PLENARY 1

CANNABINOIDS FOR SYMPTOM MANAGEMENT & CANCER THERAPY

MASCC, VIENNA

28 JUNE 2018
THERAPEUTIC APPLICATIONS OF CANNABINOIDs IN ONCOLOGY

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Levine Cancer Institute
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THE BATTLE OVER MARIJUANA

Is It Medicine?

The Risks of Legalization
The Health Effects of Cannabis and Cannabinoids
THE CURRENT STATE OF EVIDENCE AND RECOMMENDATIONS FOR RESEARCH
THERAPEUTIC EFFECTS

Conclusive/Substantial Evidence

1. Chronic Pain in Adults (Cannabis)
2. CINV (Oral Cannabinoids)
3. Multiple Sclerosis Spasticity Symptoms (Nabiximols)

Moderate Evidence

Short-Term Sleep Outcomes (Nabiximols)
<table>
<thead>
<tr>
<th>Risk</th>
<th>MODERATE</th>
<th>SUBSTANTIAL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td>+ (MVA)</td>
<td></td>
</tr>
<tr>
<td>Overdose</td>
<td>+ (Children)</td>
<td></td>
</tr>
<tr>
<td>Cognitive</td>
<td>+ (Acute Use)</td>
<td></td>
</tr>
<tr>
<td>Psychoses</td>
<td></td>
<td>+</td>
</tr>
<tr>
<td>Psych Symptoms</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Problem Use</td>
<td></td>
<td>+ Male, Young, Nicotine</td>
</tr>
<tr>
<td>Substance Abuse</td>
<td></td>
<td>+</td>
</tr>
</tbody>
</table>

National Academies, 2017
“A CERTAIN SURGEON ALWAYS TOOK SOME OPIUM,

AND

GAVE IT LIKewise TO HIS PATIENT,
WHEN HE HAD ANY CONsIDERABLE OPERATION TO PERFORM”

G. Young c.1753
INDIAN HEMP OR GUNJAH
(Cannabis Indica)

Their Effects of 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,
BROMPTON COCKTAIL

LIQUOR MORPHINI HYDROCHLORIDE  min. 15

COCAINE HYDROCHLORIDE  gr. 1:8

TINCT. CANNABIS INDICA  min.10

GIN  ml.4

SYRUP  ml.4

CHLOROFORM WATER  ad oz.1:12

Richardson, 1956
PROPOSED CLINICAL INDICATIONS

1. CNS: >50 Reports
   - Autism
   - Alzheimer’s
   - ALS
   - Epilepsy
   - Huntington’s
   - Pain Syndromes: Ca & Chronic
   - Parkinson’s

2. Medical: >150 Reports
   - Asthma & Autoimmune
   - Cancer
   - Gastrointestinal: Symptoms, IBD, IBS
   - Glaucoma
I fear I may be made out of marijuana.

I dance with the devil’s lettuce daily, from breakfast through bedtime, consuming enough of this polarizing plant to knock down an elephant. And I’m doing this to save my life—that’s **right**, marijuana is helping to keep me alive.

RECEPTOR SYSTEM

• CB1 (Delta-9-THC) - Central & Peripheral
  • Brain & Nerves: Dorsal Vagal & PAG
  • Organs incl. Gut
• CB2 (Cannabidiol) - Peripheral
  • B-Lymphocytes
  • Natural Killer Cells
CANNABINOID AGONISTS

AGONISTS (THC)  CANNABINOID RECEPTOR

---

G G G

A

(-) (-) (+)

K+

K+

Ca2+

Ca2+

CALCIUM ENTRY BLOCKED

CAMP

CAMP

K+

POTASSIUM CHANNELS OPENED

K+

CELL FIRING

NEUROTRANSMITTERS

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(Ca^{2+})
RECEPTOR SYSTEM

- **Endocannabinoids (Agonists)**
  - Anandamide
  - 2-Arachidonoylglycerol (2-AG)
- **CB1 & CB2: Pre-Synaptic G Protein**
  - Diffusely Inhibit NT Release
  - Both Excitatory & Inhibitory NT
  - Neuromodulators
# PHYSIOLOGICAL EFFECTS

<table>
<thead>
<tr>
<th>System</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>CNS</td>
<td>↓: Cognition + Coordination + Memory + Reaction time</td>
</tr>
<tr>
<td>Endocrine</td>
<td>↓: Testosterone</td>
</tr>
<tr>
<td>Heart / Vascular</td>
<td>Tachycardia; Hypotension; ↓ Cardiac Output</td>
</tr>
<tr>
<td>GUT</td>
<td>↓: Motility, Gastric Emptying</td>
</tr>
<tr>
<td>Lung</td>
<td>Bronchodilation</td>
</tr>
<tr>
<td>MFK</td>
<td>↓: Muscle Strength</td>
</tr>
<tr>
<td></td>
<td>HASHISH</td>
</tr>
<tr>
<td>----------</td>
<td>-------------------------------</td>
</tr>
<tr>
<td>Origins</td>
<td>Paste from stalk, resin</td>
</tr>
<tr>
<td>Synonym</td>
<td>Hash, Resin</td>
</tr>
<tr>
<td>Name</td>
<td>Arabic</td>
</tr>
<tr>
<td>Active</td>
<td>THC + +</td>
</tr>
<tr>
<td>Use</td>
<td>Europe/Asia</td>
</tr>
<tr>
<td>Memory</td>
<td>☑</td>
</tr>
<tr>
<td>Smoke</td>
<td>☑</td>
</tr>
<tr>
<td>Eat</td>
<td>☑</td>
</tr>
<tr>
<td>Vaporize</td>
<td>☑</td>
</tr>
<tr>
<td>Transdermal</td>
<td>☑</td>
</tr>
<tr>
<td>Plant</td>
<td>THC C. Sativa</td>
</tr>
<tr>
<td>------------</td>
<td>---------------</td>
</tr>
<tr>
<td>Active</td>
<td>Central</td>
</tr>
<tr>
<td>Receptor</td>
<td>CB1</td>
</tr>
<tr>
<td></td>
<td>Partial Agonist</td>
</tr>
<tr>
<td>Nerve Cells</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>Euphoria</td>
<td>+</td>
</tr>
<tr>
<td>Sleep</td>
<td></td>
</tr>
<tr>
<td>Psychoactive</td>
<td>+</td>
</tr>
</tbody>
</table>
Cannabis (THC 20%)
- C. Sativa
- C. Indica
- C. Ruderalis

Cannabinoids
- Phytocannabinoids
- Endogenous

Synthetic
- Dronabinol (THC)
- Nabilone (THC) x10 Potency
- Nabiximols (THC/CBD 1.08 :1 Plant Extract)
<table>
<thead>
<tr>
<th>MARIJUANA</th>
<th>DRONABINOL</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 400 Substances</td>
<td>1 Substance</td>
</tr>
<tr>
<td>&gt; 60 Cannabinoids</td>
<td>1 Cannabinoid</td>
</tr>
<tr>
<td>Carcinogens</td>
<td>No Carcinogens</td>
</tr>
<tr>
<td>Limited Research</td>
<td>More Research</td>
</tr>
</tbody>
</table>
SMOKED CNBDS IN CLINICAL PRACTICE

- Relative Benefits
  - Cost
  - Addiction
  - Side-Effects

- Good Clinical Practice & Records

- Doses Individualized By Self Titration

- Benefits V S/E

- Same Precautions as Opioids e.g. Driving

- Legal For Medical Use
  - Europe: > 10 Countries
  - USA: > 20 States
  - Federal: Illegal
CANNABIS & CANCER

• Cancer Risk
• Anti-Tumor Activity
• Toxicity Management
CANNABIS & CANCER

• Swedish Military Study
  • Cannabis > 50 Times
  • ↑ Lung CA X 2

• Kaiser Permanente Study
  • 4 Cohorts X 9 Years
  • Lung CA: Marijuana < “Never Smokers”

• Los Angeles City Epidemiology
  • Lung/Upper Airway Ca: All Marijuana Use ↓

• Population–Based Case–Control Studies
  • Marijuana ↑ Testicular Ca
CANNABINOIDs

Endocannabinoids and Cancer, Endocannabinoids, Handbook of Experimental Pharmacology, 2015
CANNABINOIDS: ANTI-TUMOR AGENTS?

- Evidence
  - In Vitro
  - Animal Models
- Actions
  - Inhibit Growth
  - Inhibit Angiogenesis & Metastasis
- Selective
  - Normal Cells Unaffected
Effects of the Endocannabinoid System in Cancer, Brit J Pharm, 2018
CANNABINOIDS & CHEMOTHERAPY

<table>
<thead>
<tr>
<th>Tumor Sites</th>
<th>Toxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Breast</td>
<td>1. Nausea &amp; Vomiting</td>
</tr>
<tr>
<td>2. Glioma’s</td>
<td>2. Neuropathic Pain</td>
</tr>
<tr>
<td>3. Lung</td>
<td>3. Cisplatin Nephrotoxicity</td>
</tr>
<tr>
<td>4. Lymphoma</td>
<td>4. Doxorubicin Cardiotoxicity</td>
</tr>
<tr>
<td>5. Pancreas</td>
<td>5. Bleomycin Lung</td>
</tr>
<tr>
<td>6. Prostate</td>
<td>6. Ocular Toxicity</td>
</tr>
<tr>
<td>7. Skin</td>
<td>7. Haemorrhagic Cystitis</td>
</tr>
</tbody>
</table>

Saraz, Cancer Res, 2008

Ostadhadi, Phytother Res, 2014
CANNABINOIDS

Triple Threat?

1. One Drug - Multiple Symptoms - Low S/E

2. Antiproliferative & Cytotoxic

3. Treatment Toxicities
MARIJUANA:
It won’t kill you... unless a bale of it falls on you.
- Willie
SIDE EFFECTS & SAFETY

• No Respiratory Depression

• Low Addiction Rate
  • Cannabis Dependence Rate 9%
  • < Alcohol, Cocaine, Heroin, Nicotine
  • Withdrawal: Mild < BZD / Opioids

• Side Effects
  • Mild at Moderate Doses
  • Both Synthetics & Cannabis
  • Psychotomimetic (CB1) Dose Limiting

• “Gateway Drug”: No Conclusive Evidence
Special Populations

- Children
- Adolescents
- Geriatric
- Survivors
- Substance Abuse
- Pregnancy/Lactation
- Occupational
- Skilled Activities
- Immunocompromised
1. Revise Schedule 1 Drug Status
2. Isolate Psychotropics (THC : CBD Ratio)
3. Opioid Synergism
4. Adjuvant Antitumor Agent
5. Immunotherapy Role
This is a painkiller.

This is a lifetime of addiction.
SUMMARY

1. Endocannabinoid System

2. Limited Clinical Evidence Base

3. Antiemetic & Appetite Stimulant & Analgesic Properties

4. Lab Data: Cytotoxic, Anti-inflammatory, Supportive Care

5. Public Debate ↔ Political Policies ↔ Patient Demand

6. Smoked CNBDS: Individualized Management

7. Change USA Drug Classification ↔ Investigational Research Agenda