Evidence-based of medical cannabis in Parkinson's disease and other movement disorders

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Disclosure

- I’ve never prescribed any preparation of medical cannabis to my patients.
- As far as I understand, there is no preparation of cannabis for medical use in my hospital.
- However, some of my patients concurrently use an oral cannabis to treat their specific symptoms together with my prescriptions.
- In addition, some parts of systematic review and recommendations are based on my team experience according to an established AAN classification of Evidence and Recommendation.

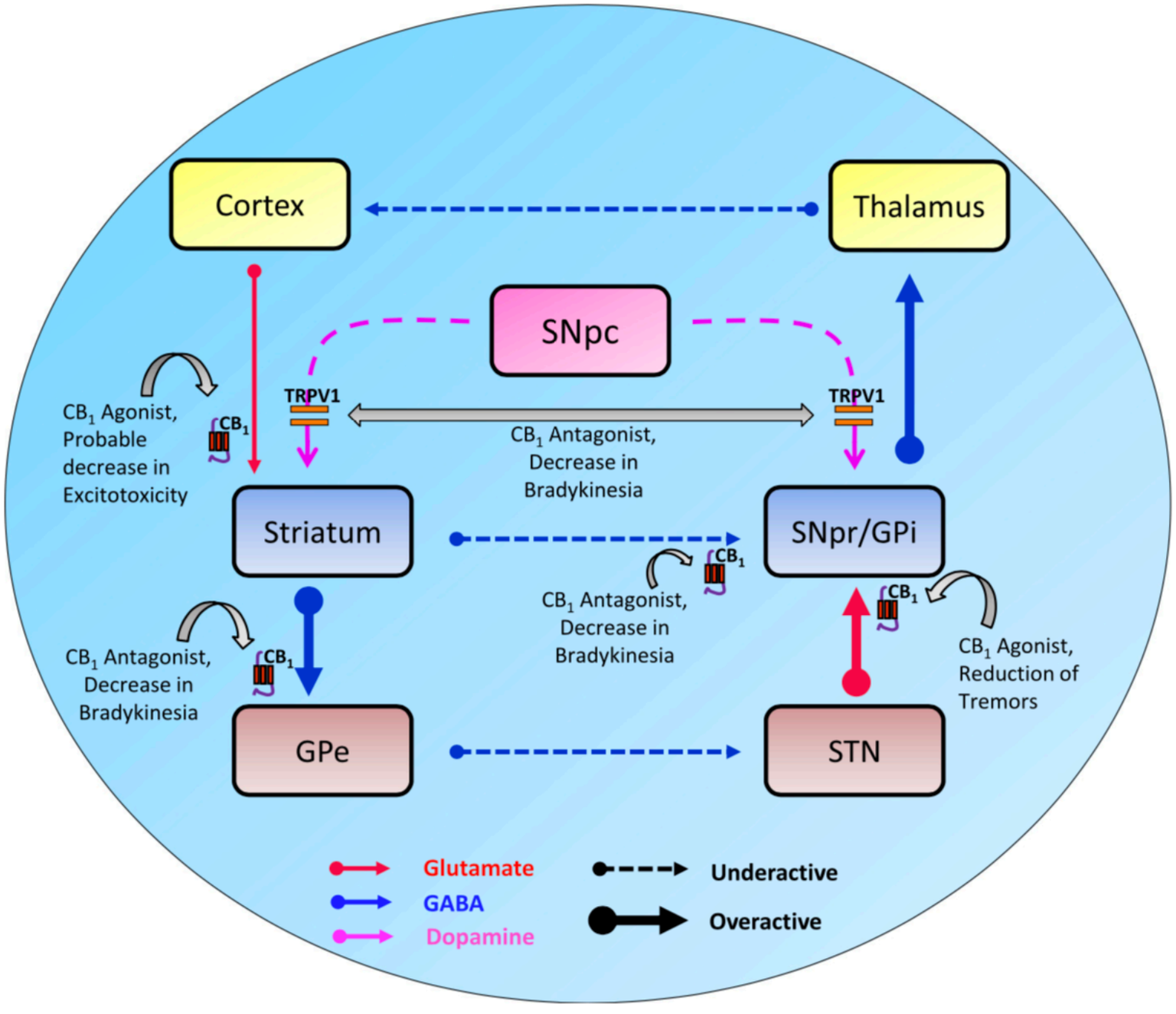
Outline of Talk

- Evidence-based of medical cannabis in Parkinson's disease
- Evidence-based of medical cannabis in other movement disorders
- Ultimate guide for managing patient expectations
- Take home message and directions for future research

Why is clinical research in medical cannabis important for medical professionals?

Evidence-based of medical cannabis in Parkinson's disease

Basal ganglial circuitry in Parkinson's disease (PD) and tentative cannabinoid targets to improve motor disability in PD



More S, et al. Molecule Degen 2015:10;17.

SPECIAL ARTICLE

AMERICAN ACADEMY OF NEUROLOGY

Systematic review: Efficacy and safety of medical marijuana in selected neurologic disorders

Report of the Guideline Development Subcommittee of the American Academy of Neurology

Included published studies up to November 2013

This evidence-based systematic review seeks to answer questions regarding safety and efficacy of cannabinoids in relieving/reducing the following:

1. Spasticity in patients with multiple sclerosis (MS)
2. Central pain and painful spasms in MS (pain could be from any etiology, including spasticity,but excluding neuropathic pain)
3. Bladder dysfunction in MS
4. Involuntary movements, including tremor, in MS
5. Dyskinesias of Huntington disease (HD), levodopa-induced dyskinesias of Parkinson disease, cervical dystonia, and tics of Tourette syndrome
6. Seizure frequency in epilepsy

Koppel B, et al. Neurology 2014;82:1556-63.

SPECIAL ARTICLE

AMERICAN ACADEMY OF NEUROLOGY

Systematic review: Efficacy and safety of medical marijuana in selected neurologic disorders

Report of the Guideline Development Subcommittee of the American Academy of Neurology

Included published studies up to November 2013

Classification of recommendation

Conclusion

Level B: Oral cannabis extract is probably ineffective for treating levodopa-induced dyskinesias in patients with Parkinson disease (1 Class I study).

Koppel B, et al. Neurology 2014;82:1556-63.

REVIEW

The Therapeutic Potential of Cannabinoids for Movement Disorders

Benzi Kluger, MD, MS,[1†*] Piera Triolo, BS,[1†] Wallace Jones, BS,[1†] and Joseph Jankovic, MD[2†]

[1]*Movement Disorders Center, Department of Neurology, University of Colorado School of Medicine, Aurora, Colorado, USA*
[2]*Parkinson's Disease Center and Movement Disorders Clinic, Department of Neurology, Baylor College of Medicine, Houston, Texas, USA*

Included published studies up to August 2014

- Endocannabinoids and the Basal Ganglia
- Preclinical neuroprotective studies of cannabinoids
- Preclinical studies assessing therapeutic symptomatic efficacy of cannabinoids for movement disorders
- Clinical studies of cannabinoids for movement disorders***Parkinson's disease, Huntington's disease, Tremor, Dystonia, Tics

Kluger B, et al. Mov Disord 2015;30:313-27.

Movement Disorder	Study Design	Sample Size	Intervention	Outcome	Reference
Parkinson's Disease	Randomized, double-blind, placebo-controlled, crossover	17	Cannador standardized to 2.5 mg of D9-THC and 1.25 mg of cannabidiol per capsule. Two treatment phases, each of 4 weeks duration separated by a 2-week washout phase.	No improvement in LID, motor symptoms, quality of life, or sleep	92
	Case series	5	One gram of marijuana (2%9% THC) smoked as a cigarette on morning of testing.	None of the patients experienced relief or demonstrated improvement of tremor after marijuana.	91
	Case series	22	After baseline assessment, patients were asked to smoke 0.5 g of cannabis. Thirty minutes later, the motor and nonmotor battery was repeated.	Significant improvement in tremor and bradykinesia	70
	Randomized, double-blind,	8	Administered 20 mg of rimonabant (CB_1	No effect on LID or motor disability	89
			mously complete a questionnaire about their possible experience with cannabis.	PD symptoms, including resting tremor and LID.	93
	Open-label pilot study.	6	A 150-mg cannabidiol tablet was administered; the dose was increased weekly by 150 mg, depending on the clinical response, for 4 weeks.	Decreased psychotic symptoms	88
	Open-label pilot study	4	Patients administered 75 to 300 mg/day of cannabidiol	Decreased RBD per patient and spouse report	90
	Randomized, double-blind, placebo-controlled study	21	Patients randomized to placebo, 75 mg/day cannabidiol, or 300 mg/day cannabidiol for 6 weeks	No change in total UPDRS or any subscales. Improvements were reported for total PDQ-39 score in 300-mg/day group.	95

9 papers were included

No classification of recommendation

Kluger B, et al. Mov Disord 2015;30:313-27.

According to previous information, are you confident for prescribing in clinical practices?

This an evidence-based systematic was conducted to answer questions regarding safety and efficacy of cannabis in relieving/reducing the following PD concerns:

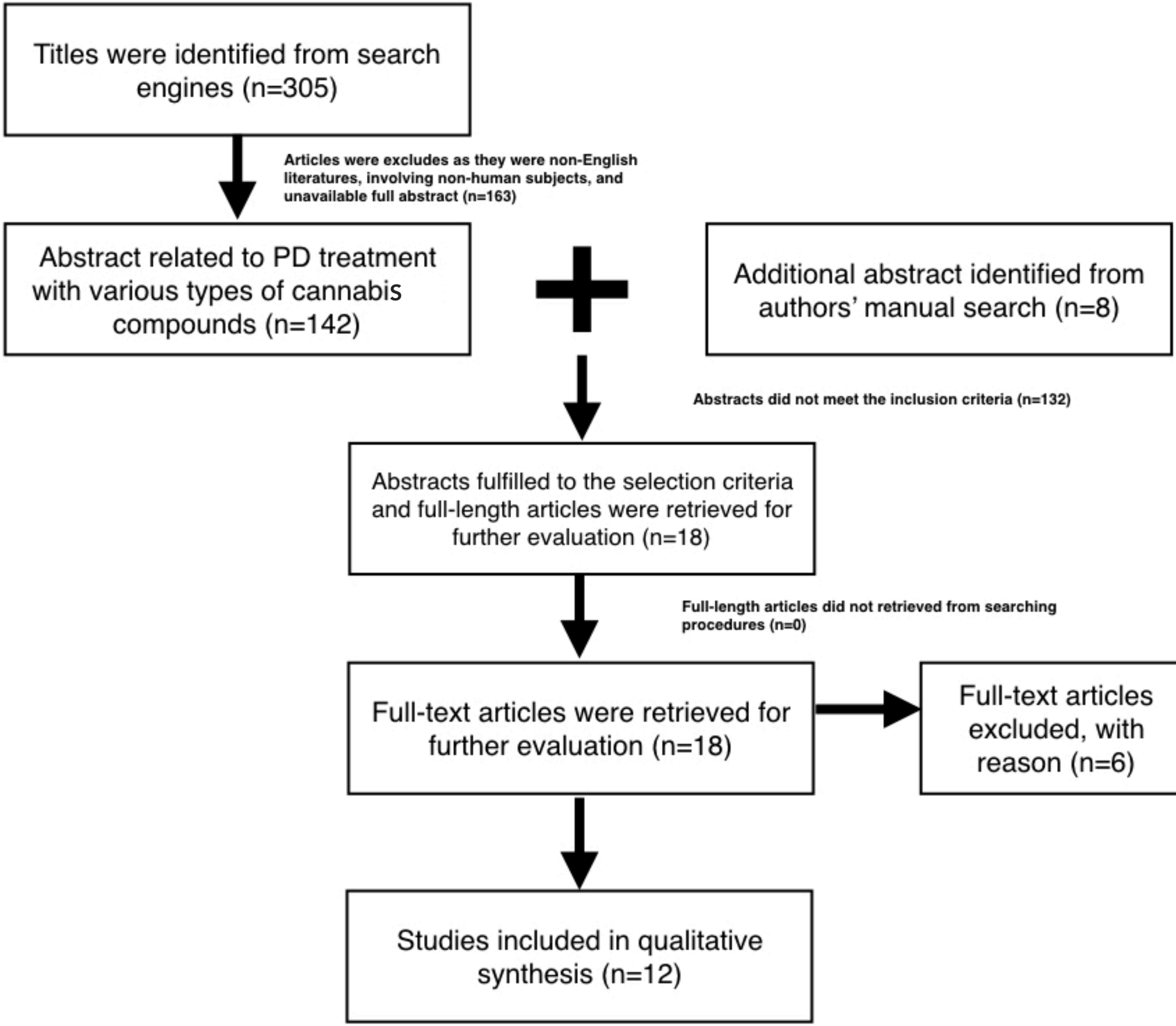
1. Does cannabis reduce levodopa-induced dyskinesia in PD patients?
2. Does cannabis improve motor symptoms in PD patients?
3. Does cannabis improve the quality of life in PD patients?
4. Does cannabis improve psychosis in PD patients?
5. Does cannabis reduce pain in PD patients?
6. Does cannabis reduce REM sleep-related disorders in PD patients?

Manuscript in preparation

Searching method for potential benefits of medical cannabis treatment in PD

Data source and search

- Literatures about the potential benefits of medical cannabis usage in Parkinson's disease were searched electronically in Pubmed, MEDLINE, life science journals, Google scholar, and online books databases at the initiation of the project. The querying keywords were including as the following: Cannabis OR Marijuana OR Cannabidiol OR Tetrahydrocannabinol OR Cannabinol OR Phytocannabinoid OR Endocannabinoid OR Nabilone OR Dronabinol OR Levonantradol OR Rimonabant OR Nabiximols OR Anandamide OR Arachidonoylglycerol
- Articles included in this review were specifically required to have the term "Parkinson's disease" AND "Parkinson" AND "Parkinsonism" in any one of the above key words within the title and/or abstract.
- The study was contained data relevant to the study about cannabis treatment in any aspects of PD. The study was available in full length in English and published before **the 30th November 2019**.
- Review articles, editorials, and clinical commentaries are excluded from the review process.


Titles were identified from search engines (n=305)
Articles were excludes as they were non-English literatures, involving non-human subjects, and unavailable full abstract (n=163)
Abstract related to PD treatment with various types of cannabis compounds (n=142)
Additional abstract identified from authors' manual search (n=8)
Abstracts did not meet the inclusion criteria (n=132)
Abstracts fulfilled to the selection criteria and full-length articles were retrieved for further evaluation (n=18)
Full-length articles did not retrieved from searching procedures (n=0)
Full-text articles were retrieved for further evaluation (n=18)
Full-text articles excluded, with reason (n=6)
Studies included in qualitative synthesis (n=12)

American Academy of Neurology Classification of Evidence and Recommendation

Therapeutic

Class I: A randomized, controlled clinical trial of the intervention of interest with masked or objective outcome assessment, in a representative population. Relevant baseline characteristics are presented and substantially equivalent among treatment groups or there is appropriate statistical adjustment for differences.

The following are also required:

a. concealed allocation
b. primary outcome(s) clearly defined
c. exclusion/inclusion criteria clearly defined
d. adequate accounting for drop-outs (with at least 80% of enrolled subjects completing the study) and cross-overs with numbers sufficiently low to have minimal potential for bias.
e. For non inferiority or equivalence trials claiming to prove efficacy for one or both drugs, the following are also required*

1. The authors explicitly state the clinically meaningful difference to be excluded by defining the threshold for equivalence or non-inferiority.
2. The standard treatment used in the study is substantially similar to that used in previous studies establishing efficacy of the standard treatment. (e.g. for a drug, the mode of administration, dose and dosage adjustments are similar to those previously shown to be effective).
3. The inclusion and exclusion criteria for patient selection and the outcomes of patients on the standard treatment are comparable to those of previous studies establishing efficacy of the standard treatment.
4. The interpretation of the results of the study is based upon a per protocol analysis that takes into account dropouts or crossovers.

Class II: A randomized controlled clinical trial of the intervention of interest in a representative population with masked or objective outcome assessment that lacks one criteria a-e above or a prospective matched cohort study with masked or objective outcome assessment in a representative population that meets b-e above. Relevant baseline characteristics are presented and substantially equivalent among treatment groups or there is appropriate statistical adjustment for differences.

Class III: All other controlled trials (including well-defined natural history controls or patients serving as own controls) in a representative population, where outcome is independently assessed, or independently derived by objective outcome measurement.**

Class IV: Studies not meeting Class I, II or III criteria including consensus or expert opinion.

Classification of Recommendations

A = Established as effective, ineffective or harmful (or established as useful/predictive or not useful/predictive) for the given condition in the specified population. (Level A rating requires at least two consistent Class I studies.)*

B = Probably effective, ineffective or harmful (or probably useful/predictive or not useful/predictive) for the given condition in the specified population. (Level B rating requires at least one Class I study or two consistent Class II studies.)

C = Possibly effective, ineffective or harmful (or possibly useful/predictive or not useful/predictive) for the given condition in the specified population. (Level C rating requires at least one Class II study or two consistent Class III studies.)

U = Data inadequate or conflicting; given current knowledge, treatment (test, predictor) is unproven.

*In exceptional cases, one convincing Class I study may suffice for an "A" recommendation if 1) all criteria are met, 2) the magnitude of effect is large (relative rate improved outcome > 5 and the lower limit of the confidence interval is > 2).

***Surveys, case reports/series, and non placebo-controlled trials were excluded.*

1

Does cannabis reduce levodopa-induced dyskinesia in PD patients?

3 papers

CME

Cannabis for dyskinesia in Parkinson disease

A randomized double-blind crossover study

C.B. Carroll, PhD, MRCP; P.G. Bain, MD, FRCP; L. Teare, BM BCh, MRCP; X. Liu, MB, PhD; C. Joint, RGN; C. Wroath, BA, RGN; S.G. Parkin, BM BCh, MRCP; P. Fox, BM BCh, MRCP; D. Wright, PhD; J. Hobart, PhD, MRCP; and J.P. Zajicek, PhD, FRCP

Reference	Drug/treatment	Class	Sample size	Study duration	Maximum dose	Scale for primary outcome	Outcome
Carroll et al. Neurology 2004	2.5mg of 9-THC + 1.25mg of CBD per capsule (titrate to maximum dose 0.25 mg/kg of THC per day) or placebo	I	19 (2 withdrawn)	4 weeks	Titrate to maximum dose 0.25 mg/kg of THC per day)	UPDRS, dyskinesia questions 32 to 34	Unchanged in dyskinesia score

Carroll C, et al. Neurology 2004;63:1245-50.

Cannabinoids reduce levodopa-induced dyskinesia in Parkinson's disease: A pilot study

Article abstract—The lateral segment of the globus pallidus (GPl) is thought to be overactive in levodopa-induced dyskinesia in PD. Stimulation of cannabinoid receptors in the GPl reduces γ-aminobutyric acid (GABA) reuptake and enhances GABA transmission and may thus alleviate dyskinesia. In a randomized, double-blind, placebo-controlled, crossover trial (n = 7), the authors demonstrate that the cannabinoid receptor agonist nabilone significantly reduces levodopa-induced dyskinesia in PD.

NEUROLOGY 2001;57:2108–2111

K.A. Sieradzan, MRCP, PhD; S.H. Fox, MRCP, PhD; M. Hill, PhD; J.P.R. Dick, FRCP, PhD; A.R. Crossman, DSc; and J.M. Brotchie, PhD

Reference	Drug/treatment	Class	Sample size	Study duration	Maximum dose	Scale for primary outcome	Outcome
Sieradzan K, et al. Neurology 2001	Nabilone or placebo (two split doses 12 hrs and 1 hr before levodopa administration)	III	9 (2 withdrawn)	20-minute intervals after levodopa (200 mg)	0.03 mg/kg	Rush dyskinesia disability scale	Significantly reduces levodopa-induced dyskinesia ($p<0.05$)

Sieradzan K, et al. Neurology 2001;57:2108-11.

Neurokinin B, Neurotensin, and Cannabinoid Receptor Antagonists and Parkinson Disease

V. Mesnage, MD, J. L. Houeto, MD,* A. M. Bonnet, MD,* I. Clavier, MD,* I. Arnulf, MD,†*
F. Cattelin MD,‡ G. Le Fur, MD, PhD,‡ P. Damier, MD, PhD,‡ M. L. Welter, MD, and Y. Agid, MD, PhD**

Reference	Drug/treatment	Class	Sample size	Study duration	Maximum dose	Scale for primary outcome	Outcome
Mesnage V, et al. Clin Neuropharmacol 2004	Cannabinoid CB1 antagonist (SR 141716) or placebo	III	16	90-minute after a single suprathreshold levodopa (+50 mg) For 16 days (9 days in placebo group)	20 mg	UPDRS IV	No significant difference in the severity of the levodopa-induced dyskinesia

Mesnage V, et al. Clin Neuropharm 2004;27:108-110.

ANS: Does cannabis reduce levodopa-induced dyskinesia in PD patients?

Suggestion

Level B: Oral cannabis is probably **ineffective** for treating levodopa-induced dyskinesias in patients with Parkinson disease (1 Class I study).

Koppel B, et al. Neurology 2014;82:1556-63.

2

Does cannabis improve motor symptoms in PD patients?

5 papers

ORIGINAL ARTICLE

Cannabis (Medical Marijuana) Treatment for Motor and Non–Motor Symptoms of Parkinson Disease: An Open-Label Observational Study

Itay Lotan, MD, Therese A. Treves, MD, Yaniv Roditi, MD, and Ruth Djaldetti, MD

Reference	Drug/treatment	Class	Sample size	Study duration	Maximum dose	Scale for primary outcome	Outcome
Lotan I, et al. Clin Neuropharm 2014	Inhaled cannabis (Participants were treated with cannabis on a daily basis for at least 2 months)	IV	22	30 min after inhale cannabis	0.5 mg	Motor symptoms in PD by UPDRS-III	-Significantly improved UPDRS-III score ($p<0.001$)

Lotan I, et al. Clin Neuropharm 2014;37:41-44.

EJP
European Journal of Pain

ORIGINAL ARTICLE

Effect of medical cannabis on thermal quantitative measurements of pain in patients with Parkinson's disease

A. Shohet[1,2], A. Khlebtovsky[1,2], N. Roizen[1,2], Y. Roditi[1,2], R. Djaldetti[1,2]

1 Movement Disorder Clinic, Department of Neurology, Rabin Medical Center – Beilinson Hospital, Petach Tikva, Israel
2 Sackler Faculty of Medicine, Tel Aviv University, Israel

Reference	Drug/treatment	Class	Sample size	Study duration	Maximum dose	Scale for primary outcome	Outcome
Shohet A, et al. Eur J Pain 2017	Inhaled cannabis (Participants were treated with cannabis on a daily basis for at least 2 months)	IV	20 (18 smoking, 2 vaporizer)	30 min after inhaled cannabis Long-term exposure up to 40 weeks (median 14 weeks)	1 mg	Motor symptoms in PD by UPDRS-III	- Significantly improved UPDRS-III score ($p<0.0001$)

Shohet A, et al. Eur J Pain 2017:486-93.

LETTERS TO THE EDITOR

Marijuana for Parkinsonian tremor

Reference	Drug/treatment	Class	Sample size	Study duration	Maximum dose	Scale for primary outcome	Outcome
Frankel J, et al. JNNP 1990	Inhaled cannabis	IV	5	Assessment after a single dose	1 g of the shredded marijuana leaf (2-9% THC by weight)	Modified Webster scale	No improvement of tremor after marijuana

Frankel J, et al. JNNP 1990;53:436-42.

Survey on Cannabis Use in Parkinson's Disease: Subjective Improvement of Motor Symptoms

Kateřina Venderová, PharmD, PhD,[1]
Evžen Růžička, MD, DSc,[2*] Viktor Voříšek, PharmD,[3]
and Peter Višňovský, MD, PhD[1]

[1]*Department of Pharmacology and Toxicology, Faculty of Pharmacy, Charles University, Hradec Králové, Czech Republic*
[2]*Movement Disorders Centre, Department of Neurology, 1st Medical Faculty, Charles University, Prague, Czech Republic*
[3]*Division of Clinical Toxicology and Mass Spectrometry, Department of Biochemistry, University Hospital Hradec Králové, Czech Republic*

Reference	Drug/treatment	Class	Sample size	Study duration	Maximum dose	Scale for primary outcome	Outcome
Vendorova K, et al. Mov Disord 2004	Medical cannabis	IV	339 (mailing responders 53.8%)	Duration of usage: 1 hr – 6 months	Unavailable data	Questionnaire on the possible use of cannabis Subjective rating in motor symptoms and dyskinesia	Significant improvement in motor symptoms such as general PD symptoms, resting tremor, bradykinesia, and muscle rigidity ($p<0.05$, all) ** only for patient who used cannabis more than 3 months

Venderova K, et al. Mov Disord 2004;19:1102-5.

ORIGINAL ARTICLE

Medical Cannabis in Parkinson Disease: Real-Life Patients' Experience

Yacov Balash,† Lihi Bar-Lev Schleider,‡ Amos D. Korczyn,† Herzel Shabtai,* Judith Knaani,* Alina Rosenberg,§ Yehuda Baruch,|| Ruth Djaldetti,†¶ Nir Giladi,*†# and Tanya Gurevich, MD*†#*

Reference	Drug/treatment	Class	Sample size	Study duration	Maximum dose	Scale for primary outcome	Outcome
Balash Y, et al. Clin Neuropharm 2017	Medical cannabis	IV	47 (telephone survey)	Duration of usage: 3-84 months	0.2-2.25 g/day	A structured ques tionnaire based on subjective global impressions of change for various parkinsonian symptoms and yes/no questions on adverse effects	Effect size (r^2) improvement for falls was 0.89, 0.73 for pain relief, 0.64 for de pression, 0.64 for tremor, 0.62 for muscle stiffness, and 0.60 for sleep.

Balash Y, et al. Clin Neuropharm 2017;40: 268–272.

ANS: Does cannabis improve motor symptoms in PD patients?

Suggestion

Level U: Data inadequate or conflicting, given current knowledge, treatment is unproven.

3

Does cannabis improve the quality of life in PD patients?

2 papers

Short report

Effects of cannabidiol in the treatment of patients with Parkinson's disease: An exploratory double-blind trial

Marcos Hortes N Chagas[1,2,3], Antonio W Zuardi[1,2], Vitor Tumas[1], Márcio Alexandre Pena-Pereira[1], Emmanuelle T Sobreira[1], Mateus M Bergamaschi[1,2], Antonio Carlos dos Santos[1,2], Antonio Lucio Teixeira[4], Jaime EC Hallak[1,2] and José Alexandre S Crippa[1,2]

Psychopharm

Journal of Psychopharmacology
2014, Vol. 28(11) 1088–1092

DOI: 10.1177/0269881114550355
jop.sagepub.com
SAGE

Reference	Drug/treatment	Class	Sample size	Study duration	Maximum dose	Scale for primary outcome	Outcome
Chagas M, et al J Psychopharm 2014	Cannabidiol or placebo	III	21	6 weeks	75 mg or 300 mg	PDQ-39	Group with CBD 300 mg/day had significantly higher total PDQ-39 scores than other groups (p=0.034)

Chagas M, et al. J Psychopharm 2014;28: 1088-92.

Complementary Therapies in Medicine 33 (2017) 99–104

Contents lists available at ScienceDirect

Complementary Therapies in Medicine

journal homepage: www.elsevier.com/locate/ctim

Cannabis use in people with Parkinson's disease and Multiple Sclerosis: A web-based investigation

John H. Kindred[a], Kaigang Li[a], Nathaniel B. Ketelhut[a], Felix Proessl[a], Brett W. Fling[a], Justin M. Honce[b], William R. Shaffer[c], Thorsten Rudroff[a,*]

[a] Colorado State University, Fort Collins, CO, 80523, USA
[b] University of Colorado Denver, Denver, CO, 80217, USA
[c] University of Colorado Health System, Fort Collins, CO, 80528 USA

Reference	Drug/treatment	Class	Sample size	Study duration	Maximum dose	Scale for primary outcome	Outcome
Kindred J, et al. Com Ther Med 2017	Medical cannabis (smoke and edible forms)	IV	454	Duration of usage: unavailable data	Dosing: unavailable data	An anonymous web-based survey was hosted on the Michael J. Fox Foundation	Cannabis users reported lower levels of disability, specifically in domains of mood, memory, and fatigue ($p < 0.05$, all)

Kindred J, et al. Com Ther Med 2017;33:99-104.

Does cannabis improve the quality of life in PD patients?

Suggestion

Level U: Data inadequate or conflicting, given current knowledge, treatment is unproven.

4

Does cannabis improve psychosis in PD patients?

1 paper

Short report

Cannabidiol for the treatment of psychosis in Parkinson's disease

Psychopharm

Journal of Psychopharmacology
23(8) (2009) 979–983

ISSN 0269-8811
SAGE Publications Ltd,
Los Angeles, London,
New Delhi and Singapore
10.1177/0269881108096519

Reference	Drug/treatment	Class	Sample size	Study duration	Maximum dose	Scale for primary outcome	Outcome
Zuardi A, et al. J Psychopharm 2009	Cannabidiol	IV	6	4 weeks	150 mg (The dose was increased weekly by 150 mg depending on the clinical response)	The Bech's version of the Brief Psychiatric Rating Scale	The psychosis symptoms evaluated by the brief psychiatric rating scale and the Parkinson Psychosis Questionnaire showed a significant decrease under CBD treatment ($p<0.05$, both)

Zuardi A, et al.J Psychopharm 2009;23:979-83.

ANS: Does cannabis improve psychosis in PD patients?

Suggestion

Level U: Data inadequate or conflicting, given current knowledge, treatment is unproven.

5

Does cannabis reduce pain in PD patients?

2 papers

ORIGINAL ARTICLE

Cannabis (Medical Marijuana) Treatment for Motor and Non–Motor Symptoms of Parkinson Disease: An Open-Label Observational Study

Itay Lotan, MD, Therese A. Treves, MD, Yaniv Roditi, MD, and Ruth Djaldetti, MD

Reference	Drug/treatment	Class	Sample size	Study duration	Maximum dose	Scale for primary outcome	Outcome
Lotan I, et al. Clin Neuropharm 2014	Inhaled cannabis (Participants were treated with cannabis on a daily basis for at least 2 months)	IV	22	30 min after inhale cannabis	0.5 mg	Visual analog scale Pain intensity scale Short-form McGill Pain questionnaire	Significantly reduced Pain intensity scale and VAS ($p<0.001$)

Lotan I, et al.Clin Neuropharm 2014;37: 41–44.

EJP
European Journal of Pain

ORIGINAL ARTICLE

Effect of medical cannabis on thermal quantitative measurements of pain in patients with Parkinson's disease

A. Shohet[1,2], A. Khlebtovsky[1,2], N. Roizen[1,2], Y. Roditi[1,2], R. Djaldetti[1,2]

1 Movement Disorder Clinic, Department of Neurology, Rabin Medical Center – Beilinson Hospital, Petach Tikva, Israel
2 Sackler Faculty of Medicine, Tel Aviv University, Israel

Reference	Drug/treatment	Class	Sample size	Study duration	Maximum dose	Scale for primary outcome	Outcome
Shohet A, et al. Eur J Pain 2017	Inhaled cannabis (Participants were treated with cannabis on a daily basis for at least 2 months)	IV	20 (18 smoking, 2 vaporizer)	30 min after inhaled cannabis Long-term exposure up to 40 weeks (median 14 weeks)	1 mg	Pain rating index VAS of the short-form McGill Pain questionnaire Thermal quantitative sensory testing (QST)	Significantly reduced Pain rating index and VAS ($p<0.05$, both) Significantly decreased cold pain threshold ($p=0.02$)

Shohet A, et al. Eur J Pain 2017:486-93.

ANS: Does cannabis reduce pain in PD patients?

Suggestion

Level U: Data inadequate or conflicting, given current knowledge, treatment is unproven.

6

Does cannabis reduce REM sleep-related disorders in PD patients?

1 paper

Journal of
Clinical Pharmacy and Therapeutics

Journal of Clinical Pharmacy and Therapeutics, 2014, **39**, 564–566 doi: 10.1111/jcpt.12179

Case Report

Cannabidiol can improve complex sleep-related behaviours associated with rapid eye movement sleep behaviour disorder in Parkinson's disease patients: a case series

M. H. N. Chagas*† MD PhD, A. L. Eckeli* MD PhD, A. W. Zuardi*† MD PhD, M. A. Pena-Pereira* MD, M. A. Sobreira-Neto* MD, E. T. Sobreira* PhD, M. R. Camilo* MD, M. M. Bergamaschi*† PhD, C. H. Schenck‡ MD, J. E. C. Hallak*† MD PhD, V. Tumas* MD PhD and J. A. S. Crippa*† MD PhD

**Department of Neuroscience and Behavior, Faculty of Medicine of Ribeirão Preto, University of São Paulo, Ribeirão Preto, Brazil, †INCT Translational Medicine (CNPq), São Paulo, and ‡Minnesota Regional Sleep Disorders Center and Department of Psychiatry, Hennepin County Medical Center and the University of Minnesota Medical School, Minneapolis, MN, USA*

Reference	Drug/treatment	Class	Sample size	Study duration	Maximum dose	Scale for primary outcome	Outcome
Chagas M, et al. J Clin Pharm Ther 2014	Cannabinoid	IV	4	6 weeks	75-300 mg/day	-PSG (3 patients) -Clinical assessment and report from patients and their spouses	Reduction in RBD-compatible symptoms were reported from all participants

Chagas M, et al. J Clin Pharm Ther 2014;39: 564-66.

ANS: Does cannabis reduce REM sleep-related disorders in PD patients?

Suggestion

Level U: Data inadequate or conflicting, given current knowledge, treatment is unproven.

Clinical research in others movement disorders

Recommendation: Surveys, case reports/series, and non placebo-controlled trials were excluded

REVIEW

The Therapeutic Potential of Cannabinoids for Movement Disorders

Benzi Kluger, MD, MS,[1†*] Piera Triolo, BS,[1†] Wallace Jones, BS,[1†] and Joseph Jankovic, MD[2†]

[1]*Movement Disorders Center, Department of Neurology, University of Colorado School of Medicine, Aurora, Colorado, USA*
[2]*Parkinson's Disease Center and Movement Disorders Clinic, Department of Neurology, Baylor College of Medicine, Houston, Texas, USA*

- Clinical studies of cannabinoids for movement disorders
  - Parkinson's disease
  - **Tics**
  - **Huntington's disease**
  - **Dystonia**
  - Tremor (Multiple Sclerosis-Related Tremor)**

Kluger B, et al. Mov Disord 2015;30:313-27.

Tics

Recommendation: Surveys, case reports/series, and non placebo-controlled trials were excluded

Tics

Movement Disorder	Study Design	Sample Size	Intervention	Outcome	Reference
Tics	Case study	1	Within 2 weeks, the daily dose was raised to 15 mg.	Improved tics by 75%. Measures: the Yale Global Tic Severity Scale	107
	Case study	1	Starting with a morning dose of 5 mg, increased D9-THC during the following 9 weeks	Improved tic with no adverse effects. Measures: Yale Global Tic Severity Scale; Gilles de la Tourette Syndrome Quality of Life Scale; and the ADHD symptoms on the Conners' Teacher Rating Scale	108
	Case study	1	Smoked cannabis (one "cone") per night for 1 year	Complete remission of tic Measures: 1-hour examination.	109
	Cross-sectional structured interviews	17	Previous cannabis use	Overall, 82% experienced a marijuana-induced improvement of their symptoms. Measures: Shapiro Tourette Syndrome Severity Scale	110
	Case study	1	Administered THC once	Tourette's Syndrome Global Scale, revealed total tic severity score was 41 before treatment and was reduced to 7 just 2 hours after treatment.	111
	Randomized, double-blind, placebo-controlled, crossover study	12	Δ9-THC or placebo was administered once. After a 4-week washout period, patients were crossed over to receive other treatment.	Scores on Global Clinical Impression Scale, Shapiro Tourette-Syndrome Severity Scale, Yale Global Tic Severity Scale, and Tourette-Syndrome Symptom List revealed dose-dependent improvement in tics.	112
	Case study	1	Combined treatment with risperidone and Δ9-THC	Scores on Global Clinical Impression Scale, Shapiro Tourette Syndrome Severity Scale, Yale Global Tic Severity Scale, and Tourette Syndrome Symptom List revealed significant improvement in tics.	113
	Randomized, double-blind, placebo-controlled	17	During 6 weeks, patients treated with up to 10 mg/day of THC	Improved tics. Measures: Tourette Syndrome Clinical Global Impressions scale, the Shapiro Tourette Syndrome Severity Scale, the Yale Global Tic Severity Scale, the self-rated Tourette Syndrome Symptom List, and a videotape-based rating scale.	113
	Case study	3	a. Self-administered smoked cannabis (1-2 cigarettes per day) for 4 weeks. b. Self-administered smoked cannabis intermittently. 3. Self-administered smoked cannabis (0.5-1.0 cigarette per day).	Improved tics	114

Muller-Vahl K, et al. Pharmacopsychiatry 2002;35: 57-61.

Muller-Vahl K, et al. J Clin Psychiatry 2003;64: 459-65.

Kluger B, et al. Mov Disord 2015;30:313-27.

7

Does cannabis reduce tics symptoms in Tourette's syndrome patients?

3 papers (same authors)

Primary outcomes

- Change in tic severity measured by use of standardised measures

K. R. Müller-Vahl[1]
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Treatment of Tourette's Syndrome with Δ^9-Tetrahydrocannabinol (THC): A Randomized Crossover Trial

Reference	Drug/treatment	Class	Sample size	Study duration	Maximum dose	Scale for primary outcome	Outcome
Muller-Vahl et al. Pharmacopsychiatry 2002**	THC (2.5- and 5.0-mg gelatin capsules) or placebo Adjusted dose of THC according to body weight, sex, age, and Hx of cannabis usage or placebo	III	12 (no dropout)	A single-dose on two days separated by a 4-week washout phase	Dose: 5 mg, 7.5 mg, and 10 mg	Tics scores according to the TSSL, STSS, YGTSS, and TSGS	Significant improvement of tics (p=0.015) and obsessive-compulsive behavior (p=0.041)

Muller-Vahl K, et al. Pharmacopsychiatry 2002;35: 57-61.

Influence of Treatment of Tourette Syndrome with Δ^9-Tetrahydrocannabinol (Δ^9-THC) on Neuropsychological Performance

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Reference	Drug/treatment	Class	Sample size	Study duration	Maximum dose	Scale for primary outcome	Outcome
Muller-Vahl et al. Pharmacopsychiatry 2001** (Using the same group of patients with previous study)	THC (2.5- and 5.0-mg gelatin capsules) or placebo Adjusted dose of THC according to body weight, sex, age, and Hx of cannabis usage or placebo	III	12 (no dropout)	A single-dose on two days separated by a 4-week washout phase	Dose: 5 mg, 7.5 mg, and 10 mg	Neuropsychological tests (performed at one hour after medication)	No significant improvement in neuropsychological tests after treatment with THC compared to placebo ** contradict result for OCB that showed a significant deterioration after THC (p=0.041)

Muller-Vahl K, et al. Pharmacopsychiatry 2001;34: 19-24.

Δ^9-Tetrahydrocannabinol (THC) is Effective in the Treatment of Tics in Tourette Syndrome: A 6-Week Randomized Trial

Kirsten R. Müller-Vahl, M.D.; Udo Schneider, M.D.; Heidrun Prevedel; Karen Theloe; Hans Kolbe, M.D.; Thomas Daldrup, M.D.; and Hinderk M. Emrich, M.D.

Reference	Drug/treatment	Class	Sample size	Study duration	Maximum dose	Scale for primary outcome	Outcome
Muller-Vahl et al. J Clin Psychiatry 2003	THC (2.5- and 5.0-mg gelatin capsules) or placebo	III	24 (7 dropout)	6 weeks	THC 10 mg	Tics scores according to the TS-CGI, STSSS, YGTSS, video rating scale and TSSL	A significant difference ($p<0.05$) or a trend toward a significant difference ($p<0.01$) between THC and placebo

Muller-Vahl K, et al. J Clin Psychiatry 2003;64: 459-65.

Systematic review and meta-analysis

Cannabinoids for the treatment of mental disorders and symptoms of mental disorders: a systematic review and meta-analysis

Nicola Black, Emily Stockings*, Gabrielle Campbell, Lucy T Tran, Dino Zagic, Wayne D Hall, Michael Farrell, Louisa Degenhardt*

	Comparator	Studies (participants)	Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	Pooled SMD (95% CI)	I^2	Favours	GRADE
Tourette syndrome											
Primary outcomes											
Change in tic or Tourette symptoms*	Placebo	2 (41)	Not serious	Not serious	Serious	Serious	Undetected	−0·46 (−1·32 to 0·40)	68%	Neither	Low
Secondary outcomes											
Change in global functioning	Placebo	2 (41)	Not serious	Not serious	Serious	Very serious	Undetected	−0·84 (−2·10 to 0·42)	68%	Neither	Very low
Cardiovascular effects	..	0 (0)	..	..	..	..	..	..	..	..	..
Weight change	..	0 (0)	..	..	..	..	..	..	..	..	..

The pooled effect from these two, small studies showed no significant benefit of pharmaceutical THC–CBD compared to placebo on Tourette symptoms

Muller-Vahl K, et al. Pharmacopsychiatry 2001;34: 19-24.
Muller-Vahl K, et al. J Clin Psychiatry 2003;64: 459-65.

Black N, et al. Lancet Psychiatry 2019;6: 99.

ANS: Does cannabis reduce tics symptoms in Tourette's syndrome patients?

Suggestion

Level U: Data inadequate or conflicting, given current knowledge, treatment is unproven.

Huntington's disease

Recommendation: Surveys, case reports/series, and non placebo-controlled trials were excluded

Huntington's disease

Movement Disorder	Study Design	Sample Size	Intervention	Outcome	Reference
Huntington's Disease	Randomized, double-blind, placebo-controlled, crossover trial	15	Cannabidiol (5 mg/kg) or placebo was given twice-daily for 6 weeks.	No effect on chorea severity	87
	Case study	1	Self-administered smoked cannabis. Then, patient was administered 1 mg of nabilone per day.	Reduction of chorea	96
	Randomized, double-blind, placebo-controlled, crossover study	37	Four assessment visits were made to each patient at their residence at 5-week intervals. Administered nabilone (1 and 2 mg) versus placebo. For the last 10 days of each treatment block, patients were taking nabilone 1 or 2 mg/day.	Improved motor coordination and chorea. Measures: UHDRS: motor scale; cognitive assessment; and behavioral assessment. No difference between taking 1 or 2 mg of nabilone.	97
	Case study	1	Patient was treated once with 1.5 mg of nabilone and, 3 hours later, was given an evaluation.	Increased chorea	98

- Consroe P, et al. Controlled clinical trial of cannabidiol in Huntington's disease. Pharmacol Biochem Behav 1991;40:701-708.
- Curtis A, et al. A pilot study using nabilone for symptomatic treatment in Huntington's disease. Mov Disord 2009;24:2254-2259.

Kluger B, et al. Mov Disord 2015;30:313-27.

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Does cannabis improve *motor (dyskinesia)* symptoms in Huntington's disease patients?

2 papers

Movement Disorders
Vol. 24, No. 15, 2009, pp. 2254–2259

A Pilot Study Using Nabilone for Symptomatic Treatment in Huntington's Disease

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Reference	Drug/treatment	Class	Sample size	Study duration	Maximum dose	Scale for primary outcome	Outcome
Curtis A, et al. Mov Disord 2009	Nabilone or placebo	I	44 (7 dropout)	5-week intervals (Four assessment visits were made to each patient at their residence)	1-2 mg/day	The total motor score of the Unified Huntington's Disease Rating Scale (UHDRS)	There was no significant difference on the primary outcome of Unified Huntington's Disease Rating Scale (UHDRS) and no difference between treatments for the UHDRS total motor score

Curtis A, et al. Mov Disord 2009;24: 2254-9.

Pharmacology Biochemistry & Behavior, Vol. 40, pp. 701–708. © Pergamon Press plc, 1991. Printed in the U.S.A. 0091-3057/91 $3.00 + .00

Controlled Clinical Trial of Cannabidiol in Huntington's Disease

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Reference	Drug/treatment	Class	Sample size	Study duration	Maximum dose	Scale for primary outcome	Outcome
Consroe P, et al. Pharmacology Biochem Behavior 1991	Cannabidiol (CBD was dissolved in sesame oil and the drug solution was incorporated into soft gelatin, amber-colored capsules)	III	15	15 weeks	10 mg/kg	Chorea severity as measured by the Marsden and Quinn's chorea severity scale* Shoulsen and Fahn's functional disability scale for HD HD staging scheme	This study found small and no statistically differences between groups on primary and secondary outcomes, including patient global impressions.

Consroe P, et al. Pharmaco Bio Behav 1991;40: 701-8.

ANS: Does cannabis improve motor (*dyskinesia)* symptoms in Huntington's disease patients?

Suggestion

Level B: Cannabinoid receptor agonist (Nabilone) is probably ineffective for treating motor symptoms in patients with Huntington's disease (1 Class I study).

Koppel B, et al. Neurology 2014;82:1556-63.

Whereas these 2 studies suggest lack of benefit, both were underpowered to detect differences, and thus no reliable conclusions can be drawn.

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Does cannabis alleviate dystonia?

Dystonia

Movement Disorder	Study Design	Sample Size	Intervention	Outcome	Reference
Dystonia	Case study	1	Smoked one "joint" in the morning once a week for 3 weeks	Self-reported improvement with dystonia.	103
	Case series.	5	Oral doses of cannabidiol rising from 100 to 600 mg/day over a 6-week period	Dystonia assessed with a standard dystonia movement scale, ranging from 0 to 120. Dose-related improvement in dystonia. Cannabidiol at doses over 300 mg/day exacerbated the hypokinesia and resting tremor.	104
	Randomized, double-blind, placebo-controlled, crossover	15	A single dose of nabilone or placebo (0.03 mg/kg) was administered.	No significant reduction in dystonia. Measures: dystonia–movement scale portion of the Burke-Fahn-Marsden Dystonia Rating Scale, adverse effects, and lying and standing blood pressure.	105
	Case study	1	Smoked cannabis 3 to 4 g/day. Patient was evaluated and reevaluated after 24-hour drug-free period.	Significantly improved dystonia. Measures: Burke-Fahn-Marsden Dystonia Rating Scale.	83
	Randomized, double-blind, placebo-controlled study	7	Dronabinol or placebo was administered daily for 3 weeks.	No improvement in dystonia.	106

Although case reports of smoked cannabis for generalized dystonia in Wilson's disease, idiopathic hemidystonia, and a case series of 5 patients with dystonia secondary to diverse causes treated with oral CBD (100-600 mg) suggest that cannabinoids may alleviate dystonia, two small randomized, placebo-controlled, **clinical trials for dystonia showed no effect**

Kluger B, et al. Mov Disord 2015;30:313-27.

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Ultimate guide for managing patient expectations

How to discuss with your patients about possible and impossible treatment expectations

- Truth telling to your patient, according to the current evidence-based guideline and your professional responsibilities
- State the limitation in development of evidence-based guidelines and recommendations
- Open for the discussion, including their current situations, expectations, willing, and confidence to use in certain medications/supplements
- Help your patients to clarify whether ‘fact’ on the internet are true
- Discuss more for future aspects or directions

Take home message and directions for future research

- Cannabis should be studied as other drugs are, to determine their efficacy, and when evidence is available, should be prescribed as other drugs are.
- To the best of my knowledge, there have been no published placebo-controlled studies of cannabis for atypical parkinsonism (PSP & MSA), genetic ataxia, myoclonus, or restless legs syndrome (RLS).
- Future clinical studies should be done in randomized fashion, adequately powered, employ appropriate methodology and outcome measures for the specific movement disorders study.

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