



Clinical outcome analysis of patients with multiple sclerosis – Analysis from the UK Medical Cannabis Registry

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ARTICLE INFO

Keywords:

Multiple sclerosis
Cannabis-based medicinal products
Cannabidiol
Tetrahydrocannabinol
Patient reported outcome measures

ABSTRACT

Introduction: Whilst disease-modifying therapies are the cornerstone for treatment of multiple sclerosis (MS), there is a need to develop novel therapeutics for the symptomatic sequelae of the disease. Cannabis-based medicinal products (CBMPs) have been suggested as a potential therapy for the associated pain, spasticity, and mental health disorders. However, there is a paucity of clinical evidence on CBMPs in MS. The aim of this study is to assess changes in MS-specific and general health-related quality of life (HRQoL) outcomes alongside adverse event incidence in patients prescribed CBMPs for MS from the UK Medical Cannabis Registry (UKMCR).

Method: Patients prescribed CBMPs for MS symptoms for longer than one month were identified from the UKMCR. The primary outcomes were changes from baseline in MS Quality of Life-54 (MSQoL-54), Generalised Anxiety Disorder-7 (GAD-7), Single-Item Sleep Quality Scale (SQS), and EQ-5D-5L scales at one month, three months and six months. $p < 0.050$ was defined as statistically significant.

Results: 141 patients met the inclusion criteria for the study. There was an improvement in the following subscales of the MSQoL-54 at 6 months: change in health scale, cognitive function, mental health composition, physical health, role limitations due to physical limitation and due to emotional problems, as well as social and sexual function ($p < 0.050$). There were also improvements in the EQ-5D-5L index value, GAD-7 and SQS ($p < 0.050$). 146 (103.55 %) adverse events were reported in total. Most were considered mild ($n = 47$; 33.33 %) and moderate ($n = 72$; 51.06 %).

Conclusions: This preliminary analysis demonstrates a possible association with improved general health-related quality of life in those prescribed CBMPs for MS. Moreover, the results suggest that CBMPs are well-tolerated in the first 6 months of treatment. However, this must be interpreted with caution considering the limitations of the observational study design.

1. Introduction

A neurodegenerative disease characterised by inflammation and demyelination; multiple sclerosis (MS) is a chronic disorder where individuals are potentially affected by a spectrum of symptoms (Filippi et al., 2018). Affecting over 120,000 individuals in the United Kingdom, the diversity of clinical manifestations can be attributed to the areas of

the central nervous system (CNS) affected by demyelinating lesions (Filippi et al., 2018; England, 2020). This is further amplified by the transient or persistent nature of lesions. However, common symptoms include pain, motor and sensory deficiencies, spasticity, and cognitive deficits (Ghasemi et al., 2017). Individuals with MS also have a higher prevalence of psychiatric disorders secondary to the significant impact on physical health, the adverse effects of steroid therapy for acute flares,

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<https://doi.org/10.1016/j.msard.2024.105665>

Received 20 December 2022; Received in revised form 1 December 2023; Accepted 3 May 2024

Available online 6 May 2024

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as well as neurobiological changes (Silveira et al., 2019). Moreover, there is often a subsequent decline in social and economic health (Filippini et al., 2018).

Disease modifying therapies are the mainstay of long-term therapy for MS to reduce progression and subsequent symptomatic burden. However, symptomatic treatment is also important to improve health-related quality of life (Kołtuniuk and Chojdak-Lukasiewicz, 2022; de Sa et al., 2011; Robertson and Moreo, 2016). Pain, including that of neuropathic and musculoskeletal aetiologies, is commonly the most prevalent indication for which symptomatic treatment is offered (Solaro et al., 2013). However, there is limited evidence for currently available analgesics, specifically in the setting of MS (Henze et al., 2006). In addition, many individuals are affected by spasticity, for which baclofen and clonidine are the first line of therapy (Chang et al., 2013). The adverse effects and limited efficacy of symptomatic treatment is a leading cause of low drug adherence in MS patients (de Sa et al., 2011). Due to this, affected individuals often seek alternative therapies to achieve improved symptom relief. As such, the development of novel therapeutics for treatment of associated symptoms in MS is essential.

Phytocannabinoids derived from the cannabis plant, of which Δ^9 -tetrahydrocannabinol (Δ^9 -THC) and cannabidiol (CBD) are the major constituents, have been identified for further evaluation for symptomatic treatment of MS (Dos Reis Rosa Franco et al., 2021). CBD and Δ^9 -THC each act predominantly via the endocannabinoid system, a complex cell-signalling system associated with a diverse range of observed effects (Khan et al., 2022). G-protein coupled cannabinoid receptor type 1 (CB1) and type 2 (CB2) are the predominant receptors and are highly expressed in the central nervous and immune systems, respectively (Kendall and Yudowski, 2016). Δ^9 -THC acts as partial agonist to CB1 and CB2, exhibiting neuroprotective and anti-oxidative properties (Maroon and Bost, 2018; Comelli et al., 2009; Dawidowicz et al., 2021). The primary mechanism of action of CBD is to inhibit the hydrolysis of anandamide, an endogenous CB1 agonist (Deutsch, 2016). In parallel, CBD acts as a non-competitive agonist of CB1, counteracting the psychotropic side effects of Δ^9 -THC whilst producing anxiolytic, analgesic, and anti-inflammatory effects (Ebbert et al., 2018; Atakan, 2012).

Nabiximols is an oromucosal spray, containing CBD and Δ^9 -THC, licensed for MS-associated spasticity in treatment-resistant populations (Serpell et al., 2013; D'Hooghe et al., 2021; Patti et al., 2016). Results from a short term randomised-controlled trial demonstrated that 40.0 % of participants achieved a clinically significant reduction in associated spasticity in those treated with nabiximols, compared to 21.9 % of those receiving a placebo (Collin et al., 2007). A subsequent trial by Novotna et al. supported this, demonstrating a significant reduction in both spasticity and sleep disruption (Novotna et al., 2011). Notcutt et al. conducted a randomised withdrawal of nabiximols for 36 patients prescribed the medication for MS-associated spasticity for 3 months or greater. Replacement of nabiximols with placebo was associated with an increased rate of treatment failure (Notcutt et al., 2012). A real-world study by Patti et al. also indicated a lasting effect of nabiximols on spasticity-associated symptoms up to 18 months (Patti et al., 2022). The most recent Cochrane review on symptomatic treatment with cannabinoids for those with MS concluded that individuals prescribed nabiximols were more 2.5 times more likely to report an improvement in spasticity compared to those receiving placebo (Filippini et al., 2022).

There is growing evidence of the role of cannabinoids and, more broadly, cannabis-based medicinal products (CBMPs) in the management of chronic pain (Wang et al., 2021; Busse et al., 2021). A recent meta-analysis concluded that non-inhaled cannabinoids were associated with a 10 % increased likelihood of achieving a clinically significant improvement in pain severity, compared to placebo (Wang et al., 2021). However, there is a paucity of data in the specific setting of MS-associated pain (Filippini et al., 2022; Wang et al., 2021). Within the Cochrane review on symptomatic MS treatment, 8 studies observed a reduction in MS-related pain, yet the certainty in this evidence was low

with a high degree of statistical heterogeneity (Filippini et al., 2022). Moreover, most studies have been conducted with nabiximols and have not considered the impact of unlicensed CBMPs on spasticity (Filippini et al., 2022).

Due to the postulated effects of CBMPs on notable symptoms of MS, in addition to reported outcomes from previously published evaluations, there is promise for the effects of CBMPs in affecting health-related quality of life (HRQoL) (Ergisi et al., 2022a; Harris et al., 2022; Ergisi et al., 2022b; Kawka et al., 2021). However, there is conflicting evidence within clinical settings for MS patients. Recent reviews both outline the lack of statistically significant changes in HRQoL after administration of CBMPs, in addition to the heterogeneity of previously published literature (Filippini et al., 2022; Haddad et al., 2022; Nielsen et al., 2018). It is crucial that the knowledge gap surrounding changes to patient reported outcome measures (PROMs) in MS after CBMP intervention is bridged to provide a detailed insight into the impact on patients' lives. This will also be able to aid clinicians in making informed decisions regarding future treatment plans.

There is a large body of evidence on the adverse event profile of nabiximols (NICE 2019), which indicates that whilst nabiximols is largely safe, loco-regional reactions, such as oral pain and ulceration are common (Erridge et al., 2022a; Yadav et al., 2014). On the contrary, there is little known about the incidence of loco-regional adverse events with vapourised or sublingually administered unlicensed CBMPs (Erridge et al., 2022a). In addition, most evaluations of nabiximols or unlicensed CBMPs have limited follow up periods, emphasising the need for longitudinal assessment of adverse events through a formalised pharmacovigilance programme (Pratt et al., 2019).

Considering the limitations of current literature describing the effects of CBMPs in patients with MS, the primary aims of this study were to therefore assess the changes in HRQoL outcomes, as well as incidence of adverse events of MS patients treated with unlicensed CBMPs in a real-world clinical setting.

2. Methods

2.1. Study design and participants

This case series was conducted using data from the UK Medical Cannabis Registry, which is managed by Curaleaf Clinic. The UK Medical Cannabis Registry has recorded pseudonymised data of patients prescribed CBMPs for any indication across the UK and Channel Islands since 1st December 2019 (Ergisi et al., 2022a; Harris et al., 2022; Erridge et al., 2022b).

The UK Medical Cannabis Registry has been afforded a favourable ethical opinion by the Health Research Authority (Central Bristol Research Ethics Committee reference 22/SW/0145). All participants provided informed consent prior to enrolment in the registry. The Strengthening the Reporting of Observational Studies in Epidemiology statement was adhered to for reporting of the study (von Elm et al., 2007).

All CBMPs that were prescribed adhered to Good Manufacturing Practice criteria (MHRA, 2020). CBMPs were produced in a broad spectrum of formulations (oil, capsules, lozenges, dried flower). The prescribed CBMPs were either isolated cannabinoids or broad/full spectrum extracts. In accordance with UK regulations, CBMPs were only initiated by specialist doctors (MHRA, 2020). The dose was decided by the treating physician in co-ordination with a multi-disciplinary team of other healthcare professionals. The rationale for any particular dosing strategy was not recorded.

2.2. Data collection

Data used in this analysis are from MS patients who participated in the UK Medical Cannabis Registry from 1st December 2019. Inclusion criteria included those with MS as the primary indication for treatment

with CBMPs. Moreover, they were required to have initiated treatment at least 1 month prior to the date of data extraction (23rd August 2022). Finally, those who did not record a PROM prior to their initial appointment were excluded from analysis due to being unable to provide a reliable baseline measure against which changes in health outcomes could be measured. Patients completed PROMs remotely at one month, three months, and six months.

At the initial appointment the primary indication for treatment was recorded. Clinicians additionally recorded relevant demographics, including age, gender, occupation, and body mass index (kg/m²). In addition, important comorbidities were recorded and the Charlson comorbidity index was calculated for each patient (Brusselaers and Lagergren, 2017). Tobacco, alcohol, and cannabis consumption were recorded as smoking pack years, weekly alcohol consumption in units, and cannabis gram years, respectively. Cannabis gram years is a metric designed to quantitatively describe the previous use of cannabis, which could potentially cause a tolerance to current cannabis medication (Colizzi and Bhattacharyya, 2018; Ramaekers et al., 2020a). Patients were counselled against purchase and consumption of non-medical cannabis; however, participants who were previous cannabis consumers were not required to demonstrate abstinence from cannabis prior to initiation of therapy. Non-prescribed cannabis use was not recorded during treatment with CBMPs. Consumption of illicit drugs, beyond cannabis, was not measured. Patients were required to record their baseline PROMs before their initial prescription for a CBMP is dispensed.

Details about CBMP prescriptions were collected throughout treatment, including brand name; formulation; route of administration; CBD and THC dosages.

2.3. Patient-reported outcome measures data

The primary outcomes were changes in PROMs from baseline. These included the EQ-5D-5L, General Anxiety Disorder-7 (GAD-7), Single-Item Sleep Quality Scale (SQS), patient global impression of change (PGIC) and Multiple Sclerosis Quality of Life-54 (MSQOL-54).

EQ-5D-5L measures the health status of patients in a single validated metric (Herdman et al., 2011). This dimension provides a 5-digit code to describe five stages of severities (1-no problems; 2-slight problems; 3-moderate problems; 4-severe problems; 5-extreme problems) on five measurements of the quality of life (mobility, self-care, usual activities, pain or discomfort, anxiety or depression) (van Hout et al., 2012). These are used to generate country-specific index values representing HRQoL (van Hout et al., 2012). The maximum index value is 1, whilst a score less than 0 is representative of HRQoL worse than death.

The GAD-7 is a measure for screening for and measuring severity of generalised anxiety disorder (Spitzer et al., 2006). The questionnaire provides a score from 0 to 21, with thresholds of ≥ 5 , ≥ 10 , and ≥ 15 indicating mild, moderate, and severe anxiety, respectively (Löwe et al., 2008). The minimal clinically important difference (MCID) in GAD-7 is determined as a change of ≥ 4 points (Toussaint et al., 2020).

The SQS scale provides a score from 0 to 10, describing the self-reported sleep quality of patients over the past seven days. A score of 10 and 0 represents an 'excellent' and 'terrible' sleep quality respectively (Snyder et al., 2018). The MCID for SQS is a 2.6-point change (Snyder et al., 2018).

Patient global impression of change (PGIC) is a measure of perceived change in symptoms since commencing therapy. It scales into seven points from 1 to 7 accordingly (L Ferguson, 2009).

Multiple Sclerosis Quality of Life-54 (MSQOL-54) measures HRQoL with specific attribution to the effects of living with MS. It includes 15 subscales encompassing both physical and mental health: 'change in health scale', 'cognitive function', 'emotional wellbeing', 'energy scale', 'health distress scale', 'health perception', 'pain scale', 'physical function', 'physical health', 'role limitations due to physical limitation', 'role limitations due to emotional problems', 'satisfaction with sexual function', 'sexual function', 'social function', and 'overall quality of life'.

These are also incorporated within the mental and physical health composite values. Each factor scales from 0 to 100 linearly with a higher value representing improved outcomes within each subscale (Vickrey et al., 1995).

2.4. Adverse events

Adverse events were reported by participants either through remote data collection contemporaneously with PROMs or during the time of the event. In addition, adverse events could be recorded during consultations with clinicians. In each instance they were recorded in accordance with the common terminology criteria for adverse events version 4.0 (Trotti et al., 2003).

2.5. Statistical analysis

Descriptive analysis was performed on patient demographics, drug and alcohol data, and reported adverse events. The Shapiro-Wilk test and graphical analysis was used to determine the distribution of studied data. Data was presented as the mean (\pm standard deviation (\pm SD)) or median (interquartile range [IQR]) depending on whether the data was normally distributed. Paired *t*-tests or the Wilcoxon rank sum test were used to analyse change in PROMs from baseline for parametric data sets and nonparametric data sets respectively. The proportion of patients who experience a MCID in GAD-7 and SQS were also reported. As no MCID values exist for MSQoL-54 or EQ-5D-5L in a population with MS these were not calculated or analysed. Statistical Package for Social Sciences (SPSS) [IBM Statistics version 26 SPSS (New York, IL), USA] was used for the data processing. Statistical significance was defined as p -value < 0.050 .

3. Results

3.1. Patient demographics and cannabis exposure

A total of 141 patients with MS were included in the study. 69 (48.94 %) patients were male and 72 (51.06 %) patients were female (Table 1). The mean age of the participants was 45.89 (\pm 11.10) years. The mean body mass index was 26.94 (\pm 7.02) kg/m². The most frequently recorded occupation was "unemployed" ($n = 69$; 48.90 %). The median Charlson comorbidity index score of the patients was 0.00 [0.00–5.00]. Full information on clinicopathological characteristics of patients at baseline can be viewed in Table 1.

Most participants were current cannabis users at baseline ($n = 78$; 55.32 %) (Table 2). Across the cohort, the median lifetime exposure to cannabis was 4.75 [1.00–12.88] gram years. The median lifetime exposure of patients to tobacco was 10.00 [5.00–20.00] gram years, whilst the median weekly alcohol consumption of participants was 0.00 [0.00–4.00] units.

3.2. Cannabis-based medicinal product dosing

The majority of patients were prescribed both THC and CBD ($n = 138$; 97.87 %) (Table 3). At the point of extraction, the median daily THC and CBD dose was 210.00 [24.00–372.50] mg and 25.00 [20.00–50.00] mg respectively. CBMP oils were prescribed to 41 (29.07 %) patients, and CBMP flowers were prescribed to 22 (15.60 %) patients. For patients prescribed both CBMP oils and flowers, the median THC and CBD dose was 220.00 [210.00–410.00] mg and 30.00 [25.00–55.00] mg respectively per day. Among those 41 patients prescribed with CBMP oils only, the median daily THC and CBD dose was 20.00 [20.00–20.00] mg and 20.00 [20.00–27.50] mg. While among those patients prescribed with CBMP flowers only, the median daily THC and CBD dose was 270.00 [200.00–408.75] mg and 10.00 [5.00–65.00] mg, respectively. The most commonly prescribed THC-predominant and CBD-predominant oils were Adven® 20 (Curaleaf International, Guernsey)

Table 1
Clinicopathological characteristics of study participants at baseline.

Baseline Characteristics	No. (%) / Mean ± SD / Median [IQR]
Gender	
Female	69 (48.94 %)
Male	72 (51.06 %)
Age	45.89 ± 11.10
Body mass index (kg/m ²)	26.94 ± 7.02
Occupation	
Unemployed	69 (48.94 %)
Unknown	27 (19.15 %)
Managers	10 (7.09 %)
Professional	10 (7.09 %)
Other occupations	9 (6.38 %)
Elementary occupations	5 (3.55 %)
Craft and related trades workers	4 (2.84 %)
Clerical support workers	3 (2.13 %)
Service and sales workers	2 (1.42 %)
Technicians and associate professionals	1 (0.71 %)
Plant and machine operators, and assemblers	1 (0.71 %)
Charlson Comorbidity Index	0.00 [0.00–5.00]
AIDS	0 (0.00 %)
Anxiety/depression	5 (3.55 %)
Arthritis	7 (4.96 %)
Cerebrovascular accident or transient ischemic attack	0 (0.00 %)
Chronic obstructive pulmonary disease	2 (1.42 %)
Congestive heart failure	0 (0.00 %)
Connective tissue disease	0 (0.00 %)
Dementia	0 (0.00 %)
Diabetes	5 (3.55 %)
Endocrine thyroid dysfunction	8 (5.67 %)
Epilepsy	4 (2.84 %)
Hemiplegia	0 (0.00 %)
Hypertension	12 (8.51 %)
Leukemia	0 (0.00 %)
Liver disease	0 (0.00 %)
Lymphoma	0 (0.00 %)
Moderate to severe chronic kidney disease	1 (0.71 %)
Myocardial infarction	2 (1.42 %)
Peptic ulcer disease	0 (0.00 %)
Peripheral vascular disease	2 (1.42 %)
Solid tumour	3 (2.13 %)
VTE	0 (0.00 %)

Table 2
Tobacco, alcohol, and cannabis exposure of patients at baseline.

Tobacco, alcohol, and cannabis status	n (%) / median [IQR]
Cannabis status	
Cannabis naïve	30 (21.28 %)
Ex-user	33 (23.40 %)
Current user	78 (55.32 %)
Cannabis consumption, gram years	4.75 [1.00–12.88]
Tobacco status	
Non-smoker	35 (24.82 %)
Ex-smoker	72 (51.06 %)
Current smoker	34 (24.11 %)
Tobacco pack years	10.00 [5.00–20.00]
Weekly alcohol consumption, units	0.00 [0.00–4.00]

and Adven® 50 (Curaleaf International, Guernsey), whilst the most commonly prescribed flower was Adven® EMT2 (Curaleaf International, Guernsey).

3.3. Patient-reported outcome measures & follow-up measures

Table 4 details, in full, paired results of PROMs from baseline to follow-up at 1, 3, and 6 months. Results demonstrate an improvement in HRQoL, as assessed by GAD-7, SQS and EQ-5D-5L measures at 1, 3 and 6 months compared to baseline ($p < 0.050$). However, there was no change in EQ-5D-5L Self Care measure at 6 months compared to baseline

Table 3
CBMP dosing of registered multiple sclerosis patients.

Medication status	Baseline
Median [IQR] CBD dosage per day (mg)	25.00 [20.00–50.00]
Median [IQR] THC dosage per day (mg)	210.00 [24.00–372.50]
Number of patients prescribed both THC and CBD	138 (97.87 %)
Number of patients prescribed THC alone	1 (0.71 %)
Number of patients prescribed CBD alone	2 (1.42 %)
Number of patients consumed both CBMP oils and flowers	78 (55.32 %)
Number of patients consumed CBMP oils only	41 (29.08 %)
Number of patients consumed CBMP flowers only	22 (15.60 %)

CBMP, Cannabis-based medicinal product; IQR, interquartile range; CBD, cannabidiol; THC, (-)-trans-delta-9-tetrahydrocannabinol.

($p = 0.112$). The median PGIC value at 1 and 3 months was 5.00 [5.00–6.00], while the median PGIC value at 6 months was 6.00 [5.00–6.00]. The proportion of individuals who reported a MCID change in GAD-7 at 1 month, 3 months and 6 months were 38.14 % ($n = 45/118$), 35.71 % ($n = 30/84$), and 40.00 % ($n = 22/55$). With respect to SQS, 37.82 % ($n = 45/110$), 32.14 % ($n = 27/84$), and 29.09 % ($n = 16/55$) of individuals reported a MCID.

The baseline and follow up scores for the MSQoL-54, including individual subscales are reported in Table 5. Statistically significant improvement was measured across multiple categories at each follow up, including the change in health scale, cognitive function, mental health composition, physical health, role limitations due to physical limitation and due to emotional problems, as well as social and sexual function ($p < 0.050$). Even though there was a statistically significant difference in satisfaction with sexual function at 1 month ($p = 0.009$), the difference was not significant at 3 and 6 months ($p > 0.050$). Furthermore, no significant change was observed for the overall quality of life measure at 1 and 3 months ($p > 0.050$); however, a significant change was observed at 6 months compared to baseline ($p = 0.005$).

3.4. Adverse events

Full information on adverse events reported by participants is displayed in Table 6. 146 (103.50 %) total adverse events were reported by 21 (14.89 %) participants. Among the 146 cases, most were considered mild ($n = 47$; 33.33 %) and moderate ($n = 72$; 51.06 %). 26 (18.44 %) adverse events were severe and 1 (0.71 %) was life-threatening/disabling. The five most frequent adverse events were fatigue ($n = 14$, 9.93 %), lethargy ($n = 10$; 7.09 %), somnolence ($n = 10$; 7.09 %), muscular weakness ($n = 9$; 6.38 %), and spasticity ($n = 9$; 6.38 %).

4. Discussion

This case series demonstrates a potential association between initiation of CBMPs and improved patient reported outcomes in sleep, anxiety and general HRQoL measures, over 6 months. This analysis indicated improvements in validated measures including EQ-5D-5L, GAD-7 and SQS over a 6-month follow up period ($p < 0.050$). Additional measures for HRQoL, including various physical and mental health subdomains assessed through the MSQoL-54, also exhibit improvements up to 6 months when compared to baseline. 146 (103.5 %) adverse events were by 14.89 % of participants, with most reported events being mild to moderate in severity ($n = 109$, 84.40 %). These findings, whilst statistically significant, must be interpreted with a high degree of caution, due to the inherent limitations in study design. As this is an observational study, a range of factors are uncontrolled including concomitant drug use, blinding, and patient selection - a key example is the reported proportion of current cannabis users at baseline (55.32 %).

In this case series, patients prescribed CBMPs presented with improvements in HRQoL as illustrated by a statistically significant difference in EQ-5D-5L, GAD-7 and SQS values between baseline and follow-up at all time points. This is consistent with previous analysis performed

Table 4
Paired baseline and follow-up patient reported outcome measures.

		n	Baseline Score	Follow-Up Score	p-value
GAD-7	1 month	118	6.00 [2.00–11.25]	3.00 [1.00–7.00]	<0.001
	3 months	84	5.00 [1.00–8.75]	2.00 [0.00–6.00]	<0.001
	6 months	55	5.00 [2.00–8.00]	3.00 [1.00–6.00]	<0.001
	1 month	119	4.00 [3.00–7.00]	7.00 [5.00–8.00]	<0.001
	3 months	84	4.50 [3.00–7.00]	7.00 [5.00–8.00]	<0.001
6 months	55	5.00 [3.00–7.00]	7.00 [4.00–9.00]	0.005	
EQ-5D-5L Mobility	1 month	119	3.00 [3.00–4.00]	3.00 [2.00–4.00]	<0.001
	3 months	84	3.00 [2.25–4.00]	3.00 [2.00–4.00]	0.003
	6 months	55	3.00 [3.00–4.00]	3.00 [2.00–4.00]	0.007
	1 month	119	2.00 [1.00–3.00]	2.00 [1.00–3.00]	0.018
	3 months	84	2.00 [2.00–3.00]	2.00 [1.00–3.00]	0.047
6 months	55	2.00 [2.00–3.00]	2.00 [1.00–3.00]	0.112	
EQ-5D-5L Usual Activities	1 month	119	3.00 [2.00–4.00]	3.00 [2.00–3.00]	<0.001
	3 months	84	3.00 [2.00–4.00]	3.00 [2.00–3.00]	<0.001
	6 months	55	3.00 [2.00–4.00]	3.00 [2.00–3.00]	0.006
	1 month	119	3.00 [3.00–4.00]	3.00 [2.00–4.00]	<0.001
	3 months	84	4.00 [3.00–4.00]	3.00 [2.00–3.00]	<0.001
6 months	55	4.00 [2.00–4.00]	2.00 [2.00–3.00]	<0.001	
EQ-5D-5L Anxiety and Depression	1 month	119	2.00 [2.00–3.00]	2.00 [1.00–3.00]	<0.001
	3 months	84	2.00 [1.00–3.00]	2.00 [1.00–2.00]	<0.001
	6 months	55	2.00 [2.00–3.00]	2.00 [1.00–3.00]	0.013
	1 month	119	0.33 [–0.02–0.61]	0.55 [0.30–0.68]	<0.001
	3 months	84	0.34 [–0.03–0.61]	0.58 [0.33–0.66]	<0.001
6 months	55	0.34 [0.05–0.59]	0.57 [0.30–0.69]	<0.001	
PGIC	1 month	-	-	5.00 [5.00–6.00]	-
	3 months	-	-	5.00 [5.00–6.00]	-
	6 months	-	-	6.00 [5.00–6.00]	-

GAD-7, Generalized Anxiety Disorder Scale; PGIC, Patient Global Impression of Change; SQS, Sleep Quality Scale.

on the UK Medical Cannabis Registry that demonstrated similar improvements in patients with a range of indications for prescribed CBMPs across a 1-to-6-month time period ($n = 312$) (Ergisi et al., 2022a). This study identified improvements in all EQ-5D-5L values excluding EQ-5D-5L Self-care at 3 and 6 months which is replicated in the present analysis ($p < 0.050$). A 2014 review of nabiximols administration for MS

Table 5
Paired baseline and follow-up patient-reported outcome measures.

		N	Baseline Score	Follow-Up Score	p-value
Change in health scale	1 month	116	25.00 [0.00–50.00]	50.00 [25.00–68.75]	<0.001
	3 months	83	25.00 [25.00–50.00]	50.00 [25.00–75.00]	<0.001
	6 months	54	25.00 [25.00–50.00]	50.00 [25.00–75.00]	0.001
	1 month	116	47.50 [25.00–70.00]	65.00 [35.00–80.00]	<0.001
	3 months	83	55.00 [30.00–75.00]	70.00 [45.00–80.00]	<0.001
	6 months	54	60.00 [28.75–71.25]	65.00 [43.75–85.00]	0.001
Cognitive function	1 month	116	47.50 [25.00–70.00]	65.00 [35.00–80.00]	<0.001
	3 months	83	55.00 [30.00–75.00]	70.00 [45.00–80.00]	<0.001
	6 months	54	60.00 [28.75–71.25]	65.00 [43.75–85.00]	0.001
Emotional wellbeing	1 month	116	56.00 [44.00–72.00]	68.00 [48.00–84.00]	<0.001
	3 months	83	64.00 [48.00–76.00]	72.00 [48.00–84.00]	0.068
	6 months	54	62.00 [48.00–73.00]	72.00 [52.00–84.00]	0.002
Energy scale	1 month	116	20.00 [8.00–36.00]	34.00 [16.00–48.00]	<0.001
	3 months	83	20.00 [12.00–36.00]	36.00 [16.00–48.00]	<0.001
	6 months	54	22.00 [12.00–37.00]	36.00 [20.00–52.00]	<0.001
	1 month	116	35.00 [15.00–58.75]	40.00 [25.00–65.00]	<0.001
	3 months	83	40.00 [15.00–65.00]	50.00 [25.00–70.00]	0.023
	6 months	54	40.00 [15.00–60.00]	55.00 [28.75–75.00]	0.003
Health distress scale	1 month	116	20.00 [10.00–35.00]	25.00 [15.00–38.75]	0.001
	3 months	83	25.00 [10.00–35.00]	25.00 [15.00–35.00]	0.024
	6 months	54	25.00 [13.75–35.00]	30.00 [15.00–50.00]	0.002
	1 month	116	29.17 [15.00–46.67]	46.67 [30.00–68.33]	<0.001
	3 months	83	30.00 [15.00–55.00]	46.67 [23.33–63.33]	<0.001
	6 months	54	29.17 [15.00–61.67]	53.33 [38.33–70.00]	<0.001
Pain scale	1 month	116	20.00 [5.00–35.00]	25.00 [6.25–43.75]	0.001
	3 months	83	20.00 [5.00–35.00]	25.00 [5.00–50.00]	0.010
	6 months	54	20.00 [8.75–36.25]	27.50 [5.00–46.25]	0.031
	1 month	116	20.00 [5.00–35.00]	25.00 [6.25–43.75]	0.001
	3 months	83	20.00 [5.00–35.00]	25.00 [5.00–50.00]	0.010
	6 months	54	20.00 [8.75–36.25]	27.50 [5.00–46.25]	0.031
Physical function	1 month	116	0.00 [0.00–25.00]	25.00 [0.00–75.00]	<0.001
	3 months	83	0.00 [0.00–25.00]	25.00 [0.00–50.00]	<0.001
	6 months	54	0.00 [0.00–25.00]	0.00 [0.00–81.25]	0.001
	1 month	116	33.33 [0.00–100.00]	50.00 [0.00–100.00]	0.019
	3 months	83	33.33 [0.00–100.00]	66.66 [0.00–100.00]	0.028
	6 months	54	0.00 [0.00–100.00]	66.66 [0.00–100.00]	0.012
Role limitations due to physical limitation	1 month	116	50.00 [0.00–75.00]	50.00 [25.00–75.00]	0.009
	3 months	73	50.00 [0.00–75.00]	50.00 [25.00–75.00]	0.394
	6 months	54	50.00 [18.75–75.00]	50.00 [25.00–75.00]	0.752

(continued on next page)

Table 5 (continued)

		N	Baseline Score	Follow-Up Score	p-value
Sexual function	1 month	116	62.50 [24.98–91.68]	66.70 [33.30–91.68]	0.012
	3 months	83	66.70 [24.98–91.68]	75.00 [33.30–100.00]	0.015
	6 months	54	66.69 [25.00–91.68]	75.01 [41.65–100.00]	0.007
Social function	1 month	116	41.67 [33.33–66.67]	54.17 [41.67–66.67]	<0.001
	3 months	83	50.00 [33.33–66.67]	58.33 [33.33–66.67]	0.004
	6 months	54	50.00 [31.25–66.67]	58.33 [33.33–75.00]	0.003
Mental health composite	1 month	116	43.04 [30.61–66.08]	56.81 [35.62–73.99]	<0.001
	3 months	83	50.54 [33.18–70.08]	58.96 [40.14–74.77]	<0.001
	6 months	54	43.53 [32.34–65.90]	60.62 [40.88–79.38]	<0.001
Physical health composite	1 month	116	27.55 [17.24–41.92]	37.13 [25.60–51.94]	<0.001
	3 months	83	27.75 [17.71–44.53]	38.50 [25.73–49.51]	<0.001
	6 months	54	28.11 [18.41–42.25]	40.31 [28.88–58.35]	<0.001
Overall quality of life	1 month	116	50.00 [41.65–58.35]	51.65 [45.00–65.00]	0.068
	3 months	83	50.00 [41.65–58.35]	51.65 [43.35–63.35]	0.068
	6 months	54	50.00 [40.00–55.41]	54.18 [45.00–69.18]	0.005

spasticity reported improvements to MSQoL physical and mental health composite scores (34.6 to 44.7 and 47.5 to 58.5 respectively) over a 12-month period (Arroyo et al., 2014). An associated decrease was also seen in measures of physical health, function and mobility over the investigated period, a pattern that is mirrored in several other studies (Ergisi et al., 2022a; Harris et al., 2022; Erridge et al., 2021). Given the nature of MS, a decline in physical health secondary to disease progression could help explain the gradual decrease in self-care values over the 6-month period. In the present study however, there were self-reported improvements in physical function which mirrors the findings from studies of other less progressive disorders (Harris et al., 2022; Ergisi et al., 2022b). These results differ from the clinical trial from Novotna et al. investigating the application of nabiximols for refractory spasticity in MS (Novotna et al., 2011). Future randomised controlled trials against active comparators or placebo will be necessary to enable accurate assessment of the positive and negative effects of CBMP therapy.

Improvements in measured anxiety were identified using the EQ-5D-5L anxiety and depression subscale and the GAD-7 that were sustained at 6 months ($p < 0.050$). There was also an improvement to the mental health composite MSQoL subscale ($P < 0.001$). This builds upon pre-clinical evidence supporting the role of the endocannabinoid system in neuropsychiatric conditions (Sarris et al., 2020; Black et al., 2019). Previous studies have also demonstrated a similar change in related PROMs (Ergisi et al., 2022a; Ergisi et al., 2022b; Erridge et al., 2022b; Erridge et al., 2021). Anxiety and depression are frequent co-morbidities in patients with MS, though less common in this cohort, and the present study suggests an improvement in anxiety symptoms, amongst others, which reinforces the potential of cannabinoids to treat the sequelae of MS (Ghasemi et al., 2017; Silveira et al., 2019; Johnston, 2002).

As pain is the most common reason for symptomatic therapy in MS, the improvements in the EQ-5D-5L pain and discomfort subscale and MSQoL-54 pain scale are clinically relevant (Solaro et al., 2013). Differences between baseline and follow-up were sustained at 6 months ($p < 0.001$). Similarly, in a recent analysis of the UK Medical Cannabis

Table 6

Adverse events reported by patients.

Adverse Event	Mild	Moderate	Severe	Life-threatening /Disabling	Total (%)
Abdominal Pain (Upper)	3	–	2	–	5 (3.55 %)
Amnesia	–	1	–	–	1 (0.71 %)
Anorexia	2	–	–	–	2 (1.42 %)
Ataxia	2	4	2	–	8 (5.67 %)
Blurred Vision	3	4	–	–	7 (4.96 %)
Cognitive Disturbance	1	4	–	–	5 (3.55 %)
Concentration Impairment	3	5	–	–	8 (5.67 %)
Confusion	1	2	1	–	4 (2.84 %)
Constipation	3	1	–	–	4 (2.84 %)
Decreased Weight	–	1	–	–	1 (0.71 %)
Diarrhoea	1	–	2	–	3 (2.13 %)
Dizziness	–	3	–	–	3 (2.13 %)
Dry Mouth	4	1	–	–	5 (3.55 %)
Dysgeusia	–	1	–	–	1 (0.71 %)
Dyspepsia	1	1	–	–	2 (1.42 %)
Fall	–	2	–	–	2 (1.42 %)
Fatigue	4	6	4	–	14 (9.93 %)
Faecal Incontinence	1	–	–	–	1 (0.71 %)
Headache	2	1	2	–	5 (3.55 %)
Hypertension	–	1	–	–	1 (0.71 %)
Insomnia	1	2	2	–	5 (3.55 %)
Lethargy	3	7	–	–	10 (7.09 %)
Muscular Weakness	–	5	4	–	9 (6.38 %)
Nausea	3	–	–	–	3 (2.13 %)
Pharyngitis	–	1	–	–	1 (0.71 %)
Pneumothorax	–	–	–	1	1 (0.71 %)
Pyrexia	1	–	–	–	1 (0.71 %)
Rash	–	1	–	–	1 (0.71 %)
Somnolence	–	8	2	–	10 (7.09 %)
Spasticity	2	4	3	–	9 (6.38 %)
Tremor	2	2	–	–	4 (2.84 %)
Upper Respiratory Infection	–	1	1	–	2 (1.42 %)
Urinary Tract Infection	–	1	1	–	2 (1.42 %)
Vertigo	3	2	–	–	5 (3.55 %)
Vomiting	1	–	–	–	1 (0.71 %)
Total	47 (33.303 %)	72 (51.06 %)	26 (18.44 %)	1 (0.71 %)	146 (103.55 %)

Registry investigating chronic pain conditions, clear changes in pain PROMs including EQ-5D-5L pain and discomfort subscale, the Brief Pain Inventory and the McGill Pain Questionnaire – Short Form neuropathic pain subscale were noted, supporting the present study findings (Harris et al., 2022). A 2018 study indicated a significant reduction in numerical rating scale scores following nabiximols administration through a 1-month period, consistent with the changes in PROMs reported in the present study (Turri et al., 2018). A 2022 observational study also noted a marked reduction in MS-associated pain, lasting up to 18 months (Patti et al., 2022). Furthermore, a systematic review and meta-analysis of randomised clinical trials indicated the administration of non-inhaled cannabinoids were associated with a 10 % increased risk difference of experiencing a clinically significant improvement in pain (Wang et al., 2021).

There were 146 adverse events (103.50 %) reported in this study. This is higher compared to previous findings from UK Medical Cannabis Registry analyses which ranged from 24.01 to 39.70 % (Ergisi et al., 2022a; Harris et al., 2022; Ergisi et al., 2022b; Kawka et al., 2021; Erridge et al., 2021). Several studies investigating nabiximols for MS also indicated lower adverse incidence rates ranging from 9.70 to 82.0 % (D’Hooghe et al., 2021; Patti et al., 2016; Collin et al., 2007; Novotna et al., 2011; Vaney et al., 2004; Pozzilli, 2013). A likely explanation for the high incidence rate is the upgrading of the adverse event reporting system, allowing for recording of adverse events through three different mechanisms (Erridge et al., 2022b). The longer duration of follow up also leads to accumulation of adverse events over the course of the treatment. Moreover, symptoms due to the underlying disease may be inaccurately reported as an adverse event. This is correlated with the five most common adverse events being fatigue, lethargy, somnolence, muscular weakness, and spasticity – all of which are common clinical manifestations of MS (Johnston, 2002; Čarnická et al., 2015; Braley and Chervin, 2010). The burden of MS treatment in parallel may also reflect the high incidence rate. Furthermore, the route of administration has been previously shown to impact the rate and type of adverse events. As a greater proportion of the cohort are prescribed oils (62.40 %), this may explain the lower incidence of oromucosal and bronchopulmonary adverse events. Despite the relatively high THC dose, there was also a low incidence of cognitive disturbance. Over half the cohort were current cannabis users and may have a tolerance to the effects of THC on cognition (Colizzi and Bhattacharyya, 2018; Ramaekers et al., 2020b). Furthermore, concomitant administration of medication to treat the sequelae of MS may disturb higher brain function, and lead to an underrepresentation of CBMP-induced cognitive disturbance. Without a randomised controlled trial, it will be difficult to ascertain the true nature of these adverse events. Most adverse events were mild to moderate in severity which is similar to previous studies over the short-to-medium term (Ergisi et al., 2022a; Harris et al., 2022; Ergisi et al., 2022b; Kawka et al., 2021; Erridge et al., 2021). However, a greater number of severe adverse events was noted compared to prior analyses.

This study has some note-worthy limitations. Firstly, the lack of a placebo control group lowered the study’s internal validity, making it difficult to establish a causative relationship between CBMP treatment and improvements (Banerjee et al., 2022). Additionally, the study’s use of PROMs introduces performance and response bias which means that patients may have exaggerated or understated their treatment effects. This consequently affects the ability to draw meaningful conclusions and questions the reliability of the data obtained. Likewise, lifetime cannabis use was quantified using cannabis gram years, but the accuracy is limited by its self-reported nature. Without appropriate controls, it is not possible to truly determine whether CBMP administration is solely responsible for the observed results. This study also experienced a high rate of patient attrition at the follow-up time points which has a significant impact on the reliability and external validity of the results. For example, loss to follow up could be secondary to a lack of therapeutic benefit, skewing the results towards a positive effect. Furthermore, sub-group analysis could not be performed for follow up time points due

to low statistical power. Future studies should aim to tackle the problem of missing data through methods such as multiple imputation.

Participants in this study had consulted a private clinic to access CBMP treatment at a given cost. This hinders the generalisability of the data to MS patients from lower socioeconomic backgrounds, as they may be unable to access such facilities. Unfortunately, this study did not obtain this data; however, 48.94 % of patients were unemployed indicating that the suggested bias for wealthy participants may not be as high as this would otherwise suggest. In future, it would be beneficial if socio-economic data is also collected, to allow researchers to assess if the study population is an accurate representation of the general population to ensure greater generalisability of results.

Due to the heterogenous nature of MS, patients often have personalised treatment plans (Rotstein and Montalban, 2019). Despite this, the UKCMR does not collect specific data on disease course or progression. This would be informative as sub-group analysis could be performed to understand treatment responses between disease courses. A clinical trial would be the best approach for this as both a larger sample size and controlled treatment regime are required. In this study, patients were prescribed CBMPs most suitable for their clinical requirements. The disparities between formulations, route of administration and dosage of the CBMPs prescribed to each patient can act as confounding variables and must therefore be taken into consideration.

In this cohort, the similar proportions of male and female individuals reduce the translatability of this study as it not representative of the global disease burden of MS. This is a common theme across conditions in the UKMCR as males are more likely to have cannabis experience than women and are therefore more likely to undergo cannabis-based therapy (Olsson et al., 2023; NIDA 2022). This selection bias not only masks gender differences, it may also lead to a lack of comparability between cannabis naïve and experienced patients. Preclinical evidence has indicated the effect of pharmacological tolerance that accompanies continuous cannabis use (Ramaekers et al., 2020a; D’Souza et al., 2008). For current cannabis users, this may reduce the likelihood of adverse events and lead to greater doses of THC and/or CBD to achieve the desired clinical effect. Moreover, prior cannabis users, may have an expectancy bias towards a positive outcome. Finally, if these individuals were consuming cannabis for health reasons this may represent a sampling bias towards inclusion of self-identified responders to therapy with cannabis. The importance of these issues cannot be understated, and steps should be taken to increase the access of CBMP treatment to all demographics.

Whilst this study followed up on MS patients after 6 months of CBMP use, investigating the long-term effects (>1 year) would be of great clinical interest and value. It will enable clinicians to make better informed decisions when prescribing CBMPs for MS as they can consider the possible long-term contraindications. Thus, carrying out a study with longer timepoints will further the knowledge regarding the safety and clinical outcomes of those prescribed CBMPs for MS-associated symptoms.

5. Conclusion

This case series is the first to assess the follow-up of MS patients prescribed unlicensed CBMPs for up to 6 months. The results obtained from this study have indicated an association between treatment with CBMPs and improved general HRQoL outcomes in the short-to-medium term. Despite there being a total of 146 adverse events reported, the results demonstrate that within the first 6 months CBMP treatment was well-tolerated by the majority of patients (85.11 %). However, the inherent limitations of this study must be taken into consideration when interpreting the results and conclusions should tentatively be drawn. This study highlights the need for future randomised controlled trials to further explore CBMP use for MS patients and clear the ambiguities surrounding the incidence of adverse events.

Funding

There was no external or commercial funding associated with this paper.

Ethical approval

The UK Medical Cannabis Registry and derivative research studies have been afforded a favourable ethical opinion by the Health Research Authority (South West - Central Bristol Research Ethics Committee reference 22/SW/0145).

Previous publication

This original paper has not been previously published or simultaneously submitted for publication elsewhere. The data has been presented as a poster at the International Cannabinoid Research Society Conference, 2022.

Principal Investigator: The authors confirm that the PI for this paper is Mikael H Sodergren and that he had direct clinical responsibility for patients.

All authors have contributed to and approved the final manuscript. All conditions as previously stated by the ICMJE have been met.

Patient consent

All participants completed written, informed consent prior to enrolment in the registry.

Permission to reproduce material from other sources

N/A.

Clinical trial registration

N/A.

CRediT authorship contribution statement

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Declaration of competing interest

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Acknowledgements

None.

References

- Arroyo, R., Vila, C., Dechant, K.L., 2014. Impact of Sativex® on quality of life and activities of daily living in patients with multiple sclerosis spasticity. *J. Comp. Eff. Res.* 3 (4), 435–444.

- Atakan, Z., 2012. Cannabis, a complex plant: different compounds and different effects on individuals. *Ther. Adv. Psychopharmacol.* 2 (6), 241–254.
- Banerjee, R., Erridge, S., Salazar, O., Mangal, N., Couch, D., Pachetti, B., et al., 2022. Real world evidence in medical cannabis research. *Ther. Innov. Regul. Sci.* 56 (1), 8–14.
- Black, N., Stockings, E., Campbell, G., Tran, L.T., Zagic, D., Hall, W.D., et al., 2019. Cannabinoids for the treatment of mental disorders and symptoms of mental disorders: a systematic review and meta-analysis. *Lancet Psychiatry* 6 (12), 995–1010.
- Braley, T.J., Chervin, R.D., 2010. Fatigue in multiple sclerosis: mechanisms, evaluation, and treatment. *Sleep* 33 (8), 1061–1067.
- Brusselsaers, N., Lagergren, J., 2017. The Charlson Comorbidity Index in registry-based research. *Methods Inf. Med.* 56 (5), 401–406.
- Busse, J.W., Vankrunkelsven, P., Zeng, L., Heen, A.F., Merglen, A., Campbell, F., et al., 2021. Medical cannabis or cannabinoids for chronic pain: a clinical practice guideline. *BMJ* 374, n2040.
- Chang, E., Ghosh, N., Yanni, D., Lee, S., Alexandru, D., Mozaffar, T., 2013. A review of spasticity treatments: pharmacological and interventional approaches. *Crit. Rev. Phys. Rehabil. Med.* 25 (1–2), 11–22.
- Čarnická, Z., Kollár, B., Šiarník, P., Krízová, L., Klobučníková, K., Turčáni, P., 2015. Sleep disorders in patients with multiple sclerosis. *J. Clin. Sleep. Med.* 11 (5), 553–557.
- Colizzi, M., Bhattacharyya, S., 2018. Cannabis use and the development of tolerance: a systematic review of human evidence. *Neurosci. Biobehav. Rev.* 93, 1–25.
- Collin, C., Davies, P., Mutiboko, I.K., Ratcliffe, S., 2007. Randomized controlled trial of cannabis-based medicine in spasticity caused by multiple sclerosis. *Eur. J. Neurol.* 14 (3), 290–296.
- Comelli, F., Bettoni, I., Colleoni, M., Giagnoni, G., Costa, B., 2009. Beneficial effects of a Cannabis sativa extract treatment on diabetes-induced neuropathy and oxidative stress. *Phytother. Res.* 23 (12), 1678–1684.
- D'Hooghe, M., Willekens, B., Delvaux, V., D'Haeseleer, M., Guillaume, D., Laureys, G., et al., 2021. Sativex® (nabiximols) cannabinoid oromucosal spray in patients with resistant multiple sclerosis spasticity: the Belgian experience. *BMC Neurol.* 21 (1), 227.
- D'Souza, D.C., Ranganathan, M., Braley, G., Gueorgieva, R., Zimolo, Z., Cooper, T., et al., 2008. Blunted psychotomimetic and amnesic effects of delta-9-tetrahydrocannabinol in frequent users of cannabis. *Neuropsychopharmacology* 33 (10), 2505–2516.
- Dawidowicz, A.L., Olszowy-Tomczyk, M., Typek, R., 2021. CBG, CBD, Δ9-THC, CBN, CBGA, CBDA and Δ9-THCA as antioxidant agents and their intervention abilities in antioxidant action. *Fitoterapia* 152, 104915.
- de Sa, J.C., Airas, L., Bartholome, E., Grigoriadis, N., Mattle, H., Oreja-Guevara, C., et al., 2011. Symptomatic therapy in multiple sclerosis: a review for a multimodal approach in clinical practice. *Ther. Adv. Neurol. Disord.* 4 (3), 139–168.
- Deusch, D.G., 2016. A personal retrospective: Elevating Anandamide (AEA) by targeting Fatty Acid Amide Hydrolase (FAAH) and the Fatty Acid Binding Proteins (FABPs). *Front. Pharmacol.* 7, 370.
- Dos Reis Rosa Franco, G., Smid, S., Viegas, C., 2021. Phytocannabinoids: general aspects and pharmacological potential in neurodegenerative diseases. *Curr. Neuropharmacol.* 19 (4), 449–464.
- Ebbert, J.O., Scharf, E.L., Hurt, R.T., 2018. Medical cannabis. *Mayo Clin. Proc.* 93 (12), 1842–1847.
- England P.H. Multiple sclerosis: prevalence, incidence and smoking status - data briefing United Kingdom: GOV.UK; 2020 [Available from: <https://www.gov.uk/government/publications/multiple-sclerosis-prevalence-incidence-and-smoking-status/multiple-sclerosis-prevalence-incidence-and-smoking-status-data-briefing#:~:text=Conclusions,-The%20purpose%20of&text=The%20estimate%20for%20the%20prevalence,cases%20per%20100%20of%20population%20respectively>].
- Ergisi, M., Erridge, S., Harris, M., Kawka, M., Nimalan, D., Salazar, O., et al., 2022a. An updated analysis of clinical outcome measures across patients from the UK Medical Cannabis Registry. *Cannabis. Cannabinoid. Res.*
- Ergisi, M., Erridge, S., Harris, M., Kawka, M., Nimalan, D., Salazar, O., et al., 2022b. UK Medical Cannabis Registry: an analysis of clinical outcomes of medicinal cannabis therapy for generalized anxiety disorder. *Expert. Rev. Clin. Pharmacol.* 15 (4), 487–495.
- Erridge, S., Salazar, O., Kawka, M., Holvey, C., Coomber, R., Usmani, A., et al., 2021. An initial analysis of the UK Medical Cannabis Registry: outcomes analysis of first 129 patients. *Neuropsychopharmacol. Rep.* 41 (3), 362–370.
- Erridge, S., Sodergren, M.H., Weatherall, M.W., 2022a. Medical cannabis in multiple sclerosis. *Br. J. Neuroscience Nurs.* 18 (Sup3), S28–S31.
- Erridge, S., Kerr-Gaffney, J., Holvey, C., Coomber, R., Barros, D.A.R., Bhoskar, U., et al., 2022b. Clinical outcome analysis of patients with autism spectrum disorder: analysis from the UK Medical Cannabis Registry. *Ther. Adv. Psychopharmacol.* 12, 20451253221116240.
- Filippi, M., Bar-Or, A., Piehl, F., Preziosa, P., Solari, A., Vukusic, S., et al., 2018. Multiple sclerosis. *Nat. Rev. Dis. Prim.* 4 (1), 43.
- Filippini, G., Minozzi, S., Borrelli, F., Cinquini, M., Dwan, K., 2022. Cannabis and cannabinoids for symptomatic treatment for people with multiple sclerosis. *Cochrane Database Syst. Rev.* 5 (5), CD013444.
- Ghasemi, N., Razavi, S., Nikzad, E., 2017. Multiple sclerosis: pathogenesis, symptoms, diagnoses and cell-based therapy. *Cell J.* 19 (1), 1–10.
- Haddad, F., Dokmak, G., Karaman, R., 2022. The efficacy of cannabis on multiple sclerosis-related symptoms. *Life* 12 (5).
- Harris, M., Erridge, S., Ergisi, M., Nimalan, D., Kawka, M., Salazar, O., et al., 2022. UK Medical Cannabis registry: an analysis of clinical outcomes of medicinal cannabis therapy for chronic pain conditions. *Expert. Rev. Clin. Pharmacol.* 15 (4), 473–485.
- Henze, T., Rieckmann, P., Toyka, K.V., 2006. Symptomatic treatment of multiple sclerosis. *Multiple Sclerosis Therapy Consensus Group (MSTCG) of the German Multiple Sclerosis Society. Eur. Neurol.* 56 (2), 78–105.
- Herdman, M., Gudex, C., Lloyd, A., Janssen, M., Kind, P., Parkin, D., et al., 2011. Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). *Qual. Life Res.* 20 (10), 1727–1736.
- Johnston, R.B. J.J., 2002. *Multiple Sclerosis: Current Status and Strategies for the Future*. National Academy Press, Washington DC, pp. 115–166.
- Kawka, M., Erridge, S., Holvey, C., Coomber, R., Usmani, A., Sajad, M., et al., 2021. Clinical outcome data of first cohort of chronic pain patients treated with cannabis-based sublingual oils in the United Kingdom: analysis from the UK Medical Cannabis Registry. *J. Clin. Pharmacol.* 61 (12), 1545–1554.
- Kendall, D.A., Yudowski, G.A., 2016. Cannabinoid receptors in the central nervous system: their signaling and roles in disease. *Front. Cell Neurosci.* 10, 294.
- Khan, H., Ghori, F.K., Ghani, U., Javed, A., Zahid, S., 2022. Cannabinoid and endocannabinoid system: a promising therapeutic intervention for multiple sclerosis. *Mol. Biol. Rep.* 49 (6), 5117–5131.
- Koitiuniuk, A., Chojdak-Lukasiewicz, J., 2022. Adherence to therapy in patients with multiple sclerosis-review. *Int. J. Environ. Res. Public Health* 19 (4).
- L Ferguson, J.S., 2009. Patient global impression of change scores within the context of a chronic pain rehabilitation program. *J. Pain* 10 (4).
- Löwe, B., Decker, O., Müller, S., Brähler, E., Schellberg, D., Herzog, W., et al., 2008. Validation and standardization of the Generalized Anxiety Disorder Screener (GAD-7) in the general population. *Med. Care* 46 (3), 266–274.
- Maroon, J., Bost, J., 2018. Review of the neurological benefits of phytocannabinoids. *Surg. Neurol. Int.* 9, 91.
- MHRA, 2020. *The supply, manufacture, importation and distribution of unlicensed cannabis-based products for medicinal use in humans 'specials'*. Available from: http://assets.publishing.service.gov.uk/media/5e58eefb86650c53a363f77c/Cannabis-Guidance_unlicensed_CBPMS_updated_2020.pdf.
- NICE. *Cannabis-based medicinal products NICE guideline United Kingdom 2019* [Available from: <https://www.nice.org.uk/guidance/ng144/resources/cannabis-based-medicinal-products-pdf-66141779817157>].
- NIDA. *Sex and gender differences in substance use 2022* [Available from: <https://nida.nih.gov/publications/research-reports/substance-use-in-women/sex-gender-differences-in-substance-use>].
- Nielsen, S., Germanos, R., Weier, M., Pollard, J., Degenhardt, L., Hall, W., et al., 2018. The use of cannabis and cannabinoids in treating symptoms of multiple sclerosis: a systematic review of reviews. *Curr. Neurol. Neurosci. Rep.* 18 (2), 8.
- Notcutt, W., Langford, R., Davies, P., Ratcliffe, S., Potts, R., 2012. A placebo-controlled, parallel-group, randomized withdrawal study of subjects with symptoms of spasticity due to multiple sclerosis who are receiving long-term Sativex® (nabiximols). *Mult. Scler.* 18 (2), 219–228.
- Novotna, A., Mares, J., Ratcliffe, S., Novakova, I., Vachova, M., Zapletalova, O., et al., 2011. A randomized, double-blind, placebo-controlled, parallel-group, enriched-design study of nabiximols* (Sativex®), as add-on therapy, in subjects with refractory spasticity caused by multiple sclerosis. *Eur. J. Neurol.* 18 (9), 1122–1131.
- Olsson, F., Erridge, S., Tait, J., Holvey, C., Coomber, R., Beri, S., et al., 2023. An observational study of safety and clinical outcome measures across patient groups in the United Kingdom Medical Cannabis Registry. *Expert. Rev. Clin. Pharmacol.* 16 (3), 257–266.
- Patti, F., Messina, S., Solaro, C., Amato, M.P., Bergamaschi, R., Bonavita, S., et al., 2016. Efficacy and safety of cannabinoid oromucosal spray for multiple sclerosis spasticity. *J. Neurol. Neurosurg. Psychiatry* 87 (9), 944–951.
- Patti, F., Chisari, C.G., Ó, Fernández, Sarroca, J., Ferrer-Picón, E., Hernández Vicente, F., et al., 2022. A real-world evidence study of nabiximols in multiple sclerosis patients with resistant spasticity: analysis in relation to the newly described 'spasticity-plus syndrome'. *Eur. J. Neurol.* 29 (9), 2744–2753.
- Pozzilli, C., 2013. Advances in the management of multiple sclerosis spasticity: experiences from recent studies and everyday clinical practice. *Expert. Rev. Neurother.* 13 (12 Suppl), 49–54.
- Pratt, M., Stevens, A., Thuku, M., Butler, C., Skidmore, B., Wieland, L.S., et al., 2019. Benefits and harms of medical cannabis: a scoping review of systematic reviews. *Syst. Rev.* 8 (1), 320.
- Ramaekers, J.G., Mason, N.L., Theunissen, E.L., 2020a. Blunted highs: pharmacodynamic and behavioral models of cannabis tolerance. *Eur. Neuropsychopharmacol.* 36, 191–205.
- Ramaekers, J.G., Mason, N.L., Theunissen, E.L., 2020b. Blunted highs: pharmacodynamic and behavioral models of cannabis tolerance. *Eur. Neuropsychopharmacol.* 36, 191–205.
- Robertson, D., Moreo, N., 2016. Disease-modifying therapies in multiple sclerosis: overview and treatment considerations. *Fed. Pract.* 33 (6), 28–34.
- Rotstein, D., Montalban, X., 2019. Reaching an evidence-based prognosis for personalized treatment of multiple sclerosis. *Nat. Rev. Neurol.* 15 (5), 287–300.
- Sarris, J., Sinclair, J., Karamacoska, D., Davidson, M., Firth, J., 2020. Medicinal cannabis for psychiatric disorders: a clinically-focused systematic review. *BMC Psychiatry* 20 (1), 24.
- Serpell, M.G., Notcutt, W., Collin, C., 2013. Sativex long-term use: an open-label trial in patients with spasticity due to multiple sclerosis. *J. Neurol.* 260 (1), 285–295.
- Silveira, C., Guedes, R., Maia, D., Curral, R., Coelho, R., 2019. Neuropsychiatric symptoms of multiple sclerosis: state of the art. *Psychiatry Investig.* 16 (12), 877–888.
- Snyder, E., Cai, B., DeMuro, C., Morrison, M.F., Ball, W., 2018. A new single-item sleep quality scale: results of psychometric evaluation in patients with chronic primary insomnia and depression. *J. Clin. Sleep. Med.* 14 (11), 1849–1857.

- Solaro, C., Trabucco, E., Messmer Uccelli, M., 2013. Pain and multiple sclerosis: pathophysiology and treatment. *Curr. Neurol. Neurosci. Rep.* 13 (1), 320.
- Spitzer, R.L., Kroenke, K., Williams, J.B., Löwe, B., 2006. A brief measure for assessing generalized anxiety disorder: the GAD-7. *Arch. Intern. Med.* 166 (10), 1092–1097.
- Toussaint, A., Hüsing, P., Gumz, A., Wingefeld, K., Härter, M., Schramm, E., et al., 2020. Sensitivity to change and minimal clinically important difference of the 7-item Generalized Anxiety Disorder Questionnaire (GAD-7). *J. Affect. Disord.* 265, 395–401.
- Trotti, A., Colevas, A.D., Setser, A., Rusch, V., Jaques, D., Budach, V., et al., 2003. CTCAE v3.0: development of a comprehensive grading system for the adverse effects of cancer treatment. *Semin. Radiat. Oncol.* 13 (3), 176–181.
- Turri, M., Teatini, F., Donato, F., Zanette, G., Tugnoli, V., Deotto, L., et al., 2018. Pain modulation after oromucosal cannabinoid spray (SATIVEX®) in patients with multiple sclerosis: a study with quantitative sensory testing and laser-evoked potentials. *Medicines* 5 (3).
- van Hout, B., Janssen, M.F., Feng, Y.S., Kohlmann, T., Busschbach, J., Golicki, D., et al., 2012. Interim scoring for the EQ-5D-5L: mapping the EQ-5D-5L to EQ-5D-3L value sets. *Value Health* 15 (5), 708–715.
- Vaney, C., Heinzel-Gutenbrunner, M., Jobin, P., Tschopp, F., Gattlen, B., Hagen, U., et al., 2004. Efficacy, safety and tolerability of an orally administered cannabis extract in the treatment of spasticity in patients with multiple sclerosis: a randomized, double-blind, placebo-controlled, crossover study. *Mult. Scler.* 10 (4), 417–424.
- Vickrey, B.G., Hays, R.D., Harooni, R., Myers, L.W., Ellison, G.W., 1995. A health-related quality of life measure for multiple sclerosis. *Qual. Life Res.* 4 (3), 187–206.
- von Elm, E., Altman, D.G., Egger, M., Pocock, S.J., Gøtzsche, P.C., Vandenbroucke, J.P., 2007. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *Ann. Intern. Med.* 147 (8), 573–577.
- Wang, L., Hong, P.J., May, C., Rehman, Y., Oparin, Y., Hong, C.J., et al., 2021. Medical cannabis or cannabinoids for chronic non-cancer and cancer related pain: a systematic review and meta-analysis of randomised clinical trials. *BMJ* 374, n1034.
- Yadav, V., Bever Jr., C., Bowen, J., Bowling, A., Weinstock-Guttman, B., Cameron, M., et al., 2014. Summary of evidence-based guideline: complementary and alternative medicine in multiple sclerosis: report of the guideline development subcommittee of the American Academy of Neurology. *Neurology* 82 (12), 1083–1092.