Medical Marijuana
A role in the Ataxias?

Terry D. Fife, MD, FAAN
Director, Balance Disorders & Otoneurology
Barrow Neurological Institute
Associate Professor of Neurology
University of Arizona College of Medicine

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National Ataxia Foundation

Presenter Disclosures

Dr. Fife has no financial relationship with any manufacturer of any commercial product and/ or provider of commercial services discussed in this CME activity.

Dr. Fife will discuss the evidence of cannabinoid use in neurological conditions for which there is not an FDA-designated indication.

National Ataxia Foundation

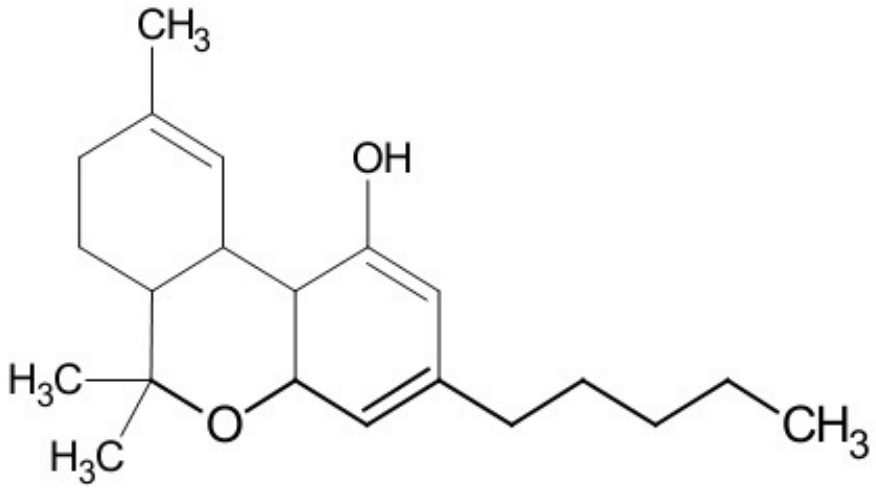
Objectives

- Be familiar with formulations of cannabinoids
- Develop a reasonable understanding of the evidence regarding use of various cannabinoids in neurological diseases and ataxia syndromes
- Be aware of a few of the legal issues associated with use of cannabinoids in medical care

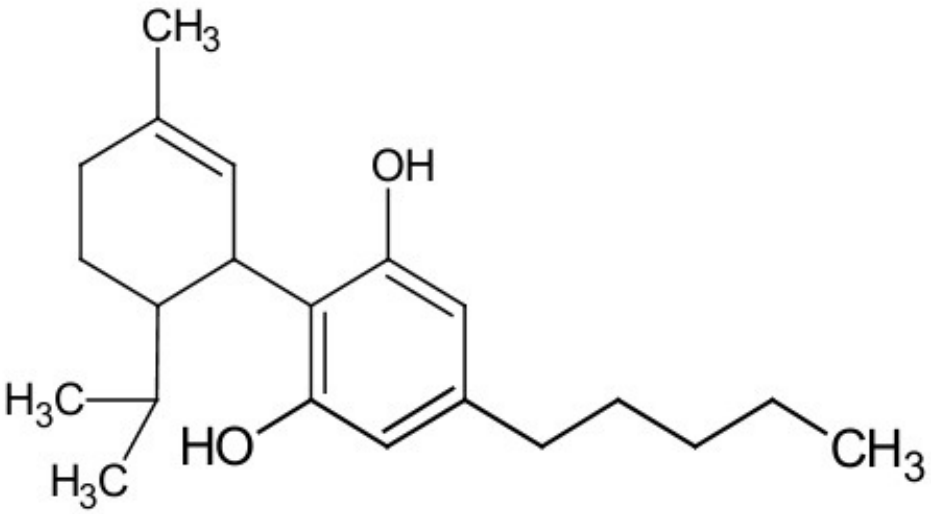
The plant: *Cannabis sativa*

Many active chemical constituents: THC (psychoactive), and cannabidiol (not psychoactive)

Hemp is fiber made from the stem of the plant and used for clothing and paper but has no medicinal value.



Tetrahydrocannabinol (THC)

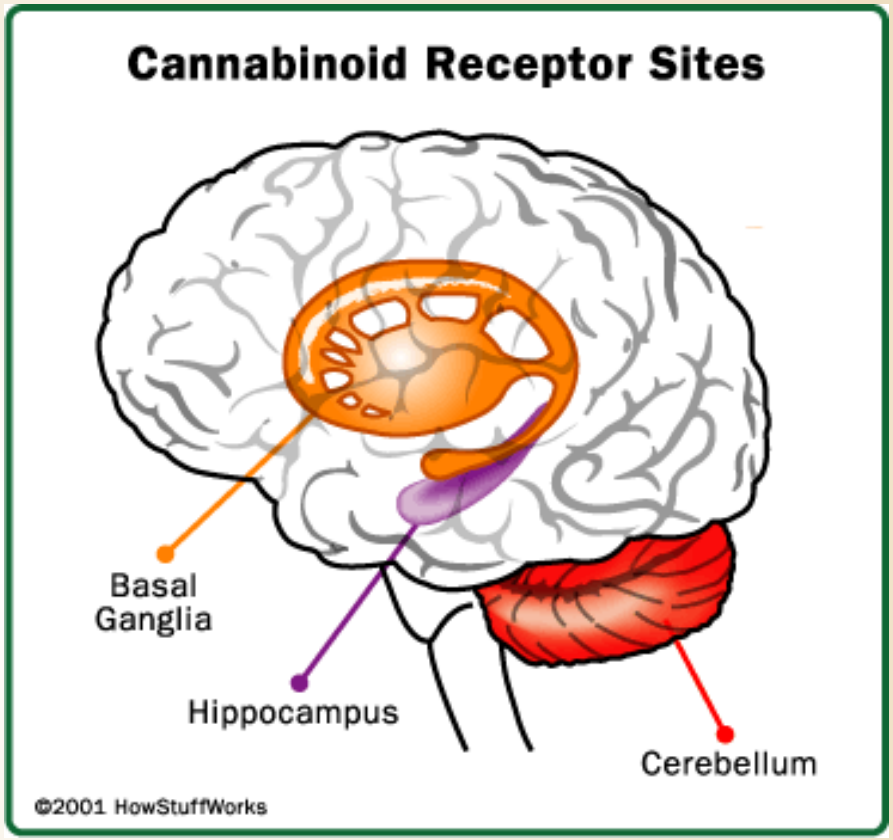


Cannabidiol (CBD)

Brain has endocannabioids which are our body's own molecules that bind to cannabinoid receptors (named CB1 and CB2).

CB1 – in CNS mainly hippocampus and cerebellum, basal ganglia, limbic system, prefrontal cortex.

CB2 – located on immune cells



Controversies of Medical Marijuana

Accounts for 75% of illegal drug use in U.S.

Two cannabinoids approved by FDA in 1985: Marinol® (Schedule III) and Cesamet™ (Schedule II).

Herbal (plant) marijuana remains illegal

FDA Schedule I drug since President Nixon signed the Controlled Substance Act in 1970 as a prelude to the "war on drugs" declaration.

Federal Law on Marijuana

Controlled Substances Act (CSA) which was signed into law as the Comprehensive Drug Abuse Prevention and Control Act of 1970 placed marijuana and its derivatives as Schedule I.

Table 2. Schedules of Controlled Substances

Schedule	Classification Criteria	Examples
C-I	Substances have a high potential for abuse, have no currently accepted medical use in treatment in the U.S., and have a lack of accepted safety for use under medical supervision	Ecstasy (MDMA), heroin, LSD, marijuana, methaqualone, peyote
C-II	Substances have a high potential for abuse, which may lead to severe psychological or physical dependence, and have a currently accepted medical use (with severe restrictions)	Hydromorphone, methadone, meperidine, oxycodone, fentanyl, morphine, opium, codeine, cocaine, amphetamine, methamphetamine, methylphenidate
C-III	Have less potential for abuse than substances in C-I or C-II, and abuse may lead to moderate or low physical dependence or high psychological dependence	Hydrocodone/acetaminophen (Vicodin), Tylenol with Codeine, buprenorphine, benzphetamine, phendimetrazine, ketamine, anabolic steroids (Depo-Testosterone)
C-IV	Have a low potential for abuse relative to substances in C-III	Alprazolam, carisoprodol, clonazepam, clorazepate, diazepam, lorazepam, midazolam, temazepam, triazolam
C-V	Have a low potential for abuse relative to substances listed in C-IV and consist primarily of preparations containing limited quantities of certain narcotics	Robitussin AC, Phenergan with Codeine, ezogabine

LSD: lysergic acid diethylamide; MDMA: 3,4-methylenedioxymethamphetamine. Source: References 4, 5.

List of states legalizing medical marijuana.

State	Year First Approved	Medical Cannabis laws only	Cannabis decriminalization and medical cannabis laws	Legal recreational cannabis and medical cannabis laws
Alaska	1998		✓	✓
Arizona	2010	✓		
California	1996		✓	
Colorado	2000			✓
Connecticut	2012		✓	
Delaware	2011	✓		
Hawaii	2000			
Illinois	2013	✓		
Maine	1999		✓	
Maryland	2014	✓		
Massachusetts	2012		✓	
Michigan	2008	✓		
Minnesota	2014		✓	
Montana	2004	✓		
Nevada	2000		✓	
New Hampshire	2013	✓		
New Jersey	2010	✓		
New Mexico	2007	✓		
New York	2014		✓	
Oregon	1998		✓	✓
Rhode Island	2006		✓	
Vermont	2004		✓	
Washington	1998			✓

So what does the science tell us?

Neurology®
THE MOST WIDELY READ AND HIGHLY CITED PEER-REVIEWED NEUROLOGY JOURNAL

The Official Journal of the American Academy of Neurology

Special Article

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

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

Barbara S. Koppel, MD, FAAN, John C.M. Brust, MD, FAAN, Terry Fife, MD, FAAN, Jeff Bronstein, MD, PhD, Sarah Youssof, MD, Gary Gronseth, MD, FAAN and David Gloss, MD

Methods

A systematic review of published literature broadly related to neurological conditions, 1947-2013

1590 Articles, 61 relevant, 23 were RCT meeting criteria, 9 were Class I

Literature Classified on the basis of potential for bias (RTC), only Class I, II and III considered.

Questions to Answer

1. What is the efficacy of cannabinoids in relieving ***spasticity in patients with MS*****?**
2. What is their efficacy in relieving ***central pain and painful spasms in MS*****?**
3. What is their efficacy in alleviating ***bladder dysfunction in MS*****?**
4. What is their efficacy in controlling involuntary movements including ***tremor in MS*****?**
5. What is their efficacy in reducing ***dyskinesias*** **of** Huntington's disease, levodopa-induced dyskinesias of Parkinson's disease, and ***tics of Tourette's syndrome*****?**
6. What is their efficacy in reducing ***seizure frequency in epilepsy*****?**

TABLE 2. Cannabinoid Formulations.*

Generic (Trade name)	Constituents	U.S. FDA Approval	Legal Under Federal/State Laws
Marijuana	THC, CBD, multiple other components	No	No/Yes (in some states)†
Dronabinol (Marinol)	THC in tablet form	Yes	Yes/Yes
Nabilone (Cesamet)	Synthetic cannabinoid in tablet form	Yes	Yes/Yes
Nabiximols (Sativex)	Oromucosal spray mixture of THC and CBD	No‡	No/No

CBD, cannabidiol; FDA, U.S. Food and Drug Administration; THC, delta-9-tetrahydrocannabinol.

* *Adapted from Koppel 2014 (1).*

† See Table 1 for states where marijuana for medical use is legal.

‡ Sativex has been approved in the United Kingdom, Spain, Canada, and New Zealand. In the United States, it is available only in FDA-approved clinical trials.

Spasticity from MS

- Cannabis extract/THC and Sativex probably effective in patient-reported (VAS/NAS) spasticity (4 Class I studies)
- Cannabis extract/THC probable ineffective for physician-assessed (Ashworth scale) spasticity (3 Class I studies)
- Smoked marijuana is of uncertain benefit in MS related spasticity (2 conflicting Class III studies).

Spasticity from MS

- Oral cannabis is established as effective to reduce patient-reported symptoms of spasticity over six weeks (Level A).
- Sativex® and THC are probably effective in reducing patient reported symptoms of spasticity over six weeks (Level B).
- Inhaled marijuana is of uncertain effect in reducing spasticity (Level U).

Medically refractory central pain in MS

Based on 5 Class I studies, 3 Class II studies:

- Oral cannabis extract is established as effective to reduce central pain of MS that has failed standard therapy (2 Class I studies), (Level A).
- THC or nabiximols are probably effective to reduce central pain or painful spasms of MS that has failed standard therapy (1 Class I study each), (Level B).

Bladder symptoms in MS

Based on 4 Class I studies, 1 Class II studies:

- Nabiximols probably effective decreasing number of bladder voids at 10 weeks (Level B).
- THC / oral Cannabis probably ineffective in reducing bladder complains (Level B).
- Nabiximols of uncertain effectiveness for overall bladder symptoms (Level U).

MS-related tremor

Based on secondary outcome measures in 2 Class I studies, 2 Class II studies:

- No benefit in tremor reduction, possibly worsens
- THC / oral cannabis extract should not be offered for MS-related tremor (Level B).

Involuntary movements

Huntington's chorea: 2 Class I studies using CBD but with different rating scales, underpowered. Benefit with secondary outcome of chorea (1 study), behavioral features (1 study). Possible modest benefit in chorea (Level B)

Levodopa-dyskinesias in PD: 1 Class I study using THC was ineffective (Level B)

Tourette's syndrome: 1 Class I, 1 Class II study, conflicting data that is overall insufficient evidence of CBD in reducing tics (Level U)

Seizure frequency in epilepsy

No Class I-III studies using cannabinoids for seizure frequency in epilepsy. All studies Class IV. No recommendation for use (Level U)

Answers to Questions

1. ***Refractory spasticity in patients with MS*?**
   Subjective improvement – YES
   Objective improvement – NO
1. ***Refractory central pain and painful spasms in MS*? YES**
2. ***Bladder dysfunction in MS*? NO (mostly)**
3. ***Tremor in MS*? NO**
4. ***Dyskinesias* of HD, dopa-dyskinesia in PD, Tics in *Tourette's syndrome*? MOSTLY NO (possible modest reduction of chorea in HD)**
5. ***Seizure frequency in epilepsy*? Unknown**

So where does that leave us?

Answer: in need of more study.

So why is it taking so long?

Answer: politics, opinions, ideologies

Some Thoughts

Disclaimer: We do not have answers to very many questions so these are my thoughts for what they are worth…

When you might consider marijuana or cannabinoids:

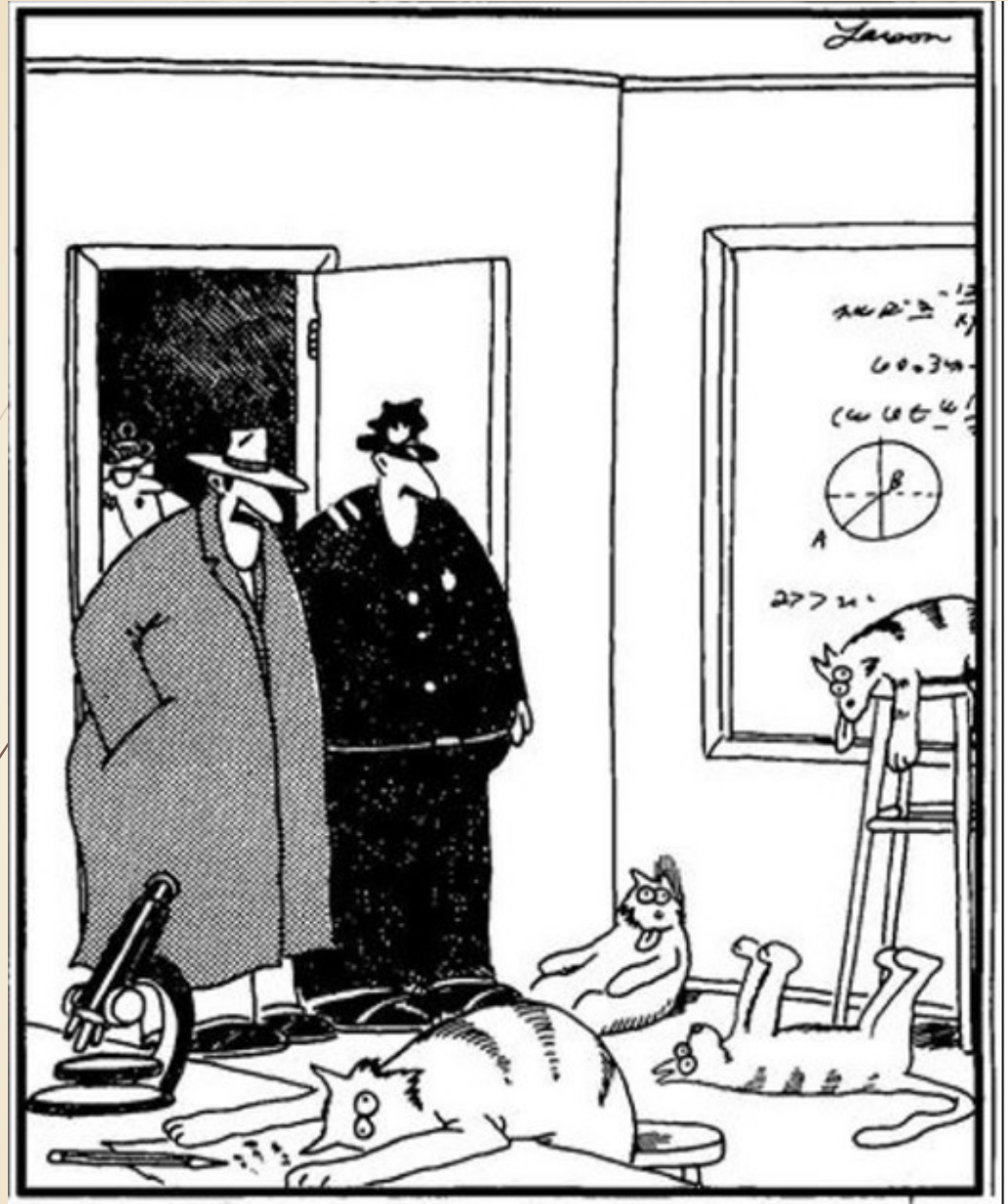
- Pain that has failed all conventional therapies
- Excessive weight loss or loss of appetite
- Nausea or motion sensitivity failing other Tx
- Anxiety, extreme emotional distress failing other Tx
- Excessive spasticity or muscle tone failing other Tx
- Oscillopsia (jittery vision) from nystagmus

When you might want to avoid marijuana or cannabinoids if you have:

- Memory or cognitive dysfunction
- Ataxia – it might worsen balance, speech
- Periods of confusion, hallucinations, disorientation

Consider the following healthful approaches:

- Minimize sedating and non-essential drugs
- Well-balance diet, hunger is permitted
- Exercise – how to achieve depends on health
- Engage with others socially, intellectually



"Notice all the computations, theoretical scribblings, and lab equipment, Norm. ... Yes, curiosity killed these cats."