the administration of both oral CBD (10 mg/kg/day for 6 weeks) and a Δ^9-THC/CBD oromucosal spray did not improve the motor, cognitive and functional symptoms of patients with HD [134, 135]. However, in a pilot study, Curtis et al. noted that nabilone enhanced chorea and cognitive problems [136]. These findings indicate that more studies are needed to establish the potential use of cannabinoids in HD.

3 Cannabinoids as Antiemetic Agents

The clinical efficacy of cannabis in this field was evaluated for the first time in 1975, when Sallan and co-workers observed that the oral administration of Δ^9-THC had antiemetic properties in patients receiving chemotherapy [137]. Since then, the antiemetic efficacy of cannabinoids has been widely reviewed.

3.1 Preclinical Studies

Darmani studied the involvement of CB_1 receptors in emesis in shrew models, demonstrating that the blockage of CB_1, but not CB_2, receptors with specific antagonists, induced emesis. Δ^9-THC and the synthetic cannabinoids CP 55,940 and WIN 55,212-2, selective agonists to CB_1 receptors, intraperitoneally administered reverted this, with CP 55,940 producing the greatest effect [138]. CP 55,940 also suppressed the emesis induced by cisplatin with median effective dose (ED_{50}) values of 0.09 mg/kg [139].

Other authors have published similar results. In shrew models of cisplatin-induced emesis, Δ^9-THC intraperitoneally administered also reduced animal vomiting (ED_{50}: 1.8 mg/kg) and the frequency of vomiting (ED_{50}: 0.36 mg/kg) [140] and these findings have also been observed in ferrets. Δ^9-THC moderated nausea (ED_{50}: 0.1 mg/kg) and vomiting (ED_{50}: 0.05 mg/Hg) via CB_1 receptors, lowering neuronal activation induced by emetic stimuli in some regions of the dorsal vagal complex [141]. Rock et al. evidenced the implication of CB_2 in emesis control with HU-308 (CB_2 selective agonist), which did not completely block but lessened nausea induced by lithium chloride in rats [142]. Finally, CBD was also described as decreasing the emesis induced by lithium chloride or cisplatin in shrews, but only at low doses (2.5–5 mg/kg) in a CB_1-independent manner. At higher doses (40 mg/kg), it exhibited emetic properties [143, 144], but this biphasic effect may be attributed to its interaction with different receptors.

The antiemetic activity of endocannabinoids has also been examined. On the one hand, studies in ferrets have

demonstrated that exogenous administration of AEA and 2-AG reduced emesis induced by morphine-6-glucuronide. While CB_1 receptors mediated AEA effect, the activity of 2-AG appeared to involve both CB_1 and CB_2 receptors [12]. However, Sticht et al. found that exogenous 2-AG decreased the vomiting induced by lithium chloride in a mechanism independent of CB_1 and Sharkey and co-workers reported that the antiemetic efficacy of AEA also involved non-cannabinoid receptors. TPRV1 involvement was suggested [145, 146]. On the other hand, the increase of endogenous endocannabinoid levels also proved to be useful, as the inhibition of endocannabinoid re-uptake transport and degradative enzymes (FAAH and MAGL) exerted antiemetic properties [12, 147, 148].

3.2 Clinical Studies

Nabilone (1 mg) has been shown to control nausea and vomiting in patients receiving chemotherapy and to be more efficient than prochlorperazine or domperidone (20 mg) orally administered before and during chemotherapy [149]. Meiri et al. observed that dronabinol (2.5 mg orally administered) showed similar efficacy to that of ondansetron (16 mg intravenously administered) to palliate nausea and vomiting caused by anticancer treatments, and that the combination of both drugs did not result in an efficacious increase [150]. However, Lane and co-workers indicated that the combination of dronabinol and prochlorperazine (10 mg every 6 h) was more efficient than either of the single drugs in diminishing these side effects, and moderated the severity and duration of the episodes. Some adverse reactions were detected in the dronabinol-treated group, although the combination with prochlorperazine lessened their frequency, suggesting that they could become a good combination therapy to treat these negative reactions to chemotherapy [151] (Table 6).

Some studies have also been performed with paediatric oncology patients (Table 7). Abrahamov et al. reported that Δ^8-THC, a plant cannabinoid with lower psychoactive activity than Δ^9-THC, orally administered (18 mg/m^2) 2 h before chemotherapy and continued every 6 h for 24 h, prevented vomiting in children (eight patients aged 3–13 years) with several blood cancers (acute lymphoblastic leukaemia, Hodgkin's lymphoma and Burkitt's lymphoma). No major adverse effects were observed, and only two children exhibited irritability and increased euphoria, reactions that are difficult to evaluate in paediatrics [152].

Dronabinol (orally administered at doses mainly of 2.5 mg/m^2 every 6 h as needed and always lower than 5 mg/m^2) also proved useful as an antiemetic agent in children (aged ≤ 18 years) with several cancers (mainly leukaemia and sarcoma) who were receiving moderate- and high-risk chemotherapy in 95% of the cases. Although 60% of the patients experienced a good response rate to this cannabinoid (0–1 emesis events), which suggests its potential use in treating chemotherapy-induced nausea and vomiting, the authors have insisted on the need for further studies using patients as their own controls to truly establish the role of dronabinol [153].

A recent study conducted in children (aged ≤ 18 years) with various cancers (including leukaemia, lymphomas, brain carcinomas and other solid tumours) demonstrated the poor effect of nabilone (orally administered) in combination with several antiemetic regimens in treating chemotherapy-induced vomiting. Notwithstanding, these differences in the efficacy of cannabinoids could be attributed to chemotherapy programmes. The common adverse effects of cannabinoids (relaxation, dizziness and euphoria) were also noted in patients receiving nabilone [154].

Finally, it is important to mention that the antiemetic efficacy of cannabinoids has also been examined in treating postoperative nausea and vomiting, and judged as ineffective. Kleine-Brueggeney and co-workers reported that the intravenous administration of Δ^9-THC (0.125 mg/kg) after surgery showed low antiemetic efficacy and, to the contrary, patients experienced relevant psychotropic side effects, which is unacceptable in the risk-benefit ratio [155]. Consequently, the use of CB_2-selective compounds would probably have a better side-effect profile.

In conclusion, Δ^9-THC-related compounds show a clear usefulness in the treatment of chemotherapy-induced nausea and vomiting. In fact, nabilone capsules are approved for this purpose in several countries (Table 1). They may also be beneficial in the paediatric oncology population, where no serious adverse effects were detected. However, additional studies are probably required in this respect.

4 Cannabinoids as Analgesics

4.1 Preclinical Studies

The ECS appears to be involved in pain and is expressed in the areas responsible for pain control, and endocannabinoids have in fact been postulated as pain modulators. In this regard, the exogenous administration of endocannabinoids has been shown to decrease painful episodes. For instance, in rodent models with both inflammatory and neuropathic pain, the two major endocannabinoids, AEA and 2-AG, displayed analgesic activity. In the case of AEA, this effect involved CB_1 and/or TPRV-1 receptors [156–158]. The increase of endogenous endocannabinoid levels (via FAAH and MAGL inhibition) also showed an analgesic effect. For example, Lichtman et al. described that the previous administration of FAAH inhibitors (10 mg/kg intravenously) promoted AEA (50 mg/kg intraperitoneally)-induced analgesia

in mouse models with inflammatory pain [159]. Similar results were later reported by Jayamanne et al., who showed that the systemic administration of FAAH inhibitors in rats reduced allodynia and thermal hyperalgesia in an inflammatory model, but not neuropathic pain. The co-administration of CB_1 and CB_2 antagonists lowered these effects, suggesting the role of these receptors in analgesic activity [160].

Some authors have also observed that, in inflammatory pain models, peroxisome proliferator-activated receptor-α blocked the analgesia induced by FAAH inhibitors, suggesting their contribution [161, 162]. Spradley and co-workers evidenced that the peripheral inhibition of MAGL and FAAH enzymes in rats lessened the pain induced by capsaicin. While the effect of MAGL inhibitors was mediated by both CB_1 and CB_2 receptors, the activity of FAAH inhibitors was blocked by CB_1 antagonists [163]. In another rat model of inflammatory pain (formalin-induced damage), similar results were also found by Guindon et al., who demonstrated that MAGL inhibition produced analgesia in CB_1 and CB_2 receptors in a dependent manner [164].

Although Jayamanne and co-workers did not note analgesic activity in neuropathic pain models, opposite results have been published by other authors. For instance, Chang et al. reported that FAAH inhibitors had an analgesic effect in both inflammatory and neuropathic models of pain, in a mechanism that also involved opioid receptors [165]. Similar results were presented by Jhaveri and co-workers in rats [166]. Woodhams and collaborators added that MAGL inhibition also had anti-nociceptive activity at the level of the spinal cord in rats [167]. Finally, Clapper and co-workers described that the rise of AEA levels via FAAH inhibition participated in pain initiation with the involvement of CB_1 receptors [168].

4.2 Clinical Studies

The results obtained in the aforementioned pre-clinical studies suggest that the ECS plays a role in pain modulation, and show the therapeutic potential of cannabinoids as analgesics for the treatment of both inflammatory and neuropathic pain. As a result, clinical research is ongoing in this field (Tables 8, 9, 10).

The oral administration of Δ^9-THC (2.2–10 mg/day) reduced pain in patients with spinal cord injury and MS [169, 170]. Lower doses of nabilone (1 mg/day) also achieved pain relief in patients with chronic upper motor neuron syndrome [171] and in patients with diabetic peripheral neuropathy [172].

The sublingual administration of Δ^9-THC/CBD spray (in a range of doses between 2.5 and 120 mg/day) effected analgesic activity in patients experiencing neuropathic pain of many origins (e.g. spinal cord injury, brachial plexus damage, limb amputation, post-herpetic neuralgia, rheumatoid arthritis and complex regional pain syndrome).

Δ^9-THC- and CBD-enriched extracts also relieved pain. However, some adverse effects were detected in cannabis-treated patients, including nervous system disorders, psychiatric effects and gastrointestinal symptoms, which are typical of cannabinoids. Moreover, in some patients receiving Δ^9-THC-enriched extracts, transient hypotension and intoxication with rapid initial dosing were observed [173–177].

Recently, an observational study in patients using Trokies® lozenges (containing *C. sativa* extracts for buccal delivery of cannabinoids) for 1–12 weeks indicated satisfactory pain relief (self-reported) in 90% of the patients. Some adverse events were observed, including dizziness, dry mouth, throat irritation and unsteadiness, but none were serious [178]. Ajulemic acid (CT-3), a synthetic analogue of a metabolite of Δ^9-THC, orally administered for 7 days (at doses of 40 mg/day for the first 4 days and 80 mg/day for the following 3 days) also lowered pain in patients with neuropathic pain compared with placebo, without major adverse effects (in some patients dry mouth and tiredness were noted) [179].

'Smoked' cannabis has also been shown to improve pain. Cigarettes containing 3.56% of Δ^9-THC were efficient in relieving pain associated with sensory neuropathy in patients with human immunodeficiency virus, with a good safety profile [180], and this has been corroborated by other authors. Ellis and co-workers, using cigarettes with a Δ^9-THC content in the range of 1–8%, also evidenced pain relief in distal sensory predominant polyneuropathy, associated with human immunodeficiency virus [181]. These cannabis formulations also reduced neuropathic pain in patients with spinal cord injury, peripheral neuropathy, complex regional pain syndrome and nerve injury, among others.

Interestingly, cigarettes with a low (3.5%) and high (7%) content of Δ^9-THC exhibited similar efficacy [182]. Lower doses (1.29% of Δ^9-THC) were also efficient, duplicating a similar analgesic effect as the formulation with a 3.5% content [183]. However, in patients with post-traumatic and post-surgical neuropathy, opposite results were found, and cigarettes with a Δ^9-THC content lower than 9.4% did not produce significant pain amelioration [184]. In patients with diabetic peripheral neuropathy, dose-dependent analgesic activity was reported with cigarettes containing 1.4% and 7% of Δ^9-THC [185]. These results suggest that the required dose might depend on pain origin.

It could also be influenced by the inconsistent bioavailability of cannabinoids. Vaporised cannabis extracts containing Δ^9-THC and both Δ^9-THC/CBD (ratio 1:1) have also been tested in cancer pain that did not respond to opioid treatments. While in the Δ^9-THC- and CBD-treated group, significant improvement in pain intensity was measured compared with placebo, in the Δ^9-THC group,

Table 6 Studies undertaken in oncology patients to evaluate the efficacy of cannabinoids in treating chemotherapy-induced nausea and vomiting in comparison with usual anti-emetic drugs

Cannabinoid-based treatments	Study type	Administration route/dosage form and dose of cannabinoids	Anti-emetic drugs	Administration schedule	Tolerability/efficacy	References
Nabilone	Interventional (controlled)	Oral/capsules/1 mg	Domperidone (20 mg PO)	Night before chemotherapy and every 8 h on each chemotherapy day for two consecutive cycles	Nabilone was more efficient in controlling nausea and vomiting induced by chemotherapy. The mean number of vomiting episodes (combination of cycles 1 and 2) was lower in nabilone-treated patients (4.53) compared with the domperidone-treated group (10.81). Nevertheless, no significant differences were detected in nausea and food intake In the cannabinoid-treated group, the incidence of adverse effects (e.g. drowsiness, dizziness and dry mouth) was higher compared with patients treated with domperidone	[149]
Dronabinol (Marinol®) alone and/or in combination	Interventional (placebo controlled)	Oral/capsules/2.5–20 mg	Ondansetron (8–16 mg IV)	Before and up to 5 d after chemotherapy patients received dronabinol and/or ondansetron	Nausea absence was higher in dronabinol- (71%) and ondansetron-treated patients (64%) compared with the placebo group (15%), showing a similar anti-emetic efficacy. The combination of both drugs did not increase their efficacy Both drugs were well tolerated	[150]
Dronabinol alone and/or in combination	Interventional (placebo controlled)	Oral/capsules/10 mg	Prochlorperazine (10 mg PO)	1 d before chemotherapy patients received dronabinol and/or prochlorperazine every 6 h. This treatment continued up to 1 d after chemotherapy	Dronabinol-treated patients experienced a higher number of nausea episodes (60%) compared with those treated with prochlorperazine (47%). However, patients that received both drugs had fewer nausea episodes (29%) Regarding vomiting, its incidence was also lower in combination-treated patients (35%) compared with those receiving dronabinol (41%) and prochlorperazine (55%) Some adverse effects occurred in dronabinol-treated patients and, interestingly, prochlorperazine decreased their frequency Some adverse effects were detected in dronabinol treated patients. Interestingly, prochlorperazine decreased their frequency	[151]

IV intravenously, *PO* orally

non-significant values were obtained. These data imply that CBD could improve the analgesic efficacy of Δ^9-THC [186].

Reports indicate that CBD exerts an inverse agonism in CB_2 receptors and this may be responsible for the analgesic efficacy of CND. Nevertheless, a small study of pain in patients with cancer noted that the sublingual administration of *C. sativa* extracts with a similar content of Δ^9-THC and CBD did not result in significant differences in pain compared with placebo. In the responder group, a two-fold higher decrease was reported in cannabinoid-treated patients, but without significance. A larger study is probably necessary [187].

Interestingly, the analgesic activity of cannabinoids as add-on therapy has also been evaluated. To this end, the administration of vaporised cannabis (cigarettes containing 3.56% of Δ^9-THC) lowered pain (around 27%) in opioid (morphine or oxycodone)-treated patients with several pathologies (arthrosis, peripheral neuropathy, musculoskeletal pain, fibromyalgia, migraine, cancer and MS). Morphine and oxycodone plasma concentrations remained unaltered [188].

Similar results were produced with dronabinol, orally administered (5–60 mg/day), in patients with cancer receiving opioid therapy (morphine, oxycodone, hydrocodone or hydromorphone). This cannabinoid appeared to decrease pain intensity and to improve overall patient satisfaction [189].

These results suggest that cannabinoids could be a good alternative as add-on therapy with opioids and might reduce the required doses of opioids and thus diminish their adverse effects. Finally, nabilone (oral administration of 2 mg/day) was also useful as an analgesic in gabapentin-treated patients with relapsing-remitting MS, reducing pain intensity (using a visual analogue score) [190]. Despite the published findings in animal models, the FAAH inhibitor PF-04457845 (4 mg orally administered) demonstrated a lack of analgesic activity in patients with osteoarthritis of the knee [191], but these effects could be attributed to the differences between species, necessitating further studies.

Finally, regarding the safety profile of cannabinoids, they were well tolerated in general, although most clinical studies in cannabinoid-treated patients have observed some adverse effects, typically related to cannabis consumption (e.g. somnolence, dizziness and gastrointestinal, drowsiness and psychedelic symptoms). The majority were classified as mild to moderate, but some patients experienced limited toxicities.

In conclusion, cannabinoids, especially Δ^9-THC- and Δ^9-THC/CBD-containing formulations, show clear utility in the treatment of neuropathic pain. In this way, nabilone capsules are approved (in Canada) as an analgesic (Table 1). Dronabinol is currently being evaluated as an analgesic in patients with bone metastases from breast cancer (early phase I study; NCT03661892) and as add-on therapy in patients with chronic pain who are taking opioids (NCT00153192).

5 Cannabinoids and Psychiatric Disorders

5.1 Post-Traumatic Stress Disorder

5.1.1 Preclinical Studies

Burstein et al. recently reported in a rat model of post-traumatic stress disorder (PTSD) that cannabinoids (specifically WIN55, 212-2) and FAAH inhibitors (URB597), intraperitoneally administered, prevented alterations (including social recognition memory, passive coping, anhedonia, fear retrieval and anxiety-like behaviour) induced by shock and situational reminders. Both agents also improved depression-like symptoms. These actions involved alterations in brain-derived neurotrophic levels, which are known to be related to these disorders [192] and whose levels were measured as lowered after cannabinoid treatments [193].

These results are in agreement with other studies, reinforcing the possible use of cannabinoids for coping with PTSD symptoms [194, 195]. Δ^9-THC alone or in combination with CBD could also be beneficial because it displayed mitigation of dysfunctional aversive memory in rat models [196].

5.1.2 Clinical Studies

Studies have shown a high prevalence of cannabis use in patients with PTSD, suggesting that cannabinoids could improve PTSD symptoms [197]. Moreover, Hill et al. recently indicated that an endocannabinoid deficiency state may imply more stress susceptibility and predisposition to the development of psychopathology associated with a trauma. This may be the biological explanation of why patients with PTSD use cannabis for coping with fear [198].

Fraser reported that the oral administration of nabilone before bedtime produced a total cessation or an improvement in nightmare severity in 72% of patients (male and female) with PTSD [199]. This was supported by Jetly et al. who emphasised the utility of nabilone in treating nightmares in a double-blind placebo-controlled trial in male military patients with PTSD in which conventional therapy was inefficient [200]. However, in the latest study, the doses necessary to achieve this effect were higher, which could be attributed to a difference in the severity of symptoms (probably higher in military patients) or to the sex of the patients (Table 11).

To recapitulate, cannabis extract could be useful in decreasing and palliating PTSD symptoms. Currently, in

Table 7 Studies undertaken in paediatric oncology patients to evaluate the efficacy of cannabinoids in treating chemotherapy-induced nausea and vomiting

Cannabinoid-based treatments	Study type	Administration route/dosage form and dose of cannabinoids	Anti-emetic drugs	Administration schedule	Tolerability/efficacy	References
Δ^8-THC	Interventional (open label)	Oral route/solution/dose of Δ^8-THC	Metoclopramide (0.3 mg/kg)	2 h before and every 6 h (for 24 h) after chemotherapy cycles	Δ^8-THC reported to block completely the emesis-induced by chemotherapy, being more efficient than metoclopramide. Δ^8-THC demonstrated a good safety profile	[152]
Dronabinol	Observational (retrospective)	Oral route/2.5–5 mg/m^2 of dronabinol	–	Every 6 h as needed	Patients showed, in general, good response rates to dronabinol	[153]
Nabilone in combination with 5-HT$_3$ antagonists	Observational (retrospective)	Oral route	5-HT$_3$ antagonists	Starting the first chemotherapy cycle and stopping 24 h after the last cycle	Nausea and vomiting control in nabilone-treated patients were poor. Some adverse effects (mild to moderate in severity) were detected in 34% of children receiving cannabis (e.g. sedation, dizziness and euphoria)	[154]

THC tetrahydrocannabinol

several states in USA, medical cannabis is approved for these purposes, but additional studies are required.

5.2 Tourette Syndrome

The potential use of cannabinoids in Tourette syndrome (TS) was suggested for the first time at the end of the 1980s, when a case report study evidenced that smoking cannabis was efficient in treating tics and behavioural symptoms in male patients with this disorder [201]. Some years later, Hemming and Yellowlees supported this with the account of the cessation for more than 1 year of symptoms in a woman with TS who smoked cannabis every night [202]. In general, numerous users of cannabis with TS have noted an improvement in symptoms.

The oral administration of cannabinoids has also proved useful. The oral administration of Δ^9-THC reduced tics in a patient with severe TS [203]. A double-blind placebo-controlled trial reported that a single oral dose of Δ^9-THC (5–10 mg) significantly reduced tics and obsessive-compulsive behaviour [204]. Finally, a case report has shown that the administration of two puffs of the Δ^9-THC/CBD oromucosal spray twice daily reduced the frequency and the severity of motor and vocal tics in a 26-year-old man with resistant TS [205] (Table 11).

The therapeutic use of cannabinoids in this disorder is not yet well confirmed and is under research. In fact, several clinical studies are ongoing with (1) Δ^9-THC/CBD oromucosal spray (NCT03087201), (2) vaporised medical cannabis with different Δ^9-THC and CBD content (NCT03247244) and (3) dronabinol and palmitoylethanolamide (NCT03066193, NCT03651726).

5.3 Anxiety Disorders

Cannabinoids have shown potential benefit in anxiolytic disorders. Cannabidiol (300 mg) has exhibited anxiolytic properties in healthy volunteers submitted to a stressful situation, specifically in the case of a simulated public speech. Cannabidiol only decreased anxiety after speaking, and was evaluated using the Visual Analogue Mood Scale and the State-trait Anxiety Inventory, while diazepam (10 mg)

reduced anxiety before and after the speech [206]. These data were supported by Bergamaschi et al. who showed that pre-treatment with CBD (at doses of 600 mg) significantly decreased anxiety, discomfort and cognitive impairment during a speech [207]. This cannabinoid was also efficient in patients with social anxiety disorder, where a significant decline in anxiety was detected [208].

However, in a controlled study performed with volunteers, Δ^9-THC (10 mg orally administered) augmented anxiety compared with placebo. Some adverse events, including sedation and psychotropic symptoms, were reported in the Δ^9-THC-treated group. In the same study, CBD demonstrated anxiolytic activity. The difference between both cannabinoids could be attributed to their effect in different areas of the brain, and the activation of limbic and paralimbic regions by CBD appeared to be responsible for its anxiolytic action [209]. However, the therapeutic potential of CBD as an anxiolytic is not well confirmed and further studies are required, especially in patients with real anxiety disorders and not in volunteers.

6 Cannabinoids as Anti-Tumour Drugs

The aberrant expression of the ECS in cancer indicates that it may be a potential target for anticancer treatments [210]. In fact, numerous cannabinoid compounds have been proven to inhibit the growth of a great number of tumours, both in vitro and in vivo, and cannabinoid receptors mediate part of these effects.

6.1 Brain Cancer

In the 2000s, the work of the Guzman group in gliomas (reviewed in [211]) reported the wide application of cannabinoids as anticancer treatments in these neoplasms. Recent studies have demonstrated that CB_1 receptors are overexpressed in glioblastomas [212] and also in paediatric low-grade gliomas, where higher levels have been related to tumour involution, as a result of apoptosis generation and cell-cycle arrest, induced by the activation of these receptors [213]. CB_2 receptors are also highly expressed in glioblastomas and astrocytomas and related to tumour grade [212, 214–216].

With respect to endocannabinoids, while some authors have observed that AEA levels are lower in gliomas, compared with non-tumour tissue [212, 217], others have detected higher levels of this endocannabinoid in gliomas and also in meningiomas [218]. Regarding 2-AG levels, they were up-regulated in both brain tumours [212, 218].

Finally, cannabinoids have shown anti-tumour activity in brain cancer. Several authors have recorded that AEA inhibited in-vitro proliferation of several glioma cells (U87, U251, C6 and H4) via apoptosis induction [219–221]. It also decreased the migration and invasion of these cells [222, 223]. In addition to AEA, 2-AG and other endocannabinoids reduced the proliferation of C6 glioma cells [224] and these effects were mediated via cannabinoid receptors [225]. Cannabidiol and Δ^9-THC, administered alone or in combination, have also displayed an anti-proliferative effect on several glioma cell lines, inducing apoptosis, with the participation of CB_2 receptors [226, 227].

6.2 Breast Cancer

The expression of the ECS has also been reported as altered in breast cancer, with CB_2 receptors overexpressed. In fact, it has been determined that more than 90% of HER-2 positive tumours have this overexpressed cannabinoid receptor [228] and this is related to a poor prognosis, probably owing to the activation of HER2 pro-oncogenic pathways [229]. Other studies associate the CB_2 receptor overexpression with major recurrence-free survival in patients with both oestrogen-receptor positive and negative mammary tumours.

AEA, 2-AG and other minor endocannabinoids applied in vitro have inhibited the proliferation of breast cancer cells, via CB_1 receptors [230, 231]. Several phytocannabinoids (including Δ^9-THC and CBD) and synthetic cannabinoids (such as WIN-55,212-2 and JWH-133) have also exhibited anti-proliferative activity in a cannabinoid receptor-dependent manner [232, 233].

The ECS plays a role in the anti-migration and anti-invasion influence of some cannabinoids. This occurs because CB_2 receptors mediate the inhibition of the invasive capacity in several breast cancer cells induced by Δ^9-THC, owing to a decrease of the activity of metalloproteinase-2 [228]. However, the anti-invasive properties of the AEA analogue methanandamide involve CB_1 receptors [234]. Last, the additive potential of cannabinoids combined with other anti-tumour drugs (including tamoxifen and cisplatin) has been proposed in the treatment of breast carcinomas [235].

6.3 Prostate Cancer

The expression of both CB_1 and CB_2 receptors is heightened as compared with normal prostatic tissue [236, 237], and the overexpression of CB_1 receptors has been associated with a major Gleason score and metastasis incidence, serving as a negative marker for the outcome in prostate cancer [238, 239]. Sundry studies have evidenced the anti-proliferative activity of cannabinoids in prostate tumours. Anandamide inhibits the proliferation of cells (PC-3, DU-145 and LNCaP) [240, 241] and primary cultures of prostate carcinoma [237] via CB_1 receptors. However, the anti-proliferative activity of CBD and Δ^9-THC does not involve cannabinoid receptors.

Table 8 Studies undertaken in patients to evaluate the potential analgesic activity of cannabinoids: oral administration of cannabinoids

Cannabinoid-based treatments	Study type	Dosage form/dose	Pain origin	Tolerability/efficacy	References
Δ^9-THC	Interventional (placebo controlled)	Capsules/5 mg	Spinal cord injury ($n=1$)	Codeine (50 mg PO) was also used in this study Both Δ^9-THC and codeine reduced pain and improved patient quality. Only Δ^9-THC improved spasticity	[169]
Dronabinol (Marinol®)	Interventional (placebo controlled)	Capsules/2.5–10 mg/d	MS	Dronabinol relieved pain (reaching significant values) compared with placebo. However, some adverse effects were recorded (e.g. dizziness, headache and tiredness), especially during the first week of treatment	[170]
Nabilone (supplied by AOP Orphan)	Interventional (placebo controlled)	Capsules/0.5 mg/d during the first week and 1 mg/d for the next 3 weeks	Chronic UMNS	Nabilone significantly reduced the neuropathic pain related to this disorder. Some adverse effects were noted (e.g. weakness and dizziness), but in general nabilone was well tolerated	[171]
Nabilone (Cesamet®)	Interventional (placebo controlled)	Capsules/1–4 mg/d (flexible dose)	Diabetic peripheral neuropathy ($n=37$)	A flexible dose of nabilone reduced the pain associated with diabetic peripheral neuropathy. Some adverse effects were observed (e.g. confusion), but nabilone was, in general, well tolerated	[172]
Ajulemic acid (CT-3) (supplied by Creapharm)	Interventional (placebo controlled)	Capsules/20 mg/d twice for the first 4 d and 40 mg/d twice for the following 3 d	Traumatic lesions	CT-3 was reported to reduce neuropathic pain compared with placebo. Adverse effects (including dry mouth tiredness, dizziness, sweating and more pain) were significantly higher in CT-3-treated patients compared with the placebo group. However, no major side effects were exhibited	[179]
Dronabinol (synthetic Δ^9-THC) in combination with opioid therapy (morphine, oxycodone, hydrocodone, hydromorphone)	Interventional (placebo controlled)	Capsules/5–60 mg/d	Cancer ($n=30$)	Dronabinol-treated patients observed a reduction in pain intensity and overall satisfaction with opioid therapy. Several adverse effects (related to dose) were present with cannabinoids, most of them classified as mild to moderate. Drowsiness, sleepiness, dizziness and dry mouth were the most frequent	[189]
Nabilone in combination with gabapentin	Interventional (placebo controlled)	Capsules/2 mg/d	MS (in relapsing-remitting phase)	Nabilone decreased pain intensity (measured by VAS) in gabapentin-treated patients. Cannabinoid therapy was in general well tolerated. No severe adverse effects appeared in cannabis-treated patients, dry mouth, dizziness, and drowsiness were the most common	[190]
PF-04457845 (FAAH inhibitor)	Interventional (placebo controlled)	Tablets/4 mg/d	Osteoarthritis of the knee ($n=74$)	No differences between placebo and PF-04457845 were demonstrated, suggesting a lack of analgesic efficacy	[191]

FAAH fatty acid amide hydrolase, *MS* multiple sclerosis, *PO* orally, *THC* tetrahydrocannabinol, *UMNS* upper motor neuron syndrome, *VAS* Visual Analogue Scale

The invasion of prostate cancer cells is also decreased by endocannabinoids. In fact, 2-AG has been postulated as a potential inhibitor of androgen prostate tumour invasion, with the involvement of CB_1 receptors [242]. Noladin ether also exerted an anti-invasive effect in this type of cancer [243]. Finally, the increase of endogenous 2-AG levels via MAGL inhibition also interfered with cancer progression. Nomura and co-workers described that MAGL inhibitors lowered the invasive capacity of prostate carcinomas and that this effect was partially reversed by the blockage of CB_1 receptors [244]. The disruption of MAGL activity also hindered epithelial growth factor-receptor expression, reducing the proliferation induced by epithelial growth factor [245].

6.4 Other Carcinomas

Although brain, breast and prostate are probably the most researched cancers relating to cannabinoids, these compounds have demonstrated anticancer activity in other types of tumours such as in lung carcinomas, where it was reported for the first time in 1975 the ability of several cannabinoids (including Δ^9-THC) to inhibit tumour growth. Cannabidiol, JWH-133 and WIN-55,512-22 also impede the proliferation of lung cancer cells [246].

In hepatocarcinoma, both CB_1 and CB_2 receptors were also found overexpressed compared with healthy liver (3.07- and 5.44-fold respectively) [247] and this overexpression has been associated with better free-survival rates [248]. Anandamide also exerted anti-proliferative activity in these tumours in a cannabinoid-receptor independent manner [249, 250]. However, the cytotoxic effect of Δ^9-THC and the synthetic cannabinoids WIN-55,512-22 and JWH-133 was mediated by CB_2 receptors [251–253]. Finally, both CB_1 and CB_2 agonists have been shown to hinder the invasion of hepatocarcinoma cells, down-regulating the expression of the metalloproteinases MMP-2 and MMP-9 [254].

The aforementioned studies suggest the participation of the ECS in cancer disease and the potential anti-tumour activity of cannabinoids, perhaps as combined therapy with other antitumor drugs. However, the possible use of cannabinoids as chemotherapy is not as clear and depends on cancer type. Among all cannabinoids, Δ^9-THC and CBD appear to be the most promising. The combination of several cannabinoids could also be beneficial, owing to their entourage effect.

Among all cancers, brain and breast carcinomas are where they have the most promising application, and it is true that these are probably the most analysed. In this respect, it is important to highlight that clinical studies have already been undertaken. In fact, a pilot clinical analysis in patients with glioblastoma multiforme noted the ability of Δ^9-THC, intratumourally administered, to reduce tumour growth and at the same time maintain a safe profile [255]. Currently, two clinical trials are being carried out to determine the efficacy and safety of Δ^9-THC/CBD in combination with temozolomide, in these tumours (NCT03529448, NCT01812603) [256]. In addition, another clinical study is now being conducted with CBD (in combination with chemotherapy) in the treatment of glioblastoma, myeloma and gastrointestinal carcinomas (NCT03607643) [257].

7 Cannabinoids and Addiction Treatments

The role of the ECS in addictions has also been examined, and cannabinoids have been postulated as alternative and co-adjuvant treatments in some abuse syndromes, mainly in ethanol and opioid abuses. A relationship between ethanol tolerance and dependence and the ECS was reported for the first time in the 1990s when Basavarajappa and co-workers demonstrated that long-term ethanol consumption decreased the expression of CB_1 receptors in the CNS [258]. Since then, other authors have also published similar results [259, 260] and have indicated that CB_1 blockage might be a good strategy in treating alcoholism [261–263].

Nevertheless, Rubio and co-workers have suggested that the inactivation of these receptors might be detrimental in ethanol withdrawal [264]. Interestingly, Hungund and Basavarajappa showed that CB_1 receptors might also be involved in voluntary ethanol intake [265] as an AEA transporter whose inhibition reduces the self-administration of ethanol [266].

In fact, the genetic deletion of CB_1 and the FAAH enzyme in mice interfered in voluntary ethanol consumption, decreasing and increasing the intake, respectively [267–271]. Ortega-Álvaro et al. also evidenced that CB_2 receptor deletion enhanced the preference and vulnerability for alcohol intake, probably owing to an increase of tyrosine hydroxylase and μ-opioid receptor sensitivity induced by ethanol [272].

Regarding endocannabinoid levels after alcohol intake, conflicting results have been recorded. While, in certain areas of the brain, short-term exposure reduced both AEA and 2-AG levels (associated with a reduction of glutamate release) [273, 274], long-term consumption provoked an increase of endocannabinoid levels [275, 276].

Finally, studies in animal models treated with cannabinoid receptor agonists (WIN 55,212-2 and CP55-940) have described an increase of ethanol intake, probably owing to the enhancement, in part, of CB_1 receptors [277–280]. With regard to CBD, it has shown an ability to prevent ethanol-induced brain injury, as a result of its neuroprotective properties [281, 282], and to reduce ethanol-reinforcing properties in mice.

Some clinical studies to evaluate the effect of cannabinoids in alcoholism treatment have also been performed.

Table 9 Studies undertaken in patients to evaluate the potential analgesic activity of cannabinoids: oromucosal administration of cannabinoids

Cannabinoid-based treatments	Study design	Dosage form/dose	Pain origin	Tolerability/efficacy	References
Nabiximols (Δ^9-THC/CBD at a ratio of 1:1) (Sativex®)	Interventional (placebo controlled)	Sublingual spray/ maximum 120 mg/d	Post-herpetic neuralgia Peripheral neuropathy Focal nerve lesion CRPS type II ($n=125$)	Sativex®-treated patients enjoyed significant pain reduction compared with the placebo group An improvement in pain disability and quality of life was also evident. However, some adverse effects (e.g. somnolence and gastrointestinal symptoms) were associated with Sativex®	[173]
Cannabis sativa extracts of: (1) Δ^9-THC enriched (2) CBD enriched (3) Δ^9-THC: CBD at a ratio of 1:1	Interventional (placebo controlled)	Sublingual spray/2.5–120 mg/d	Multiple sclerosis Spinal cord injury Limb amputation Brachial plexus damage ($n=24$)	All cannabis extracts proved useful in treating neurogenic symptoms (including pain, spasticity and spasm) associated with these pathologies compared with placebo. However, several adverse effects were described. With the Δ^9-THC-enriched extracts, some patients experienced transient hypotension and intoxication with rapid initial dosing	[174]
Nabiximols (Δ^9-THC/CBD at a ratio of 1:1) (Sativex®)	Interventional (controlled)	Sublingual spray/2.5–15 mg/d	Rheumatoid arthritis ($n=75$)	A low and significant analgesic effect was observed in Sativex®-treated patients compared with the placebo group. An improvement in movement and sleep was also reported. Most of the adverse effects with the Sativex® group were classified from mild to moderate (e.g. headache, dizziness, drowsiness and gastrointestinal symptoms)	[175]
Nabiximols (Δ^9-THC/CBD at a ratio of 1:1) [Sativex®]	Interventional (placebo controlled)	Sublingual spray/2.5–60 mg/d	Post-herpetic neuralgia, peripheral neuropathy, focal nerve lesion, radiculopathy CRPS type 2	Sativex® significantly ameliorated pain (30% at responder level) compared with placebo. An improvement of sleep, quality of life and SGIC was also evidenced in cannabinoid-treated patients	[177]
Cannabis extracts containing: (1) Δ^9-THC/CBD at a ratio of 2.7:2.5 mg (2) Δ^9-THC (2.7 mg)	Interventional (placebo controlled)	Maximum dose of $\approx$ 120 mg of Δ^9-THC and CBD	Cancer ($n=177$)	In Δ^9-THC:CBD group, a significant reduction in pain was detected compared with placebo. A > 30% reduction was detected in the 43% and 21% of Δ^9-THC:CBD and placebo-treated patients, respectively, with no significant values Although Δ^9-THC relieved pain compared with placebo, obtained results were no significant Some adverse effects (e.g. somnolence dizziness, confusion and gastrointestinal symptoms) were detected in cannabinoid-treated patients	[189]
Nabiximols (Δ^9-THC/CBD at a ratio of 1:1) [Sativex®]	Interventional (placebo controlled)	Sublingual spray/7.5–30 mg/d	Cancer ($n=16$)	No statistically significant differences between Sativex® and placebo were reported. However, in the patient responder group, a twofold reduction in pain was observed with cannabinoid- formulation-treated patients with some adverse effects (e.g. dry mouth, dizziness, gastrointestinal symptoms and fatigue)	[187]

CBD cannabidiol, *CRPS* complex regional pain syndrome, *SGIC* Subject Global Impression of Change, *THC* tetrahydrocannabinol, *UMNS* upper motor neuron syndrome, *VAS* Visual Analogue Scale

Table 10 Studies undertaken in patients to evaluate the potential analgesic activity of cannabinoids: pulmonary administration of cannabinoids

Cannabinoid-based treatments	Study design	Dose/administration schedule	Pain origin	Tolerability/efficacy	
Cannabis cigarettes (3.56% of Δ^9-THC)	Interventional (placebo controlled)		Sensory neuropathy associated with HIV ($n=24$)	More than a 30% reduction in pain was observed in 52% of cannabis-treated patients and in 24% of placebo-group patients Cannabis treatment was well tolerated and did not show serious adverse effects	[180]
Cannabis cigarettes (1–8% of Δ^9-THC)	Interventional (placebo controlled)	4 times/day for 5 consecutive days every 2 week	Distal sensory predominant polyneuropathy associated with HIV ($n=34$)	Pain reduction was higher in the cannabis-treated patients compared with the placebo group. A > 30% reduction was achieved in 46% and 18% of cannabis- and placebo-treated patients, respectively In patients receiving cannabis, some adverse effects were noted, most of them classified from mild to moderate. However, some patients experienced limiting toxicities	[181]
Cannabis cigarettes with standardised levels of Δ^9-THC: (1) low dose: 3.5% (2) high dose: 7%	Interventional (placebo controlled)	–	CRPS type I Spinal cord injury Peripheral neuropathy Nerve injury ($n=35$)	Both low and high Δ^9-THC content cigarettes showed similar analgesic activity. Minimum psychedelic effects (e.g. "feeling high" and memory disorders) were observed in cannabis-treated patients, especially in the high-dose group	[182]
Cannabis vaporized formulation with standardised levels of Δ^9-THC: (1) low content: 1.29% and (2) medium content: 3.5%	Interventional (placebo controlled)	–	CRPS type I Thalamic pain Spinal cord injury Peripheral neuropathy Radiculopathy Nerve injury	The cannabis formulation demonstrated analgesic efficacy, with no significant differences between formulations with low and medium content of Δ^9-THC Some psychoactive effects were manifested in patients treated with both formulations	[183]
Cannabis pipes with standardised levels of Δ^9-THC: 0%, 2.5%, 6% and 9.4%	Interventional (controlled)	Approximate dose range of Δ^9-THC 2–7 mg/d	Post-traumatic and post-surgical neuropathy ($n=23$)	The formulation containing 9.4% of Δ^9-THC achieved a significant reduction in pain intensity compared with the preparation with 0% of Δ^9-THC. However, the intermediate formulation showed an intermediate and non-significant efficacy Some adverse effects related to cannabis (e.g. headache, dry eyes and sedation) occurred, especially when patients received a 9.4% preparation	[184]
Cannabis formulations with standardised levels of Δ^9-THC: (1) low 1%, (2) medium 4% and (3) high 7%	Interventional (placebo controlled)	Approximately dose range of 4–28 mg	Diabetic peripheral neuropathy	A dose-dependent decrease in pain intensity was detected, attaining significant values compared with placebo	[185]
Cannabis cigarettes containing 3.56% of Δ^9-THC (in combination with morphine or oxycodone)	Interventional (open label)	–	Chronic pain ($n=21$) of various origins: arthrosis, peripheral neuropathy, musculoskeletal pain, fibromyalgia, migraine, cancer and multiple sclerosis	Cannabis cigarettes decreased chronic pain (around 27%) in patients receiving morphine or oxycodone as analgesics. The plasma concentrations of both opioids remained unaltered in the cannabis combination. No serious adverse effects were noted with cannabis treatment. Patients receiving oxycodone felt less anxiety after cannabis treatment	[188]

CRPS complex regional pain syndrome, *HIV* human immunodeficiency virus, *THC* tetrahydrocannabinol

The daily administration of rimonabant (20 mg/day for 2 weeks) was ineffective in reducing ethanol consumption [283–285] probably because of only a partial blockage of CB_1 receptors. Nevertheless, smoking cannabis decreased voluntary alcohol intake faster than in the case of cannabis non-users [286].

As we have mentioned previously, the combination of cannabinoids with opioids could be a good alternative to reduce antinociceptive doses and side effects associated with opioids. Some authors have associated cannabinoids with opioid drug reinforcement.

On the one hand, Solinas and co-workers described how CB_1 receptor agonists (specifically Δ^9-THC and WIN 55,212-2) increased heroin reinforcement, probably because of an interaction of CB_1 and μ-opioid receptors in heroin-seeking rat models [287]. On the other hand, studies in monkeys have reported that the repeated administration of Δ^9-THC not only did not enhance heroin reinforcement, but probably also decreased it [288, 289].

Other authors have also noted the involvement of CB_1 in opioid (morphine and heroin)-seeking properties [290–292]. Cannabidiol and inhibitors of AEA transport and the FAAH enzyme did not exhibit reinforcing properties and reduced morphine and heroin reinforcement, respectively [287, 293]. The dual inhibition of the FAAH and MAGL enzymes also lowered heroin-seeking behaviour [294]. Finally, the regular use of cannabis (mainly due to Δ^9-THC) during adolescence has been related to higher vulnerability to drug relapse [295] and, during opioid addiction treatment, to an increase in withdrawal duration and craving symptoms [296].

8 Cannabinoids and Retinal Diseases

The expression of the ECS in the eye suggests that it could be a potential therapeutic target for eye diseases. The lower intraocular pressure (IOP) of frequent cannabis users has led to the evaluation of cannabinoids as potential anti-glaucoma drugs [297]. In fact, it has been found that the activation of CB_1 receptors by WIN 55,212-2, topically administered, reduced IOP values rapidly [298–300]. Nevertheless, HU-308 (an agonist of CB_2 receptors) did not have the same effect, indicating the involvement of CB_1 receptors, but not CB_2, in the control of IOP [301]. The oral administration of synthetic Δ^9-THC also lowered ocular tension in patients. However, when it is administered topically, IOP decrease was achieved in animal models of glaucoma, but not in human patients [302].

As well as this, cannabinoids have also displayed a neuroprotectant effect in glaucoma, preventing retinal cell death. In animal models, Δ^9-THC has been shown not only to lower IOP, but also to moderate (by approximately 20%) the death of retinal ganglion cells [303]. Cannabidiol and WIN 55,212-2 have also exhibited neuroprotectant activity [304, 305]. Last, the inhibition of FAAH by URB597 also induced retinal ganglion cell neuroprotection, in a mechanism that involves CB_1 receptors [306]. Consequently, some cannabinoids appear to lower IOP values, and could be useful in the treatment of eye pathologies with high IOP, although this is not completely clear, and further studies are required.

9 Side Effects and Cannabis Addiction

Despite the therapeutic potential of cannabinoids in a great number of disorders, as we have already explained, the psychotropic side effects related to cannabis consumption, including euphoria and relaxation initially, and psychosis, hallucinations and depression later (Fig. 4) may limit their clinical use. Although a significantly higher adverse event rate has been detected in cannabis-treated patients compared with placebo groups, most clinical studies do not document serious events, and the side effects have been classified as low to moderate in severity, the most frequent being dizziness, dry mouth, gastrointestinal disorders and tiredness. Interestingly, no major differences have been found in the incidence and type of side effects detected among the users of cannabis vs. isolated cannabinoids and, for the most part, the studies report similar safety profiles [307].

Finally, it is important to emphasise that, owing to its ability to activate the reward system, cannabis consumption is potentially addictive and long-term use produces tolerance and dependence. Nevertheless, cannabis withdrawal symptoms are not as severe as with other recreational drugs such as alcohol or cocaine, and they are characterised by diarrhoea, insomnia, hyperhidrosis, heart rate alterations and irritability, among others [308–311].

10 Cannabinoid and Administration Routes

In most clinical trials, cannabinoids are administered orally (using capsules and oil solution as dosage forms) and, despite the fact that this route is the preferred method, it has some limitations. Cannabinoid bioavailability via this route is low (6–13%) and erratic, as a result of the first stage of metabolism. Moreover, in the liver, Δ^9-THC is transformed into 11-hydroxy-Δ^9-THC, which displays even more psychoactive activity than Δ^9-THC and triggers more undesirable effects. This erratic bioavailability could explain the differences between cannabinoid sensitivity (with respect to adverse effects) and efficacy. Oromucosal administration could be an alternative. By this route, the first stage of metabolism is avoided, and bioavailability is

Table 11 Studies undertaken in patients to evaluate the therapeutic potential of cannabinoids in psychiatric disorders

Cannabinoid-based treatments	Study design	Administration route/dosage form/administration schedule	Disorder	Tolerability/efficacy	References
Nabilone (Cesamet®)	Interventional (open label)	Oral/capsules/0.5 mg 1 h before bedtime	PTSD	72% of cannabinoid-treated patients experienced a total cessation or a reduction in the severity of nightmares	[199]
Nabilone (Cesamet®)	Interventional (placebo controlled)	Oral/capsules/0.5–3.0 mg 1 h before bedtime	PTSD	Nabilone was shown to decrease nightmares compared with placebo with no serious adverse effects in the cannabis-treated group	[200]
Δ^9-THC	Observational (case report)	Oral/start with 5 mg of Δ^9-THC. This dose was increased up to 15 mg	Tourette syndrome	An improvement in tics was detected. This study reported that Δ^9-THC could be useful as add-on therapy, specifically as add-on of methylphenidate	[203]
Δ^9-THC	Interventional (placebo controlled)	Oral/capsules/5, 7.5 or 10 mg/d	Tourette syndrome	A single-dose administration of Δ^9-THC was useful for the treatment of tics and obsessive-compulsive behaviour in Tourette syndrome with a good safety profile	[204]
Nabiximols (Δ^9-THC/CBD at a ratio of 1:1) (Sativex®)	Observational (case report)	Oromucosal/spray/two puffs twice daily (10 mg)	Tourette syndrome	Improvement of the frequency and severity of vocal tics was detected	[205]

CBD cannabidiol, *PTSD* post-traumatic stress disorder, *THC* tetrahydrocannabinol

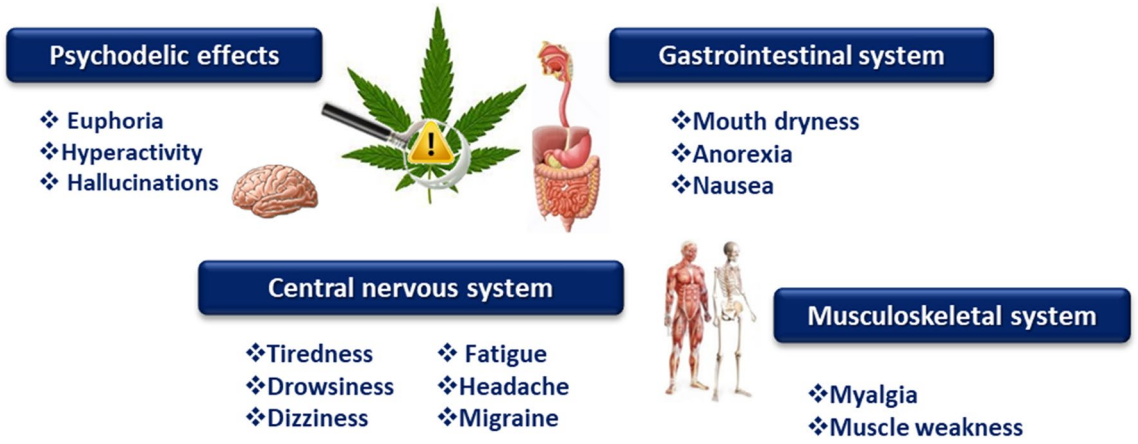

Fig. 4 Adverse effects associated with cannabis consumption

slightly increased (10–25%). In general, in MS, it is the most evaluated route.

In the case of the inhaled route, cannabinoids exhibit greater and highly erratic bioavailability (2–56%), with a rapid onset of action. For instance, it could be useful in pain treatment, and preferable to the oral route. In fact, only clinical trials for the treatment of neuropathic pain evaluate this route, using, in general, cannabis cigarettes as the method of administration. However, vaporised devices would probably be preferable because of the adverse effects associated with smoking.

11 Conclusions

The expression of the ECS has been reported to be altered in several pathologies, and it may become a potential 'new' therapeutic target for the treatment of these disorders. For example, in several neurological conditions, such as MS, PD and HD, an increased expression of CB_2 receptors (barely expressed in healthy CNS) has been detected, indicating that they may participate in disease progression. The expression of CB_1 receptors has been found lowered or up-regulated, depending on pathology origin, but also altered in most cases. In tumours, an aberrant expression of cannabinoid receptors has also been documented and associated with poor disease prognosis in most carcinomas (e.g. breast, prostate and brain tumours). With respect to endocannabinoids, levels of AEA and/or 2-AG have been shown to be augmented, probably owing to a diminished expression and/or the activity of FAAH and MAGL enzymes, suggesting a protective role of endogenous cannabinoids in these disorders. In fact, the increase of endocannabinoid levels by both their exogenous administration and the inhibition of endogenous cannabinoid degradation pathways could be a useful strategy in the treatment of several pathologies, including neurodegenerative diseases, nausea and vomiting, pain and several carcinomas.

The truth is that cannabis has been used in therapeutics since ancient times for numerous disorders, although its psychoactive properties, attributed mainly to Δ^9-THC, have limited its use. Currently, the possibility of preparing standardised formulations with an adequate dose of Δ^9-THC may overcome this limitation. Indeed, the available formulations are, in general, well tolerated and cannabinoids are attracting much more attention in medicine. Currently, some cannabis extract-based preparations, containing Δ^9-THC and CBD at different ratios, are also available and recommended for several disorders (vomiting and pain, among others).

Extensive research has been carried out with cannabinoids in a broad range of conditions (neurodegenerative diseases, cancer, psychiatric illness and neuropathic pain, among others) with promising results. Nevertheless, most of this research, such as in cancer, is still experimental, and clear evidence of cannabinoid therapeutic utility has only been established for specific compounds in specific disorders. For example, Δ^9-THC has demonstrated its usefulness for the treatment of spasticity associated with MS, the nausea and vomiting induced by chemotherapy, and neuropathy. Furthermore, CBD, via different mechanisms of action of Δ^9-THC, has been shown to be useful in epilepsy, especially in child epileptic syndromes (Lennox–Gastaut and Dravet syndromes). In fact, several cannabis-based medicines are approved for these indications.

In conclusion, cannabinoids have displayed a broad range of potential therapeutic benefits and, despite the psychoactive effects of cannabis, the possibility of preparing standardised preparations with adequate doses makes these prospective therapeutic agents. However, not all cannabinoids

are useful for all diseases, and more research is needed in this field.

Compliance with Ethical Standards

Funding No funding was received specifically for the preparation of this review.

Conflict of interest Ana Isabel Fraguas-Sánchez was granted a research fellowship (FPU14/06441) from the Spanish Ministry of Education. Ana Isabel Fraguas-Sánchez and Ana Isabel Torres-Suárez have no conflicts of interest that are directly relevant to the contents of this article.

References

1. Maule WJ. Medical uses of marijuana (*Cannabis sativa*): fact or fallacy? Br J Biomed Sci. 2015;72(2):85–91.
2. Zuardi AW. History of cannabis as a medicine: a review. Rev Bras Psiquiatr. 2006;28(2):153–7. https://doi.org/10.1590/S1516-44462006000200015.
3. Touw M. The religious and medicinal uses of *Cannabis* in China, India and Tibet. J Psychoactive Drugs. 1981;13(1):23–34. https://doi.org/10.1080/02791072.1981.10471447.
4. Kalant H. Medicinal use of cannabis: history and current status. Pain Res Manag. 2001;6(2):80–91.
5. Mikuriya TH. Marijuana in medicine: past, present and future. Calif Med. 1969;110(1):34–40.
6. Pisanti S, Bifulco M. Modern history of medical cannabis: from widespread use to prohibitionism and back. Trends Pharmacol Sci. 2017;38(3):195–8. https://doi.org/10.1016/j.tips.2016.12.002.
7. Mechoulam R. Cannabinoids as therapeutic agents. Boca Raton: CRC Press; 1986.
8. Svizenska I, Dubovy P, Sulcova A. Cannabinoid receptors 1 and 2 (CB1 and CB2), their distribution, ligands and functional involvement in nervous system structures: a short review. Pharmacol Biochem Behav. 2008;90(4):501–11. https://doi.org/10.1016/j.pbb.2008.05.010.
9. Console-Bram L, Marcu J, Abood ME. Cannabinoid receptors: nomenclature and pharmacological principles. Prog Neuropsychopharmacol Biol Psychiatry. 2012;38(1):4–15. https://doi.org/10.1016/j.pnpbp.2012.02.009.
10. Szulakowska A, Milnerowicz H. *Cannabis sativa* in the light of scientific research. Adv Clin Exp Med. 2007;16(6):807–15.
11. Kendall DA, Yudowski GA. Cannabinoid receptors in the central nervous system: their signaling and roles in disease. Front Cell Neurosci. 2016;10:294. https://doi.org/10.3389/fncel.2016.00294.
12. Van Sickle MD, Duncan M, Kingsley PJ, Mouihate A, Urbani P, Mackie K, et al. Identification and functional characterization of brainstem cannabinoid CB2 receptors. Science. 2005;310(5746):329–32. https://doi.org/10.1126/science.1115740.
13. Onaivi ES, Ishiguro H, Gong JP, Patel S, Perchuk A, Meozzi PA, et al. Discovery of the presence and functional expression of cannabinoid CB2 receptors in brain. Ann N Y Acad Sci. 2006;1074:514–36. https://doi.org/10.1196/annals.1369.052.
14. Henstridge CM. Off-target cannabinoid effects mediated by GPR55. Pharmacology. 2012;89(3–4):179–87. https://doi.org/10.1159/000336872.
15. Bisogno T, Howell F, Williams G, Minassi A, Cascio MG, Ligresti A, et al. Cloning of the first sn1-DAG lipases points to the spatial and temporal regulation of endocannabinoid signaling in the brain. J Cell Biol. 2003;163(3):463–8. https://doi.org/10.1083/jcb.200305129.
16. Bisogno T, Melck D, De Petrocellis L, Di Marzo V. Phosphatidic acid as the biosynthetic precursor of the endocannabinoid 2-arachidonoylglycerol in intact mouse neuroblastoma cells stimulated with ionomycin. J Neurochem. 1999;72(5):2113–9.
17. Cravatt BF, Giang DK, Mayfield SP, Boger DL, Lerner RA, Gilula NB. Molecular characterization of an enzyme that degrades neuromodulatory fatty-acid amides. Nature. 1996;384(6604):83–7. https://doi.org/10.1038/384083a0.
18. Dinh TP, Carpenter D, Leslie FM, Freund TF, Katona I, Sensi SL, et al. Brain monoglyceride lipase participating in endocannabinoid inactivation. Proc Natl Acad Sci USA. 2002;99(16):10819–24. https://doi.org/10.1073/pnas.152334899.
19. Fraguas-Sánchez AI, Fernández-Carballido A, Torres-Suárez AI. Phyto-, endo- and synthetic cannabinoids: promising chemotherapeutic agents in the treatment of breast and prostate carcinomas. Expert Opin Investig Drugs. 2016;25(11):1311–23. https://doi.org/10.1080/13543784.2016.1236913.
20. Schurman LD, Lichtman AH. Endocannabinoids: a promising impact for traumatic brain injury. Front Pharmacol. 2017;8:69. https://doi.org/10.3389/fphar.2017.00069.
21. Pagotto U, Marsicano G, Cota D, Lutz B, Pasquali R. The emerging role of the endocannabinoid system in endocrine regulation and energy balance. Endocr Rev. 2006;27(1):73–100. https://doi.org/10.1210/er.2005-0009.
22. Cunha P, Romão AM, Mascarenhas-Melo F, Teixeira HM, Reis F. Endocannabinoid system in cardiovascular disorders: new pharmacotherapeutic opportunities. J Pharm Bioallied Sci. 2011;3(3):350–60. https://doi.org/10.4103/0975-7406.84435.
23. Katchan V, David P, Shoenfeld Y. Cannabinoids and autoimmune diseases: a systematic review. Autoimmun Rev. 2016;15(6):513–28. https://doi.org/10.1016/j.autrev.2016.02.008.
24. Laprairie RB, Bagher AM, Denovan-Wright EM. Cannabinoid receptor ligand bias: implications in the central nervous system. Curr Opin Pharmacol. 2017;32:32–43. https://doi.org/10.1016/j.coph.2016.10.005.
25. Di Marzo V. Targeting the endocannabinoid system: to enhance or reduce? Nat Rev Drug Discov. 2008;7(5):438–55.
26. Pacher P, Mechoulam R. Is lipid signaling through cannabinoid 2 receptors part of a protective system? Prog Lipid Res. 2011;50(2):193–211. https://doi.org/10.1016/j.plipres.2011.01.001.
27. Hasenoehrl C, Taschler U, Storr M, Schicho R. The gastrointestinal tract: a central organ of cannabinoid signaling in health and disease. Neurogastroenterol Motil. 2016;28(12):1765–80. https://doi.org/10.1111/nmo.12931.
28. Ligresti A, De Petrocellis L, Di Marzo V. From phytocannabinoids to cannabinoid receptors and endocannabinoids: pleiotropic physiological and pathological roles through complex pharmacology. Physiol Rev. 2016;96(4):1593–659. https://doi.org/10.1152/physrev.00002.2016.
29. Bridgeman MB, Abazia DT. Medicinal cannabis: history, pharmacology, and implications for the acute care setting. Pharm Ther. 2017;42(3):180–8.
30. Pyszniak M, Tabarkiewicz J, Luszczki JJ. Endocannabinoid system as a regulator of tumor cell malignancy: biological pathways and clinical significance. Onco Targets Ther. 2016;9:4323–36. https://doi.org/10.2147/ott.s106944.
31. Pertwee RG. Targeting the endocannabinoid system with cannabinoid receptor agonists: pharmacological strategies and therapeutic possibilities. Philos Trans R Soc Lond B

Biol Sci. 2012;367(1607):3353–63. https://doi.org/10.1098/rstb.2011.0381.
32. Nikan M, Nabavi SM, Manayi A. Ligands for cannabinoid receptors, promising anticancer agents. Life Sci. 2016;146:124–30. https://doi.org/10.1016/j.lfs.2015.12.053.
33. Tegeder I. Endocannabinoids as guardians of metastasis. Int J Mol Sci. 2016;17(2):230. https://doi.org/10.3390/ijms17020230.
34. Benito C, Romero JP, Tolon RM, Clemente D, Docagne F, Hillard CJ, et al. Cannabinoid CB1 and CB2 receptors and fatty acid amide hydrolase are specific markers of plaque cell subtypes in human multiple sclerosis. J Neurosci. 2007;27(9):2396–402. https://doi.org/10.1523/jneurosci.4814-06.2007.
35. Jean-Gilles L, Feng S, Tench CR, Chapman V, Kendall DA, Barrett DA, et al. Plasma endocannabinoid levels in multiple sclerosis. J Neurol Sci. 2009;287(1–2):212–5. https://doi.org/10.1016/j.jns.2009.07.021.
36. Centonze D, Bari M, Rossi S, Prosperetti C, Furlan R, Fezza F, et al. The endocannabinoid system is dysregulated in multiple sclerosis and in experimental autoimmune encephalomyelitis. Brain. 2007;130(Pt 10):2543–53. https://doi.org/10.1093/brain/awm160.
37. Sanchez Lopez AJ, Roman-Vega L, Ramil Tojeiro E, Giuffrida A, Garcia-Merino A. Regulation of cannabinoid receptor gene expression and endocannabinoid levels in lymphocyte subsets by interferon-beta: a longitudinal study in multiple sclerosis patients. Clin Exp Immunol. 2015;179(1):119–27. https://doi.org/10.1111/cei.12443.
38. Baker D, Pryce G, Croxford JL, Brown P, Pertwee RG, Makriyannis A, et al. Endocannabinoids control spasticity in a multiple sclerosis model. FASEB J. 2001;15(2):300–2. https://doi.org/10.1096/fj.00-0399fje.
39. Baker D, Pryce G, Croxford JL, Brown P, Pertwee RG, Huffman JW, et al. Cannabinoids control spasticity and tremor in a multiple sclerosis model. Nature. 2000;404(6773):84–7. https://doi.org/10.1038/35003583.
40. Pryce G, Baker D. Control of spasticity in a multiple sclerosis model is mediated by CB1, not CB2, cannabinoid receptors. Br J Pharmacol. 2007;150(4):519–25. https://doi.org/10.1038/sj.bjp.0707003.
41. Pryce G, Cabranes A, Fernandez-Ruiz J, Bisogno T, Di Marzo V, Long JZ, et al. Control of experimental spasticity by targeting the degradation of endocannabinoids using selective fatty acid amide hydrolase inhibitors. Mult Scler. 2013;19(14):1896–904. https://doi.org/10.1177/1352458513485982.
42. Bernal-Chico A, Canedo M, Manterola A, Victoria Sanchez-Gomez M, Perez-Samartin A, Rodriguez-Puertas R, et al. Blockade of monoacylglycerol lipase inhibits oligodendrocyte excitotoxicity and prevents demyelination in vivo. Glia. 2015;63(1):163–76. https://doi.org/10.1002/glia.22742.
43. Hernandez-Torres G, Cipriano M, Heden E, Bjorklund E, Canales A, Zian D, et al. A reversible and selective inhibitor of monoacylglycerol lipase ameliorates multiple sclerosis. Angew Chem Int Ed Engl. 2014;53(50):13765–70. https://doi.org/10.1002/anie.201407807.
44. Feliu A, Bonilla Del Rio I, Carrillo-Salinas FJ, Hernandez-Torres G. 2-Arachidonoylglycerol reduces proteoglycans and enhances remyelination in a progressive model of demyelination. J Neurosci. 2017;37(35):8385–98. https://doi.org/10.1523/jneurosci.2900-16.2017.
45. Elliott DM, Singh N, Nagarkatti M, Nagarkatti PS. Cannabidiol attenuates experimental autoimmune encephalomyelitis model of multiple sclerosis through induction of myeloid-derived suppressor cells. Front Immunol. 2018;9:1782. https://doi.org/10.3389/fimmu.2018.01782.
46. Killestein J, Hoogervorst EL, Reif M, Kalkers NF, Van Loenen AC, Staats PG, et al. Safety, tolerability, and efficacy of orally administered cannabinoids in MS. Neurology. 2002;58(9):1404–7.
47. Ungerleider JT, Andyrsiak T, Fairbanks L, Ellison GW, Myers LW. Delta-9-THC in the treatment of spasticity associated with multiple sclerosis. Adv Alcohol Subst Abuse. 1987;7(1):39–50.
48. Zajicek J, Fox P, Sanders H, Wright D, Vickery J, Nunn A, et al. Cannabinoids for treatment of spasticity and other symptoms related to multiple sclerosis (CAMS study): multicentre randomised placebo-controlled trial. Lancet. 2003;362(9395):1517–26. https://doi.org/10.1016/s0140-6736(03)14738-1.
49. Zajicek JP, Sanders HP, Wright DE, Vickery PJ, Ingram WM, Reilly SM, et al. Cannabinoids in multiple sclerosis (CAMS) study: safety and efficacy data for 12 months follow up. J Neurol Neurosurg Psychiatry. 2005;76(12):1664–9. https://doi.org/10.1136/jnnp.2005.070136.
50. Zajicek JP, Hobart JC, Slade A, Barnes D, Mattison PG. Multiple sclerosis and extract of cannabis: results of the MUSEC trial. J Neurol Neurosurg Psychiatry. 2012;83(11):1125–32. https://doi.org/10.1136/jnnp-2012-302468.
51. Wade DT, Makela P, Robson P, House H, Bateman C. Do cannabis-based medicinal extracts have general or specific effects on symptoms in multiple sclerosis? A double-blind, randomized, placebo-controlled study on 160 patients. Mult Scler. 2004;10(4):434–41. https://doi.org/10.1191/1352458504ms1082oa.
52. Collin C, Davies P, Mutiboko IK, Ratcliffe S. Randomized controlled trial of cannabis-based medicine in spasticity caused by multiple sclerosis. Eur J Neurol. 2007;14(3):290–6. https://doi.org/10.1111/j.1468-1331.2006.01639.x.
53. Collin C, Ehler E, Waberzinek G, Alsindi Z, Davies P, Powell K, et al. A double-blind, randomized, placebo-controlled, parallel-group study of Sativex, in subjects with symptoms of spasticity due to multiple sclerosis. Neurol Res. 2010;32(5):451–9. https://doi.org/10.1179/016164109x12590518685660.
54. Notcutt W, Langford R, Davies P, Ratcliffe S, Potts R. A placebo-controlled, parallel-group, randomized withdrawal study of subjects with symptoms of spasticity due to multiple sclerosis who are receiving long-term Sativex® (nabiximols). Mult Scler. 2012;18(2):219–28. https://doi.org/10.1177/1352458511419700.
55. Novotna A, Mares J, Ratcliffe S, Novakova I, Vachova M, Zapletalova O, et al. A randomized, double-blind, placebo-controlled, parallel-group, enriched-design study of nabiximols* (Sativex®), as add-on therapy, in subjects with refractory spasticity caused by multiple sclerosis. Eur J Neurol. 2011;18(9):1122–31. https://doi.org/10.1111/j.1468-1331.2010.03328.x.
56. Rog DJ, Nurmikko TJ, Friede T, Young CA. Randomized, controlled trial of cannabis-based medicine in central pain in multiple sclerosis. Neurology. 2005;65(6):812–9. https://doi.org/10.1212/01.wnl.0000176753.45410.8b.
57. Rog DJ, Nurmikko TJ, Young CA. Oromucosal delta9-tetrahydrocannabinol/cannabidiol for neuropathic pain associated with multiple sclerosis: an uncontrolled, open-label, 2-year extension trial. Clin Ther. 2007;29(9):2068–79. https://doi.org/10.1016/j.clinthera.2007.09.013.
58. Brady CM, DasGupta R, Dalton C, Wiseman OJ, Berkley KJ, Fowler CJ. An open-label pilot study of cannabis-based extracts for bladder dysfunction in advanced multiple sclerosis. Mult Scler. 2004;10(4):425–33. https://doi.org/10.1191/1352458504ms1063oa.
59. Freeman RM, Adekanmi O, Waterfield MR, Waterfield AE, Wright D, Zajicek J. The effect of cannabis on urge incontinence in patients with multiple sclerosis: a multicentre, randomised placebo-controlled trial (CAMS-LUTS). Int Urogynecol J Pelvic Floor Dysfunct. 2006;17(6):636–41. https://doi.org/10.1007/s00192-006-0086-x.

60. Kavia RB, De Ridder D, Constantinescu CS, Stott CG, Fowler CJ. Randomized controlled trial of Sativex to treat detrusor overactivity in multiple sclerosis. Mult Scler. 2010;16(11):1349–59. https://doi.org/10.1177/1352458510378020.
61. Arevalo-Martin A, Vela JM, Molina-Holgado E, Borrell J, Guaza C. Therapeutic action of cannabinoids in a murine model of multiple sclerosis. J Neurosci. 2003;23(7):2511–6.
62. Croxford JL, Miller SD. Immunoregulation of a viral model of multiple sclerosis using the synthetic cannabinoid R + WIN55,212. J Clin Investig. 2003;111(8):1231–40. https://doi.org/10.1172/jci17652.
63. Killestein J, Hoogervorst EL, Reif M, Blauw B, Smits M, Uitdehaag BM, et al. Immunomodulatory effects of orally administered cannabinoids in multiple sclerosis. J Neuroimmunol. 2003;137(1–2):140–3.
64. Zajicek J, Ball S, Wright D, Vickery J, Nunn A, Miller D, et al. Effect of dronabinol on progression in progressive multiple sclerosis (CUPID): a randomised, placebo-controlled trial. Lancet Neurol. 2013;12(9):857–65. https://doi.org/10.1016/s1474-4422(13)70159-5.
65. Marsicano G, Goodenough S, Monory K, Hermann H, Eder M, Cannich A, et al. CB1 cannabinoid receptors and on-demand defense against excitotoxicity. Science. 2003;302(5642):84–8. https://doi.org/10.1126/science.1088208.
66. Wallace MJ, Blair RE, Falenski KW, Martin BR, DeLorenzo RJ. The endogenous cannabinoid system regulates seizure frequency and duration in a model of temporal lobe epilepsy. J Pharmacol Exp Ther. 2003;307(1):129–37. https://doi.org/10.1124/jpet.103.051920.
67. Karanian DA, Karim SL, Wood JT, Williams JS, Lin S, Makriyannis A, et al. Endocannabinoid enhancement protects against kainic acid-induced seizures and associated brain damage. J Pharmacol Exp Ther. 2007;322(3):1059–66. https://doi.org/10.1124/jpet.107.120147.
68. Naidoo V, Karanian DA, Vadivel SK, Locklear JR, Wood JT, Nasr M, et al. Equipotent inhibition of fatty acid amide hydrolase and monoacylglycerol lipase: dual targets of the endocannabinoid system to protect against seizure pathology. Neurotherapeutics. 2012;9(4):801–13. https://doi.org/10.1007/s13311-011-0100-y.
69. Shirzadian A, Ostadhadi S, Hassanipour M, Shafaroodi H, Khoshnoodi M, Haj-Mirzaian A, et al. Acute foot-shock stress decreased seizure susceptibility against pentylenetetrazole-induced seizures in mice: interaction between endogenous opioids and cannabinoids. Epilepsy Behav. 2018;87:25–31. https://doi.org/10.1016/j.yebeh.2018.06.035.
70. Hill AJ, Mercier MS, Hill TD, Glyn SE, Jones NA, Yamasaki Y, et al. Cannabidivarin is anticonvulsant in mouse and rat. Br J Pharmacol. 2012;167(8):1629–42. https://doi.org/10.1111/j.1476-5381.2012.02207.x.
71. Amada N, Yamasaki Y, Williams CM, Whalley BJ. Cannabidivarin (CBDV) suppresses pentylenetetrazole (PTZ)-induced increases in epilepsy-related gene expression. PeerJ. 2013;1:e214. https://doi.org/10.7717/peerj.214.
72. Hill TD, Cascio MG, Romano B, Duncan M, Pertwee RG, Williams CM, et al. Cannabidivarin-rich cannabis extracts are anticonvulsant in mouse and rat via a CB1 receptor-independent mechanism. Br J Pharmacol. 2013;170(3):679–92. https://doi.org/10.1111/bph.12321.
73. Iannotti FA, Hill CL, Leo A, Alhusaini A, Soubrane C, Mazzarella E, et al. Nonpsychotropic plant cannabinoids, cannabidivarin (CBDV) and cannabidiol (CBD), activate and desensitize transient receptor potential vanilloid 1 (TRPV1) channels in vitro: potential for the treatment of neuronal hyperexcitability. ACS Chem Neurosci. 2014;5(11):1131–41. https://doi.org/10.1021/cn5000524.
74. Ellison JM, Gelwan E, Ogletree J. Complex partial seizure symptoms affected by marijuana abuse. J Clin Psychiatry. 1990;51(10):439–40.
75. Mortati K, Dworetzky B, Devinsky O. Marijuana: an effective antiepileptic treatment in partial epilepsy? A case report and review of the literature. Rev Neurol Dis. 2007;4(2):103–6.
76. Gross DW, Hamm J, Ashworth NL, Quigley D. Marijuana use and epilepsy: prevalence in patients of a tertiary care epilepsy center. Neurology. 2004;62(11):2095–7.
77. Hamerle M, Ghaeni L, Kowski A, Weissinger F, Holtkamp M. Cannabis and other illicit drug use in epilepsy patients. Eur J Neurol. 2014;21(1):167–70. https://doi.org/10.1111/ene.12081.
78. Porter BE, Jacobson C. Report of a parent survey of cannabidiol-enriched cannabis use in pediatric treatment-resistant epilepsy. Epilepsy Behav. 2013;29(3):574–7. https://doi.org/10.1016/j.yebeh.2013.08.037.
79. Hussain SA, Zhou R, Jacobson C, Weng J, Cheng E, Lay J, et al. Perceived efficacy of cannabidiol-enriched cannabis extracts for treatment of pediatric epilepsy: a potential role for infantile spasms and Lennox–Gastaut syndrome. Epilepsy Behav. 2015;47:138–41. https://doi.org/10.1016/j.yebeh.2015.04.009.
80. Tzadok M, Uliel-Siboni S, Linder I, Kramer U, Epstein O, Menascu S, et al. CBD-enriched medical cannabis for intractable pediatric epilepsy: the current Israeli experience. Seizure. 2016;35:41–4. https://doi.org/10.1016/j.seizure.2016.01.004.
81. Press CA, Knupp KG, Chapman KE. Parental reporting of response to oral cannabis extracts for treatment of refractory epilepsy. Epilepsy Behav. 2015;45:49–52. https://doi.org/10.1016/j.yebeh.2015.02.043.
82. Treat L, Chapman KE, Colborn KL, Knupp KG. Duration of use of oral cannabis extract in a cohort of pediatric epilepsy patients. Epilepsia. 2017;58(1):123–7. https://doi.org/10.1111/epi.13617.
83. Maa E, Figi P. The case for medical marijuana in epilepsy. Epilepsia. 2014;55(6):783–6. https://doi.org/10.1111/epi.12610.
84. Gofshteyn JS, Wilfong A, Devinsky O, Bluvstein J, Charuta J, Ciliberto MA, et al. Cannabidiol as a potential treatment for febrile infection-related epilepsy syndrome (FIRES) in the acute and chronic phases. J Child Neurol. 2017;32(1):35–40. https://doi.org/10.1177/0883073816669450.
85. Devinsky O, Cross JH, Laux L, Marsh E, Miller I, Nabbout R, et al. Trial of cannabidiol for drug-resistant seizures in the Dravet syndrome. N Engl J Med. 2017;376(21):2011–20. https://doi.org/10.1056/NEJMoa1611618.
86. Devinsky O, Marsh E, Friedman D, Thiele E, Laux L, Sullivan J, et al. Cannabidiol in patients with treatment-resistant epilepsy: an open-label interventional trial. Lancet Neurol. 2016;15(3):270–8. https://doi.org/10.1016/s1474-4422(15)00379-8.
87. Suraev A, Lintzeris N, Stuart J, Kevin RC, Blackburn R, Richards E, et al. Composition and use of cannabis extracts for childhood eilepsy in the Australian community. Sci Rep. 2018;8(1):10154. https://doi.org/10.1038/s41598-018-28127-0.
88. O'Connell BK, Gloss D, Devinsky O. Cannabinoids in treatment-resistant epilepsy: a review. Epilepsy Behav. 2017;70(Pt B):341–8. https://doi.org/10.1016/j.yebeh.2016.11.012.
89. Reddy DS, Golub VM. The pharmacological basis of cannabis therapy for epilepsy. J Pharmacol Exp Ther. 2016;357(1):45–55. https://doi.org/10.1124/jpet.115.230151.
90. Stampanoni Bassi M, Sancesario A, Morace R, Centonze D, Iezzi E. Cannabinoids in Parkinson's disease. Cannabis Cannabinoid Res. 2017;2(1):21–9. https://doi.org/10.1089/can.2017.0002.
91. Basavarajappa BS, Shivakumar M, Joshi V, Subbanna S. Endocannabinoid system in neurodegenerative disorders. J Neurochem. 2017;142(5):624–48. https://doi.org/10.1111/jnc.14098.
92. Hurley MJ, Mash DC, Jenner P. Expression of cannabinoid CB1 receptor mRNA in basal ganglia of normal and parkinsonian

human brain. J Neural Transm (Vienna). 2003;110(11):1279–88. https://doi.org/10.1007/s00702-003-0033-7.
93. Pisani A, Fezza F, Galati S, Battista N, Napolitano S, Finazzi-Agro A, et al. High endogenous cannabinoid levels in the cerebrospinal fluid of untreated Parkinson's disease patients. Ann Neurol. 2005;57(5):777–9. https://doi.org/10.1002/ana.20462.
94. Gubellini P, Picconi B, Bari M, Battista N, Calabresi P, Centonze D, et al. Experimental parkinsonism alters endocannabinoid degradation: implications for striatal glutamatergic transmission. J Neurosci. 2002;22(16):6900–7.
95. Fernandez-Suarez D, Celorrio M, Riezu-Boj JI, Ugarte A, Pacheco R, Gonzalez H, et al. Monoacylglycerol lipase inhibitor JZL184 is neuroprotective and alters glial cell phenotype in the chronic MPTP mouse model. Neurobiol Aging. 2014;35(11):2603–16. https://doi.org/10.1016/j.neurobiolaging.2014.05.021.
96. Celorrio M, Fernandez-Suarez D, Rojo-Bustamante E, Echeverry-Alzate V, Ramirez MJ, Hillard CJ, et al. Fatty acid amide hydrolase inhibition for the symptomatic relief of Parkinson's disease. Brain Behav Immun. 2016;57:94–105. https://doi.org/10.1016/j.bbi.2016.06.010.
97. Viveros-Paredes JM, Gonzalez-Castaneda RE, Escalante-Castaneda A, Tejeda-Martinez AR, Castaneda-Achutigui F, Flores-Soto ME. Effect of inhibition of fatty acid amide hydrolase on MPTP-induced dopaminergic neuronal damage. Neurologia. 2017. https://doi.org/10.1016/j.nrl.2016.11.008 **(Epub ahead of print)**.
98. El-Banoua F, Caraballo I, Flores JA, Galan-Rodriguez B, Fernandez-Espejo E. Effects on turning of microinjections into basal ganglia of D(1) and D(2) dopamine receptors agonists and the cannabinoid CB(1) antagonist SR141716A in a rat Parkinson's model. Neurobiol Dis. 2004;16(2):377–85. https://doi.org/10.1016/j.nbd.2004.03.002.
99. González S, Scorticati C, Garcia-Arencibia M, de Miguel R, Ramos JA, Fernandez-Ruiz J. Effects of rimonabant, a selective cannabinoid CB1 receptor antagonist, in a rat model of Parkinson's disease. Brain Res. 2006;1073–1074:209–19. https://doi.org/10.1016/j.brainres.2005.12.014.
100. Kelsey JE, Harris O, Cassin J. The CB(1) antagonist rimonabant is adjunctively therapeutic as well as monotherapeutic in an animal model of Parkinson's disease. Behav Brain Res. 2009;203(2):304–7. https://doi.org/10.1016/j.bbr.2009.04.035.
101. Garcia C, Palomo-Garo C, Garcia-Arencibia M, Ramos J, Pertwee R, Fernandez-Ruiz J. Symptom-relieving and neuroprotective effects of the phytocannabinoid delta(9)-THCV in animal models of Parkinson's disease. Br J Pharmacol. 2011;163(7):1495–506. https://doi.org/10.1111/j.1476-5381.2011.01278.x.
102. Meschler JP, Howlett AC, Madras BK. Cannabinoid receptor agonist and antagonist effects on motor function in normal and 1-methyl-4-phenyl-1,2,5,6-tetrahydropyridine (MPTP)-treated non-human primates. Psychopharmacology (Berl). 2001;156(1):79–85.
103. Mesnage V, Houeto JL, Bonnet AM, Clavier I, Arnulf I, Cattelin F, et al. Neurokinin B, neurotensin, and cannabinoid receptor antagonists and Parkinson disease. Clin Neuropharmacol. 2004;27(3):108–10.
104. Carroll CB, Bain PG, Teare L, Liu X, Joint C, Wroath C, et al. Cannabis for dyskinesia in Parkinson disease: a randomized double-blind crossover study. Neurology. 2004;63(7):1245–50.
105. Chagas MH, Zuardi AW, Tumas V, Pena-Pereira MA, Sobreira ET, Bergamaschi MM, et al. Effects of cannabidiol in the treatment of patients with Parkinson's disease: an exploratory double-blind trial. J Psychopharmacol. 2014;28(11):1088–98. https://doi.org/10.1177/0269881114550355.
106. Zuardi AW, Crippa JA, Hallak JE, Pinto JP, Chagas MH, Rodrigues GG, et al. Cannabidiol for the treatment of psychosis in Parkinson's disease. J Psychopharmacol. 2009;23(8):979–83. https://doi.org/10.1177/0269881108096519.
107. Chagas MH, Eckeli AL, Zuardi AW, Pena-Pereira MA, Sobreira-Neto MA, Sobreira ET, et al. Cannabidiol can improve complex sleep-related behaviours associated with rapid eye movement sleep behaviour disorder in Parkinson's disease patients: a case series. J Clin Pharm Ther. 2014;39(5):564–6. https://doi.org/10.1111/jcpt.12179.
108. Benito C, Nunez E, Tolon RM, Carrier EJ, Rabano A, Hillard CJ, et al. Cannabinoid CB2 receptors and fatty acid amide hydrolase are selectively overexpressed in neuritic plaque-associated glia in Alzheimer's disease brains. J Neurosci. 2003;23(35):11136–41.
109. Ramirez BG, Blazquez C, Gomez del Pulgar T, Guzman M, de Ceballos ML. Prevention of Alzheimer's disease pathology by cannabinoids: neuroprotection mediated by blockade of microglial activation. J Neurosci. 2005;25(8):1904–13. https://doi.org/10.1523/jneurosci.4540-04.2005.
110. Solas M, Francis PT, Franco R, Ramirez MJ. CB2 receptor and amyloid pathology in frontal cortex of Alzheimer's disease patients. Neurobiol Aging. 2013;34(3):805–8. https://doi.org/10.1016/j.neurobiolaging.2012.06.005.
111. Koppel J, Vingtdeux V, Marambaud P, d'Abramo C, Jimenez H, Stauber M, et al. CB2 receptor deficiency increases amyloid pathology and alters tau processing in a transgenic mouse model of Alzheimer's disease. Mol Med. 2014;20:29–36. https://doi.org/10.2119/molmed.2013.00140.revised.
112. Tolon RM, Nunez E, Pazos MR, Benito C, Castillo AI, Martinez-Orgado JA, et al. The activation of cannabinoid CB2 receptors stimulates in situ and in vitro beta-amyloid removal by human macrophages. Brain Res. 2009;1283:148–54. https://doi.org/10.1016/j.brainres.2009.05.098.
113. Martin-Moreno AM, Brera B, Spuch C, Carro E, Garcia-Garcia L, Delgado M, et al. Prolonged oral cannabinoid administration prevents neuroinflammation, lowers beta-amyloid levels and improves cognitive performance in Tg APP 2576 mice. J Neuroinflamm. 2012;9:8. https://doi.org/10.1186/1742-2094-9-8.
114. Fakhfouri G, Ahmadiani A, Rahimian R, Grolla AA, Moradi F, Haeri A. WIN55212-2 attenuates amyloid-beta-induced neuroinflammation in rats through activation of cannabinoid receptors and PPAR-gamma pathway. Neuropharmacology. 2012;63(4):653–66. https://doi.org/10.1016/j.neuropharm.2012.05.013.
115. Wu J, Bie B, Yang H, Xu JJ, Brown DL, Naguib M. Activation of the CB2 receptor system reverses amyloid-induced memory deficiency. Neurobiol Aging. 2013;34(3):791–804. https://doi.org/10.1016/j.neurobiolaging.2012.06.011.
116. Aso E, Juves S, Maldonado R, Ferrer I. CB2 cannabinoid receptor agonist ameliorates Alzheimer-like phenotype in AbetaPP/PS1 mice. J Alzheimers Dis. 2013;35(4):847–58. https://doi.org/10.3233/jad-130137.
117. Esposito G, Scuderi C, Savani C, Steardo L Jr, De Filippis D, Cottone P, et al. Cannabidiol in vivo blunts beta-amyloid induced neuroinflammation by suppressing IL-1beta and iNOS expression. Br J Pharmacol. 2007;151(8):1272–9. https://doi.org/10.1038/sj.bjp.0707337.
118. Cheng D, Low JK, Logge W, Garner B, Karl T. Chronic cannabidiol treatment improves social and object recognition in double transgenic APPswe/PS1E9 mice. Psychopharmacology (Berl). 2014;231(15):3009–17. https://doi.org/10.1007/s00213-014-3478-5.
119. Cheng D, Spiro AS, Jenner AM, Garner B, Karl T. Long-term cannabidiol treatment prevents the development of social recognition memory deficits in Alzheimer's disease transgenic mice. J Alzheimers Dis. 2014;42(4):1383–96. https://doi.org/10.3233/jad-140921.

120. Aso E, Sanchez-Pla A, Vegas-Lozano E, Maldonado R, Ferrer I. Cannabis-based medicine reduces multiple pathological processes in AbetaPP/PS1 mice. J Alzheimers Dis. 2015;43(3):977–91. https://doi.org/10.3233/jad-141014.
121. Glass M, Faull RL, Dragunow M. Loss of cannabinoid receptors in the substantia nigra in Huntington's disease. Neuroscience. 1993;56(3):523–7.
122. Richfield EK, Herkenham M. Selective vulnerability in Huntington's disease: preferential loss of cannabinoid receptors in lateral globus pallidus. Ann Neurol. 1994;36(4):577–84. https://doi.org/10.1002/ana.410360406.
123. Denovan-Wright EM, Robertson HA. Cannabinoid receptor messenger RNA levels decrease in a subset of neurons of the lateral striatum, cortex and hippocampus of transgenic Huntington's disease mice. Neuroscience. 2000;98(4):705–13.
124. McCaw EA, Hu H, Gomez GT, Hebb AL, Kelly ME, Denovan-Wright EM. Structure, expression and regulation of the cannabinoid receptor gene (CB1) in Huntington's disease transgenic mice. Eur J Biochem. 2004;271(23–24):4909–20. https://doi.org/10.1111/j.1432-1033.2004.04460.x.
125. Dowie MJ, Bradshaw HB, Howard ML, Nicholson LF, Faull RL, Hannan AJ, et al. Altered CB1 receptor and endocannabinoid levels precede motor symptom onset in a transgenic mouse model of Huntington's disease. Neuroscience. 2009;163(1):456–65. https://doi.org/10.1016/j.neuroscience.2009.06.014.
126. Blazquez C, Chiarlone A, Sagredo O, Aguado T, Pazos MR, Resel E, et al. Loss of striatal type 1 cannabinoid receptors is a key pathogenic factor in Huntington's disease. Brain. 2011;134(Pt 1):119–36. https://doi.org/10.1093/brain/awq278.
127. Palazuelos J, Aguado T, Pazos MR, Julien B, Carrasco C, Resel E, et al. Microglial CB2 cannabinoid receptors are neuroprotective in Huntington's disease excitotoxicity. Brain. 2009;132(Pt 11):3152–64. https://doi.org/10.1093/brain/awp239.
128. Bisogno T, Martire A, Petrosino S, Popoli P, Di Marzo V. Symptom-related changes of endocannabinoid and palmitoylethanolamide levels in brain areas of R6/2 mice, a transgenic model of Huntington's disease. Neurochem Int. 2008;52(1–2):307–13. https://doi.org/10.1016/j.neuint.2007.06.031.
129. Bari M, Battista N, Valenza M, Mastrangelo N, Malaponti M, Catanzaro G, et al. In vitro and in vivo models of Huntington's disease show alterations in the endocannabinoid system. FEBS J. 2013;280(14):3376–88. https://doi.org/10.1111/febs.12329.
130. Lastres-Becker I, Bizat N, Boyer F, Hantraye P, Brouillet E, Fernandez-Ruiz J. Effects of cannabinoids in the rat model of Huntington's disease generated by an intrastriatal injection of malonate. Neuroreport. 2003;14(6):813–6. https://doi.org/10.1097/01.wnr.0000067781.69995.1b.
131. Lastres-Becker I, Bizat N, Boyer F, Hantraye P, Fernandez-Ruiz J, Brouillet E. Potential involvement of cannabinoid receptors in 3-nitropropionic acid toxicity in vivo. Neuroreport. 2004;15(15):2375–9.
132. Sagredo O, Ramos JA, Decio A, Mechoulam R, Fernandez-Ruiz J. Cannabidiol reduced the striatal atrophy caused 3-nitropropionic acid in vivo by mechanisms independent of the activation of cannabinoid, vanilloid TRPV1 and adenosine A2A receptors. Eur J Neurosci. 2007;26(4):843–51. https://doi.org/10.1111/j.1460-9568.2007.05717.x.
133. Maya-Lopez M, Colin-Gonzalez AL, Aguilera G, de Lima ME, Colpo-Ceolin A, Rangel-Lopez E, et al. Neuroprotective effect of WIN55,212-2 against 3-nitropropionic acid-induced toxicity in the rat brain: involvement of CB1 and NMDA receptors. Am J Transl Res. 2017;9(2):261–74.
134. Consroe P, Laguna J, Allender J, Snider S, Stern L, Sandyk R, et al. Controlled clinical trial of cannabidiol in Huntington's disease. Pharmacol Biochem Behav. 1991;40(3):701–8.
135. Lopez-Sendon Moreno JL, Garcia Caldentey J, Trigo Cubillo P, Ruiz Romero C, Garcia Ribas G, Alonso Arias MA, et al. A double-blind, randomized, cross-over, placebo-controlled, pilot trial with Sativex in Huntington's disease. J Neurol. 2016;263(7):1390–400. https://doi.org/10.1007/s00415-016-8145-9.
136. Curtis A, Mitchell I, Patel S, Ives N, Rickards H. A pilot study using nabilone for symptomatic treatment in Huntington's disease. Mov Disord. 2009;24(15):2254–9. https://doi.org/10.1002/mds.22809.
137. Sallan SE, Zinberg NE, Frei E 3rd. Antiemetic effect of delta-9-tetrahydrocannabinol in patients receiving cancer chemotherapy. N Engl J Med. 1975;293(16):795–7. https://doi.org/10.1056/nejm197510162931603.
138. Darmani NA. Delta(9)-tetrahydrocannabinol and synthetic cannabinoids prevent emesis produced by the cannabinoid CB(1) receptor antagonist/inverse agonist SR 141716A. Neuropsychopharmacology. 2001;24(2):198–203. https://doi.org/10.1016/s0893-133x(00)00197-4.
139. Darmani NA, Sim-Selley LJ, Martin BR, Janoyan JJ, Crim JL, Parekh B, et al. Antiemetic and motor-depressive actions of CP55,940: cannabinoid CB1 receptor characterization, distribution, and G-protein activation. Eur J Pharmacol. 2003;459(1):83–95.
140. Darmani NA. Delta-9-tetrahydrocannabinol differentially suppresses cisplatin-induced emesis and indices of motor function via cannabinoid CB(1) receptors in the least shrew. Pharmacol Biochem Behav. 2001;69(1–2):239–49.
141. Van Sickle MD, Oland LD, Mackie K, Davison JS, Sharkey KA. Delta9-tetrahydrocannabinol selectively acts on CB1 receptors in specific regions of dorsal vagal complex to inhibit emesis in ferrets. Am J Physiol Gastrointest Liver Physiol. 2003;285(3):G566–76. https://doi.org/10.1152/ajpgi.00113.2003.
142. Rock EM, Boulet N, Limebeer CL, Mechoulam R, Parker LA. Cannabinoid 2 (CB2) receptor agonism reduces lithium chloride-induced vomiting in Suncus murinus and nausea-induced conditioned gaping in rats. Eur J Pharmacol. 2016;786:94–9. https://doi.org/10.1016/j.ejphar.2016.06.001.
143. Kwiatkowska M, Parker LA, Burton P, Mechoulam R. A comparative analysis of the potential of cannabinoids and ondansetron to suppress cisplatin-induced emesis in the *Suncus murinus* (house musk shrew). Psychopharmacology (Berl). 2004;174(2):254–9. https://doi.org/10.1007/s00213-003-1739-9.
144. Parker LA, Kwiatkowska M, Burton P, Mechoulam R. Effect of cannabinoids on lithium-induced vomiting in the *Suncus murinus* (house musk shrew). Psychopharmacology (Berl). 2004;171(2):156–61. https://doi.org/10.1007/s00213-003-1571-2.
145. Sharkey KA, Cristino L, Oland LD, Van Sickle MD, Starowicz K, Pittman QJ, et al. Arvanil, anandamide and *N*-arachidonoyl-dopamine (NADA) inhibit emesis through cannabinoid CB1 and vanilloid TRPV1 receptors in the ferret. Eur J Neurosci. 2007;25(9):2773–82. https://doi.org/10.1111/j.1460-9568.2007.05521.x.
146. Sticht MA, Rock EM, Parker LA. 2-arachidonoylglycerol interferes with lithium-induced vomiting in the house musk shrew, *Suncus murinus*. Physiol Behav. 2013;120:228–32. https://doi.org/10.1016/j.physbeh.2013.08.015.
147. Parker LA, Limebeer CL, Rock EM, Litt DL, Kwiatkowska M, Piomelli D. The FAAH inhibitor URB-597 interferes with cisplatin- and nicotine-induced vomiting in the *Suncus murinus* (house musk shrew). Physiol Behav. 2009;97(1):121–4. https://doi.org/10.1016/j.physbeh.2009.02.014.
148. Parker LA, Niphakis MJ, Downey R, Limebeer CL, Rock EM, Sticht MA, et al. Effect of selective inhibition of

monoacylglycerol lipase (MAGL) on acute nausea, anticipatory nausea, and vomiting in rats and *Suncus murinus*. Psychopharmacology (Berl). 2015;232(3):583–93. https://doi.org/10.1007/s00213-014-3696-x.
149. Pomeroy M, Fennelly JJ, Towers M. Prospective randomized double-blind trial of nabilone versus domperidone in the treatment of cytotoxic-induced emesis. Cancer Chemother Pharmacol. 1986;17(3):285–8.
150. Meiri E, Jhangiani H, Vredenburgh JJ, Barbato LM, Carter FJ, Yang HM, et al. Efficacy of dronabinol alone and in combination with ondansetron versus ondansetron alone for delayed chemotherapy-induced nausea and vomiting. Curr Med Res Opin. 2007;23(3):533–43. https://doi.org/10.1185/030079907x167525.
151. Lane M, Vogel CL, Ferguson J, Krasnow S, Saiers JL, Hamm J, et al. Dronabinol and prochlorperazine in combination for treatment of cancer chemotherapy-induced nausea and vomiting. J Pain Sympt Manag. 1991;6(6):352–9.
152. Abrahamov A, Abrahamov A, Mechoulam R. An efficient new cannabinoid antiemetic in pediatric oncology. Life Sci. 1995;56(23–24):2097–102.
153. Elder JJ, Knoderer HM. Characterization of dronabinol usage in a pediatric oncology population. J Pediatr Pharmacol Ther. 2015;20(6):462–7. https://doi.org/10.5863/1551-6776-20.6.462.
154. Polito S, MacDonald T, Romanick M, Jupp J, Wiernikowski J, Vennettilli A, et al. Safety and efficacy of nabilone for acute chemotherapy-induced vomiting prophylaxis in pediatric patients: a multicenter, retrospective review. Pediatr Blood Cancer. 2018;26:e2737. https://doi.org/10.1002/pbc.27374 **(Epub ahead of print)**.
155. Kleine-Brueggeney M, Greif R, Brenneisen R, Urwyler N, Stueber F, Theiler LG. Intravenous delta-9-tetrahydrocannabinol to prevent postoperative nausea and vomiting: a randomized controlled trial. Anesth Analg. 2015;121(5):1157–64. https://doi.org/10.1213/ane.0000000000000877.
156. Calignano A, La Rana G, Giuffrida A, Piomelli D. Control of pain initiation by endogenous cannabinoids. Nature. 1998;394(6690):277–81. https://doi.org/10.1038/28393.
157. Guindon J, Desroches J, Beaulieu P. The antinociceptive effects of intraplantar injections of 2-arachidonoyl glycerol are mediated by cannabinoid CB2 receptors. Br J Pharmacol. 2007;150(6):693–701. https://doi.org/10.1038/sj.bjp.0706990.
158. Starowicz K, Makuch W, Osikowicz M, Piscitelli F, Petrosino S, Di Marzo V, et al. Spinal anandamide produces analgesia in neuropathic rats: possible CB(1)- and TRPV1-mediated mechanisms. Neuropharmacology. 2012;62(4):1746–55. https://doi.org/10.1016/j.neuropharm.2011.11.021.
159. Lichtman AH, Leung D, Shelton CC, Saghatelian A, Hardouin C, Boger DL, et al. Reversible inhibitors of fatty acid amide hydrolase that promote analgesia: evidence for an unprecedented combination of potency and selectivity. J Pharmacol Exp Ther. 2004;311(2):441–8. https://doi.org/10.1124/jpet.104.069401.
160. Jayamanne A, Greenwood R, Mitchell VA, Aslan S, Piomelli D, Vaughan CW. Actions of the FAAH inhibitor URB597 in neuropathic and inflammatory chronic pain models. Br J Pharmacol. 2006;147(3):281–8. https://doi.org/10.1038/sj.bjp.0706510.
161. Sagar DR, Kendall DA, Chapman V. Inhibition of fatty acid amide hydrolase produces PPAR-alpha-mediated analgesia in a rat model of inflammatory pain. Br J Pharmacol. 2008;155(8):1297–306. https://doi.org/10.1038/bjp.2008.335.
162. Jhaveri MD, Richardson D, Robinson I, Garle MJ, Patel A, Sun Y, et al. Inhibition of fatty acid amide hydrolase and cyclooxygenase-2 increases levels of endocannabinoid related molecules and produces analgesia via peroxisome proliferator-activated receptor-alpha in a model of inflammatory pain. Neuropharmacology. 2008;55(1):85–93. https://doi.org/10.1016/j.neuropharm.2008.04.018.
163. Spradley JM, Guindon J, Hohmann AG. Inhibitors of monoacylglycerol lipase, fatty-acid amide hydrolase and endocannabinoid transport differentially suppress capsaicin-induced behavioral sensitization through peripheral endocannabinoid mechanisms. Pharmacol Res. 2010;62(3):249–58. https://doi.org/10.1016/j.phrs.2010.03.007.
164. Guindon J, Guijarro A, Piomelli D, Hohmann AG. Peripheral antinociceptive effects of inhibitors of monoacylglycerol lipase in a rat model of inflammatory pain. Br J Pharmacol. 2011;163(7):1464–78. https://doi.org/10.1111/j.1476-5381.2010.01192.x.
165. Chang L, Luo L, Palmer JA, Sutton S, Wilson SJ, Barbier AJ, et al. Inhibition of fatty acid amide hydrolase produces analgesia by multiple mechanisms. Br J Pharmacol. 2006;148(1):102–13. https://doi.org/10.1038/sj.bjp.0706699.
166. Jhaveri MD, Richardson D, Kendall DA, Barrett DA, Chapman V. Analgesic effects of fatty acid amide hydrolase inhibition in a rat model of neuropathic pain. J Neurosci. 2006;26(51):13318–27. https://doi.org/10.1523/jneurosci.3326-06.2006.
167. Woodhams SG, Wong A, Barrett DA, Bennett AJ, Chapman V, Alexander SP. Spinal administration of the monoacylglycerol lipase inhibitor JZL184 produces robust inhibitory effects on nociceptive processing and the development of central sensitization in the rat. Br J Pharmacol. 2012;167(8):1609–19. https://doi.org/10.1111/j.1476-5381.2012.02179.x.
168. Clapper JR, Moreno-Sanz G, Russo R, Guijarro A, Vacondio F, Duranti A, et al. Anandamide suppresses pain initiation through a peripheral endocannabinoid mechanism. Nat Neurosci. 2010;13(10):1265–70. https://doi.org/10.1038/nn.2632.
169. Maurer M, Henn V, Dittrich A, Hofmann A. Delta-9-tetrahydrocannabinol shows antispastic and analgesic effects in a single case double-blind trial. Eur Arch Psychiatry Clin Neurosci. 1990;240(1):1–4.
170. Svendsen KB, Jensen TS, Bach FW. Does the cannabinoid dronabinol reduce central pain in multiple sclerosis? Randomised double blind placebo controlled crossover trial. BMJ. 2004;329(7460):253. https://doi.org/10.1136/bmj.38149.566979.AE.
171. Wissel J, Haydn T, Muller J, Brenneis C, Berger T, Poewe W, et al. Low dose treatment with the synthetic cannabinoid Nabilone significantly reduces spasticity-related pain : a double-blind placebo-controlled cross-over trial. J Neurol. 2006;253(10):1337–41. https://doi.org/10.1007/s00415-006-0218-8.
172. Toth C, Mawani S, Brady S, Chan C, Liu C, Mehina E, et al. An enriched-enrolment, randomized withdrawal, flexible-dose, double-blind, placebo-controlled, parallel assignment efficacy study of nabilone as adjuvant in the treatment of diabetic peripheral neuropathic pain. Pain. 2012;153(10):2073–82. https://doi.org/10.1016/j.pain.2012.06.024.
173. Nurmikko TJ, Serpell MG, Hoggart B, Toomey PJ, Morlion BJ, Haines D. Sativex successfully treats neuropathic pain characterised by allodynia: a randomised, double-blind, placebo-controlled clinical trial. Pain. 2007;133(1–3):210–20. https://doi.org/10.1016/j.pain.2007.08.028.
174. Wade DT, Robson P, House H, Makela P, Aram J. A preliminary controlled study to determine whether whole-plant cannabis extracts can improve intractable neurogenic symptoms. Clin Rehabil. 2003;17(1):21–9. https://doi.org/10.1191/0269215503cr581oa.
175. Blake DR, Robson P, Ho M, Jubb RW, McCabe CS. Preliminary assessment of the efficacy, tolerability and safety of a cannabis-based medicine (Sativex) in the treatment of pain caused by

rheumatoid arthritis. Rheumatology (Oxford). 2006;45(1):50–2. https://doi.org/10.1093/rheumatology/kei183.
176. Serpell MG, Notcutt W, Collin C. Sativex long-term use: an open-label trial in patients with spasticity due to multiple sclerosis. J Neurol. 2013;260(1):285–95. https://doi.org/10.1007/s00415-012-6634-z.
177. Serpell M, Ratcliffe S, Hovorka J, Schofield M, Taylor L, Lauder H, et al. A double-blind, randomized, placebo-controlled, parallel group study of THC/CBD spray in peripheral neuropathic pain treatment. Eur J Pain. 2014;18(7):999–1012. https://doi.org/10.1002/j.1532-2149.2013.00445.x.
178. Crowley K, de Vries ST, Moreno-Sanz G. Self-reported effectiveness and safety of Trokie® lozenges: a standardized formulation for the buccal delivery of cannabis extracts. Front Neurosci. 2018;12:564. https://doi.org/10.3389/fnins.2018.00564.
179. Karst M, Salim K, Burstein S, Conrad I, Hoy L, Schneider U. Analgesic effect of the synthetic cannabinoid CT-3 on chronic neuropathic pain: a randomized controlled trial. JAMA. 2003;290(13):1757–62. https://doi.org/10.1001/jama.290.13.1757.
180. Abrams DI, Jay CA, Shade SB, Vizoso H, Reda H, Press S, et al. Cannabis in painful HIV-associated sensory neuropathy: a randomized placebo-controlled trial. Neurology. 2007;68(7):515–21. https://doi.org/10.1212/01.wnl.0000253187.66183.9c.
181. Ellis RJ, Toperoff W, Vaida F, van den Brande G, Gonzales J, Gouaux B, et al. Smoked medicinal cannabis for neuropathic pain in HIV: a randomized, crossover clinical trial. Neuropsychopharmacology. 2009;34(3):672–80. https://doi.org/10.1038/npp.2008.120.
182. Wilsey B, Marcotte T, Tsodikov A, Millman J, Bentley H, Gouaux B, et al. A randomized, placebo-controlled, crossover trial of cannabis cigarettes in neuropathic pain. J Pain. 2008;9(6):506–21. https://doi.org/10.1016/j.jpain.2007.12.010.
183. Wilsey B, Marcotte T, Deutsch R, Gouaux B, Sakai S, Donaghe H. Low-dose vaporized cannabis significantly improves neuropathic pain. J Pain. 2013;14(2):136–48. https://doi.org/10.1016/j.jpain.2012.10.009.
184. Ware MA, Wang T, Shapiro S, Robinson A, Ducruet T, Huynh T, et al. Smoked cannabis for chronic neuropathic pain: a randomized controlled trial. CMAJ. 2010;182(14):E694–701. https://doi.org/10.1503/cmaj.091414.
185. Wallace MS, Marcotte TD, Umlauf A, Gouaux B, Atkinson JH. Efficacy of inhaled cannabis on painful diabetic neuropathy. J Pain. 2015;16(7):616–27. https://doi.org/10.1016/j.jpain.2015.03.008.
186. Johnson JR, Burnell-Nugent M, Lossignol D, Ganae-Motan ED, Potts R, Fallon MT. Multicenter, double-blind, randomized, placebo-controlled, parallel-group study of the efficacy, safety, and tolerability of THC:CBD extract and THC extract in patients with intractable cancer-related pain. J Pain Sympt Manag. 2010;39(2):167–79. https://doi.org/10.1016/j.jpainsymman.2009.06.008.
187. Lynch ME, Cesar-Rittenberg P, Hohmann AG. A double-blind, placebo-controlled, crossover pilot trial with extension using an oral mucosal cannabinoid extract for treatment of chemotherapy-induced neuropathic pain. J Pain Sympt Manag. 2014;47(1):166–73. https://doi.org/10.1016/j.jpainsymman.2013.02.018.
188. Abrams DI, Couey P, Shade SB, Kelly ME, Benowitz NL. Cannabinoid–opioid interaction in chronic pain. Clin Pharmacol Ther. 2011;90(6):844–51. https://doi.org/10.1038/clpt.2011.188.
189. Narang S, Gibson D, Wasan AD, Ross EL, Michna E, Nedeljkovic SS, et al. Efficacy of dronabinol as an adjuvant treatment for chronic pain patients on opioid therapy. J Pain. 2008;9(3):254–64. https://doi.org/10.1016/j.jpain.2007.10.018.
190. Turcotte D, Doupe M, Torabi M, Gomori A, Ethans K, Esfahani F, et al. Nabilone as an adjunctive to gabapentin for multiple sclerosis-induced neuropathic pain: a randomized controlled trial. Pain Med. 2015;16(1):149–59. https://doi.org/10.1111/pme.12569.
191. Huggins JP, Smart TS, Langman S, Taylor L, Young T. An efficient randomised, placebo-controlled clinical trial with the irreversible fatty acid amide hydrolase-1 inhibitor PF-04457845, which modulates endocannabinoids but fails to induce effective analgesia in patients with pain due to osteoarthritis of the knee. Pain. 2012;153(9):1837–46. https://doi.org/10.1016/j.pain.2012.04.020.
192. Zhang L, Li XX, Hu XZ. Post-traumatic stress disorder risk and brain-derived neurotrophic factor Val66Met. World J Psychiatry. 2016;6(1):1–6. https://doi.org/10.5498/wjp.v6.i1.1.
193. Burstein O, Shoshan N, Doron R, Akirav I. Cannabinoids prevent depressive-like symptoms and alterations in BDNF expression in a rat model of PTSD. Prog Neuropsychopharmacol Biol Psychiatry. 2018;84(Pt A):129–39. https://doi.org/10.1016/j.pnpbp.2018.01.026.
194. Ghasemi M, Abrari K, Goudarzi I, Rashidy-Pour A. Effect of WIN55-212-2 and consequences of extinction training on conditioned fear memory in PTSD male rats. Basic Clin Neurosci. 2017;8(6):493–502. https://doi.org/10.29252/nirp.bcn.8.6.493.
195. Fidelman S, Mizrachi Zer-Aviv T, Lange R, Hillard CJ, Akirav I. Chronic treatment with URB597 ameliorates post-stress symptoms in a rat model of PTSD. Eur Neuropsychopharmacol. 2018;28(5):630–42. https://doi.org/10.1016/j.euroneuro.2018.02.004.
196. Stern CA, Gazarini L, Vanvossen AC, Zuardi AW, Galve-Roperh I, Guimaraes FS, et al. Delta9-tetrahydrocannabinol alone and combined with cannabidiol mitigate fear memory through reconsolidation disruption. Eur Neuropsychopharmacol. 2015;25(6):958–65. https://doi.org/10.1016/j.euroneuro.2015.02.001.
197. Mizrachi Zer-Aviv T, Segev A, Akirav I. Cannabinoids and post-traumatic stress disorder: clinical and preclinical evidence for treatment and prevention. Behav Pharmacol. 2016;27(7):561–9. https://doi.org/10.1097/fbp.0000000000000253.
198. Hill MN, Campolongo P, Yehuda R, Patel S. Integrating endocannabinoid signaling and cannabinoids into the biology and treatment of posttraumatic stress disorder. Neuropsychopharmacology. 2018;43(1):80–102. https://doi.org/10.1038/npp.2017.162.
199. Fraser GA. The use of a synthetic cannabinoid in the management of treatment-resistant nightmares in posttraumatic stress disorder (PTSD). CNS Neurosci Ther. 2009;15(1):84–8. https://doi.org/10.1111/j.1755-5949.2008.00071.x.
200. Jetly R, Heber A, Fraser G, Boisvert D. The efficacy of nabilone, a synthetic cannabinoid, in the treatment of PTSD-associated nightmares: a preliminary randomized, double-blind, placebo-controlled cross-over design study. Psychoneuroendocrinology. 2015;51:585–8. https://doi.org/10.1016/j.psyneuen.2014.11.002.
201. Sandyk R, Awerbuch G. Marijuana and Tourette's syndrome. J Clin Psychopharmacol. 1988;8(6):444–5.
202. Hemming M, Yellowlees PM. Effective treatment of Tourette's syndrome with marijuana. J Pychopharmacol (Oxford, England). 1993;7(4):389–91. https://doi.org/10.1177/026988119300700411.
203. Hasan A, Rothenberger A, Munchau A, Wobrock T, Falkai P, Roessner V. Oral delta 9-tetrahydrocannabinol improved refractory Gilles de la Tourette syndrome in an adolescent by increasing intracortical inhibition: a case report. J Clin Psychopharmacol. 2010;30(2):190–2. https://doi.org/10.1097/JCP.0b013e3181d236ec.
204. Muller-Vahl KR, Schneider U, Koblenz A, Jobges M, Kolbe H, Daldrup T, et al. Treatment of Tourette's syndrome with delta 9-tetrahydrocannabinol (THC): a randomized crossover

trial. Pharmacopsychiatry. 2002;35(2):57–61. https://doi.org/10.1055/s-2002-25028.
205. Trainor D, Evans L, Bird R. Severe motor and vocal tics controlled with Sativex®. Australas Psychiatry. 2016;24(6):541–4. https://doi.org/10.1177/1039856216663737.
206. Zuardi AW, Cosme RA, Graeff FG, Guimaraes FS. Effects of ipsapirone and cannabidiol on human experimental anxiety. J Psychopharmacol. 1993;7(1 Suppl.):82–8. https://doi.org/10.1177/026988119300700112.
207. Bergamaschi MM, Queiroz RH, Chagas MH, de Oliveira DC, De Martinis BS, Kapczinski F, et al. Cannabidiol reduces the anxiety induced by simulated public speaking in treatment-naive social phobia patients. Neuropsychopharmacology. 2011;36(6):1219–26. https://doi.org/10.1038/npp.2011.6.
208. Crippa JA, Derenusson GN, Ferrari TB, Wichert-Ana L, Duran FL, Martin-Santos R, et al. Neural basis of anxiolytic effects of cannabidiol (CBD) in generalized social anxiety disorder: a preliminary report. J Psychopharmacol. 2011;25(1):121–30. https://doi.org/10.1177/0269881110379283.
209. Fusar-Poli P, Crippa JA, Bhattacharyya S, Borgwardt SJ, Allen P, Martin-Santos R, et al. Distinct effects of {delta}9-tetrahydrocannabinol and cannabidiol on neural activation during emotional processing. Arch Gen Psychiatry. 2009;66(1):95–105. https://doi.org/10.1001/archgenpsychiatry.2008.519.
210. Fraguas-Sanchez AI, Martin-Sabroso C, Torres-Suarez AI. Insights into the effects of the endocannabinoid system in cancer: a review. Br J Pharmacol. 2018;175(13):2566–80. https://doi.org/10.1111/bph.14331.
211. Guzman M. Cannabinoids: potential anticancer agents. Nat Rev Cancer. 2003;3(10):745–55. https://doi.org/10.1038/nrc1188.
212. Wu X, Han L, Zhang X, Li L, Jiang C, Qiu Y, et al. Alteration of endocannabinoid system in human gliomas. J Neurochem. 2012;120(5):842–9. https://doi.org/10.1111/j.1471-4159.2011.07625.x.
213. Sredni ST, Huang CC, Suzuki M, Pundy T, Chou P, Tomita T. Spontaneous involution of pediatric low-grade gliomas: high expression of cannabinoid receptor 1 (CNR1) at the time of diagnosis may indicate involvement of the endocannabinoid system. Childs Nerv Syst. 2016;32(11):2061–7. https://doi.org/10.1007/s00381-016-3243-7.
214. Sanchez C, de Ceballos ML, Gomez del Pulgar T, Rueda D, Corbacho C, Velasco G, et al. Inhibition of glioma growth in vivo by selective activation of the CB(2) cannabinoid receptor. Cancer Res. 2001;61(15):5784–9.
215. Ellert-Miklaszewska A, Grajkowska W, Gabrusiewicz K, Kaminska B, Konarska L. Distinctive pattern of cannabinoid receptor type II (CB2) expression in adult and pediatric brain tumors. Brain Res. 2007;1137(1):161–9. https://doi.org/10.1016/j.brainres.2006.12.060.
216. Schley M, Stander S, Kerner J, Vajkoczy P, Schupfer G, Dusch M, et al. Predominant CB2 receptor expression in endothelial cells of glioblastoma in humans. Brain Res Bull. 2009;79(5):333–7. https://doi.org/10.1016/j.brainresbull.2009.01.011.
217. Maccarrone M, Attina M, Cartoni A, Bari M, Finazzi-Agro A. Gas chromatography–mass spectrometry analysis of endogenous cannabinoids in healthy and tumoral human brain and human cells in culture. J Neurochem. 2001;76(2):594–601.
218. Petersen G, Moesgaard B, Schmid PC, Schmid HH, Broholm H, Kosteljanetz M, et al. Endocannabinoid metabolism in human glioblastomas and meningiomas compared to human non-tumour brain tissue. J Neurochem. 2005;93(2):299–309. https://doi.org/10.1111/j.1471-4159.2005.03013.x.
219. Contassot E, Wilmotte R, Tenan M, Belkouch MC, Schnuriger V, de Tribolet N, et al. Arachidonylethanolamide induces apoptosis of human glioma cells through vanilloid receptor-1. J Neuropathol Exp Neurol. 2004;63(9):956–63.
220. Hinz B, Ramer R, Eichele K, Weinzierl U, Brune K. Up-regulation of cyclooxygenase-2 expression is involved in R(+)-methanandamide-induced apoptotic death of human neuroglioma cells. Mol Pharmacol. 2004;66(6):1643–51. https://doi.org/10.1124/mol.104.002618.
221. Bari M, Battista N, Fezza F, Finazzi-Agro A, Maccarrone M. Lipid rafts control signaling of type-1 cannabinoid receptors in neuronal cells. Implications for anandamide-induced apoptosis. J Biol Chem. 2005;280(13):12212–20. https://doi.org/10.1074/jbc.M411642200.
222. Ma C, Wu TT, Jiang PC, Li ZQ, Chen XJ, Fu K, et al. Anticarcinogenic activity of anandamide on human glioma in vitro and in vivo. Mol Med Rep. 2016;13(2):1558–62. https://doi.org/10.3892/mmr.2015.4721.
223. Hohmann T, Grabiec U, Ghadban C, Feese K, Dehghani F. The influence of biomechanical properties and cannabinoids on tumor invasion. Cell Adh Migr. 2017;11(1):54–67. https://doi.org/10.1080/19336918.2016.1183867.
224. Fowler CJ, Jonsson KO, Andersson A, Juntunen J, Jarvinen T, Vandevoorde S, et al. Inhibition of C6 glioma cell proliferation by anandamide, 1-arachidonoylglycerol, and by a water soluble phosphate ester of anandamide: variability in response and involvement of arachidonic acid. Biochem Pharmacol. 2003;66(5):757–67.
225. Jacobsson SO, Wallin T, Fowler CJ. Inhibition of rat C6 glioma cell proliferation by endogenous and synthetic cannabinoids: relative involvement of cannabinoid and vanilloid receptors. J Pharmacol Exp Ther. 2001;299(3):951–9.
226. Massi P, Vaccani A, Ceruti S, Colombo A, Abbracchio MP, Parolaro D. Antitumor effects of cannabidiol, a nonpsychoactive cannabinoid, on human glioma cell lines. J Pharmacol Exp Ther. 2004;308(3):838–45. https://doi.org/10.1124/jpet.103.061002.
227. Marcu JP, Christian RT, Lau D, Zielinski AJ, Horowitz MP, Lee J, et al. Cannabidiol enhances the inhibitory effects of delta9-tetrahydrocannabinol on human glioblastoma cell proliferation and survival. Mol Cancer Ther. 2010;9(1):180–9. https://doi.org/10.1158/1535-7163.mct-09-0407.
228. Caffarel MM, Andradas C, Mira E, Perez-Gomez E, Cerutti C, Moreno-Bueno G, et al. Cannabinoids reduce ErbB2-driven breast cancer progression through Akt inhibition. Mol Cancer. 2010;9:196. https://doi.org/10.1186/1476-4598-9-196.
229. Perez-Gomez E, Andradas C, Blasco-Benito S, Caffarel MM, Garcia-Taboada E, Villa-Morales M, et al. Role of cannabinoid receptor CB2 in HER2 pro-oncogenic signaling in breast cancer. J Natl Cancer Inst. 2015;107(6):dvj077. https://doi.org/10.1093/jnci/djv077.
230. Bisogno T, Katayama K, Melck D, Ueda N, De Petrocellis L, Yamamoto S, et al. Biosynthesis and degradation of bioactive fatty acid amides in human breast cancer and rat pheochromocytoma cells: implications for cell proliferation and differentiation. Eur J Biochem. 1998;254(3):634–42.
231. Melck D, De Petrocellis L, Orlando P, Bisogno T, Laezza C, Bifulco M, et al. Suppression of nerve growth factor Trk receptors and prolactin receptors by endocannabinoids leads to inhibition of human breast and prostate cancer cell proliferation. Endocrinology. 2000;141(1):118–26. https://doi.org/10.1210/endo.141.1.7239.
232. Ligresti A, Moriello AS, Starowicz K, Matias I, Pisanti S, De Petrocellis L, et al. Antitumor activity of plant cannabinoids with emphasis on the effect of cannabidiol on human breast carcinoma. J Pharmacol Exp Ther. 2006;318(3):1375–87. https://doi.org/10.1124/jpet.106.105247.
233. Qamri Z, Preet A, Nasser MW, Bass CE, Leone G, Barsky SH, et al. Synthetic cannabinoid receptor agonists inhibit

tumor growth and metastasis of breast cancer. Mol Cancer Ther. 2009;8(11):3117–29. https://doi.org/10.1158/1535-7163.mct-09-0448.
234. Grimaldi C, Pisanti S, Laezza C, Malfitano AM, Santoro A, Vitale M, et al. Anandamide inhibits adhesion and migration of breast cancer cells. Exp Cell Res. 2006;312(4):363–73. https://doi.org/10.1016/j.yexcr.2005.10.024.
235. Blasco-Benito S, Seijo-Vila M, Caro-Villalobos M, Tundidor I, Andradas C, Garcia-Taboada E, et al. Appraising the "entourage effect": antitumor action of a pure cannabinoid versus a botanical drug preparation in preclinical models of breast cancer. Biochem Pharmacol. 2018. https://doi.org/10.1016/j.bcp.2018.06.025 **(Epub ahead of print)**.
236. Sarfaraz S, Afaq F, Adhami VM, Mukhtar H. Cannabinoid receptor as a novel target for the treatment of prostate cancer. Cancer Res. 2005;65(5):1635–41. https://doi.org/10.1158/0008-5472.can-04-3410.
237. Orellana-Serradell O, Poblete CE, Sanchez C, Castellon EA, Gallegos I, Huidobro C, et al. Proapoptotic effect of endocannabinoids in prostate cancer cells. Oncol Rep. 2015;33(4):1599–608. https://doi.org/10.3892/or.2015.3746.
238. Chung SC, Hammarsten P, Josefsson A, Stattin P, Granfors T, Egevad L, et al. A high cannabinoid CB(1) receptor immunoreactivity is associated with disease severity and outcome in prostate cancer. Eur J Cancer. 2009;45(1):174–82. https://doi.org/10.1016/j.ejca.2008.10.010.
239. Cipriano M, Haggstrom J, Hammarsten P, Fowler CJ. Association between cannabinoid CB(1) receptor expression and Akt signalling in prostate cancer. PLoS One. 2013;8(6):e65798. https://doi.org/10.1371/journal.pone.0065798.
240. Mimeault M, Pommery N, Wattez N, Bailly C, Henichart JP. Anti-proliferative and apoptotic effects of anandamide in human prostatic cancer cell lines: implication of epidermal growth factor receptor down-regulation and ceramide production. Prostate. 2003;56(1):1–12. https://doi.org/10.1002/pros.10190.
241. Nithipatikom K, Isbell MA, Endsley MP, Woodliff JE, Campbell WB. Anti-proliferative effect of a putative endocannabinoid, 2-arachidonylglyceryl ether in prostate carcinoma cells. Prostaglandins Other Lipid Mediat. 2011;94(1–2):34–43. https://doi.org/10.1016/j.prostaglandins.2010.12.002.
242. Endsley MP, Aggarwal N, Isbell MA, Wheelock CE, Hammock BD, Falck JR, et al. Diverse roles of 2-arachidonoylglycerol in invasion of prostate carcinoma cells: location, hydrolysis and 12-lipoxygenase metabolism. Int J Cancer. 2007;121(5):984–91. https://doi.org/10.1002/ijc.22761.
243. Nithipatikom K, Endsley MP, Isbell MA, Falck JR, Iwamoto Y, Hillard CJ, et al. 2-arachidonoylglycerol: a novel inhibitor of androgen-independent prostate cancer cell invasion. Cancer Res. 2004;64(24):8826–30. https://doi.org/10.1158/0008-5472.can-04-3136.
244. Nomura DK, Lombardi DP, Chang JW, Niessen S, Ward AM, Long JZ, et al. Monoacylglycerol lipase exerts dual control over endocannabinoid and fatty acid pathways to support prostate cancer. Chem Biol. 2011;18(7):846–56. https://doi.org/10.1016/j.chembiol.2011.05.009.
245. Cipriano M, Gouveia-Figueira S, Persson E, Nording M, Fowler CJ. The influence of monoacylglycerol lipase inhibition upon the expression of epidermal growth factor receptor in human PC-3 prostate cancer cells. BMC Res Notes. 2014;7:441. https://doi.org/10.1186/1756-0500-7-441.
246. Ramer R, Bublitz K, Freimuth N, Merkord J, Rohde H, Haustein M, et al. Cannabidiol inhibits lung cancer cell invasion and metastasis via intercellular adhesion molecule-1. FASEB J. 2012;26(4):1535–48. https://doi.org/10.1096/fj.11-198184.
247. Suk KT, Mederacke I, Gwak GY, Cho SW, Adeyemi A, Friedman R, et al. Opposite roles of cannabinoid receptors 1 and 2 in hepatocarcinogenesis. Gut. 2016;65(10):1721–32. https://doi.org/10.1136/gutjnl-2015-310212.
248. Xu X, Liu Y, Huang S, Liu G, Xie C, Zhou J, et al. Overexpression of cannabinoid receptors CB1 and CB2 correlates with improved prognosis of patients with hepatocellular carcinoma. Cancer Genet Cytogenet. 2006;171(1):31–8. https://doi.org/10.1016/j.cancergencyto.2006.06.014.
249. DeMorrow S, Glaser S, Francis H, Venter J, Vaculin B, Vaculin S, et al. Opposing actions of endocannabinoids on cholangiocarcinoma growth: recruitment of Fas and Fas ligand to lipid rafts. J Biol Chem. 2007;282(17):13098–113. https://doi.org/10.1074/jbc.M608238200.
250. DeMorrow S, Francis H, Gaudio E, Venter J, Franchitto A, Kopriva S, et al. The endocannabinoid anandamide inhibits cholangiocarcinoma growth via activation of the noncanonical Wnt signaling pathway. Am J Physiol Gastrointest Liver Physiol. 2008;295(6):G1150–8. https://doi.org/10.1152/ajpgi.90455.2008.
251. Giuliano M, Pellerito O, Portanova P, Calvaruso G, Santulli A, De Blasio A, et al. Apoptosis induced in HepG2 cells by the synthetic cannabinoid WIN: involvement of the transcription factor PPARgamma. Biochimie. 2009;91(4):457–65. https://doi.org/10.1016/j.biochi.2008.11.003.
252. Vara D, Salazar M, Olea-Herrero N, Guzman M, Velasco G, Diaz-Laviada I. Anti-tumoral action of cannabinoids on hepatocellular carcinoma: role of AMPK-dependent activation of autophagy. Cell Death Differ. 2011;18(7):1099–111. https://doi.org/10.1038/cdd.2011.32.
253. Xu D, Wang J, Zhou Z, He Z, Zhao Q. Cannabinoid WIN55, 212-2 induces cell cycle arrest and inhibits the proliferation and migration of human BEL7402 hepatocellular carcinoma cells. Mol Med Rep. 2015;12(6):7963–70. https://doi.org/10.3892/mmr.2015.4477.
254. Pourkhalili N, Ghahremani MH, Farsandaj N, Tavajohi S, Majdzadeh M, Parsa M, et al. Evaluation of anti-invasion effect of cannabinoids on human hepatocarcinoma cells. Toxicol Mech Methods. 2013;23(2):120–6. https://doi.org/10.3109/15376516.2012.730559.
255. Guzman M, Duarte MJ, Blazquez C, Ravina J, Rosa MC, Galve-Roperh I, et al. A pilot clinical study of delta9-tetrahydrocannabinol in patients with recurrent glioblastoma multiforme. Br J Cancer. 2006;95(2):197–203. https://doi.org/10.1038/sj.bjc.6603236.
256. Zogopoulos P, Korkolopoulou P, Patsouris E, Theocharis S. The antitumor action of cannabinoids on glioma tumorigenesis. Histol Histopathol. 2015;30(6):629–45. https://doi.org/10.14670/hh-30.629.
257. Ramer R, Hinz B. Antitumorigenic targets of cannabinoids: current status and implications. Expert Opin Ther Targets. 2016;20(10):1219–35. https://doi.org/10.1080/14728222.2016.1177512.
258. Basavarajappa BS, Cooper TB, Hungund BL. Chronic ethanol administration down-regulates cannabinoid receptors in mouse brain synaptic plasma membrane. Brain Res. 1998;793(1–2):212–8.
259. Thanos PK, Dimitrakakis ES, Rice O, Gifford A, Volkow ND. Ethanol self-administration and ethanol conditioned place preference are reduced in mice lacking cannabinoid CB1 receptors. Behav Brain Res. 2005;164(2):206–13. https://doi.org/10.1016/j.bbr.2005.06.021.
260. Serrano A, Rivera P, Pavon FJ, Decara J, Suarez J, Rodriguez de Fonseca F, et al. Differential effects of single versus repeated alcohol withdrawal on the expression of endocannabinoid system-related genes in the rat amygdala.

Alcohol Clin Exp Res. 2012;36(6):984–94. https://doi.org/10.1111/j.1530-0277.2011.01686.x.
261. Gallate JE, Mallet PE, McGregor IS. Combined low dose treatment with opioid and cannabinoid receptor antagonists synergistically reduces the motivation to consume alcohol in rats. Psychopharmacology (Berl). 2004;173(1–2):210–6. https://doi.org/10.1007/s00213-003-1694-5.
262. Mitrirattanakul S, Lopez-Valdes HE, Liang J, Matsuka Y, Mackie K, Faull KF, et al. Bidirectional alterations of hippocampal cannabinoid 1 receptors and their endogenous ligands in a rat model of alcohol withdrawal and dependence. Alcohol Clin Exp Res. 2007;31(5):855–67. https://doi.org/10.1111/j.1530-0277.2007.00366.x.
263. Femenia T, Garcia-Gutierrez MS, Manzanares J. CB1 receptor blockade decreases ethanol intake and associated neurochemical changes in fawn-hooded rats. Alcohol Clin Exp Res. 2010;34(1):131–41. https://doi.org/10.1111/j.1530-0277.2009.01074.x.
264. Rubio M, Villain H, Docagne F, Roussel BD, Ramos JA, Vivien D, et al. Pharmacological activation/inhibition of the cannabinoid system affects alcohol withdrawal-induced neuronal hypersensitivity to excitotoxic insults. PLoS One. 2011;6(8):e23690. https://doi.org/10.1371/journal.pone.0023690.
265. Hungund BL, Basavarajappa BS. Distinct differences in the cannabinoid receptor binding in the brain of C57BL/6 and DBA/2 mice, selected for their differences in voluntary ethanol consumption. J Neurosci Res. 2000;60(1):122–8.
266. Cippitelli A, Bilbao A, Gorriti MA, Navarro M, Massi M, Piomelli D, et al. The anandamide transport inhibitor AM404 reduces ethanol self-administration. Eur J Neurosci. 2007;26(2):476–86. https://doi.org/10.1111/j.1460-9568.2007.05665.x.
267. Poncelet M, Maruani J, Calassi R, Soubrie P. Overeating, alcohol and sucrose consumption decrease in CB1 receptor deleted mice. Neurosci Lett. 2003;343(3):216–8.
268. Wang L, Liu J, Harvey-White J, Zimmer A, Kunos G. Endocannabinoid signaling via cannabinoid receptor 1 is involved in ethanol preference and its age-dependent decline in mice. Proc Natl Acad Sci USA. 2003;100(3):1393–8. https://doi.org/10.1073/pnas.0336351100.
269. Lallemand F, de Witte P. Ethanol induces higher BEC in CB1 cannabinoid receptor knockout mice while decreasing ethanol preference. Alcohol Alcohol. 2005;40(1):54–62. https://doi.org/10.1093/alcalc/agh115.
270. Vinod KY, Yalamanchili R, Thanos PK, Vadasz C, Cooper TB, Volkow ND, et al. Genetic and pharmacological manipulations of the CB(1) receptor alter ethanol preference and dependence in ethanol preferring and nonpreferring mice. Synapse. 2008;62(8):574–81. https://doi.org/10.1002/syn.20533.
271. Vinod KY, Sanguino E, Yalamanchili R, Manzanares J, Hungund BL. Manipulation of fatty acid amide hydrolase functional activity alters sensitivity and dependence to ethanol. J Neurochem. 2008;104(1):233–43. https://doi.org/10.1111/j.1471-4159.2007.04956.x.
272. Ortega-Álvaro A, Ternianov A, Aracil-Fernandez A, Navarrete F, Garcia-Gutierrez MS, Manzanares J. Role of cannabinoid CB2 receptor in the reinforcing actions of ethanol. Addict Biol. 2015;20(1):43–55. https://doi.org/10.1111/adb.12076.
273. Ferrer B, Bermudez-Silva FJ, Bilbao A, Alvarez-Jaimes L, Sanchez-Vera I, Giuffrida A, et al. Regulation of brain anandamide by acute administration of ethanol. Biochem J. 2007;404(1):97–104. https://doi.org/10.1042/bj20061898.
274. Rubio M, McHugh D, Fernandez-Ruiz J, Bradshaw H, Walker JM. Short-term exposure to alcohol in rats affects brain levels of anandamide, other *N*-acylethanolamines and 2-arachidonoyl-glycerol. Neurosci Lett. 2007;421(3):270–4. https://doi.org/10.1016/j.neulet.2007.05.052.
275. Gonzalez S, Cascio MG, Fernandez-Ruiz J, Fezza F, Di Marzo V, Ramos JA. Changes in endocannabinoid contents in the brain of rats chronically exposed to nicotine, ethanol or cocaine. Brain Res. 2002;954(1):73–81.
276. Vinod KY, Yalamanchili R, Xie S, Cooper TB, Hungund BL. Effect of chronic ethanol exposure and its withdrawal on the endocannabinoid system. Neurochem Int. 2006;49(6):619–25. https://doi.org/10.1016/j.neuint.2006.05.002.
277. Colombo G, Serra S, Brunetti G, Gomez R, Melis S, Vacca G, et al. Stimulation of voluntary ethanol intake by cannabinoid receptor agonists in ethanol-preferring sP rats. Psychopharmacology (Berl). 2002;159(2):181–7. https://doi.org/10.1007/s002130100887.
278. Alen F, Santos A, Moreno-Sanz G, Gonzalez-Cuevas G, Gine E, Franco-Ruiz L, et al. Cannabinoid-induced increase in relapse-like drinking is prevented by the blockade of the glycine-binding site of *N*-methyl-D-aspartate receptors. Neuroscience. 2009;158(2):465–73. https://doi.org/10.1016/j.neuroscience.2008.10.002.
279. Klugmann M, Klippenstein V, Leweke FM, Spanagel R, Schneider M. Cannabinoid exposure in pubertal rats increases spontaneous ethanol consumption and NMDA receptor associated protein levels. Int J Neuropsychopharmacol. 2011;14(4):505–17. https://doi.org/10.1017/s1461145710001562.
280. Lopez-Moreno JA, Gonzalez-Cuevas G, Rodriguez de Fonseca F, Navarro M. Long-lasting increase of alcohol relapse by the cannabinoid receptor agonist WIN 55,212-2 during alcohol deprivation. J Neurosci. 2004;24(38):8245–52. https://doi.org/10.1523/jneurosci.2179-04.2004.
281. Hamelink C, Hampson A, Wink DA, Eiden LE, Eskay RL. Comparison of cannabidiol, antioxidants, and diuretics in reversing binge ethanol-induced neurotoxicity. J Pharmacol Exp Ther. 2005;314(2):780–8. https://doi.org/10.1124/jpet.105.085779.
282. Liput DJ, Hammell DC, Stinchcomb AL, Nixon K. Transdermal delivery of cannabidiol attenuates binge alcohol-induced neurodegeneration in a rodent model of an alcohol use disorder. Pharmacol Biochem Behav. 2013;111:120–7. https://doi.org/10.1016/j.pbb.2013.08.013.
283. Soyka M, Koller G, Schmidt P, Lesch OM, Leweke M, Fehr C, et al. Cannabinoid receptor 1 blocker rimonabant (SR 141716) for treatment of alcohol dependence: results from a placebo-controlled, double-blind trial. J Clin Psychopharmacol. 2008;28(3):317–24. https://doi.org/10.1097/JCP.0b013e318172b8bc.
284. Weerts EM, Kim YK, Wand GS, Dannals RF, Lee JS, Frost JJ, et al. Differences in delta- and mu-opioid receptor blockade measured by positron emission tomography in naltrexone-treated recently abstinent alcohol-dependent subjects. Neuropsychopharmacology. 2008;33(3):653–65. https://doi.org/10.1038/sj.npp.1301440.
285. George DT, Herion DW, Jones CL, Phillips MJ, Hersh J, Hill D, et al. Rimonabant (SR141716) has no effect on alcohol self-administration or endocrine measures in nontreatment-seeking heavy alcohol drinkers. Psychopharmacology (Berl). 2010;208(1):37–44. https://doi.org/10.1007/s00213-009-1704-3.
286. Metrik J, Spillane NS, Leventhal AM, Kahler CW. Marijuana use and tobacco smoking cessation among heavy alcohol drinkers. Drug Alcohol Depend. 2011;119(3):194–200. https://doi.org/10.1016/j.drugalcdep.2011.06.004.
287. Solinas M, Panlilio LV, Tanda G, Makriyannis A, Matthews SA, Goldberg SR. Cannabinoid agonists but not inhibitors of endogenous cannabinoid transport or metabolism enhance the reinforcing efficacy of heroin in rats. Neuropsychopharmacology. 2005;30(11):2046–57. https://doi.org/10.1038/sj.npp.1300754.

288. Li JX, Koek W, France CP. Interactions between delta(9)-tetrahydrocannabinol and heroin: self-administration in rhesus monkeys. Behav Pharmacol. 2012;23(8):754–61. https://doi.org/10.1097/FBP.0b013e32835a3907.
289. Maguire DR, France CP. Effects of daily delta-9-tetrahydrocannabinol treatment on heroin self-administration in rhesus monkeys. Behav Pharmacol. 2016;27(2-3 Spec Issue):249–57. https://doi.org/10.1097/fbp.0000000000000192.
290. Karimi S, Azizi P, Shamsizadeh A, Haghparast A. Role of intra-accumbal cannabinoid CB1 receptors in the potentiation, acquisition and expression of morphine-induced conditioned place preference. Behav Brain Res. 2013;247:125–31. https://doi.org/10.1016/j.bbr.2013.03.022.
291. Khaleghzadeh-Ahangar H, Haghparast A. Intra-accumbal CB1 receptor blockade reduced extinction and reinstatement of morphine. Physiol Behav. 2015;149:212–9. https://doi.org/10.1016/j.physbeh.2015.06.005.
292. Fattore L, Spano S, Cossu G, Deiana S, Fadda P, Fratta W. Cannabinoid CB(1) antagonist SR 141716A attenuates reinstatement of heroin self-administration in heroin-abstinent rats. Neuropharmacology. 2005;48(8):1097–104. https://doi.org/10.1016/j.neuropharm.2005.01.022.
293. Katsidoni V, Anagnostou I, Panagis G. Cannabidiol inhibits the reward-facilitating effect of morphine: involvement of 5-HT1A receptors in the dorsal raphe nucleus. Addict Biol. 2013;18(2):286–96. https://doi.org/10.1111/j.1369-1600.2012.00483.x.
294. Wilkerson JL, Ghosh S, Mustafa M, Abdullah RA, Niphakis MJ, Cabrera R, et al. The endocannabinoid hydrolysis inhibitor SA-57: Intrinsic antinociceptive effects, augmented morphine-induced antinociception, and attenuated heroin seeking behavior in mice. Neuropharmacology. 2017;114:156–67. https://doi.org/10.1016/j.neuropharm.2016.11.015.
295. Stopponi S, Soverchia L, Ubaldi M, Cippitelli A, Serpelloni G, Ciccocioppo R. Chronic THC during adolescence increases the vulnerability to stress-induced relapse to heroin seeking in adult rats. Eur Neuropsychopharmacol. 2014;24(7):1037–45. https://doi.org/10.1016/j.euroneuro.2013.12.012.
296. Prilutskaya M, Bersani FS, Corazza O, Molchanov S. Impact of synthetic cannabinoids on the duration of opioid-related withdrawal and craving among patients of addiction clinics in Kazakhstan: a prospective case-control study. Hum Psychopharmacol. 2017. https://doi.org/10.1002/hup.2618 **(Epub 2017 Jun 20)**.
297. Merritt JC, Crawford WJ, Alexander PC, Anduze AL, Gelbart SS. Effect of marihuana on intraocular and blood pressure in glaucoma. Ophthalmology. 1980;87(3):222–8.
298. Porcella A, Maxia C, Gessa GL, Pani L. The synthetic cannabinoid WIN55212-2 decreases the intraocular pressure in human glaucoma resistant to conventional therapies. Eur J Neurosci. 2001;13(2):409–12.
299. Chien FY, Wang RF, Mittag TW, Podos SM. Effect of WIN 55212-2, a cannabinoid receptor agonist, on aqueous humor dynamics in monkeys. Arch Ophthalmol. 2003;121(1):87–90.
300. Song ZH, Slowey CA. Involvement of cannabinoid receptors in the intraocular pressure-lowering effects of WIN55212-2. J Pharmacol Exp Ther. 2000;292(1):136–9.
301. Szczesniak AM, Maor Y, Robertson H, Hung O, Kelly ME. Nonpsychotropic cannabinoids, abnormal cannabidiol and canabigerol-dimethyl heptyl, act at novel cannabinoid receptors to reduce intraocular pressure. J Ocul Pharmacol Ther. 2011;27(5):427–35. https://doi.org/10.1089/jop.2011.0041.
302. Merritt JC, Perry DD, Russell DN, Jones BF. Topical delta 9-tetrahydrocannabinol and aqueous dynamics in glaucoma. J Clin Pharmacol. 1981;21(8–9 Suppl.):467s–71s.
303. Crandall J, Matragoon S, Khalifa YM, Borlongan C, Tsai NT, Caldwell RB, et al. Neuroprotective and intraocular pressure-lowering effects of (-)delta9-tetrahydrocannabinol in a rat model of glaucoma. Ophthalmic Res. 2007;39(2):69–75. https://doi.org/10.1159/000099240.
304. El-Remessy AB, Khalil IE, Matragoon S, Abou-Mohamed G, Tsai NJ, Roon P, et al. Neuroprotective effect of (-)delta9-tetrahydrocannabinol and cannabidiol in *N*-methyl-D-aspartate-induced retinal neurotoxicity: involvement of peroxynitrite. Am J Pathol. 2003;163(5):1997–2008.
305. Pinar-Sueiro S, Zorrilla Hurtado JA, Veiga-Crespo P, Sharma SC, Vecino E. Neuroprotective effects of topical CB1 agonist WIN 55212-2 on retinal ganglion cells after acute rise in intraocular pressure induced ischemia in rat. Exp Eye Res. 2013;110:55–8. https://doi.org/10.1016/j.exer.2013.02.009.
306. Slusar JE, Cairns EA, Szczesniak AM, Bradshaw HB, Di Polo A, Kelly ME. The fatty acid amide hydrolase inhibitor, URB597, promotes retinal ganglion cell neuroprotection in a rat model of optic nerve axotomy. Neuropharmacology. 2013;72:116–25. https://doi.org/10.1016/j.neuropharm.2013.04.018.
307. Whiting PF, Wolff RF, Deshpande S, Di Nisio M, Duffy S, Hernandez AV, et al. Cannabinoids for medical use: a systematic review and meta-analysis. JAMA. 2015;313(24):2456–73. https://doi.org/10.1001/jama.2015.6358.
308. Danovitch I, Gorelick DA. State of the art treatments for cannabis dependence. Psychiatr Clin N Am. 2012;35(2):309–26. https://doi.org/10.1016/j.psc.2012.03.003.
309. Bonnet U, Preuss UW. The cannabis withdrawal syndrome: current insights. Subst Abuse Rehabil. 2017;8:9–37. https://doi.org/10.2147/sar.s109576.
310. Soyka M, Preuss U, Hoch E. Cannabis-induced disorders. Nervenarzt. 2017;88(3):311–25. https://doi.org/10.1007/s00115-017-0281-7.
311. Wright S, Metts J. Recreational cannabinoid use: the hazards behind the "high". J Fam Pract. 2016;65(11):770–9.