TAKE HOME MESSAGES

- Marijuana remains federally illegal, but is fast gaining legitimacy at the state level.
- Medical marijuana dispensaries by and large offer non-pharmaceutical grade cannabis.
- Medical marijuana is not a single active ingredient.
- The endocannabinoid system holds rich medicinal potential.

TIMELINE

- 1851-1941: US Pharmacopoeia classifies marijuana as legitimate medical compound
- 1937: Federal government criminalizes marijuana
- 1954: Alice B. Toklas (partner to Gertrude Stein) publishes recipe for hashish fudge
- 1970: Federal Controlled Substance Act rendered it Schedule I
- 1996: CA 1st state to decriminalize medical marijuana
- 2007: NM passes 1st law to include state-regulated dispensaries

SCHEDULE I

- Not currently accepted for medical use in the US
- Lacking accepted safety profile for use under medical supervision
- High potential for abuse
FEDERALLY ILLEGAL

Recommending medical marijuana may carry a degree of Federal legal risk, mitigated by:
- Fact that practitioner is not prescribing
- Fact that there is little history of prosecution in medical marijuana states
- the Rohrabacher-Farr amendment (2014) prohibiting Justice Department from using federal funds to prevent states from implementing medical marijuana laws (although Jeff Sessions is threatening to repeal).

TYPES OF STATE MARIJUANA LAWS

- Allowing for comprehensive medical marijuana
- Allowing for recreational marijuana use (in addition to comprehensive medical marijuana)
- Allowing only cannabidiol (CBD) use
- Prohibiting marijuana use of any kind

MARIJUANA LEGAL LANDSCAPE

- 28 states and DC have medical marijuana laws
- 6 of those also have recreational marijuana laws
- 14 states have cannabidiol-only laws
- Only 8 states have no permissive medicinal marijuana laws on the books
HOW MEDICAL MARIJUANA LAWS WORK GENERALLY

- Define qualifying conditions
- Require “debilitating” symptoms
- Allow “Recommendation,” not prescription
- Stipulate permissible amount, generally ranging from 1 to 24 grams
NON-EXHAUSTIVE LIST OF QUALIFYING CONDITIONS

- AD
- ALS
- Anorexia
- Asthma
- Autism
- Cachexia
- Cancer
- Childhood AIDS
- Chronic Poly
- Cystic Fibrosis
- Epilepsy
- Fibromyalgia
- Glaucoma
- Hep C
- HIV/AIDS
- IBD
- Interstitial Cystitis
- Intractable Epilepsy
- LUPUS
- MS
- Parkinson’s
- PIH
- PTSD
- Sickle Cell
- Tourette’s
- Various Pain Syndromes

SAMPLE LIST OF DEBILITATING SYMPTOMS

- Agitation (AD)
- Cachexia
- Persistent muscle spasms
- Severe pain
- Severe nausea or vomiting
- Seizures

REGISTERED MEDICAL MARIJUANA DISPENSARIES
REGISTERED MEDICAL MARIJUANA DISPENSARIES

- Typically offer non-pharmaceutical grade preparations (not of chemical purity standard established by a recognized pharmacopeia to ensure stability, safety, and efficacy)
- Tend not to be regulated with regard to strains of marijuana and potency/types of products they offer
- Usually employ non-medical personnel who advise about products, delivery methods, dosing

MARIJUANA'S ACTIVE COMPONENTS

- >300 active components
- Phytochemicals, terpenes, phenols
- Due to regulatory hurdles, many not well vetted
- Operate through entourage effects
- Of greatest interest: Δ⁹-tetrahydrocannabinol (THC) and cannabidiol (CBD)

Δ⁹-TETRAHYDROCANNABINOL (THC)

- Main ingredient
- Responsible for marijuana’s mind-altering effects
- Also with analgesic, antiemetic, appetite-stimulating, anxiolytic, and anti-inflammatory effects
CANNABIDIOL (CBD)

- Up to 40% of cannabis sativa
- Not responsible for plant's mild-altering effects
- Administered across a wide variety of oral, intravenous & inhaled doses (in 25 human studies), no notable emotional, cognitive, psychomotor or hemodynamic side-effects
- Preclinical & clinical studies suggest anxiolytic, antipsychotic, sedative, anticonvulsive, antiemetic, anti-inflammatory, analgesic, & antineoplastic effects
- U.S. FDA has granted CBD Orphan Drug Designation for treatment of pediatric epilepsy.

PRESCRIPTION VERSUS RECOMMENDATION

<table>
<thead>
<tr>
<th>Specify</th>
<th>Prescription</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Indication</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Quantity</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Duration</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Route</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Dose</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Frequency</td>
<td>X</td>
<td></td>
</tr>
</tbody>
</table>
RECEPTORS

<table>
<thead>
<tr>
<th>CB1</th>
<th>CB2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Central and peripheral nervous system</td>
<td>Immune cells (spleen, B, T, monocytes)</td>
</tr>
<tr>
<td>Presynaptic (negative feedback)</td>
<td>Postsynaptic</td>
</tr>
<tr>
<td>G-protein-mediated calcium-channel modulator</td>
<td></td>
</tr>
</tbody>
</table>

- Brain function
  - Immune, hematopoietic, pain, GI motility & bone mass functions
- Binds endogenous ligands including anandamide & 2-arachidonoylglycerol

ENDOCANNABINOID LIFECYCLE

- Binds to various receptors CB1, CB2, G protein-coupled receptors 18 & 55
- Signaling terminated by enzymatic hydrolysis, for anandamide via fatty acid amide hydrolase (FAAH), and for 2-AG through monoacylglycerol lipase (MAGL)
**NOTE**

- Little research has been done on non-pharmaceutical-grade herbal cannabis & some dates to the 1970s before Congress categorized marijuana as schedule I.
- For this reason, presentation to continue with a brief review of pharmaceutical-grade synthetic and herbal preparations.

**SYNTHETIC CANNABINOID ANALOGS**

<table>
<thead>
<tr>
<th>Type</th>
<th>Onset (duration)</th>
<th>FDA Indications</th>
<th>Other evidence-based indications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dronabinol</td>
<td>30-60 min (4-6 hrs)</td>
<td>CINV &amp; HIV wasting syndrome</td>
<td>Spasticity in MS &amp; SCI</td>
</tr>
<tr>
<td>Nabilone</td>
<td>60-90 min (8-12 hrs)</td>
<td>CINV, Spasticity in MS &amp; SCI, Pain (chronic, neuropathic &amp; fibromyalgia-related)</td>
<td></td>
</tr>
</tbody>
</table>

*Not available at medical marijuana dispensaries

**PHARMACEUTICAL-GRADE HERBAL EXTRACTS**

<table>
<thead>
<tr>
<th>Delivery</th>
<th>Description</th>
<th>Onset (duration)</th>
<th>Evidence-based indications</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral (Cannador)</td>
<td>Δ-9 -THC &amp; cannabidiol in ratio of 2:1</td>
<td>Variable due to 1st pass metabolism</td>
<td>Not available in US</td>
<td>Approved in UK, NL, &amp; Canada in Phase III trials in the US</td>
</tr>
<tr>
<td>Sublingual metered dosed spray (nabiximols; Sativex®)</td>
<td>Δ-9 -THC &amp; cannabidiol in ratio of 1:1</td>
<td>15-40 min (2-4 hrs)</td>
<td>MS spasticity, urinary retention &amp; insomnia, Pain, particularly neuropathic</td>
<td>Approved in UK, NL, &amp; Canada in Phase III trials in the US</td>
</tr>
<tr>
<td>Oral (Epidiolex)</td>
<td>Cannabidiol Peaks in 2 hours; 24 hour ½ life</td>
<td>Not available in US</td>
<td>Dravet syndrome and pediatric epilepsy</td>
<td>Orphan drug designation in US</td>
</tr>
</tbody>
</table>

*Not available at medical marijuana dispensaries
**MEDICAL MARIJUANA**

<table>
<thead>
<tr>
<th>Quantity</th>
<th>Description</th>
<th>Method</th>
<th>Route</th>
<th>Result</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smoke</td>
<td>Smoked via cigarette or pipe</td>
<td>Immediate onset</td>
<td>Inhalation of carcinogens and toxins</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vaper</td>
<td>Heated to 175-225°C &amp; inhaled</td>
<td>Near-immediate onset</td>
<td>Cannabinoids vaporized below point of combustion</td>
<td>Theoretical risk of fungal infection</td>
<td></td>
</tr>
<tr>
<td>Oral extract</td>
<td>Ingested</td>
<td>No smoke inhalation</td>
<td>Variable onset due to 1st pass metabolism</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**SYMPTOM TRIALS**

<table>
<thead>
<tr>
<th>Symptom (population)</th>
<th>Type</th>
<th>N</th>
<th>Length (wk)</th>
<th>Route</th>
<th>Result</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bronchoconstriction (asthma)</td>
<td>RDBP* (2000)</td>
<td>8</td>
<td>8</td>
<td>Smoked</td>
<td>(+)</td>
<td>Induced symptom</td>
</tr>
<tr>
<td>Glaucoma (Chronic)</td>
<td>Retrospective observation</td>
<td>30</td>
<td>N/A</td>
<td>Smoked</td>
<td>Suggests benefit</td>
<td></td>
</tr>
<tr>
<td>Intracranial pressure (glaucoma)</td>
<td>Parallel group (n=109)</td>
<td>18</td>
<td>1</td>
<td>Smoked</td>
<td>Suggests benefit</td>
<td>However…</td>
</tr>
<tr>
<td>Nausea/vomiting (cancer)</td>
<td>Prospective observational</td>
<td>56</td>
<td>13</td>
<td>Smoked</td>
<td>Suggests benefit</td>
<td>Medication-resistant</td>
</tr>
<tr>
<td>Mood disturbance (HIV)</td>
<td>RDBP* (n=10)</td>
<td>8</td>
<td>10</td>
<td>Smoked</td>
<td>(+)</td>
<td>Statistical analysis: no details</td>
</tr>
</tbody>
</table>

* Trial employed a cross-over design

**AMERICAN ACADEMY OF OPHTAMOLOGY (2003)**

“No scientific evidence demonstrates increased benefits and/or diminished risks of marijuana use to treat glaucoma compared with available pharmaceuticals.”
VINCIGUERRA ET AL. (1988)

- Background: Financed by NY State
- Sample: NHSA non-randomize oncology patients with medication-resistant CINV who served as own controls
- Treatment method: Smoked marijuana, dose unknown
- Measure: Patient self-report
- Results: 34% experienced marijuana as very effective; 44% experienced marijuana as moderately effective
- Conclusion: Suggests benefit

SYMPTOM TRIALS

<table>
<thead>
<tr>
<th>Symptom (population)</th>
<th>Type</th>
<th>N</th>
<th>Length (days)</th>
<th>Route</th>
<th>Measure</th>
<th>Results</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Muscle spasm (MS)</td>
<td></td>
<td>26</td>
<td></td>
<td>Smoked</td>
<td></td>
<td>(1)</td>
<td></td>
</tr>
<tr>
<td>Parkinsonism</td>
<td></td>
<td>19</td>
<td></td>
<td>Oral</td>
<td></td>
<td>(1)</td>
<td></td>
</tr>
<tr>
<td>Parkinsonism</td>
<td></td>
<td>23</td>
<td></td>
<td>Smoked</td>
<td></td>
<td>(1)</td>
<td></td>
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<tr>
<td>Muscle spasm (MS)</td>
<td></td>
<td>7</td>
<td></td>
<td>Smoked</td>
<td></td>
<td>(1)</td>
<td></td>
</tr>
<tr>
<td>Parkinsonism</td>
<td></td>
<td>14</td>
<td></td>
<td>Smoked</td>
<td></td>
<td>(1)</td>
<td></td>
</tr>
</tbody>
</table>

* All trials employed a cross-over design

NEUROPATHIC PAIN TRIALS

<table>
<thead>
<tr>
<th>Type*</th>
<th>N</th>
<th>Days</th>
<th>Population</th>
<th>Route (% THC Potency)</th>
<th>Result</th>
<th>Comment</th>
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<tbody>
<tr>
<td>RDBPC</td>
<td>15</td>
<td></td>
<td></td>
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<td>RDBPC</td>
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<tr>
<td>RDBPC</td>
<td>15</td>
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</tr>
</tbody>
</table>

* All trials employed a cross-over design
EVIDENCE FOR USE IN THE “DEBILITATING CONDITIONS” HIGHLIGHTED BY MA LAW

<table>
<thead>
<tr>
<th>Indications</th>
<th># of RDBPCT*</th>
<th># of other RCTs</th>
<th># of Non-randomized Studies</th>
<th>Citations</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALS</td>
<td>1</td>
<td></td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Cancer</td>
<td>1</td>
<td>2</td>
<td></td>
<td>2</td>
</tr>
<tr>
<td>Crohn's</td>
<td>1</td>
<td></td>
<td></td>
<td>2</td>
</tr>
<tr>
<td>Glaucoma</td>
<td>1</td>
<td></td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Hep C</td>
<td>1</td>
<td></td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>HIV/AIDS</td>
<td>1</td>
<td></td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>MS</td>
<td>1</td>
<td></td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Parkinson's</td>
<td>1**</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* RDBPCT= Randomized, double-blind, placebo-controlled trial
** With negative results

COMMONLY REPORTED SIDE-EFFECTS

- Cough/ throat irritation
- Decreased concentration/ cognitive performance
- Dizziness/ lightheadedness
- Dry mouth
- Fatigue/ sedation
- Headache
- High
- Muscle weakness/ myalgia
- Nausea
- Numbness
- Paralympathies
- Palpitations
- Poor coordination
- Heavy

ADDITIONAL SIDE EFFECTS & RISKS: PHYSIOLOGIC

- Cardiovascular: acute hypertension, postural hypotension & heart rate acceleration
- Weight gain
- Hyperemia syndrome with chronic use
- Immune; immunosuppression
- Pulmonary irritation & chronic bronchitis
- Higher carcinogen exposure than tobacco smoke with possible risk of lung & testicular germ cell cancers in users & increased leukemia risk in offspring
- Abuse, tolerance & dependence (the latter in 9-17% of users)
- Withdrew (redness, irritability, insomnia, nausea, cramping, dizziness & rinoirethia)
- No direct mortality related to marijuana
ADDITIONAL SIDE EFFECTS & RISKS: NEUROPSYCHIATRIC

ACUTE
- Altered perceptions and mood, difficulty with thinking and problem solving, disrupted learning and memory
- Anxiety
- Paranoia & hallucinations
- Impaired driving

LONG-TERM
- Broad neuropsychological decline, particularly for adolescent-onset, persistent users
- Risk factor for psychosis later in life, particularly for those who start using young
- Flashbacks

ACOG: MJA IN PREGNANCY OR WITH BREASTFEEDING RISKS

- Intrauterine growth restriction
- Low birth weight
- Stillbirth
- Cognitive delays, deficits
- Poor executive function

DRUG-DRUG INTERACTIONS

- Use with tobacco synergistically ↑ heart rate and CO levels.
- Use with anticholinergics, alpha-agonists, theophylline, tricyclic antidepressants, naloxone or amphetamines synergistically ↑ heart rate.
- Central nervous system depressants potentiate sedative-hypnotic effects.
- Clinically meaningful P450 interactions have not been elucidated.
PATTERNS OF USE OF MEDICAL CANNABIS AMONG ISRAELI CANCER PATIENTS: A SINGLE INSTITUTION EXPERIENCE
WAISENGRIN ET AL 2015 JPSM 49(2) 223-230.

- An Israeli cancer center published their experience with 279 cancer patients issued permits for cannabis by a single oncologist.
- Median age 60(19-93)
- 84% with metastatic disease
- They reported improvement in:
  - Pain 70%
  - General well-being 70%
  - Appetite 60%
  - Nausea 50%

EFFECT ON CHRONIC PAIN

- Retrospective cross-sectional study of patrons of a dispensary with chronic pain found that most reported decreased opioid use (64%). Boehnke et al. (Journal of Pain 2016 Jun 17(6))
- They also reported improved side effect profile and improved quality of life.

- Prospective open label study showed improved pain and functional outcomes and decreased opioid use in cannabis users with chronic pain. Haroutounian Clin J Pain 2016 Dec 32(12)

ANTI-TUMOR EFFECTS!

- Conflicting evidence – tumor enhancing properties observed in some experimental models.
- Gliomas are tumor type with greatest cannabinoid research detailed but not clinically approved
- In vitro and animal models suggest cannabinoids decrease tumor growth
  - Induction of cell death
  - Inhibit tumor angiogenesis
  - Regulating antitumor immunity
CURRENT STUDIES

• Phase III Nabiximols and temozolomide in recurrent GBM
• Phase II CBD in solid tumors

RESEARCH LIMITATIONS

• DEA Schedule I status – access to substance
• Average THC concentration in 1980s: 4%; Average THC concentration in 2013: 15%
• Unblinding: Many so-called blinded studies probably are not
• Majority of clinical trials are of short duration (<2 weeks)

THE COLORADO EXPERIENCE

Expected Findings:
• Increased ED visits for marijuana intoxication

Unexpected:
• Increase in burns
• Cyclical vomiting
• Increase in intoxication from ingestion of edibles in children (accidental) and adults

OPIOID-RELATED MORTALITY

- Examined 13 states with medical marijuana laws in 2010.
- 24% lower mean opioid analgesia overdose mortality in states with medical marijuana laws.
- Significant drop was seen in year following medical marijuana laws and strengthened each year.


SUMMARY RECOMMENDATIONS

- Remember that, legally, healthcare providers are under no obligation to issue certifications.
- Exhaust conventional symptom management approaches before considering non-pharmaceutical grade cannabis.
- Use prudence with regard to patients with milder forms of qualifying conditions or with conditions without strong evidence base.
- Avoid recommending medical marijuana regularly or as the bulk of practice.

- Document that you have communicated to the patient: indications, risks, benefits, alternatives & duration of certification.
- Warn patient not to operate heavy machinery while under the influence.
- Consider baseline &/or periodic drug testing & in the case of patients with addiction history, psychiatric consultation prior to certifying.
- Use with caution if history of psychosis.
- Hospitals should neither dispense nor provide funds for medical marijuana, and prohibit on hospital premises.
CONCLUSIONS

• Registered marijuana dispensaries offer non-pharmaceutical grade cannabis, with fewer quality controls than pharmaceutical-grade cannabis products
• Scientific evidence base for medical marijuana is immature: Some exciting medicinal potential with regard to neuropathic pain; other indications for non-pharmaceutical cannabis based on anecdotal evidence or extrapolation from research on synthetics or pharmaceutical-grade herbals
• Concerning lack of coherence between scientific evidence base and the regulation

SUGGESTED FUTURE DIRECTIONS

• Federal regulation to ease barriers to cannabis research
• Well designed research trials with adequate sample sizes and clinically relevant durations to be done addressing cannabis’ beneficial & harmful effects
• Nabiximols to become available in the US
• MA regulation to tighten quality control standards, for instance regulating THC/CBving

T.H.

• 45-year old male MA resident, single sanitation worker
• History of IN cocaine, none in 5 years, and occasional recreational marijuana
• Chronic pain following MVA 2 years ago, occasionally impedes tasks like driving
• Relies on oxycodone prn, never abnormally but would like to substitute with medical marijuana given abuse potential
C.R.
- 32-year old, married woman, sans children, with severe MS diagnosed 4 years ago
- Symptoms include pain, spasticity, urinary retention
- Family history notable for schizophrenic mother; however no personal psychiatric history

P.S.
- 72-year old man
- Medical history significant for mild cognitive decline, MI (age 60), S/P stenting, and Parkinson’s disease (diagnosed age 70)
- PD symptoms include tremor, masked facies and depression
- Requesting marijuana as Sinemet discontinued in setting of nausea

E.H.
- 74-year old widowed Vietnam Vet with PTSD and history of several cancers including urinary and lymphoma with brain involvement
- PTSD symptoms include paranoia, irritability, flashbacks, nightmares
- Cancers largely asymptomatic and no active treatment
- Requesting marijuana for PTSD as “it helped in Vietnam”
M.P. 

- 40-year old married, father of 3 minors (age 15, 8, and 5) ultrasound technician in academic hospital with multiple myelomas 
- Treatment-related neuropathy severely impairs sleep; seeking medical marijuana for this indication 
- Hospital has drug-free policy in place for employees