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ADIS DRUG EVALUATION

Delta-9-Tetrahydrocannabinol/Cannabidiol (Sativex®): A Review of Its Use in Patients with Moderate to Severe Spasticity Due to Multiple Sclerosis

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Abstract Delta-9-tetrahydrocannabinol (THC)/cannabidiol (CBD) [Sativex®] is an oromucosal spray formulation that contains principally THC and CBD at an approximately 1:1 fixed ratio, derived from cloned *Cannabis sativa* L. plants. The main active substance, THC, acts as a partial agonist at human cannabinoid receptors (CB_1 and CB_2), and thus, may modulate the effects of excitatory (glutamate) and inhibitory (gamma-aminobutyric acid) neurotransmitters. THC/CBD is approved in a number of countries, including Germany and the UK, as an add-on treatment for symptom improvement in adult patients with moderate to severe spasticity due to multiple sclerosis 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. In the largest multinational clinical trial that evaluated the approved THC/CBD regimen in this population, 12 weeks' double-blind treatment with THC/CBD significantly reduced spasticity severity (primary endpoint) compared with placebo in patients who achieved a clinically significant improvement in spasticity after 4 weeks' single-blind THC/CBD treatment, as assessed by a patient-rated numerical rating scale. A significantly greater proportion of THC/CBD than placebo recipients achieved a ≥30 % reduction (a clinically relevant reduction) in spasticity severity. The efficacy of THC/CBD has been also shown in at least one everyday clinical practice study (MOVE 2). THC/CBD was generally well tolerated in clinical trials. Dizziness and fatigue were reported most frequently during the first 4 weeks of treatment and resolved within a few days even with continued treatment. Thus, add-on THC/CBD is a useful symptomatic treatment option for its approved indication.

Add-on delta-9-tetrahydrocannabinol (THC)/cannabidiol (CBD) [Sativex®] in patients with moderate to severe refractory spasticity due to multiple sclerosis: a summary

Self-titrated oromucosal formulation of THC and CBD (approximately 1:1 ratio) derived from *Cannabis sativa* L. plants cultivated under controlled conditions

Significantly reduces spasticity severity compared with placebo in patients who achieved a clinically significant improvement in spasticity during an initial 4 weeks' therapy

Significantly reduces spasm frequency compared with placebo

Generally well tolerated, with the majority of adverse events being mild or moderate in severity

Does not induce withdrawal syndrome or tolerance; minimal abuse potential

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1 Introduction

Spasticity (muscle stiffness) is a common symptom of multiple sclerosis (MS). According to a recently updated definition, spasticity is a "disordered sensori-motor control, resulting from an upper motor neurone lesion, presenting as intermittent or sustained involuntary activation of muscles" [1]. Spasticity is often associated with pain, sleep disturbance, inability to walk, unexpected falls and painful spasms; these symptoms can cause further complications such as pressure sores, contractures, poor personal hygiene, negative emotional impact and social isolation [2, 3]. In a survey of patients with MS ($n = 20{,}969$), 84 % of patients reported spasticity, with 34 % rating it as moderate or worse [4]. Healthcare resource use increases dramatically with increased spasticity severity [5].

Currently recommended oral medications for spasticity include baclofen, gabapentin, tizanidine, diazepam, clonazepam and dantrolene [6]. However, although spasticity is potentially treatable, systematic reviews show that evidence for the effectiveness of these medications is limited and that they provide only modest clinical benefit, with some patients not responding to treatment [2, 7]. The options for patients with treatment-refractory spasticity are limited, expensive and invasive (e.g. intrathecal baclofen) [6]. Thus, there is a need for antispasticity medications in patients who have not responded adequately to the available agents.

Illicit cannabis (*Cannabis sativa*) is often used in various forms for medicinal purposes, most commonly to alleviate sleep disorders, pain and anxiety [8] or the symptoms of MS [9]. The underlying biology of cannabinoids' therapeutic effects in spasticity is only just emerging (reviewed by Baker et al. [10]). The human endocannabinoid system comprises two major cannabinoid receptors (CB_1 and CB_2, expressed primarily in central nervous system [CNS] tissues and immune cells, respectively) and their endogenous ligands, known as endocannabinoids [10]. Under normal physiological conditions, binding of endocannabinoids to pre-synaptic CB_1 receptors acts as a presynaptic signal to inhibit further release of excitatory neurotransmitters such as glutamate [10]. In spasticity, an aberrant level of glutamatergic excitability is detected [10]. Thus, augmenting the endocannabinoid system with exogenous cannabinoid receptor agonists is a potential therapeutic approach for the control of spasticity. Indeed, a study in mice showed that CB_1 receptors play an important role in controlling spasticity and that some CB_2 receptor agonists may also have antispastic activity because of their cross-reactivity to CB_1 receptors [11].

The principal active components of cannabis extract which act as human endocannabinoid system modulators are delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD) [10]. THC is a psychoactive substance that accounts for the therapeutic effect as well as some adverse events (e.g. intoxication) of cannabis extract; whereas, CBD is a non-psychoactive substance with its own therapeutic properties and, most importantly, it is thought to alleviate the intoxicating effects of THC [10, 12]. A number of oral formulations of THC, either from cannabis extract or synthetic, have been evaluated in clinical trials with varying degrees of effectiveness in reducing spasticity in patients with MS [13].

An oromucosal spray formulation of THC and CBD (at approximately 1:1 fixed ratio) extracted from leaves and flowers of cloned *C. sativa* L. plants. (Sativex®; USAN, nabiximols; THC/CBD) cultivated under controlled conditions has been developed [12]. Each spray delivers a 100 μL volume, containing principally THC 2.7 mg and CBD 2.5 mg, prepared in a solution of ethanol, propylene glycol and peppermint oil; in addition, small quantities of other cannabinoids and non-cannabinoids are also present [12]. The rationale for the development of this formulation is that the whole-plant extract of cannabis providing THC and CBD in balanced quantities may be more effective and have a better tolerability profile than individual components, and an oromucosal formulation may be an optimal route of administration in terms of absorption, plasma concentrations and tolerability [12]. THC/CBD is the first endocannabinoid system modulator to receive approval in several countries, including the UK [14], as an add-on treatment for spasticity in patients with MS. This review focuses on the pharmacological properties, clinical efficacy and tolerability of THC/CBD in adult patients with MS-related spasticity.

2 Pharmacodynamic Properties

2.1 Mechanism of Action

The pharmacodynamic effect of THC/CBD on the physiology of muscle tone or spasticity has not been directly studied in humans, but has been demonstrated in an animal model [15]. THC acts as a partial agonist at both CB_1 and CB_2 receptors, and mimics the action of endocannabinoids (i.e. to act as a presynaptic signal); therefore, it may modulate the effects of neurotransmitters, such as reducing the effects of the major excitatory neurotransmitter, glutamate, and enhancing the effects of the inhibitory neurotransmitter, gamma-aminobutyric acid (GABA) [14, 16].

2.2 Effect on Spasticity, Early Studies

In addition to an in vivo study using a mouse model of MS [15], the clinical effects of THC/CBD on spasticity have

been initially studied in at least two phase II trials [17, 18], with published data available from one study [18] and the other study (study GWN19904) reported in the Public Assessment Report (PAR) of the UK Medicines and Healthcare Products Regulatory Agency (MHRA) [17].

THC/CBD dose-dependently reduced hind limb stiffness (a marker of spasticity) in an experimental mouse model of MS-related spasticity (chronic relapsing experimental autoimmune encephalomyelitis) [15]. The stiffness was assessed by gauging the force required to bend the hind limb to full flexion. Intravenously administered THC/CBD 5/5 and 10/10 mg/kg significantly ($p < 0.01$) reduced the stiffness within 10 min, with a peak reduction of approximately 20 and 40 % from baseline over a 2-h assessment period. The higher dose was as effective as intravenous baclofen 5 mg/kg in reducing limb stiffness [15].

In a double-blind, crossover, phase II trial ($n = 20$ evaluable; 14 with MS), add-on therapy with cannabis whole-plant extracts of THC, CBD or THC/CBD sublingual spray alleviated neurogenic symptoms, including muscle spasms and/or spasticity in patients with a range of CNS pathologies (see Fig. 1 for further trial design and dosage details) [18]. Each patient had up to five troublesome symptoms (pain, muscle spasms, spasticity, impaired bladder control and tremor) that were stable and not responsive to standard treatments. Compared with placebo, THC/CBD and THC significantly improved muscle spasm and THC also improved spasticity from baseline, as assessed by patient-rated visual analogue scale (VAS) scores (Fig. 1a). All three active treatments significantly reduced spasticity severity from baseline compared with placebo, as assessed by observer-rated numerical rating scale (NRS) scores (Fig. 1b). After 2 weeks' treatment, THC/CBD and THC also significantly ($p < 0.05$) reduced spasm frequency compared with placebo (least squares mean number of spasms per day 3.6 and 3.4 vs. 4.9 [5.5 at baseline]). Although, this study had a number of limitations such as an open-label THC/CBD treatment period and a lack of adjustment for multiplicity, the results show that THC and/or CBD may have some antispastic activity [18]. However, the GWN19904 study in 29 patients with MS or other neurological conditions did not support the efficacy of THC/CBD for the treatment of spasticity [17]. Of note, these studies were relatively small; for discussion of large phase III studies that evaluated the efficacy of THC/CBD in patients with MS-related moderate to severe spasticity see Sect. 4.

2.3 Other Effects

THC/CBD does not induce any clinically significant cardiovascular responses [14, 19]. In healthy volunteers, THC/CBD up to 18 sprays twice daily did not produce any clinically relevant changes in corrected QT (QTc), PR or QRS interval duration, heart rate or blood pressure [14]. In cannabis smokers ($n = 9$), a single dose of six sprays of THC/CBD significantly ($p < 0.001$) decreased diastolic blood pressure and increased heart rate compared with placebo, with heart rate returning to baseline by 10.5 h. However, the mean changes from baseline were considered clinically insignificant [19].

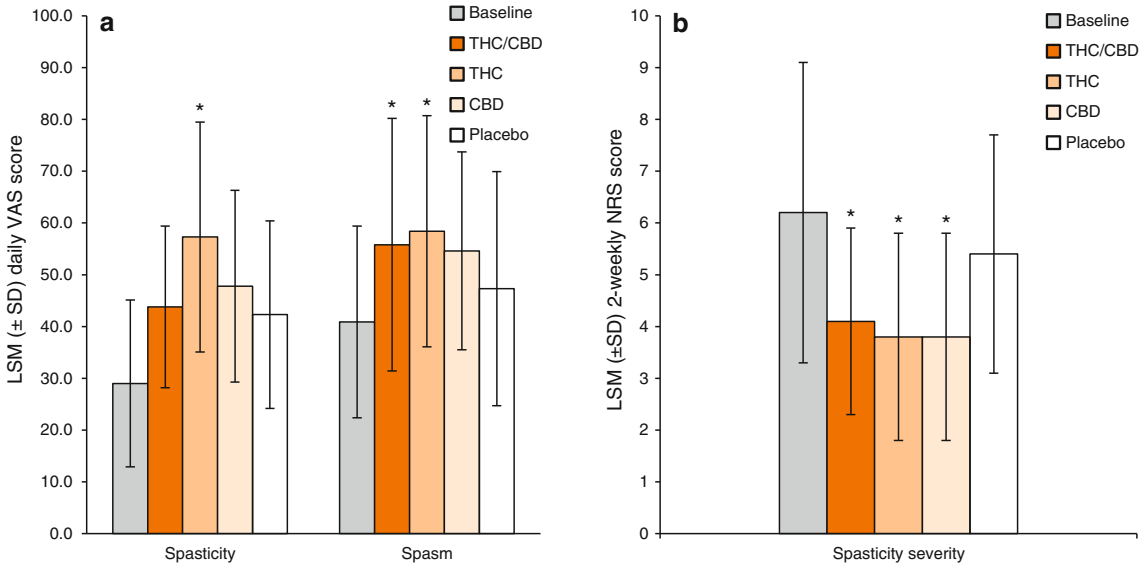

Fig. 1 Effect of delta-9-tetrahydrocannabinol (THC)/cannabidiol (CBD) on intractable spasticity and muscle spasms in patients with various neurological conditions, based on **a** patient-rated VAS scores (100 = best) for days 8–14 and **b** observer-rated NRS scores (10 = worst) after 2 weeks' treatment [18]. After 2 weeks' open-label THC/CBD, patients received THC/CBD 2.5/2.5 mg, THC 2.5 mg, CBD 2.5 mg or placebo in a double-blind manner, each for 2 weeks (cross-over). *LSM* least squares mean, *NRS* numerical rating scale, *VAS* visual analogue scale. *$p < 0.05$ vs. placebo

A single dose of up to six sprays of THC/CBD did not result in clinically significant intoxication or anxiety in cannabis smokers [19]. Patient-reported 0–100 mm VAS (0 = not at all, 100 = most ever) scores were significantly higher with two sprays of THC/CBD than with placebo for feeling 'stimulated' (average treatment difference 2.95; $p = 0.032$) and 'anxious' (>4.22; $p \leq 0.001$). With six sprays of THC/CBD, 'anxious' scores were significantly higher than with two sprays (average treatment difference >3.29; $p \leq 0.004$). Only the high dose produced 'good drug effect' compared with placebo (treatment difference 3.79; $p = 0.022$) and neither doses of THC/CBD resulted in feeling 'high'. Compared with placebo, cannabis intoxication scores (as assessed by the 12-item Marijuana scale from the Addiction Research Center Inventory [ARCI]) were significantly ($p < 0.036$) higher with both doses of THC/CBD, and state anxiety scores (as assessed by the Spielberger State–Trait Anxiety Inventory) were significantly ($p = 0.008$) higher with high-dose THC/CBD. However, the subjective drug effects of low therapeutic doses of THC/CBD seen in this study were considered to be clinically insignificant, and were generally similar to those of approximately equivalent oral THC doses [19].

In a double-blind, crossover study in recreational cannabis users ($n = 23$ evaluable), a single THC/CBD dose of four consecutive sprays did not show abuse potential, although higher single doses of 8 or 16 sprays did show some abuse potential [20]. On a dose-per-dose basis, abuse potential of THC/CBD eight or 16 sprays was lower or similar to that of equivalent oral THC doses [20].

An 8-week, double-blind, placebo-controlled, crossover trial ($n = 17$) showed that THC/CBD dosed freely (mean 8.20 sprays/day) did not significantly induce psychopathology or cognitive impairment in cannabis-naïve patients with MS [21]. These findings are generally supported by a double-blind, placebo-controlled, 12-month study ($n = 121$) that assessed the long-term effects of THC/CBD on cognition and mood in patients with moderate to severe spasticity not responding to other antispasticity drugs (presented as an abstract) [22]. The mean change from baseline in Paced Auditory Serial Addition Test 2 and 3 (a measure of cognitive function; primary endpoint) and Beck Depression Inventory-II scores at 12 months were not significantly different between THC/CBD and placebo recipients [22].

3 Pharmacokinetic Properties

Data discussed in this section are mainly from clinical trials in healthy volunteers [23–26], the UK PAR [17] and the UK summary of product characteristics (SPC) [representative PAR and SPC for the decentralized procedure in the EU] for THC/CBD [14]. Pharmacokinetics of THC/CBD oromucosal spray have not been specifically studied in children, the elderly, or in patients with significant hepatic or renal impairment [14].

3.1 Absorption and Distribution

In healthy volunteers ($n = 12$), following a single oromucosal administration of THC/CBD 10.8/10 mg (four sprays), both THC and CBD were rapidly absorbed, appearing in plasma within 15 min [14, 23]; for THC, a mean maximum plasma concentration (C_{max}) of ≈4 ng/mL was reached at 45–120 min after dosing [14].

Key pharmacokinetic parameters of THC/CBD after 9 consecutive days of once-daily dosing are summarized in Table 1. C_{max} and area under the plasma concentration-time curve (AUC) over the final dosing interval (0–24 h) [AUC_τ] for THC, 11-OH-THC (the primary metabolite of THC) and CBD increased with increasing doses, with no evidence of dose proportionality (Table 1). Exposure to CBD, but not to THC or 11-OH-THC, increased over time [26].

Table 1 Pharmacokinetic parameters of delta-9-tetrahydrocannabinol/cannabidiol oromucosal spray in healthy men [26]. Values are means after the last dose on day 9 unless stated otherwise

THC/CBD sprays od (dose)	Pt no.	THC			11-OH-THC (primary THC metabolite)			CBD		
		AUC_τ (ng·h/mL)	C_{max} (ng/mL)	t_{max} (h)	AUC_τ (ng·h/mL)	C_{max} (ng/mL)	T_{max} (h)	AUC_τ (ng·h/mL)	C_{max} (ng/mL)	T_{max} (h)
2 (5.4/5.0 mg)	6	4.06	1.36	1.64	8.96	1.53	2.25	2.52	0.49	1.64
4 (10.8/10.0 mg)	11	9.86	2.72	1.50	30.89	4.19	2.25	6.66	1.14	1.27
8 (21.6/20.0 mg)	6	39.94	6.90	3.25	99.57	11.11	2.75	20.34	3.22	2.00
Inter-subject CV % range[a]		11.7–39.4	30.8–54.2	NR	40.9–56.6	38.2–52.7	NR	29.1–46.6	42.1–75.7	NR

AUC_τ area under the plasma concentration-time curve over the final dosing interval (0–24 h), *CBD* cannabidiol, *C_{max}* maximum plasma concentration, *CV* coefficient of variation, *NR* not reported, *od* once daily, *Pt* patient, *THC* delta-9-tetrahydrocannabinol, *t_{max}* time to C_{max}

[a] Calculated over the dose range studied

Moderate inter-subject variability was seen in pharmacokinetic parameters after multiple dosing (Table 1) [26], with a high degree of intra-subject variability also noted after single and repeat dosing [14]. In 11 evaluable subjects, after nine once-daily doses of four sprays, THC C_{max} values decreased in eight subjects and increased in three subjects, and CBD C_{max} values increased in four subjects and decreased in seven subjects [14].

Food did not appear to have a clinically significant effect on the pharmacokinetics THC/CBD [25]. In 12 healthy male volunteers, following a single THC/CBD dose of 10.8/10.0 mg (four sprays), the mean C_{max} and AUC values for THC, 11-OH-THC and CBD were significantly (based on 90 % confidence interval) higher under the fed state than under the fasted state. For example, respective values for THC were: 6.48 versus 3.98 ng/mL for C_{max} and 34.99 versus 12.51 ng·h/mL for AUC from time zero infinity (AUC_{∞}). Time to C_{max} was also longer in the fed state (4.0 vs. 1.5 h in the fasted state for THC). However, the large inter-subject variability in exposure seen in these subjects suggests that these increases may not be clinically relevant [25].

There was no evidence of significant THC or CBD accumulation in patients with MS receiving stable self-titrated doses of THC/CBD over the long term [17]. During the extension phase of a phase III trial (GWMS0001; see Sect. 4), plasma concentrations of THC, 11-OH-THC and CBD were measured at two clinical visits 8 weeks apart. Pre-dose trough concentrations after long-term dosing were similar to that seen after a single dose. For example, mean (minimum–maximum) THC trough concentrations at the first and second visits were 2.53 (0.06–6.28) and 2.10 (0.63–3.56) ng/mL [17].

At equivalent doses, THC/CBD oromucosal spray produced lower plasma concentrations of THC compared with inhaled or smoked cannabinoids [14, 26, 27]. Following a single oromucosal dose equivalent to 21.6 mg THC, a C_{max} of 5.4 ng/mL was reached at 60 min after dosing [26]. Whereas, with an inhaled vaporized THC extract dose of 8 mg, a C_{max} of 118.6 ng/mL was reached at 17 min, causing significant psychoactivity [14]. Smoked cannabis at a dose equivalent to 33.8 mg THC resulted in a THC C_{max} of 162.2 ng/mL, reached at 9 min [27].

Cannabinoids are highly fat soluble [14]. Following administration of THC/CBD oromucosal spray, THC and CBD are rapidly redistributed into fatty tissues throughout the body, where they may be stored for as long as 4 weeks and released slowly into the blood stream at sub-therapeutic concentrations. Due to their lipophilic nature, cannabinoids are transferred to maternal breast milk, according to animal studies. With repeated dosing, cannabinoids are accumulated in the breast milk at concentrations 40–60 times than those seen in plasma. Plasma protein binding of THC is high (≈97 %) [14].

3.2 Metabolism and Elimination

THC is metabolized in the liver by cytochrome P450 (CYP) isoenzyme CYP2C9 into its primary metabolite 11-OH-THC, which is further metabolized by liver enzymes into other metabolites, including 11-*nor*-9-carboxy-delta-9-tetrahydrocannabinol (THC-COOH), the most abundant secondary metabolite in human plasma and urine [14]. The CYP3A subfamily catalyzes the formation of other minor metabolites of THC. Some of THC undergoes hepatic first-pass metabolism into 11-OH-THC. CBD is extensively metabolized (mainly via hydroxylation and oxidation at C-7), with more than 33 metabolites identified in urine. The major oxidized metabolite of CBD is CBD-7-oic acid containing a hydroxyethyl side chain [14].

Approximately two-thirds of the parent drugs and their metabolites are excreted in faeces and the rest in urine [17]. Based on a non-compartmental pharmacokinetic analysis, the first-order terminal elimination half-lives from plasma following the administration of two, four and eight sprays of THC/CBD were: THC 1.94, 3.72 and 5.25 h, respectively, and CBD 5.28, 6.39 and 9.36 h, respectively [14]. The prolonged terminal elimination half-life is because of the gradual release cannabinoids from fatty tissues [14].

3.3 Potential Drug Interactions

Based on in vitro studies, cannabinoids at therapeutic doses are unlikely to induce or inhibit a number of CYP enzymes [14]. However, CBD could inhibit P-glycoprotein-mediated transport of drugs, such as digoxin [14].

CYP3A4 inhibitors or inducers altered the pharmacokinetics of THC/CBD [24]. Co-administration of a single dose of four sprays of THC/CBD and ketoconazole (a CYP3A4 inhibitor) increased the C_{max} of THC, 11-OH-THC and CBD by 1.26-, 3.04- and 1.89-fold, respectively, and increased the AUC_{∞} by 2.14-, 3.51- and 1.84-fold, respectively. Conversely, co-administration with rifampicin (a CYP3A4 inducer) decreased respective C_{max} values by 36, 87 and 51 %, and AUC_{∞} values by 24, 87 and 58 %. No significant changes in the pharmacokinetic parameters of THC/CBD were observed when it was concomitantly administered with omeprazole (a CYP2C19 inhibitor). These data indicate that THC/CBD re-titration may be required when CYP3A4 inhibitors or inducers are started or stopped during treatment with THC/CBD [24].

4 Therapeutic Efficacy

The efficacy of THC/CBD oromucosal spray as an add-on treatment for symptom improvement in patients with MS-related moderate to severe spasticity has been evaluated in

four short-term (6- to 14-week) double-blind, multicentre, phase III studies: GWMS0001 [28], GWMS0106 [29], GWCL0403 [30] and GWSP0604 [31]. In these studies, patients were allowed to use a maximum THC/CBD dosage of 12 to 48 sprays/day, but had used a mean 8.3–9.4 sprays/day where reported [29–31]. This section mainly focuses on the multinational GWSP0604 trial, as it is the only pivotal trial that used the approved regimen (i.e. a maximum dosage of THC/CBD 12 sprays/day, with a formalized initial trial period of 4 weeks' therapy, as recommended in the UK SPC [14]) [see Sect. 7]. In addition, long-term efficacy data from open-label extensions of the GWMS0001 [32] and GWMS0106 [33] trials, and a double-blind, THC/CBD withdrawal study [34] are discussed. Supportive data from everyday clinical practice studies [35–39], including a German, prospective study (Mobility Improvement 2 [MOVE 2]) [37, 38], and THC/CBD safety registries [40] are also discussed. Some studies are only available as abstracts/posters [35–37].

In the exploratory GWMS001 trial ($n = 160$) [28], 39 patients with MS who had spasticity as their primary baseline symptom experienced a significant ($p < 0.001$) improvement in VAS spasticity severity scores compared with placebo. Subsequent trials [29–31] specifically assessed the change in spasticity severity using a validated, patient-rated 11-point NRS (0 = no spasticity; 10 = worst ever) in which patients rated their level of spasticity over the last 24 h on a daily basis [17].

The GWMS0106 ($n = 189$) [29] and GWCL0403 ($n = 337$) [30] trials followed a conventional randomized design in which patients received study medications for 6 and 14 weeks, following a 14- and 7-day baseline period, respectively. A significant ($p = 0.048$ vs. placebo) decrease in the spasticity severity NRS scores from baseline at the end of evaluable period in the intent-to-treat (ITT) population (primary endpoint) was seen in one trial [29]. Although, the second trial [30] did not meet its primary endpoint (change in spasticity severity NRS score in the ITT population), a significant ($p = 0.035$ vs. placebo) decrease in spasticity severity was seen in the per-protocol population (i.e. ITT population who had data for the primary endpoint and no significant protocol deviations; $n = 265$). Overall, the mean treatment effect was relatively small in both trials [14, 29, 30]. In THC/CBD and placebo groups, the proportions of clinical responders (defined as patients achieving a ≥30 % reduction in the NRS score from the baseline at the end of the evaluable period) were 40.0 vs. 21.9 % ($p = 0.014$) [29] and 31 vs. 25 % [17, 30].

A meta-analysis [41] of GWMS0001 (0–100 VAS transformed to a 0–10 scale), GWMS0106 and GWCL0403 data showed that efficacy results were generally consistent with those of the GWMS0106 and GWCL0403 trials. In the meta-analysis, the adjusted mean reduction from baseline in spasticity severity NRS scores at the end of individual study evaluable periods in the ITT population was significantly ($p = 0.026$) greater with THC/CBD than with placebo (−1.30 vs. −0.97; primary analysis), with a significantly ($p = 0.0073$) greater proportion of clinical responders in the THC/CBD group than in the placebo group (37 vs. 26 %). Based on these findings, it was postulated that a clinically useful treatment effect in a subset of patients might be masked by data from another subset of non-responders in the analyses of mean changes in NRS spasticity score [14]. Consequently, an enriched enrolment design was proposed for a large pivotal trial (GWSP0604; $n = 572$) in which only patients who had demonstrated the capacity to respond to treatment during an initial trial of therapy were eligible for randomization [31].

The pivotal GWSP0604 trial [31] included patients (mean age 48.9 years) with any MS subtype for ≥6 months and MS-related spasticity for ≥3 months (mean duration of MS and spasticity was 12.4 and 7.5 years). Patients had to have at least moderate spasticity (defined as a NRS spasticity severity score of ≥4 in a single assessment at screening) that was not completely relieved with current antispasticity medications. The most frequently used antispasticity medications were the centrally acting agents baclofen (58 % of patients) and tizanidine (17 %), antiepileptics (24 %), benzodiazepine-related derivatives (22 %) or adamantane derivatives (13 %). Current antispasticity and/or disease-modifying medications were maintained at a stable dosage 30 days prior to and throughout the study. Exclusion criteria included: concomitant disease that had spasticity-like symptoms; conditions that may affect the level of spasticity; use of cannabis or cannabinoid medications 30 days prior to study entry; history of significant psychiatric, renal, hepatic, cardiovascular or convulsive disorders; alcohol or substance abuse; diagnosed dependence disorder or current non-prescribed use of any prescription drug [31].

A schematic diagram of the key design features of the GWSP0604 trial is shown in Fig. 2. Patients remained blinded to treatment throughout the whole study [31]. A ≥20 % reduction in NRS spasticity severity score was chosen as the initial cutoff response (i.e. initial responders; ≥20 % NRS response) during the single-blind phase based on a NRS validation study [42] which showed that a 18.0 % reduction in the NRS spasticity severity score was associated with 'minimally improved' or better on the patient's global impression of change (PGIC) scale/score in patients with spasticity due to MS. A post hoc exploratory combined analysis of GWMS0106 and GWCL0403 trials showed that a 20 % NRS response during the first 4 weeks of treatment was predictive of final clinically relevant response, defined as a ≥30 % reduction in the NRS score [14], which has been shown to be associated with 'much

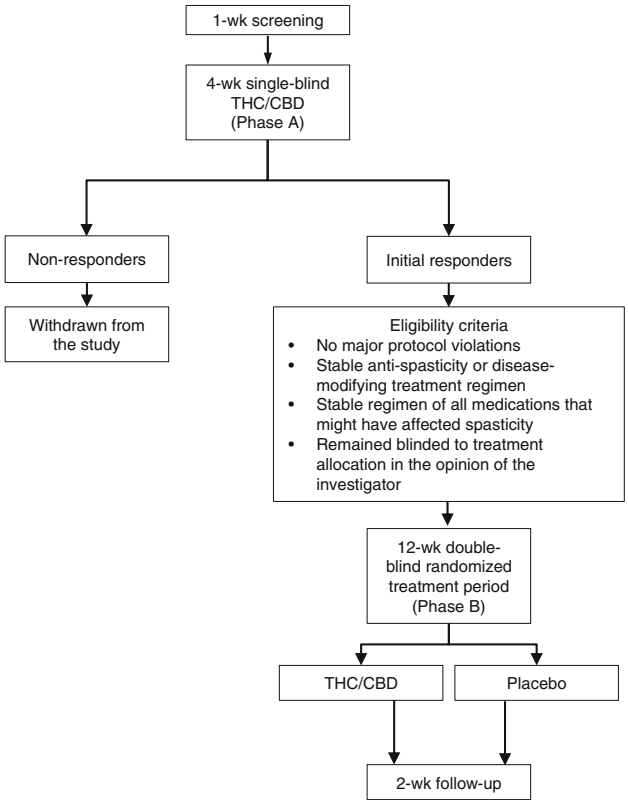

Fig. 2 Overall design of the pivotal GWSP0604 trial [31]. At the end of the 4-wk single-blind phase, initial responders were defined as patients achieving a ≥20 % reduction from screening baseline in spasticity severity based on an 11-point numerical rating scale. *CBD* cannabidiol, *THC* delta-9-tetrahydrocannabinol, *wk* week

improved' or better on PGIC scale [42]. Thus, an initial trial therapy period of 4 weeks (i.e. phase A) was chosen. Patients self-titrated the study medication to their optimal dose based on efficacy and tolerability, through a pre-defined escalation scheme over the first 10 treatment days during phase A and maintained the optimal dosage during phase B. The maximum permitted dose was restricted to 12 sprays in any 24-h period [31].

The primary endpoint was the mean change from the double-blind baseline (mean of last 7 days of phase A) in the NRS spasticity severity score at the end of the double-blind treatment period (mean of last 7 days of phase B) [31]. The primary endpoint was assessed in the ITT population [31], defined as all patients who received at least one dose of randomized study medication [17].

4.1 Effect on Spasticity

4.1.1 Clinical Studies

In GWSP0604, THC/CBD improved spasticity in patients who were classified as initial responders to THC/CBD treatment at the end of phase A [31]. The mean reduction from baseline in NRS spasticity severity score at the end of phase A was 3.01 points (Table 2). Of the 572 enrolled patients, 272 patients (48 %) achieved a ≥20 % reduction in the NRS spasticity severity score at the end of phase A, with 241 (42 %) meeting the criteria for the subsequent 12-week double-blind treatment period (phase B). After 12 weeks' double-blind treatment, the mean reduction in the NRS spasticity severity score was significantly greater in the THC/CBD than in the placebo group (primary endpoint; Table 2). Of patients who achieved a ≥20 % NRS response at the end of phase A, a significantly greater proportion of patients receiving THC/CBD than placebo achieved a ≥30 % NRS response at the end of phase B (Table 2). During study phase B, the mean change in the modified Ashworth scale (assesses spasticity on a 0–4 scale; 4 = worst) scores over 12 weeks were 0.08 and 1.83 in the THC/CBD and placebo groups (treatment difference −1.75 points; $p = 0.094$) [31].

The efficacy of THC/CBD in improving the spasticity severity was maintained in the long term [32–34], with relatively few patients discontinuing treatment because of lack of efficacy.

Of 160 patients who participated in the GWMS0001 trial, 137 entered its open-label extension, 79 (58 %) patients continued treatment for a mean duration of 434 days and 58 (42 %) patients discontinued the study, with 24 (18 %) patients discontinuing because of lack of efficacy [32]. Among patients who had completed at least 1 year's treatment and had data at each time point, spasticity VAS scores continued to improve (severity decreased) until 10 weeks and was maintained through week 82 (mean VAS scores 69.5, 34.2 and 31.8 at double-blind baseline, week 10 and week 82, respectively; $n = 66$) [32].

In the open-label extension [33] of the GWMS0106 trial, 146 patients elected to enter the open-label phase (mean treatment duration 334 days for all patients; average dosage 7.3 sprays/day), 59 (40 %) patients received the treatment for ≥1 year, and 52 (36 %) withdrew from the study in the first year, with 13 (9 %) withdrawals because of lack of efficacy. In patients with continuous data for up to 52 weeks ($n = 55$), the mean weekly NRS spasticity severity score decreased from 5.6 at the double-blind baseline to 4.0 at 52 weeks, with a plateau reached at ≈8 weeks of open-label treatment (data estimated from graph) [33].

In the withdrawal study [34], patients with MS-related spasticity receiving THC/CBD for ≥12 weeks (mean duration 3.6 years; mean daily dose 8.25 sprays) were randomized to THC/CBD ($n = 18$) or placebo ($n = 18$) for 28 days, following a 7-day baseline (open-label THC/CBD treatment) period. The primary endpoint was time to

Table 2 Efficacy of delta-9-tetrahydrocannabinol/cannabidiol as add-on therapy in patients with moderate to severe spasticity associated with multiple sclerosis. Results from the pivotal multinational GWSP0604 trial in which patients received ≤12 sprays/day (i.e. the recommended dosage) [31]. See Fig. 2 for further design details

Study phase (treatment duration; week)	Treatment	No. of evaluable pts[a]	Mean no. of sprays/day (SD)	Mean spasticity score[b]			Response rate[c] (% of pts)
				Baseline	Change at endpoint	Estimated treatment difference	
Sb phase A (4)	THC/CBD	572	6.9 (1.78)	6.91	−3.01		
Db phase B (12)	THC/CBD	124	8.3 (2.43)	3.87[d]	−0.19[e]	−0.83*	74*
	PL	117	8.9 (2.31)	3.92[d]	+0.64[e]		51

CBD cannabidiol, *Db* double-blind, *NRS* numerical rating scale, *PL* placebo, *pt(s)* patient(s), *Sb* single-blind, *THC* delta-9-tetrahydrocannabinol

* $p < 0.001$ vs. PL

[a] Enrolled pts in phase A; intent-to-treat population in phase B (i.e. all randomized pts who received ≥1 dose of study medication)

[b] Assessed on a pt-rated 0–10 point NRS (0 = no spasticity; 10 = worst ever spasticity)

[c] Proportion of pts with ≥30 % reduction from screening baseline in mean NRS spasticity severity score at study end (i.e. week 16)

[d] Mean of the last 7 days of phase A

[e] Primary endpoint

treatment failure (TF). TF was defined as cessation of the randomized treatment before day 28, worsening of spasticity (a mean ≥20 % increase in NRS score over the last 7 days of treatment period and ≥1 unit increase from baseline) or a clinically relevant increase in or addition to existing antispasticity or disease-modifying regimen after randomization. Overall, 17 patients completed the treatment (15 in the THC/CBD group and 2 in the placebo group) and 25 patients experienced TF (8 and 17 patients per group), with some patients who completed treatment having TF (5 and 1 patients per group). The time to TF (i.e. number of days from randomization to the first day of TF) was significantly longer with THC/CBD than with placebo (hazard ratio 0.335; 95 % CI 0.162–0.691; $p = 0.013$). Thus, the maintenance of THC/CBD efficacy seen in this study supports the findings of the open-label extension studies [32, 33].

4.1.2 Everyday Clinical Practice Studies

Results from the GWSP0604 trial are generally supported by the MOVE 2 study [38], in which adult patients with MS-related moderate or severe spasticity who had started THC/CBD treatment in accordance with the product label within the previous 7 days were enrolled, with response to treatment assessed at months 1 (4 ± 2 weeks) and 3 (12 ± 2 weeks). Of 216 patients evaluable at month 1, 90 (41.7 %) achieved a ≥20 % NRS response, and of 75 evaluable patients at month 3, 30 (40 %) achieved a ≥30 % NRS clinically relevant response, using a mean number of 6.9 and 6.7 sprays/day at months 1 and 3, respectively [38]. The mean NRS spasticity severity scores significantly ($p < 0.0001$) decreased from baseline in patients who achieved a ≥20 % NRS response at month 1 (from 6.4 to 3.9) and in those who achieved a ≥30 % NRS response at month 3 (from 6.5 to 3.4) [38]. The mean modified Ashworth scale scores also significantly ($p < 0.0001$) decreased from baseline in the entire study population at 1 month (from 3.0 to 2.7; $n = 260$), and were maintained at 2.6 after 3 months ($p < 0.0001$ vs. baseline; $n = 95$) [38]. An extension to the MOVE 2 study showed that the efficacy of THC/CBD was maintained through 12 months in at least 50 % of initial responders [37]. The extension study included 104 patients who were deemed to have had a clinical response at month 3 by their treating physician, and 52 patients were evaluable at 12 months [37]. In the evaluable patients, the mean NRS spasticity severity score decreased from 6.2 at baseline to 4.6 at month 12 ($p < 0.0001$), with 53 and 41 % of patients achieving a ≥20 and ≥30 % reduction from baseline in the NRS spasticity severity score at 12 months, respectively [37].

The efficacy of THC/CBD in patients with MS-related spasticity in routine clinical practice settings has also been reported from studies conducted in Germany [39], the UK [35] and Spain [36]. In the German study [39], after a mean follow-up of 9 months, 120 of 166 patients (72 %) remained on THC/CBD, including 95 patients receiving add-on THC/CBD and 25 patients receiving THC/CBD monotherapy (off-label use) [39]. In clinical responders, the mean NRS spasticity severity score decreased from 7.0 at baseline to 3.0 at 10 days (57 % reduction), with a mean THC/CBD use of four sprays/day [39]. In the UK study [35], 22 of 39 patients (56 %) reported a 35 % reduction in spasticity severity NRS score at 4 weeks (mean dosage eight sprays/day) and in the Spanish study [36], 13 of 19 patients (68 %) reported a 28 % reduction in the NRS score after 4–6 weeks' treatment (mean dosage seven

sprays/day). Taken together, these data suggest that more patients achieved a higher initial NRS response with a lower THC/CBD dosage, compared with that seen in the GWSP0604 trial. The higher initial NRS responder rate in real life is further supported by interim data from the UK and Spain THC/CBD safety registries which indicated that >70 % of patients who were prescribed THC/CBD continued to take it for ≥6 months [40].

4.2 Other Endpoints

In addition to spasticity severity, THC/CBD also improved other spasticity-related symptoms such as spasm frequency and sleep disruption in clinical responders to the treatment [31, 38]. In the GWSP0604 trial [17, 31], at the end of phase B, the adjusted mean reduction from the double-blind baseline in the number of spasms per day was significantly ($p = 0.005$) greater with THC/CBD than with placebo (−0.03 [5.61 at baseline] vs. +2.56 [5.29]). At same timepoint, the adjusted mean reduction in patient-rated sleep disruption was significantly ($p < 0.0001$) greater with THC/CBD than with placebo (−0.13 [1.96 at baseline] vs. +0.75 [2.07] on an 11-point NRS sleep disruption scale) [17, 31]. These results were supported by data from the MOVE 2 study in which mean sleep disruption NRS scores decreased significantly from baseline in patients who achieved a ≥20 % NRS response at month 1 (from 3.9 to 2.6; $p < 0.0001$) and in those who achieved a ≥30 % NRS response at month 3 (from 3.7 to 2.1; $p = 0.0098$) [38]. A slight improvement in patient-rated sleep quality (assessed on a 5-point categorical scale) and sleep disturbance (times woken per night) was also noted in the open-label extension of the GWMS0106 trial [29].

In the GWSP0604 trial, compared with placebo, THC/CBD treatment was associated with a significant improvement in the Barthel Activities of Daily Living index (odds ratio 2.04; $p = 0.0067$) and global impression of change as rated by patients (1.70; $p = 0.023$), carers (impression of function 2.40; $p = 0.005$) and physicians (1.96; $p = 0.005$) [14, 31]. During phase B, the mean change in 10-m walk time over 12 weeks was −0.13 and +3.22 s in the THC/CBD and placebo groups (treatment difference −3.34 s; $p = 0.069$) [31]; at the same timepoint, the mean change in health-related quality of life (assessed using the 36-item Short Form health survey, EQ-5D Health state index and EQ-5D Health status VAS) was not significantly different between THC/CBD and placebo recipients [31].

5 Tolerability

This section focuses mainly on the tolerability data for THC/CBD presented in an integrated analysis of clinical trials comparing THC/CBD ($n = 805$) with placebo ($n = 741$) in patients with MS, available in the UK PAR [17]. In addition, everyday clinical practice data from the MOVE 2 study [38] and a long-term, observational, post-approval, UK/German registry study, presented as an abstract [43], are discussed, along with supplemental data from the UK SPC [14].

5.1 General Tolerability Profile

THC/CBD was generally well tolerated in patients with MS-related spasticity in placebo-controlled and noncomparative clinical trials [17] and in everyday clinical practice studies [38, 43], with the overall incidence of adverse events being generally lower in the latter.

5.1.1 Placebo-Controlled Trials

Overall, ≥1 all-cause adverse event was reported in 78.0 % of THC/CBD recipients and 66.4 % of placebo recipients [17]. However, the majority of these events were mild or moderate in severity. Severe adverse events were reported in 15.3 and 8.5 % of patients in THC/CBD and placebo groups, but only two adverse events were reported as severe in >1 % of patients: dizziness (2.9 vs. 0.4 %) and asthenia (1.1 vs. 0.3 %) [17].

The most commonly (incidence >10 %) reported adverse events in the first 4 weeks' THC/CBD treatment were dizziness (occurring mainly during the initial titration period) and fatigue, both being generally mild to moderate in severity and resolving within a few days even with continued treatment [14]. The other most common adverse events in placebo-controlled trials, all typically mild or moderate in severity, included nausea, urinary tract infection, somnolence, vertigo, headache, dry mouth, asthenia and diarrhoea (Fig. 3). With the dosage and titration schedule used in the 4-week, single-blind, therapeutic trial period (phase A) of the GWSP0604 trial, the incidence of the most common adverse events, including dizziness and fatigue, appeared to be lower than the incidence of these events reported in earlier trials in which a less gradual up-titration of the THC/CBD dose was used [17], although such comparisons across trials should be interpreted with caution. For instance, in THC/CBD recipients in GWSP0604, the incidences of dizziness and fatigue were 14.0 and 5.9 % during phase A, and were reduced to 3 and 5 % during phase B [31].

Overall, all-cause treatment-emergent serious adverse events were reported in 4.6 and 3.2 % of patients in the THC/CBD and placebo groups, with the most frequently reported events including urinary tract infection (0.6 vs. 0.5 %) and MS relapse (0.4 vs. 0.4 %) [17]. In individual trials, serious adverse events that were considered to be

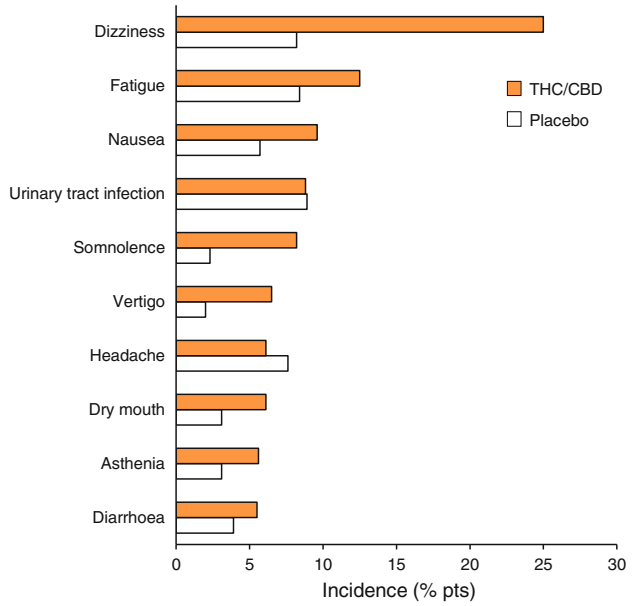

Fig. 3 Tolerability of delta-9-tetrahydrocannabinol (THC)/cannabidiol (CBD) in patients with multiple sclerosis-related spasticity. Most common (incidence ≥5 %) adverse events in an integrated analysis of trials comparing THC/CBD ($n = 805$; mean exposure 67 days) with placebo ($n = 741$; mean exposure 71 days). *Pts* patients [17]

possibly related to or related to THC/CBD treatment included vomiting (one patient) [29], psychiatric disorders (three patients) and urinary tract infection (one patient) [30]. All cases of psychiatric disorders and urinary tract infection resolved [30].

The overall rate of treatment discontinuation because of adverse events was low in clinical trials, with an approximately twofold higher rate in the THC/CBD group than in the placebo group (9.8 vs. 4.7 %) [17]. The primary reasons for treatment discontinuation was CNS-related adverse events and application-site reactions [17]. Only 3 % of patients discontinued treatment because of adverse events in phase A or B of the GWSP0604 trial [31].

5.1.2 Noncomparative Trials

An integrated analysis of noncomparative studies ($n = 1{,}016$) [17], including long-term open-label extensions of the placebo-controlled trials and single-blind THC/CBD treatment, indicated that the tolerability profile of THC/CBD in patients with MS was generally consistent with that seen in placebo-controlled trials, with no new safety signals identified. In open-label trials, serious adverse events that were considered possibly related to THC/CBD were seizures (two patients, one died subsequently from aspiration pneumonia) and lack of balance (one patient) [32] and those that were considered treatment-related included aspiration pneumonia (two patients, one subsequently died) and one case each of abnormal liver function test, convulsions, dizziness, paraesthesia, tremor, nausea, delusion perception and paranoia [33].

5.1.3 Everyday Clinical Practice Studies

The safety population of the MOVE 2 study included 325 patients, with treatment-related adverse events reported in 51 (15.7 %) patients [38]. These events were reported as mild in 47 of the 51 patients. The most frequently reported adverse events were dizziness (4 %), fatigue (2.5 %), drowsiness (1.9 %), nausea (1.9 %) and dry mouth (1.2 %). Only four of 325 patients reported serious adverse events that were considered to be related to treatment, including despondency, fatigue, weakness, worsened walking ability, dizziness, headache, muscle spasm, and urinary tract infection; all patients recovered. THC/CBD was discontinued in 11.4 % of patients because of adverse events [38].

Interim safety analysis of the UK/German registry included 687 patients with MS-related spasticity who had received at least one prescription of THC/CBD (median dosage four sprays/day; median duration of exposure 570 days) [43]. The most frequently reported adverse events were fall (4.9 % of patients), depression (3.3 %), dizziness (1.9 %), MS (1.9 %), urinary tract infection (1.5 %), MS relapse (1.3 %), fatigue (1.3 %), anxiety (1.3 %) and nausea (1.3 %). A total of 26 % of patients discontinued the THC/CBD treatment [43].

THC/CBD did not appear to affect driving ability according to the UK/German registry study [43] and a pilot, 4–6 week observational study ($n = 33$) in patients with MS-related spasticity (presented as an abstract [44]).

5.2 Adverse Events of Special Interest

Administration of THC/CBD to oral mucosa can result in application site-type reactions, consisting of mostly mild to moderate stinging at the time of administration. Common (incidence ≥1/100 to <1/10) application-site reactions included application-site pain, oral discomfort or pain, dysgeusia, mouth ulceration and glossodynia [14].

THC/CBD treatment is associated with psychiatric symptoms in some patients, possibly because of its transient effect on the CNS [14]. These symptoms were generally mild to moderate in severity, well tolerated and can be expected to disappear when the THC/CBD dose is reduced or treatment is interrupted. Commonly (incidence ≥1/100 to <1/10) reported psychiatric symptoms that were considered possibly related to THC/CBD were depression, disorientation, dissociation and euphoric mood. Symptoms such as hallucination (unspecified, auditory or visual), illusion, paranoia, suicidal ideation and delusional perception were uncommon (incidence ≥1/1000 to <1/100).

Some of the psychiatric symptoms seen in patients with MS receiving THC/CBD could also be part of the underlying disease [14].

Falls are common in patients with MS. According to the UK national audit of services for people with MS 2011 report, 449 of 565 (79 %) respondents reported a fall in the last year [45]. There might be an increased risk of fall in patients who have had spasticity reduction but do not have adequate muscle strength to maintain posture or gait [14]. The incidence of fall was low in placebo-controlled trials (1.5 and 0.5 % in THC/CBD and placebo groups) [17]. However, in the long-term UK/German registry study in which assessment of the incidence of fall was one of the specific objectives, fall was the most common adverse event (see Sect. 5.1.3).

Abrupt cessation of long-term THC/CBD treatment did not appear to cause withdrawal-type symptoms in patients with MS-related spasticity [32, 34]. No withdrawal syndrome was observed in the randomized withdrawal study (see Sect. 4.1.1 for trial design) [34]. No consistent pattern or time profile of withdrawal-type symptoms was observed in a predesigned 2-week drug interruption substudy [32] performed in 25 patients receiving THC/CBD for ≥1 year during the open-label extension phase of the GWMS0001 trial. About half (44 %) of patients experienced some withdrawal-type symptoms, including interrupted sleep, hot and cold flushes, and tiredness (16 % each), low mood (12 %), decreased appetite (8 %), and emotional lability, vivid dreams and intoxication (4 % each) [32]. However, no patient met the criteria for cannabis withdrawal syndrome [17].

Patients do not appear to develop tolerance to THC/CBD with long-term use, as demonstrated by a lack of increasing dose requirements in the long-term open-label trials [32, 33]. The mean number of THC/CBD sprays used per day remained almost constant from week 4 (8.6 sprays) to 52 ($n = 30$) [33] or decreased from 12.3 sprays at week 26 to 10.6 sprays at week 82 ($n = 80$; data estimated from graph) [32], while efficacy was maintained (see Sect. 4.1.1). Indeed, in everyday clinical practice studies [38, 43], patients appeared to use lower daily dosages of THC/CBD compared with the pivotal trial (4.0–6.7 vs. 8.3 sprays/day) [31]. The lack of increase in daily dosage, along with low levels of patient-reported intoxication after long-term dosing (3.14 mm at week 52 on a 0–100 mm VAS; 100 = highest [33]), also indicate that dependence on THC/CBD is unlikely with long-term use [14].

6 Pharmacoeconomic Considerations

This section focuses on cost-utility analyses of THC/CBD as an add-on therapy in patients with MS-related moderate to severe spasticity who did not respond adequately to standard of care (oral antispasticity medications), performed from the perspective of the UK National Health Service [46], or German or Spanish healthcare payer [5].

Using a Markov model and following clinical practice, the analyses evaluated the cost effectiveness of THC/CBD plus standard of care compared with standard of care alone, over a 5-year horizon with an annual discount rate of 3.5 % [5, 46]. The year of costing was 2009 [46] or 2010 [5]. Age of patients on model entry was 50 years in the UK study (not reported in the German and Spanish study). The UK study [46] used three health states: responders on treatment, withdrawn from treatment (because of lack of efficacy or other reasons) and death, while the German and Spanish study [5] used four states: mild, moderate and severe spasticity (based on 0–10 NRS score), and death. In both studies, clinical efficacy and utility (EuroQol-5D) data were derived from the GWPS0604 trial, open-label extensions of the phase III trials and/or the withdrawal study (see Sect. 4). Only direct medical costs, reflective of local clinical practice, were included. In base-case analysis, a constant THC/CBD dosage of 8.3 sprays/day was used in the UK study, whereas, the German and Spanish study applied a linear decrease in dosage to model long-term dose adjustments, gradually reducing to 4.2 sprays/day (a dosage approximately similar to that seen in the UK/German registry).

Add-on THC/CBD treatment did not appear to be cost effective compared with standard antispasticity treatment in the UK, but it was cost effective in Germany and dominant in Spain (Table 3). In the UK [5], the base-case incremental cost-effectiveness ratio (ICER) of £49,257 per quality-adjusted life-year (QALY) gained was well above the NICE willingness-to-pay threshold range of £20,000–30,000 [47]. In Germany, the base-case ICER per QALY gained (€11,214) was below commonly accepted threshold such as that established by NICE. In Spain, add-on THC/CBD treatment was associated with a cost saving of €3,496 per person and a QALY gain of 0.32 per person over 5 years (Table 3). The cost saving in Spain was partly because of improved spasticity severity resulting in reduced consumption of resources such as physiotherapy and medications; furthermore, the unit cost of THC/CBD was lower in Spain than in Germany (€440 excluding tax in hospital pharmacies vs. €597 including tax in street pharmacies, per 3 × 10 mL vial pack) [5].

ICER was most sensitive to the costs of THC/CBD in all three evaluations [5, 46]. Sensitivity analyses of the UK model showed that the ICER would be less than £30,000 if four sprays/day was as effective as eight sprays/day or if the price of THC/CBD was 40 % lower than its current listed price [46]. On the other hand, in the German and Spanish models, increasing the THC/CBD dosage from the

Table 3 Cost effectiveness of delta-9-tetrahydrocannabinol/cannabidiol as an add-on therapy in patients with multiple sclerosis-related moderate to severe spasticity who did not respond adequately to standard of care (oral antispasticity medications)

Study	Country (currency)	Total average cost per pt[a]		QALYs gained		IC per QALYs gained
		THC/CBD + SoC	SoC	THC/CBD + SoC	SoC	THC/CBD + SoC vs. SoC
Lu et al. [46]	UK (£)	8,925	1,298	2.37	2.22	49,257
Slof et al. [5]	Germany (€)	42,489	38,892	2.71	2.39	11,214
Slof et al. [5]	Spain (€)	31,510[b]	35,006	2.71	2.39	Dominant

Analyses were based on a Markov model, estimated the cost utility of THC/CBD + SoC (oral antispasticity medications) versus SoC per patient over a 5-year horizon and were conducted from the perspective of UK National Health Service [46] or German and Spanish healthcare payer [5]. Clinical outcome data were from the pivotal GWSP0604 trial [31] and other long-term studies. Costs and benefits were discounted at 3.5 % annually; year of costing was 2009 [46] or 2010 [5]

CBD cannabidiol, *IC* incremental costs, *pt* patient, *QALY* quality-adjusted life year, *SoC* standard of care, *THC* delta-9-tetrahydrocannabinol

[a] Direct medical costs including those reflective of local clinical practice for the management of the disease

[b] Cost was less versus SoC because of improved spasticity severity thereby reducing resource consumption (e.g. physiotherapy and medications)

8.3–4.2 gradual decrease to 8.3 sprays/day still produced an ICER of less than £30,000 (€29,258 in Germany and €2,361 in Spain) [5].

7 Dosage and Administration

THC/CBD oromucosal spray is approved as an add-on treatment for symptom improvement in adult patients with moderate to severe spasticity due to MS in a number of countries in Europe, including the UK [14], and other countries [48]. THC/CBD should be used only 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 [14]. THC/CBD is not recommended for use in children or adolescents aged <18 years, as there are no adequate efficacy and safety data for this population [14].

The UK SPC-recommended treatment with THC/CBD involves a 14-day self-titration period to reach the optimal dosage and a 4-week initial trial of therapy to identify responders to the treatment [14]. Patients should gradually increase the dose following the pattern prescribed in the SPC starting with a single spray on day 1 (evening) to a maximum of 12 sprays (5 in the morning and 7 in the evening) on day 14, with at least a 15-min gap between sprays. During the titration period, physicians should maintain or reduce the dose, or interrupt the treatment at least temporarily, based on the seriousness and severity of adverse events, particularly drowsiness. The optimum dosage identified during the titration period should be maintained thereafter, but the timing of sprays may be distributed throughout the day based on individual response and tolerability. Physicians should review the response to THC/CBD after the 4-week trial of therapy, and if a clinically significant reduction in spasticity (defined as a ≥20 % improvement in 0–10 NRS spasticity severity score) is not achieved in this period, the treatment should be discontinued. In patients who continue the treatment for long term, physicians should re-evaluate the effectiveness of THC/CBD periodically. Re-titration of THC/CBD may be necessary based on changes in symptom severity, concomitant medications or tolerability [14].

In order to mitigate application-site reactions, patients should change the site of application within the oromucosal surface each time the THC/CBD spray is used [14]. THC/CBD should be taken the same way in relation to food each time (i.e. with or without food) to minimize variations in bioavailability. THC/CBD is contraindicated in patients with psychotic illness, severe personality disorder or certain significant psychiatric disorders, breast feeding mothers (as cannabinoids can accumulate in breast milk, see Sect. 3.1) and in patients with hypersensitivity to cannabinoids or to any of the excipients of THC/CBD [14].

Local prescribing information should be consulted for detailed information, including contraindications, warnings and precautions, special patient populations and potential drug interactions.

8 Current Status of Delta-9-Tetrahydrocannabinol/Cannabidiol in Multiple Sclerosis-Related Spasticity

NICE clinical guidelines [6] recommend a stepwise approach to treating spasticity and spasms in patients with MS, with specific active interventions recommended only if the symptoms are causing pain or distress, or further limiting the patient's independence and activities. Specific goal(s) should be set for active interventions, but will seldom include improved performance in activities [6]. Oral baclofen (a $GABA_{\beta}$ agonist) or gabapentin (a GABA analogue) are recommended as initial pharmacotherapy for bothersome spasticity or spasms, and if this treatment is

unsuccessful or not tolerated, tizanidine, diazepam, clonazepam or dantrolene (all oral) may be used. A combination of these and other medications such as anticonvulsants can also be used after seeking specialist advice. For patients whose symptoms remain inadequately controlled with oral treatments, pharmacological options include intrathecal baclofen, phenol injection to motor points or intrathecally, or intramuscular botulinum toxin [6], all of which are invasive and/or expensive, with the latter reserved only for localized spasticity that is not responding to other treatments. NICE is currently reviewing the use of THC/CBD oromucosal spray for MS-related spasticity, and a decision is expected in 2014 [49].

A consensus document of the Spanish Society of Neurology demyelinating diseases working group [50] recommends THC/CBD as an add-on second-line treatment option for the treatment of MS-related generalized spasticity in patients who responded inadequately to first-line baclofen or tizanidine monotherapy (recommendation graded as A based on the Scottish Intercollegiate Guidelines Network [SIGN] grading system); nonresponders to THC/CBD can be switched to a combination of baclofen plus tizanidine. THC/CBD treatment should follow an initial trial of therapy similar to that recommended by the UK SPC (see Sect. 7). According to the German guidelines, well documented medications for MS-related spasticity include baclofen, tizanidine, gabapentin (for painful spasms) and THC/CBD, with THC/CBD categorized as having the highest evidence class [50].

Spasticity has multiple clinical manifestations, and is not readily and accurately measureable [17]. The Ashworth Scale, the most widely used assessment tool for spasticity, is potentially controversial with respect to its reliability and validity [17]. According to a Cochrane review [7], relatively few placebo-controlled studies and none of the active comparator studies were able to demonstrate a significant treatment effect of antispastic agents, using the Ashworth scale. Therefore, most clinical trials of THC/CBD used a patient-rated 0–10 NRS to assess the severity of spasticity. The validity and reliability of this NRS has been demonstrated in validation analyses of data from two clinical trials (GWMS0106 and GWCL0403) of THC/CBD [17]. Furthermore, of three spasticity grading scales (modified Ashworth scale, NRS and Penn Spasm frequency scale) assessed, NRS had the highest evidence level and recommendation grade (Grade A) based on the SIGN levels of evidence and grading, and NRS is the recommended best practice based on the clinical experience of the Spanish Society of Neurology demyelinating diseases working group [50].

The therapeutic efficacy of THC/CBD is thought to result mainly from THC modulating the effects of excitatory and inhibitory neurotransmitters (Sect. 2.1), with CBD possibly ameliorating some of the psychoactive effects of THC [12]. The efficacy of THC/CBD was assessed in several double-blind phase III studies, including a study (GWSP0604) that used the approved treatment regimen. In GWSP0604, self-titrated THC/CBD ($\leq$12 sprays/day allowed; patients had used a mean 8.3 sprays/day) significantly reduced spasticity severity (primary endpoint) compared with placebo in patients with MS-related spasticity that was not fully relieved with other antispasticity medication and who had demonstrated a clinically significant improvement in spasticity during a 4-week initial trial of therapy (Sect. 4.1.1). Among initial responders, a significantly greater proportion of THC/CBD than placebo recipients achieved a clinically relevant $\geq$30 % reduction from screening baseline in spasticity severity at 12 weeks (Table 2). In addition to reduction in spasticity severity, THC/CBD recipients also had significantly fewer spasms per day compared with placebo recipients (Sect. 4.2). These data indicate that THC/CBD is effective in reducing MS-related spasticity, albeit only in a subset of the whole population. The benefit of THC/CBD treatment was maintained in the long term for up to at least 3.6 years (Sect. 4.1.1). The efficacy of THC/CBD was also demonstrated in the everyday clinical practice setting, with a large observational study (MOVE 2) showing that THC/CBD treatment improves MS-related spasticity and sleep disturbances (Sects. 4.1.2 and 4.2). In everyday clinical practice, patients used fewer THC/CBD sprays per day than in clinical trials (see Sect. 5.2), suggesting that increasing the number of sprays does not necessarily improve the response to the treatment.

In the GWSP0604 trial, only those patients achieving a minimum clinically relevant reduction in spasticity severity based on their own assessment during the initial single-blind trial of therapy were randomized to THC/CBD or placebo. This may have introduced a patient preselection bias in favour of THC/CBD. However, this design meant that initial nonresponders were not exposed to the potential adverse effects of THC/CBD [31]. This design also reflects the everyday clinical practice for symptomatic treatments in which nonresponders are unlikely to continue treatment for a prolonged period and thus, demonstrates the efficacy that is likely to be seen in this setting [31].

A hypothetical limitation of the GWSP0604 trial is the potential unblinding of patients because of the psychoactivity of THC/CBD [31]. Single-blind treatment during the initial 4 weeks and the investigator's judgement about the blinding at the end this period (see Fig. 2) was used to maintain the blinding during the double-blind period [31]. Although not directly assessed in the GWSP0604 trial,

various indirect evidence suggest that unblinding may not have been widespread and that unblinded patients were unlikely to have been biased in terms of differentiating between the efficacy of THC/CBD and placebo [17].

Overall, THC/CBD was generally well tolerated in clinical trials, with the majority of adverse events being mild or moderate in severity (Sect. 5). The most common adverse events reported during the first 4 weeks were mild to moderate dizziness and fatigue, which resolved within a few days even with continued treatment. The tolerability profile of THC/CBD in long-term open-label studies was consistent with that of short-term pivotal studies. In the UK/German registry study approximately one-quarter of patients discontinued the THC/CBD treatment over $\approx$1.5 years (Sect. 5.1.3).

Add-on THC/CBD (applying a linear decrease from 8.3 to 4.2 sprays/day) was predicted to be cost effective compared with standard antispasticity treatment in Germany and it was dominant in Spain; when a constant dosage of 8.3 sprays/day was applied, THC/CBD still remained cost effective in these countries (Sect. 6). However, the ICER in a UK model (applying a constant THC/CBD dosage of 8.3 sprays/day) was outside the generally accepted willingness-to-pay threshold. These cost-utility analyses were modelled on clinical trials (including GWSP0604) and everyday clinical practice data over a 5-year horizon, and were conducted from the healthcare payer perspective. The acquisition cost of THC/CBD was the major driver of costs in all three countries. In Spain, the total average cost per patient was lower with add-on THC/CBD than with standard treatment alone partly because of reduced resource consumption resulting from improved spasticity severity. As with all pharmacoeconomic analyses, cost-utility analyses of THC/CBD are subject to limitations, such as the input data may differ from real-life situations. Furthermore, base-case results of cost-effectiveness analyses may differ between countries because of differences in healthcare systems, clinical practice and units costs.

In conclusion, add-on THC/CBD is an effective and well tolerated treatment for patients with MS-related spasticity who have not responded adequately to other antispasticity medications. A $\geq$20 % reduction in spasticity severity on an 11-point NRS during an initial 4-week trial of therapy is a reliable predictor of continued response to THC/CBD. Further clinical trials comparing THC/CBD with active treatments would help fully define the place of add-on THC/CBD in the management of treatment resistant MS-related spasticity. In the meantime, add-on THC/CBD is a useful symptomatic treatment option for MS-related resistant spasticity in patients who demonstrate a clinically significant improvement in spasticity after 4 weeks' initial therapy.

Data selection sources: Relevant medical literature (including published and unpublished data) on delta-9-tetrahydrocannabinol/cannabidol (Sativex®) was identified by searching databases including MEDLINE (from 1946) and EMBASE (from 1996) [searches last updated 21 February 2014], bibliographies from published literature, clinical trial registries/databases and websites. Additional information was also requested from the company developing the drug.
Search terms: delta-9 tetrahydrocannabinol/cannabidiol, tetrahydrocannabinol and cannabidiol, nabiximols, Sativex, oromucosal spray, spasticity, muscle spasticity, multiple sclerosis.
Study selection: Studies in patients with spasticity due to multiple sclerosis who received delta-9-tetrahydrocannabinol/cannabidol. When available, large, well designed, comparative trials with appropriate statistical methodology were preferred. Relevant pharmacodynamic and pharmacokinetic data are also included.

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