Utah Department of
Health & Human Services
Center for Medical Cannabis

Department of Health and Human Services

Guidance on the suggested use of medical cannabis

Multiple sclerosis

About this document: The following information on the use of medical cannabis serves as a suggested use guide for those participating in the Utah Medical Cannabis Program. The intended audience for this document includes qualified medical providers, pharmacy medical providers, patients intending to use medical cannabis, and caregivers of patients intending to use medical cannabis.

This document details the guidance on the use of medical cannabis for multiple sclerosis. This document does not include general instructions on the use of medical cannabis, contraindications, warnings, precautions and adverse reactions to using cannabis and drug-to-drug interactions which could be found in the extended guidance document titled *Guidance on the Suggested Use of Medical Cannabis.* The extended guidance document can be found on the Department of Health and Human Services Center for Medical Cannabis website (www.medicalcannabis.utah.gov).

About the authors: This document was authored by the Utah Cannabis Research Review Board and Department of Health and Human Services staff.

About the Utah Cannabis Research Review Board: Under Utah Health Code 26B-1-420, the Cannabis Research Review Board is a board of medical research professionals and physicians who meet on a voluntary basis to review and discuss any available scientific research related to the human use of cannabis, cannabinoid product or an expanded cannabinoid product that was conducted under a study approved by an Institutional Review Board (IRB) or was conducted and approved by the federal government.

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IMPORTANT NOTE: As always, in the event of significant side effects, stop use of medical cannabis until side effects have resolved, and then reduce to previous, best-tolerated dose. To avoid unwanted psychoactive side effects, "start low and go slow" especially when using cannabis products for the first time or using new dosages or types of products.

There is substantial evidence[a] to support the conclusion that cannabis and cannabinoids are effective in improving patient-reported multiple sclerosis spasticity symptoms (oral cannabinoids[b]). This is based on supportive findings from good-quality studies with very few or no credible opposing findings.

There is moderate evidence to support the conclusion that cannabis or cannabinoids are effective in treating neuropathic pain in patients with multiple sclerosis (oral cannabinoids[b]).

There is limited evidence to support the conclusion that cannabis or cannabinoids may be effective in reducing overactive bladder symptoms in people with MS, including nocturia, daily void frequency, and patient-reported incontinence (nabiximols[b]).

There is insufficient evidence to support or refute the conclusion that cannabis or cannabinoids are effective in treating tremor in people with multiple sclerosis.

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.

[a] Developed using level of evidence categories from the 2017 National Academies of Sciences, Engineering, and Medicine report on cannabis (National Academies of Sciences, Engineering, and Medicine, 2017*d*).
[b] Indicates the type of cannabis or cannabinoids studied in most clinical trials. Oral cannabinoids typically included cannabis extracts (predominantly delta-9-tetrahydrocannabinol [THC]), nabiximols (1:1 THC:CBD [cannabidiol] oromucosal spray), or synthetic THC analogs.

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Multiple sclerosis (MS) is an autoimmune disease in which the immune system attacks myelin sheaths of neurons present in the central nervous system. Resulting damage to myelinated neurons of the central nervous system can result in sensory deficits, neuropathic pain (hyperalgesia and allodynia), motor weakness and paralysis involving both striated and smooth muscles, and upper motor neuron hyperreflexia and spasticity. Several biologic-based disease-modifying agents, immune antagonists, and symptom-based therapies are approved for the treatment of this chronic and often progressive debilitating disorder.

Cannabis or cannabinoids may be effective for treatment of some MS symptoms. The following summarizes clinical efficacy evidence from recent systematic reviews (SRs), primarily of randomized controlled trials (RCTs), for treatment of MS with cannabis-based therapies.

- **Spasticity:**
    - Pooled data from 5 RCTs including about 1100 patients shows short-term (up to 14 weeks) treatment with nabiximols (1:1 THC:CBD oromucosal spray) or oral cannabis extract significantly increases the odds of reporting a clinically significant spasticity symptom reduction (by 30%) compared to placebo. Nabiximols also modestly improve mean change in spasticity compared to placebo in the short term (from 7 RCTs of about 1200 patients) (Filippini et al., 2022). Long-term treatment evidence is limited, but spasticity benefits from nabiximols may persist for at least 12 months based on observational studies (Martinez-Paz et al., 2023). Evidence for treating spasticity with whole-plant cannabis and routes of administration other than oral/oromucosal is limited. Overall, the moderate-certainty RCT evidence supports oral cannabinoids as add-on therapy option for patients with moderate-to-severe MS spasticity insufficiently responsive to other treatment options (Filippini et al., 2022). When reported, mean maintenance doses of nabximols in RCTs and observational studies reached about 11-23 mg of THC and 10-21 mg of CBD daily (Ergul et al., 2022; Filippini et al., 2022; Longoria et al., 2022).
- **Chronic neuropathic pain:**
    - Add-on treatment with oral cannabinoids may modestly improve short-term neuropathic pain compared to placebo, based on a meta-analysis of 8 RCTs. One small RCT demonstrated a clinically significant (pain reduction of 50% from baseline) reduction in pain with dronabinol versus placebo at 3 weeks. However, the evidence was

rated as low or very-low certainty by a recent SR due to risk of bias and inconsistency, or serious imprecision (Filippini et al., 2022).

- **Overactive bladder:**
    - Two moderate-size RCTs demonstrated short-term benefits from nabiximols (mean of about 24 mg THC/21 mg CBD) or oral THC (max 25 mg) for improving some overactive bladder symptoms compared to placebo. Nabiximols were superior to placebo for secondary outcomes of nocturia frequency and number of daily voids but failed to demonstrate superiority for the primary outcome of daily incontinence episode frequency. Oral THC and oral cannabis extract significantly reduced patient-reported urge incontinence episodes versus placebo, but a difference compared to placebo was not demonstrated on any domain of the King's Health Questionnaire (a validated bladder-specific health-related quality of life measure) (Bapir et al., 2022; Filippini et al., 2022).
- **Tremor:**
    - Tremor symptom improvement with oral cannabinoids over placebo was not observed in 4 short-term (up to 12 week) trials. Improvement in patient-reported tremor symptoms was observed in extended follow-up of 1 trial of oral THC (max 25 mg daily) at 27 and 52 weeks (Pourmohammadi et al., 2022). Overall, evidence for treating tremor is inconclusive.
- **Sleep quality:**
    - **o** Oral cannabinoids (primarily nabiximols) may modestly improve short-term sleep quality compared to placebo, based on a pooled estimate of 7 RCTs with substantial heterogeneity (Filippini et al., 2022). In an observational study, benefits of cannabinoids for sleep correlated with pain relief (Longoria et al., 2022).
- **Patient's Global Impression of Change (PGIC) in Heath Status and Health-related Quality of Life (HRQoL)**
    - Oral cannabinoids probably increase the number of patients with MS reporting 'very much' or 'much' improvement in health status after 4–48 weeks of treatment based on a pooled analysis of 8 RCTs (moderate-certainty evidence). Nonetheless, the combined evidence from 8 trials demonstrated little to no improvement in HRQoL from baseline after 3–48 weeks with cannabinoids compared to placebo (low-certainty evidence) (Filippini et al., 2022).

Evidence for disease-modifying and neuroprotective effects of cannabis in preclinical models of multiple sclerosis (Pryce et al., 2015) supports the use of medical cannabis in the early treatment of MS. However, a single placebo-controlled study of pure synthetic THC (dronabinol) administered to 498 patients with chronic and progressive MS (Zajicek et al., 2013) failed to demonstrate an improvement in disability or neuropathology.

Safety Concerns

Treatment with oral cannabinoids in people with MS increases the odds for nervous system adverse events (AEs), such as dizziness, somnolence and headache compared to placebo (Filippini et al., 2022).

Based primarily on pre-clinical *in vivo* and *in vitro* studies, THC and CBD may suppress parts of the innate and acquired immune system (eg, affecting leukocyte propagation, macrophage and T-cell viability, and pro-inflammatory cytokine secretion) (Katchan et al., 2016). Little is known about whether combined treatment with immunosuppressive disease-modifying therapies (DMTs) for MS and cannabis increases the risk for serious infections. Approximately 60% of patients with MS were receiving DMTs (glucocorticoids, interferons, or other agents) during a 14-week RCT of oromucosal nabiximols (maximum of 32.4 mg THC and 30 mg CBD daily) for treatment of neuropathic pain. In this short-term trial, no severe infections were reported, and the rate infections/infestations was 20% in the THC/CBD arm compared to 16% in the placebo arm (Langford et al., 2013). Newer DMTs for MS were not used by patients in that trial. Combined immunosuppressive risks of cannabis with DMTs, particularly for newer DMTs, is unknown.

The impact of cannabis use on cognition in people with MS is an important safety concern. SRs of RCTs and observational studies suggest that cognitive AEs are rare among people with MS who receive nabiximols at recommended doses (maximum of about 32 mg THC and 30 mg CBD daily) for up to 12 months (very low to low certainty evidence) (Dykukha et al., 2022; Motaghi et al., 2023) Nonetheless, multiple observational studies found impaired cognition on neuropsychological tests after cannabis or cannabinoid use, with the most consistently reported effects of impaired attention and working memory, especially with whole-plant cannabis use (Landrigan et al., 2022). One cross-sectional study reported that prolonged use of ingested or inhaled cannabis was associated with poorer performance on various cognitive domains (e.g. information processing speed, working memory, executive function, and visuospatial perception) in patients with MS (Honarmand et

al., 2011). In a small (n=20), non-blinded, randomized withdrawal trial, people with MS who regularly smoked cannabis (mean dose 2g/day for >5 years) and 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 (Landrigan et al., 2022). Available evidence is highly heterogenous in terms of type and dose of cannabinoid used, route of administration, and duration of use, precluding firm conclusions (Landrigan et al., 2022; Wieghorst et al., 2022). While most high-quality evidence suggests any negative impact of cannabinoids on cognition in people with MS is relatively small, the possibility of worsened cognition from some cannabis/cannabinoid exposures and from long-term use cannot be excluded (Wieghorst et al., 2022).

Summary, Limitations, and Suggestions

In summary, clinical evidence supports the use of medical cannabis for symptomatic treatment of MS-associated moderate-severe spasticity of both striated and smooth muscles, and neuropathic pain in patients with MS. Cannabinoids might improve overactive bladder symptoms of nocturia, daily void frequency, and patient-reported incontinence in the short-term; however, evidence is limited to only 2 clinical trials, and mixed results were observed for the number of incontinence episodes. Clinical evidence is insufficient to recommend cannabis/cannabinoids treatment of tremor in people 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 (Chiurchiù et al., 2018).

Providers considering cannabis treatment for people with MS should weigh the limitations and uncertainties of available evidence. Many trials among people with MS are considered to have at least some bias concerns, which is reflected in lower certainty evidence ratings for some symptoms/outcomes. SR authors reported additional limitations of co-treatment with other therapies during RCT follow-up, potentially confounding the cannabis treatment results, and the limited long-term trial data (Filippini et al., 2022). In addition, the majority of RCT evidence is for oral cannabinoids, particularly nabiximols; whether patients will experience similar benefits using available medical cannabis formulations is unknown.

For most patients with MS, cannabis/cannabinoids should not be a first-line symptomatic treatment. Cannabinoids/cannabis may be an option after insufficient

benefit from first- or second-line therapies when the potential benefits outweigh concerns due to adverse effects and uncertainties in the evidence.

When recommending medical cannabis for treatment of MS, inform the patient of possible adverse reactions including the possibility of decreased cognitive performance associated with long-term use of cannabis, and do appropriate clinical monitoring of cognitive function.

Cannabinoid use may cause sedation, dizziness, or other neurologic adverse effects. People with MS may be sensitive to these effects, increasing the risk for falls or other adverse events. We suggest that providers assess potential risks from sedation or dizziness before starting cannabis and provide appropriate counseling and clinical monitoring to mitigate risks. Follow general dosing guidance for cannabis, including starting at a low dose and up-titrating slowly.

For dosing guidance for treatment of MS, please refer to the general dosing suggestions at the beginning of the document titled Guidance on the Suggested Use of Medical Cannabis found on the Department of Health and Human Services Center for Medical Cannabis website (www.medicalcannabis.utah.gov).

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DISCLAIMER

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This document is a summary of available peer-reviewed literature concerning potential therapeutic uses and harmful effects of cannabis and cannabinoids. With the ongoing nature of cannabis and cannabinoid research, it is not meant to be complete or comprehensive and should be used as a limited complement to other reliable sources of information. This document is not a systematic review or meta-analysis of the literature and has not rigorously evaluated the quality and weight of the available evidence. There is a lack of controlled clinical trials yielding high-level evidence of predictable therapeutic benefits for any given condition other than those for FDA-approved formulations. This document includes warnings and risks related to the use of cannabis including cannabis use disorder, potentially irreversible brain damage/mental illness, legal liability for DUI, and potential for adverse work-related consequences.

All patrons participating in the Utah Medical Cannabis Program are advised to use this document and any such document produced from this original document as informational and educational. The use of medical cannabis is at one's own risk. **Medical cannabis is NOT a first-line therapy for most medical conditions.**

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