COLLEGE OF PHARMACY
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EVIDENCE REVIEW:

Experimental Evidence for the Treatment of Spasticity or Spasms with Cannabis-based Products

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I have no conflicts of interest to disclose

BRIEF EVIDENCE REPORT OBJECTIVE & METHODS

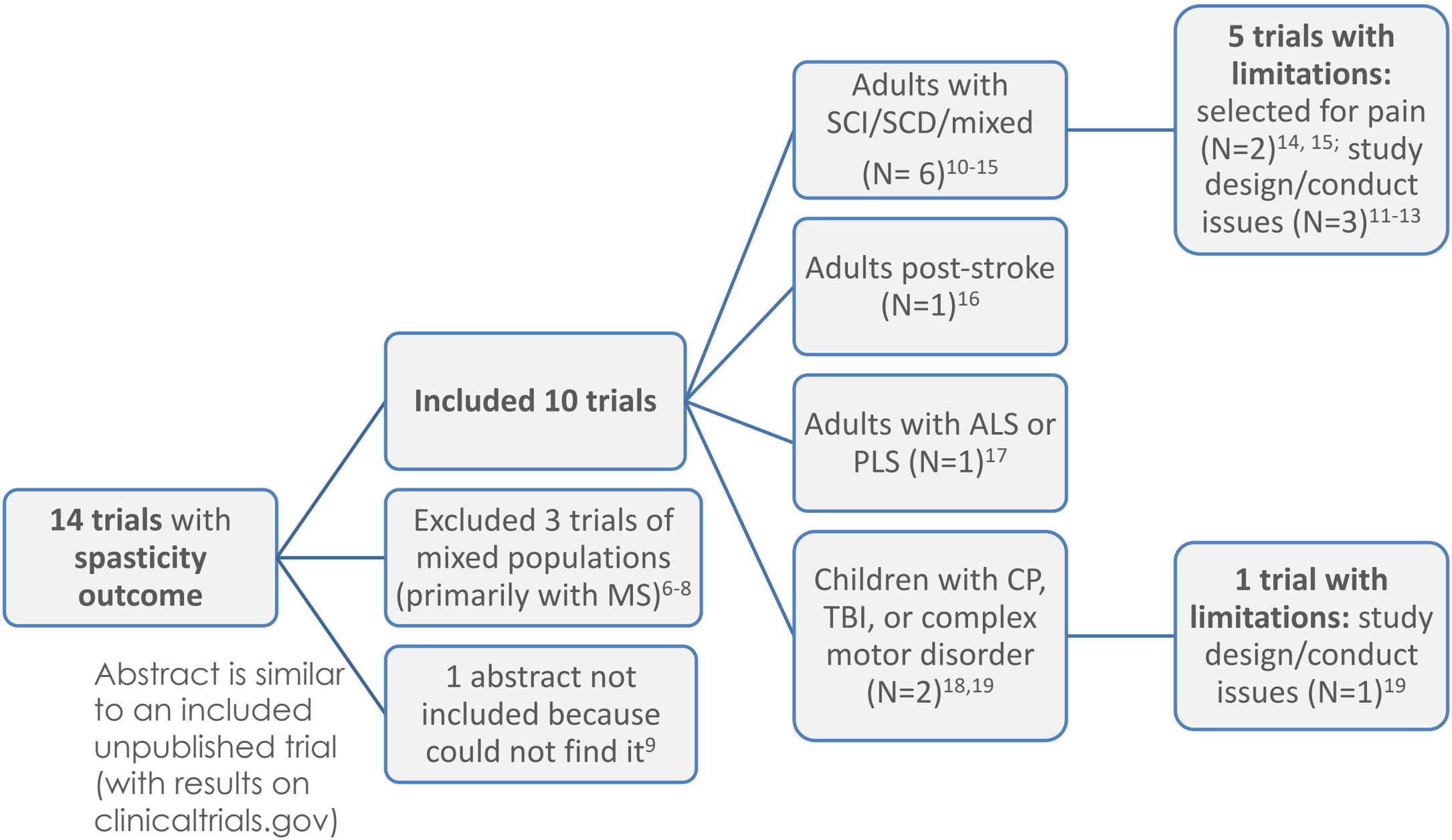
- **Objective:**
  - Summarize recent clinical evidence for the treatment of (1) spasticity or (2) spasms associated with upper motor neuron syndrome (UMNS) with CBPs using a hierarchy-of-evidence approach
  - Assist the CRRB with drafting and/or updating guidance

- **Methods:**
  - Searched for SRs of experimental trials (ETs) published since 2018 or ETs (eg, RCTs) published since 2020*
  - Included ETs of any design with:
    - Patients with spasticity and/or spasms associated with UMNS, with most patients having disorders other than MS (<40% of patients with MS)
    - Treatment with CBP for any duration; with a spasticity/spasm outcome
  - Summarized spasticity or spasm efficacy outcomes and safety outcomes

*Narrowed RCT search dates to 2020-2023 based on the search dates of SRs[1-5]

Abbreviations: CBP, cannabis- or cannabinoid-based product; CRRB, Utah Cannabis Research Review Board; ET, experimental trials; MS, multiple sclerosis; RCT, randomized controlled trial; SR, systematic review; UMNS, upper motor neuron syndrome;

INCLUDED TRIALS



Abbreviations: ALS, amyotrophic lateral sclerosis; CP, cerebral palsy; MS, multiple sclerosis; PLS, primary lateral sclerosis; SCI, spinal cord injury; TBI, traumatic brain injury;

OVERVIEW OF SCI/SCD TRIALS

Trial and design	Population (total n)	Approx. Tx. Duration
Pooyania et al 2010[10] Crossover RCT#	Adults with SCI & tetra/paraplegia with **mod. spasticity** (n=12)	4 weeks
Hagenbach et al 2007*[11] RCT with failed randomization and 2 initial open-label periods	Adults with SCI & tetra/paraplegia with **mod. spasticity without meds** (n=25)	6 weeks
Kogel et al 1995*[12] Unclear; probably a non-randomized before-after trial#	Adults with SCI & quadriplegia with **spasticity resistant to other meds** (n=5)	Unknown, possibly 5 days
Maurer et al 1990*[13] n-of-1 RCT#	Adult with SCI from tumor, walks with assistance; **persistent spasticity** (n=1)	18 sequences of 3 different treatments over 5 months
Wilsey et al 2016*[14] Crossover RCT#	Adults with SCI (69%) or SCD and **neuropathic pain** (≥4/10) with involved neurological level of cervical, thoracic, or lumbar (n=42)	Up to 7 hours
Jazz Pharma 2012*[15] **(unpublished)** Parallel RCT#	Adults with SCI and **neuropathic pain** (≥ 4/10) (n=116)	3 weeks

#Stable antispastic medications and/or other treatments allowed

*Trial with limitations

Abbreviations: Approx. approximate; mod., moderate; n, number; Pharma, pharmaceuticals; RCT, randomized controlled trial; SCD, spinal cord disease; SCI, spinal cord injury; tx., treatment;

SCI/SCD TRIAL EFFICACY RESULTS

Study	Intervention(s)	Efficacy – mAS or AS	Efficacy – Spasticity NRS	Efficacy – Other
Adults with SCI or mixed population including SCI, selected for spasticity				
Pooyania 2010[10] n=12	NAB 0.5 mg–1 mg/day vs PBO	+, most involved muscle group (1)	+/- trend toward NAB	+/- **Spasm frequency** scale
Hagenbach 2007*[11] n=25	Dronabinol (~31 mg) vs PBO	+, summed for 6 joints (1)	+/- most days	
	Dronabinol vs rectal THC-HS (~43 mg)	+/-, summed for 6 joints (1)	NR	
Kogel 1995*[12] n=5	Dronabinol 10 mg–60 mg/day vs no treatment	NR	NR	Mixed descriptive results on **knee pend. drop test** (2 improved, 1 unchanged, 1 variable, 1 worsened)
Maurer 1990*[13] n=1	THC 5 mg orally vs PBO	NR	+, at 4 timepoints	
	THC 5 mg orally vs codeine 50 mg	NR	+, at 4 timepoints	

Key: *trial with limitations; + (green), efficacy favors CBP over comparator (statistically); +/- (red); efficacy favors neither CBP or PBO (statistically); mixed result descriptively (blue); 1=specified as the primary outcome

Abbreviations: AS, Ashworth scale; CBP, cannabinoid- or cannabis-based product; mAS, Modified ashworth scale; n, number of patients; NAB, nabilone; NR, not reported; NRS, numeric rating scale; PBO, placebo; pend., pendulum; SCI, spinal cord injury; THC, delta-9-tetrahydrocannabinol; THC-HS, THC-hemisuccinate;

SCI/SCD TRIAL EFFICACY RESULTS

Study	Intervention(s)	Efficacy – mAS or AS	Efficacy – Spasticity NRS	Efficacy – Other
Adults with SCI or mixed population including SCI, selected for neuropathic pain				
Wilsey 2016,[14] N=42	Vaporized cannabis 6.7% THC vs PBO	NR	+/-	+/-
	Vaporized cannabis 2.9% THC vs PBO	NR	+, at 7h only (not earlier)	+, at 7h only using **PGIC**
Unpublished, [15] N=116	Nabiximols vs PBO	+/-, trend toward nabiximols	+/-	+/- for **multiple spasm measures, % days with spasticity, and spasticity severity**

Key: *trial with limitations; +, efficacy favors CBP over comparator (statistically) [green]; +/-, efficacy favors neither CBP or PBO [red]; mixed result descriptively [blue]; 1 = specified primary outcome

Abbreviations: AS, Ashworth scale; CBP, cannabinoid- or cannabis-based product; mAS, Modified ashworth scale; n, number of patients, NR, not reported; NRS, numeric rating scale; PBO, placebo; PGIC, Patient's Global Impression of Change; THC, delta-9-tetrahydrocannabinol;

SCI/SCD TRIAL SAFETY RESULTS

- Safety outcome details variably reported

Studied CBP	Select Safety Results
Nabilone 0.5-1 mg daily[10]	• Common AEs (>placebo): drowsiness, asthenia, mild vertigo
Oral THC (10-15 mg to 60 mg daily)[13-15] or rectal THC-HS[13]	• THC generally associated with fatigue, increased or decreased anger, dry mouth, anxiety, and dysphoria • Patients receiving oral or rectal THC d/c treatment due to: • Anxiety (8%), decreased attention or mood (4%), apoplexy (4%), increased pain (30%)
Oromucosal nabiximols (1:1 THC: CBD spray) at an unknown dose[17]	• Any AE: nabiximols (82%) versus placebo (48%) • Serious AE: nabiximols (5.4%) versus placebo (3.3%) • Common AEs (> placebo): nausea, URTI, dizziness, dysgeusia, somnolence
Vaporized inhaled cannabis with 2.9% or 6.7% THC[16]	• No serious AEs or discontinuations due to AEs • One patient with syncope that resolved without sequelae

Abbreviations: AE, adverse event; CBD, cannabidiol; CBP, cannabinoid- or cannabis-based product; d/c, discontinued; THC, delta-9-tetrahydrocannabinol; THC-HS, THC-hemmisuccinate; URTI, upper respiratory tract infection;

ROB OR QUALITY ASSESSMENT OF SCI TRIALS BY SR

- ROB or quality ratings by an SR was available for 4 of 6 trials
  - No trials considered to have a low ROB or to be of high quality

- Trials assessed using a Cochrane ROB tool:
  - Some concerns/unclear ROB (N=2)[1,4, 12,13]

- Trials assessed using the NIH quality tool:
  - Poor quality (N=1)[1,14] , or fair quality (N=1)[1,16]

- Trials without quality assessment:
  - Maurer et al: n-of-1 randomized, double-blind, active and placebo-controlled trial[15]
  - Jazz Pharma unpublished: randomized, quadruple-blinded, placebo-controlled, parallel group trial[17]

Abbreviations: NIH, National Institute of Health; ROB, risk of bias; SCI, spinal cord injury; SR, systematic review;

OVERVIEW OF ALS/PLS OR POST-STROKE TRIALS

Trial and design	Population (total n)	Approx. Tx. Duration
Adults with ALS or PLS		
Riva et al 2019[18] Parallel, phase 2 RCT#	Adults with possible, probable, or definite or upper-motor neuron dominant ALS (74.6%), or PLS (23.7%) and **spasticity (mAS ≥ 1 in 2+ muscle groups)*** (n=59)	6 weeks
Adults post-stroke		
Marinelli et al 2022[19] Crossover RCT#	Adults with an ischemic (62%) or hemorrhagic stroke (n=38%) ≥ 3 months ago, with an acceptable cardiovascular profile (including CHA_2DS_2VASc score <7) **and spasticity (mAS 1-3)* in 1+ sites (wrist, elbow, or foot plantar flexors; or knee extensors)** (n=41)	4 weeks

#Stable antispastic medications and/or other treatments allowed

*The mAS is assessed on a 6-point scale from 0 (no increased muscle tone, least severe) to 4 (muscle is rigid in flexion or extension), including 1+ between 1 and 2

Abbreviations: ALS, amyotrophic lateral sclerosis; mAS, modified Ashworth scale; n, number; PLS, primary lateral sclerosis; RCT, randomized controlled trial; Tx., treatment;

ALS/PLS OR POST-STROKE TRIAL EFFICACY RESULTS

Study	Intervention(s)	Efficacy – mAS or AS	Efficacy – Spasticity NRS	Efficacy – Other
Adults with ALS or PLS				
Riva 2019[18] n=59	Nabiximols vs PBO	+, summed for muscle groups (1)	+/-	+/-, **spasm frequency** NRS +/-, caregiver's GIC +/-, neurologist's GIC
				+, patient's GIC
Adults post-stroke (≥3 months ago)				
Marinelli 2022[19] n=41	Nabiximols vs PBO	+/-, for wrist flexors; trend toward favoring nabiximols	+/- (1)	+/-, stretch reflex amplitude (1) +/-, **daily spasms score**

Key: *trial with limitations; + (green), efficacy favors CBP over comparator (statistically); +/- (red), efficacy favors neither CBP or PBO; mixed result descriptively (blue); 1 = specified as primary outcome

Abbreviations: ALS, amyotrophic lateral sclerosis; AS, Ashworth scale; CBP, cannabinoid- or cannabis-based product; GIC, global impression of change; mAS, modified ashworth scale; n, number of patients; NR, not reported; NRS, numeric rating scale; PBO, placebo; PLS, primary lateral sclerosis; THC, delta-9-tetrahydrocannabinol;

ALS/PLS OR STROKE SAFETY RESULTS

Studied CBP	Select Safety Results
Adults with ALS or PLS	
Oromucosal self-titrated nabiximols (mean 21.6 mg THC and 19.2 mg CBD)[18]	• Any AEs: nabiximols (76%) versus placebo (27%) • Most common AEs with nabiximols: asthenia, somnolence, vertigo, nausea (mostly mild-moderate severity) • Two patients *temporarily* d/c nabiximols due to nausea or anxiety • Less frequent AEs during open-label extension period if prior nabiximols use
Adults post-stroke	
Oromucosal self-titrated nabiximols (mean 24.3 mg THC and 22.5 mg CBD)[19]	• Most common AEs with nabiximols: confusion and dizziness • Serious AEs: 2 in nabiximols arm, with 1 considered drug-related (nausea) • Acceptable CV profile per investigators; no significant changes in BP, HR, or adverse CV or cerebrovascular events

Abbreviations: AE, adverse event; ALS, amyotrophic lateral sclerosis; BP, blood pressure; CBD, cannabidiol; CV, cardiovascular; d/c, discontinued; HR, heart rate; PLS, primary lateral sclerosis; THC, delta-9-tetrahydrocannabinol;

ROB OR QUALITY ASSESSMENT FOR ALS/PLS AND POST-STROKE TRIALS BY SR

- ROB ratings by an SR was available for 1 of 2 trials
- Riva et al rated as having a low ROB on all Cochrane 2.0 ROB domains[4,18]
- Trials without ROB/quality assessment by a SR:
  - Marinelli et al: a double-blind, crossover pilot RCT[19]
    - Insufficient details reported about randomization, and high attrition (83% of patients completed the trial)
    - No sample size reported

Abbreviations: ALS, amyotrophic lateral sclerosis; PLS, primary lateral sclerosis; ROB, risk of bias; SR, systematic review;

OVERVIEW OF CP/TBI TRIALS

Trial and design	Patients (total n)	Approx. Tx. Duration
Fairhurst et al 2020[18] Parallel, RCT (2 nabiximols: 1 PBO allocation)[#]	• **Children 8-18 years old** (weight >15 kg) with CP (89%) or non-progressive CNS injury (n=72) • **Spasticity (mAS ≥ 2 in 1+ muscle groups and average NRS ≥ 4) that failed 1+ year of medication** • Physical impairments that usually require a wheelchair	12 weeks
Libzon et al 2018[19] Parallel pilot trial with unclear design; likely a non-randomized before-after trial[*]	• **Children 1-18 years old** with a complex motor disorder including CP (76%), neurogenetic syndrome (40%) or TBI (4%) (n=25) • ***Dystonia or spasticity or both*** • Physical impairments that usually require a wheelchair	5 months

[#]Stable antispastic medications and/or other treatments allowed.

*Libzon et al appears to have allowed changes in concurrent antispastic medications during the trial

Abbreviations: CNS, central nervous system; CP, cerebral palsy; mAS, modified Ashworth scale; NRS, numerical rating scale; PBO, placebo; PLS, primary lateral sclerosis; RCT, randomized controlled trial; TBI, traumatic brain injury;

CP OR TBI TRIAL EFFICACY RESULTS

Study	Intervention	Efficacy – mAS or AS	Efficacy – Spasticity NRS	Efficacy – Other
Children with cerebral palsy or traumatic brain injury				
Fairhurst 2020,[18] N=72	Nabiximols (mean 16 mg THC and 14.5 mg CBD) vs PBO	+/-, summed for 5 muscle groups	+/-, rated by caregivers	+/-, maximum muscle reading on MTS
Libzon 2018*,[19] N=25	CBD 5% oil orally with a CBD:THC ratio of 6:1 or 20:1	NR	+ (within-group change from BL) for both, rated by caregivers	--

Key: *trial with limitations; + (green), efficacy favors CBP over comparator (statistically) [green]; +/- (red), efficacy favors neither CBP or PBO; mixed result descriptively (blue); 1=specified as primary outcome

Abbreviations: AS, Ashworth scale; BL, baseline; CBP, cannabinoid- or cannabis-based product; mAS, Modified ashworth scale; MTS, Modified Tardieu Scale; NR, not reported; PBO, placebo; THC, delta-9-tetrahydrocannabinol;

CP OR TBI TRIAL SAFETY RESULTS

Studied CBP	Select Safety Results
Oromucosal caregiver-titrated nabiximols[18] (mean 16 mg THC and 14.5 mg CBD)	• Common AEs vs placebo (mostly mild-moderate severity): retching, nasopharyngitis, and poor sleep quality • Serious AEs: nabiximols (12%) versus placebo (9%) • Three events of hallucinations with nabiximols; 1 event led to a suicide attempt
Oral CBD-rich oil[19]: • CBD: THC 6:1 (mean 38 mg and 6.3 mg), or • CBD: THC 20:1 (mean 92 mg and 3.7 mg)	• Safety details poorly reported, and no placebo comparator • Behavioral changes of excitation (n=1) and somnolence (n=1) among patients receiving 6:1 oil • Mood changes with concurrent methylphenidate and cannabis (n=1) in patient receiving 20:1 oil • Worsened previously controlled seizures (n=2; with unknown cannabis product)

Abbreviations: AE, adverse event; CBD, cannabidiol; CBP, cannabinoid- or cannabis-based product; CP, cerebral palsy; TBI, traumatic brain injury; THC, delta-9-tetrahydrocannabinol;

ROB OR QUALITY ASSESSMENT FOR CP OR TBI TRIALS BY SR

- ROB or quality ratings by an SR available for both trials
  - No trials considered to have a low ROB

- Trials assessed using a Cochrane ROB tool:
  - Some concerns/unclear risk on 2 domains and low risk on other domains (Fairhurst et al)[3,18]
  - Low risk on 1 domain, and some concerns/unclear risk on all other domains (Libzon et al)[5,19]

Abbreviations: CP, cerebral palsy; ROB, risk of bias; SR, systematic review; TBI, traumatic brain injury;

EVIDENCE REVIEW DISCUSSION AND SUMMARY

- Ten RCTs, including 6 for adults with a SCI/SCD (n=201),[10-15] 1 for adults with ALS/PLS (n=59),[17] 1 for adults post-stroke (n=41),[16] and 2 for children primarily with CP (n=242)[18,19]

- **Mixed efficacy for treating spasticity**:
  - 4 of 6 (66.6%) SCI trials[10,11,13,14] + mixed descriptive results in 1 trial[12]
  - 1 (100%) ALS/PLS trial[17]
  - 1 of 2 (50%) of children with CP trials[19]
- Studies (N=4) failed to show benefit for nabilone or nabiximols to reduce the frequency of spasms[10,15-17]

- Short-term CBP use appears to be associated with primarily mild-moderate severity events
  - AEs information is underreported by many trials
  - In children with CP, nabiximols was associated with retching, and 3 patients reported hallucinations that resulted in a suicide attempt for 1 patient[18]

Abbreviations: ALS, amyotrophic lateral sclerosis; CBP, cannabinoid- or cannabis-based product; CP, cerebral palsy; PLS, primary lateral sclerosis; SCD, spinal cord disease; SCI, spinal cord injury;

ROB AND HETEROGENEITY

- 7 of 10 trials considered to have a low (N=1)[4,17] or unclear ROB (N=4),[3,5,10,11,18,19] or have poor (N=1)[1,12] and fair (N=1) quality,[1,14] per SRs

- Studies limited by small sample sizes, quality concerns, short durations, and significant heterogeneity
- Cannot make firm conclusions about the impact of a particular source of heterogeneity on the results

- Examples of potential sources of heterogeneity:
  - Within trial and between-trial differences in spasticity, and degree of concurrent pain
  - Co-medications for spasticity
  - Variability in the outcome measures used, and how the same outcomes were assessed
    - mAS/AS scales possibly with poor reliability[4,20,21]

Abbreviations: AS, Ashworth scale; mAS, Modified ashworth scale; ROB, risk of bias; SR, systematic review;

CONCLUSIONS FROM SRS AND A 2018 CANADIAN PRIMARY CARE GUIDELINE

- Conclusion of an SR of experimental and observational studies of mostly poor to fair quality[1]:
  - Cannabinoids might reduce spasticity in SCI patients in the short-term
  - Investigators unsure if the effects were clinically significant
- SRs of experimental studies declined to make conclusions due to too few trials among patients with SCI, ALS/PLS, or CP[4,5]

- Canadian primary care guideline[22]:
  - Weakly recommends adjunctive medical cannabinoids for treatment-resistant spasticity in patients with SCI or MS
  - Strongly recommends against medical cannabinoids for for disorders other than MS or SCI, and against treatment of spasticity with cannabis for any disorder (lack of evidence)
  - Recommendations do not apply to spasms

Abbreviations: ALS, amyotrophic lateral sclerosis; CP, cerebral palsy; MS, multiple sclerosis; PLS, primary lateral sclerosis; SCI, spinal cord injury; SR, systematic review;

CURRENT UTAH CRRB GUIDANCE

Evidence for treatment of patients with SCI is included in the current MS guidance statement:

"There is insufficient evidence to support or refute the conclusion that cannabis or cannabinoids are effective in treatment of spasticity in patients with paralysis due to spinal cord injury"(page 2)[23]

- This statement was probably based on the evidence rating assigned by the 2017 NASEM report[24]
  - NASEM selected this rating because they did not consider the results from 3 unpublished trials cited by an included SR

Abbreviations: CRRB, (Utah) Cannabis Research Review Board; MS, multiple sclerosis; NASEM, National Academies of Science, Engineering, and Medicine; SCI, spinal cord injury; SR, systematic review;

CONSIDERATIONS FOR SPASMS/SPASTICITY GUIDANCE BY THE CRRB

- The CRRB may consider grading conclusions separately for conditions and outcomes, as appropriate

- Option to combine with MS guidance, or as a separate document

- Considerations for *graded* conclusions (using NASEM LOE rating):
  - For treatment of spasticity:
    - Insufficient evidence: adults post-stroke, children with CP or TBI
    - Limited evidence: adults with SCI/SCD, adults with ALS/PLS

  - For treatment of spasms:
    - Insufficient evidence among adults with spasticity or neuropathic pain due to SCI, ALS/PLS, or stroke

Abbreviations: ALS, amyotrophic lateral sclerosis; CP, cerebral palsy; CRRB, Utah Cannabis Research Review Board; LOE, level of evidence; MS, multiple sclerosis; PLS, primary lateral sclerosis; SCD, spinal cord disease; SCI, spinal cord injury; TBI, traumatic brain injury;

CONSIDERATIONS FOR SPASMS/SPASTICITY GUIDANCE BY THE CRRB

- Additional considerations for elaboration in guidance:
  - Overall, trials tended to include participants with moderate to severe spasticity despite other treatment
  - CBPs were used as an adjunctive therapy to antispastic medications in nearly all trials
  - Experimental evidence limited to short-term treatment (range from 1 day to 20 weeks with a median of 6 weeks)
  - Information about studied CBPs, divided by condition type

Abbreviations: CBP, cannabinoid- or cannabis-based product; CRRB, Utah Cannabis Research Review Board;

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Extra slides

NATIONAL ACADEMIES LOE RATINGS*[24]

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).
"For this level of evidence, there are many supportive findings 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).
Substantial Evidence
"There is strong evidence to support the conclusion that cannabis or cannabinoids are an effective or ineffective treatment for the health endpoint of interest" (page 7).
"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).

*LOE ratings for therapeutic effects from the 2017 National Academies of Sciences, Engineering, and Medicine report.

Abbreviations: LOE, level of evidence;

NATIONAL ACADEMIES LOE RATINGS*[24]

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).
"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).
Limited Evidence
"There is weak evidence to support the conclusion that cannabis or cannabinoids are an effective or ineffective treatment for the health endpoint of interest" (page 8).
"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).

*LOE ratings for therapeutic effects from the 2017 National Academies of Sciences, Engineering, and Medicine report.

Abbreviations: LOE, level of evidence;

NATIONAL ACADEMIES LOE RATINGS*[24]

No or Insufficient Evidence
"There is no or insufficient evidence to support the conclusion that cannabis or cannabinoids are an effective or ineffective treatment for the health endpoint of interest" (page 8).
"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).

*LOE ratings for therapeutic effects from the 2017 National Academies of Sciences, Engineering, and Medicine report.

Abbreviations: LOE, level of evidence;

OVERVIEW OF STUDIED CBPS

Trial	Studied Cannabinoid- or Cannabis-based Product (CBP)
Adults with SCI or mixed population with SCI, selected for spasticity	
Pooyania et al 2010[10]	Oral nabilone 0.5 daily or 0.5 mg twice daily
Hagenbach et al 2007[11]	Oral dronabinol starting at 10 mg daily and titrated to effect (mean of 31 mg daily), or rectal THC-HS 20-60 mg daily (mean of 43 mg daily)
Kogel et al 1995[12]	Oral dronabinol 5 mg twice daily to 20 mg three times daily
Maurer et al 1990[13]	Oral THC 5 mg daily
Adults with SCI or mixed population with SCI, selected for pain	
Wilsey et al 2016[14]	Vaporized 400 mg cannabis with 2.9% THC or 6.7% THC administered with the Foltin puff procedure at a dose of 4 puffs followed by 4-8 puffs four hours later
Jazz Pharma 2012[15] (unpublished)	Oromucosal nabiximols (Sativex; 2.7 mg THC: 2.5 mg CBD per spray) to a maximum of 48 sprays daily

Abbreviations: CBD, cannabidiol; CBP, cannabinoid- or cannabis-based product; SCI, spinal cord injury; THC, delta-9-tetrahydrocannabinol; THC-HS, THC-hemisuccinate;

OVERVIEW OF STUDIED CBPS

Trial	Studied Cannabinoid or Cannabis-based Product (CBP)
Adults with ALS or PLS	
Riva et al 2019[17]	Oromucosal nabiximols (Sativex; 2.7 mg THC/2.5 mg CBD per spray) titrated over 14 days to a max of 12 sprays per day. • Used a mean of 8 sprays (21.6 mg THC and 20 mg CBD) daily
Adults post-stroke	
Marinelli et al 2022[16]	Oromucosal nabiximols (Sativex) titrated over 14 days to a max of 12 sprays per day. • Used a mean of 9 sprays (24.3 mg THC and 22.5 mg CBD) daily
Children with cerebral palsy or traumatic brain injury	
Fairhurst et al 2020[18]	Oromucosal nabiximols (Sativex) titrated over 14 days to a max of 12 sprays per day. • Used a mean of 5.8 sprays (15.7 mg THC and 14.5 mg CBD) daily among children with a mean weight of 34 kg
Libzon et al 2018[19]	Oral (or by feeding tube) CBD-rich oil (with 6:1 or 20:1 CBD:THC); mean daily doses of CBD and THC ranged from 38 mg (3.7 mg/kg) and 6.3 mg (0.6 mg/kg in the 6:1 group, and 92 mg (5.5 mg/kg) and 3.7 mg (0.28 mg/kg) in the 20:1 group.

Abbreviations: ALS, amyotrophic lateral sclerosis; CBD, cannabidiol; CBP, cannabinoid- or cannabis-based product; PLS, primary lateral sclerosis; THC, tetrahydrocannabinol;

OUTCOMES OF EXCLUDED TRIALS WITH SCI PATIENTS

Trial and design (total n)	Overview of spasm/spasticity efficacy results
Mixed population of adults with SCI, MS (≥40%), or other, selected for spasticity, muscle spasms, other neurological symptoms, and/or pain (varied by trial)	
Wade et al 2003[25] Double-blind, crossover RCT (n=24) 16.7% SCI patients	• THC and THC/CBD spray (not CBD only) **reduced PR-spasms and spasm frequency** vs placebo • THC (not THC/CBD or CBD only) **reduced PR-spasticity** vs placebo • THC, CBD, and THC:CBD **reduced spasticity on NRS (not AS)** versus placebo
Wissel et al 2006[26] Double-blind, crossover RCT (n=13) 23.1% SCI patients	• Nabilone treatment resulted in **numerical, but not statistically significant reductions in spasticity on the AS scale** versus placebo
Hansen et al 2023[27] Blinded, parallel RCT (n=134) 11.2% SCI patients	• **No significant differences** between THC, CBD, THC:CBD versus placebo for **spasticity on NRS** • Underpowered (aimed to enroll 448)

Abbreviations: AS, Ashworth scale; CBD, cannabidiol; n, number of patients; PR, patient-reported; SCI, spinal cord injury; THC, delta-9-tetrahydrocannabinol;