Utah Department of
Health & Human Services
Center for Medical Cannabis

Department of Health and Human Services

Guidance on the suggested use of medical cannabis

Persistent and debilitating muscle spasms

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.

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.

Persistent and debilitating muscle spasms may result from a variety of distinct clinical conditions in adult and pediatric patients.

There is limited evidence to support the conclusion that cannabis or cannabinoids (oral cannabinoids, vaporized cannabis, or nabiximols) are an effective treatment for spasticity in adults with spinal cord injury, amyotrophic lateral sclerosis, or primary lateral sclerosis.

There is insufficient evidence to support the conclusion that cannabis or cannabinoids (nabiximols) are an effective treatment for spasticity in adults who have had a stroke

There is insufficient evidence to support the conclusion that cannabis or cannabinoids (CBD rich oil or nabiximols) are an effective treatment for spasticity children with traumatic brain injury or cerebral palsy.

[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*).

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Persistent and debilitating muscle spasms[1] may result from a variety of distinct clinical conditions in adult and pediatric patients such as spinal cord injury (SCI)/spinal cord disease (SCD), amyotrophic lateral sclerosis (ALS), primary lateral sclerosis (PLS), traumatic brain injury (TBI), stroke, and cerebral palsy (CP) among others. Guidance for use of medical cannabis in treating multiple sclerosis is detailed separately.

The terms muscle spasms and spasticity are not always used consistently in medical literature. Spasticity is an increase in muscle tone that worsens with movement resulting from upper motor neuron dysfunction.[2,3] The term spasm is less specific and may be used by patients and providers to describe painful cramps, spasticity, clonus, dystonia, or other conditions.[4]

Spasticity is often assessed using the clinician-administered modified Ashworth scale (mAS), which grades symptoms on a 6-point scale from 0 (no increased muscle tone, least severe) to 4 (muscle is rigid in flexion or extension), or the originator 5-point Ashworth scale (AS). The mAS updated the AS by adding a "1+" intermediary score that is halfway between 1 and 2 on the AS scale.[5] Decreases by at least 1 point on the mAS are estimated to be clinically meaningful to patients.[6] Patient-reported spasticity assessed per numeric rating scales (NRSs) or visual rating scales (VRSs) are other common spasticity outcome measures.[7]

In animal models of MS spasticity, agonism of cannabinoid type 1 (CB_1) receptors improves spasticity.[8]It has been proposed that cannabinoids, particularly delta-9-tetrahydrocannabinol (THC), could improve spasticity by reducing excitatory glutamatergic neurotransmission.[8,9] Nabiximols (Sativex), an oromucosal spray of cannabis plant extract containing an approximately 1:1 mixture of THC and cannabidiol (CBD), has received regulatory approval for treatment-resistant spasticity in adults with MS in many countries other than the United States.[9,10]

Non-cannabinoid pharmacologic options for symptomatic management of spasticity include oral agents (eg, baclofen, tizanidine, benzodiazepines, dantrolene), intrathecal baclofen, and botulinum neurotoxin A injection.[11] According to experts, use of these therapies is limited by adverse effects and tolerance.[8]

The following summarizes clinical efficacy evidence from recent systematic reviews (SRs), primarily of randomized controlled trials (RCTs), for treatment of spasms with cannabis-based therapies.

- **Spasticity from SCI/SCD:**
    - Six unclear to high risk-of-bias or poor to fair quality trials (only assessed for 4 trials)[6,26,27] demonstrated mixed efficacy of cannabinoids or cannabis (oral nabilone, dronabinol, or THC; oromucosal nabiximols; vaporized cannabis; or rectal THC-HS) for reducing spasticity in the short-term among patients with SCI/SCD, many of whom were paraplegic or quadriplegic (neurological injury

level was not reported by all trials).[12-17,25]

- If only results from the 4 trials who selected patients for spasticity at baseline are considered, spasticity was significantly reduced compared to placebo for at least 1 outcome measure in 3 of 4 trials.[12-15] Spasticity was significantly improved in 1 of the 2 other trials of patients with pain at baseline (albeit not until 7 hours after the first dose, and only for the lower cannabis dosage),[16] and spasticity on the modified Ashworth scale improved numerically with nabiximols compared to placebo in the other trial.[17] There is uncertainty about findings from the trials due to potential bias, confounding, and small sample sizes.

- **ALS or PLS**
  - A randomized controlled trial with a low risk-of-bias met its primary outcome, showing that nabiximols significantly reduced mean spasticity scores on the mAS (calculated as a sum of multiple muscle groups) compared to placebo at 6 weeks (adjusted mean difference: –0.32 [95%CI –0.57 to –0.07]). Change on the Patient's Global Impression of Change (but not Neurologists' or Caregivers') scale also significantly favored nabiximols over placebo.[18] There is some uncertainty due to the small sample size and evidence being limited to a single trial.
- **Stroke**
  - In a small, randomized, cross-over, triple-blinded pilot trial, nabiximols did not significantly improve mean spasticity on a numerical rating scale from baseline to 4 weeks compared to placebo among adults who had a stroke and low pain at baseline. The co-primary outcomes of change in stretch reflexes per electromyographic recordings also did not improve with nabiximols compared to placebo. While no formal risk-of-bias assessment by a systematic review was performed for this trial, we note there is an unclear risk-of-bias arising from randomization (sufficient detail not reported) and attrition during the trial (only 83% of patients completed the trial). There is uncertainty due to the small sample size, the possible lack of statistical power (no power calculation was performed since it was a pilot trial), and bias.[19]
- **Children with CP or TBI**
  - Two experimental trials primarily among children with CP found conflicting results for the treatment of spasticity with cannabis. Nabiximols did not significantly reduce mean spasticity scores from baseline to 12 weeks on a caregiver reported scale compared to placebo in a randomized controlled trial with some risk-of-bias concerns (Fairhurst et al 2020)[26]; changes from

baseline in secondary outcome spasticity measures also did not differ from placebo.[20] In contrast, in the second trial with poorly reported methods and an unclear risk-of-bias (Libzon et al 2018),[29] CBD rich oil at 2 different dosages improved caregiver-reported spasticity at 5 months compared to baseline.[21] Both trials were small, and the trial by Libzon et al carries uncertainty due to bias from the unknown randomization and blinding methods, confounding, and the lack of a placebo comparator.

Nearly all experimental trials studied cannabis-based treatments as an adjunct to other therapies (eg, skeletal muscle relaxants like baclofen and/or physical therapy).[12,14-16,18-21] Only one trial that included patients with SCI tapered off other treatments before starting oral THC or rectal THC-HS during the trial.[13]

Trials used a variety of cannabinoid products including oral nabilone (N=1),[12] oral dronabinol or THC (N=3),[13-15] oromucosal nabiximols spray (N=4),[17-20] CBD-rich cannabis oil (N=1),[21] rectal THC-HS (N=1),[13] and inhaled cannabis (N=1).[16]

Safety Concerns

Cannabinoid product tolerability and the degree of safety details reported varied between trials. In the 4 trials that administered patient-titrated oromucosal nabiximols, nabiximols generally had an acceptable safety and tolerability profile, with an expected increased incidence of mild to moderate adverse events (e.g., nausea, dizziness, somnolence, asthenia, vertigo) compared to placebo.[17-20] While nabiximols was tolerated by medically complex children in the trial by Fairhurst et al in general, some children considered the nabiximols formulation to be unpalatable; 12.8% of children in the nabiximols arm reported retching compared to 0% in the placebo arm.[20] Moreover, while evidence is limited, children with CP/TBI might be more susceptible to neuropsychiatric events with nabiximols compared to adults with MS, stroke, and ALS/PLS who received nabiximols in clinical trials. Three pediatric patients experienced hallucinations while receiving nabiximols, which led to a suicide attempt in one instance.[20] Another trial (Libzon et al) that enrolled children compared two oral CBD-enriched oils with a 6:1 or 20:1 CBD: THC ratio, and considered CBD-based oils to be well-tolerated and safe for up to 5 months. The clarity of AE reporting by Libzon et al was poor, but it is described that AEs among the 25 included children were limited to 2 events of worsened seizures (possibly attributable to underlying conditions or changes to anti-seizure

medications), 2 events of behavioral changes, and 1 event of somnolence.[21] In the Fairhurst et al trial, serious AEs of seizures occurred in 2 patients (7.4%) in the nabiximols arm and 1 patient (4%) in the placebo arm.[20]

Oral THC/dronabinol, rectal THC-HS, or nabilone were studied in 4 trials of adults with SCI: most of these trials poorly reported safety information. Few severe AEs occurred with nabilone, and common AEs associated with nabilone included drowsiness, asthenia, and mild vertigo.[12] In 2 trials that used high oral THC doses (range 10-15 to 60 mg daily), THC was generally associated with fatigue, increased or decreased anger, dry mouth, anxiety, and dysphoria.[13,14] A high proportion of patients who received oral THC in one trial (23%) reported increased pain, which led to 80% of affected patients (4 of 5) discontinuing the oral THC.[13] The final trial studied 2 doses of vaporized cannabis among patients with SCI and reported little detail about AEs.[16] Patients who used vaporized cannabis did not discontinue the treatment due to AEs and no serious AEs occurred; 1 patient experienced temporary syncope that resolved without sequelae.[16]

An association between cannabis exposure and stroke, primarily ischemic, has been reported among people with or without other stroke risk factors in observational and descriptive studies.[30,31] One included small, short-term RCT studied nabiximols oromucosal spray among older adults (median age of 68 years) with a history of a stroke, including ischemic stroke in 62% of people who completed the trial. Enrolled patients passed cardiovascular screening (blood pressure, electrocardiogram, and echocardiogram) at baseline.[19] No adverse effects on blood pressure or heart rate were observed after 4 weeks of treatment, nor did any ischemic or hemorrhagic events occur among the population with a median of 4.2 years since their stroke.[28]

Summary, Limitations, and Suggestions

In summary, it is our opinion that evidence for treatment of *spasticity* with cannabis or cannabinoids could be considered *limited* for adults with SCI or ALS/PLS, and *insufficient* for adults who had a stroke, and children with TBI or CP.

Available experimental evidence is limited to *short-term treatment* with CBPs,

ranging from 1 day to about 20 weeks with a median of 6 weeks across the 10 trials.

Cannabinoid use may cause sedation, dizziness, or other neurologic adverse effects.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 persistent or debilitating muscle spasms, 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

The following information on the use of medical cannabis serves as a suggested use guide for those participating in the Utah Medical Cannabis Program. This document has been vetted and approved by the Utah Cannabis Research Review Board under Utah Health Code 26B-1-420.

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.

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