Cannabis and the Future of Psychiatry

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Robert P. Walton, MD, PhD (1905-1971)
Professor and Chairman of MUSC Department of Pharmacology from 1942

Published in 1938, Walton’s tome was the premier publication on cannabis for the first half of the 20th century.
Disclaimer 1: Ethan Russo, MD

• Disclosure: Almost nothing discussed herein is FDA-approved. The interventions discussed in this program are for educational purposes. If such therapies are applied, outcomes will vary.
There is a world of difference between recreational studies of cannabis wherein the intention is to attain intoxication, release, or an altered state of consciousness, as compared to its therapeutic application, wherein the intent is to attain symptom relief at much lower dosages without adverse events including psychiatric symptoms.
Cannabis sativa and the Endocannabinoid System

- It began with a plant called cannabis----
- Cannabis makes glandular trichomes, that in turn produce THC

THC binds to a receptor, CB₁ that also binds endogenous cannabinoids, the "endocannabinoids," anandamide and 2-arachidonylglycerol.

- Endocannabinoid tone is a function of endocannabinoid levels, the status of the receptors and enzymes
CB₁ Expression in Brain

CB₁ is highly expressed in nociceptive areas, cerebellum, **limbic system**, basal ganglia and reward pathways, but not in medullary respiratory centers.

Stimulation of CB₁ inhibits release of neurotransmitters (e.g., glutamate or GABA) and thus is neuromodulatory.
Emperor Shên-Nung Pên-tsao Ching, 2700 BCE

Ma Fen [Herba Cannabis Sativae]---
Taking much of it may make one behold ghosts and frenetically run about. ---Protracted taking may make one fat, strong, and never senile.

We tell of the five kingdoms of herbs headed by Soma; may it and kuca grass, and bhanga and barley, and the herb saha release us from anxiety.

Passage: 11,6,15
translation, G.A. Grierson, India Hemp Drugs Commission Report, 1894.
“It is said that bhang is one of the best of God’s gifts, --- It quickens the fancy, deepens thought and sharpens judgment.”
Jamaica 1975

- 60 Hospitalized Adult Males
- Intake of >3 spliffs/day for >10 years
- Assay range 0.7-10.3% THC, average 2.8%
- NSD EEG, hematology
- Slight downward trend in FVC & FEV₁, NSD
- NSD Neuropsych except users had increased WAIS digit span
Greece, 1977

- 60 Subjects smoking hashish >10 years
- Hashish 4-5% THC, mixed with tobacco
- Slight increase in bronchitis sx. (concomitant tobacco)
- Fewer EEG changes
- Neuropsych: Users > control on WAIS Similarities, Digit Symbol Substitution & VIQ:
  - “These observations do not provide evidence of deterioration of mental abilities in the hashish users.”
Costa Rica, 1980

- 41 Subjects smoking >10 years
- Average 2 grams of cannabis/day
- THC content 1.27-3.72%, average 2.2%
- Users had > bronchodilation
- No immunological or endocrine changes (testosterone, fertility)
- Neuropsych: “We failed to uncover significant differences between user & nonuser groups—even in those subjects who had consumed cannabis for over 18 years.”
Jamaica 1982/1997

WORKING MEN AND GANJA
Marijuana Use in Rural Jamaica
Melanie Creagan Dreher

“Roots daughter” smoking ganja. Photo supplied by Melanie Dreher.

<table>
<thead>
<tr>
<th>Pt.</th>
<th>Age/Gender</th>
<th>Qualifying Condition</th>
<th>IND Approval/Cannabis usage</th>
<th>Daily Cannabis/THC content</th>
<th>Current Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>62/F</td>
<td>Glaucoma</td>
<td>1988 25 years</td>
<td>8 grams/3.80%</td>
<td>Disabled Operator/Singer/Activist/Vision stable</td>
</tr>
<tr>
<td>B</td>
<td>52/M</td>
<td>Nail-Patella Syndrome</td>
<td>1989 27 years</td>
<td>7 grams/3.75%</td>
<td>Disabled Laborer/Factotum/Ambulatory</td>
</tr>
<tr>
<td>C</td>
<td>48/M</td>
<td>Multiple Congenital Exostoses</td>
<td>1982 26 years</td>
<td>9 grams/2.75%</td>
<td>Full time Stockbroker/Disabled Sailor/Ambulatory</td>
</tr>
<tr>
<td>D</td>
<td>45/F</td>
<td>Multiple Sclerosis</td>
<td>1991 11 years</td>
<td>9 grams/3.50%</td>
<td>Disabled clothier/Visual impairment/Ambulatory aids</td>
</tr>
</tbody>
</table>
MRI scan of the brain
Pulmonary function tests (Spirometry)
Chest X-ray, P-A & lateral (Patients A-C)

Neuropsychological tests

- Wechsler Adult Intelligence Scale-3rd Edition (WAIS-III)
- Wechsler Memory Scale-3rd Edition (WMS-III)
- California Verbal Learning Test (CVLT)
- Halstead-Reitan Battery
  - Trail Making Test A & B
  - Grooved Peg Board
  - Finger Tapping and Category Subtests
- Controlled Oral Word Association Test
- Thurstone Word Fluency Test
- Category Fluency Test (animal naming)
- Wisconsin Card Sorting Test (WCST)
- Conner’s Continuous Performance Test-2nd Edition (CPT-II)
- Beck Depression Inventory-2nd Edition (BDI-II).

Endocrine assays
- FSH, LH, prolactin, estradiol, estrone, estrogen, testosterone, progesterone

Immunological assays
- CBC, CD4 count

Electroencephalography (EEG) (Patients A-C)
P300 testing (Patients A-C)
Neurological examination

Tests Performed: Chronic Cannabis IND Study

Neuropsychological Summary: Undertaken while medicating

- Patients A-D: mild difficulty with attention and concentration
- At least minimal impairment of acquisition of complex new verbal material (CVLT)
- Higher level executive functions WNL in 2/4
- No depressive symptoms in any
- No attributable sequelae to cannabis


• 2018 Follow-up:

• Patients A (79), B (69), and D (62) lost access to NIDA cannabis, but A continued daily use from other sources.

• Patients B and D reported as cognitively intact via long-term nurse.

• Patients A & C mentally sharp via neurologist.

• Patient C is active vice president of an investment firm.

- Compared current (n=63) and past heavy users (n=45) with light past users (N=72) as controls
- Neuropsychological test battery applied sequentially after abstinence
- Some *cognitive deficits* were detectable in current heavy users for 7 days (memory of word lists), but were totally reversible by 30 days.
- “----our findings do not support the hypothesis that long-term heavy cannabis use causes irreversible cognitive deficits---.” p. 914

“The results of our meta-analytic study failed to reveal a substantial, systematic effect of long-term, regular cannabis consumption on the neurocognitive function of users who were not acutely intoxicated.” p. 685

“---these findings are not likely to generalize to more limited administration of cannabis compounds, as would be seen in a medical setting.” p. 686

- 69 study of 2152 cannabis users, mean age 20.6, and 6575 controls
- Small overall effect size, $d \, -0.25$, $p<0.001$, for reduced cognitive function in frequent or heavy users.
- However, in studies examining abstinence of $>72$ h, $d \, -0.08$, NSD from abstainers.
- “---all effect sizes in this study were below one-third of a standard deviation.” p. 591
- “---previous studies of cannabis in youth may have overstated the magnitude and persistence of cognitive deficits associated with use. Reported deficits may reflect residual effects from acute use or withdrawal.” p. 585
- “---these results do not support a heightened risk for poor cognitive outcomes in cannabis-using adolescents compared with adults---.” p. 591
Medical cannabis and mental health: A guided systematic review

Zach Walsh a, Raul Gonzalez b, Kim Crosby d, Michelle S. Thiessen e, Chris Carroll f, Marcel O. Bonn-Miller g

HIGHLIGHTS

- Mental health conditions are prominent among the reasons for medical cannabis use.
- Cannabis has potential for the treatment of PTSD and substance use disorders.
- Cannabis use may influence cognitive assessment, particularly memory.
- Cannabis use does not appear to increase paranoia.
- More research is needed.

Marijuana Makes You Crazy, Says New Study (Yeah, Tell us Something we Don't Know)
Neurocognition

- Improved executive functioning at 3 months follow-up
- 2 study of therapeutic use*
- CTP users did not differ from controls with regard to neurocognitive functioning at one-year follow-up
- 6 Reviews of non-medical
  - Mixed findings for decision-making and inhibitory control
    - Some deficits in attention and memory
    - Acute deficits in short term memory
  - No evidence of long term, persistent neurocognitive deficits after cessation of use

*Courtesy of Zach Walsh, PhD
Smoked NIDA cannabis in 50 subjects TID for 5 days

- All required to have previous cannabis smoking experience

Results
  - decreased daily pain (p=0.03)
  - hyperalgesia (p=0.05)
  - 52% with >30% pain reduction vs. placebo (p=0.04)

- AEs in smoking group (psychoactive effects) were prominent

### Adjusted estimates

<table>
<thead>
<tr>
<th></th>
<th>Cannabis, mean (95% CI)</th>
<th>Placebo, mean (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anxiety*</td>
<td>0.25 (0.14, 0.44)</td>
<td>0.10 (0.05, 0.22)</td>
</tr>
<tr>
<td>Sedation†</td>
<td>0.54 (0.36, 0.81)</td>
<td>0.08 (0.04, 0.17)</td>
</tr>
<tr>
<td>Disorientation†</td>
<td>0.16 (0.07, 0.34)</td>
<td>0.01 (0.00, 0.04)</td>
</tr>
<tr>
<td>Paranoia</td>
<td>0.13 (0.03, 0.45)</td>
<td>0.04 (0.01, 0.14)</td>
</tr>
<tr>
<td>Confusion†</td>
<td>0.17 (0.07, 0.39)</td>
<td>0.01 (0.00, 0.06)</td>
</tr>
<tr>
<td>Dizziness†</td>
<td>0.15 (0.07, 0.31)</td>
<td>0.02 (0.01, 0.05)</td>
</tr>
<tr>
<td>Nausea</td>
<td>0.11 (0.04, 0.30)</td>
<td>0.03 (0.01, 0.14)</td>
</tr>
</tbody>
</table>

Side effects were rated three times daily on a 0 to 3 scale (0 = none, 1 = mild, 2 = moderate, 3 = severe).

* p, 0.05; † p < 0.001.
Neuropathic Pain in Multiple Sclerosis

• Double blind, randomised, parallel group placebo controlled study of nabiximols in central neuropathic pain in MS

• Single UK Centre Study N = 66 Treatment duration: 5 weeks

• All patients remain on current medication throughout trial

• Primary endpoint
  • Change from baseline in pain score averaged over last 7 days, evaluated from daily pain diaries and measured on a Numerical Rating Scale (NRS, 0-10) of pain severity. Pain in nabiximols was significantly improved (p<0.005)

• NSD in Hamilton Anxiety, Depression and Guy’s Neurological Disability Scale

• Improvement was noted in Selective Reminding Test portion (p=0.009) of the Brief Repeatable Battery of Neuropsychological Tests

Nabiximols Safety Profile: Adverse Events, Incidence >3%

Most AE’s are early and transient

Improved safety profile as result of modified “lower and slower” dose titration regimen

**Tolerance and Intoxication**

**No evidence of tolerance**

**Examples: Intoxication Scores**

<table>
<thead>
<tr>
<th>Study Week Number</th>
<th>Intoxication Scores (Clinic Visits)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo Crossover to THC:CBD</td>
</tr>
</tbody>
</table>

**Nabiximols vs THC vs Placebo**

<table>
<thead>
<tr>
<th></th>
<th>nabiximols</th>
<th>THC</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pre-Dose</strong></td>
<td>6.45</td>
<td>8.22</td>
<td>6.59</td>
</tr>
<tr>
<td><strong>2 hours</strong></td>
<td>9.75</td>
<td>11.2</td>
<td>8.41</td>
</tr>
<tr>
<td><strong>4 hours</strong></td>
<td>9.63</td>
<td>12.1</td>
<td>7.44</td>
</tr>
</tbody>
</table>

- Examined 150 patients in clinical studies and 900 in post-marketing
- “---in practice average doses used by patients tended to be lower than those reported in clinical studies (5-6.4 vs. >8 sprays/day), and effectiveness was maintained in the majority of patients---.” (p. 4)
- 33 patients were specifically examined: “The mean spasticity 0-10 NRS score decreased from 6.0 (±1.76) at baseline to 3.6 (±1.73) at final visit (p<0.0001)” (p. 6)
- “There was one case of suicidal ideation, in a subject taking placebo.” (p. 7)
- “---long-term treatment with THC:CBD spray was not associated with cognitive decline, depression or significant changed in mood.” (p. 7)
- “At 6 months 69% of the initial patients were continuing with THC:CBD oromucosal spray and the equivalent number was 66% at 1-year.” (p. 8)
Driving skills


No cognitive sequelae

but, clear improvement in functional status

---

**Fig. 2.** Effects of THC:CBD oromucosal spray and placebo on cognitive ability of MS patients with spasticity treated for 50 weeks.

**Fig. 3.** Effects of THC:CBD oromucosal spray and placebo on patient, physician and caregiver Global Impression of Change (GIC) in MS patients with spasticity treated for 50 weeks. * p = 0.0042; ** p = 0.0014; *** p < 0.001.

**Table 3. Safety findings of special interest from the Spanish registry**

<table>
<thead>
<tr>
<th>Tolerability</th>
<th>Incidence (n = 196)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any AE, % (n)</td>
<td>19.9% (39)</td>
</tr>
<tr>
<td>Significant psychiatric or psychotic event</td>
<td>2.4% (5)</td>
</tr>
<tr>
<td>Reduced driving ability</td>
<td>0.5% (1)</td>
</tr>
<tr>
<td>Fall requiring medical attention</td>
<td>0% (0)</td>
</tr>
<tr>
<td>Suicidal thoughts/attempted suicide</td>
<td>0% (0)</td>
</tr>
<tr>
<td>Abuse/misuse</td>
<td>0% (0)</td>
</tr>
<tr>
<td>Other</td>
<td>16.8% (33)</td>
</tr>
</tbody>
</table>

More than two-thirds of patients reported deriving benefit from THC:CBD spray, despite having spasticity resistant to treatment with current oral antispasticity agents.

- High doses of $\Delta^8$-THC up to 0.64 mg/kg/dose given to 8 children with hematological malignancies, ages 3-13, up to 114 treatments (divided QID).
- Almost universally effective in 480 total applications with minimal side effects.
- Dose of $\Delta^8$-THC in children was 18 mg/m$^2$ as compared to usual recommended dose of 5-10 mg/m$^2$ $\Delta^9$-THC in adults.

- 188 patients, most taking oil with average 79.5 mg CBD, 4 mg THC TID
- After 6 months, 86.6% continued Tx., with positive mood 63.5%, improved ADLs 42.9%, good sleep 24.7%, and good concentration 14% (all p<0.001)
- 80% of patents reported moderate or significant improvement
Effect of Sativex on Sleep

Summary of Impact of Sativex on Sleep Quality / Disturbance

*compared to placebo

PTSD and the ECS

• Previous research has elucidated the role of the ECS in:
  • Extinction of aversive memories (Marsicano 2002)
  • Stress-induced analgesia (Hohmann 2005)
  • A central anandamide deficiency that predicts stress-induced anxiety (Bluett 2014)

Posttraumatic Stress Disorder

4 studies of medical use

Substantial portion treat PTSD symptoms with cannabis
Self-report of good outcomes
Effective for improving sleep and reducing nightmares

Courtesy of Zach Walsh, PhD

- 46 WTC survivors were assessed
- Serum 2-AG was significantly reduced in PTSD victims vs. those without PTSD, especially those with direct exposure, promoting retention of aversive memories
- A negative relationship was also noted between AED levels and intrusive symptoms
- Results to date suggest a good correlation of lower serum AEA levels to increased CB₁ receptor binding sites in CNS.
Depression

9 Cross-sectional studies of therapeutic

7 noted mood improvement

1 reported positive association between depression severity and problematic cannabis use

4 Reviews of nonmedical

Small positive association between cannabis and depression – no causation
Missoula Chronic Use Study
Beck Depression Inventory-II

• Mild Depression: 18 (mean)
• Moderate Depression: 27
• Severe Depression: 34

Steer et al. (2001) *Psychol Rep* 88: 1075-.

Results:

Patient A: 6
Patient B: 0
Patient C: 0
Patient D: 0

Psychosis/Schizophrenia

6 Reviews of non-medical use

Evidence of an association between cannabis and psychosis among at-risk groups

Individuals at risk for developing schizophrenia may treat prodromal symptoms
Hickman, M., et al 2009. If cannabis caused schizophrenia--how many cannabis users may need to be prevented in order to prevent one case of schizophrenia? England and Wales calculations. *Addiction, 104*(11), 1856-1861.

- In male heavy cannabis users, the number needed to prevent (NNP) schizophrenia ranged from 2800 to 4700 depending on age.

- In female heavy cannabis users, the NNP for schizophrenia ranged from 5470 to 10,870.

- Cannabidiol 800 mg po per day vs. amisulpride in 42 patients for 4 weeks.
- Positive and Negative Syndrome Scores (PANSS) were improved in each (p=0.001), but negative symptoms were notably better on CBD (p=0.001) with fewer extrapyramidal AEs (p=0.006), less weight gain (p=0.01) and prolactin elevation (p=0.001).

- 45 controls on anti-psychotics vs. 43 on 1000 mg CBD divided BID over 6 weeks.
- Positive psychotic sx. decreased on CBD (p=0.019)
- Clinician ratings favored CBD (p=0.018)
- Motor speed favored CBD (p<0.05)
Results imply a markedly better therapeutic index and safety margin for nabiximols (THC/CBD extracts) over pure THC.


Anxiety

8 Cross-sectional studies of medical
- 8 reported relief of anxiety as a primary or secondary benefit
- 1 reported anxiety returned after cessation of use

2 Reviews of non-medical
- Small positive association between cannabis use and anxiety – no causation

Courtesy of Zach Walsh, PhD

- 3723 Americans in the National Epidemiological Survey on Alcohol and Related Conditions, over 4 years.
- 1.76% of patients with anxiety disorder used cannabis throughout (“Cannabis Use Disorder”).
- NSD in anxiety remission rates noted compared to other users or non-users.
- NSD in 3 groups on suicidality.
- On Quality of Life (QOL), mean scores on emotional and mental health subscales and mental functioning scale were significantly higher in cannabis users than abstainers.

- “Nearly half of the ANX sample [N=888] (49%) reported substituting a prescribed medication with CMP to some degree, of whom 61% indicated that cannabis had completely (100%) replaced a drug prescribed---.” p. 137

- “The most frequently replaced drugs included psychotropics (antidepressants and benzodiazepines) and pain relievers.” p. 137

- Open-label study of 176 Israeli chronic pain patients qualifying for adjunctive cannabis treatment, completing 6 months of study.
- Average cannabis intake 1.5 grams/day by various routes, mostly smoking.
- S-TOPS pain symptom score improved from 83.3 to 75 (p<0.001), along with family-social disability, role-emotional disability, satisfaction with outcome, and sleep problem index.
- Of 73 pts. on opioids, 32 (44%) discontinued them (p<0.001), and median oral morphine equivalent dose decreased from 60 to 45 mg (NSD).

![Graph showing change in BPI pain severity and interference]

Change in BPI pain severity median (7.5 to 6.25) and Pain interference score (8.14 to 6.71) (both p<0.001)

In study 118 patients, cannabis use led to a 64% reduction in opioids and a 45% increase in QOL measures (possibly due to fewer opioid-associated AEs).

Of 344 patients (33.9%) on opioids at onset, 36% were able to discontinue them, 9.9% decreased their dose, only 1.1% increased and 51% continued on a stable dosage.

Anxiety and depression declined 84.2%.

- 26 pts. in Israel getting mean dose of 26 g. of cannabis/month (<1 g/d)
- 46% reported increase in work capacity or return to work
- Substantial opioid sparing and decreased use of adjunctive drugs was noted.

**TABLE 3. Meds Consumed Prior to and Under MC Treatment**

<table>
<thead>
<tr>
<th>Medication</th>
<th>Prior to MC Treatment</th>
<th>Under MC Treatment</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Simple analgesics</td>
<td>12 (~46)</td>
<td>3 (~15)</td>
<td>0.000</td>
</tr>
<tr>
<td>NSAIDs</td>
<td>19 (~73)</td>
<td>2 (~8)</td>
<td>0.000</td>
</tr>
<tr>
<td>Simple opiates</td>
<td>4 (~15)</td>
<td>0 (0)</td>
<td>0.055</td>
</tr>
<tr>
<td>Pregabalin</td>
<td>7 (~27)</td>
<td>0 (0)</td>
<td>0.005</td>
</tr>
<tr>
<td>Strong opiates</td>
<td>20 (~77)</td>
<td>5 (~19)</td>
<td>0.000</td>
</tr>
<tr>
<td>Benzodiazepines</td>
<td>7 (~27)</td>
<td>1 (~5)</td>
<td>0.027</td>
</tr>
<tr>
<td>Tricyclics</td>
<td>4 (~15)</td>
<td>0</td>
<td>0.055</td>
</tr>
<tr>
<td>Other antidepressants</td>
<td>8 (~31)</td>
<td>3 (~12)</td>
<td>0.107</td>
</tr>
</tbody>
</table>

NSAIDs indicates nonsteroidal anti-inflammatory drugs.
Cannabis Synergy: Psychopharmacology

• Depression: THC/CBD/CBG + Limonene
• Anxiety: CBD + limonene/linalool
• Sedation: THC/CBN + Myrcene
• Agitation/Alzheimer Disease:
  THC/CBD + Limonene/Pinene/Linalool
• Sleep:
  THC + Caryophyllene/Linalool/Myrcene
• Addiction: CBD + Caryophyllene
Thanks!