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REVIEW

Cannabinoids therapeutic use: what is our current understanding following the introduction of THC, THC:CBD oromucosal spray and others?

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ABSTRACT

Introduction: The complexity of the endocannabinoid (eCB) system is becoming better understood and new drivers of eCB signaling are emerging. Modulation of the activities of the eCB system can be therapeutic in a number of diseases. Research into the eCB system has been paralleled by the development of agents that interact with cannabinoid receptors. In this regard it should be remembered that herbal cannabis contains a myriad of active ingredients, and the individual cannabinoids have quite distinct biological activities requiring independent studies.

Areas covered: This article reviews the most important current data involving the eCB system in relation to human diseases, to reflect the present (based mainly on the most used prescription cannabinoid medicine, THC/CBD oromucosal spray) and potential future uses of cannabinoid-based therapy.

Expert commentary: From the different therapeutic possibilities, THC/CBD oromucosal spray has been in clinical use for approximately five years in numerous countries world-wide for the management of multiple sclerosis (MS)-related moderate to severe resistant spasticity. Clinical trials have confirmed its efficacy and tolerability. Other diseases in which different cannabinoids are currently being investigated include various pain states, Alzheimer's disease, Parkinson's disease, Huntington's disease and epilepsy. The continued characterization of individual cannabinoids in different diseases remains important.

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1. Historical introduction

Extracts of cannabis (*Cannabis sativa* or *Cannabis indica*) have been used for centuries in folklore medicine, for recreational purposes and also for potential therapeutic benefit. The therapeutic possibilities of cannabis were mentioned by Shen Nung in China in about 2700 BC and were first documented in the Egyptian Ebers Papyrus and Rh-Ya Chinese Pharmacopoeia in about 1500 BC [1]. Yet, it was only in the 1960s that the major cannabinoid constituents of cannabis, including the main psychoactive component Δ^9-tetrahydrocannabinol (THC), were isolated and structurally elucidated (Table 1) [2]. It was followed by the identification and cloning of two cannabinoid receptors in the 1980s (CB_1) and the early 1990s (CB_2), and by the identification of endocannabinoids (eCBs) shortly thereafter [1]. It is now known that the cannabis plant is a unique source of >60 different cannabinoid-related compounds, collectively called 'phytocannabinoids', as well as >400 other substances that might interact, alone or in combination, in the human body with the possibility of producing physiological/medical effects [1,2]. Moreover, *C. sativa* and *C. indica* cannabinoids have different chemical fingerprints and we now refer to them as 'chemovars' rather than 'cultivars' [3]. Among these substances, THC and cannabidiol (CBD) (both shown in Table 1) have been widely recognized as the main bioactive constituents [1–3]. THC is a partial agonist of CB_1 and CB_2 receptors while CBD has little binding affinity for cannabinoid receptors, although it is able to antagonize some effects of THC on CB_1 receptors [4]. Cannabinoids such as cannabinol (CBN), tetrahydrocannabivarin (THCV), cannabigerol (CBG), cannabidivarin, cannabichromene (CBC), and others are still under investigation.

2. The eCB system

Shortly after its identification, THC was demonstrated to act stereospecifically in the central nervous system (CNS) due to its ability to bind specifically to a G-protein-coupled receptor (GPCR) called type-1 cannabinoid receptor (CB_1). Interestingly, CB_1 is the most abundant GPCR in the human brain (for a review, see Ref. [5]). The type-2 cannabinoid receptor (CB_2) was discovered in peripheral blood cells a few years later, and it was also shown to be expressed within the CNS [6], although the lack of selective antibodies makes it difficult to study [7]. CB_1 and CB_2

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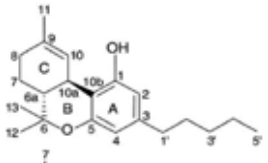
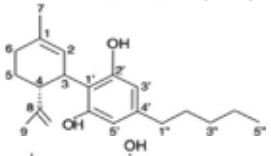
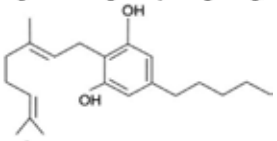
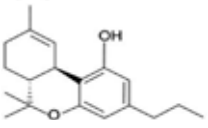
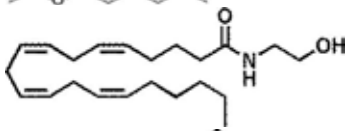
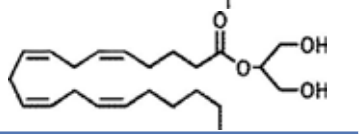
Table 1. Major phytocannabinoids and endocannabinoids with a role in experimental MS figures reproduced with permission from Wiley [2].

Name (abbreviation)	Chemical structure
Δ^9- THC	
CBD	
CBG	
Δ^9- THCV	
N-arachidonoylethanolamine (Anandamide, AEA)	
2-AG	

CBD: Cannabidiol; THC: tetrahydrocannabinol; CBG: cannabigerol; THCV: tetrahydrocannabivarin; 2-AG: 2-arachidonoylglycerol.

receptors trigger multiple signal transduction pathways, for example, they inhibit the formation of the second messenger cyclic adenosine monophosphate and modulate extracellular regulated kinases, β-arrestin, nitric oxide synthase, and ion channels. Unsurprisingly, endogenous ligands of CB receptors (eCBs) such as *N*-arachidonoylethanolamine (anandamide, AEA) and 2-arachidonoylglycerol (2-AG) have been identified (Table 1); both being derivatives of arachidonic acid (AA). AEA and 2-AG have been shown to be a partial agonist and a full agonist of CB_1 and CB_2 receptors, respectively. Since their discovery in the 1990s they have remained the best studied members of an ever-growing family of bioactive signaling lipids [1–3]. The individual levels of AEA and 2-AG vary between species, tissues, developmental stages, and pathophysiological conditions, with 2-AG generally being 10–1000-fold more abundant than AEA. Despite their different chemical structures, THC, AEA, and 2-AG share the same pharmacophore in their 3D structures, thus explaining why they bind to the same receptor targets [8]. This was recently confirmed following the determination of the crystal structure of the CB_1 receptor [9,10]. AEA and 2-AG are also endogenous ligands of transient receptor potential vanilloid type-1 (TRPV1) ion channels, whose activation may have detrimental effects on neuronal survival, and they can activate the purported 'CB_3' receptor GPR55, GPR119, and nuclear transcription factors like peroxisome proliferator-activated receptors (PPARs) [5]. The cannabinoid receptors can also be targeted by synthetic agonists and antagonists, not just plant substances, with different affinities and effects, opening the door to the study of very diverse medical uses with different active principles and combinations.

The neurophysiological actions of eCBs depend on specific proteins that synthesize, transport, bind, and degrade them. Indeed, unlike other neurotransmitters, eCBs are not stored in vesicles but are produced 'on demand' following different biological stimuli, to act paracrinally or autocrinally. The most studied pathway for AEA synthesis involves its release from membrane precursors via *N*-acylphosphatidylethanolamine (NAPE)-specific phospholipase D. Fatty acid amide hydrolase (FAAH) is the enzyme largely responsible for the cleavage of AEA into AA and ethanolamine. In contrast, 2-AG is formed by the action of two diacylglycerol lipases, DAGLα and DAGLβ, and is primarily degraded into AA and glycerol by monoacylglycerol lipase. These enzymes, together with eCB-binding transporters and receptors, comprise the eCB system, and their distinct distribution in neuronal cells is schematically depicted in Figure 1 (for a review, see Ref. [5]). Of note, factors such as membrane lipid composition can drive eCB signaling; for example, CB_1 receptors are localized in specialized microdomains in the cell membrane called lipid rafts [11], and FAAH is modulated by membrane cholesterol [12]. In addition, eCB intracellular transporters (EITs) and intracellular eCB storage sites like adiposomes can contribute to fine tuning of eCB signaling (Figure 1) [5]. Finally, it is becoming apparent that the activity of distinct elements of the eCB system is regulated at the gene expression level through epigenetic mechanisms including DNA methylation, histone modifications, and microRNAs [13].

3. Herbal cannabis and cannabinoid-based medicines

3.1. Herbal cannabis

Nonmedical use: The increase in the consumption of *C. sativa* derivatives among adolescents and young adults is a cause for concern given the association between continued use and academic failure [14], problem behaviors [15], and traffic accidents [16]. Furthermore, subsequent possible abuse and dependence on drugs such as cocaine or heroin [17,18], and the possibility of depressive and psychotic episodes, are added concerns [19–21]. The progressive popularization of home-grown 'indoor cannabis', which can be up to 10–15 times more potent than the 'classical herb' from a THC-related psychoactive point of view, and also synthetic forms of cannabis, usually called *spice*, which seem much more dangerous than the 'indoor' varieties, has exacerbated the problem [22]. Of particular concern to health authorities and professionals working in the area of addiction are the possible future consequences of this behavior, both psychopathological and organic. This may not only be reflected in significantly increased numbers of 'problem' cases, but also a changing clinical presentation. A very worrying aspect in recent years has been the gradual trivialization of the risks associated with cannabis usage in western societies, mainly in adolescent

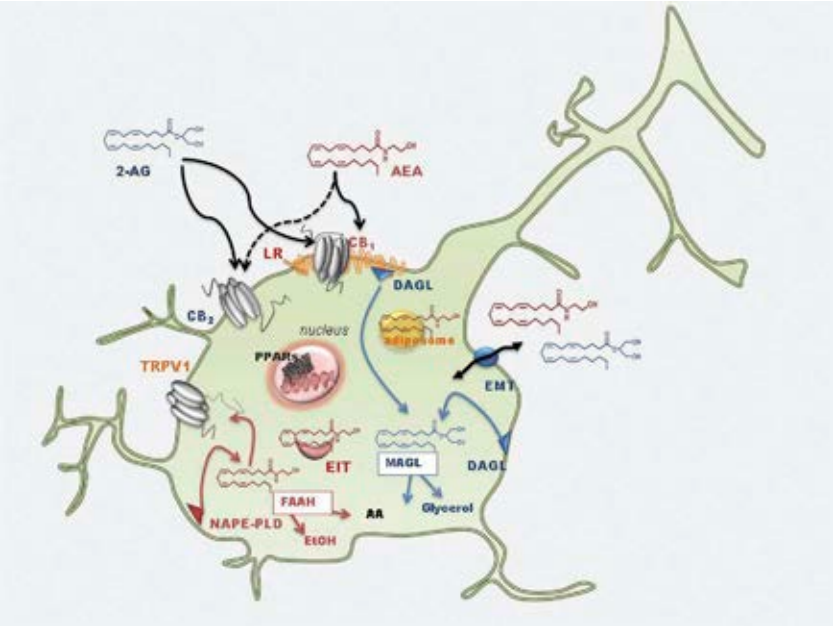


Figure 1. The eCB system in the CNS.
eCB signaling is orchestrated by target receptors (CB_1, CB_2, TRPV1 and PPARs), biosynthetic (NAPE-PLD and DAGL) and degradative (FAAH and MAGL) enzymes, transmembrane transport mechanisms (like the putative EMT), intracellular trafficking by EITs like fatty acid binding proteins, heat shock protein 70, and FAAH-like AEA transporter, as well as by storage organelles like adiposomes. Altogether, these proteins regulate the endogenous tone of eCBs, and hence their biological activity. It should be noted that, unlike other eCB-binding receptors, CB_1 appears to be located in cholesterol-enriched membrane microdomains termed LRs, and that CB_2 is expressed in neurons upon brain injury.
EITs: eCB intracellular transporters; CB_1/CB_2: G-protein coupled type-1 and type-2 cannabinoid receptors; DAGL: diacylglycerol lipase α/β; eCBs: endocannabinoids; EMT: putative endocannabinoid transmembrane transporter; FAAH: fatty acid amide hydrolase; LRs: lipid rafts; MAGL: monoacylglycerol lipase; NAPE-PLD: *N*-acylphosphatidylethanolamine-specific phospholipase D; PPARs: peroxisome proliferator-activated nuclear receptors; TRPV1: transient receptor potential vanilloid 1 channels.

populations that consume it in an experiential–exploratory–festive context, typical of this age group [23]. Factors such as a movement toward 'liberalization of recreational consumption' [24]; misinterpretation of the legitimate medical use of cannabis, as a plant without the dangers usually attributed to so-called illegal drugs [25]; and social acceptability based upon witnessing parental usage of small amounts of cannabis in the 1960/70s [26] may all have contributed to this.

Unfortunately, most prevention programs implemented in the last couple of decades do not seem to have had a great effect on reducing recreational consumption of herbal cannabis. This is particularly the situation for vulnerable populations such as adolescents with neurodevelopmental disorders, Attention Deficit Hyperactivity Disorder, learning disorders, and disruptive behaviors, all of them inducing school problems, challenging behaviors, and risk of social exclusion [27]. The net result might be a dramatic increase in the consumption of herbal cannabis in the years ahead, and it remains to be determined whether this will be limited to certain genetic-mediated 'high-risk' groups of people [28] and could decrease over time, or whether such uptake will spread further afield as was the case with tobacco in the last century [29].

Along with the significant increase in consumption in the general population, herbal cannabis use among chronic psychiatric patients has also grown exponentially in recent decades. This is probably due firstly to an increase in the personal autonomy that these patients now have and which allows them to access substances that previously were very difficult to obtain as a result of their previous worst clinical situation or asylum lifestyle [30]. The situation is likely exacerbated by an increase in the supply of, and easier access to, illicit substances, which can currently be obtained more easily and at more affordable prices. Because of the link between herbal cannabis usage and psychotic episodes, it is surprising to find that up to 70% of schizophrenic patients consume herbal cannabis [30]. Since it is difficult to believe that these patients use the herbal cannabis aiming to worsen their condition, it is hypothesized that they have a biological 'risk-activities' seeking predisposition caused by the chronic mental illness, and/or it might also be an attempt to 'self-medicate', taking advantage of the anxiolytic, antidepressant, and/or antipsychotic effects that have been described for some of the psychoactive substances present in the plant, such as CBD and others [31,32].

It should be noted that a number of internationally controlled clinical trials are being conducted at present to study the beneficial psychotropic effects of specific cannabinoids [33]. This research is useful to help us better understand the beneficial effects of the different cannabinoids on both organic and psychic disorders. However, it is also important to recognize the addictive properties of herbal cannabis and its capacity to provoke or to exacerbate psychiatric pathologies, which may lie silent in the adolescent population. There is sufficient scientific evidence to support the dangerousness of herbal cannabis in younger persons, and consumption might lead to a deterioration of basic psychic functions (attention, concentration and abstraction), difficulties in the construction and course of thought, paranoia, and alteration of the sensory-perceptive processes, with

hallucinatory phenomena and delusions [27]. In addition, while there is no conclusive data on the possible shift from 'misuse' to 'dependence', it is expected as is the case in other addictive processes that between 12% and 15% of herbal cannabis users will become chronic consumers. These considerations justify prohibiting the use of herbal cannabis in younger persons (adolescents) in whom the processes of cerebral maturation are active.

3.2. Cannabinoid-based medicines

A variety of cannabinoid-based preparations with medicinal effects are currently available; some of them are approved for clinical use. They can be classified as

- Natural cannabinoids (phytocannabinoids):
  - Full plant extracts with multiple different cannabinoids composition (Bedrocan® and others, not approved label).
  - Two purified cannabinoids (THC/CBD) extracted from the plant as active principles (nabiximols, Sativex®, with approved label).
  - Single purified cannabinoid (CBD) extracted from the plant as active principle (Epidiolex®, label studies ongoing, but recently granted Orphan Drug status by the US FDA).
- Synthetic cannabinoids, including dronabinol (synthetic THC, Marinol®), nabilone (THC analog, Cesamet®), both with approved label, and levonantradol (THC analog, 30 times more potent) [34].

The route of administration of these preparations can be oral (i.e. mixed with food or made into tea), sublingual/oromucosal, topical, smoked, or inhaled. Each composition will have different pharmacokinetic properties and pharmacodynamic effects which would need to be tested in appropriate studies. Because of possible neuromodulatory, neuroprotective, and/or anti-inflammatory properties, several indications of cannabinoid preparations have been postulated, and a number of outcomes have been explored in clinical studies (Table 2).

Nausea and vomiting associated with chemotherapy, appetite stimulation in HIV/AIDS, spasticity due to MS, neuropathic pain in MS, and cancer pain unresponsive to opioids are currently approved indications in a number of countries [35,36].

A recent systematic review and meta-analysis analyzed all randomized clinical trials (RCTs) that compared cannabinoids with usual care, placebo, or no treatment for 10 clinical conditions, and non-randomized clinical studies with at least 25 patients, published in the last 40 years (1975–2015, [36]). This review pooled data from studies of cannabinoid-based medications performed with different types and concentrations of active principles, which is a methodological limitation of the analysis. Despite the potential limitation of pooling and comparing such data, the vast majority of the randomized and placebo-controlled trials showed superiority of cannabinoid-based medications over placebo for most of the studied clinical conditions and outcomes considered. The exception was depression, wherein placebo was reported to be more effective than preparations containing THC in one clinical trial [37] and no apparent differences in two additional studies. In clinical trials in patients with nausea and vomiting due to chemotherapy, HIV/AIDS, chronic pain (neuropathic pain and cancer pain), spasticity due to multiple sclerosis or paraplegia, anxiety disorder, sleep disorder, psychosis and Tourette's syndrome, cannabinoid-based medications were generally reported to be more efficacious than placebo on the primary outcomes of the selected studies. Studies assessing the effects of THC/CBD generally scored higher in the GRADE (Grades of Recommendation Assessment, Development and Evaluation) ratings, indicating better quality of evidence [36]. Cannabinoids were associated with a greater risk of any AE, serious AEs, withdrawals due to AEs, and a number of specific AEs, but because only pooled data of very different compounds and doses were presented, this limits the value of the information. Another systematic review evaluated the efficacy and safety data of the medical use of cannabinoids published between 1948 and 2013 in RCTs that compared herbal cannabinoids to placebo in three neurological disorders (MS, epilepsy, and movement disorders) [35]. The quality of the evidence was rated according to the American Academy of Neurology methods and showed that only THC/CBD in MS spasticity provided A-rated scientific evidence.

Six Cochrane reviews, each looking at cannabinoid treatment for one medical condition, have been published in the 2013–2016 period. Clinical conditions of interest were fibromyalgia [38], chemotherapy-induced nausea and vomiting [39], cannabis dependence [40], epilepsy [41], HIV/AIDS [42],

Table 2. Approved and potential indications for cannabinoids.

Cannabinoid	Approved and potential indications
THC	Chemotherapy-induced nausea and vomiting* Appetite stimulant (HIV/AIDS)* MS-spasticity Neuropathic pain in MS Cancer pain unresponsive to opioids Other pain conditions (i.e. postherpetic neuralgia, postoperative pain)
THC/CBD	Spasticity due to multiple sclerosis*, to paraplegia, to amyotrophic lateral sclerosis Neuropathic pain in MS Cancer pain unresponsive to opioids Other pain conditions (i.e. postherpetic neuralgia, postoperative pain)
CBD	Childhood epilepsy: tuberous sclerosis complex seizures, Lennox–Gastaut syndrome, Dravet syndrome, and infantile spasms
THC, THC/CBD, other cannabinoids	Intraocular pressure in glaucoma, depression, anxiety disorder, sleep disorder, psychosis, tics of Tourette syndrome, tremor due to MS, bladder dysfunction due to MS, dyskinesias of HD, levodopa-induced dyskinesias in PD, cervical dystonia, epilepsy, and AD

AD: Alzheimer's disease; CBD: cannabidiol; HD: Huntington's disease; MS: multiple sclerosis; THC: Δ^9-tetrahydrocannabinol.
*Approved indications.

and schizophrenia [30]. Various cannabinoid preparations were analyzed together, and quality of evidence was considered to be generally inconclusive or insufficient.

Thus, overall, a large volume of published papers exist on the topic of medical use of cannabinoid-based preparations, but no clear distinction is made among the various preparations. No head-to-head trials comparing cannabinoid-based compounds in the same indication (e.g. spasticity due to MS, or pain) have been performed so far, and only in a few indications have the available data been sufficient to gain approval by the regulatory authorities.

4. Preclinical and clinical evidence

4.1. Experimental MS

There is a need for novel therapeutic strategies for MS. Different cannabinoids have been shown to exert immunomodulatory, antioxidant, neuroprotective, and oligoprotective effects which may be beneficial in neuroinflammatory pathologies such as MS [43]. Table 3 summarizes some of the interesting research findings with different cannabinoids in experimental MS models [43–50]. In addition, THC/CBD reduced spasticity in an experimental mouse model of MS and in this model, it was as effective as baclofen (Table 2) [48].

4.2. MS symptoms

4.2.1. THC/CBD oromucosal spray (Sativex®): current indications

In clinical trials and following its first regulatory approvals in 2011, THC/CBD 1:1 ratio oromucosal spray has been used for more than 45,000 patient/years [51], mainly in MS-related spasticity and, to a lesser degree, in patients with neuropathic pain or bladder dysfunction. Findings from MS spasticity pivotal clinical trials supported its approval in numerous countries for 'symptom improvement in adult patients with moderate-to-severe MS-related spasticity who have not responded adequately to other anti-spasticity medication and who demonstrate clinically significant improvement in spasticity related symptoms during an initial trial of therapy'. Other indications (children spasticity, pain, etc.) are still being studied.

In a recent review of the medical use of cannabinoids in selected neurologic disorders, the authors stated that for spasticity treatment, THC/CBD and THC are probably effective in reducing patient-centered measures; while for treatment of central pain or painful spasms, THC/CBD could probably be effective [35]. Yadav et al. in their evidence-based guidelines on complementary and alternative medicine in MS recommended THC/CBD for spasticity symptoms and pain [52]. In two recent reviews THC/CBD was rated as effective in patients with an inadequate response to first-line antispasticity medications [53,54] and there was supportive data relating to its use in central neuropathic pain (CNP) and bladder dysfunction [54].

4.2.2. THC/CBD in MS spasticity: pivotal and observational studies

Basic treatment of MS-related spasticity is physiotherapy followed by oral muscle relaxant drugs: baclofen, tizanidine, and, if neuropathic pain is present, gabapentin as first-line. For severe spasticity, intrathecal baclofen (especially spastic paraparesis) or botulinum toxin A (in focal spasticity) should be used [55]. Previously, cannabinoids were not recommended since THC and a herbal cannabis extract had shown no significant reduction of spasticity in several studies. This could, in part, be due to the studies using nonoptimal doses and/or the most appropriate cannabinoid active principles. Additionally, the main spasticity outcome measure was the Modified Ashworth Scale which is now viewed as not valid or reliable, and the 0-10 spasticity numeric rating scale (NRS) is considered a better option [56,57]. Furthermore, no assessment of responders and nonresponders was performed. Nevertheless, many patients have reported positive effects on overall mobility and on subjective impression of pain reduction [58]. In a meta-analysis of three studies with THC/CBD spray, it was found that treatment yielded a statistically significant greater proportion of clinically relevant responders versus placebo (37% vs. 26%, respectively; $p = 0.0073$) [59].

4.2.2.1. THC/CBD: pivotal studies. Because of possible underestimation of THC/CBD efficacy in early studies, Novotna et al. used an enriched design in a pivotal multicenter, double-blind RCT in MS patients with spasticity not relieved by usual drug therapy. After 4 weeks single-blind add-on treatment with THC/CBD oromucosal spray in all patients, only those with a 20% improvement in spasticity ('responders', 272 of 572 patients treated) were eligible for a 12-week randomized placebo-controlled phase. Of the 272 responders, 241 were randomized to THC/CBD or placebo. THC/CBD produced a statistically significant reduction ($p = 0.0002$) in the mean spasticity NRS score as well as significant improvements in the spasm frequency score, sleep disturbances, and patient,

Table 3. Effects of phytocannabinoids in experimental MS.

Compound	Model	Effects	Reference
THC	Chronic relapsing EAE	Amelioration of tremor and spasticity, immunosuppression, Th17 responses, disease progression	[44] [45]
CBD	Chronic relapsing EAE and chronic-progressive EAE (TMEV-IDD)	Inhibition of pathogenic T cells and microglial activity, leukocyte infiltration, neuroprotection	[46] [43] [47]
THC/CBD	Chronic relapsing EAE	Amelioration of spasticity THC/CBD 10/10 mg/kg equivalent to baclofen 5 mg/kg	[48]
CBG quinone	Chronic relapsing EAE	Alleviation of neuroinflammation, immunosuppression	[49] [50]

EAE: Experimental autoimmune encephalomyelitis; TMEV-IDD: Theiler's murine encephalomyelitis virus-induced demyelinating disease; CBD: cannabidiol; THC: Δ^9-tetrahydrocannabinol; CBG: cannabigerol.

caregiver and clinician Global Impression of Change NRS scores, with an acceptable tolerability profile [60]. Overall, THC/CBD was an effective antispastic agent in this RCT, and the enriched study design more closely reflects clinical practice since only patients likely to benefit from THC/CBD therapy actually received it. These results were verified in a *post-hoc* analysis of this study which concluded that THC/CBD oromucosal spray provided consistent relief in MS spasticity patients irrespective of pretreatment with other antispasticity drugs [61]. Additional evidence for the efficacy of THC/CBD arises from a controlled 5-week withdrawal study in patients on long-term treatment with THC/CBD who were blindly randomized to THC/CBD or placebo. Time to treatment failure was significantly in favor of THC/CBD ($p = 0.013$) [62].

In a recent review, the efficacy of THC/CBD spray in MS patients with resistant moderate-to-severe spasticity was also confirmed. The authors emphasized the benefits of self-adaptable dosing which allows patients to optimize treatment to their personal needs and helps them to control the relief of symptoms, adverse effects, and factors that may influence their quality of life (QoL) [63].

4.2.2.2. THC/CBD: observational studies. To build upon the results from the pivotal RCTs' program, several observational studies have been performed with THC/CBD in everyday clinical practice. In a recent review involving patients with moderate-to-severe resistant MS-related spasticity, the effectiveness of THC/CBD oromucosal spray was confirmed and a positive impact on QoL was highlighted [63]. Long-term studies of up to 2 years' duration confirmed the stable and sustained effect of THC/CBD treatment. Furthermore, in patients with secondary progressive MS and a mean Expanded Disability Status Scale of 7.5, similar reductions in NRS ratings occurred in patients treated with THC/CBD add-on therapy as those on THC/CBD monotherapy. During long-term use, the dosage of THC/CBD tended to be stable or to decrease over time [64]. In observational studies involving patients with moderate-to-severe MS-related spasticity, the effectiveness and tolerability of THC/CBD oromucosal spray was confirmed in 144 patients treated in a single-center in Milan [65] and in 1534 patients treated at 30 specialized MS centers across Italy [66]. Similar findings were also observed in more than 900 patients in United Kingdom, Germany, and Switzerland [51].

Despite spasticity often having a negative impact on mobility, objective gait parameters are not commonly measured in studies with cannabinoids. However, in one observational study of THC/CBD in 20 MS patients suffering from spasticity-induced restricted gait, improvements in both subjective (NRS-based) and objective assessments of movement, including increased speed (+15%), cadence (+6%), stride length (10%), and a reduction of Gait Profile Score by 10%, were recorded. More physiologic values for proximal leg and knee movements were also observed [67].

4.2.3. THC/CBD in neuropathic pain in MS

CNP is a frequent symptom of MS and cannot always be controlled using anticonvulsant drugs, antidepressants, or opioids. Therefore, THC/CBD may be potentially useful in this clinical setting.

In a phase III RCT in 339 MS patients (167 THC/CBD; 172 placebo) with insufficient analgesia from existing medication, there was a large number of responders to both THC/CBD and placebo during 14 weeks' double-blind treatment. However, 58 patients entered a consecutive 14-week open-label treatment plus a 4-week double-blind randomized withdrawal phase and there was an increased time to treatment failure in THC/CBD patients compared to placebo [68]. Furthermore, 57% of patients receiving placebo failed treatment versus 24% of patients from the THC/CBD group ($p = 0.04$). The mean change from baseline in pain NRS ($p = 0.028$) and sleep quality NRS ($p = 0.015$) scores were also statistically significant compared to placebo.

In a review that included data on efficacy and tolerability of THC/CBD in MS-related neuropathic pain, the authors stated that THC/CBD can be an appropriate treatment for pain patients particularly those resistant to their current pharmacological interventions [69].

4.2.4. THC/CBD tolerability and safety

Findings from two phase III pivotal studies [70,71] and a study by Wade and colleagues [72] were combined in a meta-analysis [59], and adverse events (AEs) were reported by 79.3% of THC/CBD patients and 55.8% of placebo patients [63]. AEs were mostly mild to moderate with dizziness being the most common. A total of 11.0% patients on THC/CBD and 3.6% on placebo withdrew from pivotal studies, mainly due to nausea, dizziness, or vertigo. Serious AEs occurred in 5.8% of THC/CBD-treated patients versus 4.3% in the placebo group and resolved without consequence [63]. In accordance with these results, dizziness and fatigue were the most common treatment-related AEs in observational studies involving THC/CBD [63].

In an observational study to determine the effects of THC/CBD oromucosal spray on driving ability, 33 MS patients underwent 5 driving test procedures from a validated computerized test battery before and after 4–6 weeks treatment with THC/CBD (titrated up to a maximum of 12 sprays/day; mean dosage at the end of the study was 5.1 sprays/day). The findings demonstrated that the drug does not negatively impact on driving ability [73].

4.3. Epilepsy

It has long been known that certain cannabinoids have anticonvulsant properties and could be effective in treating partial epilepsies and generalized tonic–clonic seizures (also known as grand mal seizures) [74]. The evidence for this is largely anecdotal, based on the observation that some individuals who smoked marijuana to treat their epilepsy, and who ceased cannabis use, reported a reemergence of convulsive seizures. Furthermore, it was reported that seizure control was reestablished when cannabis consumption was resumed. Multiple studies in experimental models have confirmed the efficacy of certain cannabinoids such as CBD in preventing seizures and reducing mortality in epilepsy; however, the mechanisms underpinning this pharmacological effect are not fully understood [75,76]. Activation of the eCB system prevents seizure-induced neurotoxicity and is neuroprotective. In addition, activation of CB_1 receptors reduces seizure

severity [75]. Rosenberg and colleagues reviewed data from preclinical seizure models in 13 studies and found that modulation of the eCB system resulted in anticonvulsant activity in 46.2%, a mixed effect in 23.1%, and no effect in 30.8% of them. CB_1 receptor agonists produced anticonvulsant activity in 68.1%, proconvulsant activity in 2.9%, a mixed effect in 7.2%, and no effect in 21.7% of studies [75].

Published clinical trial data are currently insufficient to provide support for the efficacy of cannabinoids for reducing seizure frequency [74]. Interestingly, a pharmaceutical formulation of CBD in oral solution (Epidiolex®) has recently completed two phase III randomized, placebo-controlled, clinical trials for the treatment of Lennox–Gastaut syndrome (n = 171, n = 225) [77], a rare and severe form of childhood-onset epilepsy. CBD has also been evaluated in a phase III study in children with resistant seizures (n = 120) associated with Dravet syndrome [78], a rare genetic epileptic encephalopathy, as well as a study which included some children with the disorder [79,80]. Based on these findings, CBD has been granted Orphan Drug status by the FDA for the treatment of Lennox–Gastaut and Dravet syndromes. Other studies in childhood epilepsy are ongoing for tuberous sclerosis complex seizures, Lennox–Gastaut syndrome, Dravet syndrome, and infantile spasms [80]. In the last couple of years, including presentations at the American Epilepsy Society Annual Meeting (6 December 2015), a number of studies relating to a physician-sponsored Expanded Access Program for Epidiolex have been presented, and these reported promising efficacy and tolerability data for the drug in about 260 patients [74,77,78,81].

4.4. Alzheimer's disease

Several studies have reported that the eCB system is a promising target for the treatment of Alzheimer's disease (AD) which is characterized by the presence of amyloid-β deposition and neuronal tau hyperphosphorylation in the brain associated with oxidative stress, neuroinflammation, and energy failure [82]. AD is associated with profound changes in the eCB system, most notably increased levels of CB_2 receptors in AD postmortem brain samples, predominantly in astrocytes and the microglia surrounding the amyloid-β plaques [83,84]. Pharmacological activation of CB_2 receptors has been shown to produce beneficial effects in several experimental models of AD. In animal models of the disease, CB_2 stimulation was shown to facilitate removal of amyloid-β plaques [85,86] and reduce neuroinflammation [86–92], oxidative stress damage [92,93], and tau hyperphosphorylation [92–94]. Improvements in cognitive deficits have also been reported [86,91,92,94]. It was previously shown that CB_2 receptor null in amyloid precursor protein (APP) transgenic mice had exacerbated amyloid-β production and plaque deposition as well as microgliosis associated with amyloid plaques [93]. Interestingly, the same mouse model was also associated with decreased total soluble tau, collectively demonstrating that CB_2 receptors have a modulatory role in the two main pathophysiological processes in AD [93].

Several studies have reported that the administration of different *C. sativa* derivatives has beneficial effects in animal models of AD. Indeed, THC enhanced mitochondrial function and decreased amyloid-β aggregation at extremely low concentrations in a dose-dependent manner in cells expressing amyloid-β protein precursor [95]. CBD administration ameliorated neuroinflammation [88,89], microgliosis, and cognitive deficits [96] in mice injected with amyloid-β in the hippocampus. CBD administration also reversed the social recognition deficit and improved several cognitive tasks in APP/PS1 transgenic mice, a well-established rodent model of AD [97,98].

Interestingly, a combination of THC and CBD produced greater benefit than either cannabinoid alone in *in vivo* rodent models of AD. Thus, the THC/CBD combination preserved memory and reversed learning impairment in APP/PS1 transgenic mice when administered during the early symptomatic stage, and the individual phytocannabinoids produced less benefit in this model [94,99]. Behavioral improvement was associated with reduced astrogliosis, microgliosis, levels of inflammatory-related molecules, and a decrease in soluble amyloid-β levels, the most toxic form of amyloid-β [99]. The mechanisms involved in the beneficial effects of the THC/CBD combination are not fully understood since individually they act on different pharmacological targets and intracellular signaling pathways [2,100]. However, several mechanisms could account for these neuroprotective effects, such as blockade of excitotoxicity, reduction in calcium influx, antioxidant effects, enhanced trophic factor support, and a decrease in pro-inflammatory mediators, among others [101].

4.5. Parkinson's disease

Cannabinoids have been investigated against neurodegeneration due to their ability to modify the activity of CB_1 and/or CB_2 receptors, in addition to strong antioxidant properties of some compounds. A combination THC/CBD improved the behavioral alterations and neurological deficits in parkin-null, human tau overexpressing (PK−/−/TauVLW) mice, a model of complex frontotemporal dementia, Parkinsonism, and lower motor neuron disease [102]. This improvement was associated with a decrease in gliosis and reduction in the levels of phosphorylated tau in the cerebral cortex and striatum, and deposition of amyloid-β in the cerebral cortex, together with an improvement in dopamine metabolism and redox state [102]. Furthermore, CBD and THCV (Table 1) exhibited neuroprotective effects along with the ability to reduce symptoms in different animal models of Parkinson's disease, thus highlighting a promising pharmacological profile that might be useful to design future novel anti-Parkinsonian therapies [103].

4.6. Huntington's disease

The beneficial effects of THC and CBD alone, or in combination, have been investigated in several animal models of Huntington's disease (HD). Their action was reported to be mediated by multiple targets, including CB_1/CB_2 receptors, additional eCB-binding receptors like PPARs, or even non-eCB targets [103]. In addition, controversial results have been obtained with phytocannabinoids in clinical trials of HD, and a recent phase II clinical trial with THC/CBD oromucosal spray

reported no benefit [103]. The effects of CBG, a non-psychotropic phytocannabinoid (Table 1), have been investigated in mouse models of HD, where it prevented striatal neuron death and neurological deterioration. Although these mechanisms are responsible for the beneficial effects of CBG, a direct interaction with CB_1 and/or CB_2 receptors seems unlikely, as CBG is known to have low affinity for both receptor types [103].

4.7. Pain treatment

The eCB system plays a crucial role in the control of nociceptive transmission acting at peripheral, spinal, and supraspinal levels [104]. At the periphery, CB_1 receptors located in nociceptive terminals and CB_2 receptors in immune cells inhibit nociceptive transmission [105]. CB_1 receptors expressed in the dorsal root ganglia and spinal cord inhibit neurotransmitter release and pain transmission, whereas CB_2 receptors modulate the immune responses leading to neuronal sensitization in the spinal cord during chronic pain [106]. At the supraspinal level, CB_1 stimulation inhibits ascending pain transmission, mainly at the thalamus level, improves the emotional pain component acting in the limbic and cortical areas, and activates the descending inhibitory pathway at the level of the periaqueductal gray matter and nucleus raphe magnus [104,106].

Numerous studies have reported the antinociceptive effects of several cannabinoids in different pain models. Early studies have reported the antinociceptive effects of THC [4,107] that has been shown to play a predominant role in the analgesic effects of *C. sativa* derivatives [108]. The effectiveness of cannabinoids in acute experimental models of pain is often lower than that exhibited by opioid agonists [109]. Other phytocannabinoids contained in *C. sativa* also produce analgesic effects in different experimental models, including CBD, CBG, CBN, CBC, and THCV and D9-tetrahydrocannabiorcol (THCO) [110].

CBD is the second most studied phytocannabinoid. A plethora of molecular targets have been proposed to explain the still unknown mechanism of action of CBD [111]. The anti-inflammatory and analgesic effects of CBD have been reported in multiple studies and experimental models of chronic inflammatory and neuropathic pain [4,111–113].

Different cannabinoids have shown pain relief-related effects in various animal models: CBN, CBC, and CBG. CBN produces anti-inflammatory and analgesic effects in rodents [114]. This phytocannabinoid has low affinity for CB_1 and CB_2 receptors and has agonist properties on the TRPV2 thermosensor, which underlines its potential interest in the treatment of burns [115]. CBC been reported to produce anti-inflammatory [116,117] and analgesic effects [118] in rodents. The analgesic effects of this phytocannabinoid seem to be mediated via activation of the descending antinociceptive pathway at the level of the periaqueductal gray matter [119], probably through an inhibition of anandamide uptake [120]. CBG produces analgesic effects in acute pain models in rodents [114]. This phytocannabinoid has a weak partial agonist effect at CB_1 and CB_2 receptors, has affinity for transient receptor potential cation channel, subfamily A, member 1 (TRPA1) channels, α2-adrenoreceptors and $5HT_{1A}$ serotonergic receptors, and is a strong inhibitor of GABA and anandamide uptake [4].

THCV antagonizes the antinociceptive effects of THC [110], probably due to its neutral antagonist properties on CB_1 and CB_2 receptors [121]. However, THCV induces important anti-inflammatory and analgesic effects in several models of acute, neuropathic, and inflammatory pain [112], possibly due to its ability to activate CB_2 receptors at high concentrations [122]. THCO also produces antinociceptive effects in several acute pain models acting at the spinal level [123]. This phytocannabinoid activates and desensitizes TRPA1 channels involved in pain transmission.

Preclinical studies have underlined the potential interest of cannabinoid compounds mainly in animal models that mimic two particular chronic pain conditions, that is, neuropathic and inflammatory pain [104,106]. Indeed, genetic studies using knockout mice have reported a crucial role of CB_2 receptors in the development of the nociceptive manifestations of neuropathic pain [124,125], whereas CB_1 receptors seem mainly involved in the affective component [126]. Both, CB_1 and CB_2 agonists attenuate the nociceptive manifestations of neuropathic pain, as well as the phytocannabinoids THC and CBD given alone or in combination [127]. The effectiveness of cannabinoid compounds on neuropathic pain has been shown in multiple animal models including constriction injury, sciatic and spinal nerve ligation, as well as diabetic, chemotherapy, lysolecithin, and viral-induced neuropathy [127].

CB_2 receptors have also been reported to play a major role in the development of the nociceptive manifestations of osteoarthritis pain [128], whereas CB_1 has a predominant role in the affective component of this chronic pain condition [129]. Both CB_1 and CB_2 agonists improve the nociceptive and emotional manifestations of osteoarthritis pain, whereas CB_1 agonists also improve the cognitive impairment produced by this chronic pain [129]. Interestingly, these studies using genetically modified mice suggest that CB_2 seems to be mainly involved in the development of neuropathic and osteoarthritis pain rather than in the manifestations of these chronic pain conditions [104,128]. In a recent study, administration of the CB_2 agonist JWH015 was shown to have opioid-sparing effects in rodent models of inflammatory, postoperative, and neuropathic pain, but not in a model of nociceptive pain [130].

5. Experts commentary

The last couple of decades have witnessed significant growth in research efforts involving the eCB system following the identification of cannabinoid receptors and ligands that interact with these receptors. We now have a greater understanding of the physiological functions that the eCB system performs, and how modulation of its activities holds therapeutic promise in a wide range of different diseases. The complexity of the eCB system is becoming better understood and new drivers of eCB signaling are emerging. For instance, membrane lipid composition can influence eCB signaling as in the case of CB_1 receptors which are localized in specialized microdomains on the cell surface called lipid rafts and FAAH that is modulated by membrane cholesterol. In addition, EITs and eCB storage sites like adiposomes can contribute to fine tuning of eCB signaling. All these new players are potential points of action for the development of properly targeted different innovative therapeutics. For example, a substantial proportion of CB_1 in the brain is localized intracellularly, and this may

significantly impact on the efficacy of CB_1-directed drugs. This research into the eCB system has been paralleled by the development of agents that interact with cannabinoid receptors. In this regard, it should be remembered that herbal cannabis contains a complex mixture of active ingredients (most notably THC and CBD) in varying amounts, and the individual components have quite distinct biological activities. Consequently, the 'polypharmacology' concept, whereby multiple receptors are targeted by multiple active principles at the same time, causing different effects (medicinal and/or unwanted) has to be taken into account. Such a concept appears relevant for the study of cannabinoids and exemplifies what might be needed for the research into future medicines [131]. Notably, cannabinoids like CBD and CBG are epigenetic regulators of gene expression [132], and this type of control seems to be important in experimental MS [133]. This observation may be relevant for developing personalized medicines. Indeed, different individual responses to the same dose of medicine can be due to different epigenomes, whereby the protein targets can be expressed to different extents in different subjects.

The analgesic effects of THC and other cannabinoids have been widely reported in multiple animal studies. Two chronic pain conditions, neuropathic and inflammatory pain, are of particular interest for the possible development of effective treatments based on cannabinoid derivatives. CB_2 receptors located in immune cells are specifically involved in the processes underlying the development of chronic neuropathic and osteoarthritis pain, rather than in the manifestations of these chronic pain conditions. Therefore, the potential interest of certain cannabinoids at different doses in preventing the development of these chronic pain conditions merits investigation. The effectiveness of some cannabinoids in acute pain conditions is often lower than that exhibited by opioid compounds, which must be taken into consideration for the future design of appropriate clinical trials in order to be able to reveal the potential beneficial effects of cannabinoid derivatives in pain treatment. Two specific cannabinoids, THC and CBD, have been reported to produce beneficial effects in several animal models of AD. Interestingly, the combination of THC and CBD produces greater overall benefit versus either cannabinoid administered alone, with the added advantage of reducing psychoactivity [134]. The mechanisms underlying the beneficial effects of the THC/CBD combination in AD have not been clarified and deserve further investigation. However, the specific beneficial effects obtained with this combination in early stages of the disease in rodents suggest that clinical trials should also be designed in patients with early stage disease. Other diseases in which the cannabinoids are being investigated include Parkinson's disease, HD, and epilepsy. Recently, CBD has been granted Orphan Drug status by the FDA for the treatment of Lennox–Gastaut and Dravet syndromes and additional studies in childhood epilepsy are ongoing for tuberous sclerosis complex seizures, Lennox–Gastaut syndrome, Dravet syndrome, and infantile spasms [80].

For clinical usage, it is important that any cannabinoid preparation studied should be strictly standardized since cultivation conditions, extraction procedures, and formulation can markedly impact on the biological activity of the final product. THC/CBD (Sativex®) is a plant-derived cannabinoid preparation that is cultivated under strictly controlled conditions and produced using standardized procedures [135] to deliver an oromucosal formulation that has received regulatory approval in a number of countries for the treatment of MS-related spasticity. THC/CBD oromucosal spray has been in clinical use for approximately 5 years in numerous European and other countries worldwide for the management of moderate-to-severe resistant MS spasticity. Reviewing all the current evidence, Otero-Romero and colleagues concluded that THC/CBD can have a beneficial effect as add-on therapy in patients with a poor response and/or intolerance to first-line oral treatments like baclofen, tizanidine, and gabapentin [136]. Nevertheless, its efficacy as monotherapy/first-line use has not been examined sufficiently. Findings as an add-on drug in neuropathic pain are encouraging but require confirmation. AEs are usually mild.

6. Five-year view

While we have come a long way in our understanding of the eCB system over the last 10–20 years, we still have much to learn about the relationship between receptor signaling and specific pathological changes. In the next 5 years, we will likely see a much greater focus on research aimed at identifying the link between the eCB system and specific pathologies. For example, CB_2 receptor expression is induced in patients with AD and targeting CB_2 receptors may prove beneficial. In animal models of AD, CB_2 receptor agonists have been shown to improve cognitive performance. Considering the pleiotropic effects of CB_2 receptors and the lack of undesirable psychoactive effects, compounds acting at this level might represent a promising therapy against AD. Nevertheless, we have no information regarding the efficacy of drugs specifically targeting CB_2 receptors in the clinical setting. The same considerations apply to a number of diseases such as epilepsy, the development of neuropathic and osteoarthritic pain, Parkinson's disease, and HD to name a few. In parallel with this research, we will likely see the introduction of newer agents aimed at specific targets within the eCB system.

In the case of THC/CBD oromucosal spray over the next 5 years, we should get a clearer understanding of its overall benefits and safety, particularly when used for extended treatment periods (>5 years) and in different spasticity or pain states. Another aspect of its potential usage will likely relate to formal assessment of its use as monotherapy since this is how some patients are currently choosing to use it.

Clearly, one of the most important aspects relating to a new clinical approach is to fully establish the therapeutic benefits, safety, and tolerability that each cannabinoid agent or combination possesses, so as to minimize the inappropriate use of products, aimed at achieving medicinal results, but containing active principles with mixed properties. Findings with THC/CBD oromucosal spray are reassuring, and the same level of thoroughness needs to be applied to research with the different cannabinoid chemical entities in each disease setting that is being researched.

Key issues

- Identification of cannabinoid receptors and their endogenous ligands has triggered an upsurge in research in the endocannabinoid (eCB) system and its functioning in health and disease.
- The complexity of the eCB system is becoming better understood and new drivers of eCB signaling are emerging and this raises the possibility of new treatment modalities.
- Research into the eCB system has been paralleled by the development of agents that interact with cannabinoid receptors. In this regard it should be remembered that herbal cannabis contains a complex mixtures of active ingredients (most notably THC and CBD), and the individual components have quite distinct biological activities.
- Herbal cannabis use has a number of relevant risks, especially in younger individuals such as adolescents.
- Pharmacological research is expanding to investigate the role of the eCB system in other pathologies including various pain states, Alzheimer's disease, Parkinson's disease, Huntington's disease and epilepsy.
- Clinically, THC/CBD oromucosal spray has been in use for over five years in some countries for the management of moderate to severe resistant MS spasticity and it has proven to be beneficial as add-on therapy in patients with a poor response and/or intolerance to first-line oral treatments like baclofen, tizanidine and gabapentin.
- Future research will likely focus on gaining a better understanding of the role of the eCB system in other diseases which could benefit for cannabinoid-based therapy.

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