VCU Health

Benign Essential Blepharospasm Research Foundation

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

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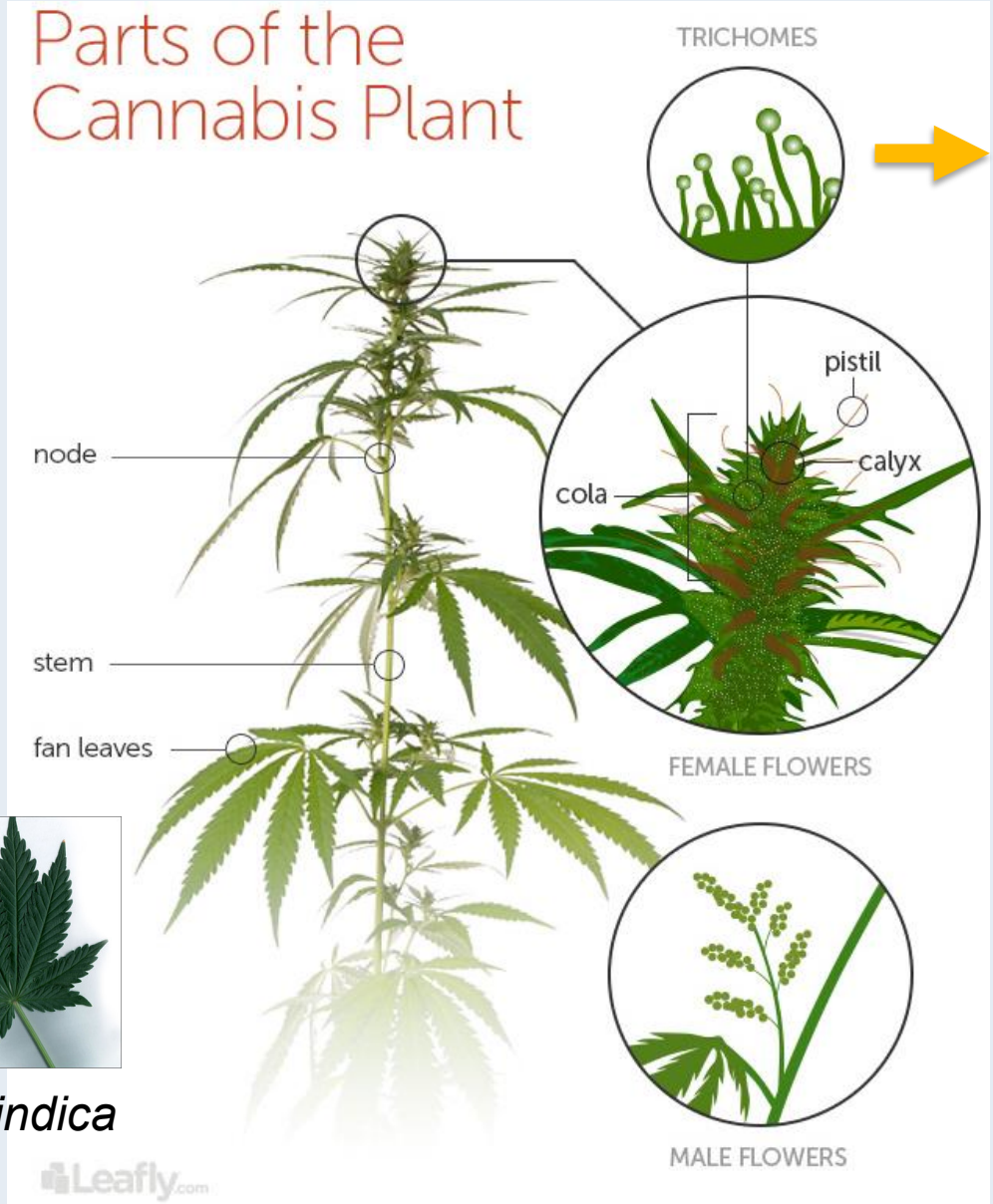
- Cultivated from prehistoric times in China, India, Egypt
- Planted in Virginia in 1611, Plymouth Colony in 1632



Hairs on the surface of the plant produce the cannabinoids and terpenes.

C. sativa and *C. indica*

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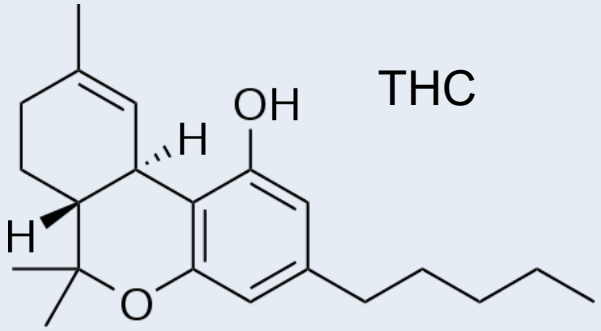
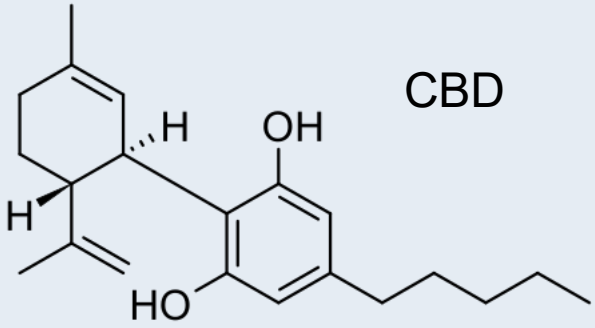
What's in it?

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+)



THC



CBD

Early medical uses

- Analgesic, anticonvulsant (O'Shaugnessey, 1842)
- Insomnia, neuralgia, dysmenorrhea (Reynolds, 1890)
- Regarding migraine, "Cannabis indica is probably the most satisfactory remedy." (Osler, 1915)

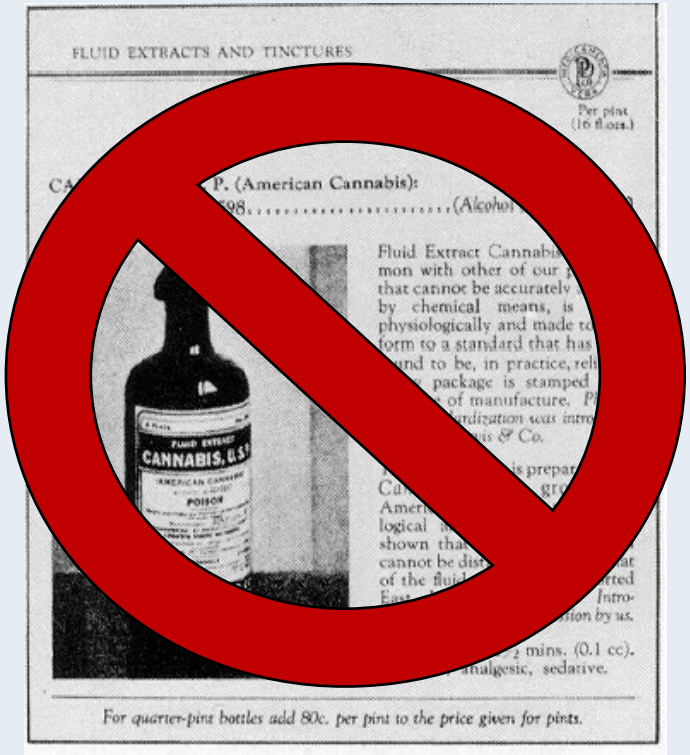
Marijuana Tax Act, 1937

- Removed 28 cannabis-containing medicines from U.S. usage
- Opposed by AMA

Removal from US Pharmacopoeia, 1942

Controlled Substances Act, 1970

- Schedule I



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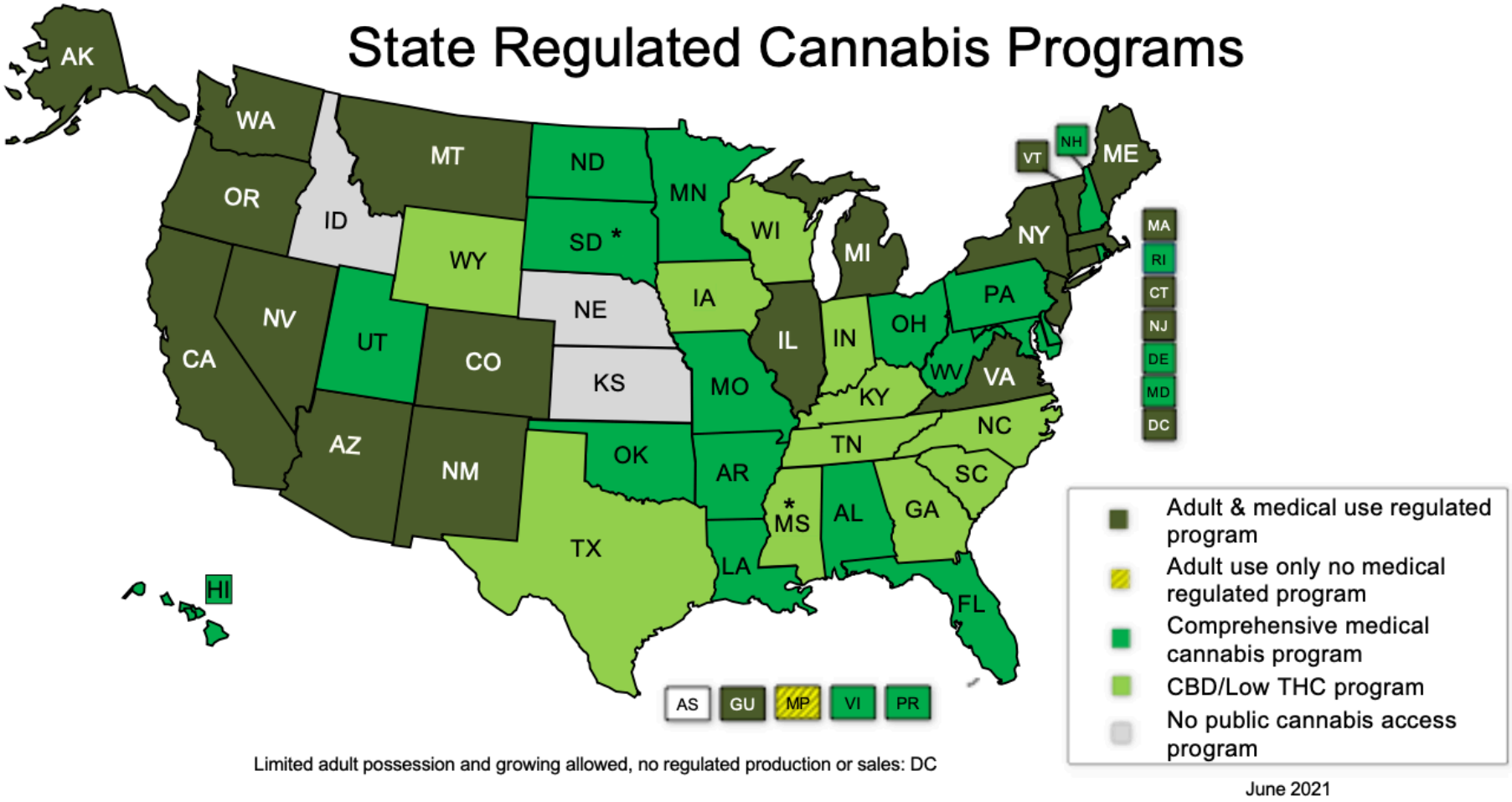
Prescription forms

- 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



Limited adult possession and growing allowed, no regulated production or sales: DC

June 2021

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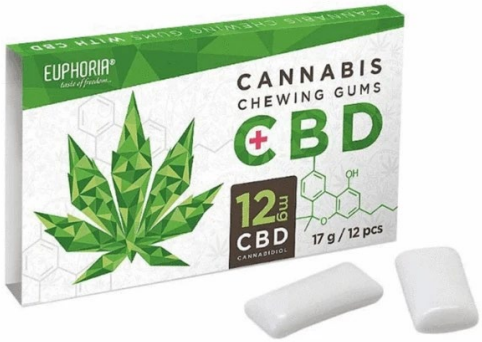
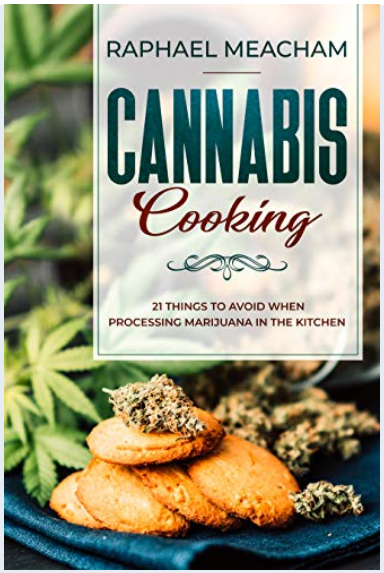
OTC forms





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Uses

- 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 cannabinodiols (CBN, CBND): Anti-inflammatory, antibiotic, sedative, anti-convulsant.
- Others: Includes cannabicyclols (CBL), cannabielsoins (CBE), cannabitriols (CBT) and other miscellaneous types.

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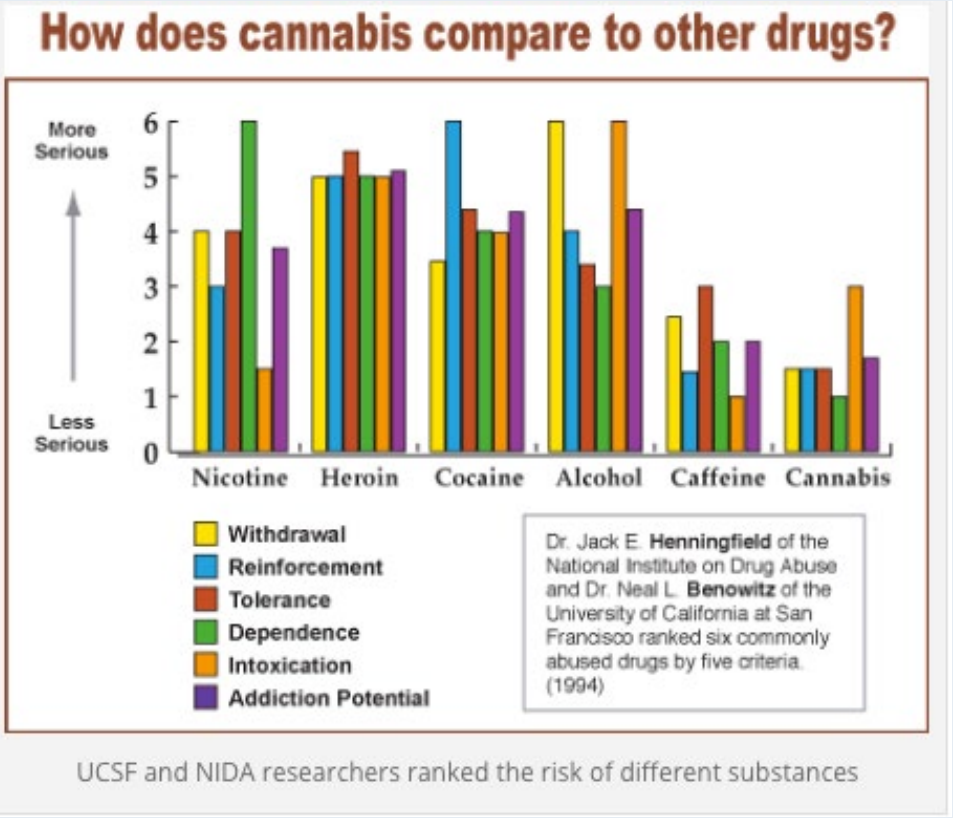
Safety



UCSF and NIDA researchers ranked the risk of different substances

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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 BEBRF Survey

Complementary Therapies	Yes	No/Blank	
Tried Complementary:	142	188	330
Current Complementary:	56		

Tried Other:* (excluded 4 for Dry Eyes)			
Farias/neuroplascity	9	light therapy, sacral cranial therapy	1
meditation	5	magneuam/peroxide drips	1
massage	4	Neurofeedback	1
homeopathic remedies	2	neuroplascity, meditation	1
Reiki	2	positive attitude/yoga	1
acupressure for cervical dystonia	1	psychologist counseling/zoloft until insura	1
cognitive behavior therapy	1	psychoterapy	1
cultural/religious rituals	1	sudafed, claritin d	1
eye/eyelid exercises	1	TMJ Treatments	1
Frankisencense essential oil	1	topical cream applied around the eyes	1
		yoga, accupressure, speech therapy, phys	1
			38

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2020 BEBRF Survey

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

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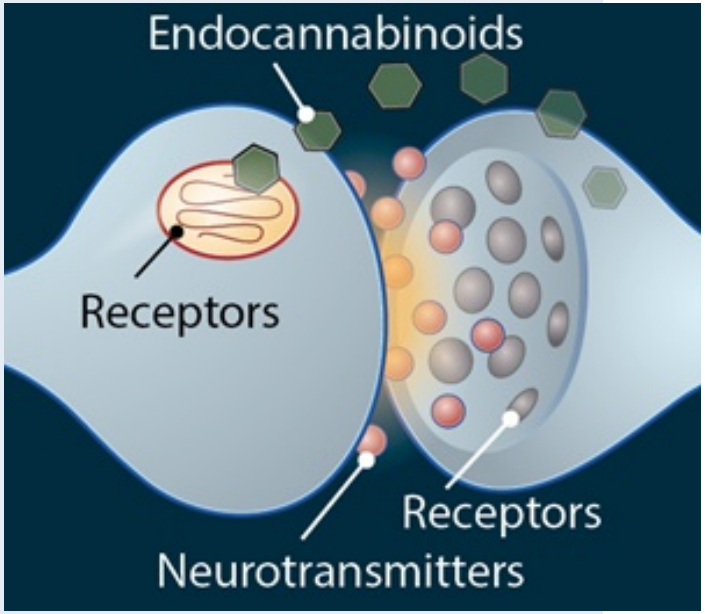
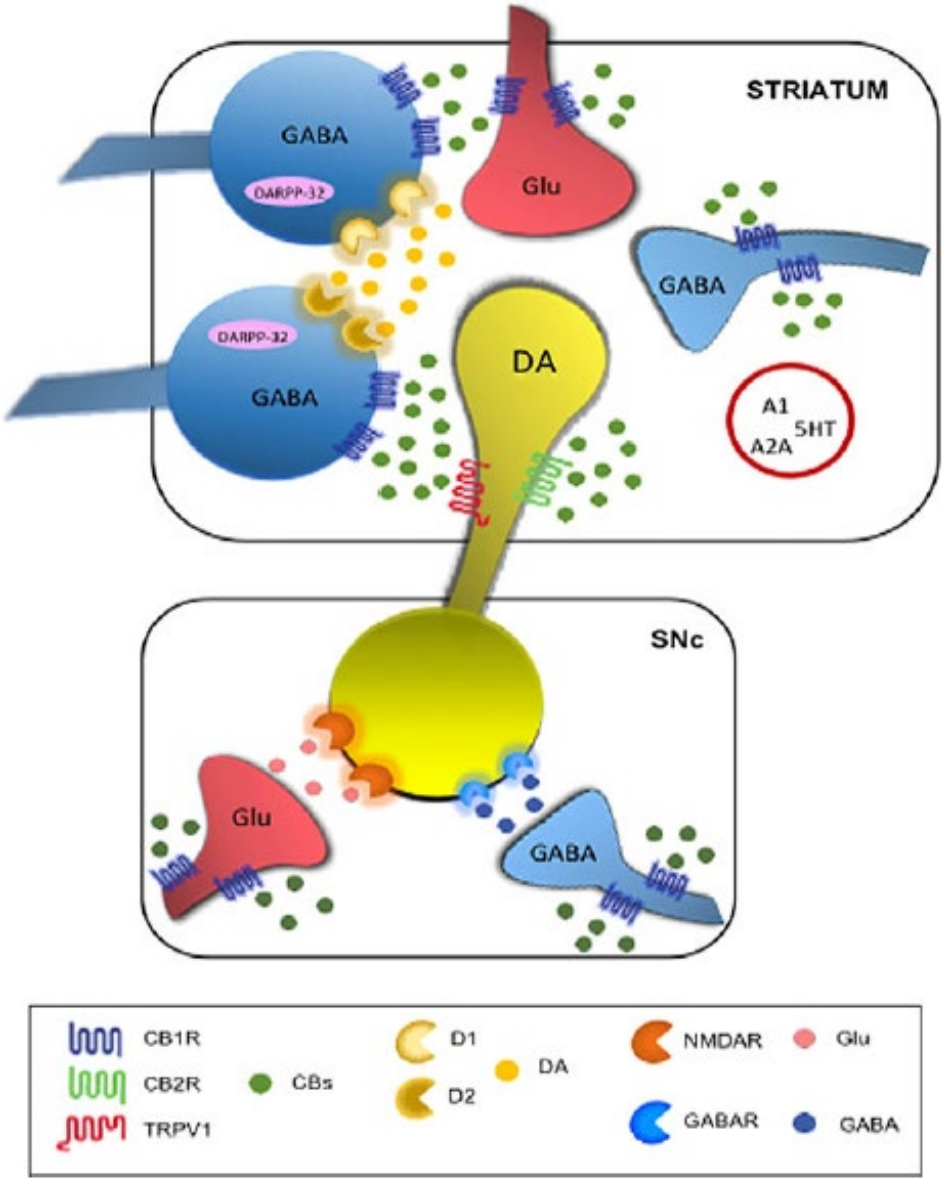
25 tried and stopped

Mechanism of action





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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?

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Parkinson disease

Study design	Number of patients	Cannabinoids	Results	Authors
Patient survey	84	Smoked cannabis	Forty-six percent of patients described some benefit; 31% reported improvement of rest tremor, 45% of bradykinesia and 14% of LID	Venderová et al.[88]
Patient survey	9	Cannabis	Seven patients (78%) reported improvement of mood and sleep, two patients reported improved motor symptoms, not specifically dyskinesias	Finseth et al.[89]
Case series	5	Smoked cannabis, 1 g cannabis (2–9% THC)	No benefit for tremor following single administration	Frankel et al.[90]
Open-label	22	Smoked cannabis, 0.5 g cannabis	Thirty minutes after smoking cannabis, patients reported improvement in tremor, rigidity, bradykinesia, pain, and sleep	Lotan et al.[91]
Four-week open-label	6	CBD up to 400 mg/day	Improvements on the Brief Psychiatric Rating Scale and Parkinson Psychosis Questionnaire	Zuardi et al.[92]
Case series	4	CBD 75 or 300 mg/day	Benefits for rapid eye movement sleep behavior disorder	Chagas et al.[93]
Randomized, double-blind, placebo-controlled crossover	5	Nabilone	Significant reduction of the Rush Dyskinesia Disability Scale and total LID time; two patients reported improvement in painful off-dystonia	Sieradzan et al.[94]
Four-week randomized, double-blind, placebo-controlled crossover	17	Cannador (1.25 mg CBD and 2.5 mg THC)	No improvement of LIDs on multiple outcomes. No significant changes for motor symptoms (UPDRS-III), quality of life (PDQ-39) or sleep	Carroll et al.[95]
Randomized, double-blind, placebo-controlled	8	Rimonabant	No effect on motor symptoms or LID (UPDRS and standardized videotape)	Mesnage et al.[96]
Randomized, double-blind, placebo-controlled	21	CBD 75 or 300 mg/day	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	Chagas et al.[97]

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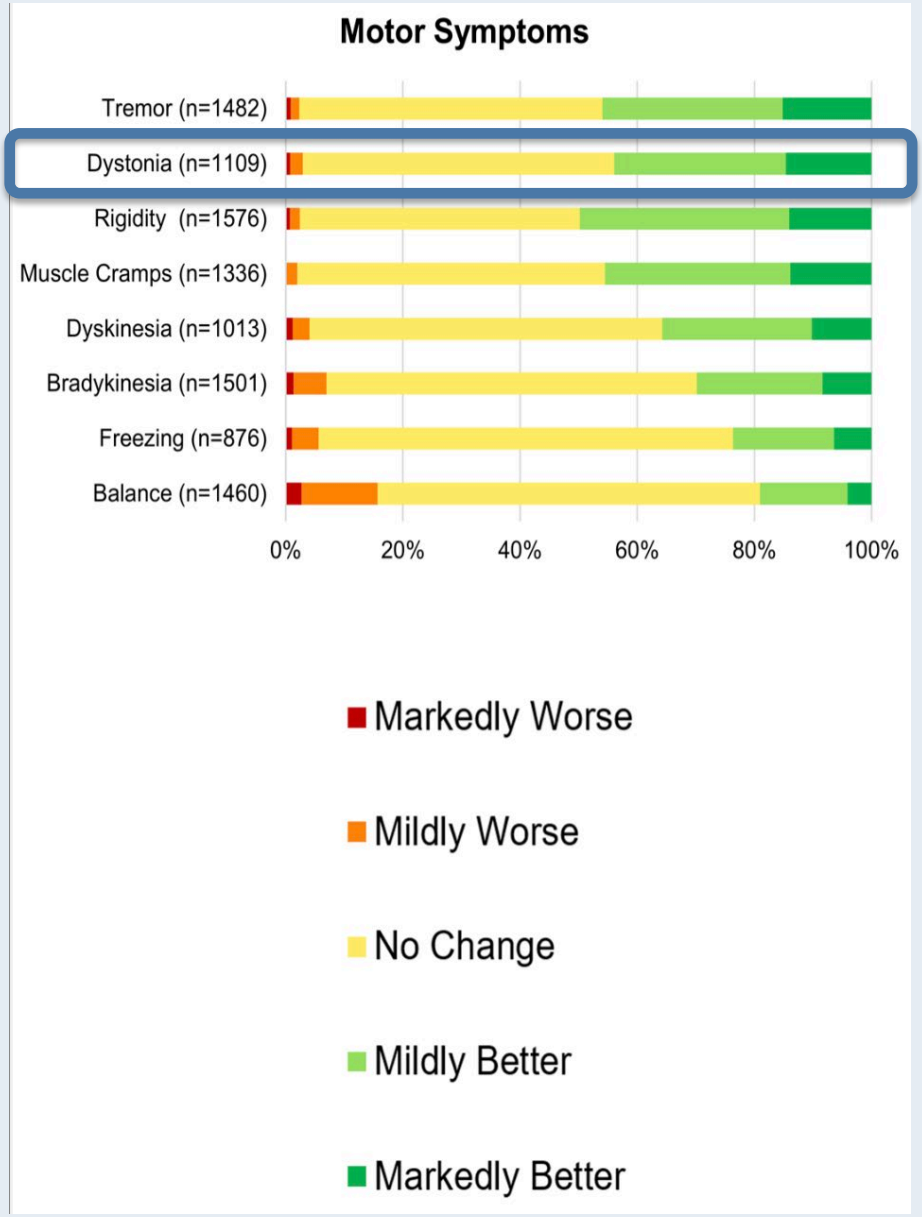
Parkinson disease

Fox Insight Cannabis Survey (N=1881)



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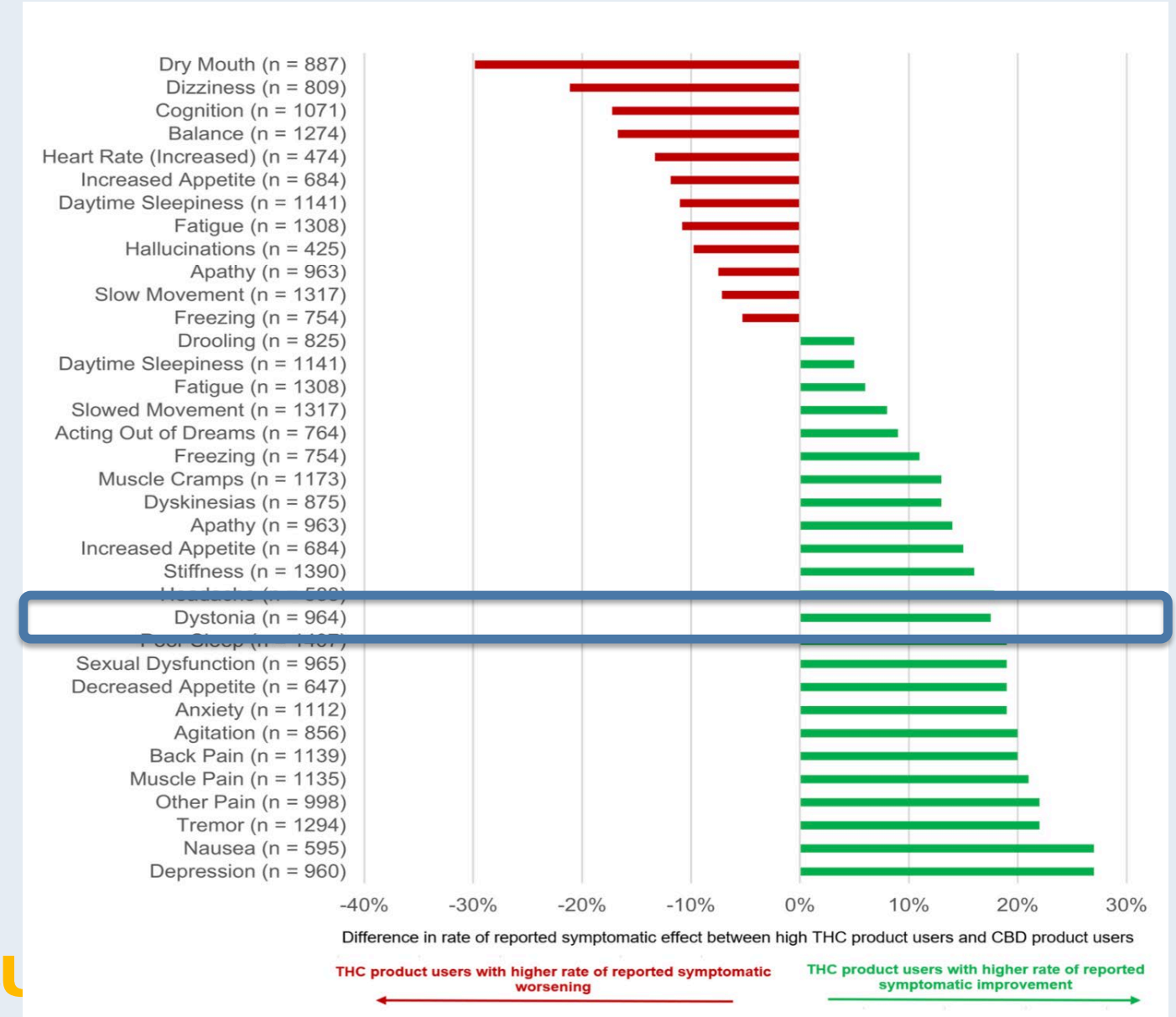
Parkinson disease



Cannabinoid studies in dystonia

Open label (1986) evaluation of Cannabidiol in dystonic movement disorders. Consroe P., Sandyk R., Snider S. R. Int. J. Neurosci. 30, 277–282.

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

Randomized, double-blind, placebo-controlled trial (2002) to assess the potential of cannabinoid receptor stimulation in the treatment of dystonia. Fox SH, Kellett M, Moore AP, Crossman AR, Brotchie JM. Mov Disord. 17(1):145-9.

- 15 patients with segmental and generalized dystonia treated with synthetic nabilone showed no improvement

Cannabinoid studies in blepharospasm

Medical Cannabis, a Beneficial High in Treatment of Blepharospasm? An **Early Observation (2017).** Radke PM, Mokhtarzadeh A, Lee MS, Harrison AR. Neuroophthalmology. 2017;41(5):253-258.

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

Cannabinoid agonists in the treatment of blepharospasm – a **case report (2004)** study. Gauter B, Rukwied R, Konrad C. Neuro Endocrinol Lett 25:45–48.

- Dronabinol improved pain and social life in single patient

Cannabinoid studies in blepharospasm

Cannabinoids and dystonia: an issue yet to be defined.

Marcello Mario Mascia, Daniele Carmagnini, Giovanni Defazio. Neurol Sci. 2020 Apr;41(4):783-787.

- 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

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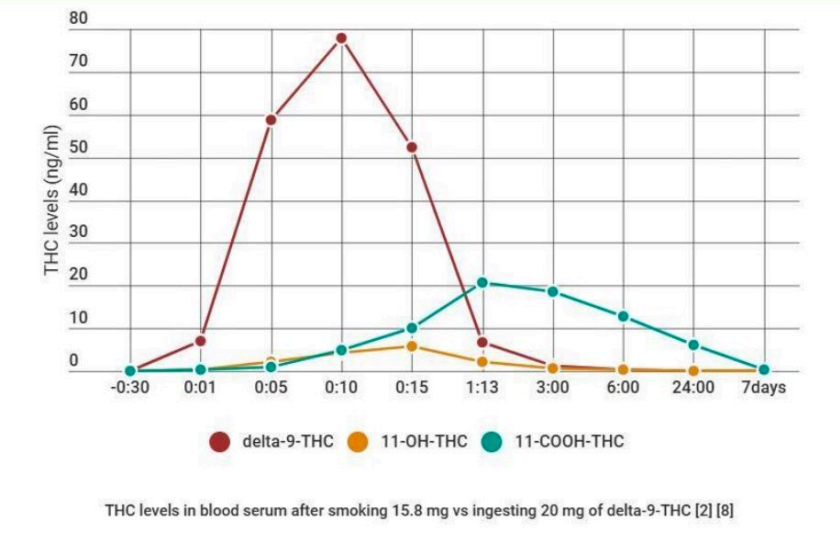
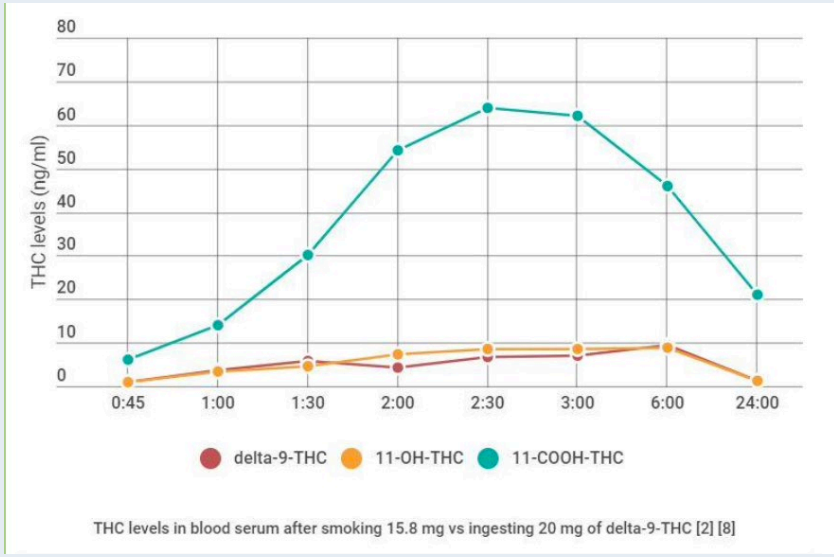
Recommendations?

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



THC levels in blood serum after smoking 15.8 mg vs ingesting 20 mg of delta-9-THC [2] [8]



THC levels in blood serum after smoking 15.8 mg vs ingesting 20 mg of delta-9-THC [2] [8]

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WHAT YOU LOOK LIKE WHEN
YOUR BOTOX DOESN'T TAKE AT THE SAME TIME
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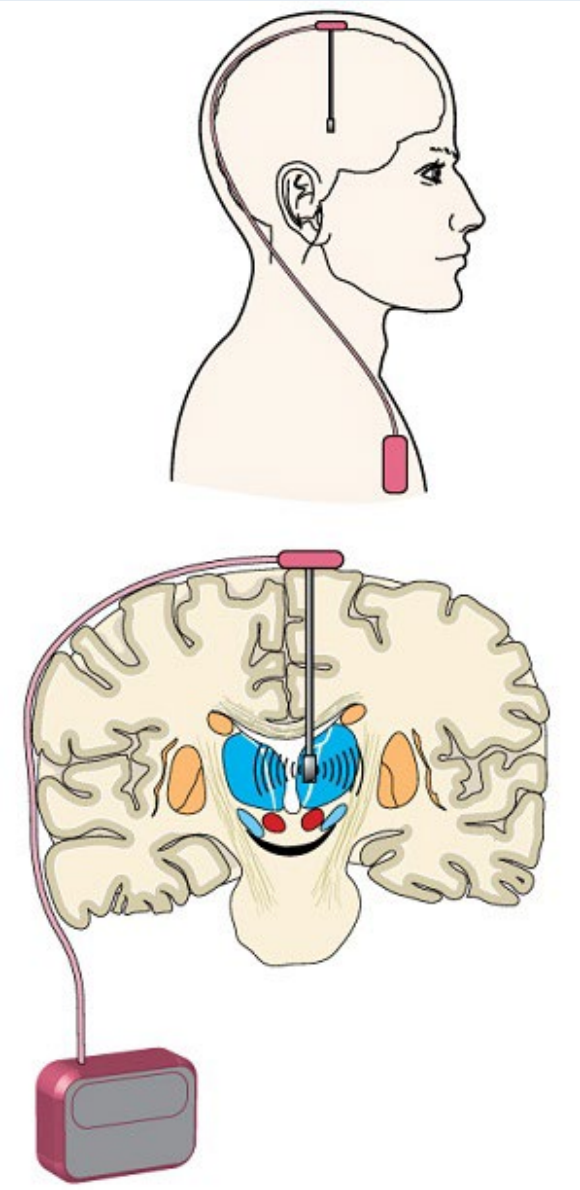
Deep brain stimulation



- 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

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Deep brain stimulation in blepharospasm

References	Type of patient	Number of patients	Site of stimulation	Therapeutic effect
Muta et al. (132)	MS	1	GPi	Improvement while remaining refractory to pharmacotherapy and bilateral thalamotomy
Foote et al. (126)	MS	1	Gpi	Improvement at 6-month follow up
Houser and Waltz (125)	MS	1	Gpi	Substantial improvement
Ostrem et al. (123)	MS	6	Gpi	Improvement of dystonia and slight worsening of motor function was reported in previously non-dystonic body regions in four patients
Hebb et al. (124)	MS	1	Gpi	Sustained relief of dystonia 1 year after cessation of DBS
Blomstedt et al. (121)	MS	1	Gpi	No improvement in axial symptoms but blepharospasm was abolished
Loher et al. (133)	MS	1	Gpi	Long-term symptomatic and functional improvement
Sensi et al. (134)	MS	9	Gpi	Significant improvement at 6 months and better outcome
Woehrle et al. (135)	MS	1	Gpi	Improvement
Inoue et al. (116)	MS	1	Gpi	Sustained long-term improvement (N80%) for 10 years
Ghang et al. (136)	MS	11	Gpi	Effective for intractable MS without significant side effects
Lyons et al. (137)	MS	4	Gpi	Effective for medically refractory MS
Markaki et al. (18)	MS	1	Gpi	Improvement by 70% in movement score and 93.33% in disability score
Romito et al. (138)	MS	1	Gpi	Progressive and sustained improvement of dystonia at 38-month follow-up
Sako et al. (119)	MS	5	Gpi	Significant improvement in movement and disability scales
Reese et al. (120)	MS	12	Gpi	Good effect persisting for up to 6 years
Tai et al. (139)	MS	1	Gpi	Good effect persisting for 36 months
Limotai et al. (140)	MS	6	Gpi	Low-frequency stimulation (100 Hz) was effective in two patients, with two patients experiencing a 20% benefit
Sobstyl et al. (141)	MS	3	Gpi	Burke-Fahn—Marsden dystonia rating scale total disability score was reduced by 34% and 47% at short- and long-term follow-ups, respectively
Bae et al. (142)	MS	1	Gpi	Excellent improvement in speech with no adverse events
Wang et al. (130)	MS	4	Gpi or STN	Significant improvement
Zhao et al. (143)	OMD	1	STN GPi	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.
Yamada et al. (144)	BSP	9	GPi	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.
Santos et al. (145)	BSP	1	GPi	Blepharospasm improved
Sobstyl et al. (104)	MS	6	Gpi	Significant improvement
Luthra et al. (146)	BSP	1	Gp	This case illustrates successful treatment of blepharospasm with pallidal stimulation.
Zhan et al. (147)	MS	15	STN	Immediate improvement in symptoms after stimulation; four adverse events recorded in three patients, all of which were resolved without permanent sequelae
Horisawa et al. (129)	MS	16	Gpi	Significant improvement
Aires et al. (128)	MS	2	Gpi	Dystonia was improved by 68% in Patient 1 and by 96% in Patient 2, whereas disability was improved by 77%–92% at 24-month follow-up
Yao et al. (127)	MS	15	STN	MS patients ($n = 14$) showed improved BFMDRS score
Shu et al. (148)	MS	1	Gpi	Significant improvement in symptoms
Wang et al. (149)	MS	20	Gp or STN	Good outcome in nine patients and poor outcome in 11 patients
Tian et al. (150)	MS	17	Gpi or STN	Both the STN and Gpi could be effective targets of DBS for MS.
Hao et al. (151)	MS	22	GPi	Bilateral pallidal neurostimulation is a beneficial therapeutic option for refractory MS, which could improve the motor symptoms except for depression and sleep quality.
Ouyang et al. (152)	MS	15	STN	STN-DBS was not only able to improve patients' motor symptoms, but also their sleep status.

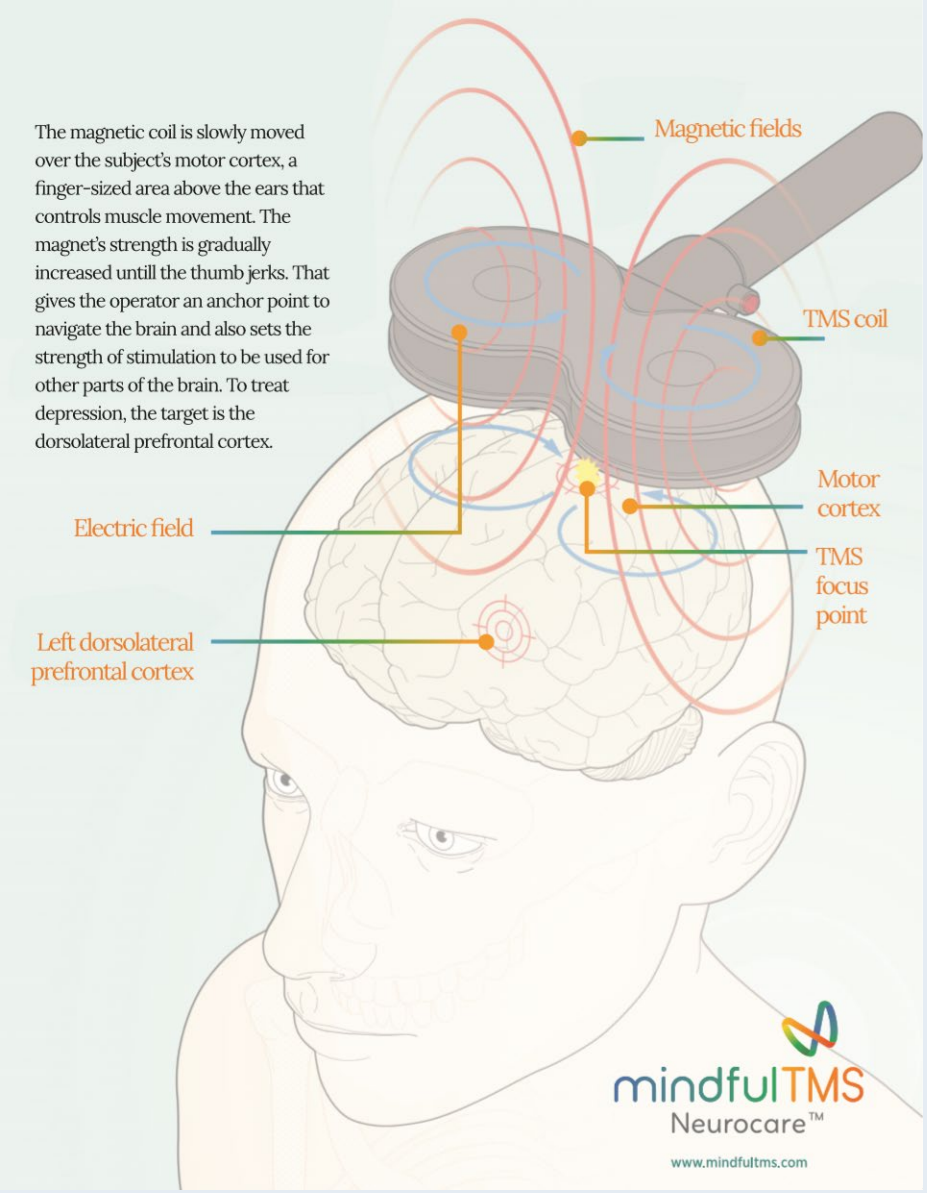
DBS, deep brain stimulation; GPi, globus pallidus internal; STN, subthalamic nucleus; MS, Meige syndrome; BSP, Blepharospasm; OMD, oromandibular dystonia.

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

Deep brain stimulation for Meige syndrome: a meta-analysis with individual patient data. J Neurol 266, 2646–2656 (2019).

Blepharospasm, Oromandibular Dystonia, and Meige Syndrome: Clinical and Genetic Update Front Neurol. 2021 Mar 29;12:630221.

How about something less invasive?



FDA device permits

2008 Major depression
2013 Migraine
2018 OCD
2020 Smoking cessation
2020 Bipolar depression
2021 Anxiety in depression

TMS in blepharospasm

October 19, 2010; 75 (16) ARTICLES

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

CORRESPONDENCE | VOLUME 11, ISSUE 3, P645-647, MAY 01, 2018

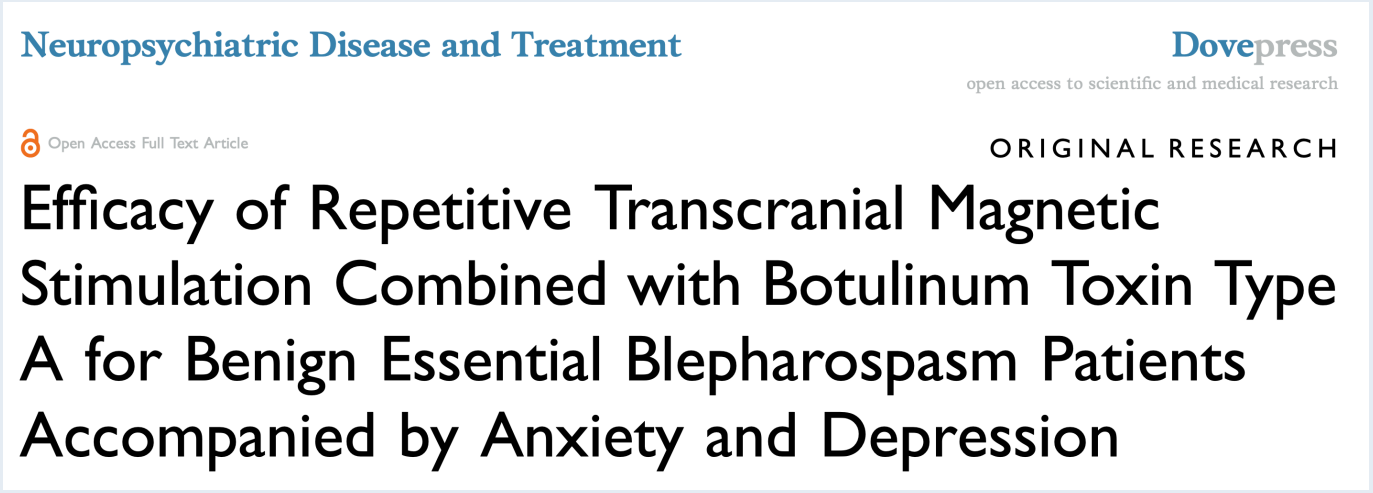
Combined effects of rTMS and botulinum toxin therapy in benign essential blepharospasm

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 • Check for updates

- 2 weeks of rTMS given 6 weeks after BoNT showed improvement 2 weeks after TMS but not at 6 weeks

TMS in blepharospasm



Neuropsychiatric Disease and Treatment

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ORIGINAL RESEARCH

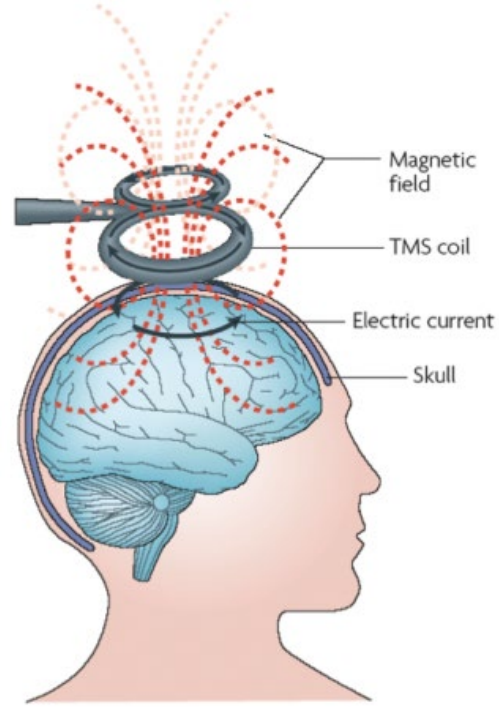
Efficacy of Repetitive Transcranial Magnetic Stimulation Combined with Botulinum Toxin Type A for Benign Essential Blepharospasm Patients Accompanied by Anxiety and Depression

August 2021

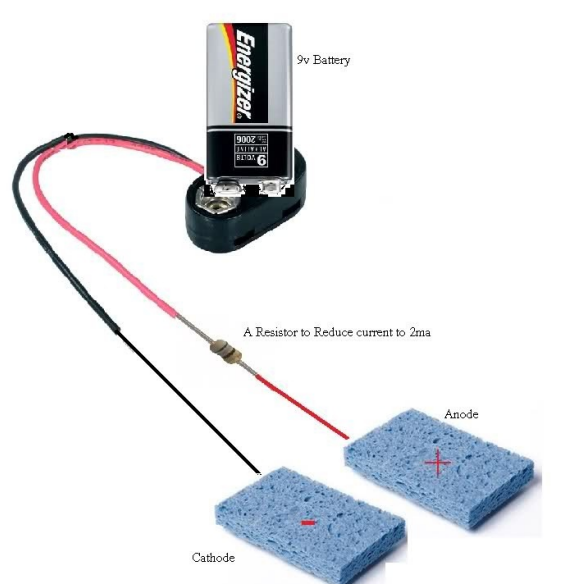
- BoNT combined with 20-minute sessions of rTMS over 20 days improved symptoms in 35 patients with anxiety/depression compared to 28 patients treated BoNT only.
  - Improved Efficacy: 94.29% vs 92.86%
  - Increased Duration: 16.9 weeks vs 13.0 weeks

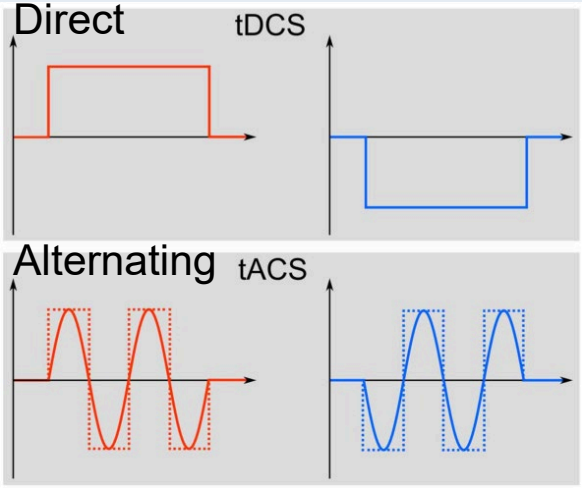
Transcranial Magnetic vs Electrical stimulation

Magnetic (TMS)



Electrical (TES)





TES in blepharospasm

Case Reports > Neurol Sci. 2017 Jan;38(1):201-202. doi: 10.1007/s10072-016-2703-x. Epub 2016 Sep 26.

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]

Case Reports > Neurophysiol Clin. 2020 Oct;50(5):391-392. doi: 10.1016/j.neucli.2020.09.006. Epub 2020 Sep 30.

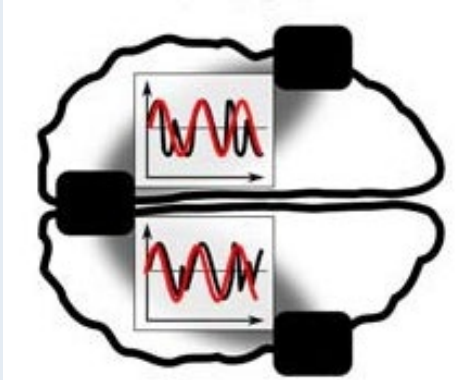
Treatment of cervical dystonia and blepharospasm by anodal tDCS of cerebellar hemispheres. A case report

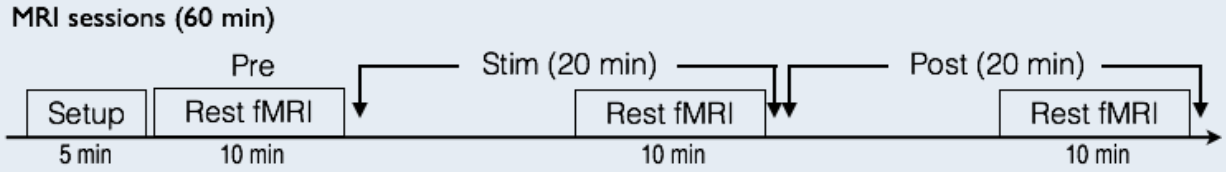
Jean-Paul Nguyen [1], Alcira Suarez [2], Catherine Malineau [2], Véronique Dixneuf [2], Gilles Mazaltarine [2], Philippe Damier [3]

TACS in cervical dystonia

SCHOOL OF MEDICINE
Department of Neurology
UNIVERSITY OF COLORADO ANSCHUTZ MEDICAL CAMPUS

Mary Rossick Kern
and Jerome H. Kern





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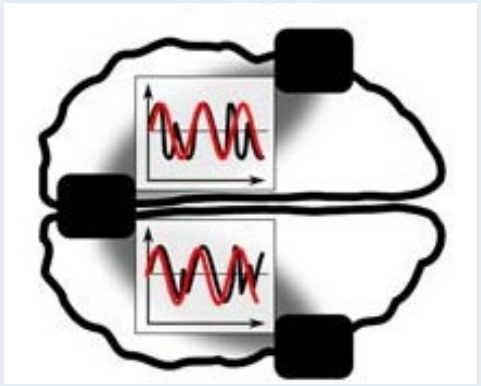
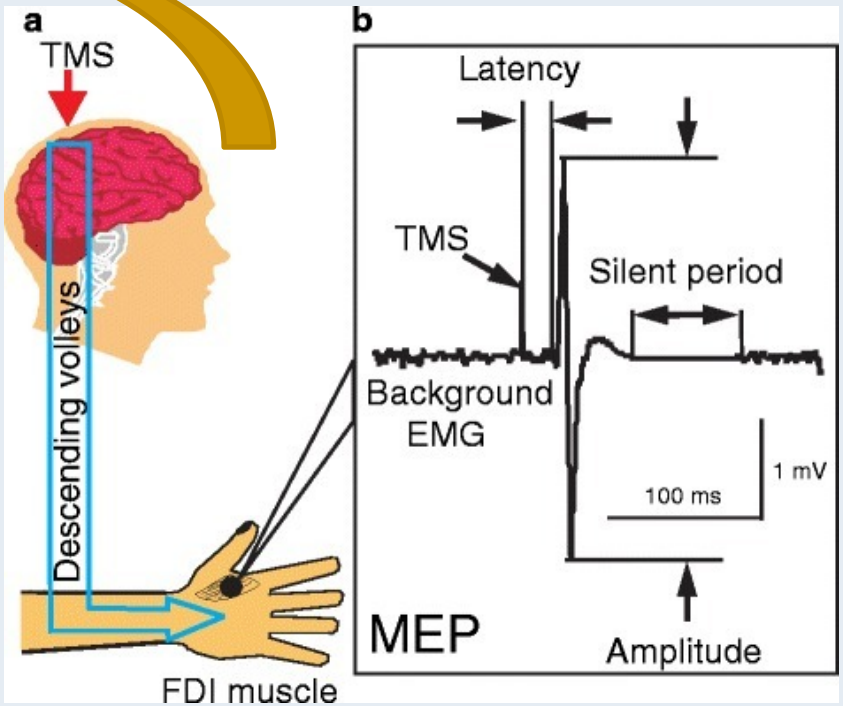
TACS in cervical dystonia



X 5 days



Change in symptoms or motor excitability?

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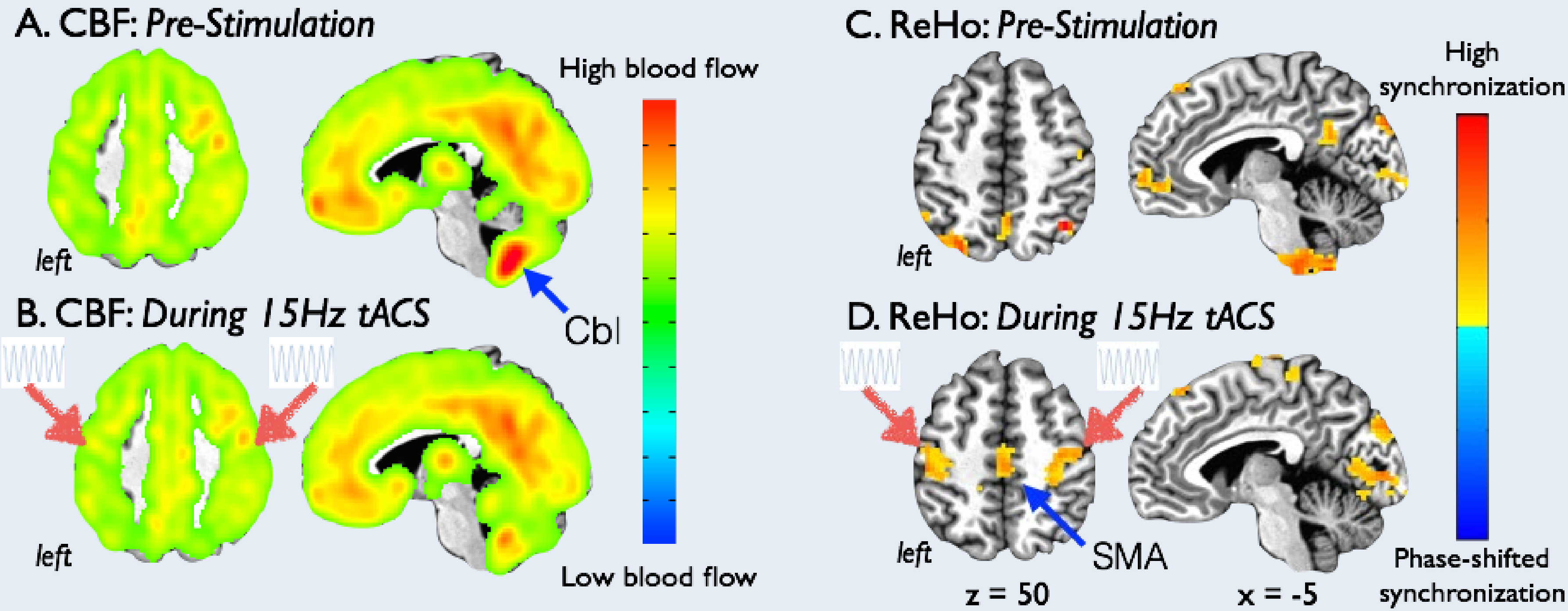
TACS effects on motor network



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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)

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Benign Essential Blepharospasm Research Foundation

Thank you!

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DYSTONIA COALITION

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