CANNABIS, CANNABIS-BASED PRODUCTS, OR CANNABINOIDS BRIEF EVIDENCE REPORT:

EVIDENCE FROM RECENT SYSTEMATIC REVIEWS ON THE TREATMENT OF MULTIPLE SCLEROSIS

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ABBREVIATIONS

AE	Adverse event
BL	Baseline
CBD	Cannabidiol
CBP	Cannabinoid- or cannabis-based product
CNS	Central nervous system
CRRB	Cannabis Research Review Board
F/u	Follow up
HRQoL	Health-related quality of life
LOE	Level of Evidence
MA	Meta-analysis
MD	Mean difference
MS	Multiple sclerosis
NRS	Numeric rating scale
OR	Odds ratio
PBO	Placebo
RCT	Randomized controlled trial
ROB	Risk of bias
SAE	Serious adverse event
SMD	Standardized mean difference
SR	Systematic review
THC	(delta-9-)tetrahydrocannabinol

1.0 OBJECTIVE

This brief evidence report summarizes recent clinical evidence for the treatment of patients with multiple sclerosis (MS) with cannabis- or cannabinoid-based products (CBPs) using a hierarchy-of-evidence approach.

Information from this report may be considered for updates to the Cannabis Research Review Board (CRRB) guidance for use of cannabis to treat MS (see Section 5 for recommendations). The current CRRB guidance for treatment of MS concluded:

- "There is substantial evidence to support the conclusion that cannabis and cannabinoids are effective in importing patient-reported multiple sclerosis spasticity symptoms (oral cannabinoids). This is based on supportive findings from good-quality studies with very few or no credible or opposing findings" (page 4).[1]
- "There is moderate evidence to support the conclusion that cannabis or cannabinoid are effective in treatment neuropathic pain in patients with multiple sclerosis" (page 4).[1]
- "There is insufficient evidence to support or refute the conclusion that cannabis or cannabinoids are effective in treating spasticity in patients with paralysis due to spinal cord injury (National Academies of Sciences, Engineering, and Medicine, 2017)" (page 4).[1]

References cited in current CRRB guidance were published from 2013-2018; the 2017 National Academy of Sciences Report[2] on evidence for cannabis use was included.[1] The CRRB guidance also describes:

> "…clinical evidence supports the use of medical evidence for symptomatic treatment of MS-associated spasticity of both striated and smooth muscles, pain, and sleep disturbances in patients with MS. Preclinical data from MS models in animals suggest the possibility that medical cannabis may also be effective in MS as a disease-modifying agent and may have neuroprotective effects, but clinical trials using medical cannabis as a disease-modifying agent are lacking" (page 6).[1]

Due to the comprehensiveness and quality of the systematic review (SR), this summary will focus on results from the recent SR by the Cochrane organization (Filippini et al 2022).[3] Refer to the methods section for details of the methodology used for this brief evidence report.

2.0 RECENT COCHRANE SYSTEMATIC REVIEW: FILIPPINI ET AL (2022)

2.1 Review Methods

Filippini et al (2022) conducted a SR of randomized controlled trials (RCTs) on the efficacy and safety of CBPs (including synthetic cannabinoids) versus active or placebo comparator for the *symptomatic treatment* of MS. Patient populations were adults ages ≥ 18 years old diagnosed with MS (ie, including relapsing-remitting or progressive types). "Critical outcomes" addressed include spasticity, chronic neuropathic pain, and tolerability based on patient withdrawal from trials due to adverse events (AEs). Additional symptomatic efficacy outcomes and safety outcomes (eg, serious AEs and types of AEs) were also collected. A systematic literature search was performed including queries of multiple major bibliographic databases (CENTRAL, MEDLINE, Embase, CINAHL, LILACS, Physiotherapy Evidence Database [PEDro]) and sites with registered trials (WHO, Clinicaltrials.gov, EU clinical trials at clinicaltrialsregister.eu, and the Internal Association for Cannabinoid Medicines [IACM] databank). Searches were executed in December 2021. The Cochrane ROB 2.0 tool was used to assess the risk of bias (ROB) among included RCTs. The ROB 2.0 tool consideration bias arising from multiple documents (ie, from randomization, deviations from the intended treatment, missing outcome data, and selecting outcomes for report); additional considerations were made for any cross-over trials (eg, carry-over effects). RCTs were rated as having a low ROB if each ROB domain was rated as low risk; some concerns if no domain was high risk and at least 1 domain had some ROB concerns; or high risk, if at least 1 domain was rated as high risk or multiple critical domains were rated as some concerns. Direct random-effects meta-analysis (MA) was performed when appropriate and feasible. Statistical heterogeneity was assessed using the I^2 metric. Due to how data was reported among included trials, Filippini et al were unable to conduct a statistical evaluation of clinical heterogeneity.[3]

2.2 Review Results

2.2.1 Included Study Characteristics[3]

- Included 25 RCTs with 3763 total participants (2290 of whom received a cannabinoid)
  - 18 parallel group RCTs and 7 crossover RCTs with samples sizes ranging from 14 to 657 people
  - RCT duration (number of studies): 2-4 weeks (n=5); 4-12 weeks (n=10); 12-26 weeks (n=7); and long-term (n=2; 50-week study and 156-week study)
  - Most studies were conducted in the UK or a European country; 1 study was from the US and 1 from Canada
  - Participant characteristics:
    - Ages ranged from 18-60 years and were predominantly female (% female range, 50-88%)
    - Most studies allowed any type of MS; 4 studies included patients with a particular MS type. Among the 4 trials reporting numeric scale spasticity outcomes, most (range 55%-100%) participants had progressive MS.
    - Studies excluded patients with major medical conditions

    - Most studies of patients with spasticity required patients to have moderate-severe symptoms with residual symptoms after current treatment; pain studies required pain to be refractory to other pharmacologic treatments.
    - Ten studies reported on prior cannabis use history, reporting a positive history among 6%-80% of participants.
- Studied interventions:
    - Nabiximols (Sativex, THC:CBD oromucosal spray): 13 RCTs (52% of trials)
    - Oral synthetic THC analogs: 5 RCTs, including dronabinol (n=3), nabilone (n=1), or namisol (n=1)
    - Oral THC plant extract: 3 RCTs
    - Inhaled herbal cannabis: 1 RCT
    - Studies comparing more than 1 cannabinoid included 1 RCT of dronabinol vs THC extract vs placebo, and 1 RCT of dronabinol vs inhaled herbal cannabis vs placebo.
- Studied co-interventions:
    - Spasticity outcome studies permitted patient use of other anti-spasticity medications at stable doses.
    - Pain outcome studies permitted patient use of stable doses of other medications for neuropathic pain, and 3 studies allowed rescue pain medications.

2.2.2 Efficacy Results from Meta-Analysis

Table 1. Select Efficacy Results from Filippini et al (2022)[3]

Outcome	Number of Included Studies, # of participants	Result
Spasticity ('critical outcome')		
Reduction of spasticity by 30% from BL	5, n=1143	OR 2.51 (95% CI 1.56 to 4.04; I^2= 67%; P=0.02 for heterogeneity), for nabiximols or Cannador vs PBO with f/u of 6 to 14 wks
		Moderate certainty evidence
		ROB rating: all some concerns
Mean spasticity change from BL on NRS	7, n=1262	MD –0.55 (95% CI –0.94 to –0.17; I^2= 68%; P=0.004 for heterogeneity), for nabiximols vs PBO with f/u of 2 to 14 wks
		Moderate certainty evidence
		ROB rating: some concerns; 1 trial high risk
Chronic pain ('critical outcome')		
Reduction of pain by 50% from BL	1, n=48	OR 4.23 (95% CI 1.11 to 16.17), for dronabinol vs PBO with f/u of 3 wks
		Very-low certainty evidence; insufficient evidence
		ROB rating: high risk
Mean pain change from BL on NRS-PI	8, n=1451	MD –0.54 (95% CI –0.91 to –0.18; I^2= 62%; P=0.01 for heterogeneity), for nabiximols, cannabis extract, or synthetic THC vs PBO with f/u of 3 to 16 wks
		Low certainty evidence
		ROB rating: some concerns; 1 trial high risk
Patient's Global Impression of Change ('important outcome')		
Number of patients reporting PGIC score improvement	8, n=1215	OR 1.80 (95% CI 1.37 to 2.36; I^2=0%; P=0.53 for heterogeneity), for nabiximols, cannabis extract or synthetic THC vs PBO with f/u of 4 to 48 wks
		Moderate certainty evidence
		ROB rating: all with some concerns; at least 1 'high risk' domain (3 trials)
Health-related Quality of Life ('important outcome')		
Mean change in HRQOL score from baseline	8, n=1942	SMD –0.08 (95%CI –0.17 to 0.02; I^2 = 0%; P=0.59 for heterogeneity), for cannabinoids vs PBO with f/u of 3 to 48 wks
		Low certainty evidence
		ROB rating: all with some concerns; 3 trials with at least 1 'high risk' domain

Abbreviations: BL, baseline; CI, confidence interval; f/u, follow-up; HRQOL, health-related quality of life; MD, mean difference; NRS, Numeric rating scale ; PBO, placebo; ROB, Risk of Bias using the Cochrane 2.0 scale; SMD, standardized mean difference; THC, tetrahydrocannabinol; wks, weeks;

2.2.3 Safety Results from Meta-Analysis

Table 2. Select Safety Results from Filippini et al (2022)[3]

Outcome	Number of Included Studies (# participants)	Result
Tolerability ('critical outcome')		
Trial withdrawal due to AEs	19, n=3110	OR 2.41 (95% CI 1.51 to 3.84; I^2= 17%; P=0.25 for heterogeneity), for Cannabis-based treatment (63.2% nabiximols) vs PBO with f/u of 3 to 48 wks
		Low certainty evidence
		ROB rating: some concerns; 1 trial high risk
Serious Adverse Events ('important outcome')		
Patients reporting SAE	20, n=3124	OR 1.38 (95% CI 0.96 to 1.99; I^2= 64%; P=0.60 for hetergeneity), for cannabinoids vs PBO with f/u of 3 to 48 wks
		Low certainty evidence
		ROB rating: some concerns; 2 trials high risk
Nervous system Adverse Events ('important outcome')		
Patients reporting nervous system AEs	7, n=1154	OR 2.61 (95% CI 1.53 to 4.44; I^2= 64%; P=0.01 for heterogeniety), for cannabinoids vs PBO with f/u of 4 to 48 wks
		Low certainty evidence
		ROB rating: some concerns; 2 trials high risk

Abbreviations: AE, adverse event; CI, confidence interval; f/u, follow-up; MD, mean difference; ; PBO, placebo; ROB, Risk of Bias using the Cochrane 2.0 scale SAE, serious adverse event; wks, weeks;

2.2.4 Discussion and Conclusions

According to Filippini et al (2022), there is moderate-quality evidence from RCTs that add-on treatment with CBPs significantly reduces spasticity of MS by at least 30% in the short-term (up to 14 weeks) and significantly increases the proportion of patient's reporting global symptom improvement compared to placebo. The certainty of evidence was rated as low or very low for management of other MS symptoms with CBPs, and for AEs of CBPs (eg, at least 50% reduction in neuropathic pain, AEs, and health-related quality of life). Effects rated as low- or very-low certainty reflect the author's assessment of the high likelihood that the true effect is substantially different than what was determined by MA. Thus, based on this comprehensive SR, confidence in the benefits of CBPs for treating symptoms other than spasticity, or the risks of AEs with CBPs in patients with MS is low. Filippini et al concluded that CBPs, particularly nabiximols, have a place in therapy for management of moderate to severe spasticity in patients with MS insufficiently managed with other pharmacologic or nonpharmacologic options. Additionally, Filippini et al advised weighing benefits of using CBPs against the possible harms such as

intolerability and neuropsychiatric AEs, particularly since evidence of short- and long-term risks of CBPs is insufficient.[3]

Regarding CBPs for treatment of chronic neuropathic pain in people with MS, Filippini et al prioritized the 'critical' pain outcome of achieving at least a 50% reduction in pain. Only 1 small (n=48) trial reported this outcome, which demonstrated a significant benefit with dronabinol compared to placebo after 3 weeks with a very wide confidence interval, leading Filippini et al to conclude there was insufficient evidence for this outcome. Pain outcomes were also assessed by Filippini et al in 2 other ways: change from baseline in pain scores, and achievement of a ≥30% reduction in pain. For the 8 trials reporting change in baseline pain, the point estimate for the effect direction in nearly all studies (7 of 8) favored a modest benefit with cannabinoids (nabiximols, cannabis extract, or synthetic THC) compared to placebo. Certainty of the evidence for change in pain scores was downgraded 2 levels by the SR authors due to ROB and inconsistency. Another RCT reported a pain outcome of proportion of 339 patients achieving a ≥ 30% reduction in pain after 10 weeks, finding a benefit for nabiximols compared to placebo.[3]

Filippini et al described the evidence applicability to patients with varying characteristics and identified limitations of their review. Evidence from the SR by Filippini et al is most applicable to adults with various types of MS (progressive MS for spasticity) receiving cannabinoids as an adjunctive therapy when prior treatments were insufficient. It is inconclusive whether the results can be generalized to people without a history of cannabis use. There was substantial clinical and statistical heterogeneity, which may limit translation of the results to all patients with MS. Most concerns arising from the ROB analysis concerned "deviations from intended interventions", "measurement of outcome" or blinding. Many (50%) cross-over trials were judged as having a high risk of carry-over effects between treatment periods. Limitations of the SR were the inability to exclude bias from non-reporting, the possibility of inadequate reporting by included studies (SR authors did not reach out for clarification, etc.), and not accounting for the cross-over design in the meta-analysis.[3]

3.0 ADDITIONAL EVIDENCE FROM LITERATURE SEARCH

To supplement information from Filippini et al (2022), we searched for other recent SRs or RCTs including patients with MS treated with CBPs. No relevant RCTs published since 2022 were found; nine recent SRs were included. Refer to Appendix A Table A1 for an overview of other included SRs. Other SRs tended to be less comprehensive and rigorous than Filippini et al. In most cases, other SRs missed experimental studies included by Filippini et al (refer to Appendix A Table A2), so relative to Filippini et al, conclusions from other SRs may be biased due to not having a representative sample. Nonetheless, comparisons of the conclusions between Filippini et al 2002 and other recent SRs for primary outcomes addressed by the other SRs or select other efficacy outcomes are discussed below.

3.1 Spasticity

Other recent SRs reporting spasticity outcomes reached similar conclusions as Filippini et al for treatment of spasticity. All SRs consistently reported a statistically significant reduction in spasticity with CBPs versus comparator, primarily after short-term (eg, <12 weeks) treatment among people with MS.[4-6] Most of the evidence is from clinical studies using nabiximols (ie, 1:1 THC:CBD oromucosal spray containing 2.7 mg THC and 2.5 mg CBD per spray).[5,6] According to Martinez-Paz et al, who only included

studies from the past 5 years, the mean daily dose of nabiximols in recent RCTs and observational studies was 4-7 sprays, or approximately 11-19 mg of THC and 10-17.5 mg of CBD daily.[6] Details of the clinical trial population were not reported by each SR. Martinez-Paz et al described 2 RCTs of nabiximols as an add-on therapy to stable doses of 1-2 other medications for spasticity (oral baclofen and/or tizanidine)[6]; this aligns with Filippini et al's conclusion that their results are most applicable to patients considering cannabinoids when other therapies are insufficient.[3] Based on observational studies, benefits of nabiximols for spasticity may be maintained for at least 12 months of treatment.[6]

3.2 Chronic pain

Of recent SRs, only Longoria et al (2022) addressed pain outcomes among studies of people with MS treated with cannabis or cannabinoids. Like Filippini et al (2022), who included more RCTs,[3] Longoria et al found CBP treatment reduced pain intensity on numeric or visual analog rating scales after 1-6 months in 5 studies (1 RCT and 4 observational/descriptive studies all studying nabiximols oromucosal spray) among patients with MS.[5] Several of the studies included by Longoria et al were single-arm cohort studies lacking a comparator group, so the results should be interpreted cautiously. One single-arm cohort study reported many patients refractory to gabapentin for neuropathic pain benefited from adding nabiximols (57% demonstrated improvement from baseline at 1 month).[5]

3.3 Tremor

Filippini et al (2022) reported results from 1 small cross-over trial (n=14) of oral cannabis extract (Cannador, 2.5 mg THC per capsule) titrated to a maximum of 0.125 mg/kg of THC twice daily compared to placebo, which found no significant improvements in upper limb tremors with cannabis.[3] Pourmohammadi et al (2022) also found a lack of benefit from THC/CBD oromucosal spray (max of 48 sprays of 2.7 mg THC/2.5 mg CBD per spray; daily sprays during trial not reported) for 6 weeks or cannabis extract (Cannador oral capsules of THC 2.5 mg/CBD 1.25 mg/<5% other cannabinoids, titrated to a maximum of THC 25 mg/day) for 12 weeks for tremor compared to placebo. However, after long-term follow-up of the cannabis extract study (52 weeks), patient-reported tremor improved with oral cannabis extract compared to placebo. According to Pourmohammadi et al, results are inconclusive, but possibly, CBPs become effective for tremor after longer treatment.[7] Notably, tremor was not a primary outcome in the study demonstrating possible benefit.

3.4 Cognition

Autoimmune-mediated damage to the CNS in people with MS can lead to cognitive dysfunction.[8] Although the overall impact of cannabis use on cognitive function is debated,[9] cannabis use has also been associated with cognitive impairment (eg, impaired attention or short-term memory).[8,9] Therefore, the impact of CBPs on cognitive function in people with MS is an important safety consideration.

Filippini et al (2022) examined the cognitive effects of CBPs only in conjunction with other nervous system AEs (eg, dizziness, somnolence, headache), finding low certainty evidence that the combined odds of experiencing at least one of the AEs was increased in people with MS treated with cannabis compared to placebo.[3] Several recent SRs focused on cognitive outcomes only, providing a more in-depth evaluation than Filippini et al.

Four SRs evaluated cognitive outcomes in observational and experimental clinical studies of patients with MS receiving nabiximols (1:1 THC:CBD oromucosal spray) for a maximum of approximately 12 months.[8-11] Most SRs reported cognitive outcomes from specific cognitive instruments measuring various domains, finding that nabiximols treatment was not associated with worsened cognition[8-11] based on very-low quality evidence for both RCTs and observational studies per 1 SR.[10] The incidence of cognitive AEs (eg, 'disturbed attention' or 'memory impairment' reported without using a specific cognitive measurement tool) was evaluated by 1 SR for nabiximols compared to placebo among 13 RCTs within a maximum follow up of 48 weeks. Overall, the incidence of cognitive AEs with nabiximols were rare among RCTs (AEs occurred in 6 of 13 RCTs with only 32 overall events reported), but by meta-analysis, nabiximols treatment resulted in a significantly higher odds of disturbed attention compared to placebo. Most (94%) cognitive AEs in nabiximols clinical trials occurred in trials for off-label uses (primarily due to using higher than recommended maximal dosages, or for non-spasticity indications).[10] In one small (n=20) uncontrolled observational study, nabiximols treatment was associated with improved processing speed and auditory verbal memory in people with MS; however, the results should be interpreted cautiously given the small size, lack of control group, and inconsistencies with other studies.[11] Overall, SR authors suggested that nabiximols treatment at recommended dosages (eg, maximum of 12 sprays per day) poses minimal risk of increased cognitive AEs in patients with MS, at least for up to 12 months of treatment.[10,11]

Based on SRs including studies of non-nabiximols CBPs, the possibility of increased cognitive AEs among people with MS receiving cannabis cannot be excluded. Two SRs evaluated experimental or observational studies including a few exposures to other cannabinoid/cannabis types such as full-spectrum cannabis oils, smoked whole-plant cannabis (only 1 dose), oral cannabis extracts, or unknown cannabis (cross-sectional studies of people reporting cannabis use).[8,9] Heterogeneous cannabis products with incomplete reporting of details of cannabis exposures and some inconsistencies among studies prevents definitive conclusions about the impact of whole-plant cannabis on cognition.[8] Nonetheless, Landrigan et al found multiple instances of cognitive impairment, particularly impaired attention and working memory, among studies of chronic cannabis use in patients with MS. A neuroimaging study of people with MS found patients with ongoing regular cannabis use had more memory and attention deficits than matched control MS patients without cannabis use. Additionally, in a small (n=20), non-blinded, randomized withdrawal study among people with MS regularly using smoked cannabis (mean dose 2g/day for >5 years), people who stopped cannabis use for 28 days demonstrated significant improvements in multiple cognitive domains (ie, verbal and visuospatial memory, auditory and working memory, processing speed, verbal fluency) compared to similar patients randomized to continue cannabis use.[8] Landrigan et al concluded that "Existing data suggest that cognition may be differentially impacted in [people with MS] depending on the type of product, the duration use, and the indication" (page 1).[8] Similar to Landrigan et al, Wieghorst et al concluded that it is impossible to make definitive conclusions about the effects of CBPs on cognitive function; while most high-quality evidence suggests any negative impact is relatively small, a long-term negative cognitive impact cannot be excluded.[9]

SR authors Wieghorst et al (2022) suggested that CBPs containing low-moderate doses of THC (eg, THC <19 mg) are unlikely to affect cognition based on 2 cross-over RCTs of patients using inhaled cannabis for neuropathic pain.[9] Another SR of only studies of MS patients receiving nabiximols found that dosages exceeding the maximal recommended nabiximols dose were associated with cognitive adverse effects.[10] However, Motaghi et al identified inconsistencies in the THC dosages eliciting cognitive adverse effects

in people with MS; multiple studies of THC doses from nabiximols exceeding 19 mg did not find negative effects on cognition.[11] Overall, results from these SRs are insufficient to conclude there is a clear threshold THC dose where doses below the threshold prevent long-term cognitive adverse effects, particularly since the supportive trials cited by Wieghorst et al likely measured acute effects on cognition and included few patients with MS.[12,13]

3.5 Neurogenic Bladder Symptoms

Lower urinary tract symptoms (eg, urinary frequency, urgency, reflex or urge incontinence) are common among people with MS, frequently caused by detrusor muscle overactivity.[14] Multiple receptors modulated by cannabinoids (eg, cannabinoid [CB_1 and CB_2], or transient receptor potential vanilloid 1 [TRPV1]) are expressed in the urinary tract lining, detrusor muscle and/or bladder motor or sensory neurons.[15]

Bapir et al conducted a SR of various treatments (cannabinoids and others) for overactive bladder among people with neurological diseases, concluding that THC or CBD may improve incontinence, nocturia, and daytime void frequency in patients with MS based on 2 trials.[16] Add-on therapy with nabiximols (mean 8.91 sprays of 2.7 mg THC/2.5 mg CBD per spray) for 8 weeks in a parallel group RCT among 135 patients with MS and an overactive bladder who had failed first-line treatments did not improve the number of urinary incontinence episodes compared to placebo (the primary outcome). However, improvements in secondary bladder symptoms of number of daily nocturia episodes, number of daily voids, and Patient's Global Impression of Change were observed for nabiximols compared to placebo.[3] A second placebo-controlled RCT evaluated treatment with oral THC (n=174) or oral cannabis extract (n=181) for 15 weeks as a treatment for urge incontinence in a subgroup of a larger trial originally designed for evaluating spasticity. Both THC and cannabis extract significantly reduced the frequency of patient-reported (by diary) urinary incontinence versus placebo (adjusted percent reduction from baseline rate: THC, 33%; cannabis extract, 38%; placebo, 18%); however, there were no differences between groups in incontinence symptoms per the King's Health questionnaire.[14]

3.6 Disease-Modifying Outcomes

We did not find any recent RCTs or SRs of disease-modifying outcomes in people with MS treated with CBPs. One SR which was excluded by this review due to the lack of relevant studies searched for studies reporting neuroprotective outcomes (eg, measuring myelination and disability) in patients with MS.[17] According to that SR, there is a lack of human studies using CBPs for those outcomes published through at least January 2020.[17]

One included SR primarily reviewed animal or other preclinical studies to examine the potential disease-modifying effect of cannabinoids on MS. They concluded that cannabinoids might modify the MS disease process by suppressing immune-mediated CNS destruction, exerting anti-inflammatory neuroprotective effects, or promoting remyelination, based on preclinical research.[5] This SR also included one small (n=33 including 19 responders and 14 non-responders) observational study that examined the change in whole-blood transcriptome profile of patients receiving nabiximols (mean 7-8 sprays daily) for moderate-severe spasticity between baseline and 4 weeks. Results from this small study suggest that response to nabiximols treatment is associated with upregulation of protein synthesis genes, and downregulation of genes associated with the immune system (primarily), cell migration, nervous system,

and some cancers. According to the authors of that study, the immunomodulatory changes suggested a role of nabiximols in inhibiting pro-inflammatory cytokines, regulating T-cell differentiation, and downregulating migratory leukocytes, in agreement with prior animal studies.[18]

4.0 RECRUITING CLINICAL TRIALS

ClinicalTrials.gov was queried for registered clinical trials of cannabis or cannabinoids in patients with MS, yielding 36 search results. The following 3 studies with a "recruiting" status that involve cannabis or cannabinoids as a treatment in patients with MS were identified:

- NCT05092191: "Cannabis as a Complementary Medicine in Multiple Sclerosis (CAN-SEP)" Phase 2 randomized trial comparing cannabis oil to placebo for management of spasticity in adults. Anticipated to be completed in March 2025.[19]
- NCT05269628: "Mechanisms of Cannabidiol in Persons with MS: the Role of Sleep and Pain Phenotype." Phase 2 randomized trial with THC, CBD, or placebo interventions for management of sleep in adults with MS. Anticipated to be completed in June 2026.[20]
- NCT03944447: "Outcomes Managed National Integration with Cannabis with Medicine." Phase 2 non-randomized trial of a cannabis inhaler device to chronic pain (including some patients with MS) among people ≥ 7 years. Anticipated to be completed in December 2025.

These studies may be of interest at future follow up of this topic.

5.0 CONSIDERATIONS FOR UPDATES TO THE CRRB GUIDANCE DOCUMENT

The following are considerations for possible updates to the CRRB guidance document on the suggested use of medical cannabis for the treatment of MS based on the evidence reviewed in the report.

5.1 Considerations for Graded Conclusions

- The CRRB may consider reaffirming or revising the evidence grades for graded statements in current guidance. Previously, the CRRB used the National Academies of Sciences, Engineering, and Medicine (NASEM) level of evidence (LOE) categories for therapeutic effects from their 2017 report on cannabis.[2] Refer to Appendix B for details about the NASEM criteria for each LOE.
    - Current statements for management of MS *spasticity* and *neuropathic pain* are graded (respectively) as *substantial* and *moderate* in quality. Current guidance also addresses cannabis use for spasticity among people without MS; because this population was not addressed by this review, we suggest waiting to evaluate that statement.
        - *Spasticity:* Results from recent SRs[3,5,6] support the CRRB's prior conclusion that there is substantial evidence of benefit from oral cannabinoids for reducing spasticity of MS.
        - *Neuropathic pain:* Previously, the CRRB considered there to be moderate evidence for treatment of neuropathic pain of MS with CBPs. Filippini et al (2022) reviewed RCTs of treatment of neuropathic pain with CBPs and graded the evidence as low- or very-low-quality depending on the pain outcome. Despite the low evidence grades (due to ROB, inconsistency, and/or imprecision) for pain outcomes, Filippini et al reported that nearly all trials with data appropriate for their analysis found a direction of effect favoring CBPs to

placebo for pain reduction.[3] Overall, the moderate evidence designation for this outcome (per NASEM ratings[2]) is reasonable. Nonetheless, given the quality concerns identified by Filippini et al, the CRRB may wish to perform their own evaluation about the continued appropriateness of the moderate evidence designation.

- As desired, the CRRB may consider adding graded conclusions for outcomes included by recent SRs not previously addressed in CRRB guidance, such as tremor and overactive bladder symptoms. Alternatively, the CRRB could elaborate on clinical evidence for these outcomes as non-graded statements in the guidance document.
  - Current guidance cites recommendations from the 2013 Health Canada review, which found pre-clinical studies support a benefit of THC, CBD and nabiximols for improving tremor, and limited evidence from clinical studies showing cannabinoids (dronabinol, nabiximols, THC/CBD) improve bladder dysfunction symptoms.[1] However, we found 4 clinical studies included by 2 SRs addressing tremor,[3,7] which could support a statement about tremor in CRRB guidance. Refer to Section 3.3 and Appendix A for information about tremor. Two trials evaluated bladder outcomes in people with MS treated with CBPs[3,16]; refer to Section 3.5 for information about those studies.

5.2 Additional Considerations

As desired, the CRRB may consider adding additional details from clinical studies of CBPs for patients with MS as non-graded summary text in the revised guidance document. For example, the following information might be useful to address in guidance:

- Cognitive outcomes
  - Cognitive concerns are addressed in the current guidance by referencing a single, small, cross-sectional study showing cognitive adverse effects with (primarily) smoked cannabis; patients in this study started cannabis at an early age (mean 17 years) and reported high-intensity use (ie, long duration, with 72% reporting daily use) of unknown cannabis quality.[21] The cross-sectional study was included in the recent SR by Landrigan et al (2022), who also described cognitive outcomes from 17 additional experimental or observational studies.[21] Refer to Section 3.4 and Appendix A for information from multiple recent SRs addressing cognition that may be used to supplement cognitive information in the guidance document. Current guidance also advises providers to monitor for adverse cognitive events in people with MS receiving cannabis, particularly with long-term use,[1] which is reasonable based on available evidence.
  - Additional details about treating spasticity with CBPs (eg, CBP types and dosages, and clinical trial patient characteristics)
    - Based on the Filippini et al (2022) SR of RCTs, most evidence for treating MS spasticity is for nabiximols (61.5% of trials with spasticity outcomes). Other studied interventions in RCTs were primarily oral THC products (eg, dronabinol, or THC extract). Only 2 RCTs cited by Filippini et al evaluated inhaled herbal cannabis; one of these studies only evaluated outcomes at 3 days, and the other was terminated early due to insufficient recruitment.[3] Evidence for treating spasticity with whole-plant cannabis and routes of administration other than oral or oromucosal is limited.
    - When reported, the mean daily number of nabiximols oromuscosal sprays for treating spasticity ranged from approximately 4-8.5 daily,[3,5,6] for a dose of approximately 11-23 mg

of THC with 10-21 mg of CBD daily. RCTs included by Filippini et al reported a mean range of 6.4 to 8.5 sprays daily (median of 6.4 sprays daily in 1 trial),[3] which is similar to the daily 4-7 range reported by 2 other SRs also including observational studies.[5,6]

- According to Filippini et al, most RCTs for treatment of spasticity enrolled patients with MS who had moderate-to-severe spasticity symptoms insufficiently responsive to other oral spasticity treatment options. Studies of patients with MS and chronic pain typically required patients to have failed other treatment options.[3]

6.0 METHODS

This brief evidence report focused on results from the SR by Filippini et al (202)2 from the Cochrane organization.[3] To supplement the findings by Filippini et al, two major bibliographic databases (Ovid-Medline and Embase) were searched for SRs or RCTs published after the Filippini et al review (2022-2023). Literature searches of Ovid-Medline and Embase were based on the search strategy of Filippini et al, modified to include additional free text and controlled vocabulary terms for cannabis or cannabinoids. Search results were filtered for SRs and RCTs using a broadened SR filter developed by McMaster University for Ovid-Medline,[22] an independently-derived SR filter for Embase, and RCT filters from the Cochrane Organization for both databases.[23] Conference reports were excluded from the RCT search of Embase. Refer to Appendix C for details of the searches of Ovid-Medline and Embase. The ClinicalTrials.gov database was queried on April 21st of 2023 for studies of patients with multiple sclerosis treated with cannabis, cannabidiol, tetrahydrocannabinol, nabiximols, or Sativex.

Literature search results were reviewed by a single author for inclusion. SRs of clinical studies including patients with MS receiving any type of cannabis or cannabinoid (plant-based or synthetic) and that included at least one experimental study were included. Reviews not including details of their search strategy and/or not using a systematic process were excluded. In addition, since multiple relevant SRs of primary studies were identified, SRs exclusively including systematic reviews were excluded.

Primary results, methodology, and conclusions were extracted from Filippini et al (2022). Results relevant to the treatment of patients with MS and brief notes about study methodology were extracted from other included SRs and summarized. Search results from ClinicalTrials.Gov were filtered for studies with the “recruiting” status, and brief details about plans for those studies planning to use a CBP in patients with MS were extracted. All data extraction was performed by a single author.

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APPENDIX A – EVIDENCE FROM OTHER RECENT SYSTEMATIC REVIEWS

Table A1. Overview of Methodology and Results from Recent Systematic Reviews of Studies of Patients with MS Treated with a Cannabis- or Cannabinoid-based Product

Author, Publication Year N included studies n included participants	Study Design Databases Searched Date of Last Literature Search	Objective/PICOS	Included CBP Interventions	Author Conclusions
Martinez-Paz C et al 2023[6] N = 5 (2 RCTs; 2 observational; 1 SR of observational studies) n = 42-3989 patients per study (total = 4604)	SR PubMed, Scopus, EMBASE, WOS, Cochrane Library August 2022 (varied by database)	**P:** MS with resistant spasticity **I:** cannabinoids (synthetic modified cannabinoids and 'Hemp' products with <0.3% THC excluded) **C:** any comparator **O:** Ashworth scale (NRS) for spasticity severity (range from 0 to 4, with 4 indicating severe symptoms) **S:** Experimental, Observational, or SR published from 2017-2022. Studies meeting <50% of the study-design specific reporting checklist criterion (CONSORT for RCTs, STROBE for observational, and PRISMA for SRs) were excluded.	Nabiximols (N=5), the mean daily dose was 4-7 sprays among all studies. Duration: range 12 weeks (observational and RCTs), and a median of 30 days to 4.5 years (SR)	In both RCTs, add-on therapy to stables doses of 1-2 other medications (oral baclofen and/or tizanidine) with nabiximols significantly reduced spasticity; onset of benefit versus placebo was at about 2 weeks, and this benefit persisted until the end of the 12-week trial. Most results from observational studies were reported descriptively, so it's unclear if significant benefits were achieved. Descriptively, most patients achieved clinically significant improvements in spasticity and/or improvements in activities of daily living. According to the SR of observational studies, spasticity benefits were maintained for at least 12 months. Regarding safety, mostly mild-moderate AEs were reported in RCTs with the most frequent AEs (listed in order of most to least frequent) being vertigo, somnolence, dizziness, diarrhea, nausea; one SAE occurred, which was considered unrelated to THC/CBD. SAEs in observational studies were rare (<1%), with most SAEs being CNS-related. One observational study descried 7% of patients exceeding the maximum recommended dose, but Martinez-Paz described that "…despite this, no studies have reported cases of abuse or dependence on treatment" (page 7).[6] Further, authors described "The discontinuation rate for these treatments is around 40% due to lack of effectiveness and adverse events" (page 1).[6] *Quality assessment:* This SRs did not report these details for each study. Studies not reporting adequate details were excluded.
Motaghi E et al 2023[11] N = 10 (2 cross-over trials, 3 parallel-group trials, 2 observational; 7 studies of people with MS) n = 16-160 per study (total = 510)	SR PubMed, Scopus, Web of Sciences September 2022	**P:** Any (including healthy or health condition) **I:** THC and CBD together, oromucosal **C:** placebo or non-administered control (eg, baseline measurement) **O:** Cognition **S:** Human studies with a statistical comparison of THC/CBD to control. Abstracts, editorials, and non-peer-reviewed articles were excluded.	Nabiximols (N=9) Whole-plant extract (N=1) Duration: range 1 to 365 days	Nearly all studies found THC:CBD did not significantly different from placebo (true in patients with MS, HD, and healthy patients) for assessed cognitive domains (eg, attention, working memory, orientation, memory recall, processing speed, episodic memory). Only 1 RCT among people with MS (4 weeks, at a dose of THC 25.9 and CBD 24 mg/day) reported a potentially detrimental cognitive effect of THC/CBD, and that was limited to long-term memory storage during a selective reminding test. Other cognitive domains tested in that trial were not significantly affected by THC/CBD compared to placebo. One observational study found a potentially beneficial effects of THC/CBD on processing speed and auditory verbal memory (in contrast to other included studies measuring those domains). *ROB rating:* Clinical trials rated as having a low to unclear ROB
Bapir et al 2022[16] N = 52, with 10 studies included in the MA (2 RCTs addressing CBPs) n with bladder symptoms = 135-522	SRMA PubMed, Embase April 2022	**P:** People with neurologic conditions with overactive bladder symptoms (the CBP trials were patients with MS) **I:** Any pharmacologic or non-pharmacologic treatment for overactive bladder **C:** Not reported; CBP trials used a placebo comparator. **O:** Various overactive bladder outcomes including frequency of daytime and nighttime voids, frequency of incontinence or urgency episodes, quality of life, and urodynamic measurements **S:** Single- or double-blinded RCTs	Nabiximols (N=1), mean 8.91 sprays; Oral THC or cannabis extract (2.5 mg THC and 1.25 mg CBD per capsule), both titrated to max of 25 mg THC daily (N=1)	Add-on therapy with nabiximols for 8 weeks was not superior to placebo for the number of urinary incontinence episodes (primary outcome). Improvements in secondary bladder symptoms of number of daily nocturia episodes, number of daily voids, and Patient's Global Impression of Change were observed with nabiximols compared to placebo. In the second trial, both THC and cannabis extract significantly reduced the frequency of patient-reported (by diary) urinary incontinence versus placebo (adjusted percent reduction from baseline rate: THC, 33%; cannabis extract, 38%; placebo, 18%). No MA was performed with these trials. In the trial of cannabis extract, the treatments were reportedly well-tolerated. In the other trial, dizziness, disorientation, and dissociation occurred numerically more frequently with nabiximols compared to placebo. *ROB rating (Cochrane ROB scale):* Both trials were rated as low risk on 4 domains and some concerns on the remaining 2 domains. Bapir et al concluded that THC or CBD *may* improve incontinence, nocturia, and daytime void frequency in patients with MS based on the 2 trials.

Abbreviations: AE, adverse event; C, comparator; CBP, cannabis- or cannabinoid-based product; CBD, cannabidiol; CI, confidence interval; CNS, central nervous system; GRADE, Grading of Recommendations, Assessment, Development, and Evaluations; I, intervention; MA, meta-analysis; MS, multiple sclerosis; O, outcome; OR, odds ratio; P, population; RCT, randomized controlled trial; ROB, risk of bias; S, study design; SAE, serious adverse event; SR, systematic review; THC, tetrahydrocannabinol;

Dykukha et al 2022[10] N = 17 (13 DBPCT, and 4 observational studies) n = 22-160 per study (total = 2,321)	SRMA with qualitative summary of RCTs and observational studies reporting cognitive assessment outcomes; and SRMA of RCTs reporting the incidence of cognitive AEs PubMed, CENTRAL, Epistemonikos, Physiotherapy Evidence Database, Google Scholar, ClinicalTrials.Gov, EudraCT (European clinical trials database) April 2021	**P:** People with MS and spasticity **I:** Nabiximols oromucosal spray **C:** Any comparator **O:** Cognitive function using any instrument or measurement **S:** Any study design published as full text or in an official study register	Nabiximols (N=17), in RCTs the maximal allowed dose ranged from 12 sprays daily to 48 sprays daily Duration: 3 to 48 weeks	*Qualitative summary of cognitive assessment (3 RCTs and 4 observational studies):* Most RCTs and observational studies did not find statistically significant differences between nabiximols and placebo for cognitive assessments (eg, processing speed, executive functions, verbal memory, visual memory, attention). One observational study reported a beneficial effect of nabiximols on one cognitive domain (verbal memory), and another observational study reported decreased executive functions, but only when tested along with a postural test. *Quantitative and qualitative summary from up to 13 RCTs only:* Cognitive AEs with nabiximols were reported by 6 of 13 RCTs, with 'disturbed attention' being the most common type of cognitive AE (19 events, 59%). Most cognitive AEs (93.8%) were reported by studies using maximal nabiximols doses exceeding the maximal recommended labeled dose (12 sprays daily). Random effects meta-analysis of the incidence of memory impairment, impaired psychomotor skills, or disturbed attention only found a significantly impaired attention with nabiximols versus placebo (OR 7.06, 95% CI 1.86 to 26.77). The point estimate for memory and psychomotor skills impairment favored greater impairment with nabiximols versus placebo, but this was not statistically significant, and the confidence interval was very wide, suggesting high imprecision. *Evidence GRADE Rating:* Low for incidence of adverse cognitive effects (eg, 'disturbed attention', 'memory impairment') in RCTs (13 RCTs with 2040 patients). Very low for cognitive function measured using specific instruments in RCTs (3 RCTs with 312 participants). Very low for cognitive function measured using specific instruments in observational studies (4 studies, 3 prospective and 1 retrospective, with 514 participants). *ROB rating for RCTs:* Overall moderate ROB
Ergul et al 2022[4] N = 10, including 1 randomized crossover cannabis trial with an 11-day washout period n = 30 (cannabis trial only)	SR PubMed, Scopus, Web of Science, Elsevier, Proquest, Sage Journals, Psysiotherapy Evidence Database, and Cochrane Library March-June 2019	**P**: People with confirmed MS **I:** Pharmacologic of non-pharmacologic interventions for spasticity **C:** Any control including placebo, active, or no treatment **O:** Spasticity using a spasticity scale, walking tests, balance on the Berg balance scale, or Time Up and Go **S:** RCTs or interventional studies using a pre-post design published 1964 to 2019. To be included, studies must have assessed multiple outcome domains of interest (ie, spasticity, functional mobility, balance, and gait ability and gait speed).	Smoked cannabis once daily Duration: 3 days	In the short crossover trial, cannabis cigarettes significantly improved spasticity on the Modified Ashworth scale (by an average of 2.74 points) and pain on the Visual Analog Scale (by an average of 5.28 points) compared to placebo. Cannabis cigarettes were not significantly better than placebo cigarettes for the timed walking test. Authors of this SR concluded that few experimental studies of people with MS and spasticity have assessed functional clinical outcomes. *ROB rating:* The cannabis trial was rated as having a low ROB for all assessed domains on the Cochrane ROB scale except for "Clarity of the Intervention details", which was rated as high ROB.

Abbreviations: AE, adverse event; C, comparator; CBP, cannabis- or cannabinoid-based product; CBD, cannabidiol; CI, confidence interval; CNS, central nervous system; GRADE, Grading of Recommendations, Assessment, Development, and Evaluations; I, intervention; MA, meta-analysis; MS, multiple sclerosis; O, outcome; OR, odds ratio; P, population; RCT, randomized controlled trial; ROB, risk of bias; S, study design; SAE, serious adverse event; SR, systematic review; THC, tetrahydrocannabinol;

Landrigan et al 2022[8] N = 18 (7 cross-sectional, 5 crossover, 3 RCTs, 1 observational, 1 retrospective real-world data) n = 6-396 per study, all except 1 with <100 participants; (total = 787)	SR MEDLINE, PsychINFO, EMBASE, CENTRAL, CINAHL June 2020	**P:** People diagnosed with MS (per physician and/or per McDonald criteria) **I/E:** Past month cannabis or cannabinoid use **C:** Any or no comparator (ie, normative data comparison) **O:** Cognition measured using a validated tool **S:** Primary human studies reporting empirical data	Nabiximols (N=5), nabilone (N=1), oral capsule cannabis extract (N=1), THC as Namisol (N=1), medical cannabis cigarettes (N=1), recreational or street cannabis use (N=7) Administered by oromucosal spray (N=5), smoking (N=9), or orally (N=3) Duration not specified by SR (N=7); randomized withdrawal from cannabis, 28 days (N=1); duration range 1 dose to a mean of 43 ± 15 months in remaining studies.	Included studies were heterogenous in terms of their design, cannabinoid intervention, and duration, among other factors, which prevented the authors from performing a MA and prevents definitive conclusions from the study. While not performed for every study, the SR authors thought most studies attempted to control for confounding. Underreported issue by studies were details of the cannabis use, and whether patients were also receiving benzodiazepines. Studies of medicinal cannabinoid preparations (eg, nabiximols) did not report the amount of time between cannabinoid ingestion and cognitive testing, unlike most whole-plant cannabis studies. Overall, most studies of short-term treatment nabiximols found no cognitive impairments versus controls. Results were mixed, but overall, studies of whole-plant cannabis found negative effects of cannabis on cognition (primarily on attention and working memory), especially after chronic use. A neuroimaging study observed reduced grey and white matter volumes in areas of the brain affecting cognition (medial and lateral temporal, thalamus, basal ganglia, prefrontal cortex) in patients with MS who smoked cannabis; cannabis use was also associated with slower information processing. Notably, the brain imaging study included patients apparently using cannabis recreationally. Studies of whole-plant cannabis (recreational or medical) were hampered by a lack of detail about cannabis exposures; this also complicated indirect comparisons of outcomes between studies of different dosage forms. In a small study (n=20) of people with MS with a history of using cannabis (mean 2 grams/day) ≥4 times per week who were randomized to continue or withdraw cannabis that performed cognitive tests outside the peak acute effects of cannabis, people who stopped cannabis for 28 days performed significantly better on some memory, processing speed, and executive function tests than people who continued cannabis. *Quality rating (expressed as the average % of quality criteria met on the Mixed Methods Appraisal Tool for an individual study):* Range 40-100%, with all studies except for 1 rated as high (MMT average % score >75%).
Longoria et al 2022[5] N = 28 (14 clinical studies and 14 non-clinical studies; of the clinical studies, included 5 RCTs and 9 observational or descriptive studies) n = 15-427 per study (total = 2749)	SR PubMed, EBSCO Host, ProQuest Unknown search date; included articles for the past 15 years (2007+), and received for publication in Jan 2022	**P:** People with MS, or animal studies using experimental MS (or similar) models **I:** Cannabis or cannabinoids **C:** Any or no comparator **O:** Spasticity, pain, sleep quality, neurogenic bladder outcomes, inflammation (primary); disability, AEs, drug interactions (secondary). **S:** Experimental, observational, or descriptive studies.	In clinical studies: Nabiximols oromucosal spray (N=13). When reported, mean daily sprays ranged from 3.8 to ~8. One trial allowed up to 48 sprays daily. Self-reported variable cannabis formulations classified by the THC/CBD ratio (N=1) Duration: range 4 weeks to 12 months (not reported for the cross-sectional survey)	Studies (N=9) evaluating change in spasticity reported a clinically significant benefit from treatment for some patients, or a statistically significant reduction in spasticity (range –0.5 to –0.83 difference from comparator on the numerical rating scale). Modest benefits of nabiximols for improving pain were also observed (5 studies). Studies reporting lower urinary tract dysfunction outcomes (n=3) did not fine a benefit of nabximols for urinary incontinence, but nabximols treatment was associated with improvements in some other urinary symptoms (eg, bladder dysfunction, number of daily voids, and daily nocturia episodes). Improvements in self-reported sleep quality were reported by 1 RCT, a descriptive study, and a cross-sectional survey. Longoria et al concluded: "Medical marijuana studies conducted between 2007 and 2021 have demonstrated, with moderate certainty of evidence, that add-on therapy with 1:1 CBD/THC cannabinoid oromuscosal spray mixtures is effective within a narrow therapeutic window to modestly improve primarily subjective measures of spasticity, pain, and bladder- and sleep-related quality of life in responders within weeks of stating treatment. Some benefits are maintained beyond 6 months to 12 months, but some effects may wane with prolonged use" (pages 22-23).[5] *ROB ratings (based on attrition and performance bias):* For spasticity outcomes, rated as not serious for 9/9 articles. For pain outcomes, rated as not serious for 3/5 articles and serious for the remaining 2 articles. For lower urinary tract dysfunction, rating as not serious for 3/3 studies. For sleep disturbance outcomes, rates as serious for 1 article and not serious for the remaining articles. Nearly all articles were rated as having a serious risk of confounding due to concomitant medications; the remaining two articles were rated as having a very serious or unknown risk of confounding. *Evidence quality ratings (using GRADE):* For spasticity, rated as low (3 studies) to moderate (6 studies). For pain, rated as very low (1 study), low (2 studies) or moderate (2 studies). For lower urinary tract dysfunction, rated as low (1 study) to moderate (2 studies). For sleep disturbances, rated as low (1 study) to moderate (1 study)

Abbreviations: AE, adverse event; C, comparator; CBP, cannabis- or cannabinoid-based product; CBD, cannabidiol; CI, confidence interval; CNS, central nervous system; GRADE, Grading of Recommendations, Assessment, Development, and Evaluations; I, intervention; MA, meta-analysis; MS, multiple sclerosis; O, outcome; OR, odds ratio; P, population; RCT, randomized controlled trial; ROB, risk of bias; S, study design; SAE, serious adverse event; SR, systematic review; THC, tetrahydrocannabinol;

Pourmohammadi et al 2022[7] N = 26; 4 CBP trials (3 PCDBT and 1 PC parallel trial) n (for CBP trials, the patient subset with tremors) = 14-391 (total = 787)	SR PubMed, Scopus, Embase, Web of Science March 2021	**P:** Adults with MS **I**: Any pharmacologic treatment (CBPs were one of several) **C:** Placebo or control **O:** Tremor measured using a validated method; and adverse effects **S:** Randomized or non-randomized clinical trials	Cannador (cannabis extract with 2.5 mg THC per capsule; Sativex THC/CBD oromucosal spray, 2.5-120 mg of each daily; and dronabinol (THC) or cannabis extract containing 2.5 mg THC/1.25 mg CBD per capsule, both titrated to a maximum of 25 mg/THC per day (this was studied in 2 trials, including a 52-week follow-up of the initial 15-week trial) Duration: range 2-52 weeks	The 3 trials of acute (2-15 weeks) treatment with oral or oromucosal Cannador, Sativex and or cannabis extract did not show a benefit for the CBPs compared to placebo for tremor in people with MS. However, the longer follow-up of the oral cannabis extract trial (maximum of THC 25 mg daily), which contained only people who voluntarily continued treatment, demonstrated a benefit of treatment for tremor at 27 and 52 weeks (presumably compared to baseline). All trials reported minor AEs in patients receiving the CBPs. Examples of AEs (reported by at least 1 trial): drowsiness and lightheadedness, memory disturbance, dysphoria, euphoria, increased appetite, dry mouth, cognitive and behavioral changes, constipation, and diarrhea. In at least 1 trial, the rate of any serious AEs was similar between the active and placebo group. Authors of this SR concluded that none of the studied treatments for tremor, including CBPs, have demonstrated significant and consistent benefits for tremor; additional trials with large sample sizes are needed. *ROB rating per the JADAD scale:* The 4 publications were rated as having a low ROB (scores between 3-5 on the JADAD scale). *Methodological quality rating per the Critical Appraisal Skills Programme RCT checklist:* The 4 publications were rated as having a moderate (1 trial) to high (3 trials) status.
Wieghorst 2022[9] N = 23 (16 RCTs, 1 case-control study, and 6 pre-post studies; 11 studies were only patients with MS) n = 11-160 per study (total = 917)	SR EMBASE, PsycINFO, PubMed, Scopus April 2021 (final search)	**P:** Any human adults except for people with severe neurodegenerative diseases or cancer-related pain **I:** Medical cannabis **C:** People serving as own control (eg, cross-over design) **O**: Cognitive functions **S:** Studies using patients as own control reporting measures using a recognized cognitive test, and that reported sufficient details about the cannabis dose. Must have been published during or after 1996.	Nabiximols (N=8); Epidiolex (N=2); Aerosolized granulated cannabis plant with primarily THC via the Synqe inhaler (N=1); sublingual spray with 2.5 mg THC and/or CBD (N=1); gelatin capsules of primarily THC 2.5-5 mg (N=3); smoking/vaping cannabis (N=5); full-spectrum cannabis oil (N=1); choice of smoking, inhalation or oil products containing 1:1-3:1 THC:CBD; and a randomized withdrawal from regular cannabis use Among the studies, when reported, the max dose of THC was about 34 mg.	Among studies of nabiximols of which all studies except 1 included people with MS, the majority (6/8) did not show significant differences in cognition. One nabiximols study showed cognitive improvement in processing speed auditory verbal memory at 6 months, and the remaining study showed executive function impairment with nabiximols, but only when tested simultaneously with a postural sway test. Another study of patients with MS who were randomized to stop regular cannabis use showed cognitive improvements 28 days after stopping cannabis compared to people who continued cannabis. One 2-week crossover RCT of people with MS found people receiving THC had impaired orientation, memory and concentration, attention, working memory and processing speed after a single dose of 4 inhalations of 4% smoked cannabis. Most remaining studies among patients without MS did not report cognitive impairments, except for 3 studies of smoked/vaporized cannabis among people with chronic pain. *Global quality ratings (among all included studies):* weak (5, 22%), moderate (9, 39%), strong (9, 39%)

Abbreviations: AE, adverse event; C, comparator; CBP, cannabis- or cannabinoid-based product; CBD, cannabidiol; CI, confidence interval; CNS, central nervous system; GRADE, Grading of Recommendations, Assessment, Development, and Evaluations; I, intervention; MA, meta-analysis; MS, multiple sclerosis; O, outcome; OR, odds ratio; P, population; RCT, randomized controlled trial; ROB, risk of bias; S, study design; SAE, serious adverse event; SR, systematic review; THC, tetrahydrocannabinol;

Table A2. Comparison of Experimental Studies of Cannabinoids in Patients with MS included by SRs[a]

Author, Publication Year	Zajiceck 2003	Wade 2003	Fox 2004	Vaney 2004	Wade 2004	Kurzthaler 2005	Rog 2005	Zajicek 2005	Freeman 2006	Collin 2007	Aragona 2009	Collin 2010	Kavia 2010	Novotna 2011	Corey-Bloom 2012	Notcutt 2012	Langford 2013	Vachova 2014	Leocani 2015	Van Amerongen 2017	Markova 2019	Feinstein 2019	Meuth 2020	NCT01-606176
Martinez-Paz et al, 2023																					X		X	
Motaghi et al, 2023		X			X		X				X							X						
Bapir et al, 2022									X				X											
Conte et al, 2022														X							X			
Dykukha et al, 2022					X		X			X	X		X	X		X	X	X	X		X			X
Ergul et al, 2022															X									
Landrigan et al, 2022			X	X		X	X				X				X					X		X		
Longoria et al, 2022										X		X	X	X			X							
Pourmohammadi et al, 2022	X		X		X			X																
Wieghorst et al, 2022		X		X	X		X				X				X			X				X		
Filipinni et al, 2022[b]	X	Excl	X	X	X	Excl	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	Excl	X	X

[a] 'X' indicates that experimental study was included by the SR. Primary studies were classified as experimental based on the description by SRs, which may be inaccurate. Note that SRs other than Filippini et al focused on a subset of outcomes, which explains some differences in included trials.

[b] Other studies included by Filippini et al only: Killestein 2002; NCT00682929; Schimrigk 2017; Svendesen 2004; Turcotte 2015; Zajicek 2012; and Zajicek 2013. Note that although Filippini et al identified these studies, not all studies were included in meta-analyses.

Abbreviations: Excl, excluded; MS, multiple sclerosis; NCT, National Clinical Trial number; SR, systematic review

APPENDIX B – NATIONAL ACADEMIES LEVEL OF EVIDENCE CATEGORIES

Historically, the CRRB used level of evidence (LOE) categories from the 2017 National Academies of Sciences, Engineering, and Medicine (NASEM) report for therapeutic recommendations in guidance documents.[2] Criteron for each LOE according to the NASEM report are shown in Table B1.

Table B1. Levels of Evidence for Therapeutic Effects from the 2017 NASEM Cannabis Report

Conclusive Evidence
• "There is strong evidence from randomized controlled trials to support the conclusion that cannabis or cannabinoids are an effective or ineffective treatment for the health endpoint of interest" (page 7).[2] • "For this level of evidence, there are many supportive finfings from good-quality studies with no credible opposing findings. A firm conclusion can be made, and the limitation of the evidence, including chance, bias, and confounding factors, can be ruled out with reasonable confidence" (page 7).[2]
Substantial Evidence
• "There is strong evidence to support the conclusion that cannabis or cannabinoids are an effective or inffective treatment for the health endpoint of interest" (page 7).[2] • "For this level of evidence, there are several supportive findings from good-quality studies with very few or no credible opposing findings. A firm conclusion can be made, but minor limitations, including chance, bias, and confounding factors, cannot be ruled out with reasonable confidence" (page 7).[2]
Moderate Evidence
• "There is some evidence to support the conclusion that cannabis or cannabinoids are an effective or ineffective treatment for the health endpoint of interest" (page 8).[2] • "For this level of evidence, there are several supportive findings from good- to fair-quality studies with very few or no credible opposing findings. A general conclusion can be made, but limitations, including chance, bias, and confounding factors, cannot be ruled out with reasonable confidence." (page 8).[2]
Limited Evidence
• "There is weak evidebce to support the conclusion that cannabis or cannabinoids are an effective or ineffective treatment for the health endpoint of interest" (page 8).[2] • "For this level of evidence, there are supportive findings from fair-quality studies or mixed findings with most favoring one conclusion. A conclusion can be made, but there is significant uncertainty due to chance, bias, and confounding factors" (page 8).[2]
No or Insufficient Evidence
• "There is no or insufficient evidence to support the conclusion that cannabs or cannabinoids are an effective or ineffective treatment for the health endpoint of interest" (page 8).[2] • "For this level of evidence, there are mixed findings, a single poor study, or health endpoint has not been studied at all. No conclusion can be made because of substantial uncertainty due to chance, bias, and confounding factors" (page 8).[2]

Abbreviations: NASEM, The National Academies of Sciences, Engineering, and Medicine

APPENDIX C – LITERATURE SEARCHES

Ovid-Medline Search for Relevant Systematic Reviews, or Randomized Controlled Trials published from 2022-March 2023

Search date: March 13, 2023

Database(s): **Ovid MEDLINE(R) and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations and Daily** 1946 to March 10, 2023

Search Strategy:

#	Searches	Results
1	exp Multiple Sclerosis/	68996
2	Myelitis, Transverse/	1696
3	Demyelinating Diseases/	12848
4	Encephalomyelitis, Acute Disseminated/	2124
5	exp Optic Neuritis/	10299
6	("multiple sclerosis" or "neuromyelitis optica" or "transverse myelitis" or encephalomyelitis or devic or "optic neuritis" or "demyelinating disease*" or "acute disseminated encephalomyelitis").ti,ab,kw,kf.	114334
7	1 or 2 or 3 or 4 or 5 or 6	132521
8	exp animals/ not (exp animals/ and exp human/)	5101357
9	exp Cannabis/ or exp cannabinoids/ or exp Medical Marijuana/ or exp "Marijuana Use"/ or exp Marijuana Abuse/	37036
10	(mari?uana or pot or hash* or bhang* or gan?a* or weed* or hemp*).ti,ab,kw,kf.	82972
11	(Tetrahydrocannab* or cannabi* or THC or CBD or CBN or CBG or CBC, or THCV or CBDV or CBCV or CBGV or THCA or CBDA or CBGA or CBNA).ti,ab,kw,kf.	63832
12	(THC and (analog* or enantiomer* or isomer*)).ti,ab,kw,kf.	618
13	(nabilone or dronabinol or marinol or syndros or cesamet or epid#olex or nabiximol* or Sativex or bedrocan or bedrobinol or bedica or bediol or bedrolite or dexanbinol).ti,ab,kw,kf.	1190

14	9 or 10 or 11 or 12 or 13	143500
15	7 and 14	1334
16	limit 15 to yr="2022 -Current"	102
17	meta-analysis/ or (metaanaly$ or meta-analy$).ti,ab,kw,kf. or "systematic review"/ or ((sytematic* adj3 review*) or (systematic* adj2 search*) or cochrane$ or (overview adj4 review)).ti,ab,kw,kf. or (cochrane$ or systematic review?).jw.	459100
18	(MEDLINE or Embase or Pubmed or systematic review).tw. or meta analysis.pt.	473955
19	17 or 18	571663
20	16 and 19	14
21	(randomized controlled trial or controlled clinical trial).pt. or randomi?ed.ab. or placebo.ab. or clinical trials as topic.sh. or randomly.ab. or trial.ti.	1553837
22	7 and 14 and 22	228
23	limit 40 to yr="2022 -Current"	12

Embase Search for Relevant Systematic Reviews, or Randomized Controlled Trials published from 2022-March 2023

Search date: March 13, 2023

#	Searches	Results
1	**'encephalomyelitis'**/exp OR **'demyelinating disease'**/exp OR **'multiple sclerosis'**/exp OR **'myelooptic neuropathy'**/exp	236,318
2	**'multiple sclerosis'**:ti,ab OR **'neuromyelitis optica'**:ti,ab OR **encephalomyelitis**:ti,ab OR **devic**:ti,ab	160,792
3	#1 OR #2	250,504
4	**'cannabinoid'**/exp OR **'cannabis use'**/exp OR **'cannabis smoking'**/exp OR **'cannabis addiction'**/exp	98,323

5	**mari?uana**:ti,ab,kw OR **pot**:ti,ab,kw OR **hash***:ti,ab,kw OR **bhang***:ti,ab,kw OR **gan?a***:ti,ab,kw OR **weed***:ti,ab,kw OR **hemp***:ti,ab,kw	104,235
6	**tetrahydrocannab***:ti,ab,kw OR **cannabi***:ti,ab,kw OR **thc**:ti,ab,kw OR **cbd**:ti,ab,kw OR **cbn**:ti,ab,kw OR **cbg**:ti,ab,kw OR **cbc**:ti,ab,kw OR **thcv**:ti,ab,kw OR **cbdv**:ti,ab,kw OR **cbcv**:ti,ab,kw OR **cbgv**:ti,ab,kw OR **thca**:ti,ab,kw OR **cbda**:ti,ab,kw OR **cbga**:ti,ab,kw OR **cbna**:ti,ab,kw	97,193
7	**thc**:ti,ab,kw AND (**analog***:ti,ab,kw OR **enantiomer***:ti,ab,kw OR **isomer***:ti,ab,kw)	809
8	**cannabi***:ti,ab,kw AND (**analog***:ti,ab,kw OR **enantiomer***:ti,ab,kw OR **isomer***:ti,ab,kw)	2,535
9	**nabilone**:ti,ab,kw OR **dronabinol**:ti,ab,kw OR **marinol**:ti,ab,kw OR **syndros**:ti,ab,kw OR **cesamet**:ti,ab,kw OR **epid?olex**:ti,ab,kw OR **nabiximol***:ti,ab,kw OR **sativex**:ti,ab,kw OR **bedrocan**:ti,ab,kw OR **bedrobinol**:ti,ab,kw OR **bedica**:ti,ab,kw OR **bediol**:ti,ab,kw OR **bedrolite**:ti,ab,kw OR **dexanabinol**:ti,ab,kw	1,887
10	**#4** OR **#5** OR **#6** OR **#7** OR **#8** OR **#9**	220,843
11	**cochrane***:jt OR **'systematic review*'**:jt OR **'meta analysis'**/exp OR **'systematic review'**/exp OR ((**systematic*** NEAR/3 **review***):ti,ab,kw) OR ((**systematic*** NEAR/2 **search***):ti,ab,kw) OR **'meta analys*'**:ti,ab,kw OR **metaanalys***:ti,ab,kw OR ((**overview** NEAR/4 (**review** OR **reviews**)):ti)	681,532
12	**#3** AND **#10** AND **#11**	218
13	**#3** AND **#10** AND **#11** AND [2022-2023]/py	37
14	**#3** AND **#10**	3,284
15	**#3** AND **#10** AND [2022-2023]/py	250
16	**#15** NOT **#13**	213
17	**#16** NOT **'conference abstract'**/it	175
18	(**'crossover procedure'**:de OR **'double-blind procedure'**:de OR **'randomized controlled trial'**:de OR **'single-blind procedure'**:de OR **random***:de,ab,ti OR **factorial***:de,ab,ti OR **crossover***:de,ab,ti OR ((**cross** NEXT/1 **over***):de,ab,ti) OR **placebo***:de,ab,ti OR ((**doubl*** NEAR/1 **blind***):de,ab,ti) OR ((**singl*** NEAR/1 **blind***):de,ab,ti) OR **assign***:de,ab,ti OR **allocat***:de,ab,ti OR **volunteer***:de,ab,ti) NOT (**'conference abstract'**/it OR **'conference review'**/it)	2,503,700
19	**#3** AND **#10** AND **#18**	556
20	**#3** AND **#10** AND **#18** AND [2022-2023]/py	40