Cannabis and the Future of Psychiatry

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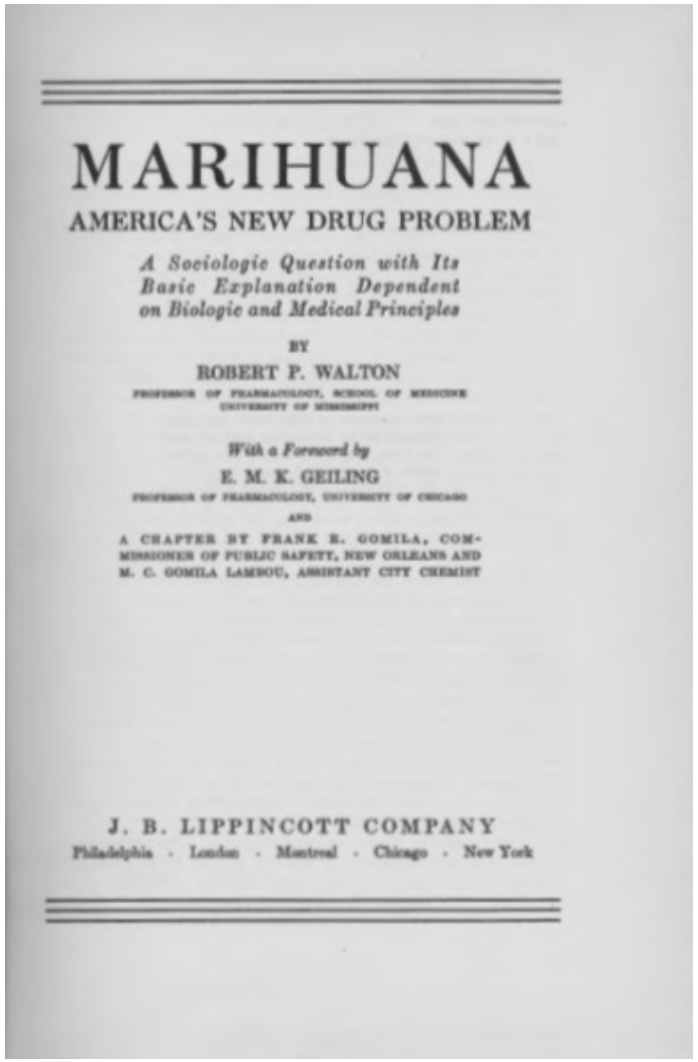
Robert P. Walton, MD, PhD (1905-1971)

Professor and Chairman of MUSC Department of Pharmacology from 1942

Courtesy of Jane Brown, Waring Library, 2003



MARIHUANA

AMERICA'S NEW DRUG PROBLEM

A Sociologic Question with Its Basic Explanation Dependent on Biologic and Medical Principles

BY

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With a Foreword by

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A CHAPTER BY FRANK R. GOMILA, COMMISSIONER OF PUBLIC SAFETY, NEW ORLEANS AND M. C. GOMILA LAMBOU, ASSISTANT CITY CHEMIST

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Published in 1938, Walton's tome was the premier publication on cannabis for the first half of the 20th century.

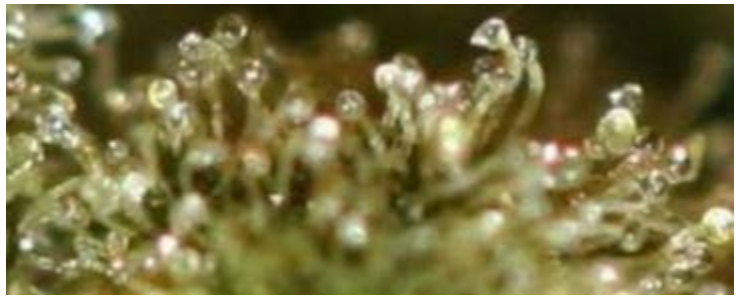
Disclaimer 1: Ethan Russo, MD

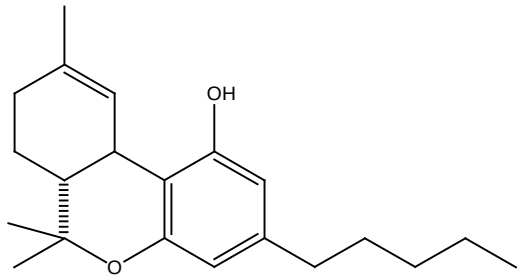
- Disclosure: Almost nothing discussed herein is FDA-approved. The interventions discussed in this program are for educational purposes. If such therapies are applied, outcomes will vary.

Disclaimer 2: Ethan Russo, MD

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.

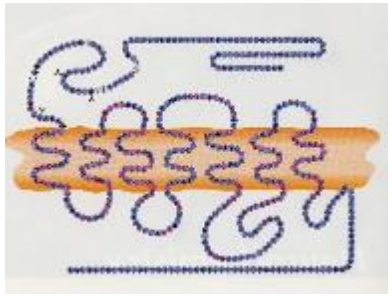
Cannabis sativa and the Endocannabinoid System



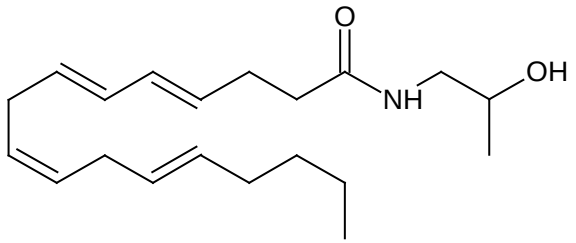


delta-9-tetrahydrocannabinol (THC)

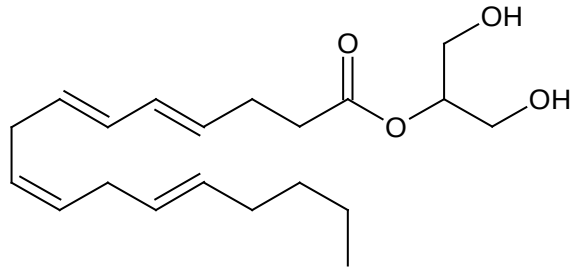
- It began with a plant called cannabis----
- Cannabis makes glandular trichomes, that in turn produce THC



CB_1



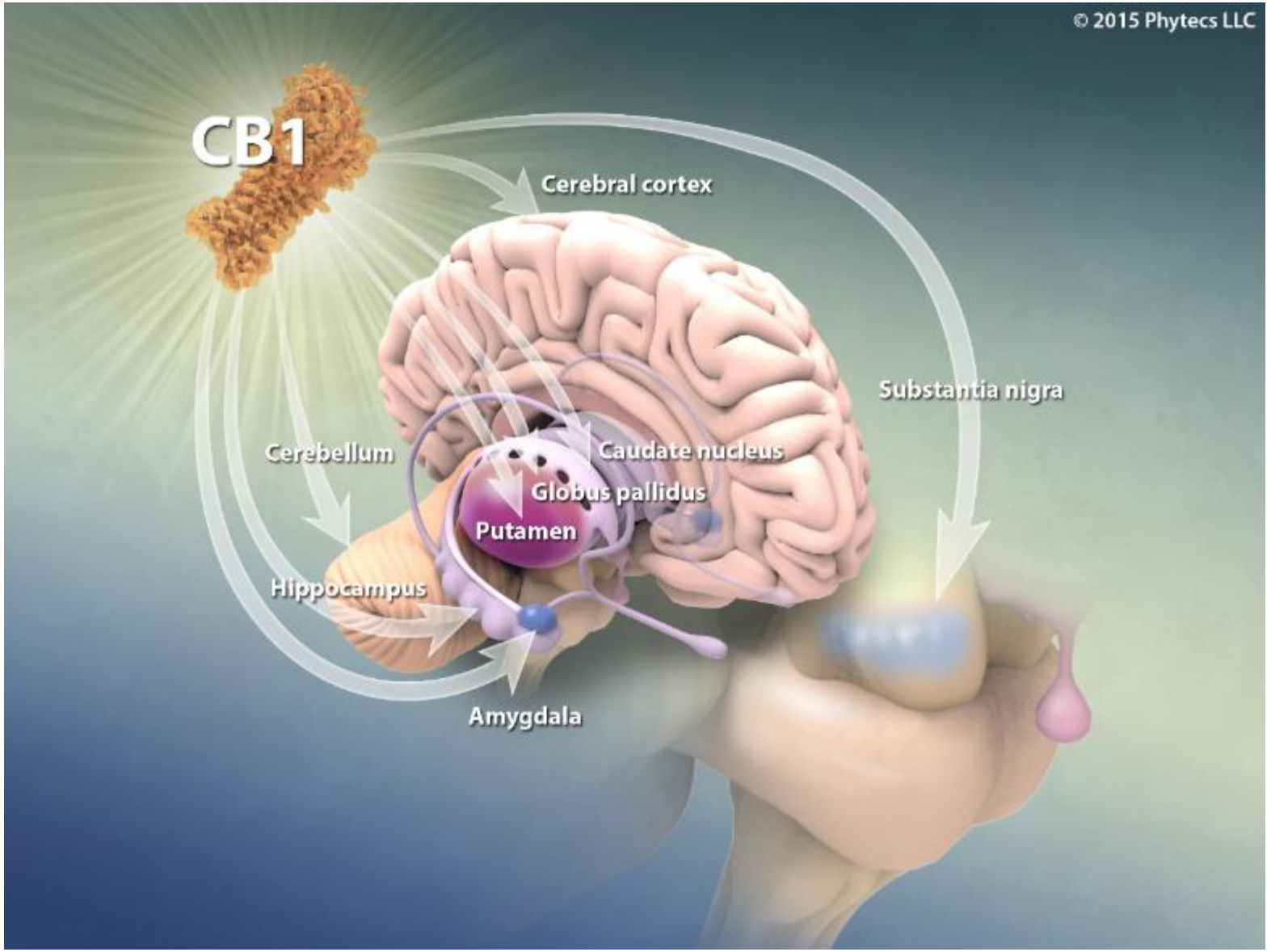
anandamide



2-arachidonylglycerol

- THC binds to a receptor, CB_1 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

CB_1 Expression in Brain



CB_1 is highly expressed in nociceptive areas, cerebellum, **limbic system,** basal ganglia **and reward pathways, but not in medullary respiratory centers.**

Stimulation of CB_1 inhibits release of neurotransmitters (e.g, glutamate or GABA) and thus is neuromodulatory.

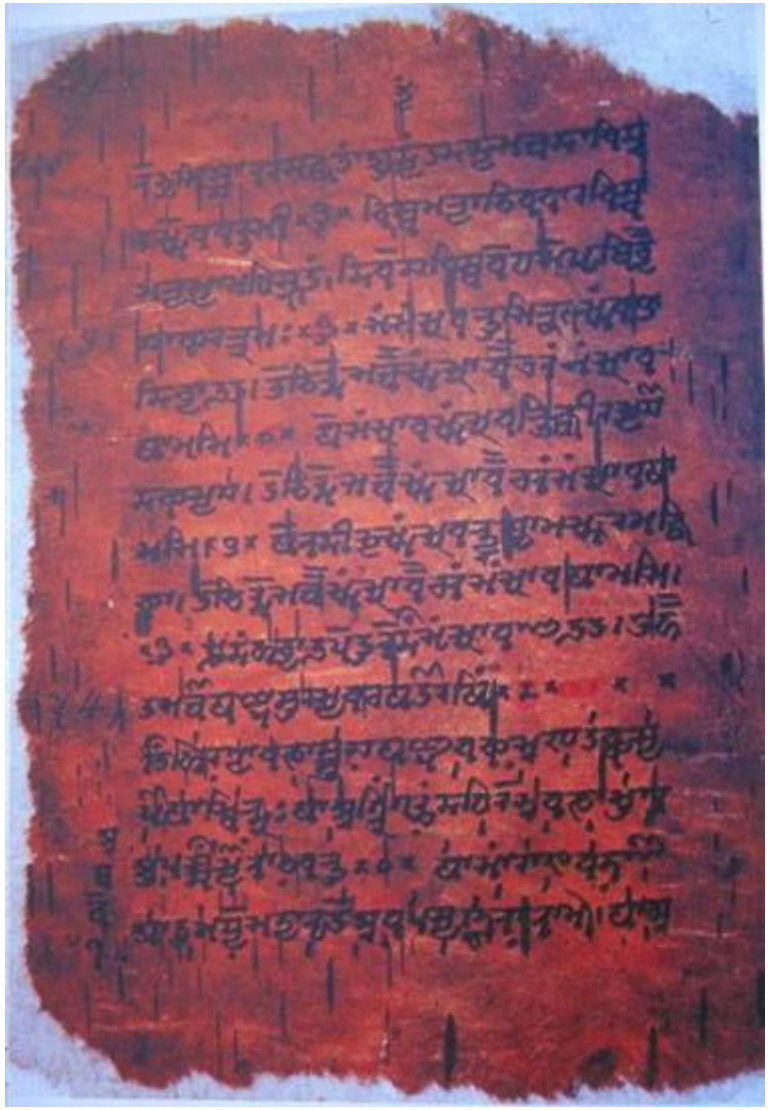
Emperor Shên-Nung *Pên-tsao Ching*, 2700 BCE

麻

***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.**

Shou-zhong, Y. 1997. The divine farmer's materia medica: A translation of the *Shen Nong Ben Cao Jing.* Boulder, CO: Blue Poppy Press.

Atharva Veda, 16th Century BCE

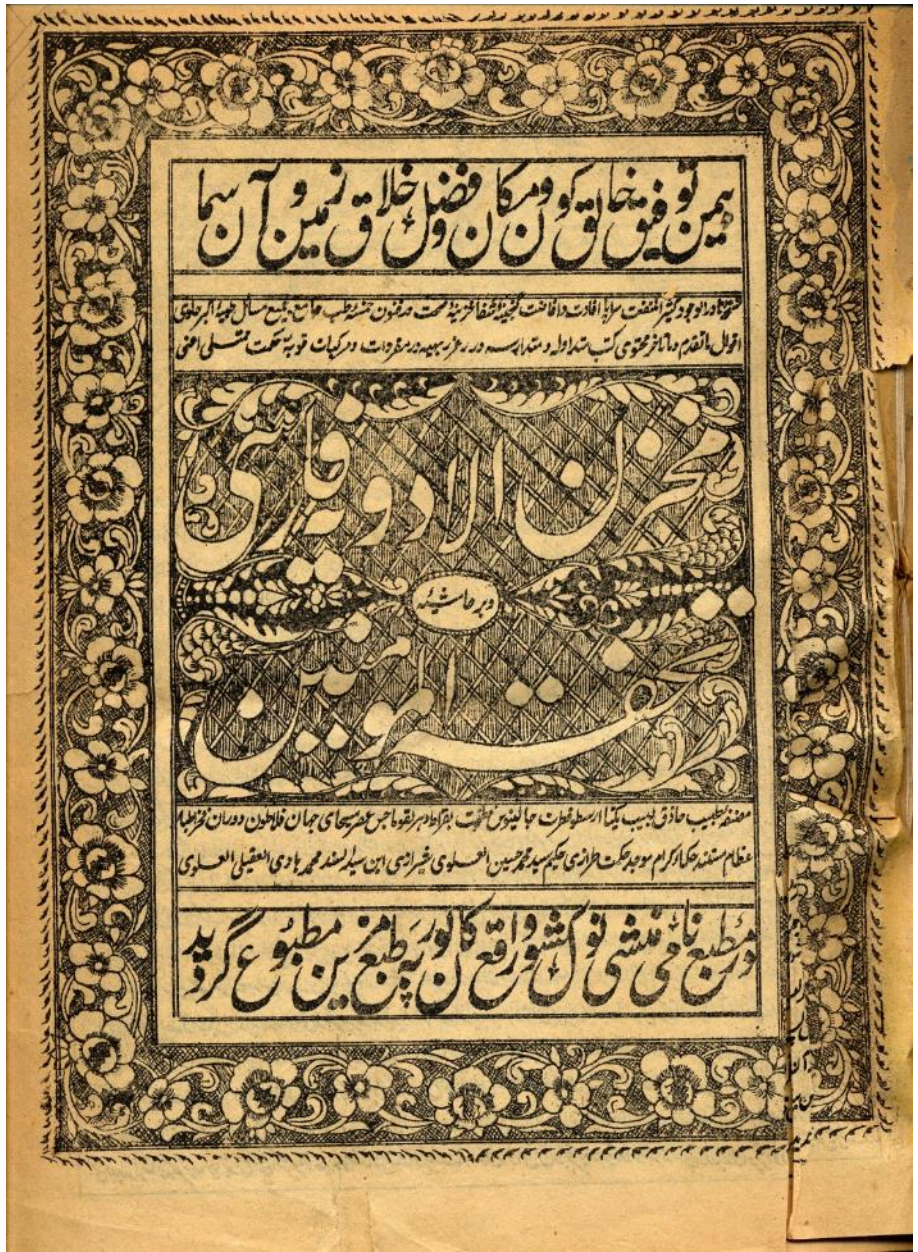


We tell of the five kingdoms of herbs headed by Soma; may it and *kuca* grass, and ***bhanga*** and barley, and the herb *saha* **release us from anxiety.**

Passage: 11,6,15

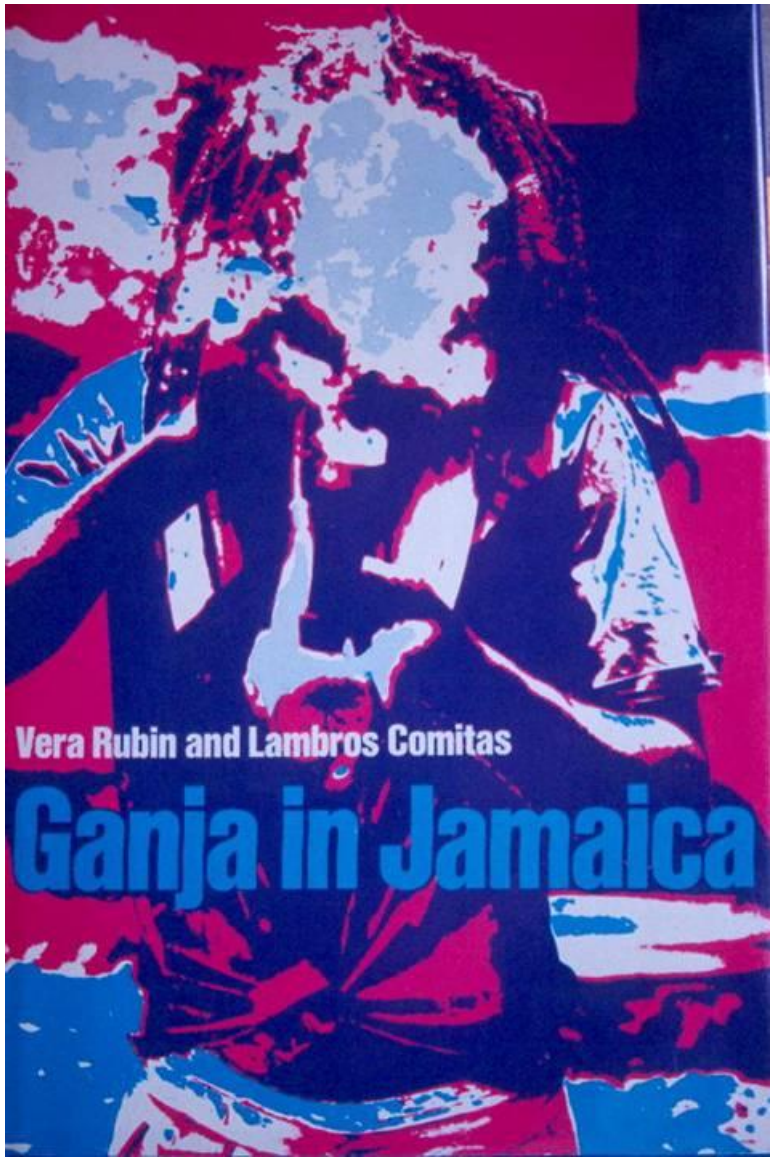
translation, G.A. Grierson, *India Hemp Drugs Commission Report,* 1894.

Makhzan al-adwiya, 18th Century



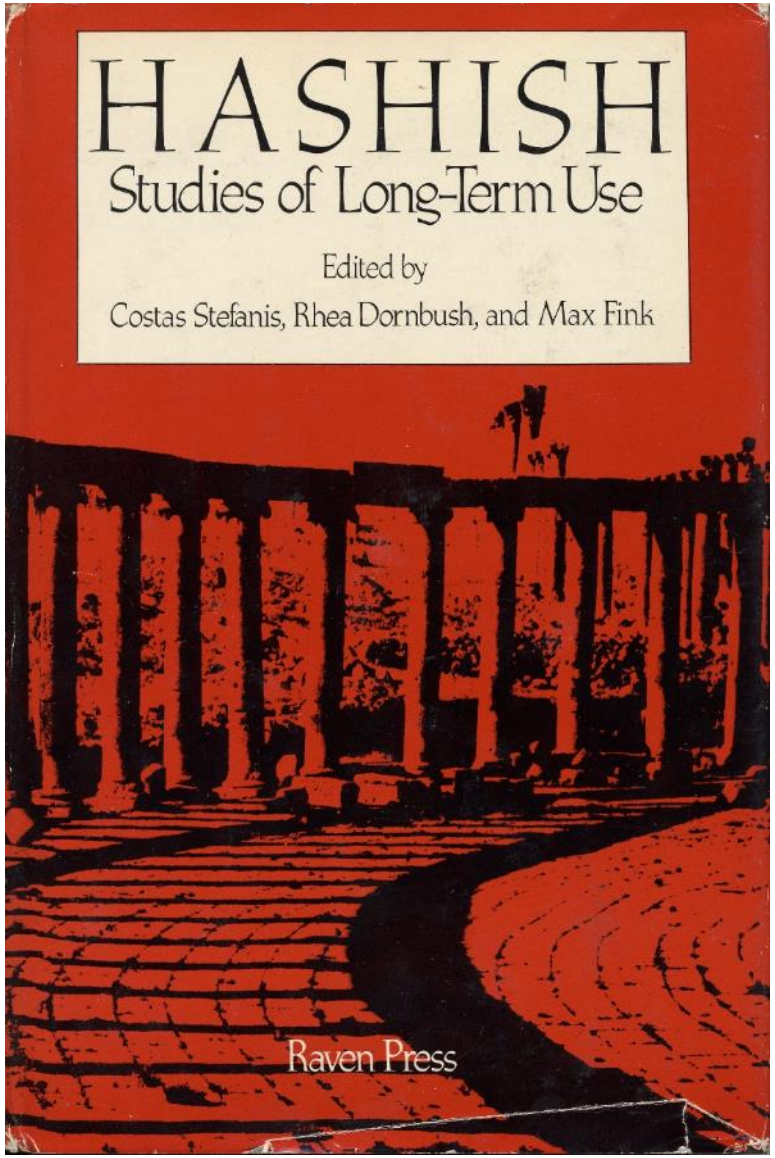
"It is said that bhang is one of the best of God's gifts, --- It quickens the fancy, deepens thought and sharpens judgment."

Jamaica 1975



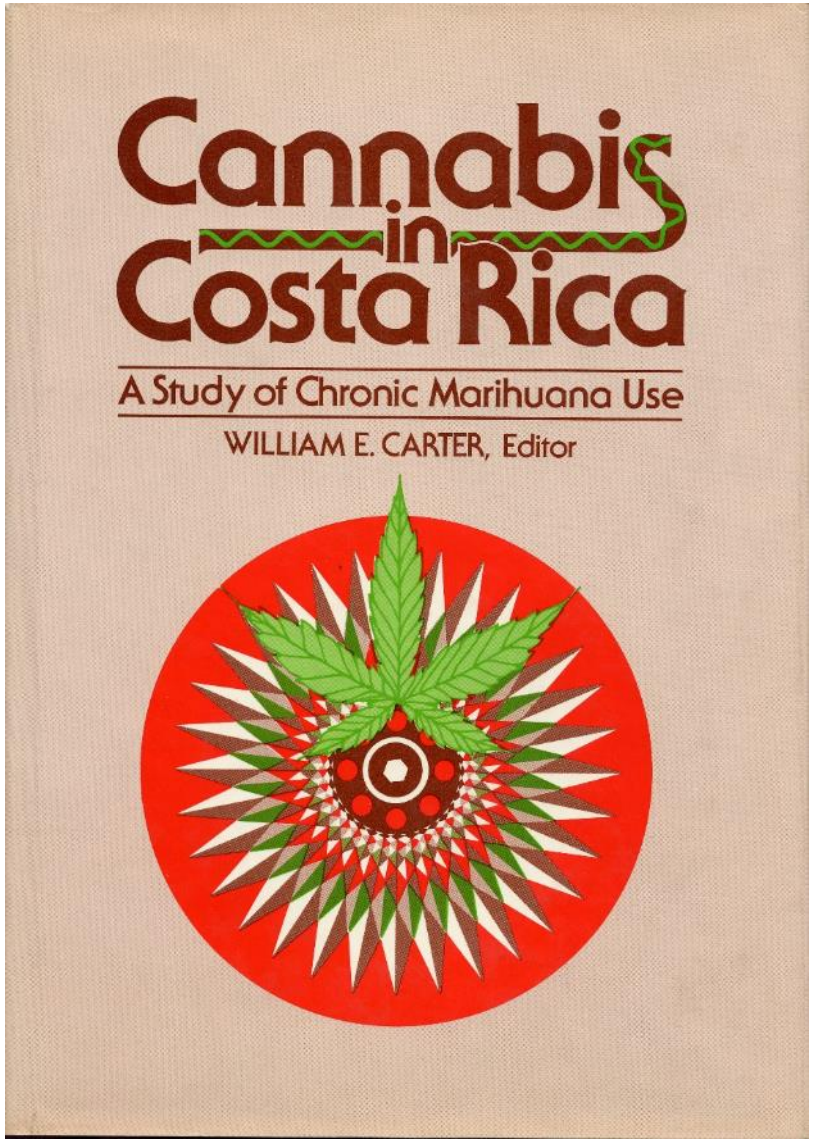
- 60 Hospitalized Adult Males
- Intake of >3 spliffs/day for >10 years
- Assay range 0.7-10.3% THC, average 2.8%
- NSD EEG, hematology
- Slight downward trend in FVC & FEV_1, NSD
- **NSD Neuropsych except users had increased WAIS digit span**

Greece, 1977



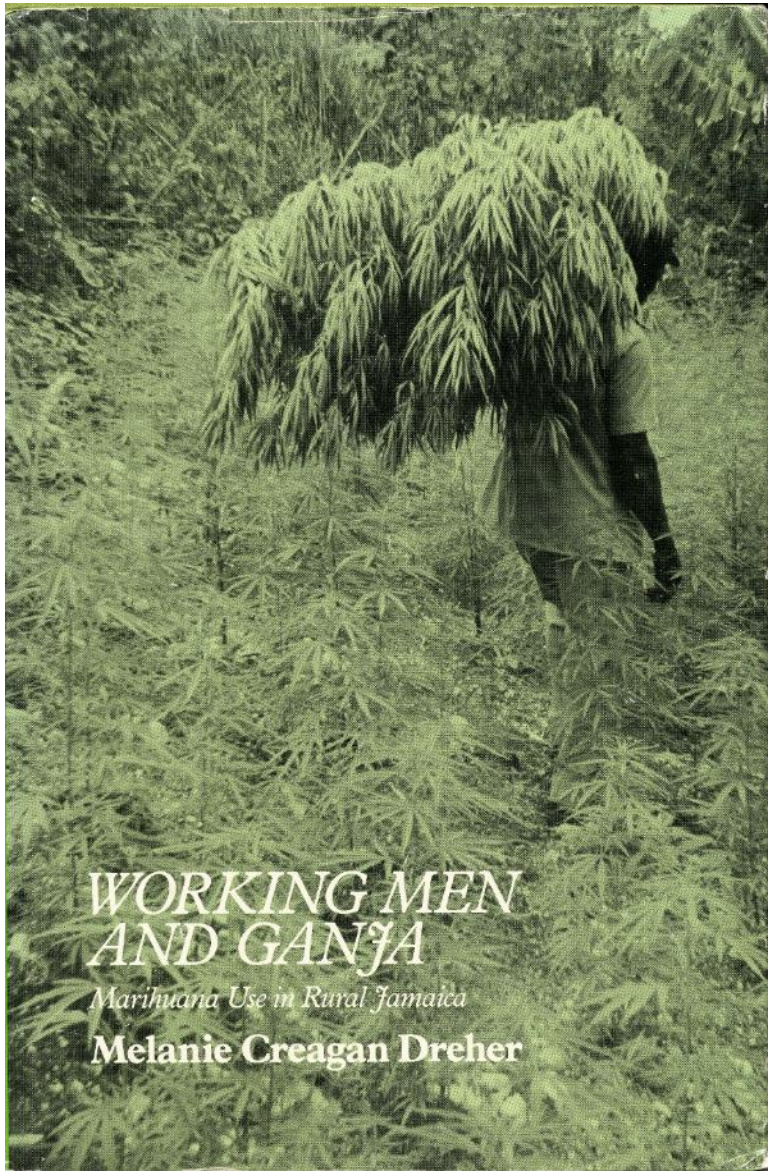
- 60 Subjects smoking hashish >10 years
- Hashish 4-5% THC, mixed with tobacco
- Slight increase in bronchitis sx. (concomitant tobacco)
- Fewer EEG changes
- **Neuropsych: Users > control on WAIS Similarities, Digit Symbol Substitution & VIQ:**
- **“These observations do not provide evidence of deterioration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

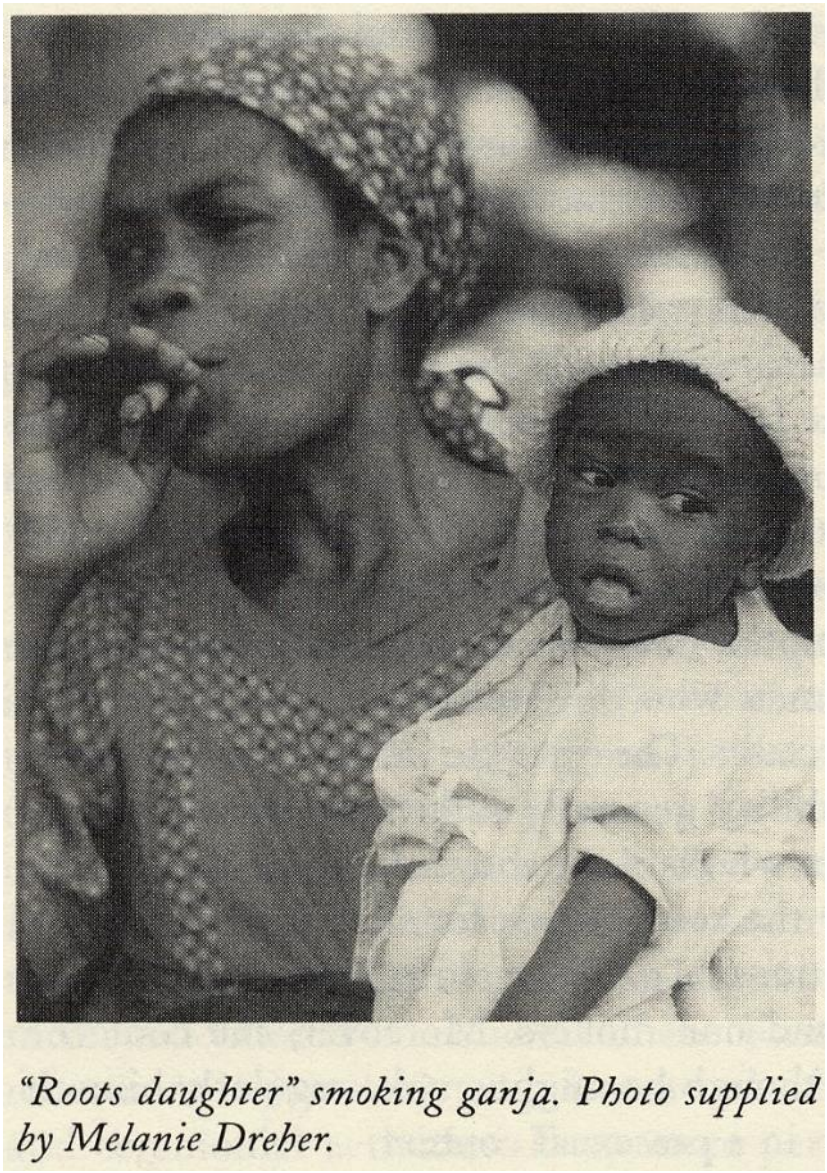
Costa Rica, 1980



- 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."**

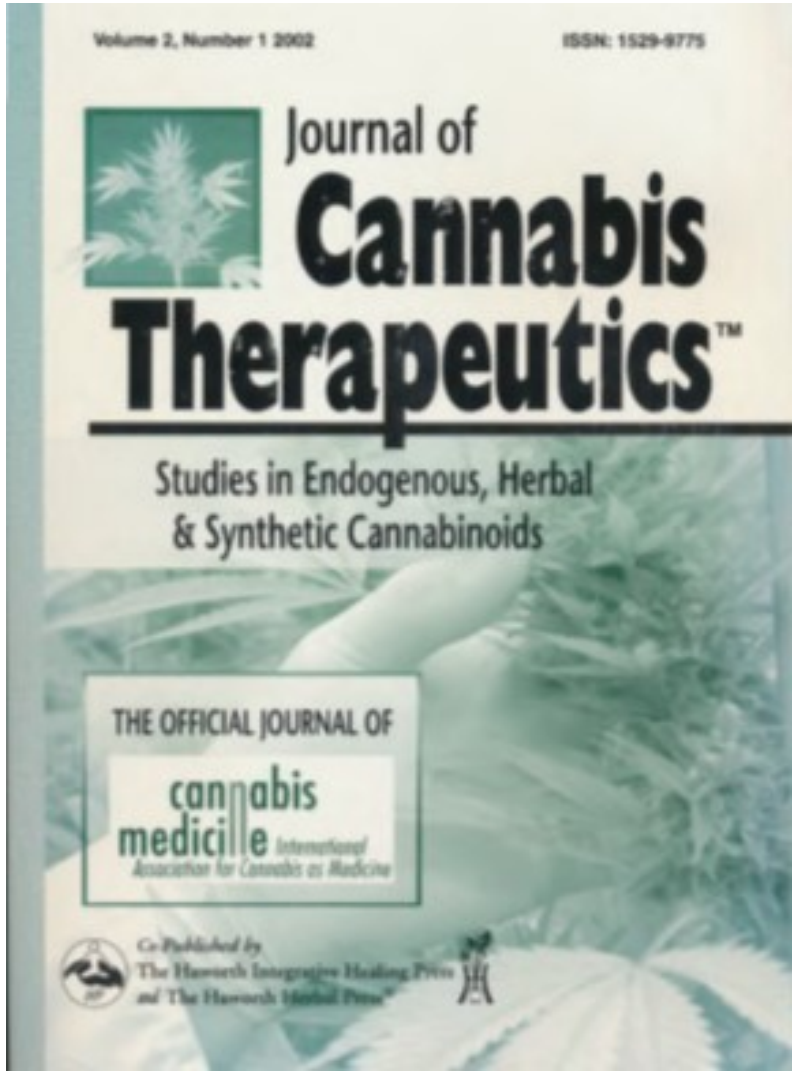
Jamaica 1982/1997





"Roots daughter" smoking ganja. Photo supplied by Melanie Dreher.

Russo, E.B. et al. 2002. Chronic cannabis use in the Compassionate Investigational New Drug Program: An examination of benefits and adverse effects of legal clinical cannabis. *Journal of Cannabis Therapeutics* 2(1), 3-57.



Pt.	Age/Gender	Qualifying Condition	IND Approval/ Cannabis usage	Daily Cannabis/ THC content	Current Status
A	62/F	Glaucoma	1988 25 years	8 grams/ 3.80%	Disabled Operator/ Singer/ Activist/ Vision stable
B	52/M	Nail-Patella Syndrome	1989 27 years	7 grams/ 3.75%	Disabled Laborer/ Factotum/ Ambulatory
C	48/M	Multiple Congenital Cartilaginous Exostoses	1982 26 years	9 grams/ 2.75%	Full time Stockbroker/ Disabled Sailor/ Ambulatory
D	45/F	Multiple Sclerosis	1991 11 years	9 grams 3.50%	Disabled clothier/ Visual impairment/ Ambulatory aids

Chronic Cannabis IND Patient Demographics

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

Russo, E.B. et al. 2002. Chronic cannabis use in the Compassionate Investigational New Drug Program: An examination of benefits and adverse effects of legal clinical cannabis. *Journal of Cannabis Therapeutics* 2(1), 3-57.

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

Russo, E.B. et al. 2002. Chronic cannabis use in the Compassionate Investigational New Drug Program: An examination of benefits and adverse effects of legal clinical cannabis. *Journal of Cannabis Therapeutics* 2(1), 3-57.

Russo, E.B. et al. 2002. Chronic cannabis use in the Compassionate Investigational New Drug Program: An examination of benefits and adverse effects of legal clinical cannabis. *Journal of Cannabis Therapeutics* 2(1), 3-57.

- 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.

Pope HG, et al. Neuropsychological performance in long-term cannabis users. *Arch Genl Psychiatr* 2001;58(10):909-15.

- 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

Grant I. et al. Non-acute (residual) neurocognitive effects of cannabis use: a meta-analytic study. *J Int Neuropsychol Soc* 2003. 9(5):679-89.

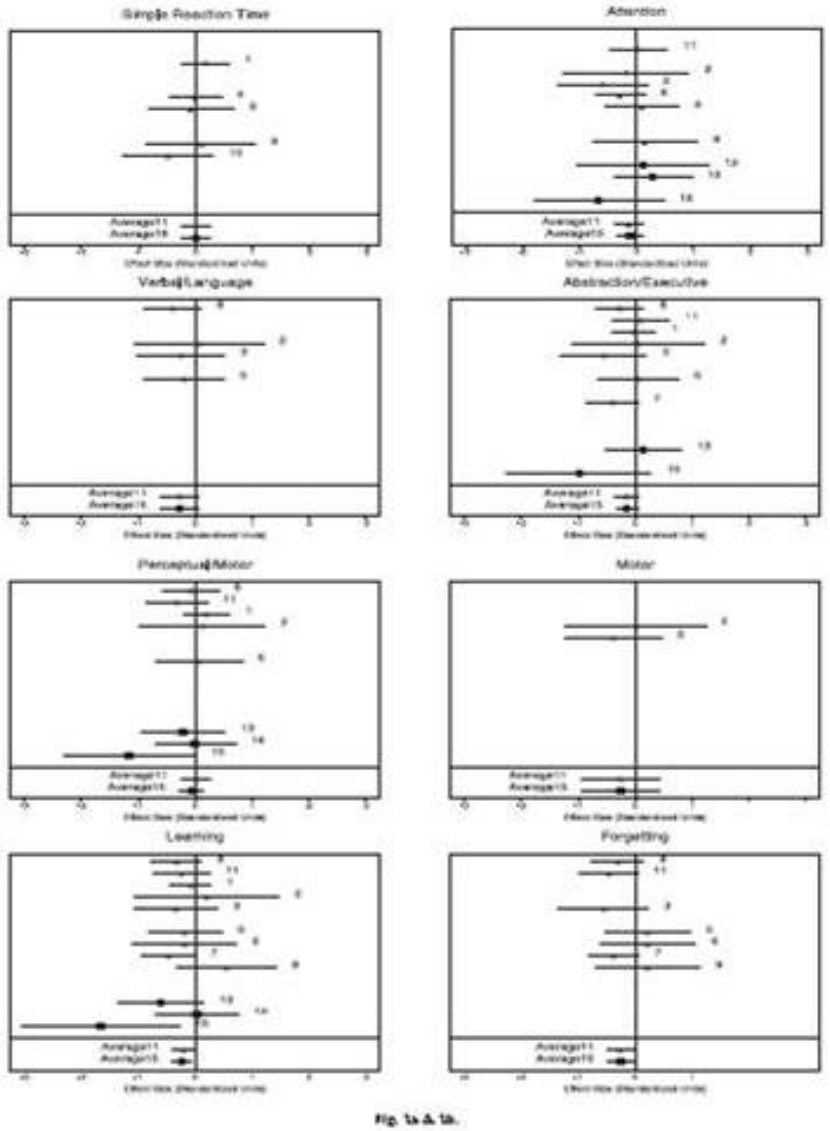


Table 4. Effect sizes and estimate of heterogeneity within domains, across studies

Domain	Effect size (99% CI)	*Q*-statistic	*df* for *Q*	*p*-value for *Q*
Attention	−.11 (−.34, .12)	11.26	8	.19
	−.083 (−.32, .15)	9.30	7	.23
Abstraction/Executive	−.15 (−.34, .032)	14.24	8	.08
	−.13 (−.32, .052)	10.73	7	.15
Forgetting/Retrieval*	−.27 (−.49, −.044)	10.81	6	.09
Learning*	−.24 (−.41, −.064)	23.09	11	.02
	−.21 (−.39, −.040)	14.60	10	.15
Motor	−.26 (−.96, .43)	.55	1	.46
Perceptual–Motor	−.065 (−.28, .15)	12.80	7	.15
	−.026 (−.25, .20)	5.57	6	.47
Simple Reaction Time	.0086 (−.25, .26)	4.54	4	.34
Verbal/Language	−.28 (−.62, .060)	1.30	3	.73

Note. * denotes a significant effect size; Rows with two sets of numbers contain the values obtained before and after the removal of an outlier study (i.e., Wig & Varma), in the respective order; *df* = degrees of freedom.

"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

Scott, J. C., et al. (2018). Association of Cannabis With Cognitive Functioning in Adolescents and Young Adults: A Systematic Review and Meta-analysis. *JAMA Psychiatry*, *75*(6), 585-595.

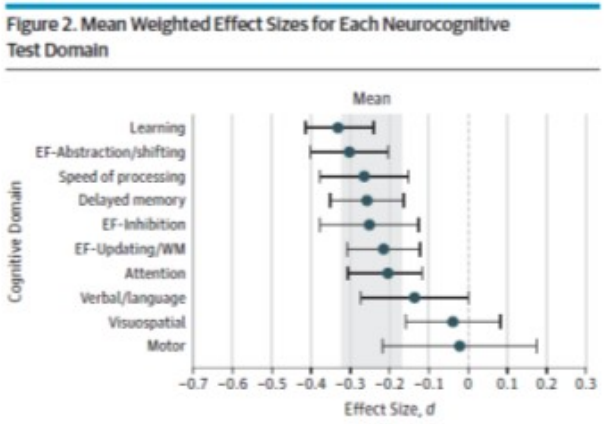


Figure 2. Mean Weighted Effect Sizes for Each Neurocognitive Test Domain

The mean value shown is the grand mean effect size of 69 included studies; *d* is the standardized mean difference. The shaded area indicates the 95% CI around the mean, −0.247. EF indicates executive functioning; SIP, speed of information processing; WM, working memory. Blue circles indicate the domain effect size *d*; gray bands, the overall means; error bars, 95% CIs.

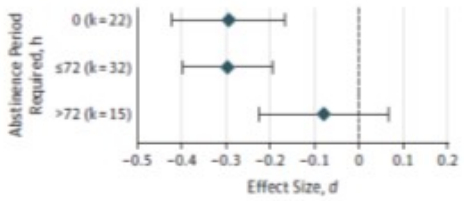


Figure 3. Mean Weighted Effect Sizes for Varying Abstinence Criteria

Subgroup analyses compared effect sizes (standardized mean difference *d*) from studies with abstinence periods longer than 72 hours to effect sizes from studies with abstinence lengths equal to or less than 72 hours. Data from all 3 groups are presented here to show that the subgroup of studies with unknown or 0 abstinence are not the primary contributor to reported subgroup differences. Blue diamonds indicate the domain effect size *d*; error bars, 95% CIs.

- 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

Clinical Psychology Review 51 (2017) 15–29

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journal homepage: www.elsevier.com/locate/clinpsychrev

Review

Medical cannabis and mental health: A guided systematic review

Zach Walsh [a,*], Raul Gonzalez [b], Kim Crosby [a], Michelle S. Thiessen [a], Chris Carroll [a], Marcel O. Bonn-Miller [c]

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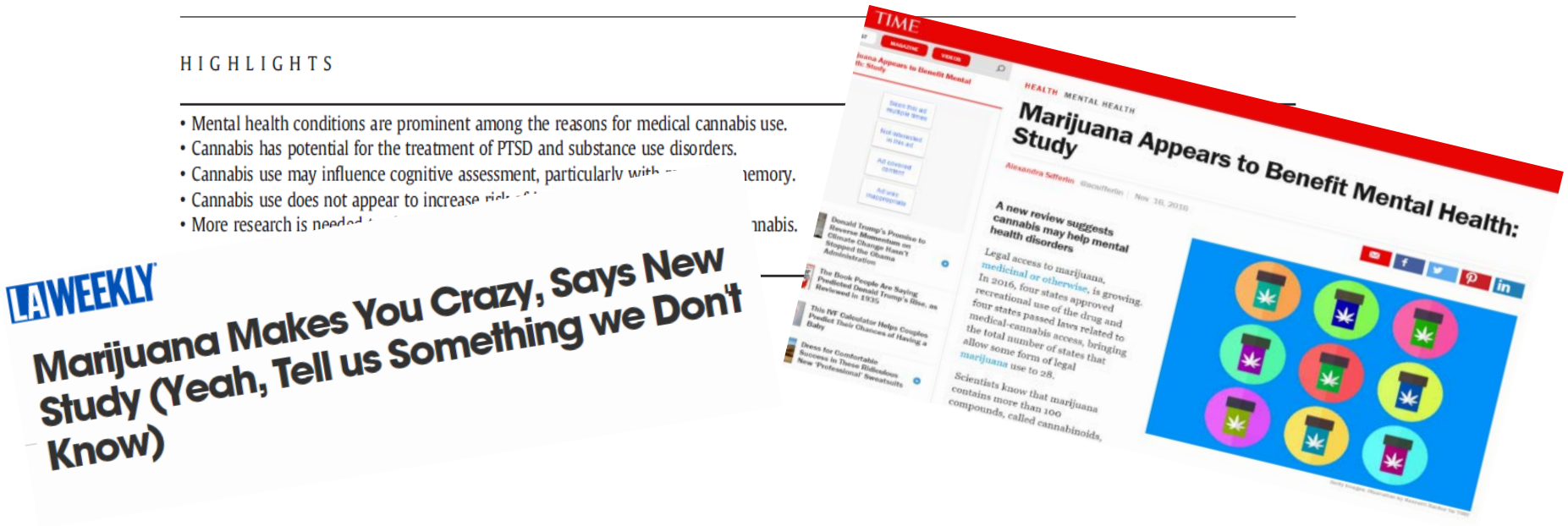
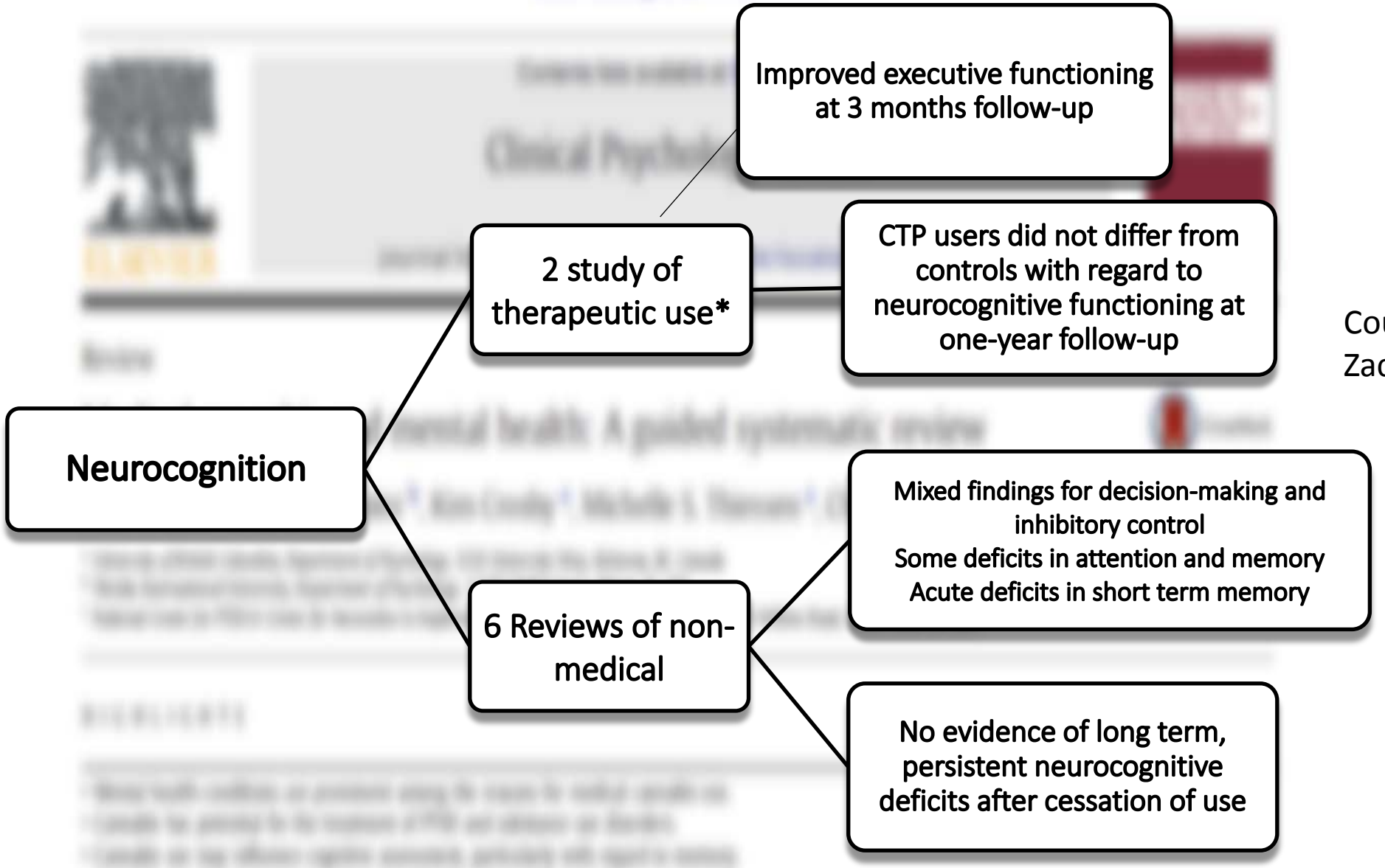
[b] Florida International University, Department of Psychology, 11200 SW8th Street, Miami, FL, USA
[c] National Center for PTSD & Center for Innovation to Implementation, VA Palo Alto Health Care System, 795 Willow Road, Menlo Park, CA., USA

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 with [illegible] memory.
- Cannabis use does not appear to increase [illegible]
- More research is needed [illegible] nabis.



Courtesy of
Zach Walsh, PhD



Courtesy of
Zach Walsh, PhD

Abrams DI, et al. Cannabis in painful HIV-associated sensory neuropathy: a randomized placebo-controlled trial. *Neurology.* 2007;68(7):515-21.

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

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

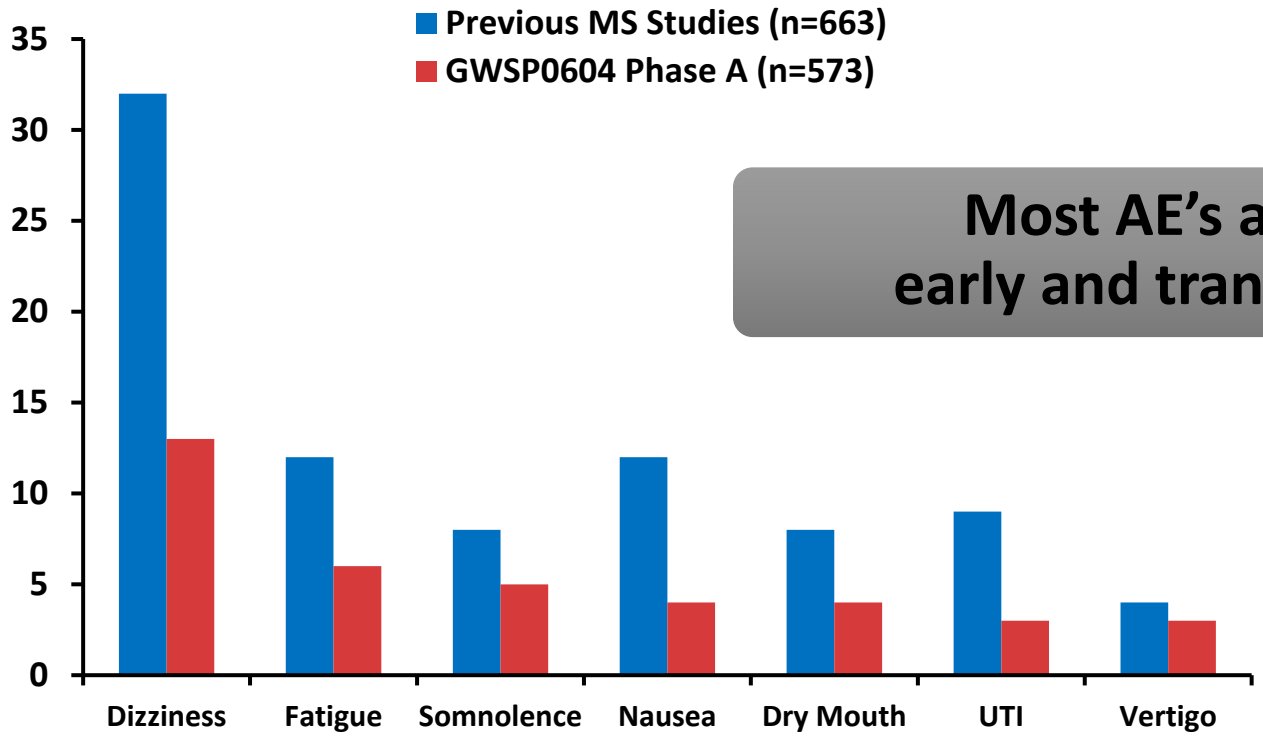
* p, 0.05; † $p < 0.001$.

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 Repeatbale Battery of Neuropsychological Tests**

Rog DJ et al. Randomized controlled trial of cannabis based medicine in central neuropathic pain due to multiple sclerosis. *Neurology.* 2005;65(6):812-9.

Nabiximols Safety Profile: Adverse Events, Incidence >3%

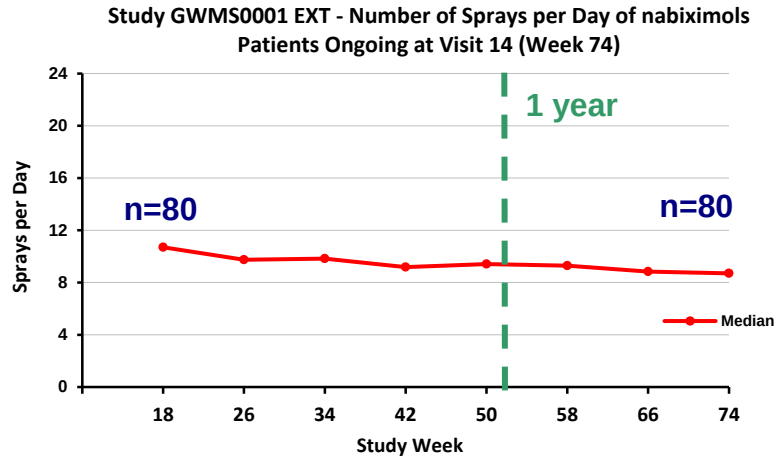


Most AE's are early and transient

MacCallum, C. & Russo, E.B. 2018. Practical considerations in cannabis dosing and administration. *Europ J Intl Med* 49:12-19

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

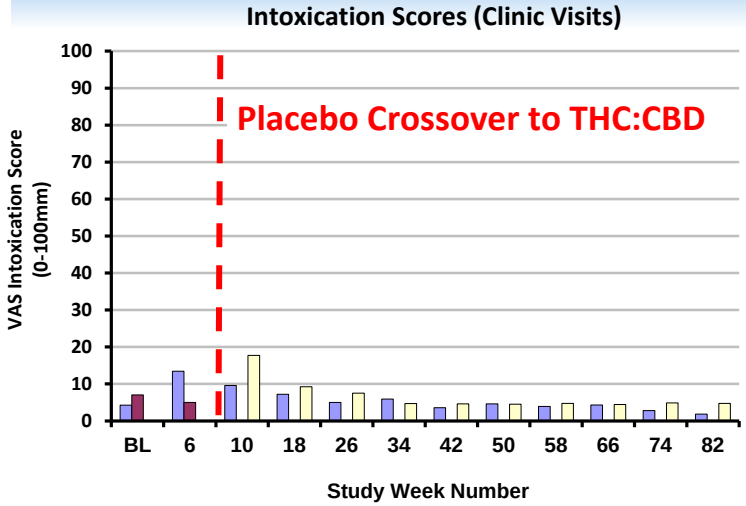
Tolerance and Intoxication



No evidence of tolerance

Wade DT, Makela PM, House H, Bateman C, Robson PJ. Long-term use of a cannabis-based medicine in the treatment of spasticity and other symptoms in Multiple sclerosis. *Multiple Sclerosis*. 2006;12:639-645.

Examples: Intoxication Scores



Nabiximols vs THC vs Placebo

	nabiximols	THC	Placebo
Pre-Dose	6.45	8.22	6.59
2 hours	9.75	11.21	8.41
4 hours	9.63	12.17	7.44

Rekand T (2014). THC:CBD spray and MS spasticity symptoms: data from latest studies. *European Neurology* 71 Suppl 1: 4-9.

- 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)

Rekand T (2014). THC:CBD spray and MS spasticity symptoms: data from latest studies. *European Neurology* 71 Suppl 1: 4-9.

Driving skills

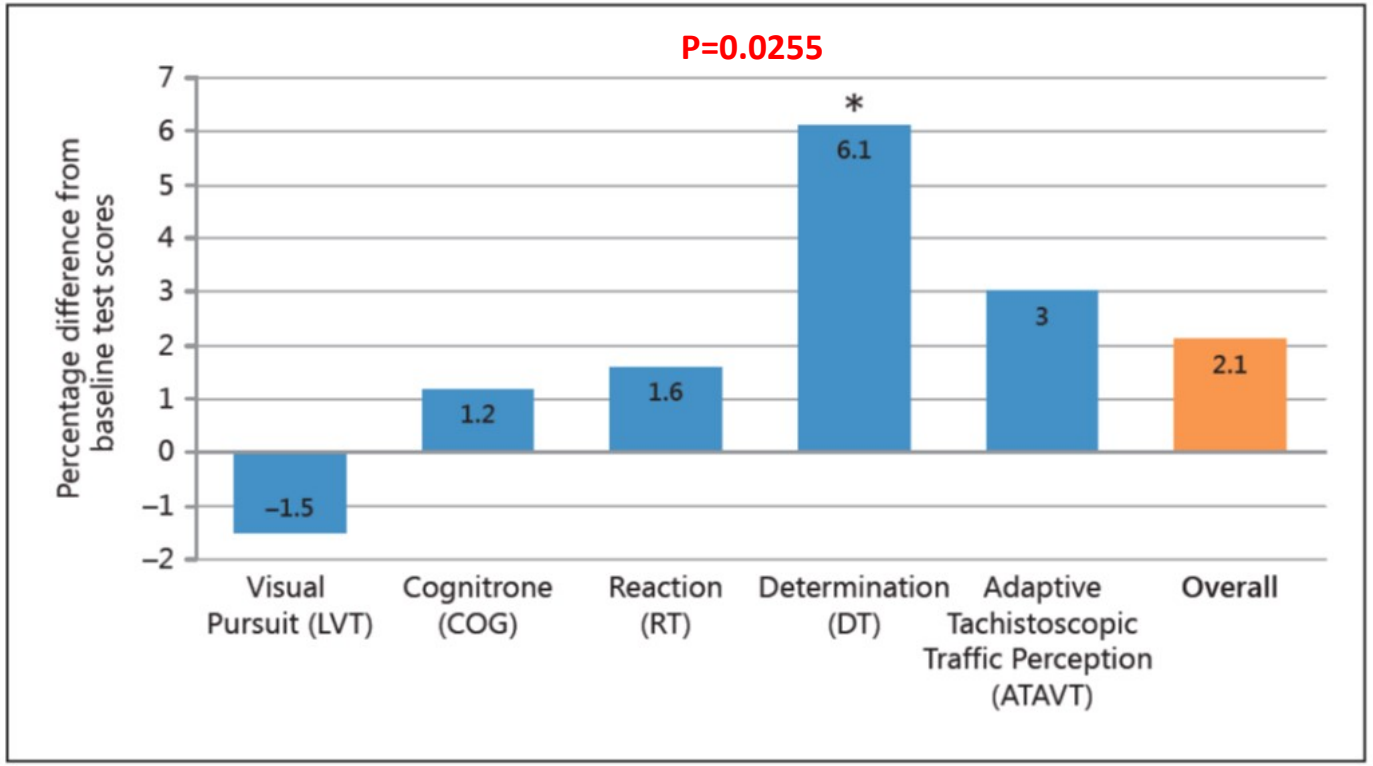


Fig. 1. Effect of THC:CBD oromucosal spray on 5 specific driving-related ability dimensions in patients with moderate to severe resistant MS-related spasticity. * p = 0.0255 versus baseline.

Rekand T (2014). THC:CBD spray and MS spasticity symptoms: data from latest studies. *European Neurology* 71 Suppl 1: 4-9.

No cognitive sequelae

but, clear improvement in functional status

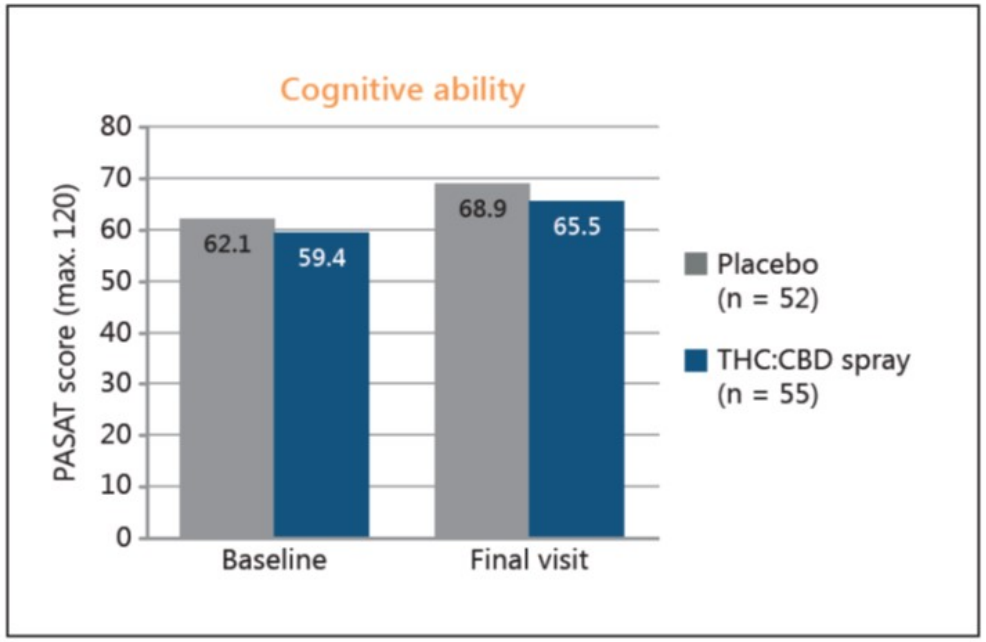


Fig. 2. Effects of THC:CBD oromucosal spray and placebo on cognitive ability of MS patients with spasticity treated for 50 weeks.

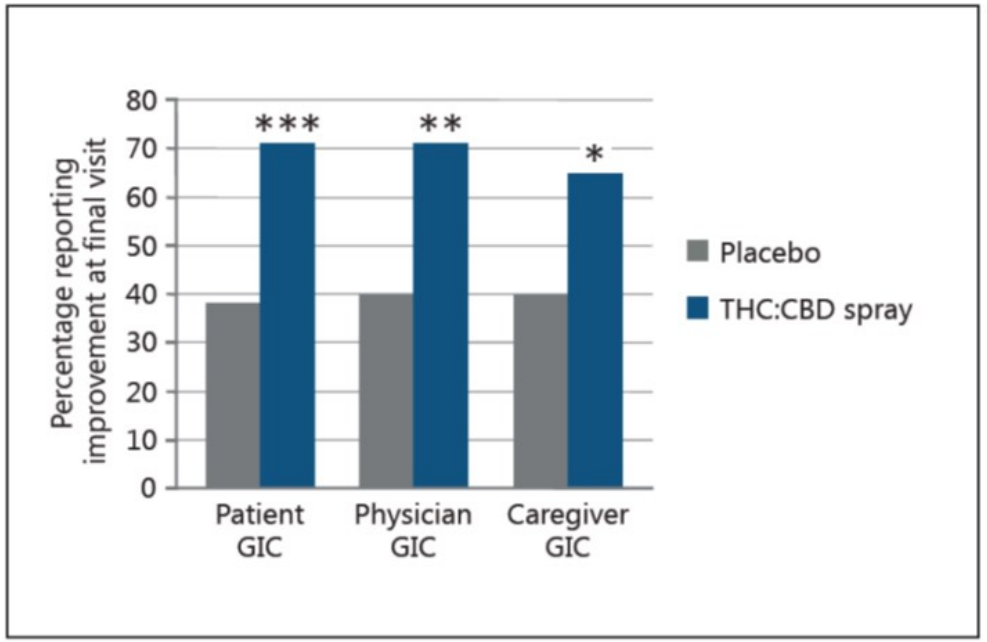


Fig. 3. Effects of THC:CBD oromucosal spray and placebo on patient, physician and caregiver Global Impression of Change (GIC) in MS patients with spasticity treated for 50 weeks. * $p = 0.0042$; ** $p = 0.0014$; *** $p < 0.001$.

Rekand T (2014). THC:CBD spray and MS spasticity symptoms: data from latest studies. *European Neurology* 71 Suppl 1: 4-9.

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

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

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

Abrahamov, A., and R. Mechoulam. 1995. An efficient new cannabinoid antiemetic in pediatric oncology. *Life Sci* 56 (23-24):2097-102.

- High doses of Δ^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 Δ^8-THC in children was 18 mg/m^2 as compared to usual recommended dose of 5-10 mg/m^2 Δ^9-THC in adults.**

Bar-Lev Schleider, L., et al. 2019. Real life Experience of Medical Cannabis Treatment in Autism: Analysis of Safety and Efficacy. *Sci Rep*, *9*(1), 200.

	Sleep			Eating with Appetite			Concentration on daily tasks			Bowel Activity		
	Before	During	p value	Before	During	p value	Before	During	p value	Before	During	p value
Severe difficulty	44 (47.3)	2 (2.2)		2 (2.2)	1 (1.1)		75 (80.6)	21 (22.6)		3 (3.2)	2 (2.2)	
Moderate difficulty	18 (19.4)	27 (29.0)		6 (6.5)	13 (14.0)		11 (11.8)	41 (44.1)		13 (14.0)	17 (18.3)	
No difficulty	28 (30.1)	39 (41.9)	<0.001	59 (63.4)	47 (50.5)	0.751	2 (2.2)	11 (11.8)	<0.001	71 (76.3)	54 (58.1)	0.242
Good	2 (2.2)	15 (16.1)		10 (10.8)	16 (17.2)		0	10 (10.8)		5 (5.4)	13 (14.0)	
Very Good	1 (1.1)	8 (8.6)		16 (17.2)	14 (15.1)		0	3 (3.2)		1 (1.1)	4 (4.3)	

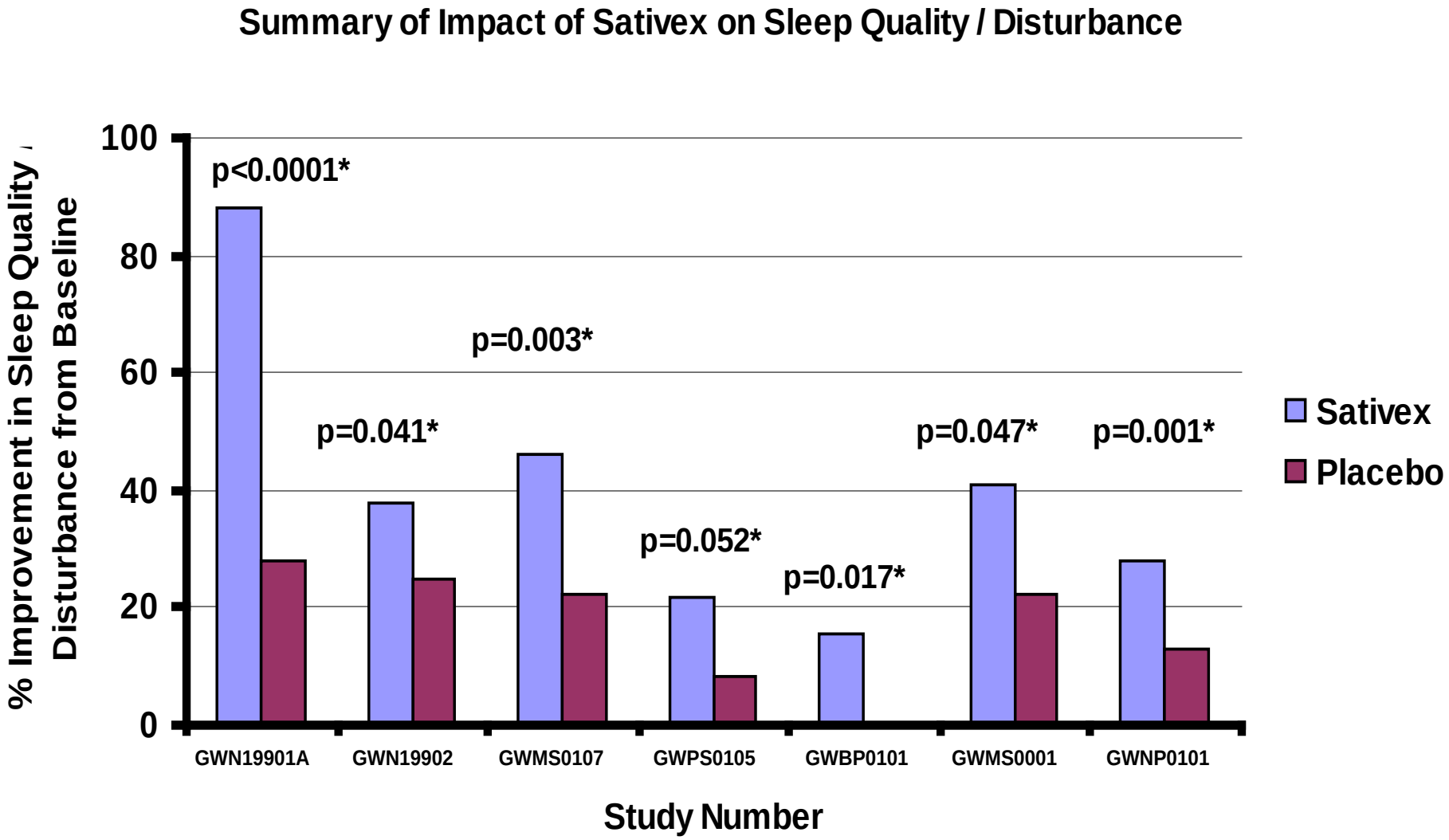
Table 3. Assessment of daily activities. Ability to perform activities of daily living was assessed prior to and six months after initiation of cannabis treatment. Numbers in parenthesis represent the % of patients.

	Intake	Change at six months follow-up				
Medication family	Total	Stopped taking this medication	Dosage decreased	Has not changed	Dosage increased	New medication
Antipsychotics, n (%)	55	11 (20)	3 (5)	41 (75)	0	0
Antiepileptics, n (%)	46	6 (13)	0	35 (76)	2 (4.5)	3 (6.5)
Antidepressants, n (%)	10	3 (30)	0	4 (40)	1 (10)	2 (20)
Hypnotics and sedatives, n (%)	10	2 (20)	1 (10)	7 (70)	0	0
Anxiolytics, n (%)	7	2 (28)	0	5 (72)	0	0

Table 4. Concomitant medications. Concomitant medications use at the baseline and six months follow up in patients responding to the six-month questionnaire.

- 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



*compared to placebo

Russo, E. B. et al. 2007. Cannabis, pain, and sleep: lessons from therapeutic clinical trials of Sativex, a cannabis-based medicine. *Chem Biodivers*, 4, 1729-43.

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)

Russo, E. B. 2016. Clinical endocannabinoid deficiency reconsidered: Current research supports the theory in migraine, fibromyalgia, irritable bowel, and other treatment-resistant syndromes. *Cannabis and Cannabinoid Research, 1*, 154-165.

Posttraumatic Stress Disorder

4 studies of medical use

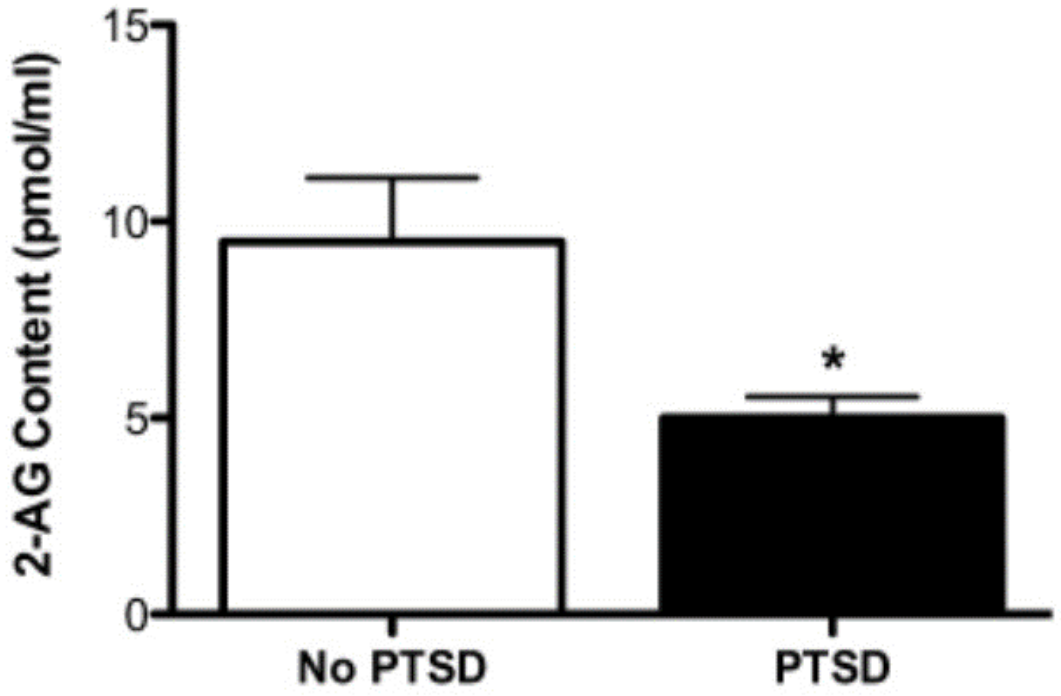
Substantial portion treat PTSD symptoms with cannabis

Self-report of good outcomes

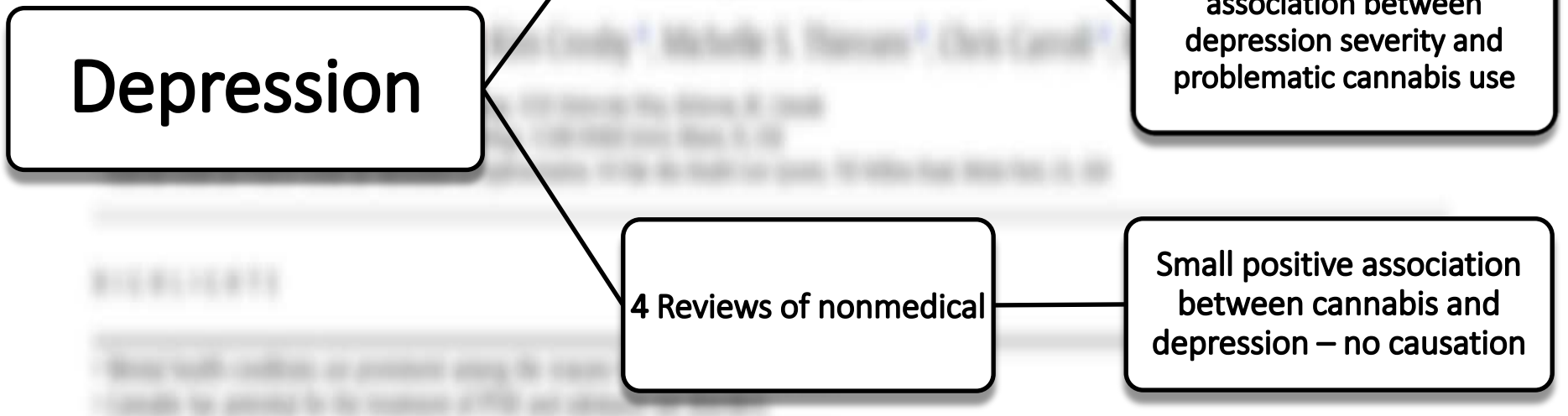
Effective for improving sleep and reducing nightmares

Courtesy of
Zach Walsh, PhD

HILL, M. N., et al. 2013. Reductions in circulating endocannabinoid levels in individuals with post-traumatic stress disorder following exposure to the World Trade Center attacks. *Psychoneuroendocrinology,* 38**,** 2952-61.



- 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 CB_1 receptor binding sites in CNS.



Courtesy of Zach Walsh, PhD

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-.

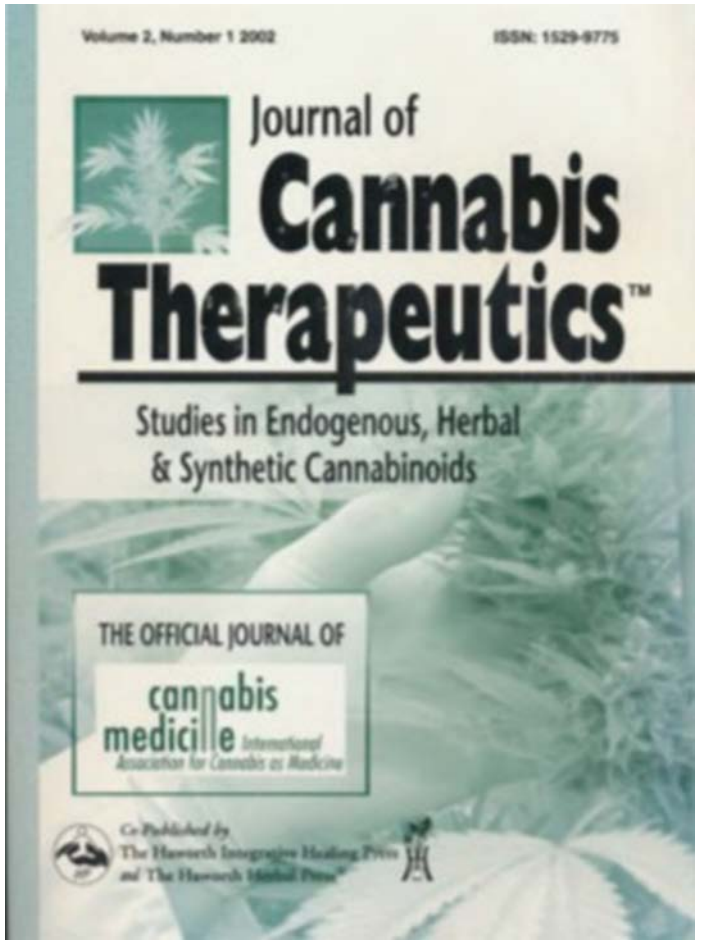
Results:

Patient A: 6

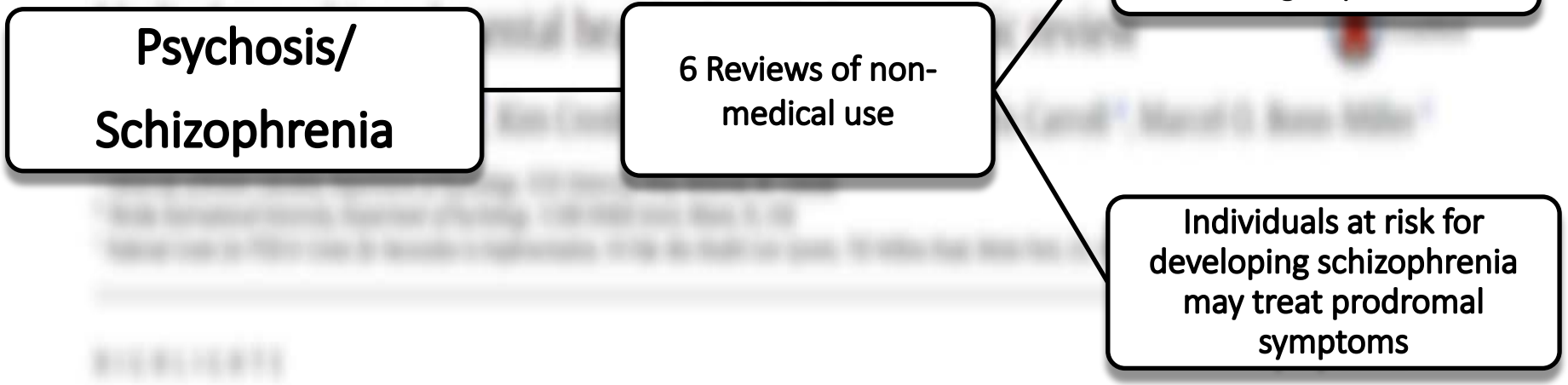
Patient B: 0

Patient C: 0

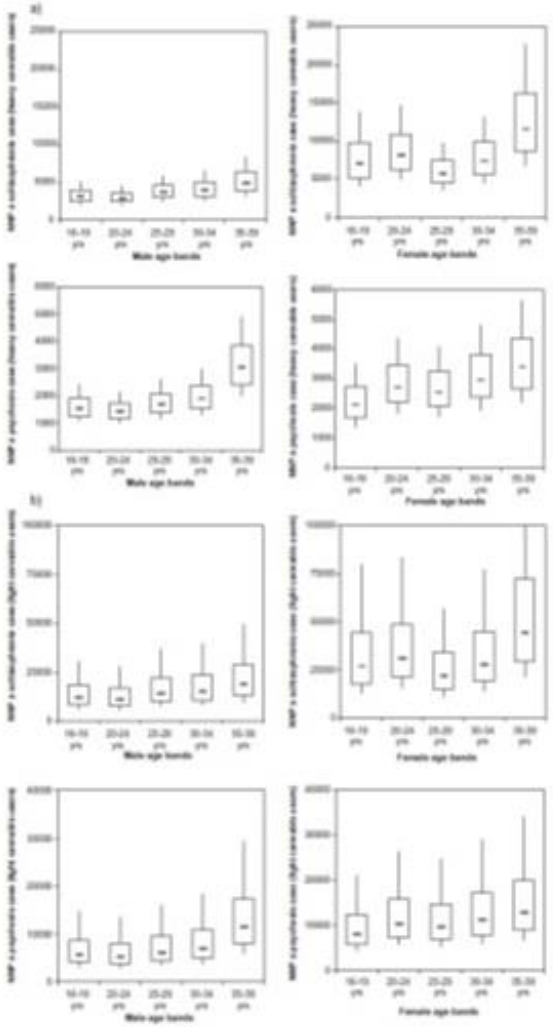
Patient D: 0



Russo, E.B. et al. 2002. Chronic cannabis use in the Compassionate Investigational New Drug Program: An examination of benefits and adverse effects of legal clinical cannabis. *Journal of Cannabis Therapeutics* 2(1), 3-57.


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.

Leweke, F.M. et al. 2012. Cannabidiol enhances anandamide signaling and alleviates psychotic symptoms of schizophrenia. *Transl Psychiatry* 2, e94.

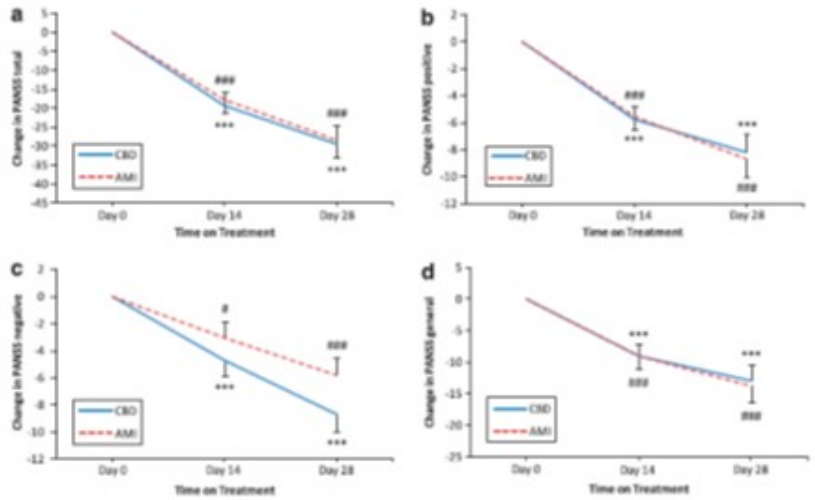
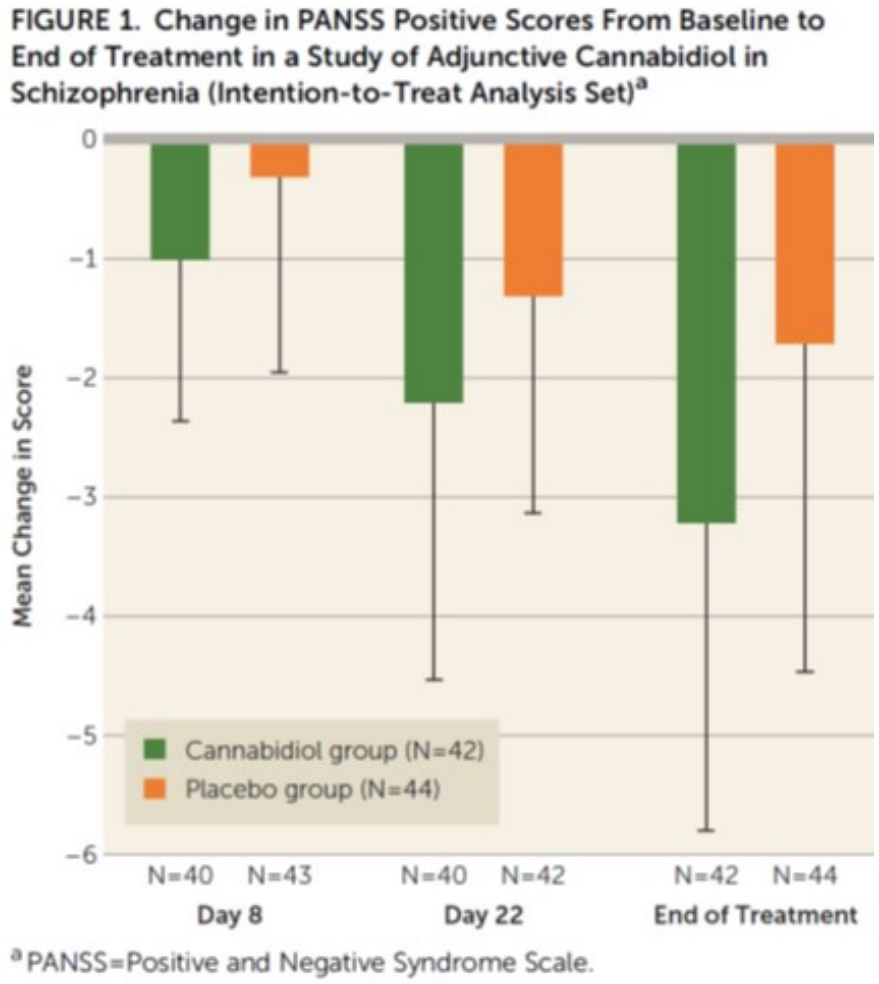


Figure 2 Changes from baseline in Positive and Negative Symptoms Scale (PANSS) scores determined using mixed effects repeated measures model analysis (adjusted for baseline). (**a**) PANSS total score. (**b**) PANSS-positive score. (**c**) PANSS-negative score. (**d**) PANSS general score. Data show predicted means and s.e. at each week. Statistical significance is calculated between groups ($^{\dagger}P<0.05$, $^{\dagger\dagger}P<0.01$ and $^{\dagger\dagger\dagger}P<0.001$) and vs baseline (that is, 0; *CBD, #AMI; $^{*,\#,\dagger}P<0.05$, $^{**,\#\#,\dagger\dagger}P<0.01$, $^{***,\#\#\#,\dagger\dagger\dagger}P<0.001$).

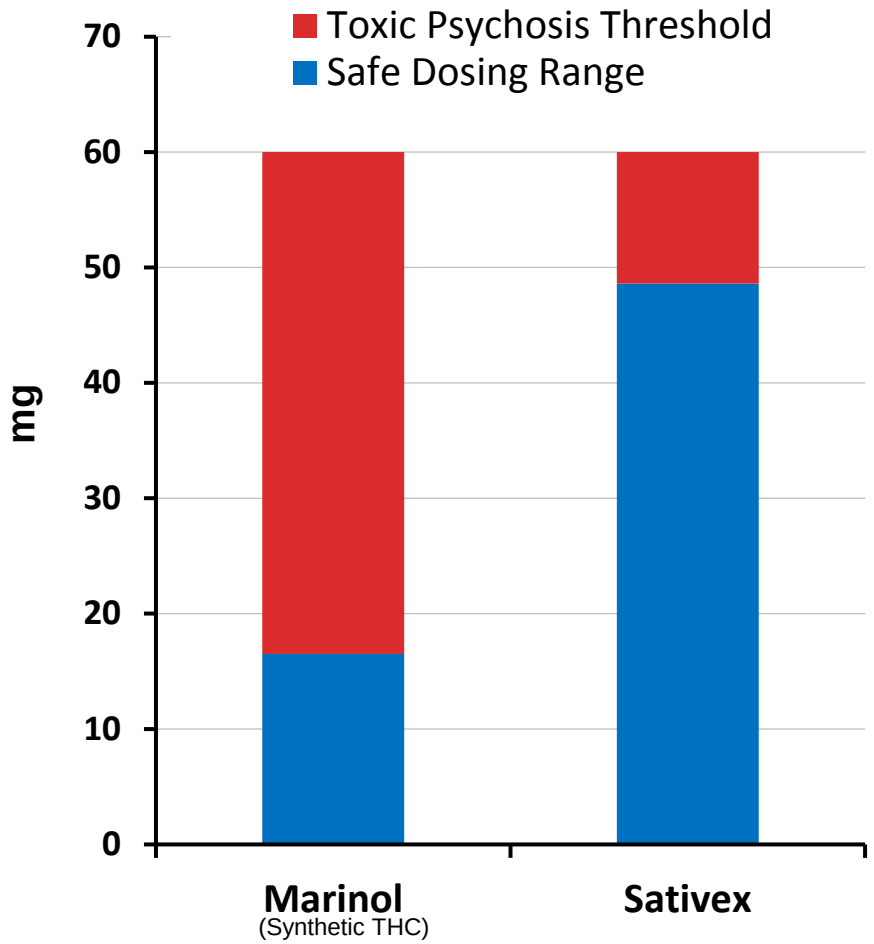
- Cannabidiol 800 mg po per day vs. amisulpride in 42 patients for 4 weeks.
- Positive and Negative Syndrome Scores (PANSS) were improved in each (p=0.001), but negative symptoms were notably better on CBD (p=0.001) with fewer extrapyramidal AEs (p=0.006), less weight gain (p=0.01) and prolactin elevation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

McGuire, P., et al. 2018. Cannabidiol (CBD) as an Adjunctive Therapy in Schizophrenia: A Multicenter Randomized Controlled Trial. *Am J Psychiatry* 175(3), 225-231.



- 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 ($p<0.05$)

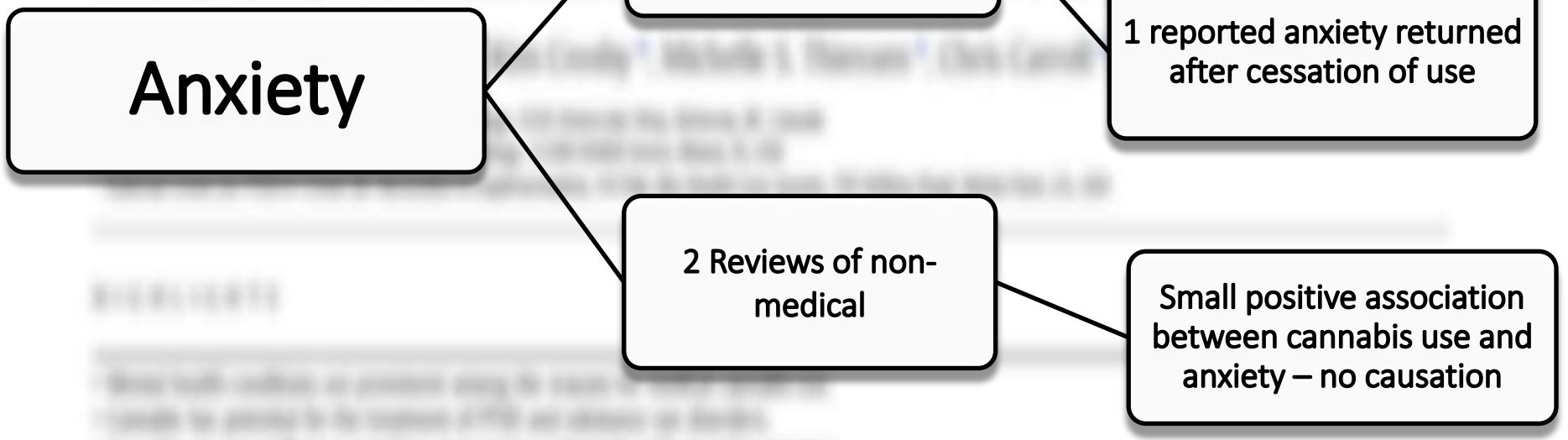
Sellers, E. M., et al. 2013. A Multiple-Dose, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group QT/QTc Study to Evaluate the Electrophysiologic Effects of THC/CBD Spray. *Clinical Pharmacology in Drug Development* 2 (3):285-294.



Results imply a markedly better therapeutic index and safety margin for nabiximols (THC/CBD extracts) over pure THC

MacCallum, C. & Russo, E.B. 2018. Practical considerations in cannabis dosing and administration. *Europ J Intl Med* 49:12-19

Marinol info from: Favrat B, et al. Two cases of “cannabis acute psychosis” following the administration of oral cannabis. *BMC Psychiatry.* 2005:5:17.



Courtesy of Zach Walsh, PhD

Feingold, D. et al. 2018. Clinical and functional outcomes of cannabis use among individuals with anxiety disorders: A 3-year population-based longitudinal study. *Depress Anxiety* 6:490-501.

- 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.

Turna, J., et al. 2019. Cannabis use behaviors and prevalence of anxiety and depressive symptoms in a cohort of Canadian medicinal cannabis users. *J Psychiatr Res*, *111*, 134-139.

Table 3
Proportion of the ANX sample replacing a prescribed medication with medicinal cannabis (n = 888).

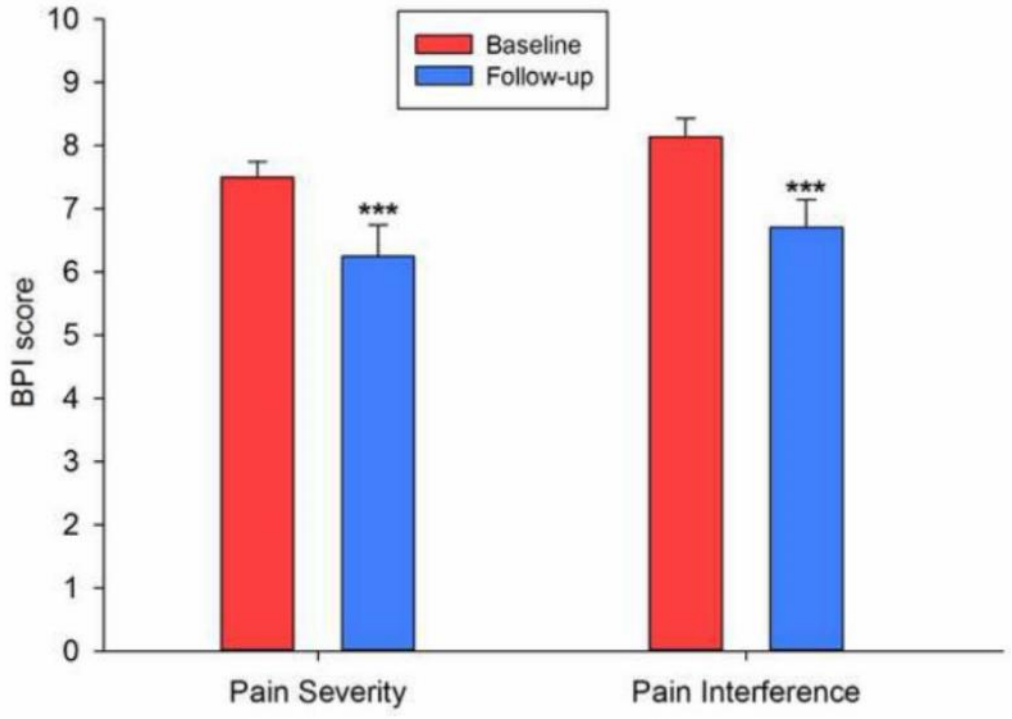
Drug Class	%
Antidepressants	23.8
Opioid	19.2
Benzodiazepine	15.8
NSAIDs	6.1
Antiepileptic	5.0
Sedative-Hypnotic	4.2
General Analgesic	3.9
Psychostimulant	3.7
Antipsychotic	3.0
All others	15.3

Table 4
Frequencies of primary condition for which CMP has been authorized by a medical doctor.

Indication	ANX group (n = 888)	All respondents (n = 2032)
Mental Health (Stress, Anxiety, Depression, PTSD, eating disorders)	52.9%	30.6%
Chronic Pain	17.2%	26.7%
Insomnia	8.0%	9.4%
Other	5.0%	8.9%
Arthritis	3.5%	7.7%
All others	13.4%	16.7%

- "Nearly half of the ANX sample [N=888] (49%) reported substituting a prescribed medication with CMP so 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

Haroutounian S, et al. The Effect of Medicinal Cannabis on Pain and Quality of Life Outcomes in Chronic Pain: A Prospective Open-label Study. *Clin J Pain*. 2016.



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

- 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).**

Boehnke, K. F. et al. 2016. Medical Cannabis Use Is Associated With Decreased Opiate Medication Use in a Retrospective Cross-Sectional Survey of Patients With Chronic Pain *J Pain* 17: 739-44.

Outcome of Interest	Entire Set of Questionnaires (N = 244)
FM score	9.23 (5.52)
Opioid use change	–63% (46%)
Degree to which side effects of medication affect daily function (before using medical cannabis); scale from 1 to 10	6.44 (2.91)
Degree to which side effects of medication affect daily function (after using medical cannabis); scale from 1 to 10	2.77 (2.35)
Number of medication classes used (before cannabis use)	2.35 (1.43)
Number of medication classes used (after cannabis use)	1.82 (.94)
Quality of life change	45% (28%)

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)

Bar-Lev Schleider, L., et al. 2018. Prospective analysis of safety and efficacy of medical cannabis in large unselected population of patients with cancer *Eur J Intern Med*, 49: 37-43.

Table 2
Concomitant medications use at the baseline and six month follow up.

	Intake	Change at six month follow-up					
Medication family	Total	I stopped taking this medication	Dosage decreased	Has not changed	Dosage increased	Other	New medication
Opioids, n (%)	344	124 (36.0)	34 (9.9)	176 (51.1)	4 (1.1)	6 (1.7)	32
Other analgesics and antipyretics, n (%)	177	56 (31.6)	15 (8.4)	102 (57.6)	~	4 (2.2)	2
Anxiolytics, n (%)	155	37 (23.8)	3 (1.9)	113 (72.9)	1 (0.6)	1 (0.6)	5
Hypnotics and sedatives, n (%)	114	29 (25.4)	7 (6.1)	76 (66.6)	~	2 (1.7)	3
Corticosteroids for systemic use, plain, n (%)	85	27 (31.7)	6 (7.0)	49 (57.6)	~	3 (3.5)	7
Antiemetics and antinauseants, n (%)	49	33 (67.3)	1 (2.0)	15 (30.6)	~	~	~
Laxatives, n (%)	38	12 (31.5)	2 (5.2)	23 (60.5)	~	1 (2.6)	2

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%.

Habib, G., and S. Artul. 2018. Medical Cannabis for the Treatment of Fibromyalgia *J Clin Rheumatol*

TABLE 3. Meds Consumed Prior to and Under MC Treatment

	Prior to MC Treatment	Under MC Treatment	
Medication	**No. Patients (%)**	**No. Patients (%)**	***P***
Simple analgesics	12 (~46)	3 (~15)	0.000
NSAIDs	19 (~73)	2 (~8)	0.000
Simple opiates	4 (~15)	0 (0)	0.055
Pregabalin	7 (~27)	0 (0)	0.005
Strong opiates	20 (~77)	5 (~19)	0.000
Benzodiazepines	7 (~27)	1 (~5)	0.027
Tricyclics	4 (~15)	0	0.055
Other antidepressants	8 (~31)	3 (~12)	0.107

NSAIDs indicates nonsteroidal anti-inflammatory drugs.

- 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.

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

IvanArt, Bern, Switzerland, 2010 http://www.ivanart.net/index.html