Medical Marijuana for Blepharospasm (and a bit on Transcranial Stimulation as well)

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Professor of Neurology
October 9, 2021
WELCOME TO THE 2016 BEBRF SYMPOSIUM!

Brian D. Berman, MD, MS
Associate Professor of Neurology
University of Colorado Anschutz Medical Campus
2017, 2018, 2019...
VCU Parkinson’s and Movement Disorders Center
2020 – Present
Objectives

- Discuss history and use of medical marijuana
- Review the potential of cannabinoids to treat blepharospasm
- Provide update on magnetic and electrical stimulation approaches for blepharospasm
Hairs on the surface of the plant produce the cannabinoids and terpenes.

- Cultivated from prehistoric times in China, India, Egypt
- Planted in Virginia in 1611, Plymouth Colony in 1632

C. sativa and C. indica
What’s in it?

Chemical compounds: >500

- **Cannabinoids (100+)**
  - *Tetrahydrocannabinol (THC)*
    - *High* concentrations
    - Major psychoactive component
  - **Cannabidiol (CBD)**
    - Up to 40% of plant’s extract
    - Does not cause a high (limits it)
- **Terpenes (200+)**
Early medical uses

- Analgesic, anticonvulsant (O’Shaughnessey, 1842)
- Insomnia, neuralgia, dysmenorrhea (Reynolds, 1890)
- Regarding migraine, “Cannabis indica is probably the most satisfactory remedy.” (Osler, 1915)

Marijuana Tax Act, 1937
- Removed 28 cannabis-containing medicines from U.S. usage
- Opposed by AMA

Removal from US Pharmacopoeia, 1942

Controlled Substances Act, 1970
- Schedule I
Prescription forms

- **Dronabinol** (Marinol™)
  - Synthetic THC
  - Nausea, appetite stimulation, MS pain
- **Cannabidiol** (Epidiolex™)
  - CBD extract
  - Epilepsy (Dravet, LG)
- **Nabiximols** (Sativex™)
  - 1:1 THC:CBD
  - Pain in MS and cancer
State Regulated Cannabis Programs

- Adult & medical use regulated program
- Adult use only no medical regulated program
- Comprehensive medical cannabis program
- CBD/Low THC program
- Limited adult possession and growing allowed, no regulated production or sales: DC

June 2021
- Cannabidiols (CBD): Painkiller, anti-inflammatory, antioxidant, anxiety reducer, antipsychotic, suppresses muscle spasms.
- Tetrahydrocannabinols (THC): Painkiller, anti-inflammatory, antioxidant, euphoriant, suppresses nausea and vomiting.
- Cannabigerols (CBG): Painkiller, anti-inflammatory, antibiotic, antifungal.
- Cannabichromenes (CBC): Painkiller, anti-inflammatory, antibiotic, antifungal.
- Cannabinols and cannabinoildols (CBN, CBND): Anti-inflammatory, antibiotic, sedative, anticonvulsant.
- Others: Includes cannabicyclols (CBL), cannabielsoins (CBE), cannabitrions (CBT) and other miscellaneous types.
Safety

**How does cannabis compare to other drugs?**

UCSF and NIDA researchers ranked the risk of different substances.
She looked
So awake... So alive!

Was it caffeine or botox?
Acute/adverse effects

- Redness of the eyes
- Increased appetite and thirst
- Decreased salivation
- Increased heart rate and blood pressure
- Slow heart rate and low standing blood pressure (high doses)
- Urinary frequency
- Decreased intraocular pressure

- Euphoria, relaxation
- Dysphoria, anxiety, panic
- Subjective time slowing
- Depersonalization, altered sense of body proportion
- Auditory/visual illusions and hallucinations
- Impaired balance and coordination
- Impaired memory and problem solving
## 2020 BEBREF Survey

<table>
<thead>
<tr>
<th>Complementary Therapies</th>
<th>Yes</th>
<th>No/Blank</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tried Complementary:</td>
<td>142</td>
<td>188</td>
<td>330</td>
</tr>
<tr>
<td>Current Complementary:</td>
<td>56</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Tried Other: (excluded 4 for Dry Eyes)

- Farias/neuroplascty: 9
- meditation: 5
- massage: 4
- homeopathic remedies: 2
- Reiki: 2
- acupressure for cervical dystonia: 1
- cognitive behavior therapy: 1
- cultural/religious rituals: 1
- eye/eyelid exercises: 1
- Frankisencense essential oil: 1
- light therapy: 1
- sacral cranial therapy: 1
- magnesium/peroxide drips: 1
- neurofeedback: 1
- neuroplascty, meditation: 1
- positive attitude/yoga: 1
- psychologist counseling/zoloft until insura: 1
- psychoterapy: 1
- sudafed, claritin d: 1
- TMJ Treatments: 1
- topical cream applied around the eyes: 1
- yoga, accupressure, speech therapy, phys: 1

Total: 38
## 2020 BEBRF Survey

<table>
<thead>
<tr>
<th>Patient #</th>
<th>% MM Eff</th>
<th>Taking MM?</th>
<th>IF MM Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>18</td>
<td>50</td>
<td>Extract &amp; Liquid &amp; Capsule, all forms on survey</td>
<td>1:1, 2:1 (depends on botox length)</td>
</tr>
<tr>
<td></td>
<td>75</td>
<td>All but Topical extract liquid</td>
<td>8:1 CBD/THC</td>
</tr>
<tr>
<td></td>
<td>0</td>
<td>no relief yet pill liquid</td>
<td>CBD:THC 0:1 (100% THC)</td>
</tr>
<tr>
<td></td>
<td>50</td>
<td>80% CBD edible, liquid, pill</td>
<td>CBD:THC 0:1 (100% THC)</td>
</tr>
<tr>
<td></td>
<td>60</td>
<td>not sure liquid</td>
<td>CBD:THC 1:0 (100% CBD)</td>
</tr>
<tr>
<td>N/A</td>
<td>30</td>
<td>answer not provided edible, liquid, pill, cream</td>
<td>CBD:THC 1:0 (100% CBD)</td>
</tr>
<tr>
<td></td>
<td>27</td>
<td>Yes CBD oil</td>
<td>CBD:THC 1:0 (100% CBD)</td>
</tr>
<tr>
<td></td>
<td>15</td>
<td>Pill</td>
<td>CBD:THC 1:0 (100% CBD)</td>
</tr>
<tr>
<td></td>
<td>50</td>
<td>27 inhaled, edible</td>
<td>CBD:THC 1:3 (25% CBD, 75% THC)</td>
</tr>
<tr>
<td></td>
<td>25</td>
<td>edible liquid inhaled, liquid, pill</td>
<td>CHD TCH 1:1</td>
</tr>
<tr>
<td>too soon to tell</td>
<td>extract</td>
<td>Hempwork CBD at :01 THC</td>
<td>no answer</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>not sure type</td>
</tr>
</tbody>
</table>

25 tried and stopped
Mechanism of action
So, do cannabinoids work for blepharospasm?

Scientific literature provides some good evidence for:

- Pain relief
- Muscle spasticity (in MS)
- Nausea control
- Appetite enhancement
- Short-term sleep disturbance
- Epilepsy (specific types)

What’s the evidence in Movement Disorders?
# Parkinson disease

<table>
<thead>
<tr>
<th>Study design</th>
<th>Number of patients</th>
<th>Cannabinoids</th>
<th>Results</th>
<th>Authors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient survey</td>
<td>84</td>
<td>Smoked cannabis</td>
<td>Forty-six percent of patients described some benefit; 31% reported improvement of rest tremor, 45% of bradykinesia and 14% of LID</td>
<td>Venderová et al.</td>
</tr>
<tr>
<td>Patient survey</td>
<td>9</td>
<td>Cannabis</td>
<td>Seven patients (78%) reported improvement of mood and sleep, two patients reported improved motor symptoms, not specifically dyskinesias</td>
<td>Finseth et al.</td>
</tr>
<tr>
<td>Case series</td>
<td>5</td>
<td>Smoked cannabis, 1 g cannabis (2–9% THC)</td>
<td>No benefit for tremor following single administration</td>
<td>Frankel et al.</td>
</tr>
<tr>
<td>Open-label</td>
<td>22</td>
<td>Smoked cannabis, 0.5 g cannabis</td>
<td>Thirty minutes after smoking cannabis, patients reported improvement in tremor, rigidity, bradykinesia, pain, and sleep</td>
<td>Lotan et al.</td>
</tr>
<tr>
<td>Four-week open-label</td>
<td>6</td>
<td>CBD up to 400 mg/day</td>
<td>Improvements on the Brief Psychiatric Rating Scale and Parkinson Psychosis Questionnaire</td>
<td>Zuardi et al.</td>
</tr>
<tr>
<td>Case series</td>
<td>4</td>
<td>CBD 75 or 300 mg/day</td>
<td>Benefits for rapid eye movement sleep behavior disorder</td>
<td>Chagas et al.</td>
</tr>
<tr>
<td>Randomized, double-blind, placebo-controlled crossover</td>
<td>5</td>
<td>Nabilone</td>
<td>Significant reduction of the Rush Dyskinesia Disability Scale and total LID time; two patients reported improvement in painful off-dystonia</td>
<td>Sieradzan et al.</td>
</tr>
<tr>
<td>Four-week randomized, double-blind, placebo-controlled crossover</td>
<td>17</td>
<td>Cannador (1.25 mg CBD and 2.5 mg THC)</td>
<td>No improvement of LIDs on multiple outcomes.</td>
<td>Carroll et al.</td>
</tr>
<tr>
<td>Randomized, double-blind, placebo-controlled</td>
<td>8</td>
<td>Rimonabant</td>
<td>No significant changes for motor symptoms (UPDRS-III), quality of life (PDQ-39) or sleep</td>
<td>Mesnage et al.</td>
</tr>
<tr>
<td>Randomized, double-blind, placebo-controlled</td>
<td>21</td>
<td>CBD 75 or 300 mg/day</td>
<td>No effect on motor symptoms or LID (UPDRS and standardized videotape)</td>
<td>Chagas et al.</td>
</tr>
<tr>
<td>Randomized, double-blind, placebo-controlled</td>
<td></td>
<td></td>
<td>No changes for total UPDRS or any subscales. Improvement for total PDQ-39 score and activities of daily living subscores for the CBD 300 mg/day group</td>
<td></td>
</tr>
</tbody>
</table>
Parkinson disease

Fox Insight Cannabis Survey (N=1881)

Motor Symptoms

- Tremor (n=1482)
- Dystonia (n=1109)
- Rigidity (n=1576)
- Muscle Cramps (n=1336)
- Dyskinesia (n=1013)
- Bradykinesia (n=1501)
- Freezing (n=876)
- Balance (n=1460)

- Markedly Worse
- Mildly Worse
- No Change
- Mildly Better
- Markedly Better
Parkinson disease

Difference in rate of reported symptomatic effect between high THC product users and CBD product users

THC product users with higher rate of reported symptomatic worsening

THC product users with higher rate of reported symptomatic improvement

- Dystonia (n = 964)
Cannabinoid studies in dystonia

- 5 patients (2 with PD) had dystonia improved with CBD

- 15 patients with segmental and generalized dystonia treated with synthetic nabilone showed no improvement
Cannabinoid studies in blepharospasm


- Out of 5 patients surveyed, 3 of 4 had improvement (4 discontinued use)


- Dronabinol improved pain and social life in single patient
Cannabinoids and dystonia: an issue yet to be defined.

- Cannabinoids seem to be effective in single cases, but further studies are required to determine their role as complementary treatment in dystonia.
2019 BEBRF Research Grant

Effect of Non-psychoactive Cannabidiol as an Adjunct to Botulinum Toxin in Blepharospasm - a prospective double-masked cross-over study

Investigators
Rona Z Silkiss, MD, FACS
Arvind Chandna, MD, DO, FRCS, FRCOphth
Christopher Tyler B.A., M.Sc., Ph.D., D.Sc.
Jayson Koppinger, MD
Recommendations?

Generally safe to try but with some caution.

- Start low and go slow (dose to response)
- Start with 100% CBD or low concentrations of THC
- Be aware of adverse effects
- Be aware of drug-drug interactions
- Caution about tolerance and dependence
- Ingestion form matters
WHAT YOU LOOK LIKE WHEN

YOUR BOTOX DOESN'T TAKE AT THE SAME TIME
Deep brain stimulation

- Relieves motor symptoms in patients with dystonia (average ↓ ~50%)
- Benefit can take weeks to months, and effect may last weeks to months after turned off
- Adverse effects can limit effectiveness
Deep brain stimulation in blepharospasm

<table>
<thead>
<tr>
<th>References</th>
<th>Type of patient</th>
<th>Number of patients</th>
<th>Site of stimulation</th>
<th>Therapeutic effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Muta et al. (132)</td>
<td>MS</td>
<td>1</td>
<td>Gpi</td>
<td>Improvement while remaining refractory to pharmacotherapy and bilateral thalamotomy</td>
</tr>
<tr>
<td>Foote et al. (126)</td>
<td>MS</td>
<td>1</td>
<td>Gpi</td>
<td>Improvement at 6-month follow up</td>
</tr>
<tr>
<td>Houser and Waltz (129)</td>
<td>MS</td>
<td>1</td>
<td>Gpi</td>
<td>Substantial improvement</td>
</tr>
<tr>
<td>Ostrem et al. (123)</td>
<td>MS</td>
<td>6</td>
<td>Gpi</td>
<td>Improvement of dystonia and slight worsening of motor function was reported in previously non-dystonic body regions in four patients</td>
</tr>
<tr>
<td>Hedayat et al. (124)</td>
<td>MS</td>
<td>1</td>
<td>Gpi</td>
<td>Sustained relief of dystonia 1 year after cessation of DBS</td>
</tr>
<tr>
<td>Bloem et al. (121)</td>
<td>MS</td>
<td>1</td>
<td>Gpi</td>
<td>No improvement in axial symptoms but blepharospasm was abolished</td>
</tr>
<tr>
<td>Loher et al. (133)</td>
<td>MS</td>
<td>1</td>
<td>Gpi</td>
<td>Long-term symptomatic and functional improvement</td>
</tr>
<tr>
<td>Sensi et al. (134)</td>
<td>MS</td>
<td>9</td>
<td>Gpi</td>
<td>Significant improvement at 6 months and better outcome</td>
</tr>
<tr>
<td>Woolf et al. (135)</td>
<td>MS</td>
<td>1</td>
<td>Gpi</td>
<td>Improvement</td>
</tr>
<tr>
<td>Inoue et al. (116)</td>
<td>MS</td>
<td>1</td>
<td>Gpi</td>
<td>Sustained long-term improvement (N80%) for 10 years</td>
</tr>
<tr>
<td>Gang et al. (130)</td>
<td>MS</td>
<td>11</td>
<td>Gpi</td>
<td>Effective for intractable MS without significant side effects</td>
</tr>
<tr>
<td>Lyons et al. (137)</td>
<td>MS</td>
<td>4</td>
<td>Gpi</td>
<td>Effective for medically refractory MS</td>
</tr>
<tr>
<td>Marziali et al. (118)</td>
<td>MS</td>
<td>1</td>
<td>Gpi</td>
<td>Improvement by 70% in movement score and 93.33% in disability score</td>
</tr>
<tr>
<td>Romito et al. (130)</td>
<td>MS</td>
<td>1</td>
<td>Gpi</td>
<td>Progressive and sustained improvement of dystonia at 36-month follow-up</td>
</tr>
<tr>
<td>Saiko et al. (119)</td>
<td>MS</td>
<td>5</td>
<td>Gpi</td>
<td>Significant improvement in movement and disability scores</td>
</tr>
<tr>
<td>Paese et al. (123)</td>
<td>MS</td>
<td>12</td>
<td>Gpi</td>
<td>Good effect persisting for up to 6 years</td>
</tr>
<tr>
<td>Tel et al. (139)</td>
<td>MS</td>
<td>1</td>
<td>Gpi</td>
<td>Good effect persisting for 36 months</td>
</tr>
<tr>
<td>Limoli et al. (140)</td>
<td>MS</td>
<td>6</td>
<td>Gpi</td>
<td>Low-frequency stimulation (100 Hz) was effective in two patients, with two patients experiencing a 50% benefit</td>
</tr>
<tr>
<td>Sobityl et al. (141)</td>
<td>MS</td>
<td>3</td>
<td>Gpi</td>
<td>Burke-Fahn– Marsden dystonia rating scale total disability score was reduced by 34% and 47% at short- and long-term follow-ups, respectively</td>
</tr>
<tr>
<td>Else et al. (142)</td>
<td>MS</td>
<td>1</td>
<td>Gpi or STN</td>
<td>Excellent improvement in speech with no adverse events</td>
</tr>
<tr>
<td>Wang et al. (130)</td>
<td>MS</td>
<td>4</td>
<td>Gpi or STN</td>
<td>Significant improvement</td>
</tr>
<tr>
<td>Zhao et al. (143)</td>
<td>MS</td>
<td>1</td>
<td>STN</td>
<td>STN-DBS seemed to induce dyskinesia, which made the patient felt uncomfortable although stimulation was slight. On the contrary, GPI-DBS stimulation relieved her discomfort.</td>
</tr>
<tr>
<td>Yamada et al. (144)</td>
<td>MS</td>
<td>9</td>
<td>Gpi</td>
<td>15 months after the operation, his preoperative scores on the Burke-Fahn–Marsden Dystonia Rating Scale (=8 points) decreased to 1 (87.5% improvement). The present study demonstrates the applicability of GPI-DBS for treating blepharospasm presenting as focal dystonia.</td>
</tr>
<tr>
<td>Sato et al. (145)</td>
<td>MS</td>
<td>1</td>
<td>Gpi</td>
<td>Improvement</td>
</tr>
<tr>
<td>Sobityl et al. (140)</td>
<td>MS</td>
<td>6</td>
<td>Gpi</td>
<td>Significant improvement</td>
</tr>
<tr>
<td>Luffa et al. (146)</td>
<td>MS</td>
<td>1</td>
<td>Gpi</td>
<td>This case illustrates successful treatment of blepharospasm with pallidal stimulation.</td>
</tr>
<tr>
<td>Zhan et al. (147)</td>
<td>MS</td>
<td>15</td>
<td>STN</td>
<td>Immediate improvement in symptoms after stimulation; four adverse events recorded in three patients, all of which were resolved without permanent sequelae</td>
</tr>
<tr>
<td>Horisawa et al. (129)</td>
<td>MS</td>
<td>16</td>
<td>Gpi</td>
<td>Significant improvement</td>
</tr>
<tr>
<td>Aires et al. (128)</td>
<td>MS</td>
<td>2</td>
<td>Gpi</td>
<td>Dystonia was improved by 88% in Patient 1 and by 98% in Patient 2, whereas disability was improved by 77%—82% at 24-month follow-up</td>
</tr>
<tr>
<td>Yio et al. (127)</td>
<td>MS</td>
<td>15</td>
<td>STN</td>
<td>MS patients (n = 14) showed improved BMFDRS score</td>
</tr>
<tr>
<td>Shu et al. (148)</td>
<td>MS</td>
<td>1</td>
<td>Gpi</td>
<td>Significant improvement in symptoms</td>
</tr>
<tr>
<td>Wang et al. (149)</td>
<td>MS</td>
<td>20</td>
<td>Gpi or STN</td>
<td>Good outcome in nine patients and poor outcome in 11 patients</td>
</tr>
<tr>
<td>Tian et al. (150)</td>
<td>MS</td>
<td>17</td>
<td>Gpi or STN</td>
<td>Both the STN and GPI could be effective targets of DBS for MS</td>
</tr>
<tr>
<td>Hao et al. (151)</td>
<td>MS</td>
<td>22</td>
<td>Gpi</td>
<td>Bilateral pallidal neurostimulation is a beneficial therapeutic option for refractory MS, which could improve the motor symptoms except for depression and sleep quality.</td>
</tr>
<tr>
<td>Ouyang et al. (152)</td>
<td>MS</td>
<td>15</td>
<td>STN</td>
<td>STN-DBS was not only able to improve patients’ motor symptoms, but also their sleep status.</td>
</tr>
</tbody>
</table>

- Meta-analysis in Meige syndrome showed improvement:
  - in dystonia
    - (BFM-M: 21.5 vs 8.6, p<0.001)
  - in disability
    - (BFM-D: 6.4 vs 2.9, p<0.001)


How about something less invasive?

The magnetic coil is slowly moved over the subject's motor cortex, a finger-sized area above the ears that controls muscle movement. The magnet's strength is gradually increased until the thumb jerks. That gives the operator an anchor point to navigate the brain and also sets the strength of stimulation to be used for other parts of the brain. To treat depression, the target is the dorsolateral prefrontal cortex.

FDA device permits
2008 Major depression
2013 Migraine
2018 OCD
2020 Smoking cessation
2020 Bipolar depression
2021 Anxiety in depression
TMS in blepharospasm

Transcranial magnetic brain stimulation modulates blepharospasm
A randomized controlled study
G. Kranz, E.A. Shamim, P.T. Lin, G.S. Kranz, M. Hallett

- 15-minute session of rTMS improved symptoms in patients

Combined effects of rTMS and botulinum toxin therapy in benign essential blepharospasm
Aparna Wagle Shukla, Wei Hu, Joseph Legacy, Wissam Deeb, Mark Hallett
Published: February 17, 2018 • DOI: https://doi.org/10.1016/j.brs.2018.02.004

- 2 weeks of rTMS given 6 weeks after BoNT showed improvement 2 weeks after TMS but not at 6 weeks
BoNT combined with 20-minute sessions of rTMS over 20 days improved symptoms in 35 patients with anxiety/depression compared to 28 patients treated BoNT only.

- Improved Efficacy: 94.29% vs 92.86%
- Increased Duration: 16.9 weeks vs 13.0 weeks
Transcranial Magnetic vs Electrical stimulation

Magnetic (TMS)

Electrical (TES)

Direct tDCS

Alternating tACS
TES in blepharospasm

Transcranial direct current stimulation for patients with benign essential blepharospasm: a case report

Vincent Trebossen ¹, Noomane Bouaziz ², René Benadhira ¹, Dominique Januel ¹

Treatment of cervical dystonia and blepharospasm by anodal tDCS of cerebellar hemispheres: A case report

Jean-Paul Nguyen ¹, Alcira Suarez ², Catherine Malineau ², Véronique Dixneuf ², Gilles Mazaltarine ², Philippe Damier ³
TACS in cervical dystonia

Mary Rossick Kern
and Jerome H. Kern
TACS in cervical dystonia

X 5 days

Change in symptoms or motor excitability?
TACS effects on motor network

A. CBF: Pre-Stimulation

B. CBF: During 15Hz tACS

C. ReHo: Pre-Stimulation

D. ReHo: During 15Hz tACS

High blood flow

Low blood flow

Cbl

High synchronization

Phase-shifted synchronization

left

z = 50

SMA

x = -5

left

left

left

left

left

left

left
2018 BEBRF Research Grant

Non-invasive inhibitory neurostimulation for the treatment of blepharospasm: A pilot study

Investigators
Brian D. Berman, MD, MS
Brice McConnell, MD

Enrolled
N = 8 BSP
N = 9 HC
(N = 11 CD)
Thank you!