Cannabis and Parkinson’s Disease: Weeding out the details

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Assistant Professor of Neurology
Division of Movement Disorders
Outline

• Cannabis
• Endocannabinoid system
• What the current research shows
• Safety issues/side effects
• Recommendations
• The future of medicinal cannabis
The typical brazier and burnt stones in ancient Pamirs
ON THE PREPARATIONS
OF THE
INDIAN HEMP, OR GUNJAH,*
(Cannabis Indica)

Their Effects on the Animal System in Health, and their Utility in the Treatment of Tetanus and other Convulsive Diseases.

By W. B. O'Shaughnessy, M.D., Bengal Army, Late Professor of Chemistry and Materia Medica in the Medical College of Calcutta.
[Concluded from p. 847.]

Experiments by the Author—Inferences as to the Action of the Drug on Animals and Man.

Such was the amount of preliminary information before me, by which I was guided in my subsequent twenty minutes was ridiculously drunk; in four hours his symptoms passed away, also without harm.

Expts. 3, 4, and 5.—Three kids had ten grains each of the alcoholic extract of gunjah. In one no effect was produced; in the second there was much heaviness, and some inability to move; in the third a marked alteration of countenance was conspicuous, but no further effect.

Expt. 6.—Twenty grains were given, dissolved in a little spirit, to a dog of very small size. In a quarter of an hour he was intoxicated; in half an hour he had great difficulty of movement; in an hour he had lost all power over the hinder extremities, which were rather stiff but flexible; sensibility did not seem to be impaired, and the circulation was natural. He readily acknowledged calls by an attempt to rise up.
Sir William Gowers

- *Manual of Diseases of the Nervous System (1888)*
  - oral consumption of an “Indian hemp” extract quieted tremors temporarily
Terminology

- **Cannabis:**
  - Hemp (low resin)- a type of cannabis plant with <0.3% THC
  - Marijuana (high resin)
    - phyto-cannabinoids –a class of compounds that act on the endo-cannabinoid system
    - THC
    - CBD=cannabidiol
Cannabis

- Contains >60 phyto-cannabinoids
  - THC (tetrahydrocannabinol)-
    - primary psychotropic compound
    - may help nausea, pain or muscle spasms
    - can affect mood, behavior, and thinking
  - CBD (cannabidiol)
    - does not cause mind-altering effects
    - can lessen the psychoactive effects of THC
    - may help ease anxiety, insomnia
Contains >100 Terpenoids
- The aromatic component of plant essential oils
- Increases BBB permeability
- May have serotonin reuptake inhibitor properties

Common Terpenes & Terpenoids

- **PINENE** (Pines)
- **CARYOPHYLLENE** (Peppercorns)
- **CARENE** (Cedar, Rosemary)
- **LIMONENE** (Citrus Lemon)
- **LINALOOLE** (Mints, Lavender)

**Terpeneols**
- **TERPINEOLS** (Junipers, Orange Peel)
- **NEROL** (Lemongrass)
- **HUMULENE** (Hops)
- **CERANOL** (Roses, Wine Grapes)
- **MYRCENE** (Myrtles & Cannabis)
Endocannabinoid System

• Cannabinoid receptors
  • a molecular **switch** on the outside of a cell that makes something happen inside a cell when activated

+ 

• Endogenous cannabinoids
  • Naturally made in the human body
Endocannabinoid System

HYPOTHALAMUS
Controls appetite, hormonal levels and sexual behavior

BASAL GANGLIA
Involved in motor control and planning, as well as the initiation and termination of action

AMYGDALA
Responsible for anxiety, emotion and fear

BRAINSTEM AND SPINAL CORD
Important in the vomiting reflex and the sensation of pain

NEOCORTEX
Responsible for higher cognitive functions and the integration of sensory information

HIPPOCAMPUS
Important for memory and the learning of facts, sequences and places

CEREBELLMUM
Center for motor control and coordination
Cannabinoid Receptors

- Cannabinoid receptor type 1 (CB1)
  - Highly expressed in the brain (basal ganglia)
  - Increase GABAergic (inhibitory) activity and inhibit glutaminergic activity (excitatory-?neuroprotective)

Cannabinoid Receptors

- Cannabinoid receptor type 1 (CB1)
  - CB1 agonists generate motor inhibition
  - Inhibits dopamine release
  - THC binds to CB1 receptors
  - CBD has low affinity for cannabinoid receptors
Cannabinoid Receptors

• Cannabinoid receptor type 2 (CB2)
  • Expressed primarily in the immune system
  • Found in smaller concentrations in the central nervous system
  • May play a role in neuroinflammation or neuroprotection
Cannabinoid Receptors

- Other receptors
  - TRPV1- may play a role in inflammatory and thermal pain processing
  - GPR55, PPAR, abnormal CBD receptor
- A very complex system!!
The Endocannabinoid System (ECS) in Parkinson’s disease

• Models of PD show:
  • increased ECS activity
  • increased CB1 receptor protein levels
  • decreased cannabinoid clearance
Potential use of cannabinoid-based products

1. Symptom-relieving substances
   • Tremor
   • Dyskinesias
   • Pain
   • Sleep
   • Anxiety

2. Neuroprotective molecules able to slow down disease progression
FDA Approved Cannabinoid-Based Medicine

- Plant-derived cannabinoid (CBD)
- Dravet syndrome
- Lennox-Gastaut syndrome

- Synthetic cannabinoid (THC)
- Chemo induced nausea/vomiting
- AID related weight loss

- Synthetic cannabinoid (THC)
- Chemo induced nausea/vomiting

Keck School of Medicine of USC
European Cannabinoid-Based Medicine
Phytocannabinoids (plant based)
<table>
<thead>
<tr>
<th>Movement disorder</th>
<th>Study Design</th>
<th>Sample Size</th>
<th>Intervention</th>
<th>Outcome</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parkinson’s disease</td>
<td>Randomized, double-blind, placebo-controlled crossover.</td>
<td>17</td>
<td>Cannabinoid standardized to 2.5 mg of D9-THC and 1.25 mg of cannabidiol per capsule. 2 treatment phases, each of 4 weeks duration separated by a 2-week washout phase.</td>
<td>No improvement in LID, motor symptoms, quality of life or sleep.</td>
<td>59</td>
</tr>
<tr>
<td>Case series.</td>
<td>5</td>
<td>One gram marijuana (7–9% THC) smoked as a cigarette on morning of testing.</td>
<td>None of the patients experienced relief or demonstrated improvement of tremor following marijuana.</td>
<td>138</td>
<td></td>
</tr>
<tr>
<td>Case series.</td>
<td>22</td>
<td>After baseline assessment, patients were asked to smoke .5 g of cannabis. 30 minutes later the motor and non-motor battery was repeated.</td>
<td>Significant improvement in tremor and bradykinesia.</td>
<td>135</td>
<td></td>
</tr>
<tr>
<td>Randomized, double-blind, placebo-controlled study.</td>
<td>8</td>
<td>Administered 20 mg rimonabant (CB1 antagonist) or placebo for 9 or 16 days and then gave levodopa challenge.</td>
<td>No effect on LID or motor disability in on or off state.</td>
<td>38</td>
<td></td>
</tr>
<tr>
<td>Randomized, double-blind, placebo-controlled, crossover trial.</td>
<td>5</td>
<td>Nabilone or placebo was administered in 2 split doses 12 hours and 1 hour before levodopa challenges 2 weeks apart.</td>
<td>Rush Dyskinesia Disability Score and LID time was significantly reduced with nabilone vs. control.</td>
<td>60</td>
<td></td>
</tr>
<tr>
<td>Cross-sectional survey.</td>
<td>84</td>
<td>PD registered at Prague Movement Disorders Centre were asked to anonymously complete a questionnaire about their possible experience with cannabis.</td>
<td>39 patients described mild or substantial improvement of PD symptoms, including resting tremor and LID.</td>
<td>61</td>
<td></td>
</tr>
<tr>
<td>Open-label pilot study.</td>
<td>6</td>
<td>150 mg cannabidiol tablet was administered; the dose was increased weekly by 150 mg depending on the clinical response for 4 weeks.</td>
<td>Decreased psychotic symptoms.</td>
<td>57</td>
<td></td>
</tr>
<tr>
<td>Open-label pilot study.</td>
<td>4</td>
<td>Patients administered 75–300 mg/day of cannabidiol.</td>
<td>Decreased REM Behavior disorder per patient and spouse report</td>
<td>139</td>
<td></td>
</tr>
<tr>
<td>Randomized, double-blind, placebo-controlled study.</td>
<td>21</td>
<td>Patients randomized to placebo, 75 mg/day cannabidiol or 300 mg/day cannabidiol for 6 weeks.</td>
<td>No change in total UPDRS or any subscales. Improvements were reported for total PDQ-39 score in 300 mg/day group.</td>
<td>140</td>
<td></td>
</tr>
</tbody>
</table>
CONCLUSIONS:
Orally administered cannabis extract resulted in no objective or subjective improvement in dyskinesias or parkinsonism.

*Side effects: dry mouth, poor concentration, drowsy, vivid dreams

• After 6 weeks there was no improvement in:
  • Tremor
  • Slowness/stiffness
  • Dyskinesias
• An improvement in quality of life was seen in the CBD 300mg vs. placebo (emotional well being, body discomfort)
Research

• Rodrigues GG et al (2009)->open label, CBD 150-400mg/day
  • Reduced psychotic symptoms, no change in cognitive or motor tests, no SE

• Sobriera ET et al (2014)->case series, CBD, 4 PD pts
  • Reduced events related to REM sleep behavior disorder
# Table: Evidence for Safety and Effectiveness of Medical Marijuana

<table>
<thead>
<tr>
<th>Findings, by Disorder and Drug Formulation</th>
<th>Strength of Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>PD: Temporary, Uncontrolled Movements</td>
<td></td>
</tr>
<tr>
<td>OCE</td>
<td>Moderate</td>
</tr>
<tr>
<td>• Probably does <strong>not</strong> help lessen abnormal movements caused by levodopa</td>
<td></td>
</tr>
</tbody>
</table>
Retrospective Study, AAN, 2019

- 204 people >75 y/o, enrolled in New York State's Medical Marijuana Program (average age of 81)
- various ratios of THC /CBD for an average of four months
- taken by mouth as a liquid extract tincture, capsule or in an electronic vaporizer
Retrospective Study, AAN, 2019

- Initially, 34% of participants had side effects. After an adjustment in dosage, only 21% had SE.
- Most common SE were:
  - Sleepiness in 13% of patients.
  - Balance problems in 7%.
  - Gastrointestinal disturbances in 7%.
  - 3% of the participants stopped taking the medical marijuana due to the side effects.
Retrospective Study, AAN, 2019

- **69 %** of participants experienced some symptom relief
- The most common conditions that improved were:
  - pain (49 % experiencing relief)
  - sleep symptoms (18 % experiencing relief)
  - neuropathy (15 %)
  - anxiety (10 %)
- Opioid pain medication was reduced in 32 % of participants
Potential Side Effects

- Low blood pressure
- Vertigo
- Visual Hallucinations
- Dizziness
- Somnolence
- Mood and behavioral changes
*84 products (from 31 companies)
*42.85% of products were underlabeled
*26.19 were overlabeled
*30.95% were accurately labeled
*vaporization liquid most frequently mislabeled (87.50%)
*oil most frequently labeled accurately (45%)
* THC was detected (up to 6.43 mg/mL) in 18 of the 84 samples tested
<table>
<thead>
<tr>
<th>Cannabidiol Extract Products</th>
<th>Oil (n = 40)</th>
<th>Tincture (n = 20)</th>
<th>Vapourization Liquid (n = 24)</th>
<th>Total (N = 84)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Label accuracy, No. of products (%) [95% CI]</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Accurate</td>
<td>18 (45.00) [30.71-60.17]</td>
<td>5 (25.00) [11.19-46.87]</td>
<td>3 (12.50) [4.34-31.00]</td>
<td>26 (30.95) [22.08-41.49]</td>
</tr>
<tr>
<td>Under</td>
<td>10 (25.00) [14.39-40.19]</td>
<td>8 (40.00) [21.88-61.34]</td>
<td>18 (75.00) [56.18-88.00]</td>
<td>36 (42.65) [32.82-53.53]</td>
</tr>
<tr>
<td>Over</td>
<td>12 (30.00) [18.67-45.43]</td>
<td>7 (35.00) [18.12-56.71]</td>
<td>3 (12.50) [4.34-31.00]</td>
<td>22 (26.19) [17.38-36.48]</td>
</tr>
<tr>
<td>Labeled concentration, mg/mL</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (95% CI)</td>
<td>56.15 (14.23-99.07)</td>
<td>11.14 (5.60-16.60)</td>
<td>26.15 (12.56-39.74)</td>
<td>36.86 (16.21-57.51)</td>
</tr>
<tr>
<td>Median (range)</td>
<td>22.29 (2.50-800.00)</td>
<td>8.33 (1.33-30.00)</td>
<td>18.33 (2.00-160.00)</td>
<td>15.00 (1.33-800.00)</td>
</tr>
</tbody>
</table>

Deviation of labeled content from tested value, mg/mL

| Median (range) [% of deviation] | 2.76 (0.11-14.73) [12.11] | 1.48 (0.91-22.30) [16.12] | 4.52 (0.14-66.07) [67.34] | 3.17 (0.10-144.73) [26.42] |

* Cannabidiol content tested within 10% of labeled value.

* Cannabidiol content exceeded labeled value by more than 10%.

* Cannabidiol content tested more than 10% below labeled value.
Limitations in research

- Marijuana is a **schedule 1** drug (defined as having no currently acceptable medical use and a high potential for abuse)
- Variable CBD, THC, etc concentrations
- Lack of standardized or known doses
- Various formulations and routes of administration
Ongoing Clinical Trials

- University of Colorado, Denver
  - to assess the **efficacy** of **CBD** on motor symptoms (tremor) of Parkinson's Disease (PD), and secondarily to study the **safety and tolerability**
  - 1.25 mg/kg/day and 2.5 mg/kg/day of CBD
  - enroll 75 people
  - randomize 30 to placebo and 30 to CBD
Ongoing Clinical Trials

• University Health Network, Toronto
  • to assess safety and tolerability of different formulations of cannabis oil for pain in Parkinson's disease
  • 15 patients- 5 patients per group
  • 3 different formulations of Δ-9THC and cannabidiol
    • 18:0; 10:10; and 1:20
Future Clinical Trials

- Parkinson’s UK/Kings College London (early 2020)
  - **CBD** for PD **psychosis**
  - 6-week pilot study to find optimum dose
    - Oral capsules of up to **1,000mg daily**
  - 120 people, 12 week placebo controlled study
Dose Gradually

• start with low doses of a CBD-rich remedy (low THC)
• increase the dosage (and, if necessary, the amount of THC) step-by-step
• oral administration - it can take **60 to 90 minutes** before the effects of a single dose are felt and can last **4hrs**
CBD may be more effective when working with other constituents of plants (terpenes and phytocannabinoids).

Check labels for brands that use the “whole plant” or “full spectrum”
Certificate of Analysis

- Ask brands for a “Certificate of Analysis”
- This should come from an independent testing facility
- Should include analysis of CBD and THC levels and screening for any contaminants
- Test batches should be less than 15lbs of cannabis flower per analysis
Certificate of Analysis

The client sample was analyzed for plant-based cannabinoids by Convergence Chromatography (CC). The collected data was compared to data collected for certified reference standards at known concentrations.

<table>
<thead>
<tr>
<th>ID</th>
<th>Weight %</th>
<th>Conc.</th>
</tr>
</thead>
<tbody>
<tr>
<td>D9-THC</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>THCV</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>CBD</td>
<td>64.14 wt %</td>
<td>641.37 mg/g</td>
</tr>
<tr>
<td>CBDV</td>
<td>3.47 wt %</td>
<td>34.70 mg/g</td>
</tr>
<tr>
<td>CBG</td>
<td>4.40 wt %</td>
<td>43.99 mg/g</td>
</tr>
<tr>
<td>CBC</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>CBN</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>THCA</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>CBD-A</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>CBGA</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>Total</td>
<td>72.01 wt %</td>
<td>720.05 mg/g</td>
</tr>
<tr>
<td>Max THC</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Max CBD</td>
<td>64.14 wt %</td>
<td>641.37 mg/g</td>
</tr>
</tbody>
</table>

Max THC (and Max CBD) are calculated values for total cannabinoids after heating, assuming complete decarboxylation of the acid to the neutral form. It is calculated based on the weight loss of the acid group during decarboxylation: Max THC = (0.877 x THCA) + THC. ND = None detected above the limits of detection (LLD)
Going Forward

• AAN, MJFF support reclassification of marijuana from Schedule 1 to schedule II to allow for medical research
• FDA just held a meeting to discuss cannabis
Discussion

- The Michael J Fox Foundation (MJFF)
  - The work to date on marijuana and cannabinoids has given promising but conflicting signals on potential benefit for dyskinesias, motor, and non-motor symptoms
  - This therapy may represent a future treatment option for PD, but the correct dose and formulation are not clear, full side effects and drug interactions are unknown, and benefits have not been rigorously determined
  - Future studies should be large and well designed to provide clear data on the safety and efficacy of marijuana and cannabinoids in Parkinson's
Though most available studies have not shown a benefit, that does not mean that there will not be a benefit. Much more research will be needed to understand which patients, which symptoms, and how best to safely administer medical marijuana, especially over the long-term. It may turn out that non-motor features such as depression, anxiety, and pain respond best, but studies are desperately needed to sort this out. Be aware of the effects on the lungs, the dangers of driving, and accidental overdoses (particularly with food items). States will need to develop training programs for doctors and medical teams prescribing marijuana.
Conclusion

“Despite the widespread **publicity** about the medical benefits of cannabinoids, further **research** is needed to better characterize the **pharmacological, physiological**, and **therapeutic** effects of this class of drugs in movement disorders.”

Websites for more information

- MJFF
- Parkinon’s Foundation
- Project CBD
- ???
But most health professionals know little about CBD or cannabis therapeutics and they lack sufficient expertise to adequately counsel patients regarding dosage, modes of administration, CBD/THC synergies, and any risk factors, including interactions with other drugs.