Marijuana, Cannabinoids, and Epilepsy: Where’s the evidence?

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Saturday November 14, 2015
Learning Objectives

• Describe the history, use, and pharmacological mechanisms of marijuana
• Identify the potential therapeutic role of cannabinoids in the treatment of epilepsy
• Discuss the current evidence supporting and challenging the use of cannabinoids in patients with epilepsy
Disclosures

- I have no disclosures
Marijuana

- **Cannabis** genus of flowering plants
  - Comprises mainly *sativa* and *indica* species
- Indigenous to Central & South Asia
- Composed of more than 500 compounds
  - Those unique to cannabis plant are called cannabinoids
- 2 major neuroactive components
  - $\Delta^9$-tetrahydrocannabinol ($\Delta^9$-THC)
  - Cannabidiol (CBD)
- Rising potency of marijuana
  - $\Delta^9$-THC concentration
    - 4% in 1980s
    - 14.5% in 2012
- Most marijuana sold illegally has no or very low amounts of CBD
History of Medical Marijuana Use

- Medicinal preparations from flowers & resin of *C. sativa* have been used in China since ~2,700 BCE
  - Menstrual disorders
  - Gout
  - Rheumatism
  - Malaria
  - Constipation
  - Absent-mindedness

- Medieval times used by Islamic physicians
  - Nausea & vomiting
  - *Epilepsy*
  - Inflammation
  - Pain
  - Fever

*Shen Nung, the Father of Chinese medicine and one of the first documented users of cannabis.*
History of Medical Marijuana Use

• Western medicine used cannabis widely in 1800s
  – Prior to Aspirin, it was a common analgesic drug
• Cannabis was available over-the-counter in US pharmacies until 1941
  – Passage of Marijuana Tax Act of 1937: limited its access
  – Controlled Substances Act of 1970: classified cannabis as Schedule I, making its use illegal
    • “no currently accepted medical use”
Medical Marijuana

• Best evidence for efficacy currently:
  – Painful HIV-associated sensory neuropathy
  – Chronic pain
  – Chemotherapy-induced nausea & vomiting
  – Spasms in patients with multiple sclerosis

*No significant evidence marijuana is superior to FDA approved medications currently available to treat these conditions*

Use in epilepsy in modern era

- Late 19th century, English neurologists including Reynolds & Gowers used cannabis to treat epilepsy

**Russell Reynolds and William Gowers on Cannabis for Epilepsy**

*Cannabis indica*, which was first recommended in epilepsy by Dr. Reynolds, is sometimes, though not very frequently, useful. It is of small value as an adjunct to bromide, but is sometimes of considerable service given separately. It may be noted that the action of Indian hemp presents many points of resemblance to that of belladonna; it is capable of causing also delirium and sleep, first depression and then acceleration of the heart, and also dilates the pupil. The cerebral excitement is relatively more marked, and the effect on the heart and pupil much less than in the case of belladonna.

**John K., aged 40, came under treatment in 1868, having suffered from fits for 25 years.** They occurred during both sleeping and waking, at intervals of a fortnight. There was a brief warning, vertigo, then loss of consciousness, and tonic and clonic spasm followed by some automatism;—“acts strangely and cannot dress himself.” The attacks ceased for a time on bromide, but recurred when he discontinued attendance. He came again in October, 1870; scruple doses of bromide of potassium three times a day had now no effect, and the fits, at the end of 4 months’ treatment, were as frequent as ever. Ext. *cannabis indicae* gr. (~9.8 g), three times a day, was then ordered; the fits ceased at once, “a wonderful change” the patient declared. He had no fit for 6 months, and then, having discontinued attendance, the fits recurred, but were at once arrested by the same dose of Indian hemp. He continued free from fits for some months, until, during my absence, bromide was substituted for the Indian hemp; the fits immediately recurred, and he left off treatment. He returned to the hospital in 6 months’ time, and on Indian hemp passed 2 months without an attack. In the third month another fit occurred, and the patient again ceased to attend, and did not return.
Use in epilepsy in modern era

• Use of cannabis for epilepsy remained very limited despite anecdotal successes
• Cannabis received scant or no mention from English-language epilepsy texts in late 19th & early to mid-20th centuries
• 4 “controlled” studies examined the effect of CBD on seizures
Pharmacology

• *C. sativa* produces more than 80 terpenophenolic compounds called cannabinoids
• CBD was first isolated in 1940 & its structure identified in 1963
• $\Delta^9$-THC was isolated & characterized in 1964
  – For next 30 years, most chemical & pharmacologic research focused on $\Delta^9$-THC
  – Not until early 1990s that $\Delta^9$-THC was found to bind to 2 G-protein-coupled cell membrane receptors
    • Cannabinoid type 1 (CB$_1$) receptor
      – Brain predominantly
    • Cannabinoid type 2 (CB$_2$) receptor
      – Immune & hematopoietic cells
Pharmacology

• Endocannabinoids (endogenous ligands) to CB$_1$ identified in 1992
  – Anandamide
  – 2-arachidonoyl glycerol (2-AG)
    • Produced on demand during excessive neuronal excitation
    • Part of natural dampening feedback loop
• THC is a partial agonist at CB$_1$ & CB$_2$ receptors
• CB$_1$ receptors
  – Present in inhibitory $\gamma$-aminobutyric acid (GABA)ergic & excitatory glutamatergic neurons
Pharmacology

• Unlike THC, CBD does not activate CB\textsubscript{1} & CB\textsubscript{2} receptors
  – CBD can diminish effects of CB\textsubscript{1} activation
  – Mechanism by which CBD exerts its anti-epileptic effects is not well defined
    • “multitarget” drug
      – *Modulation*: equilibrative nucleoside transporter, orphan G-protein-coupled receptor, & transient receptor potential of melastatin type 8 channel
        » Also modulates intracellular Ca\textsuperscript{2+} concentration & inhibits T-type calcium channels
      – *Agonist*: 5HT\textsubscript{1a} and α3 & α1 glycine receptors; and transient receptor potential of ankyrin type 1
      – *Activates*: nuclear peroxisome proliferator-activated receptor-γ, transient receptor potential of vanilloid type 1 (TRPV1) & TRPV2 channels
      – *Inhibits*: cellular uptake & degradation of endocannabinoid anandamide
  – CBD also been shown to have anti-apoptotic, neuroprotective, and anti-inflammatory effects
    • Modulation of TNF-α release
Endocannabinoid Signaling in CNS

Plasticity of Endocannabinoid System

- Endocannabinoids have important influence on development of neuronal networks
  - $\text{CB}_1\text{R}$-mediated plasticity of excitatory synapses in hippocampus occur in immature but not mature brain
- Cannabis has adverse effects in children under 15
  - Risk for psychosis
  - Long-term impairment of executive function
  - Neurotoxic effects when brain is undergoing critical development
Marijuana & Children/Adolescents

• According to CDC data, more teens now smoke marijuana than cigarettes
• MRI brain studies in young recreational marijuana users:
  – Structural abnormalities occur in areas of brain associated with drug craving & dependence
  – Reduced density of gray matter in prefrontal cortex (decision-making abilities)
• Chronic adolescent users
  – Researchers in New Zealand administered IQ tests to 1037 individuals at age 13 (before cannabis use)
    • Assessed their patterns of cannabis use at ages 18, 21, 26, 32, & 38
    • Repeat IQ testing at age 38
  – Results:
    • Heavy use in teens: Drop of 8 points in IQ
    • Regular or heavy use after age 18: minor declines in IQ
    • Never used marijuana: no decline in IQ
  – Cessation of cannabis use (>1 year) did not fully restore neuropsychological functioning

-Meier MH et al. Persistent cannabis users show neuropsychological decline from childhood to midlife. Proc Natl Acad Sci USA 2012 Oct 2;109(40):E2657-64.
Adverse Effects of Marijuana Use

• Review of Class I-III medical marijuana studies (1948-Jan 2013) to address treatment of multiple sclerosis, epilepsy, and movement disorders
• 1,619 patients treated with cannabinoids for less than 6 months
  – 6.9% stopped medication due to AEs
• 1,118 patients treated with placebo
  – 2.2% stopped medication due to AEs
• Adverse effects reported in cannabinoid users
  – Nausea
  – Increased weakness
  – Behavioral or mood changes
  – Suicidal ideation or hallucinations
  – Dizziness or vasovagal symptoms
  – Fatigue
  – Feelings of intoxication
• One death “possibly related” to treatment
  – Seizure followed by fatal aspiration pneumonia

Pre-clinical models of Seizures & Epilepsy

- $\Delta^9$-THC has primarily anti-convulsant properties
  - In some naïve, seizure susceptible rats & rabbits, $\Delta^9$-THC actually provoked epileptiform activity
- CBD is more consistently anti-convulsant
  - Follow bell-shaped dose-response curve
  - Less preclinical evidence for CBD’s effects in animal models of chronic epilepsy
Whole cannabis: Contradictory evidence

• Plant is complex
  – 489 known constituents
    • ~80 are cannabinoids
    • Remainder constituents are potentially neuroactive substances capable of crossing blood brain barrier
• Significant variability of strain-specific ratios of THC & CBD
  – Concentration can vary based on plant clones, weather, soil & other factors
• Mode of administration likely affects bioavailability & neuroactivity
• Attractive to isolate a single compound
  – But it is likely that combination of neuroactive substances taken together responsible for any potential anti-epileptic effect
Cannabidiol pharmacology in humans

- Potential routes of administration
  - Inhaled route
    - ~31% bioavailability
  - Oral route
    - Oil based capsule
    - ~6% bioavailability
- Distribution: highly lipophilic; high volume of distribution; highly protein bound
- Metabolism & elimination: CBD is metabolized extensively by the liver
  - CYP450 system: CYP3A, CYP2C
  - Half life: 18-32 hours
- Safety in humans
- Drug-Drug Interactions
  - Potent inhibitor of CYP2C and CYP3A
  - Repeated administration may induce CYP2B
    - Valproate & clobazam are metabolized by these routes
Cochrane Review 2014

- Assessed efficacy & safety of cannabinoids when used as monotherapy or add-on treatment for people with epilepsy
- Randomized controlled trials (blinded or not)
- Primary outcome: seizure freedom at ≥ 1 year or 3x longest inter-seizure interval
- Secondary outcomes: responder rate at ≥ 6 months, objective quality of life data, & adverse events
- Main results: 4 randomized trial reports that included total of 48 patients
  - Each used CBD as treatment agent
  - 1 report was an abstract & another was letter to the editor
  - No study assessed the primary outcome
  - All reports were considered “low quality”

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatments (subjects per group)</th>
<th>Duration</th>
<th>Outcome</th>
<th>Toxicity</th>
<th>Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mechoulam and Carlini, (1978)⁷²</td>
<td>TRE – CBD 200 mg/day (4) TRE – Placebo (5)</td>
<td>3 months</td>
<td>CBD: 2 seizure free; 1 partial improvement; 1 no change</td>
<td>None</td>
<td>No baseline seizure frequency, no definition of improvement; unclear if AEDs were changed; small N/limited power; not truly randomized-blinded; unknown if groups were matched</td>
</tr>
<tr>
<td>Cunha et al. (1980)⁷³</td>
<td>TRE-TLE CBD (7)⁴⁵        TRE-TLE Placebo (8)⁴⁶</td>
<td>200–300 mg/day for 3–18 weeks</td>
<td>Last visit: 4 CBD, 1 placebo</td>
<td>Somnolence</td>
<td>Not clearly blinded, since one patient transferred groups and doses were adjusted in CBD, but no mention of this in placebo group and CBD group received had longer average treatment</td>
</tr>
<tr>
<td>Ames and Cridland (1986)⁷⁴</td>
<td>IDD-TRE CBD (16)⁴⁶       IDD-TRE Placebo (16)⁴⁶</td>
<td>CBD 300/day × 1 week; 200/day × 3 weeks</td>
<td>No difference between CBD v. Placebo</td>
<td>Somnolence</td>
<td>This was a letter to the editor and details are lacking</td>
</tr>
<tr>
<td>Trembly and Sherman (1990)⁷⁵</td>
<td>TRE (10 or 12)⁴⁶</td>
<td>3 months baseline; 6 months placebo: Randomized to either 6 months placebo v. CBD 100 t.i.d.; then crossover for 6 months on alternative treatment</td>
<td>No change in seizure frequency or cognitive/behavioral tests</td>
<td>None</td>
<td>Only truly double blind study. Unclear why sample size differed in two reports. Data reported is incomplete</td>
</tr>
</tbody>
</table>

TRE, treatment-resistant epilepsy; TLE, temporal lobe epilepsy; IDD, intellectual/developmental disability.

⁴Frequent convulsions for ≥1 year; 1 GTCSz per week.
⁵One patient transferred from placebo to treatment after 1 month.
⁶12 subjects were divided into two groups, but distribution uncertain.
⁷Abstract and subsequent book chapter have different N’s (10 and 12).
“End of the Road”

• Many patients have turned to medical marijuana when traditional AEDs have “failed”

• Accounts of dramatic improvements with cannabis-based products with high CBD:THC (>20:1) ratios in popular press
Charlotte’s Web

• Charlotte Figi
• First seizure was prolonged status epilepticus at 3 months of age
• Confirmed SCN1A gene mutation, Dravet Syndrome
• Lost milestones and by age 5
  – Cognitive & motor delays
  – Feeding tube
  – Struggled to walk and talk
  – Full assist with her activities of daily living
• Tried on and failed multiple AEDs & ketogenic diet
  – Levetiracetam, oxcarbazepine, topiramate, zonisamide, valproate, clobazam, clonazepam, & valium
• Experiencing up to 50 generalized tonic-clonic seizures per day

Charlotte’s Web

- Charlotte’s mother started adjunctive therapy with a high concentration CBD:THC cannabis strain
- Baseline frequency of 300+ convulsions per week
  - 3 months into treatment, Charlotte had >90% reduction in convulsions
    - Had also been weaned from her other AEDs (clobazam)
  - 20 months into treatment, Charlotte has only 2-3 nocturnal convulsions per month
    - Improved development: eating & drinking, autistic behaviors improved, walking & talking again
- Strain of cannabis named “Charlotte’s Web” (CW)
- Families have moved from across the country & internationally to Colorado for treatment with CW
On July 20, 2014, Gov. Quinn signed Senate Bill 2636, which amended the Compassionate Use of Medical Cannabis Act to allow children under 18 to be treated with non-smokable forms of medical marijuana for the same conditions originally approved for adults. An underage patient’s parent or guardian must serve as caregiver, and signatures from two doctors are required. The bill, which becomes effective Jan. 1, 2015, also added seizures, including those related to epilepsy, to the list of approved conditions.
Survey on support of medical marijuana & CBD

• *Epilepsia* online survey
  – seeking opinions about use of medical marijuana & CBD for people with epilepsy
• May 20\(^{th}\) to Sept 1\(^{st}\), 2014
• 8 questions
• 776 started the survey
  – 58% were patients from North America
  – 22% were epileptologists & general neurologists (Epil/Neurol) from Europe & North America
  • 529 (68%) completed the survey

Results of Survey

Science is a religion held by a small minority

- Orrin Devinsky, MD
Dravet Syndrome

- Most often results from mutations in the SCN1A gene
- Healthy, developmentally normal children present within first year of life with convulsive status epilepticus (SE)
- Further episodes of SE, hemiclonic or generalized recur after first year of life
  - Other seizure types develop
- Seizures are typically refractory to standard AEDs
- Affected children develop an epileptic encephalopathy resulting in cognitive, behavioral, & motor impairment
Dravet Syndrome

• More effective early control of epilepsy is associated with better developmental outcomes

• Avoiding drugs that can worsen seizures (e.g. carbamazepine & lamotrigine)

• Prescribe effective drugs (e.g. valproic acid, clobazam, topiramate, stiripentol)

• Dietary therapies (ketogenic or modified Atkins diet)
Lennox Gastaut Syndrome (LGS)

• Rare epilepsy syndrome with diverse etiologies
• Presents in children 1-8 years old
  – Typically 3-5 years old
• Multiple refractory seizures despite multiple AEDs
• Example of an “epileptic encephalopathy”
• Morbidity is significant with frequent head injuries due to drop attacks
Lennox Gastaut Syndrome (LGS)

• EEG findings
  – Interictal (waking and sleep)
    • Slowed posterior dominant background rhythm
    • Awake: diffuse slow spike wave (1 to 2.5 Hz)
      – Typically generalized synchronous pattern (can be lateralized)
    • Bursts of fast rhythms (10Hz) that could occur frequently, sleep-activated, and associated with tonic seizure
    • May see multi-focal spikes
Lennox Gastaut Syndrome (LGS)

- EEG findings
  - Ictal
    - Tonic seizure*
      - Diffuse, rapid, low amplitude activity pattern that progressively decreased in frequency & increases in amplitude
    - Atypical absence seizure
      - Diffuse, slow, and irregular spike waves
    - Atonic, massive myoclonic, or myoclonic-atonic seizure
      - Slow spike waves, polyspike waves, or rapid diffuse rhythms
    - Absence status epilepticus
      - Continuous spike wave discharges, usually at a lower frequency than at baseline
Lennox Gastaut Syndrome (LGS)
Join this group to see the discussion, post and comment.

The Pediatric Cannabis Therapy group is a support and education group regarding the use of medical cannabis for pediatric patients. This group is designed for Parents/Caretakers of pediatric patients only.
Dravet Syndrome & Lennox-Gastaut Syndrome

• Recent survey of 19 parents who explored use of CBD-enriched cannabis therapy
  – 13 of whom had children with Dravet Syndrome
  – Age range 2-16 years
  – Treatment resistant epilepsy for >3 years prior to trying CBD-enriched cannabis
  – Average of 12 failed AEDs
  – Seizure frequency range: 2 per week to 250 per day
  – Dosages of CBD: 0.5mg/kg/day-28.6mg/kg/day
  – Dosages of THC: 0.0mg/kg/day-0.8mg/kg/day

Dravet Syndrome & Lennox Gastaut Syndrome

• Results:
  – 84% of parents reported reduction in their child’s seizure frequency
    • 2 noted complete seizure freedom
    • 8 reported >80% seizure reduction
    • 6 reported 25-60% seizure reduction
    • 3 parents reported no change
• Other positive effects: better mood (15/19), improved alertness (14/19), improved sleep (13/19)
• Negative effects: fatigue (3/19) & drowsiness (7/19)
Epidiolex®

- Purified 98% oil-based CBD plant extract
- 25 mg/mL and 100 mg/mL in the form of a viscous liquid to be dispensed in syringe droppers
- Contains no THC
- Considered schedule 1 substance by US Food & Drug Administration
- Closely monitored and restricted by both the FDA and US Drug Enforcement Agency
- Considered “investigational drug” that has not been approved for use by FDA
- Orphan drug designation in 2014 was obtained for Dravet Syndrome & Lennox Gastaut Syndrome
FDA Approves Cannabis Extract Study in Pediatric Epilepsy

• NYU & UCSF (preliminary data)
  – 23 patients treated with Epidiolex®
    • Dravet syndrome (n = 9)
    • Remaining patients had treatment-resistant epilepsies
  – Average age 10.4 years (only 1 adult aged 26)
  • Epidiolex® was added to current AEDs
    – On average, patients were taking 2.7 other AEDs
  • Median overall reduction in seizure frequency (convulsive & non-convulsive) compared to baseline seizure frequency: 32%
    • 39% obtained at least 50% reduction in seizure frequency
    • 17% of patients were seizure free (3/9 Dravet, 1/14 other)

"These results are encouraging, especially since they involved a group of children & young adults with very treatment-resistant epilepsy. However, we await the planned double-blind study to truly assess the safety & efficacy of Epidiolex”

-Orrin Devinsky, MD

Devinsky O, et al. Efficacy and Safety of Epidiolex (Cannabidiol) in Children and Young Adults with Treatment-Resistant Epilepsy: Initial Data from an Expanded Access Program. American Epilepsy Society Annual Meeting. (Abst. 3.303), 2014
Safety of Epidiolex®

- Safety data based on 151 patients
  - Represents approximately 50 patient-years of exposure
- Most common adverse events (occurring in at least 10% of patients)
  - Somnolence: 19%
  - Fatigue: 11%
  - Other: diarrhea, decreased appetite, increased appetite
- 2 withdrawals from treatment due to adverse reactions
  - 1 patient with Dravet syndrome had marked seizure worsening
- 4 withdrawals from treatment due to lack of clinical effect
- Serious adverse events were reported in 26 patients
  - 2 deaths
    - Sudden unexpected death in epilepsy-SUDEP
    - Respiratory failure from aspiration

http://www.gwpharm.com/GW%20Pharmaceuticals%20Announces%20New%20Physician%20Reports%20of%20Epidiolex%20Treatment%20Effect%20in%20Children%20and%20Young%20Adults%20with%20Treatment-Resistant%20Epilepsy.aspx
Potential Drug-Drug Interactions with Epidiolex®

• 33 patients (median age 10)
  – Taking average of 3 different AEDs
    • Clobazam (54.5%)
    • Valproate (36.4%)
    • Levetiracetam (30.3%)
    • Felbamate (21.2%)
    • Lamotrigine (18.2%)
    • Zonisamide (18.2%)
  – Baseline AED concentrations were established & taken after addition of Epidiolex

Potential Drug-Drug Interactions

- 8.30% for Clobazam
- 8.40% for Valproate
- 9.80% for Levetiracetam
- -8.60% for Felbamate
- -21% for Lamotrigine

Of patients taking clobazam, 7 (41%) required a dose reduction following CBD addition because of excessive sedation.

Future Directions

• CBD trial at Rush with Dr. Lubov Romantseva as Principal Investigator
• Multi-center, US based, randomized, double-blind, placebo-controlled phase 3 trial of a synthetic (non-plant based) CBD in 2 populations of medically refractory epilepsy
  – Dravet Syndrome: up to age 18
  – Lennox Gastaut Syndrome: up to age 30
• Primary endpoints: change in frequency of motor seizures involving trunk or extremities
• Secondary endpoints:
  – change in overall seizure frequency & severity
  – change in global functional status of LGS patients taking CBD
• To be run in outpatient setting
• Trial duration: 12 weeks with opportunity to roll over into open label extension trial
• Expected enrollment starting soon

For more information, contact the PI, Dr. Lubov Romantseva Lubov_Romantseva@rush.edu or research coordinator: Susan Rohde Susan_Rohde@rush.edu
Future Directions

• Prospective study
• Anonymous survey of patients in an adult epilepsy clinic
  – Prevalence of current marijuana use
    • Frequency of use
  – Reasons for marijuana use
  – Concomitant AED use
  – Change in seizure frequency
• Conducted by Ruby Upadhyay, MD & myself
American Epilepsy Society Position on Medical Marijuana

AES Position on Medical Marijuana

Three million Americans live with epilepsy. One-third of these people have ongoing treatment-resistant seizures. As the leading organization of clinical and research professionals specializing in the treatment of this challenging spectrum of disorders, the American Epilepsy Society (AES) supports all well-controlled studies that will lead to a better understanding of the disease and the development of safe and effective treatments for epilepsy.

The recent anecdotal reports of positive effects of the marijuana derivative cannabidiol for some individuals with treatment-resistant epilepsy give reason for hope. However, we must remember that these are only anecdotal reports, and robust scientific evidence for the use of marijuana is lacking. The lack of information does not mean that marijuana is ineffective for epilepsy. It merely means that we do not know if marijuana is a safe and effective treatment for epilepsy, which is why it should be studied using the well-founded research methods that all other effective treatments are. Every case of epilepsy is different and the disease is highly variable. Scientific studies help the entire epilepsy community to understand how and why various treatments work and for whom they are effective. Research also helps us understand the correct dose, side effects, and potential interactions with other medications. At present, the epilepsy community does not know if marijuana is a safe and effective treatment nor do we know the long-term effects that marijuana will have on learning, memory and behavior, especially in infants and young children. This knowledge gap is of particular concern because both clinical data in adolescents and adults and laboratory data in animals demonstrate that there are potential negative effects of marijuana on these critical brain functions.

AES understands first-hand the medical complexity of epilepsy and the difficult decisions facing people with epilepsy and their families. AES urges all people touched by epilepsy to consult with an epilepsy specialist and explore the many existing treatment options, so that they can make informed decisions with their specialist that weigh the risks and benefits of the different treatment options.
Illinois Medical Cannabis Pilot Program
Physician Written Certification Form

ATTESTATIONS

I __________________________ (the physician), have made or confirmed a diagnosis of a debilitating medical condition, as defined in the Compassionate Use of Medical Cannabis Pilot Program Act, for the qualifying patient and (ITEMS 1 THROUGH 4 BELOW MUST BE INITIALED):

1. Have established a bona-fide physician-patient relationship with the qualifying patient applicant. The qualifying patient is under my care, either for his/her primary care or for his/her debilitating medical condition, as specified on this form. This bona fide physician-patient relationship is not limited to a recommendation for the patient to use medical cannabis or a consultation simply for that purpose.
   Initial: __________________

2. Have conducted an in-person physical examination of the qualifying patient within the last 90 calendar days. I completed an assessment of the qualifying patient’s current medical condition, including symptoms, signs and diagnostic testing, related to the debilitating medical condition I diagnosed or confirmed. I understand the Illinois Department of Public Health may request additional confirmation of the assessment(s) performed for this qualifying patient’s debilitating medical conditions.
   Initial: __________________

3. Have completed an assessment of the qualifying patient’s medical history, including the review of medical records from other treating physicians from the previous 12 months. I have established a medical record for the qualifying patient with regard to his/her medical condition and his/her continued treatment for the condition(s) under my care.
   Initial: __________________

4. Have explained the potential risks and benefits of the medical use of cannabis to the qualifying patient.
   Initial: __________________

I __________________________ (the physician), hereby certify I am a physician duly licensed to practice medicine in the state of Illinois. It is my professional opinion that the qualifying patient is likely to receive therapeutic or palliative benefit from the use of medical cannabis to treat or alleviate the patient’s debilitating medical condition or symptoms of the debilitating medical condition. The qualifying patient has the debilitating medical condition(s) specified, and the patient is under my treatment for the debilitating condition(s) and/or their primary care. It is my professional opinion the potential benefits of the medical use of cannabis would likely outweigh the health risks for this patient. I attest the information provided in this written certification is true and correct.

Physician signature (no stamps accepted) __________________________ Date of signature (mm/dd/yyyy) __________________________
Thank you