Evidence for the efficacy and effectiveness of THC-CBD oromucosal spray in symptom management of patients with spasticity due to multiple sclerosis

Uwe K. Zettl, Paulus Rommer, Petra Hipp and Robert Patejdl

Abstract: Spasticity, one of the main symptoms of multiple sclerosis (MS), can affect more than 80% of MS patients during the course of their disease and is often not treated adequately. δ-9-Tetrahydrocannabinol-cannabidiol (THC-CBD) oromucosal spray is a plant-derived, standardized cannabinoid-based oromucosal spray medicine for add-on treatment of moderate to severe, resistant multiple sclerosis-induced spasticity. This article reviews the current evidence for the efficacy and safety, with dizziness and fatigue as the most common treatment-related adverse events, being mostly mild to moderate in severity. Results from both randomized controlled phase III studies involving about,1600 MS patients or 1500 patient-years and recently published studies on everyday clinical practice involving more than 1000 patients or more than,1000 patient-years are presented.

Keywords: cannabinoids, CBD, multiple sclerosis, nabiximols, spasticity, THC

Introduction

Multiple sclerosis (MS) is a progressive, chronic, immune-mediated disease of the central nervous system (CNS) [Zettl *et al*. 2012; Kutzelnigg and Lassmann, 2014], diagnosed predominantly in young adults with approximately 500,000 patients in Europe and more than 2.3 million people worldwide [Flachenecker and Stuke, 2008; Browne *et al*. 2014]. It is the most common neurological disease in young and middle-aged adults resulting in marked physical disability, inability to work or early retirement, significantly impaired quality of life (QoL) and a substantial burden on society in terms of associated costs as it evolves [Zettl *et al*. 2013; Svensson *et al*. 2014]. MS is characterized by a broad range of signs and symptoms, the most common being restricted mobility, spasticity, fatigue, sensory deficits, palsy, pain, bladder dysfunction, cognitive dysfunction, depression and visual impairment [Rizzo *et al*. 2004; Goldenberg, 2012].

Spasticity is one of the more common symptoms of MS, as it affects more than 80% of MS patients during the course of the disease [Barnes *et al*. 2003; Beard *et al*. 2003; Rizzo *et al*. 2004]. Spasticity can be defined from the pathophysiological perspective as a 'disordered sensorimotor control resulting from an upper motor neuron lesion, presenting as intermittent or sustained involuntary activation of muscles' [Stevenson, 2010]. It is perceived by the patients as continuous muscle stiffness, often associated with exacerbating spasms, and further restricting the already MS compromised mobility, fatigue, bladder dysfunction, pain or impaired sexual activities [Hobart *et al*. 2006; Crayton and Rossman, 2006; Zwibel *et al*. 2009; Flachenecker *et al*. 2014a].

The impact of MS-induced spasticity on QoL was examined by a Swedish retrospective, cross-sectional study involving 105 patients. Health-related QoL measured by generic EuroQol (EQ-5D) and 0-100 Visual Analogue Scale (VAS) significantly decreased with increased severity of spasticity. Mean quality-adjusted life-year (QALY) weight was 0.36 compared with 0.82 in the healthy Swedish population, with 21 patients

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displaying a value below 0 (worse than death). QALY weight decreased with increased severity. This study emphasizes the negative impact of spasticity on QoL [Svensson *et al.* 2014].

The association between severity of MS spasticity and QoL was also confirmed by a recent Spanish multicenter, cross-sectional study where the SF-12® questionnaire was used to assess QoL, which was correlated to the modified Ashworth scale and a 0-10 Numerical Rating Scale (NRS) used to assess severity of spasticity [Arroyo *et al.* 2013]. The results showed an association between severity of spasticity and QoL for both scales ($p \leq$ 0.002), where the correlation was stronger with the NRS in patients with MS. A second Spanish cross-sectional study has shown a direct correlation between increasing severity of spasticity and worsening of spasticity-related symptoms, especially day and nighttime spasms ($p < 0.001$), urinary dysfunction ($p < 0.001$) and sleep disturbances ($p = 0.015$). The study involved 2029 MS patients; 65.7% suffered from spasticity, with 40% of them moderate to severe [Oreja-Guevara *et al.* 2013].

Costs for society increase with severity of spasticity, being 2.4 times higher in MS patients with severe spasticity than to those with mild spasticity [Svensson *et al.* 2014].

Severity of spasticity is difficult to quantify. Even mild spasticity may cause restrictions of the patient's physical capacities in comparison with persons with no motor neuron damage [Henze *et al.* 2006]. First of all, an intensive anamnestic and neurological evaluation is key to identifying spasticity in MS patients. In addition to neurophysiological methods [Voerman *et al.* 2005] and biomechanical techniques [Wood *et al.* 2005], objective but often applicable only in experimental settings, reliable, responsive and validated clinical scales can be applied [Platz *et al.* 2005]. The most widely used scale reflecting the healthcare professional's perspective is the (modified) Ashworth Scale [Ashworth, 1964; Bohannon and Smith, 1987], but its validity and reliability have been questioned [Fleuren *et al.* 2010; Sunnerhagen, 2010]. This is because, although an increase in score represents more spasticity, the difference in spasticity between two consecutive scores is not the same across the whole scale (categorical scale, no linearity). Therefore, the differences in scores and changes during time obtained with this scale and possible analyses (for

example, central or dispersion tendency measures such as means and standard deviations) are likely to be imprecise.

The 0-10 NRS reflects the severity of spasticity from patient's perspective [Farrar *et al.* 2008; Anwar and Barnes, 2009], displayed as mean perception over time. It is both reliable and valid for the measurement of spasticity, and it substantially increases the likelihood of making an accurate diagnosis and assessment of the level of severity. The scale has a moderate to high level of correlation with other clinician rated instruments used to assess spasticity. It allows simplified patient self-rating of spasticity and provides more details on the severity of spasticity-associated symptoms experienced by patients who are also influenced by the presence of spasticity.

Two other important scales to measure spasticity are the Penn Spasms Scale, which is a two component self-report measure of frequency with a five-point scale and of severity with a three-point scale to quantify spasticity severity [Penn *et al.* 1989] and the Multiple Sclerosis Spasticity Scale (MSSS-88), a validated self-assessment tool, retrieving 88 items [Hobart *et al.* 2006; Henze *et al.* 2014]. Due to its extent, use of the MSSS-88 scale in daily practice is limited. However, so far no single standard method or a direct comparison between scales is available.

Management of MS-induced spasticity

The most important treatment goals in patients with MS-induced spasticity are avoidance or elimination of triggers which may initiate or enhance spasticity, pain reduction, improvement or maintenance of functional abilities, QoL and facilitation of nursing. If physiotherapy, as a generally accepted basic treatment option, is not sufficient, drugs should be tried [Henze *et al.* 2006]. Depending on the severity of spasticity, drug treatment varies widely, reliant on approved drugs which may differ between geographical regions. Commonly used medications like baclofen, tizanidine, gabapentin or dantrolene are administered orally. Their mode of action varies, but all cause muscle relaxation.

There is limited evidence of the effectiveness and efficacy of these four anti-spasticity drugs. According to a number of reviews, they appear to be approximately equally effective at reducing spasticity when assessed clinically, but there is no

convincing proof of functional benefit [Beard *et al.* 2003; Stevenson, 2010]. Clinical studies date back to the 1970s and spasticity measured by the (modified) Ashworth Scale might not have led to valid and reliable results [Fleuren *et al.* 2010; Sunnerhagen, 2010].

A systematic review by the Cochrane Group concluded that the absolute and comparative efficacy, as well as tolerability of classical antispasticity medication, is limited [Shakespeare *et al.* 2003]. The most commonly used medication, oral baclofen, yielded a moderate effectiveness score of 3.68 (±0.97) in a rating carried out by patients on a 1 to 5 categorical rating scale from (3 = no change and 4 = a little better; Rizzo *et al.* 2004). Further limitations are mainly due to a high occurrence of side effects such as muscle weakness with risk of falls, sedation, cognitive difficulties, withdrawal syndrome or dizziness at patient required doses.

However, the evaluation of the efficacy of a symptomatic treatment in the context of a chronic disease like MS might be afflicted with methodological problems. Spasticity is a very complex and not yet fully understood condition. As the extent of upper motor neuron damage varies from patient to patient, the response to a peripheral or centrally acting antispasticity medication cannot be predicted and can vary. An overlap of various symptoms can influence the detection of the improvement of one specific symptom. Therefore psychometric qualities of the selected instruments need to be reliable and valid. An instrument with poor psychometric properties will be less likely to detect treatment effects.

Invasive medication like intrathecal baclofen pumps for resistant spasticity [Smyth and Peacock, 2000] or intramuscular injections of botulinum toxin A for focal cases [Kabus *et al.* 2006] are used only for a small number of patients. Few patients are treated with intrathecal triamcinolone-acetonide [Kamin *et al.* 2014]. Surgical interventions are applied only very rarely [Beard *et al.* 2003].

There is ample evidence that spasticity is not being managed adequately in everyday clinical practice. Various published cross-sectional European survey-based studies showed that only about half of the patients with MS-related spasticity were receiving antispasticity medication. In Spain, 42.4% of patients with moderate and 52.6% with severe spasticity received spasticity related medication [Oreja-Guevara *et al.* 2013]. In Germany, 55.1% of MS patients with spasticity were treated with antispasticity medication [Zettl *et al.* 2013]. The number of prescribed drugs increased with severity of spasticity, indicating insufficient effectiveness [Flachenecker *et al.* 2014a]. These results are confirmed by a North American study. About one-third of the patients reported their level of spasticity as moderate or worse despite ongoing single or multiple drug use [Rizzo *et al.* 2004]. Additionally, in the North American Research Committee on Multiple Sclerosis (NARCOMS) study, it was shown that MS patients showed a continuous worsening of spasticity through MS disease evolution despite available treatments [Kister *et al.*, 2013].

Recent burden-of-disease studies [Zettl *et al.* 2013] confirm those early findings. MOVE 1 (MObility ImproVEment), a cross-sectional and retrospective study from Germany, has shown low satisfaction with the effectiveness of the currently available pharmacotherapy of spasticity in a total of 414 MS patients with mild (27.3%), moderate (44.0%) and severe spasticity (28.7%); 36.1% of the patients under pharmacotherapy and 41.3% of the participating physicians were partially or fully dissatisfied with the effectiveness of the medication used (including baclofen, tolperisone or tizanidine). In both groups, dissatisfaction increased with increasing severity of spasticity [Flachenecker *et al.* 2014a]. Similar trends are seen in the MOVE 1 EU study, with 300 participating patients from seven countries: 48.0% physicians and 34.0% patients are at least partly dissatisfied with spasticity relief from current drug treatment [Vermersch, 2014].

Considering these limitations, there was an urgent need to find alternative drugs. Since 2011, δ-9-tetrahydrocannabinol-cannabidiol (THC-CBD) oromucosal spray [US Adopted Name (USAN nabiximols; trade name Sativex®] is available as add-on therapy for patients with moderate to severe treatment-resistant spasticity in a growing number of European countries.

Role of the endocannabinoid system in spasticity

The search for alternative antispasticity drugs reignited the interest in *Cannabis sativa*, one of the oldest herbal plants in the history of medicine [von Linnaeus, 1753]. Smoked or otherwise

processed cannabis has been used for medical purposes for a long time either to achieve or to investigate antispastic, muscle relaxant and analgesic effects [Killestein and Polman, 2004; Russo and Guy, 2006]. However, concerns were raised regarding cannabinoid tolerability, in particular with respect to the contribution to psychiatric or cognitive disorders by repeated use [Johns, 2001; Arseneault *et al.* 2004; Solowij *et al.* 2002].

After the discovery of the human endocannabinoid system, the identification of the cannabinoid receptors CB_1 and CB_2 and of the endogenous cannabinoids including anandamide and 2-arachidonoylglycerol, its role was extensively examined [DiMarzo and Petrosino, 2007]. One important action of endocannabinoids is their interaction with presynaptic cannabinoid receptors, predominantly present in the CNS on both GABAergic and glutamatergic synapses. CB_1 receptor-mediated inhibition of ion channels is associated with a reduced release of the excitatory glutamatergic and the inhibitory GABAergic neurotransmitters [Pertwee, 2006]. It has been shown that the CB_1 receptors in the aforementioned pathways are the main cannabinoid target to deliver an antispastic effect [Pryce and Baker, 2007]. The stimulation of the endocannabinoid system has an impact on many different effects including a reduction of the severity of both MS-induced spasticity and pain [Pertwee, 2006]. This gave rise to the development of specifically combined cannabinoids for the treatment of MS-induced spasticity [Ware *et al.* 2005; Pertwee, 2009; Perez and Ribera, 2008].

THC-CBD oromucosal spray for the management of MS-induced spasticity

A THC-CBD oromucosal spray is available as add-on therapy for patients with moderate to severe treatment-resistant spasticity in a growing number of European countries for patients who are not satisfactorily relieved with their current first-line antispastic therapy. Two exogenous endocannabinoid agonists, the phytocannabinoids THC [Gaoni and Mechoulam, 1964] and CBD [Guy and Stott, 2005], derived from cloned *Cannabis sativa* chemovars, are the main components of this oromucosal spray. They have both inhibitory and excitatory effects on different neurotransmitter systems [Hoffman and Lupica, 2000]:

THC is a partial agonist at both human CB_1 and CB_2 receptors. Its main pharmacological effects at different doses include analgesia, muscle relaxation, anti-emesis or appetite stimulation as well as psychotropic effects which limited its clinical use [Pertwee, 2000].

CBD has little activity at the CB_1 receptor but greater activity at the CB_2 receptor [Showalter *et al.* 1996]. It also stimulates vanilloid pain receptors (VR1) and inhibits the uptake of anandamide, while also weakly inhibiting its breakdown [Bisogno *et al.* 2001]. Studies have also shown that it can have anti-inflammatory, neuroprotective, anticonvulsant, muscle relaxant, antioxidant and anti-psychotropic effects at different doses [Russo and Guy, 2006; Perez, 2006].

Figure 1 illustrates the mode of action of cannabinoids. They modulate the human endocannabinoid system and act synergistically to increase the analgesic effects on muscles. Mimicking the negative feedback mechanism of endocannabinoids [Pertwee, 2006], a modulation of the transmission of impulses at synapses in the central and peripheral nervous system is therefore ensured [Di Marzo and Petrosino, 2007]. THC binds to the CB_1 receptor which is predominantly present in the CNS at glutamatergic synapses. This reduces the effects of the excitatory glutamate typical for spasticity [Pertwee, 1999; Izzo *et al.* 2009]. The mode of action of THC has been studied in an *in vivo* MS mouse model [Baker *et al.* 2000]. As CBD alleviates the psychotrophic effects of THC, a higher dose of THC can be administered and thus a higher benefit can be achieved [Pertwee, 2000; Russo and Guy, 2006]. The synergistic potential in MS-induced spasticity was proven in an *in vivo* MS mouse model where THC-CBD dose dependently reduced spasticity to the same extent as baclofen [Hilliard *et al.* 2012].

THC-CBD oromucosal spray contains a standardized, fixed 1:1 ratio of THC and CBD and is so far the only cannabinoid approved as add-on treatment for MS induced spasticity. Other orally administered cannabinoid-containing medications such as dronabinol (synthetic THC) or nabilone (THC analog) lack CBD and are not approved for this indication.

A summary of pharmacokinetic data from five phase I studies [Guy and Robson, 2003; Karschner *et al.* 2011; Stott *et al.* 2013a, 2013b, 2013c] was published recently in a review
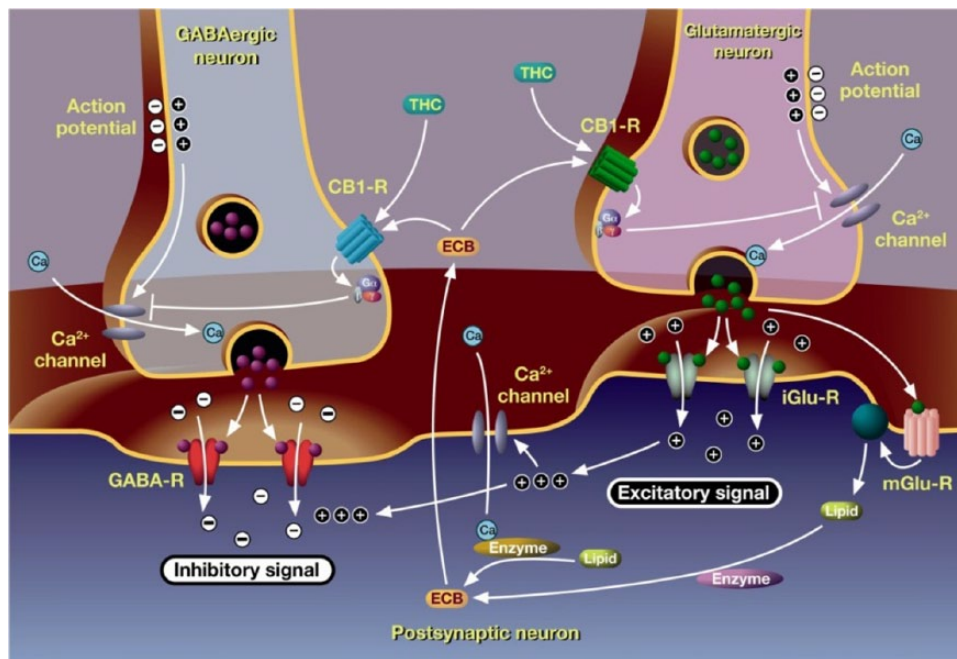
Figure 1. Endocannabinoid system and mode of action of cannabinoids.
Endo- and phytocannabinoids mediate neuronal signaling. The neurotransmitters glutamate and γ-aminobutyric acid (GABA) are released after an action potential has induced calcium ions to flow into the axonal terminal bulb. Glutamate binding to its ionotropic receptor (iGluR) leads to membrane depolarization in the postsynaptic neuron and an excitatory signal. GABA binding to its receptor leads to an inhibitory signal. Synthesis of endocannabinoids (ECBs) is induced by the activation of postsynaptic metabotropic glutamate receptors (mGlu-R) and high cytoplasmic calcium levels. ECBs activate presynaptic G-protein-coupled CB_1 receptors, thus inhibiting presynaptic calcium influx and neurotransmitter release. Tetrahydrocannabinol (THC) mimics the action of the ECB anandamide (Perez, J. Combined cannabinoid therapy *via* an oromucosal spray. *Drugs of Today* 2006; 42:495-501. Copyright© 2006-2014 Prous Science, S.A.U. or its licensors. All rights reserved. DOI NUMBER: 10.1358/dot.2006.42.8.1021517].

[Garcia-Merino *et al.* 2014]. Both THC and CBD are absorbed rapidly and appear in the plasma within 15 minutes of a single oromucosal administration. A mean plasma concentration C_{max} of about 4 ng/ml was reached about 45–120 minutes after a single dose administration of 4 sprays in a row. As cannabinoids are highly lipophilic, they are quickly absorbed and distributed into body fat. From there they are slowly released at subtherapeutic levels back into the blood stream. Then they are metabolized in the liver and excreted *via* the urine and feces [Karschner *et al.* 2011]. Food does alter the relative bioavailability of the THC-CBD oromucosal spray; however, variations in bioavailability caused by food are less than the intersubject variations observed and therefore the findings are unlikely to be clinically relevant [Stott *et al.* 2013b]. A comparison between the THC-CBD oromucosal spray and smoked cannabis confirmed that the likelihood of achieving psychoactive effects is minimal due to a much lower C_{max} compared with inhaled THC [Stott *et al.* 2008].

Clinical efficacy of THC-CBD oromucosal spray in pivotal and recent studies

The THC-CBD spray clinical study program included basically three pivotal randomized, double blind, placebo-controlled, multicenter phase III efficacy studies [Collin *et al.* 2007, 2010; Novotna *et al.* 2011], one supporting phase II pilot study and its open label extension [Wade *et al.* 2004, 2006], one long-term extension study [Serpell *et al.* 2013], one withdrawal study [Notcutt *et al.* 2012] and one safety phase IV study [Vachova *et al.* 2014] in MS patients with moderate to severe treatment-resistant spasticity. Inclusion criteria were in line with the Summary of Product Characteristics (SmPC).

THC-CBD spray is approved as to be used in addition to the patient's current antispastic medication. Usually, the NRS was used to determine spasticity in the studies, only early studies applied the 0–100 mm VAS, which is a horizontal line on which patients mark the point that they feel represents the perception of their current state. Efficacy

outcomes have been summarized and discussed in detail in other publications [Sastre-Garriga *et al.* 2011; Leussink *et al.* 2011; Garcia-Merino *et al.* 2014; Syed *et al.* 2014] and are only briefly discussed here. Table 1 summarizes the main characteristics and key efficacy results.

In a phase II pilot study (*n* = 160 patients), THC-CBD spray showed a significant improvement in the 100 mm VAS compared with placebo (*p* = 0.0001) after 10 weeks [Wade *et al.* 2004]. This effect was maintained in 137 patients in a subsequent extension study for up to 82 weeks without significant changes in mean dosages [Wade *et al.* 2006].

In the first pivotal study (*n* = 337 patients), the primary endpoint was the change in the patient-rated, mean spasticity NRS score from baseline after 6 weeks [Collin *et al.* 2007]. It was statistically significant in favor of THC-CBD spray in the intention-to-treat (ITT) population (difference 0.52 points, *p* = 0.048). A responder analysis (≥30% NRS reduction at study end) of the primary variable was presented as a secondary outcome measure. In the THC-CBD group, 40% of patients reported at least a 30% improvement in spasticity compared with 20% in the placebo group (*p* < 0.01). The mean daily spray number was 9.6 ± 6.4. The secondary endpoint [a composite Ashworth Scale and Motricity Index in muscles affected by spasticity score, mean daily spasm scores and patient Global Impression of Change (GIC)] was in favor of THC-CBD spray, but did not reach statistical significance. In a subsequent noncomparative, open-label extension study to provide safety and tolerability information on the long-term use of THC-CBD, a total of 146 patients from the previous parent study were enrolled [Serpell *et al.* 2013]. All patients with continuous data up to 52 weeks of treatment were analyzed. Of these patients, 90% (*n* = 55 patients) reported continued benefit over a mean treatment time of 334 (± 209) days on mean spasticity NRS score, the subjective effect in spasticity and quality of sleep. Only 10% of patients withdrew from the study due to lack of efficacy.

Using results from the study by Collin and colleagues [Collin *et al.* 2007], Farrar and colleagues proved the validity, reliability and clinical relevance of the spasticity NRS [Farrar *et al.* 2008]. The minimal clinically important difference was defined by a reduction of 18% in spasticity NRS score and the clinically important difference was

defined by a reduction of 29.5%. A ≥20% spasticity NRS improvement was therefore considered an initial response and a ≥30% improvement as clinically relevant response in the following studies.

The second pivotal study by Collin and colleagues included 335 patients in the ITT analysis and 265 patients in the per protocol (PP) analysis after 15 weeks [Collin *et al.* 2010]. The primary endpoint, the change in mean spasticity NRS score from baseline, was in favor of THC-CBD in the PP population (difference -0.46 points, *p* = 0.035), but not statistically significant in the ITT population (difference -0.23 points; *p* = 0.219). Responder analysis at the 30% spasticity reduction level showed nonsignificant treatment differences in the ITT population (*p* = 0.23); in the PP analysis, however, 36% of patients reported at least a 30% improvement in spasticity compared with 21% in the placebo group (*p* = 0.04). The difference between ITT and PP outcome was thought to be attributed to a group of 72 patients in the verum group who terminated treatment early and had a poor treatment response. This group potentially masked the response in the ITT population, while it was excluded in the PP analysis. It was shown that a 20% reduction in spasticity NRS score during the first 4 weeks (initial responder) was predictive of the clinically relevant response of a ≥30% reduction in spasticity NRS score (clinically relevant responder). The mean daily spray number was 8.5 (range 1–22). QoL, measured by the generic QoL questionnaire EQ-5D and the disease-specific QoL questionnaire MSQoL-54, showed a positive trend in favor of THC-CBD spray.

A meta-analysis of the studies by Collin and colleagues [Collin *et al.* 2007, 2010] and Wade and colleagues [Wade *et al.* 2004] proved that treatment with THC-CBD spray (*n* = 356) yielded a statistically significant greater proportion of clinically relevant responders *versus* placebo (*n* = 296) (37% *versus* 26%, respectively; *p* = 0.0073) at study end with an odds ratio (OR) in favor of THC-CBD spray [OR = 1.62; 95% confidence interval (CI): 1.15–2.28] [Wade *et al.* 2010].

Based on the findings from these three studies [Collin *et al.* 2007, 2010; Wade *et al.* 2010], an enriched study design with two phases (single blind trial period followed by randomized phase of the trial period responders) was developed. This design was accepted by the European

Table 1. Main efficacy results from pivotal THC-CBD spray clinical phase III studies.

Study	Design	Study period	Number of patients (n)	Mean duration since MS diagnosis in years ± SD (min-max)	Mean duration of spasticity in years ± SD (minimum–maximum)	Mean daily sprays in active group ± SD	Key efficacy outcome	Key efficacy results
Collin *et al.* [2007]	R, DB, PC, MC	6 weeks	THC-CBD: n = 124 Placebo: n = 65	13.6 ± 8.6 12.2 ± 7.7	n.a.	9.6 ±6.4*	Primary: efficacy (change in mean spasticity NRS score) Secondary: Ashworth Scale, subjective measure of spasm	Statistically significant reduction of mean spasticity NRS in THC-CBD group (ITT analysis). Treatment difference of 0.52 points (95% CI: -1.029 to -0.004 points; *p* < 0.0001) in favor of THC-CBD Responder analysis favored THC-CBD group: 40% of patients achieved ≥30% reduction in mean NRS score *versus* placebo at study end (*p* = 0.014). No statistical significance in Ashworth Scale or subjective measure of spasm.
Collin *et al.* [2010]	R, DB, PC, MC	15 weeks	THC-CBD: n = 167 Placebo: n = 170 (ITT, n = 335) (PP, n = 265)	15.2 ± 8.41	7.73 ± 5.33	8.5 (range 1–22)$	Primary: efficacy (change in mean spasticity NRS score) Secondary: responder analysis 30% improvement in NRS spasticity; timed 10 metre walk, Barthel Index, carer GIC	Numeric, but no statistically significant reduction of mean spasticity NRS in THC-CBD group (ITT analysis). Treatment difference of 0.23 points (*p* = 0.219) in favor of THC-CBD. Statistically significant reduction of mean spasticity NRS in THC-CBD group (PP analysis). Treatment difference of 0.46 points (*p* = 0.035) in favor of THC-CBD. No difference between treatment groups in 30% responder analysis. Significant change in carer GIC (*p* = 0.013) and timed 10 metre walk (*p* = 0.042).

(Continued)

Table 1. (Continued)

Study	Design	Study period	Number of patients (n)	Mean duration since MS diagnosis in years ± SD (min-max)	Mean duration of spasticity in years ± SD (minimum– maximum)	Mean daily sprays in active group ± SD	Key efficacy outcome	Key efficacy results
Novotna *et al.* [2011]	R, DB, PC, MC, enriched	Phase A: 4 weeks Phase B: 12 weeks	Phase A: n = 572 Phase B (ITT): n = 241 (THC-CBD n = 124, placebo n = 117)	12.4 ± 7.66 (0.5–42.4)	7.5 ± 5.86 (0.2–40.4)	8.3 ±2.43‡	Primary: efficacy (change in mean spasticity NRS score in phase B) Secondary: responder analysis >30% improvement in spasticity, subjective measure of spasm, sleep disruption, Barthel Index, physician GIC, patient GIC, carer GIC	Statistically significant reduction of mean spasticity NRS in THC-CBD group (ITT analysis). Treatment difference in phase B: 0.84 points (95% CI: -1.29 to -0.40 points; *p* = 0.0002) in favor of THC-CBD. Significant differences were found in favor of THC-CBD in the responder analysis (*p* = 0.0003), spasm frequency (*p* = 0.005), sleep disruption (*p* <0.0001), Barthel Index (*p* =0.0067), physician GIC: (*p* = 0.005), patient GIC (*p* = 0.023) and carer GIC (*p* = 0.005).

*Maximum of 48 sprays per day.
$Maximum of 24 sprays per day.
‡Maximum of 12 sprays per day.
CI, confidence interval; DB, double blind; GIC, Global Impression of Change; ITT, intention-to-treat; MS, multiple sclerosis; MC, multicenter studies; n.a., not available; NRS, Numerical Rating Scale; PC, placebo-controlled; PP, per protocol; R, randomized; SD, standard deviation; THC-CBD, δ-9-tetrahydrocannabinol-cannabidiol.

Medicines Agency (EMA) for the conduction of the third pivotal study [Novotna *et al.* 2011]. This enriched study design is a well-accepted concept often used in analgesic studies [Hewitt *et al.* 2011].

In a single blind, 4 week trial period, all patients (n = 522) received THC-CBD. Only those patients achieving an improvement of ≥20% in their spasticity NRS score were selected and continued into a 12 week double blind randomized phase. Of the patients who completed the week phase, 47% (n = 271) were initial responders. In this trial period, the mean spasticity NRS of the early responder MS patients with moderate to severe spasticity improved by 3.01 points [standard deviation (SD) ± 1.38] from 6.91 ± 1.25 to 3.90 ± 1.51 points. The mean daily spray number was 6.9 (±1.78). A total of 241 patients were randomized. The primary endpoint, the change in mean spasticity NRS score from beginning of randomization phase, was statistically significant in favor of THC-CBD (difference of 0.85, *p* = 0.0002). Responder analysis (≥30% NRS reduction at study end compared with screening) was presented as a secondary outcome measure. In the THC-CBD group, 74% of patients reported at least a 30% improvement in spasticity compared with 51% in the placebo group (*p* = 0.0003). The mean daily spray number was 8.3 (±2.43) in the active group compared with 8.9 (±2.31) in the placebo group.

In addition, secondary endpoints were statistically significant in favor of THC-CBD *versus* placebo, including spasm frequency ($p = 0.0005$), sleep disturbance ($p < 0.0001$), Barthel Index of Daily Living ($p = 0.0067$), physician GIC ($p = 0.005$), subject GIC ($p = 0.023$) and carer GIC in function ($p = 0.005$). The secondary endpoints modified Ashworth Scale ($p = 0.094$) and timed 10 metre walk ($p = 0.069$) were in favor of THC-CBD spray but did not reach statistical significance, while QoL measured by the generic questionnaires EQ-5D and SF-36 showed 19–37% improvement in initial responders.

In a randomized, double blind, placebo-controlled, long-term multicenter phase IV study with 121 patients, long-term tolerability (cognition and mood) and efficacy was investigated over 50 weeks [Vachova *et al.* 2014]. Efficacy of spasticity was measured using the GIC determined by patients, physicians and carers, and in all analysis the THC-CBD arm was significantly improved compared with placebo ($p = 0.002$; $p = 0.0001$ and $p = 0.014$, respectively). From the first to the last 3 months of the study, the mean daily spray number decreased from 7.6 ± 3.1 to 6.4 ± 3.1 sprays per day in the THC-CBD group.

The phase III studies and the phase IV study provide conclusive evidence of the efficacy of THC-CBD spray in MS-induced, moderate to severe spasticity that cannot be fully relieved with first-line therapies. Initial responders can be identified in a 4 week trial period. About 40% of previously unsuccessful treated MS patients reached a clinically relevant mean spasticity NRS score improvement of at least 30% with a mean daily spray number of around eight.

There are some relevant aspects to be considered in the interpretation of the results. Not all these previously resistant patients profited from a treatment with THC-CBD spray. THC-CBD did not show significant benefit in the four points observer rated spasticity modified Ashworth Scale secondary endpoint, although a number of other spasticity related end points such as the patient-rated NRS, spasm frequency or the patient, carer and clinician GICs improved significantly. Regarding the mode of action, it is potentially related to inhibitory signals in the GABAergic system, but patient's perception and an analgesic effect of THC-CBD cannot be excluded completely. Moreover, the therapeutic gain (active arm effect minus placebo effect) seems limited if the trial period gains are not considered.

Clinical effectiveness of THC-CBD spray: results from observational studies

Evidence-based medicine relies on randomized controlled clinical studies to evaluate efficacy, safety and tolerability of new drugs. Nevertheless, well-designed observational post approval studies to monitor use in everyday clinical practice are important to confirm results obtained under experimental conditions. All observational studies described here included only patients with moderate to severe spasticity not responding to first-line oral antispastic treatment, in alignment with the THC-CBD approved label. The main characteristics and key effectiveness results with effectiveness as 'efficacy in real-life or under conditions of an observational study' are described and are summarized in Table 2.

MOVE 2 German observational study

MOVE 2 was an observational, prospective, multicenter, noninterventional study. It included 276 patients for a follow-up period of 3–4 months [Flachenecker *et al.* 2014b]. The main objective of this study was to provide longitudinal data on the effectiveness and tolerability of the THC-CBD oromucosal spray from everyday clinical practice. The initial response rate (NRS $\geqslant 20\%$ *versus* baseline after 4 weeks trial period) was 41.7%. Analysis for all endpoints was done for the total sample, the 20% NRS responders (MCID) and the 30% NRS responders (CID). After 1 month, the mean spasticity NRS score decreased significantly in the total sample group ($p < 0.0001$), in the 20% responder group ($p < 0.0001$) and the 30% responder group ($p < 0.0001$) compared with study start. Similarly, the mean spasticity NRS constantly decreased in all groups after 3 months in the total sample group ($p < 0.0001$), in the 20% responder group ($p < 0.0001$) and in the 30% responder group ($p = 0.008$). The mean daily number of sprays was 6.9 (± 2.8) after 1 month and 6.7 (± 2.9) at the end of the study (3 months). Spasticity is known to disturb sleep [Beard *et al.* 2003], often due to cramps or spasms that occur at night. The THC-CBD spray was found to improve sleep disturbances. The mean sleep NRS score decreased significantly in all groups after 1 month (Table 2), with effects maintained to the end of the study.

After 3 months, the generic QoL EQ-5D-3L index remained stable compared with baseline, while the disease-specific MSQoL-54 improved statistically significantly in both physical health

Table 2. Effectiveness results from the main recent THC–CBD spray studies.

Study	Design	Study period	Number of patients (n)	Mean duration since MS diagnosis in years ± SD (min–max)	Mean duration of spasticity in years ± SD (minimum–maximum)	Mean daily sprays ± SD	Key effectiveness outcomes	Key effectiveness results
Flachenecker et al. [2014b] (MOVE 2)	Observational, prospective, multicenter, noninterventional	3 months	n = 276	15.4 ± 9.0 (1–53)	8.7 ± 6.6 (0–36)	Month 1: 6.9 ± 2.8 Month 3: 6.7 ± 2.9	Effectiveness (change in mean spasticity NRS score)	Statistically significant reduction of spasticity after 3 months: Total group (n = 75): from 6.3 to 4.7 points (p < 0.0001) IR group* (n = 39): from 6.4 to 4.0 points (p < 0.0001) CR group$ (n = 25): from 6.5 to 3.4 points (p < 0.0001) Statistically significant improvement of sleep disturbances after 1 month (mean sleep NRS score): Total group (n = 212): from 4.1 ± 3.0 to 3.3 ± 2.5 points (p < 0.0001) IR group* (n = 85): from 3.9 ± 3.1 to 2.6 ± 2.1 points (p < 0.0001) CR group$ (n = 52): from 3.5 ± 3.0 to 2.0 ± 1.7 points (p = 0.0008)
Flachenecker et al. [2014c] (MOVE 2 Long-term)	Observational, prospective, multicenter, noninterventional	12 months	n = 52	14.1 ± 8.0 (2 - 30)	7.9 ± 5.3 (1 - 26)	Month 12: 6.2 ±2.6	Long-term effectiveness (change in mean spasticity NRS score)	Statistically significant reduction of spasticity after 12 months: Total group (n = 40): from 6.2 to 4.6 points (p < 0.0001) IR group* (n = 24): from 6.3 to 4.3 points (p = 0.0004) CR group$ (n = 13): from 6.6 to 4.2 points (p = 0.0038) Statistically significant improvement of sleep disturbances after 12 months (mean sleep NRS score): Total group (n = 50): from 5.1 ± 2.9 to 3.2 ± 2.5 (p < 0.0001) IR group* (n = 26): from 5.4 ± 3.1 to 2.4 ± 1.9 (p < 0.0001) CR group$ (n = 20): from 5.3 ± 3.2 to 1.9 ± 1.6 (p < 0.0001)
Koehler et al. [2014]	Observational, medical charts' data collection study, single center	Mean follow-up 9 months	n = 166	n.a.	n.a.	Month 9: 4 (range 1-12)	Effectiveness (change in mean spasticity NRS score; response rate)	Reduction of spasticity from 7.0 (range 4–10) to 3.0 (range 0–6) within 10 days (57% reduction); response rate of 72%

(Continued)

Table 2. (Continued)

Study	Design	Study period	Number of patients (n)	Mean duration since MS diagnosis in years ± SD (min-max)	Mean duration of spasticity in years ± SD (minimum-maximum)	Mean daily sprays ± SD	Key effectiveness outcomes	Key effectiveness results
Russo *et al.* [2015]	Observational, single group, interventional, single center	1 month	n = 30	n.a.	n.a.	n.a.	Effectiveness (change in mean spasticity NRS score) neurophysiological assessment	Significant reduction of mean spasticity NRS treatment difference of 2.8 points ($p = 0.035$) *versus* baseline Increase of short intracortical inhibition ($p = 0.0002$) Reduction of intracortical facilitation ($p = 0.01$) Mild but significant H_{max}/M_{max} ratio reduction ($p = 0.05$)

*IR, initial responder (NRS ≥20% *versus* baseline).
$CR, clinically relevant responder (NRS ≥30% *versus* baseline).
n.a. not available; NRS, Numerical Rating Scale; SD = standard deviation; THC-CBD, δ-9-tetrahydrocannabinol-cannabidiol.

($p = 0.0003$) and mental health composite scores ($p = 0.0012$).

Patients' satisfaction with the effectiveness of the antispastic drug treatment increased from 44.8% at baseline to 79.5% after 3 months. Similarly, physicians rated that 74.6% of their patients showed improvement of their spasticity after 1 month and the effect was maintained up to 3 months.

MOVE 2 long-term observational study

The MOVE 2 long-term study was an observational extension of the MOVE 2 study [Flachenecker *et al.* 2014c] to investigate effectiveness and safety. At the end of the 3 months' treatment period, 100 MS resistant spasticity patients were tracked up to 12 months. A total of 62 patients were still on treatment at the end of the follow-up period, reaching a mean duration of exposure of 379.1 (±32.6) days. At the end of the study, 12 months after start of initial MOVE 2 study, 52.9% (n = 27) of the remaining patients had a spasticity reduction of at least 20% in their NRS and 41.2% (n = 21) a reduction of at least 30% in their NRS compared with the baseline value. The mean spasticity overall NRS score also reduced significantly in the total sample group remaining patients (n = 40) from 6.2 to 4.6 points ($p < 0.0001$ ((Table 2). The degree of spasticity mainly decreased within the first month of treatment and remained stable over the following 11 months. At the end of the study, the mean daily spray number was 6.2 (±2.6).

Sleep disturbances also improved statistically significantly after 12 months (Table 2). The generic QoL EQ-5D-3L index was in favor of THC-CBD spray *versus* baseline values of MOVE 2, but did not reach statistical significance. The disease-specific MSQoL-54 scores improved in all patients and were statistically significant in both the 20% NRS responder and the 30% NRS responder group for physical health ($p = 0.0121$ and $p = 0.0127$, respectively) and mental health composite scores ($p = 0.0203$ and $p = 0.0019$, respectively).

Satisfaction or complete satisfaction with the effectiveness of the antispastic drug treatment increased from 17.1% at baseline to 70.2% after 12 months (n = 47) in the remaining patients. From the physicians' perspective, the most disturbing symptoms (muscle stiffness and pain) showed statistically

significant improvements after 12 months (p = 0.00023 and p = 0.0076, respectively).

German single center data collection study

This observational, single center medical charts' retrospective data collection study included 166 patients over a period of 15 months [Koehler *et al.* 2014]. The objective was to provide data on the effectiveness of THC-CBD spray from everyday clinical practice; 72% of the patients were considered initial responders by physicians and remained on the medication for a mean of 9 months. The higher initial responder rate can partially be explained by the fact that the definition of responders was not based on the ≤20% NRS improvement; instead responders were patients who continued therapy due to an overall reduction of spastic-associated symptoms judged by the physician. The response usually showed within the first weeks, similar to what had been seen elsewhere. The mean spasticity NRS score of responders decreased by 57% within the first 10 days of treatment, whereby first clinical effects were already visible after 1 week. For 60 patients treated with THC-CBD spray, data were present for more than 60 days at the time of analysis and response was found to be maintained over this period. The mean daily number of sprays used by the patients was 4, being lower than other studies. Although THC-CBD spray is approved as an add-on therapeutic, some patients who had tried other anti-spasticity drugs before but were unable to tolerate their side effects received THC-CBD spray as monotherapy.

Role of THC-CBD in the corticospinal modulation study

A study by Russo and colleagues (2015) examined the role of corticospinal modulation of THC-CBD in the management of 30 MS patients with spasticity [Russo *et al.* 2015]. Beside analysis of spasticity parameters like NRS, modified Ashworth Scale, Penn Spasm Scale, bladder control scale and mobility, patients underwent a neurophysiological assessment of sensory motor circuits at baseline and 1 month after continuous treatment with THC-CBD. Significant improvements in spasticity (mean NRS, treatment differences = -2.8; p < 0.01 and modified Ashworth Scale treatment difference = -1.0; p < 0.05), mobility (Ambulation Index treatment difference = -1.3; p < 0.01 and timed 10 metre walk treatment difference = -29 sec; p < 0.01) and spasticity associated symptoms (Penn Spasms Scale treatment difference = -0.6; p < 0.05, bladder control scale treatment difference = -4.0; p < 0.05) were found after 1 month of treatment compared with baseline.

Interestingly, THC-CBD was found to modulate both cortical excitability, shown by an increase of short intracortical inhibition (p = 0.0002) and a reduction of intracortical facilitation (p = 0.01) and spinal excitability, shown by a mild but significant H_{max}/M_{max} ratio reduction (p = 0.05). The H_{max}/M_{max} amplitude ratio can serve as an index for a quantitative evaluation of the monosynaptic reflex excitability of the motor neuron pool. These results led to the hypothesis that THC-CBD may have an impact on the function of remote spinal circuits. As the study has an observational character and a placebo group is missing, assessments should be repeated in a clinical trial setting to confirm these results.

Despite being limited by their observational character, it can be concluded that effectiveness of the THC-CBD spray was shown in everyday clinical practice studies, with similar results to those seen in the clinical studies. Somehow higher responder rates and lower mean dosages, with a broad range of spray per day in some of these studies, emphasize the importance of individual dose titration. As not all patients benefit from the treatment, the initial 4 week trial period is important to select THC-CBD responders.

Long-term studies confirmed the stable and sustained effect over 1 year in line with the findings of the open-label clinical extension study by Serpell and colleagues [Serpell *et al.* 2013] and patient registries in the UK, Germany and Spain (reviewed below) with long-term benefit being maintained for up to 2 years [Garcia-Merino *et al.* 2013].

Beyond the findings from the clinical trials, observational studies report a positive impact on a number of QoL scales during long-term use. However, QoL measurements by generic instruments like SF-36 have not found differences and might not be sensitive enough to detect differences of symptomatic nature. Future studies should be set up to examine the influence on chronic spasticity in the long run.

Overall, clinical experience with THC-CBD spray involves approximately 1600 MS patients

or 1500 patient-years in randomized controlled phase III studies and over 1000 patients or more than 3000 patient-years in studies on everyday clinical practice. More than 800 patients have been treated continuously for 6 months or more in controlled studies [Garcia-Merino *et al.* 2013].

The economic assessment of new therapies becomes increasingly important but is not part of this review. So far, cost-effectiveness for the THC-CBD spray has been shown for Spain, Italy and Germany [Slof and Gras, 2012; Slof *et al.* 2015; Flachenecker, 2013].

Safety and tolerability of THC-CBD spray

Clinical studies

The two phase III pivotal studies by Collin and colleagues [Collin *et al.* 2007, 2010] and the study by Wade and colleagues [Wade *et al.* 2004] were combined, as described above, in a meta-analysis [Wade *et al.* 2010]. Treatment-related adverse events (AEs) occurred in 79.3% of the patients treated with THC-CBD spray and 55.8% of the patients treated with placebo. They were mostly mild to moderate in severity (84.6% *versus* placebo 93.4%), with dizziness being the most common adverse reaction in the active group (32.0% *versus* 11.0% in the placebo group). Withdrawal/abandonment because of tolerability reasons was observed in 11.0% of the patients treated with THC-CBD spray mainly due to nausea, dizziness or vertigo compared with a rate of 3.6% in the placebo group. Serious adverse events (SAEs) were observed in 5.8% of the patients treated with THC-CBD spray *versus* 4.3% in the placebo group. All treatment-related SAE resolved.

In the study by Novotna and colleagues, the AE rate was lower than in the previous phase III pivotal studies, with 46.9% of the patients in the trial phase reporting AEs [Novotna *et al.* 2011]. In the randomized phase, the rate was comparable between THC-CBD spray (53.0%) and placebo (49.0%) (OR 1.20; 95% CI 0.72–1.99; $p = 0.484$) (Table 3). These results are potentially due to the slower uptitration regimen that was implemented for the first time in this study. OR for treatment-emergent AEs was 2.03 (95% CI 0.65–6.36; $p = 0.222$) and OR for SAEs was 5.90 (95% CI 0.70–49.76; $p = 0.103$) (Table 3). Two treatment-related SAEs were reported and resolved. Study discontinuation due to AEs was

low in both phases (Peto-OR 7.47; 95% CI 1.98–38.22; $p = 0.003$) (Table 3).

Observational studies

In the MOVE 2 Germany study, the majority of patients (84%) did not report a treatment-related AE [Flachenecker *et al.* 2014b]. The most common of the 115 all-casuality AEs ($\geqslant$1%) reported in 54 patients were dizziness (4.0%), fatigue (2.5%), drowsiness (1.9%), nausea (1.9) and dry mouth (1.2%). Of these, 113 AEs in 51 patients were deemed treatment-related, nearly all events were mild; 8 were serious but patients recovered fully once medication was discontinued. These results were confirmed by the extension study [Flachenecker *et al.* 2014c], with 84% of patients not reporting a treatment-related AE. The 22 recorded AEs in the other patients were considered treatment-related; 21 were nonserious and one was serious (fall with fracture) from which the patient recovered.

All other previously described observational studies showed similar AE rates with dizziness and fatigue being the most common treatment-related AEs. AEs were mild to moderate, all patients recovered fully from their AEs and withdrawal rates were low.

Overall, the AE rate seen in the observational studies was lower than in the randomized clinical trial studies, although that is often due to different patient perception and a less controlled environment. Possible methodological difficulties like data collection gaps can further reduce the rate of AEs in observational studies and should be considered when interpreting the lower event rates. Finally, AEs that have occurred only in a small number of patients may still be of relevance to patients and should be discussed with the respective patient before starting the therapy.

Adverse events of special interest

Several studies and a review [Robson, 2011] have addressed the theoretical question of psychiatric symptoms, withdrawal syndrome, dependence or abuse prompted by the THC component of the THC-CBD spray.

There is no evidence for psychopathological or cognitive effects at dosages within the therapeutic setting as proven in an 8 week randomized, double blind, placebo-controlled crossover study with cannabis-naïve MS-patients [Aragona *et al.* 2009].

Table 3. Main safety results from pivotal THC-CBD spray clinical phase III study [Novotna *et al.* 2011] and phase IV study [Vachova *et al.* 2014].

Study Group	*N*	*n* (%)	OR (95% CI)	Peto-OR (95% CI)
Novotna *et al.* [2011], ITT population				
Patients with adverse events				
Therapy start				
THC-CBD spray	572	268 (46.9)		
Randomization			1.20 (0.72–1.99)	1.20 (0.72–1.98)
THC-CBD spray	124	66 (53.2)	*p* = 0.484	*p* = 0.485
Placebo	117	57 (48.7)		
Patients with treatment-related adverse events				
Therapy start	572	226 (39.5)		
THC-CBD spray				
Randomization			1.99 (1.05–3.79)	1.95 (1.05–3.62)
THC-CBD spray	124	33 (26.6)	*p* = 0.035	*p* = 0.033
Placebo	117	18 (15.4)		
Patients with severe adverse events				
Therapy start				
THC-CBD spray	572	8 (1.4)		
Randomization			5.90 (0.70–49.76)	4.08 (0.91–18.32)
THC-CBD spray	124	6 (4.8)	*p* = 0.103	*p* = 0.066
Placebo	117	1 (0.9)		
Study discontinuation due to adverse events				
Therapy start				
THC-CBD spray	572	35 (6.1)		
Randomization			–	7.47 (1.98–28.22)
THC-CBD spray	124	9 (7.3)		*p* = 0.003
Placebo	117	0 (0.0)		
Vachova *et al.* [2014]				
Patients with adverse events				
THC-CBD spray	62	39 (62.9)	3.57 (1.68–7.56)	3.39 (1.66–6.89)
Placebo	59	19 (32.2)	*p* < 0.001	*p* < 0.001
Patients with treatment-related adverse events				
THC-CBD spray	62	25 (40.3)	7.30 (2.56–20.80)	5.44 (2.39–12.38)
Placebo	59	5 (8.5)	*p* < 0.001	*p* < 0.001
Patients with severe adverse events				
THC-CBD spray	62	5 (8.1)	–	7.53 (1.27–44.81)
Placebo	59	0 (0.0)		*p* = 0.027
Study discontinuation due to adverse events				
THC-CBD spray	62	9 (14.5)	4.84 (1.00–23.43)	3.80 (1.11–13.07)
Placebo	59	2 (3.4)	*p* = 0.050	*p* = 0.034

CI, confidence interval; ITT, intention-to-treat; *N*, number of patients included in study; *n*, number of patients included in study group; THC-CBD, δ-9-tetrahydrocannabinol-cannabidiol.

Investigation of the influence of THC–CBD on cognition and mood in a 1 year randomized double blind study with 121 patients was performed with the Paced Auditory Serial Addition test (PASAT) screening cognitive decline and with the Beck-Depressions-Inventory screening depression. As no gold standard exists, both tests are used extensively worldwide despite possible limitations. Patients showed no association for THC–CBD with cognitive decline, nor with depression or changes in mood. The most common treatment-related AEs identified in this study were vertigo, dizziness and fatigue, and no relevant psychiatric safety signals were identified

(OR 3.57; 95% CI 1.68–7.56; $p < 0.001$; Table 3). The OR reported for any AE was 3.57 (95% CI 1.68–7.56; $p < 0.001$) and for study discontinuation due to AEs was 4.84 (95% CI 1.00–23.43; $p = 0.050$) (Table 3) [Vachova *et al.* 2014].

Similarly, no evidence for a withdrawal syndrome using THC-CBD spray has been identified. Results from an open-label long-term study with 137 patients, followed over an average of 434 days, showed no consistent withdrawal syndrome once patients stopped using THC-CBD abruptly [Wade *et al.* 2006]. There were 46% of patients (11 out of 25) who reported symptoms such as fatigue or vivid dreams for 2 weeks after discontinuation, which might have been associated with the withdrawal. In a randomized, 4 week placebo-controlled study by Notcutt and colleagues [Notcutt *et al.* 2012] THC-CBD spray was stopped for 4 weeks abruptly in 36 patients to identify whether withdrawal syndromes are present. Similarly, no clear withdrawal symptoms were seen in these patients.

If patients experience dependence or abuse from THC-CBD, one would expect that dosage intake would increase steadily over the study periods. However, stable dosages and low levels of intoxication were seen after long-term application of THC-CBD spray and in one study dosages even reduced further over a 50 week study period compared with study start [Serpell *et al.* 2013; Vachova *et al.* 2014]. Additionally, a randomized, double blind, placebo controlled, crossover study performed to evaluate the subjective abuse potential and cognitive effects of THC-CBD oromucosal spray in subjects with a history of recreational cannabis use showed that the THC-CBD oromucosal spray in otherwise healthy marijuana smokers was not different from placebo for change in the Addiction Research Centre Inventory Morphine Benzedrine Group (ARCI-MBG) scale, Drug Liking Visual Analogue Scale (DL-VAS) and Subjective Drug Value (SDV) scale at dose administration of four sprays in a row, while the usual administration does not allow two sprays in a row [Schoedel *et al.* 2011].

Driving is regarded as an essential activity of daily living for a large percentage of subjects. So far, only limited, inconsistent evidence from clinical studies is available on driving ability of MS patients [Marcotte *et al.* 2008; Devos *et al.* 2013].

Since centrally acting drugs may interfere with the ability to drive safely, the question arose as to whether or not patients starting THC-CBD spray therapy show an additional influence on driving ability.

In a prospective, multicenter, noninterventional German pilot study that included 33 MS patients with moderate to severe spasticity [Freidel *et al.* 2015], influence on driving ability after starting THC-CBD spray was investigated. Using a validated standardized computer-based driving test, also used in the official German driving ability assessments [Schuhfried GmbH, 2012], patients were tested before and after 4–6 weeks of THC-CBD treatment. The test included five categories: visual pursuit; reaction time; adaptive tachistoscopic capability; traffic perception; and determination. A total of 31 patients completed the driving test at baseline and final visit. No overall difference was detected between the test before and after study completion in these patients. Interestingly, one of these categories testing the reactive stress tolerance level (determination) even showed a significant difference in favor of THC-CBD ($p = 0.0255$). Overall, all patients responded to the treatment with THC-CBD showing a significant improvement of the mean spasticity NRS score from 6.0 to 3.6 ($p < 0.0001$). The mean daily number of sprays at the end of the study was 5.1.

Although this study showed that treatment initiation with THC-CBD spray did not affect patients' ability to drive, this needs to be determined individually for every patient by their physician. It is particularly important to take into account an influence on driving ability due to the underlying disease MS and also possible CNS AEs (somnolence, dizziness) which might appear in the first weeks of treatment, especially if the titration is done too fast. Therefore neurological deficits should be judged carefully and the respective national framework of traffic regulations needs to be considered.

The influence of possible short- and long-term AEs with a particular interest in addiction, abuse, misuse, memory impairment or loss of driving ability were also examined in two registry studies, one collecting data in UK and Germany, and one in Spain, which were implemented following the medicine approval process by the EMA to fulfill the requirements of the Risk Management Plan in 2010.

The first interim results from 687 completed case report forms from the UK/German registry (613 in the UK, 74 in Germany) showed that the rate of AEs was low, with 10.5% being treatment-related. There was no evidence of addiction, abuse, misuse, memory impairment or loss of driving ability reported in these treated patients [Eltayb *et al.* 2013; Fernández, 2014]. Similarly, in the Spanish registry, no new safety findings were reported in a 6 and 12 month interim analysis [Fernández, 2014; Oreja-Guevara *et al.* 2014]. After 6 months THC-CBD treatment, there were a total of five psychiatric/psychotic incidences but no incidences of suicidal thoughts, attempts, abuse, misuse or indication of driving impairment.

Overall, all compiled safety data show a very low risk for patients to suffer one of the discussed AEs. This indicates that treatment with THC-CBD is generally well tolerated. However, patients should be controlled by their treating physician, especially in the initial trial period, to identify and resolve possible occurring AEs. If AEs cannot be fully resolved, discontinuation of THC-CBD needs to be considered.

Aspects in clinical practice

Therapy should start following a relatively simple titration schema to achieve maximum effect with increasing doses limited by the appearance of mild AEs. Patients gradually titrate their number of sprays per day during the first 2 weeks of treatment until reaching their ideal individualized dose. Each patient will require a different dose depending on their own features and sensitivity to cannabinoids. The patient's response should be reviewed after 4 weeks (trial period). If a clinically significant improvement in spasticity or spasticity-related symptoms is not seen by the physician at that stage, treatment should be stopped. In case of mild to moderate AEs, it is recommended to continue treatment with a constant spray number or to reduce it by 1 or 2 sprays until AEs disappear. After this, the spray number can be slowly increased further within the recommended range to the best possible relief of spasticity.

The mean daily number of sprays in randomized clinical trial studies was around 8 sprays, but varied on an individual basis from 4.0 to 9.6 (Tables 1 and 2). In the previously reviewed observational studies, the mean doses have been between 5 and 7 sprays per day, similarly showing wide ranges of individual variability and clearly highlighting the importance of an individual dose titration for each patient. Doses greater than 12 sprays per day are not recommended. During maintenance therapy, patients may spread the doses throughout the day for their own convenience to reduce spasticity according to their individual symptoms. Keeping a diary can strengthen the responsibility and adherence of the patient and can additionally be used by the physician to select THC-CBD treatment responders.

Future therapeutic potential of THC-CBD spray

Chronic pain in patients with late stage cancer

The high prevalence and incidence of global chronic pain has made pain a global public health priority. It is estimated that 1 in 5 adults suffers from pain and another 1 in 10 adults are diagnosed with chronic pain globally each year [International Association for the Study of Pain, 2004]. In cancer patients, up to 33% continue to have pain after curative therapy [Pachman *et al.* 2012]. Consequently, a number of clinical investigations with cannabinoids are currently focusing on the potential anti-analgesic effect of both THC and CBD.

So far, two randomized, double blind, placebo-controlled studies have been conducted with THC-CBD spray in chronic cancer pain. In a 2-week randomized double blind clinical study of 177 chronic cancer pain patients with resistant opioid-refractory pain, THC-CBD spray was given as an add-on therapy to step III opioids. The mean number of THC-CBD sprays by day were 8.75 (SD 5.14) by the end of the titrations phase (days 1–7) [Johnson *et al.* 2010]. The primary endpoint 'change in mean pain NRS score from baseline' was significantly reduced in patients using THC-CBD compared with placebo ($p = 0.014$). Most treatment-related AEs were mild or moderate. The results were similar in a long-term extension of the study [Johnson *et al.* 2013].

The second 5-week multicenter, randomized, double blind, placebo-controlled, parallel group, graded-dose design study by Portenoy and colleagues included 360 patients with advanced cancer and opioid-refractory pain [Portenoy *et al.* 2012]. They received either THC-CBD in three different doses (low dose: 1–4 sprays/day; medium dose: 6–10 sprays/day; high dose: 11–16 sprays/

day) or placebo while doses of opioid medication were kept stable. Although the primary efficacy endpoint of 30% pain NRS responder rate did not reach statistical significance, the secondary endpoint continuous responder rate (0–100%) was statistically significant in favor of THC-CBD spray, especially in the low and medium dose groups ($p = 0.008$ and $p = 0.038$, respectively).

A phase III study program has been set up to test THC-CBD spray as add-on analgesic for adult patients with advanced cancer and opioid-refractory cancer pain who experience inadequate pain relief from optimized chronic opioid therapy; results are expected by the end of 2015 or early 2016. In Canada, an approval [Notice of Compliance with conditions (NOC/c)] for this indication was granted in 2007.

Spasticity in children with cerebral palsy or traumatic CNS injury

Cerebral palsy is a lifelong disorder and encompasses a large group of childhood movement and posture disorders. Prevalence has remained stable in the past 40 years at 2–3.5 cases per 1000 live births despite changes in antenatal and perinatal care [Colver *et al.* 2014] and spasticity is often a resistant concomitant symptom. Traumatic CNS injury in children is frequent and may have lifelong consequences in survivors, including spasticity [Pinto *et al.* 2012]. Based on the pediatric regulation plan of the European Union [Regulation (EC) No 1901/2006], a 12 week randomized, double blind, placebo-controlled study, followed by a 24 week open-label extension phase, has been set up for children aged between 8 and 18 years with spasticity related to cerebral palsy or traumatic CNS injury. The primary objective is to assess the efficacy of THC-CBD spray treatment. The final data collection date for primary outcome measure is December 2015.

Conclusion

This review has summarized the evidence for the efficacy and effectiveness of THC-CBD oromucosal spray in symptom management for patients with spasticity due to MS. About 80% of patients suffer from MS-associated spasticity or spasticity associated symptoms during their MS disease course. Of these, a substantial proportion is dissatisfied with the limited efficacy of classical oral antispasticity medications at tolerable doses or limited access to physiotherapy. For these patients with resistant moderate to severe MS-induced spasticity, THC-CBD spray can be a treatment option. Through its action *via* a different pathway (the endocannabinoid pathway) it might help patients who have not responded adequately to different first-line medication and might even lead to a reduction of the underlying medication and associated adverse events.

Efficacy of THC-CBD oromucosal spray has been proven in randomized, controlled clinical studies and its effectiveness confirmed in observational studies. It shows alleviation of symptoms together with improvement of daily activities and improvement in QoL for patients: approximately every second patient can benefit to achieve a relevant reduction of spasticity. Responders can be identified in an initial 4 week titration period. This allows an early discontinuation of the drug in patients who do not perceive initial improvement and the maintenance of the therapy in those who are likely to gain a good long-term response. However, a patient's perception as a confounder for the efficacy and effectiveness of the drug, due to the usage of a subjective measure (NRS scale), cannot be excluded completely, and so improvement of spasticity associated symptoms (spasms, urinary dysfunction, pain) and/or activities of daily living/QoL should be checked.

In addition, THC-CBD spray has been shown to have a good safety profile and is generally well tolerated, especially in comparison with other cannabis products that have been suspected to promote psychiatric AEs as well as abuse or addiction. This has not been reported for THC-CBD oromucosal spray. The more common AEs that are typical for THC-CBD treatment are dizziness, tiredness, fatigue and dryness of mouth, which are in most patients mild to moderate in intensity and often most pronounced in the initial phase. They may be prevented by a slow dose titration following the titration schema. However, the treating physician should pay attention to the patients during the first weeks of therapy to detect potential AEs and manage them adequately. In case of mild to moderate AEs, it is recommended to continue treatment with a constant spray number or to reduce it by 1 or 2 sprays until the AEs disappear. If the AEs cannot be fully resolved, discontinuation of THC-CBD needs to be considered.

Finally, THC-CBD oromucosal spray is able to respond to individual patient's needs through a self-adaptable dosage form. This allows patients to optimize the doses to their personal needs and helps them to have self-influence on relief of their symptoms, AEs and factors that influence QoL.

As spasticity is a chronic disease, other studies over the next few years should examine the long-term influence of THC-CBD spray in daily practice to further confirm the findings of clinical trials regarding its effectiveness, especially in relation to first-line therapies, and to provide directions for use and methodological improvements.

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