Medical Marijuana and Epilepsy: Separating the Myths from Reality

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“"We shall, by and by, want a world of hemp more for our own consumption." John Adams, 2nd U.S. President

Historical Medicinal Use Of Cannabis

Why Consider Medical Marijuana In The Treatment Of Epilepsy?

- People
  - High prevalence
    - 50 million worldwide (0.71%)
    - 2.2 million US
  - High incidence
    - 200,000 / year in US
    - 30% in children
  - Increase in Drug-Resistant Epilepsy
    - 27-34% in US
    - 24 approved AED in the US alone
  - High prevalence similar to people
    - 0.62% to 0.8% reported
    - Translates to 583,100 dogs in US
  - Increase in Drug-Resistant Epilepsy
    - 20-30%

Regulatory Issues Related To Medical Marijuana

The legal status of cannabis (marijuana) and cannabidiol (CBD) under U.S. law

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Cannabis Horticulture

- Annual plant with ubiquitous growth in various climates throughout world
- Rapid indoor growth in 9 weeks to optimal flowering stage
- Non-cannabinoid components
  - Primary plant metabolites directly involved in plant growth
- Cannabinoid components
  - Secondary plant metabolites indirectly involved in plant growth
  - Known as terpenophenolic compounds
  - Highest concentration found in unpollinated all female floral material and upper leaf foliage
  - Found in glandular trichomes on epidermal appendages

Exogenous Cannabinoids

- Cannabinoids are chemical substances isolated from C. Sativa, and to its derivatives and transformation products
- 85 terpenophenolic compounds identified
- Phytoannabinoids compounds that are plant derived, of which 11 sub-types have been defined.
- Psychotropic forms, which contain ∆9-tetrahydrocannabinol (THC)
- Non-psychotropic forms, which do not contain ∆9-THC
- Global effect on body

The Unknown Variables

<table>
<thead>
<tr>
<th>Specimen</th>
<th>ME-L (leaves)</th>
<th>ME-M (flowers)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endo-THC</td>
<td>1.16</td>
<td>2.50</td>
</tr>
<tr>
<td>CBD</td>
<td>0.03</td>
<td>0.29</td>
</tr>
<tr>
<td>ME-M 21 WEEKS</td>
<td>1.16</td>
<td></td>
</tr>
<tr>
<td>ME-M 25 WEEKS</td>
<td>2.50</td>
<td></td>
</tr>
</tbody>
</table>

Endocannabinoid System

- Anandamide (AEA)
- 2-Arachidonoylglycerol (2-AG)
- CB1 receptor agonist
- Ubiquitous reduction in presynaptic neurotransmission
- Local effect in brain

Signal direction for neurotransmission

Signal direction for endocannabinoids

Less likely to fire

More likely to fire

G-protein coupled calcium influx inhibition

Less likely to fire

More likely to fire

Endocannabinoids

- CB1 receptor activation
- Decrease glutamate: Depolarization Induced Suppression Of Excitation (pyramidal cells)

- Decrease GABA: Depolarization Induced Suppression Of Inhibition

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Decrease

Excitation

GLUTAMATE

GABA

Depolarization

Threshold

Human Endocannibinoid System

CB1

CB2

Canine Endocannibinoid System

Spatial distribution of cannabinoid receptor type 1 (CB1) in normal canine central and peripheral nervous system

Jessica Freundt-Revilla*, Kristel Kegler*, Wolfgang Baumgartner, Andrea Tippold

PLOS ONE | https://doi.org/10.1371/journal.pone.0181064

CB1 IHC staining:
- Neuropil of the cerebral cortex, Cornu Ammonis (CA) and dentate gyrus of the hippocampus, midbrain, cerebellum, medulla oblongata and
- Grey matter of the spinal cord.
- Globus pallidus and substantia nigra surrounding immunonegative neurons.
- Astrocytes were constantly positive in all regions.
- CB1 labelled neurons and satellite cells of the dorsal root ganglia, and myelinating Schwann cells in the PNS.

Psychotropic Forms

<table>
<thead>
<tr>
<th>CB1 receptor</th>
<th>CB2 receptor</th>
</tr>
</thead>
<tbody>
<tr>
<td>∆-9 THC Main constituent</td>
<td>Partial agonist</td>
</tr>
<tr>
<td>∆-8 THC</td>
<td>Partial agonist</td>
</tr>
<tr>
<td>Cannabinol</td>
<td>Minimal partial agonist</td>
</tr>
<tr>
<td>∆-9 THC</td>
<td>Partial antagonist</td>
</tr>
</tbody>
</table>

Non-Psychotropic Forms

Mechanisms Of Action:
△-9 THC And Cannabidiol (CBD)

<table>
<thead>
<tr>
<th>Action/Effect</th>
<th>∆-9 THC</th>
<th>CBD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cannabinoid type 1 receptor</td>
<td>Psychotropic</td>
<td>Partial Agonist</td>
</tr>
<tr>
<td>Cannabinoid type 2 receptor</td>
<td>Neuroprotection</td>
<td>Partial Agonist</td>
</tr>
<tr>
<td>Serotonin receptors (serotonin) Increase serotonin</td>
<td>Inactive</td>
<td>Agonist</td>
</tr>
<tr>
<td>TRPA 1 cation receptor</td>
<td>Decrease calcium flux</td>
<td>Inactive</td>
</tr>
<tr>
<td>Docile receptors (alpha 1 and 3) Increase interneuron inhibition (Analgesic)</td>
<td>Inactive</td>
<td>Agonist</td>
</tr>
<tr>
<td>Adenosine uptake</td>
<td>Anti-inflammatory</td>
<td>Inactive</td>
</tr>
<tr>
<td>Fatty acid amide hydrolase</td>
<td>Anti-oxidant</td>
<td>Inactive</td>
</tr>
</tbody>
</table>
Neuroprotective Mechanisms

Cannabinoid Receptor Dependent

Cannabinoid Receptor Independent

Summary of Potential Anti-Convulsant Mechanisms of Action

- Decrease seizure onset
- Decrease glutamate mediated excitation
- Decrease seizure propagation
- Increase glycine mediated inhibition
- Decrease intracellular calcium
- Negative feedback through G-coupled receptor proteins
- Potentiates endocannabinoid system
- Vanilloid (TRPV1) receptor blocker
- Improved therapeutic safety by reducing THC psychotropic effects
- Potentiates THC anti-seizure effect

Comparison Of CBD Pharmacokinetics Between Human And Dog

<table>
<thead>
<tr>
<th></th>
<th>Human</th>
<th>Oral</th>
<th>Dog</th>
<th>IV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bioavailability</td>
<td></td>
<td>6%</td>
<td>3 dogs: 0</td>
<td>6-10</td>
</tr>
<tr>
<td>First pass effect through liver</td>
<td></td>
<td>0 to NR</td>
<td>3 dogs: 13-19</td>
<td></td>
</tr>
<tr>
<td>Concentration max (ug/L)</td>
<td>2.8 +/- 1.3</td>
<td>0 to NR</td>
<td>13.6</td>
<td></td>
</tr>
<tr>
<td>T max (hour)</td>
<td>3.2 +/- 1.3</td>
<td>0 to NR</td>
<td>NR</td>
<td></td>
</tr>
<tr>
<td>Volume of distribution (L/kg)</td>
<td>32</td>
<td>0 to NR</td>
<td>100</td>
<td></td>
</tr>
<tr>
<td>Terminal elimination half-life (hour)</td>
<td>18-22</td>
<td>0 to NR</td>
<td>9</td>
<td></td>
</tr>
<tr>
<td>Primary method of metabolism</td>
<td>Cytochrome P450</td>
<td>Cytochrome P450</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clearance (ml/min)</td>
<td>960-1560</td>
<td>0 to NR</td>
<td>265-288</td>
<td></td>
</tr>
<tr>
<td>Protein binding</td>
<td>High</td>
<td>High</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

$\Delta-9$ THC Distribution

<table>
<thead>
<tr>
<th></th>
<th>Human</th>
<th>Canine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Higher concentration without tolerance</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Liver, kidney, brain, heart and lymph nodes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4%S in the brain</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cerebral and cerebellar gray matter</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mitochondria</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lower concentration after tolerance</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pituitary and putamen</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Synaptic vesicles</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Safety: Therapeutic Index (TI)

- $\Delta-9$ THC: Lower TI
  - Decreased psychomotor performance
  - Impaired glucose tolerance
  - Hepatotoxicity
  - Autonomic dysfunction: Heart, GI, vision
  - Decreased T-lymphocyte function
  - Physiologic addiction

- CBD: Higher TI
  - Sedation primary adverse effect
  - Non-lethal
  - No other known adverse effects

CBD And Epilepsy

- Historical
- Laboratory: in vitro and in vivo
- Anecdotal
- Clinical studies
Historical

- First documentation of treatment of a drug-resistant epileptic patient
- Refractory bromide therapy
- Treated with C. indica extracts three times per day
- “Fits ceased at once” without recurrence for 6 months when the patient discontinued treatment, but remitted once treatment was restarted

William Gowers  John Russell Reynolds

Reynolds JR. Therapeutic uses and toxic effects of Cannabis indica. Lancet, 1868;1:637-638

Endocannabinoids Are Altered In Epilepsy

- Cause? Human (n= 6)
  - Romp et al. Epilepsia 2010
  - Newly diagnosed, untreated patients with temporal lobe epilepsy
  - Hypothesis is that normal AEA needed to prevent onset of seizures
- Effect? Canine (n= 40)
  - Gesell et al. BMC Vet Research 2013
  - Evaluation of new onset and chronic (treated) epileptics
  - Hypothesis is that an increase in AEA represents a counter-regulatory process with chronic epilepsy to decrease glutamate neurotransmission

Human Studies: Anecdotal

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Open Label, Randomized Clinical Studies

- 3 studies performed
  - Mechanism and Context, 1978; Cunha et al., 1980; Arom and Crittalton, 1986
  - N = 17 treated and 19 placebo
  - Duration: Weeks to months (all < 1 year)
  - Outcome: 4/17 (24%) reported to have reduction in seizure frequency
- Detractors
  - Heterogeneous patient population
  - No details on randomization
  - Varying dose schedule
  - No reliable conclusions

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Double-Blinded, Randomized Clinical Studies

<table>
<thead>
<tr>
<th>N</th>
<th>20 mg/kg</th>
<th>10 mg/kg</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lennox-Gastaut (1)</td>
<td>86</td>
<td>44*</td>
<td>---</td>
</tr>
<tr>
<td>Lennox-Gastaut (2)</td>
<td>73</td>
<td>42*</td>
<td>37*</td>
</tr>
<tr>
<td>Dravet (3)</td>
<td>59</td>
<td>39*</td>
<td>---</td>
</tr>
</tbody>
</table>

Epilepsy plus current AED therapy for all studies. Results are % median monthly seizure reduction; * Significant difference from placebo

Can Dogs Benefit From And Contribute To The Study Of Cannabis In Chronic Epilepsy?

Pro
- High prevalence unprovoked seizures
- High prevalence DRE
- Similar response to AED
- Similar endocannabinoid system and receptors

Con
- Unknown pharmacokinetics
- Unknown tolerance
- Wide variety of homeopathic agents

Issues For Veterinary Use
- Unregulated use in states with legalized marijuana
- 100% increase in report of canine toxicity in 2 Colorado veterinary hospitals
- Dogs have a low threshold for psychoactive effects
- Sensationalist social media results preys on owners desire to help their epileptic pets
- Discrepancy between public perception and scientific reality
- Validity issues for translational research from rodent to dog to human
- Difficulty in obtaining medical grade drug to establish controlled studies in the US

Summary
- CBD has a proven anticonvulsant effect in vitro and in rodent animal models
- Dogs have a high first past effect of CBD through liver which limits distribution to the brain
- Endocannabinoid system alterations exist in canine epilepsy that could indicate that pharmacologic manipulation of this system may be a therapeutic option
- Phase II and III clinical trials in severely affected epileptic children indicates promise for future studies
- Double-blinded, randomized clinical trials are extremely important to remove the placebo effect in veterinary medicine

Industrial hemp
- Stalk, fiber, oil and sterilized seed
- Less than 0.3% THC
- Claim of high concentration of CBD but no information on label
- Other terpenoids and flavonoids of unknown type and concentration
- No published scientific papers
- No oversight in production