Drugs (2017) 77:563–574
DOI 10.1007/s40265-017-0720-6

ADIS DRUG EVALUATION

Delta-9-Tetrahydrocannabinol/Cannabidiol Oromucosal Spray (Sativex®): A Review in Multiple Sclerosis-Related Spasticity

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Published online: 14 March 2017

Abstract Delta-9-tetrahydrocannabinol (THC)/cannabidiol (CBD) oromucosal spray (THC/CBD, Sativex®, nabiximols) is available in numerous countries worldwide for the treatment of multiple sclerosis (MS)-related moderate to severe spasticity in patients 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. Twelve weeks' therapy with THC/CBD improved MS-related spasticity in patients with an inadequate response to other anti-spasticity agents who had undergone a successful initial trial of THC/CBD therapy, according to the results of a pivotal phase 3 trial. Improvements in spasticity were maintained in the longer term with THC/CBD with no evidence of dose tolerance, and results of real-world studies confirm the effectiveness of THC/CBD in everyday clinical practice. Improvements in health-related quality of life and activities of daily living were also seen with THC/CBD. THC/CBD is generally well tolerated; adverse effects such as dizziness may occur whilst the THC/CBD dosage is being optimized. THC/CBD has low abuse potential and a low risk of psychoactive effects. In conclusion, THC/CBD oromucosal spray is a useful option for the treatment of MS-related spasticity not completely relieved with current anti-spasticity medication.

Delta-9-tetrahydrocannabinol/cannabidiol (Sativex®): clinical considerations in MS-related spasticity
Oromucosal spray containing THC and CBD in an ≈1:1 fixed ratio
Individually titrated to an optimal dosage during an initial trial of therapy
Following a successful initial trial, improves MS-related spasticity in patients with an inadequate response to other anti-spasticity agents, with improvements maintained in the longer term
Real-world studies confirm the effectiveness of THC/CBD in everyday clinical practice
Generally well tolerated
Low abuse potential and low risk of psychoactive effects

1 Introduction

The majority of patients (>80%) with multiple sclerosis (MS) report spasticity during the course of the disease, which they experience as continuous muscle stiffness [1–3]. Spasticity is also associated with spasms and worsening of other MS symptoms, such as impaired mobility, fatigue or pain, and has a significant impact on health-

The manuscript was reviewed by: ***W. Notcutt***, Department of Pain Management, James Paget University Hospital, Great Yarmouth, Norfolk, UK; ***F. Patti***, Department of Medical, Surgical Science and Advanced Technology "GF Ingrassia", University of Catania, Catania, Italy; ***C. Solaro***, Rehabilitation Unit, ML Novarese Hospital, Moncrivello, Italy; ***M. Trojano***, Department of Basic Medical Sciences, Neurosciences and Sense Organs, University of Bari "Aldo Moro", Bari, Italy.

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related quality of life (HR-QOL) and activities of daily living (ADL) [1, 2].

Oral agents commonly used in the treatment of MS-related spasticity include baclofen, tizanidine, dantrolene and gabapentin [3]. However, patients and physicians frequently express dissatisfaction with these treatment options [1, 2], most commonly because of inadequate efficacy or adverse events [2]. Thus, there has been a need for additional anti-spasticity agents to treat MS-related spasticity.

Delta-9-tetrahydrocannabinol (THC)/cannabidiol (CBD) oromucosal spray (Sativex®, nabiximols, hereafter referred to as THC/CBD) comprises extracts of *Cannabis sativa* L., with each 100 μL spray containing 2.7 mg of THC and 2.5 mg of CBD (i.e. an approximately 1:1 fixed ratio) [4, 5]. THC/CBD is available in about 20 countries worldwide for the treatment of MS-related moderate to severe spasticity in patients 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 THC/CBD therapy. This narrative review summarizes the pharmacological properties of THC/CBD, as well as providing an overview of its clinical efficacy and tolerability in MS-related spasticity.

2 Pharmacological Properties

2.1 Mechanism of Action

Different endocannabinoid receptors have been described. CB_1 receptors are abundantly expressed in the CNS, with the highest levels found in the basal ganglia, cerebellum, hippocampus and cortex [3, 6, 7]. CB_1 receptors are also found in afferent and efferent nerve pathways in the peripheral nervous system and at the neuromuscular junction, meaning that cannabinoids can affect both central and peripheral sites within the nervous system [3, 6]. CB_2 receptors are primarily located in immune cells [8].

The most common endocannabinoids anandamide and 2-arachidonoylglycerol act as retrograde synaptic messengers, activating presynaptic CB_1 receptors and inhibiting the release of excitatory neurotransmitters such as glutamate and inhibitory neurotransmitters such as γ-aminobutyric acid [3, 6, 9]. Limiting excessive glutamatergic signalling may help limit symptoms of MS, such as spasticity [6].

THC is the main psychoactive constituent of cannabis, whereas CBD is a non-psychoactive component that may reduce the effects of THC (including its psychoactive effects) [6, 9, 10]. Other effects of THC include analgesia, muscle relaxation, anti-emesis and appetite stimulation [3]. THC mimics the effects of endocannabinoids and acts as a partial agonist at both CB_1 and CB_2 receptors, whereas CBD has little activity at CB_1 receptors, but greater activity at CB_2 receptors [3, 11]. It has been suggested that THC/CBD reduces spasticity via the modulation of both cortical and spinal circuits [12, 13].

2.2 Pharmacodynamic Profile

2.2.1 Effects on Spasticity

CB receptor agonists demonstrated activity in animal models of MS and spasticity, improving limb stiffness (a marker of spasticity) and motor function [4, 14]. For example, a dose-dependent reduction in hind limb stiffness was seen with THC/CBD in a mouse model of MS [14].

The beneficial effects of THC/CBD on spasticity in patients with MS-related spasticity are discussed in Sect. 3. Several studies have examined structural or neurophysiological correlates that may explain these beneficial effects [13, 15–20]. Although spasticity improved in ten patients with MS-related spasticity who received THC/CBD for 12 months, the improvement was not correlated with changes in magnetic resonance imaging (MRI) features, the central motor conduction time or the ratio between H-reflex and M-wave amplitudes [15]. By contrast, an association between THC/CBD therapy and an increase in global brain connectivity on functional MRI was seen in 12 patients with MS-related spasticity [19], and results of a larger study ($n = 57$) indicated that the stretch reflex may be a useful neurophysiological measure of response to THC/CBD [20]. In addition, results of a recent study ($n = 55$) indicate that ultrasound elastography may be useful in terms of evaluating MS-related spasticity and the response to THC/CBD anti-spasticity treatment [21]. A significant ($p < 0.001$) correlation was found between the Ashworth Scale score (a measure of spasticity used in the clinical setting) and the Muscle Elastography Multiple Sclerosis score (MEMSs) in patients with MS-related spasticity. A significant ($p < 0.0001$) improvement from baseline in MEMSs was seen in 39 patients who responded to 1 month's therapy with THC/CBD [21].

Gait analysis demonstrated significant ($p < 0.001$) improvements from baseline in speed, cadence and stride length in patients with MS-related spasticity who received THC/CBD for 1 month [22].

2.2.2 Other Effects

Long-term treatment with therapeutic doses of THC/CBD was not associated with cognitive decline, according to the results of a randomized, double-blind, placebo-controlled, multicentre study (see also Sects. 3.1.2 and 4.2) [23]. Patients with MS associated with at least moderate

spasticity that was not completely relieved with current anti-spasticity medication were randomized to receive THC/CBD ($n = 62$) or placebo ($n = 59$) [maximum 12 sprays per day]. Following a 2-week titration period, patients entered a 46-week maintenance period. The mean number of daily THC/CBD sprays was 7.6 in the first 3 months of the study versus 6.4 in the last 3 months of the study. THC/CBD was deemed noninferior to placebo in terms of the mean change from baseline to the end of treatment in the Paced Auditory Serial Addition Test-I and -II combined total score (+6.02 vs. +7.49; primary endpoint) [23]. Moreover, no cognitive impairment or psychopathological symptoms were seen in 17 cannabis-naïve patients with MS who received THC/CBD (mean 8.2 sprays per day) for 3 weeks in a randomized, double-blind, placebo-controlled, crossover study [24]. Significant cognitive impairment and psychoactive effects have been reported with the administration of supratherapeutic doses of THC/CBD (18 sprays over 20 min twice daily) [4].

In terms of subjective drug effects, administration of two or six sprays of THC/CBD at one time to cannabis smokers did not result in subjects feeling 'high', although a significant ($p = 0.022$ vs. placebo) 'good drug effect' was reported with six sprays of THC/CBD, according to the results of a crossover study [10]. Two sprays of THC/CBD was significantly ($p = 0.032$) more 'stimulating' than placebo, and six sprays of THC/CBD induced significantly ($p \leq 0.004$) more 'anxiety' than two sprays of THC/CBD [10].

None of six primary measures of abuse potential significantly differed between recreational cannabis users who received four sprays of THC/CBD at one time or placebo, and most primary endpoints were significantly ($p < 0.05$) lower with this THC/CBD dose than with 20 or 40 mg of the synthetic THC dronabinol [25]. With administration of eight sprays or a supratherapeutic dose of 16 sprays of THC/CBD at one time, two and five primary measures of abuse potential, respectively, were significantly ($p < 0.05$) greater than with placebo, and these THC/CBD doses showed similar or significantly ($p < 0.05$) lower abuse potential than equivalent oral doses of dronabinol (i.e. 20 or 40 mg) [25]. It should be noted that the maximum number of THC/CBD sprays per day should not exceed 12, and these should be spread throughout the day (Sect. 5) [4].

The EU summary of product characteristics (SPC) states that the use of THC/CBD is not recommended in patients with serious cardiovascular disease [4]. However, no clinically relevant changes in the corrected QT, PR or QRS intervals, heart rate or blood pressure were reported in healthy volunteers who received THC/CBD (up to 18 sprays administered over 20 min twice daily) [4]. In addition, administration of two or six sprays of THC/CBD to cannabis smokers did not affect cardiovascular responses (heart rate, systolic and diastolic blood pressure) to a clinically significant extent [10].

2.3 Pharmacokinetic Profile

Both THC and CBD were rapidly absorbed following oromucosal administration of a single dose of THC/CBD 10.8/10 mg (i.e. four sprays) to healthy subjects; a mean peak plasma concentration (C_{max}) for THC of $\approx$4 ng/mL was reached after 45–120 min and a mean C_{max} for CBD of $\approx$1.2 ng/mL was reached after 45–135 min [26]. Pharmacokinetic parameters for THC/CBD showed a moderate to high degree of variability both between and within healthy volunteers [26]. When a single dose of THC/CBD was administered to healthy volunteers with food versus under fasting conditions, C_{max} and area under the plasma concentration-time curve values were increased 1.6- and 2.8-fold, respectively, for THC and 3.3- and 5.1-fold, respectively, for CBD, although marked inter-subject variability means that these increases in exposure were considered unlikely to be clinically relevant (see Sect. 5) [27].

Plasma THC concentrations were numerically lower following oromucosal administration of THC/CBD than after inhalation of similar doses of cannabinoids [26, 28]. For example, THC C_{max} values were 5.40 ng/mL with oromucosal administration of THC 21.6 mg (as THC/CBD), 118.6 ng/mL with inhaled vaporized THC extract providing THC 8 mg and 162.2 ng/mL with smoked cannabis providing THC 33.8 mg [4, 26, 28].

Cannabinoids are highly lipophilic, with THC and CBD being stored in fatty tissues and slowly released back into the blood stream at subtherapeutic concentrations [29, 30]. THC is $\approx$97% protein bound [30].

THC is metabolized by cytochrome P450 (CYP) 2C9 to its primary metabolite 11-OH-THC, which undergoes further hepatic metabolism [30, 31]. CYP3A isozymes also catalyse the formation of other hydroxylated minor metabolites [30, 31]. CBD also undergoes extensive hepatic metabolism, primarily via hydroxylation and oxidation at C-7 [30, 32].

Oral cannabinoids undergo biphasic elimination, with a prolonged elimination half-life reflecting their gradual release from fatty tissue [4]. Following oromucosal administration of two, four or eight sprays of THC/CBD, the first-order terminal elimination half-life was 1.94, 3.72 and 5.25 h, respectively, for THC and 5.28, 6.39 and 9.36 h, respectively, for CBD [4, 26].

Data are lacking concerning the use of THC/CBD in patients with renal or hepatic impairment [4]. The effects of THC/CBD may be exaggerated or prolonged in patients with significant renal or hepatic impairment, and frequent clinical evaluation by a clinician is recommended [4].

2.4 Potential Drug Interactions

Given that coadministration of the CYP3A4 inhibitor ketoconazole increased the exposure of THC [33], the main THC metabolite (11-OH-THC) and CBD, re-titration of the THC/CBD dose (see Sect. 5) may be required if CYP3A4 inhibitors (e.g. ketoconazole, itraconazole, ritonavir, clarithromycin) are started or stopped during treatment with THC/CBD [4].

Coadministration of the CYP3A4 inducer rifampicin decreased the exposure of THC, 11-OH-THC and CBD [33], meaning that coadministration of THC/CBD and strong CYP3A4 inducers [e.g. rifampicin, carbamazepine, phenytoin, phenobarbital, hypericum (St. John's wort)] should be avoided [4]. If concomitant therapy is considered necessary, careful titration of THC/CBD is recommended, particularly within the 2 weeks after the CYP3A4 inducer has been stopped [4].

No interactions are anticipated between THC/CBD and CYP3A4 substrates, given that in vitro inhibition of CYP3A4 and CYP2C19 occurred at THC/CBD concentrations much higher than peak concentrations seen in clinical trials [4].

The EU SPC recommends care when coadministering THC/CBD with hypnotics, sedatives and drugs with potential sedating effects, given that additive effects on sedation and muscle relaxation may occur [4]. In addition, care is also recommended when coadministering anti-spasticity agents with THC/CBD, given that a reduction in muscle tone and power may occur, leading to an increased risk of falls [4].

Patients should avoid alcohol whilst receiving THC/CBD, particularly at the beginning of treatment or when changing the THC/CBD dosage, as THC/CBD may interact with alcohol, affecting co-ordination, concentration and the ability to respond quickly [4].

3 Therapeutic Efficacy

3.1 Comparisons with Placebo

Results of an exploratory trial suggested that THC/CBD had efficacy in spasticity associated with MS [34]. Subsequent 6-week [35] and 15-week [36] randomized, double-blind, multicentre trials included patients with MS-related spasticity ($n = 189$ [35] and 337 [36]). In these trials (which did not use an enriched study design), patients were randomized to receive THC/CBD or placebo; the primary endpoint in both trials was the change from baseline in the spasticity Numerical Rating Scale (NRS) score. The mean change from baseline in the spasticity NRS score significantly ($p = 0.048$) favoured THC/CBD versus placebo recipients in the 6-week trial [35], although there was no significant difference between THC/CBD and placebo recipients in the 15-week trial [36]. Longer-term follow-up of the exploratory trial [34] indicated that the efficacy of THC/CBD was maintained in patients who experienced benefit during the initial 10-week trial [37]. Accordingly, the main focus of this section is a large, pivotal phase 3 trial that used an enriched study design [38].

3.1.1 Enriched Trial Design and Results

The large, pivotal, multinational phase 3 trial included a 4-week single-blind treatment period (phase A) during which all patients received THC/CBD [38]. Phase A enrolled patients who had MS (any subtype) for ≥6 months and MS-related spasticity for ≥3 months ($n = 572$). Spasticity had to be of at least moderate severity [spasticity NRS score of ≥4; scores range from 0 (no spasticity) to 10 (maximal spasticity)] and not completely relieved with current anti-spasticity medication. During the first 10 days, patients self-titrated to their optimal dose using a pre-defined up-titration scheme (maximum 12 sprays in any 24-h period). Among the patients enrolled in phase A, the mean durations of MS and spasticity were 12.4 and 7.5 years and the mean spasticity NRS score at baseline was 6.9 [38].

With THC/CBD, a ≥20% reduction from screening baseline to the end of phase A in the spasticity NRS score occurred in 272 patients (48% of the baseline sample), and the mean spasticity NRS score was reduced from screening baseline by 3.01 points (Table 1) [38]. Of these patients, 241 entered phase B, which was a 12-week double-blind treatment period during which patients were randomized to receive THC/CBD ($n = 124$) or placebo ($n = 117$). In phase B, patients randomized to THC/CBD received a mean 8.3 sprays per day (Table 1) [38].

Concomitant anti-spasticity and disease-modifying medications had to have been maintained at stable dosages for ≥30 days prior to and throughout the study [38]. The majority of randomized patients (73%) were also receiving centrally-acting agents [including baclofen (58%), tizanidine (17%)], with anticonvulsants, benzodiazepine-related derivatives and adamantane derivatives administered to 24, 22 and 13% of patients, respectively. Medications taken for reasons other than spasticity included antidepressants (>32% of patients), analgesics (>30%), proton pump inhibitors (16%), urinary antispasmodics (20%) and lipid-lowering agents (>10%) [38].

The primary endpoint was the change from double-blind baseline (i.e. mean of the last 7 days of phase A) to the end of phase B in the spasticity NRS score [38]. Efficacy was assessed in the intent-to-treat population [38].

In phase B, the mean change from double-blind baseline to the end of week 12 in the spasticity NRS score was

Table 1 Efficacy of delta-9-tetrahydrocannabinol/cannabidiol oromucosal spray in patients with multiple sclerosis-related spasticity: results of the pivotal, phase 3, enriched-design trial [38]

Study phase (duration; weeks)	Treatment	No. of evaluable pts	Mean no. of sprays per day	Mean NRS spasticity score		≥30% reduction in the spasticity NRS score[a] (% of pts)
				Baseline	Change at endpoint	
Phase A (4)	THC/CBD	572	6.9	6.91[b]	−3.01	
Phase B (12)	THC/CBD	124	8.3	3.87[c]	−0.19*[d]	74*
	PL	117	8.9	3.92[c]	+0.64[d]	51

NRS numerical rating scale, *PL* placebo, *pts* patients, *THC/CBD* delta-9-tetrahydrocannabinol/cannabidiol

* $p < 0.001$ vs. PL

[a] Reduction from screening baseline

[b] Screening baseline

[c] Double-blind baseline (mean of the last 7 days of phase A)

[d] Primary endpoint

−0.19 points among patients receiving THC/CBD and +0.64 points among patients receiving placebo (Table 1), with the estimated between-group difference in the mean spasticity NRS score significantly favouring THC/CBD recipients (−0.83 points; $p = 0.0002$) [38]. In addition, significantly ($p = 0.0003$) more THC/CBD than placebo recipients achieved a ≥30% reduction from screening baseline to the end of phase B in the spasticity NRS score (odds ratio 2.73; 95% CI 1.59–4.69) (Table 1) [38].

During phase B, changes in spasm frequency, the sleep disruption NRS score, the Barthel ADL index, the Subject Global Impression of Change (SGIC) score, the Carer Global Impression of Change (CGIC) impression of function score and the Physician Global Impression of Change (PGIC) score all significantly ($p < 0.05$) favoured patients receiving THC/CBD versus placebo [38]. No significant between-group differences were seen in terms of changes in the Modified Ashworth Scale score, the Motricity index (arm and leg), the timed 10-m walk, the European Quality of Life-5 Dimension (EQ-5D) health state index, the EQ-5D health status visual analogue scale (VAS) score, the 36-item Short-Form Health Survey domain scores and the CGIC ease of transfer score [38].

A post hoc analysis demonstrated that THC/CBD improved spasticity regardless of patients' anti-spasticity treatment history [39]. This analysis distributed the study patients between those with at least one previous failed anti-spasticity therapy attempt with baclofen or tizanidine (group 1; $n = 162$) or at least two previous failed anti-spasticity therapy attempts with baclofen and tizanidine (group 2; $n = 57$). In both groups 1 and 2, significantly ($p < 0.05$) more patients receiving THC/CBD than placebo had an improvement in the spasticity NRS score of ≥18% (87.3 vs. 66.3% in group 1 and 92.9 vs. 65.5% in group 2) and ≥30% (74.7 vs. 51.8% in group 1 and 82.1 vs. 55.2% in group 2) [39].

3.1.2 Longer-Term Trials

An enriched enrolment randomized withdrawal study included patients with MS-related spasticity who had been experiencing long-term benefit from THC/CBD therapy [40]. Patients in this multicentre study had to have been receiving THC/CBD for ≥12 weeks prior to screening and had to be considered to be experiencing benefit; other anti-spasticity medications had to have been maintained at stable dosages for ≥3 months prior to study entry [40].

All patients continued to use THC/CBD during a 1-week baseline period, after which patients were randomized to receive THC/CBD ($n = 18$) or placebo ($n = 18$) for 4 weeks [40]. Prior to randomization, the mean duration of THC/CBD use was 4.2 years in patients randomized to THC/CBD and 3.0 years in patients randomized to placebo, with use of a mean 7.3 and 9.2 sprays per day in the corresponding treatment groups. The primary endpoint was the time to treatment failure (TTF; defined as either cessation of treatment before day 28, or a worsening of spasticity or a clinically relevant increase in or addition to anti-spasticity medication or disease-modifying medication) [40].

The efficacy of THC/CBD was maintained in the longer term, with TTF significantly favouring THC/CBD versus placebo recipients (hazard ratio 0.335; 90% CI 0.162–0.691; $p = 0.013$) [40]. At the end of the 4-week withdrawal period, treatment failure had occurred in 94% of placebo recipients compared with 44% of THC/CBD recipients [40].

In another longer-term study (see Sect. 2.2.2 for study details), mean changes from baseline to week 48 (the end of treatment) in the SGIC, CGIC and PGIC scores all significantly ($p < 0.05$) favoured patients receiving THC/CBD versus placebo [23]. However, mean changes from baseline to week 48 in the Modified Ashworth Scale score

and the timed 10-m walk did not significantly differ between patients receiving THC/CBD and those receiving placebo. It should be noted that this study was not powered for these endpoints as it was primarily designed to examine effects on cognition [23].

3.2 Real-World Studies

The efficacy of THC/CBD has been confirmed in several prospective, non-interventional studies conducted in real-world settings. The MOVE 2 studies included patients with moderate to severe MS-related spasticity (defined as spasticity causing limitations to ADLs or activities in a social environment, or where there is a risk of spasm-related complications) who received THC/CBD in routine care outpatient settings. The first MOVE 2 study was conducted in Germany [41, 42]. Results of the subsequent MOVE 2 EU study [43] and an interim analysis of Italian data from MOVE 2 EU [44] have also been reported. In the MOVE 2 analyses, use of other anti-spasticity medications was reported in the majority of patients at baseline [41, 43, 44]. Additional real-world studies include the Italian Medicines Agency (AIFA) registry study [45], a multicentre Spanish study [46], and single-centre Italian [47, 48] and German [49] studies. Patients were receiving THC/CBD for MS-related spasticity [45–49] of moderate to severe severity [45, 46, 48], and had an inadequate response to other anti-spasticity medications [45, 46, 48, 49]. One study also included patients receiving THC/CBD monotherapy because they did not tolerate other anti-spasticity drugs [49].

In MOVE 2 Germany, physicians judged THC/CBD to have provided relief of MS-related spasticity in 206 of 276 patients (74.6%) after 1 month of treatment [41]. The mean spasticity NRS score was significantly improved at this time point in the overall population and in initial responders (i.e. those with a ≥20% improvement from baseline in the spasticity NRS score) (Table 2). An extension of the German analysis showed that the significant improvement in the mean spasticity NRS score was maintained at 12 months (Table 2) [42]. The proportion of patients with a ≥20 or ≥30% improvement from baseline in the spasticity NRS score at 1, 3 and 12 months is shown in Table 2 [41, 42]. In terms of other endpoints, significant ($p < 0.001$) improvements from baseline to 1 month were reported in the mean sleep disruption NRS score and ADL impairment, and there were significant ($p < 0.05$) reductions from baseline in the proportion of patients reporting pain, muscle stiffness, bladder disorders and restricted mobility as their most disturbing symptom [41]. At 3 months, significant ($p < 0.01$) improvements from baseline were reported in Multiple Sclerosis Quality of Life-54 physical and mental health composite scores [41].

Over 80% of patients had an initial response to THC/CBD at 1 month in MOVE 2 EU [43], as well as in the interim Italian analysis of MOVE 2 EU [44] (Table 2). In MOVE 2 EU, the mean spasticity NRS score was significantly improved at 3 months, and 30.6% of patients had a ≥30% improvement from baseline in the spasticity NRS score (Table 2) [43]. In the overall population and in initial responders in MOVE 2 EU, there were significant ($p < 0.05$) improvements from baseline to month 3 in the daily spasm count, the sleep impairment NRS score, the number of spasticity-related awakenings per night, the fatigue NRS score, the pain NRS score, the number of weekly urinary incontinence events and the EQ-5D VAS score for overall current state of health [43].

An initial response (i.e. a ≥20% improvement from baseline in the spasticity NRS score) occurred in 70.5% of patients in the Italian AIFA registry study (1615 enrolled patients; Table 2) [45]. The mean spasticity NRS score was significantly reduced from baseline by 23, 32 and 35% after 1, 3 and 6 months' follow-up, respectively (Table 2) [45].

In the Spanish study ($n = 205$), 68 and 60% of patients were considered by the treating physician to have derived sufficient clinical benefit from THC/CBD to continue with treatment after 6 and 12 months' follow-up, respectively (Table 2) [46].

In patients receiving THC/CBD in the single-centre Italian studies (144 [48] and 102 [47] enrolled patients), the mean spasticity NRS score was significantly reduced from baseline at 1 month and in the longer term (up to 48 weeks [48] or 12 months [47] of follow-up) (Table 2). A significant improvement in the timed 25-foot walk test was seen at 1 month in one study (Table 2) [47]. In the other study, the proportion of patients with a ≥20% improvement from baseline in the spasticity NRS score at 4 weeks and a ≥30% improvement from baseline in the NRS spasticity score at 14 weeks is shown in Table 2 [48].

Of the 166 patients who started treatment with THC/CBD in the single-centre German study, 120 remained on treatment (response rate of 72%), including 25 patients receiving THC/CBD monotherapy, after a mean duration of follow-up of 9 months [49]. The change from baseline in the mean spasticity NRS score in responders is shown in Table 2 [49].

4 Tolerability

4.1 General Adverse Event Profile

THC/CBD oromucosal spray is generally well tolerated in patients with MS-related spasticity. Adverse events such as dizziness may occur whilst the THC/CBD dosage is being optimized [4]. For example, during phase A of the pivotal

Table 2 Results of prospective studies examining the efficacy of delta-9-tetrahydrocannabinol/cannabidiol oromucosal spray in patients with multiple sclerosis-related spasticity in real-world settings

Study[a] (no. of enrolled pts)	Time point	Mean no. of sprays per day	Findings
MOVE 2 Germany [41, 42] (335)	1 month	6.9	≥20 and ≥30% ↓ in NRS spasticity score in 41.7 and 25.5% of evaluable pts ($n = 216$)
			Mean NRS spasticity score ↓ from 6.1 (BL) to 5.2*** ($n = 216$)
			Mean NRS spasticity score ↓ from 6.4 (BL) to 3.9*** in IRs[b] ($n = 90$)
	3 months	6.7	≥20 and ≥30% ↓ in NRS spasticity score in 58.7 and 40.0% of evaluable pts ($n = 75$)
	12 months	6.2	≥20 and ≥30% ↓ in NRS spasticity score in 52.9 and 41.2% of evaluable pts ($n = 51$)
			Mean NRS spasticity score ↓ from 6.2 (BL) to 4.6*** ($n = 51$)
			Mean NRS spasticity score ↓ from 6.7 (BL) to 3.3*** in IRs[b] ($n = 27$)
MOVE 2 EU [Italian analysis] [44] (322)	1 month	6.1	≥20% ↓ in NRS spasticity score in 82.9% of evaluable pts ($n = 322$)
	3 months	5.1	≥30% ↓ in NRS spasticity score in 24.6% of evaluable pts ($n = 203$)
			Mean NRS spasticity score ↓ from 6.8 (BL) to 5.5*** ($n = 166$)
MOVE 2 EU [43][c] (433)	1 month	≈6	≥20% ↓ in NRS spasticity score in 80.6% of evaluable pts ($n = 433$)
	3 months	≈6	≥30% ↓ in NRS spasticity score in 30.6% of evaluable pts ($n = 281$)
			Mean NRS spasticity score ↓ from 6.9 (BL) to 5.4*** ($n = 433$)
			Mean NRS spasticity score ↓ from 6.9 (BL) to 5.3*** in IRs[b] ($n = 349$)
Italian AIFA registry [45] (1615)	1 month	6.8	≥20 and ≥30% ↓ in NRS spasticity score in 70.5 and 28.3% of evaluable pts ($n = 1432$)
			Mean NRS spasticity score ↓ from 7.5 (BL) to 5.9*** ($n = 1432$)
	3 months	6.5	Mean NRS spasticity score ↓ from 7.5 (BL) to 5.1*** ($n = 889$)
	6 months	6.3	Mean NRS spasticity score ↓ from 7.5 (BL) to 4.8*** ($n = 593$)
Spanish study [46] (207)	6 months	6.6	Physicians judged 68% of 205 pts had sufficient clinical benefit to continue treatment
	12 months	6.6	Physicians judged 60% of 205 pts had sufficient clinical benefit to continue treatment
Italian study [47] (102)	1 month	6.5	Mean NRS spasticity score ↓ from 8.7 (BL) to 6.2*** ($n = 102$)
			Timed 25-foot walk test improved from a mean 28.1 s (BL) to 22.6 s* ($n = 52$)
	3–12 months		Mean NRS spasticity score ↓ from 8.7 (BL) to 5.9***, 6.1*** and 6.2*** at 3, 6 and 12 months, respectively ($n = 102$)
Italian study [48] (144)	4 weeks	6.5/7.7[d]	≥20% ↓ in NRS spasticity score in 71.7% of evaluable pts ($n = 138$)
			Mean NRS spasticity score ↓ from 7.6 (BL) to 5.2** in IRs[b] ($n = 99$)
	14 weeks	6.4	≥30% ↓ in NRS spasticity score in 61.9% of evaluable pts ($n = 90$)
			Mean NRS spasticity score ↓ to 5.0[†]
	48 weeks	6.2	Mean NRS spasticity score ↓ to 4.9*** ($n = 41$)
German study [49] (166)	9 months[e]	4	Response seen in 72% of evaluable pts ($n = 166$)
			In responders, mean NRS spasticity score ↓ from 7.0 (BL) to 3.0 within 10 days

BL baseline, *IRs* initial responders, *NRS* numerical rating scale, *pts* patients, ↓ reduction/decreased

* $p < 0.01$, ** $p < 0.001$, *** $p < 0.0001$ vs. BL; [†] $p = 0.03$ vs. week 4

[a] Studies were of multicentre [41–46] or single-centre [47–49] design

[b] IRs were defined as patients with a ≥20% ↓ in NRS spasticity score at 1 month

[c] MOVE 2 EU included patients from Italy ($n = 423$), Norway ($n = 8$) and Denmark ($n = 2$)

[d] Values in IRs/non-responders

[e] Mean duration of delta-9-tetrahydrocannabinol/cannabidiol treatment

phase 3 trial by Novotna et al., the most commonly occurring adverse events were dizziness (14.0% of THC/CBD recipients), fatigue (5.9%), somnolence (5.1%), dry mouth (4.2%), nausea (4.0%) and vertigo (3.7%) [38]. Adverse events were usually of mild to moderate intensity and resolved within a few days, even with continued THC/CBD treatment [4]. Use of the recommended schedule for slow up-titration of the THC/CBD dose (Sect. 5) markedly reduces the occurrence of adverse events such as dizziness and fatigue during the first 4 weeks of treatment [4].

The tolerability profile of THC/CBD did not differ much from that of placebo. In patients randomized to THC/CBD

or placebo during phase B of the pivotal phase 3 trial, the most commonly occurring adverse events included urinary tract infection (7 vs. 10%), muscle spasms (6 vs. 7%), vertigo (6 vs. 1%), fatigue (5 vs. 1%), back pain (4 vs. 3%) and nausea (4 vs. 2%) [38].

Application site-type reactions have been reported in patients receiving THC/CBD oromucosal spray, including application-site pain, oral pain and discomfort, dysgeusia, mouth ulceration and glossodynia [4, 5]. Varying the site of THC/CBD application in the mouth is advised if patients experience application-site discomfort or ulceration. In the event of lesions or persistent soreness, treatment with THC/CBD should be interrupted until complete resolution occurs [4].

The tolerability profile of THC/CBD oromucosal spray in the longer term was generally consistent with that observed in shorter-term studies [23, 42, 45–48, 50]. The majority of adverse events were of mild to moderate intensity [23, 46, 48], and the incidence of adverse events decreased over time [46, 48]. No new safety concerns emerged in the longer term [46, 50]. For example, a retrospective UK, German and Swiss safety registry included 941 patients receiving THC/CBD; 729 (78%) patients were receiving THC/CBD for MS, three-quarters of whom had a confirmed diagnosis of MS-related spasticity [50]. The mean treatment duration was 954 days among the 848 patients for whom the duration of THC/CBD exposure was recorded [50]. The most common treatment-related adverse events were dizziness (2.3%) and fatigue (1.7%). Of the 305 patients who stopped THC/CBD treatment, 25% did so because of adverse events [50]. Of the patients who discontinued THC/CBD in other longer-term real-world trials, 16–46% did so because of adverse events [42, 45, 47].

Abrupt cessation of THC/CBD treatment was not associated with withdrawal syndrome [37, 40].

4.2 Adverse Events of Special Interest

There have been infrequent reports of psychiatric symptoms such as anxiety, changes in mood and paranoid ideas in patients receiving THC/CBD [4, 45, 46, 50]. Such symptoms, which are usually of mild to moderate intensity, are thought to be the result of transient CNS effects, and can be expected to remit if the THC/CBD dose is reduced or if treatment is interrupted [4]. THC/CBD was deemed noninferior to placebo in terms of the mean change from baseline to the end of treatment in the Beck Depression Inventory (BDI)-II scale score (−2.84 vs. −2.55), according to the results of a longer-term study (see Sects. 2.2.2 and 3.1.2) [23]. In addition, BDI scores did not differ between THC/CBD and placebo recipients during the pivotal phase 3 trial by Novotna et al. [38]. Depressive symptoms were reported infrequently in safety studies [46, 50], with most depressive events considered unrelated to treatment with THC/CBD in one analysis [50].

There have also been infrequent reports of disorientation (or confusion), hallucinations and delusional beliefs or transient psychotic reactions in patients receiving THC/CBD [4, 45, 46]. Treatment with THC/CBD should be stopped immediately if such symptoms occur, and the patient should be monitored until complete resolution of symptoms has occurred [4]. There were no reports of suicidal ideation or attempted suicide in a longer-term study (median duration of THC/CBD therapy of 336 days) [23] or in the Spanish safety study (follow-up period of 1 year) [46], although cases of suicidal ideation or attempted suicide have been reported in other large registry studies [45, 50]. The SPC notes that a causal association between the administration of THC/CBD and instances of suicidal ideation could not be ruled out in a few cases [4].

THC/CBD has not shown clinically relevant abuse potential [7] (see also Sect. 2.2.2). Patients with a history of substance abuse may be more prone to abuse THC/CBD [4], although there were no signals indicating abuse, diversion or dependence in registry studies [45, 50].

Falls are not uncommon in patients with MS [51]. Falls were reported infrequently (and were usually considered mild) in patients receiving THC/CBD in the Spanish safety study [46], although a serious fall with fracture was reported in the long-term extension of MOVE 2 Germany [42], and fall-related injury requiring medical attention was reported in 6% of patients in a safety registry [50].

THC/CBD did not appear to impair driving ability in patients with MS-related spasticity [46, 50, 52], although patients are advised not to drive if they are experiencing any significant CNS effects (e.g. dizziness, somnolence) [4]. It should be noted that oral fluid tests for THC may be positive in patients receiving THC/CBD [53].

5 Dosage and Administration

THC/CBD oromucosal spray is approved in the EU for symptomatic improvement in adults 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 [4].

THC/CBD should be individually titrated to reach the optimal dosage [4]. The number of sprays should be gradually increased (with doses administered in the morning and evening) over an up to 14-day titration period until optimum relief of symptoms has been achieved. If undesirable effects (e.g. dizziness) occur during the titration period, consideration should be given to maintaining the current THC/CBD dose, reducing the THC/CBD dose

or temporarily interrupting the THC/CBD dose, depending on the seriousness and intensity of the undesirable effect. The maximum number of sprays per day should not exceed 12, and there should be a gap of ≥15 min between sprays. Following the titration period, patients should be advised to maintain their optimum THC/CBD dosage and to spread the doses throughout the day based on response and tolerability [4]. As far as possible, administration of THC/CBD should be standardized in relation to food intake in order to minimize variability in bioavailability (Sect. 2.3) [4].

Patient response to THC/CBD should be reviewed by the physician after 4 weeks' therapy [4]. If a clinically significant improvement in symptoms related to spasticity is not seen within this initial trial of therapy, treatment with THC/CBD should be stopped. The value of long-term THC/CBD therapy should also be re-evaluated periodically [4].

THC/CBD is contraindicated in patients with any known or suspected history or family history of schizophrenia or other psychotic illness, or with a history of severe personality disorder or other significant psychiatric disorder other than depression associated with their underlying condition [4]. THC/CBD is also contraindicated in breast feeding women [4].

Local prescribing information should be consulted for more information regarding dose titration, contraindications, warnings and precautions related to THC/CBD.

6 Place of THC/CBD Oromucosal Spray in the Management of MS-Related Spasticity

The goals of treatment in MS-related spasticity include improving functionality (e.g. gait, mobility), reducing pain, preventing complications such as contractures, improving ADLs (e.g. hygiene, feeding) and relieving associated symptoms (e.g. spasms, bladder dysfunction, pain, sleep disorders) [54, 55].

Spanish guidelines recommend the initial use of measures such as avoidance of triggers, appropriate positioning, physiotherapy, occupational therapy and orthosis in patients with MS-related spasticity [56]. In patients who require drug therapy despite these measures, treatment with baclofen or tizanidine is recommended for generalized spasticity. The addition of THC/CBD or combination therapy with baclofen plus tizanidine is recommended in patients who do not respond to initial therapy [56]. Guidelines from Germany and Sweden also include THC/CBD as a second- or third-line combination option in patients with MS-related spasticity [54, 55].

In the pivotal phase 3 trial by Novotna et al. [38], THC/CBD improved MS-related spasticity in patients with an inadequate response to other anti-spasticity agents who had undergone a successful initial trial of THC/CBD therapy (Sect. 3.1.1). Improvements in spasticity were maintained in the longer term with THC/CBD with no evidence of dose tolerance (Sect. 3.1.2), and results of real-world studies confirm the effectiveness of THC/CBD for the treatment of MS-related spasticity in everyday clinical practice (Sect. 3.2). Limitations of these non-interventional real-world studies (such as the need to align data collection and the use of scales measuring outcomes with usual clinical practice, and the potential for selection bias), should be kept in mind [41, 43, 44, 46].

Improvements in various other outcomes, including ADLs, the frequency of spasms and sleep quality, were reported in patients receiving THC/CBD in the pivotal phase 3 trial [38] (Sect. 3.1.1), with improvements in MS-specific HR-QOL and ADLs also reported with THC/CBD in real-world settings (Sect. 3.2).

THC/CBD was generally well tolerated in the pivotal phase 3 trial [38], with adverse events such as dizziness occurring most commonly during dose titration (Sect. 4.1). The favourable tolerability profile of THC/CBD was maintained in the longer term and in real-world settings (Sect. 4.1). In general, administration of therapeutic dosages of THC/CBD did not appear to be associated with cognitive decline, and had a low risk of clinically significant psychoactive effects or abuse potential (Sects. 2.2.2 and 4.2). The low risk of psychoactive effects corresponds with the much lower THC C_{max} values seen with oromucosal administration of THC/CBD versus smoked cannabis (Sect. 2.3). Prescribers should be aware that there have been infrequent reports of psychiatric symptoms in patients receiving THC/CBD (Sect. 4.2).

MS-related spasticity imposes a significant economic burden on society [57]. The severity of spasticity is directly correlated with the cost of care, meaning that the ability of THC/CBD to improve moderate to severe spasticity has implications for healthcare resource utilization [58].

Being able to maintain efficacy with fewer sprays of THC/CBD also has cost-effectiveness implications [23]. A mean 8.3 sprays per day of THC/CBD was administered in the pivotal phase 3 trial [38] (Sect. 3.1.1). However, over the course of a longer-term study, the mean number of daily THC/CBD sprays decreased from 7.6 to 6.4 (Sect. 2.2.2) [23]. Similarly, the mean number of THC/CBD sprays administered each day tended to be lower in real-world studies (e.g. 4 to ≈7 sprays per day after 3–12 months' follow-up; Table 2).

Spanish [59], German [59], Italian [60] and Welsh [58] pharmacoeconomic analyses concluded that treatment of MS-related spasticity with THC/CBD plus standard of care was cost effective compared with standard of care alone, with dominance shown in some settings [58–60]. By contrast, a UK pharmacoeconomic analysis concluded that THC/CBD was unlikely to be considered cost effective

[61]. Various factors, including differences in the models used and country costs, account for these differing results. One contributing factor may be that the UK cost-effectiveness analysis modelled THC/CBD costs based on the continuous use of ≈8 sprays per day, whereas Spanish [59], German [59] and Italian [60] models assumed there would be a decrease in the number of daily THC/CBD doses administered over time.

In conclusion, THC/CBD oromucosal spray is an important option for the treatment of MS-related spasticity not completely relieved with current anti-spasticity medications.

Data selection Delta-9-Tetrahydrocannabinol/ Cannabidiol Oromucosal Spray: 199 records identified	
Duplicates removed	48
Excluded at initial screening (e.g. press releases; news reports; not relevant drug/indication)	16
Excluded during initial selection (e.g. review; case report; not randomized trial)	19
Excluded by author (e.g. not randomized trials; review; duplicate data; small patient number; phase 1/2 trials)	55
Cited efficacy/tolerability articles	23
Cited articles not efficacy/tolerability	38
Search Strategy: EMBASE, MEDLINE and PubMed from 2014 to present. Previous Adis Drug Evaluation published in 2014 was hand-searched for relevant data. Clinical trial registries/databases and websites were also searched for relevant data. Key words were Nabiximols, Sativex, delta-9-THC, delta-9-tetrahydrocannabinol, tetrahydrocannabinol, dronabinol, cannabidiol, Nabidiolex, Tetranabinex, spasticity. Records were limited to those in English language. Searches last updated 20 February 2017.	

Acknowledgements During the peer review process, the manufacturer of delta-9-tetrahydrocannabinol/cannabidiol oromucosal spray was also offered an opportunity to review this article. Changes resulting from comments received were made on the basis of scientific and editorial merit.

Compliance with Ethical Standards

Funding The preparation of this review was not supported by any external funding.

Conflict of interest Gillian Keating is a salaried employee of Adis/Springer, is responsible for the article content and declares no relevant conflicts of interest.

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