Swiss Task Force for Cannabinoids in Medicine, STCM
Bern, January 22nd, 2013

Cannabinoids in Medicine – An Option? Psychiatric Diseases

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•S•S•A•M•

William Brooke O'Shaughnessy (1808 – 1889)

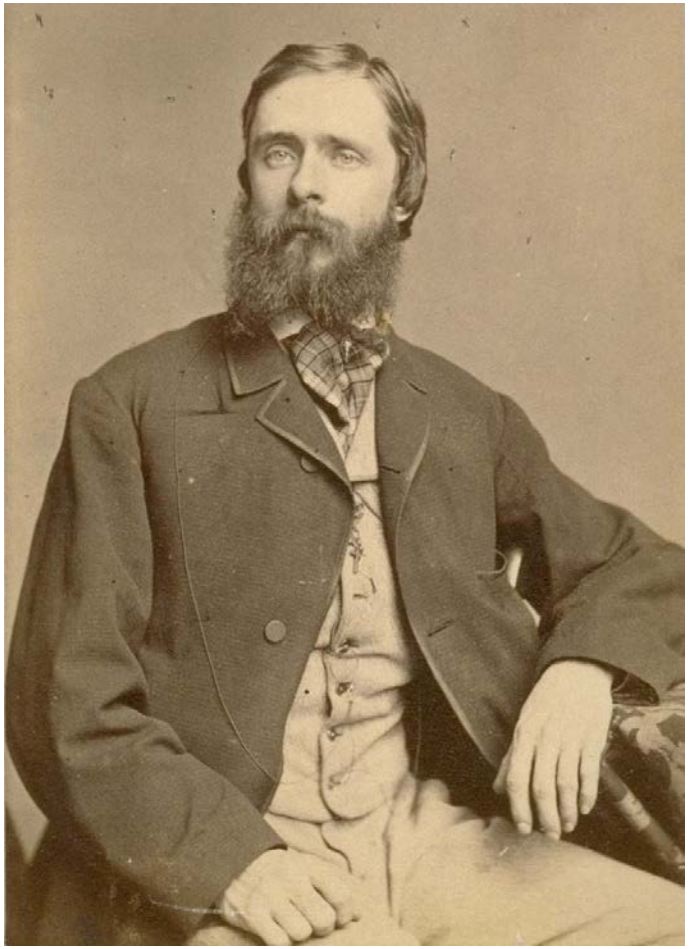
- Introduced *cannabis indica* into Western medicine (1841)
  - relieving the pain of rheumatism
  - convulsions
  - muscle spasm of tetanus and rabies

Jacques-Joseph Moreau (1804–1884), nicknamed "Moreau de Tours"

- 1845 "Du Hachisch et de l'aliénation mentale" ("Hashish and insanity").
- Moreau theorized that psychoactive substances could treat or replicate mental illness in a way to help cure patients.

Fitz Hugh Ludlow (1836 – 1870)

- «***The Hasheesh Eater***» (1857)
- "[a]t last, thought ran with such terrific speed that I could no longer write at all."[



Does Cannabis use cause schizophrenia?

Psychological Medicine (2012), **42**, 1321–1328. © Cambridge University Press 2011
doi:10.1017/S0033291711002078

ORIGINAL ARTICLE

Cannabis, schizophrenia and other non-affective psychoses: 35 years of follow-up of a population-based cohort

E. Manrique-Garcia[1]*, S. Zammit[2], C. Dalman[3], T. Hemmingsson[4], S. Andreasson[5] and P. Allebeck[1]

- **Results**. Odds ratios for psychotic outcomes among frequent cannabis users compared with non-users were 3.7 [95 % confidence interval (CI) 2.3–5.8] for schizophrenia, 2.2 (95 % CI 1.0–4.7) for brief psychosis and 2.0 (95 % CI 0.8–4.7) for other non-affective psychoses. Risk of schizophrenia declined over the decades in moderate users but much less so in frequent users. The presence of a brief psychosis did not increase risk of later schizophrenia more in cannabis users compared with non-users.
- **Conclusions**. Our results confirm an increased risk of schizophrenia in a long-term perspective, although the risk declined over time in moderate users.

Contents lists available at SciVerse ScienceDirect

Neuroscience and Biobehavioral Reviews

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

Review

Confounders of excessive brain volume loss in schizophrenia

N.E. Van Haren *, W. Cahn, H.E. Hulshoff Pol, R.S. Kahn

There is convincing evidence that schizophrenia is characterised by progressive brain volume changes during the course of the illness. In a large longitudinal study it was shown that different age-related trajectories of brain tissue loss are present in patients compared to healthy subjects, suggesting that brain maturation that occurs in the third and fourth decade of life is abnormal in schizophrenia. However, studies show that medication intake and cannabis use are important confounding factors when interpreting brain volume (change) abnormalities. Indeed, continues use of cannabis, but not cigarette smoking, is associated to a more pronounced loss of grey matter in the anterior cingulated and the prefrontal cortex. … Moreover, independent of antipsychotic medication intake, the brain volume abnormalities appear associated to the outcome of the illness.

Schizophrenia Research 143 (2013) 84–89

Contents lists available at SciVerse ScienceDirect

Schizophrenia Research

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

Cannabis use and premorbid functioning as predictors of poorer neurocognition in schizophrenia spectrum disorder

P. Andreas Ringen [a,*], Ingrid Melle [a,b], Akiah O. Berg [a,b], Ingrid Agartz [a,b,c], Olav Spigset [d,e], Carmen Simonsen [a], Kjetil Sundet [a,f], Ole A. Andreassen [a,b]

- **Results**: Cannabis was detected in the urine of 21 patients, who had significant dysfunction in several neurocognitive domains independent of a current diagnosis of cannabis abuse. However, level of premorbid functioning explained the associations for all measures.

Contents lists available at SciVerse ScienceDirect

Psychiatry Research

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

Effects of cannabis use status on cognitive function, in males with schizophrenia

Rachel A. Rabin[a,b,*], Konstantine K. Zakzanis[c], Zafiris J. Daskalakis[a,d,e], Tony P. George[a,b,d]

- … Cross-sectional comparisons suggest that lifetime cannabis users demonstrate better processing speed than patients with no lifetime dependence. Exploratory analyses indicated that patients with current dependence exhibited robust negative relationships between cumulative cannabis exposure and cognition; these associations were absent in former users. …

Psychiatry Research (2012), http://dx.doi.org/10.1016/j.psychres.2012.11.019

TABLE 1—*The median and the range of potencies of cannabinoids (% w/w) in resin (n = 169), herbal cannabis (n = 35), sinsemilla (n = 247) and cannabis powder (n = 1), seized in five constabularies in England in 2004/5 (total n = 452).*

Type	THC	CBD	CBC	THCV	CBG	CBN
Resin						
Median	**3.54**	**4.17**	**0.34**	**0.10**	**0.29**	**1.55**
Minimum	0.44	0.36	<0.10	<0.10	<0.10	0.38
Maximum	10.76	6.97	0.66	0.29	1.05	4.30
Herbal						
Median	**2.14**	**<0.10**	**0.22**	**0.17**	**0.21**	**0.55**
Minimum	0.28	<0.10	<0.10	<0.10	<0.10	<0.10
Maximum	11.81	1.97	0.42	0.43	0.76	3.62
Sinsemilla						
Median	**13.98**	**<0.10**	**0.20**	**<0.03**	**0.41**	**0.16**
Minimum	1.15	<0.10	<0.10	<0.10	<0.10	<0.10
Maximum	23.17	0.56	1.41	2.74	2.16	2.98
Powder	**40.63**	**0.18**	**0.41**	**0.29**	**1.59**	**0.57**

The cannabinoids studied, in addition to THC, CBD and CBN, were CBC (cannabichromene), THCV (tetrahydrocannabivarin) and CBG (cannabigerol).

Potter DJ, Clark P, Brown MB. J Forensic Sci. 2008 Jan;53(1):90-4.

Current Pharmaceutical Design

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DOI: 10.2174/138161212802884780

Acute Effects of a Single, Oral dose of d9-tetrahydrocannabinol (THC) and Cannabidiol (CBD) Administration in Healthy Volunteers

R. Martin-Santos, J. A. Crippa, A. Batalla, S. Bhattacharyya, Z. Atakan, S. Borgwardt, P. Allen, M. Seal, K. Langohr, M. Farre, AW. Zuardi and P. K. McGuire

Pages 4966-4979 (14)

- **Results**: Relative to both placebo and CBD, administration of THC was associated with anxiety, dysphoria, positive psychotic symptoms, physical and mental sedation, subjective intoxication (AUC and effect at 2 hours: $p<0.01$), an increase in heart rate ($p<0.05$). There were no differences between CBD and placebo on any symptomatic, physiological variable.
- **Conclusions**: In healthy volunteers, THC has marked acute behavioural and physiological effects, whereas CBD has proven to be safe and well tolerated.

Psychological Medicine, Page 1 of 13. © Cambridge University Press 2012
doi:10.1017/S0033291712001924

ORIGINAL ARTICLE

Cannabis affects people differently: inter-subject variation in the psychotogenic effects of Δ^9-tetrahydrocannabinol: a functional magnetic resonance imaging study with healthy volunteers

Z. Atakan[1]*, S. Bhattacharyya[1], P. Allen[1], R. Martín-Santos[2], J. A. Crippa[3], S. J. Borgwardt[4], P. Fusar-Poli[1], M. Seal[5], H. Sallis[6], D. Stahl[6], A. W. Zuardi[3], K. Rubia[7] and P. McGuire[1]

- **Conclusions**. In this first demonstration of inter-subject variability in sensitivity to the psychotogenic effects of THC, we found that the presence of acute psychotic symptoms was associated with a differential effect of THC on activation in the ventral and medial temporal cortex and cerebellum, suggesting that these regions mediate the effects of the drug on psychotic symptoms.

Rev Bras Psiquiatr. 2012;34(Supl1):S104-S117

ELSEVIER

Revista Brasileira de Psiquiatria

RBP Psychiatry

Official Journal of the Brazilian Psychiatric Association

Volume 34 • Supplement 1 • June/2012

ARTICLE

Cannabidiol, a *Cannabis sativa* constituent, as an anxiolytic drug

Alexandre Rafael de Mello Schier,[1] Natalia Pinho de Oliveira Ribeiro,[1] Adriana Cardoso de Oliveira e Silva,[1,2,4] Jaime Eduardo Cecilio Hallak,[3,4] José Alexandre S. Crippa,[3,4] Antonio E. Nardi,[1,4] Antonio Waldo Zuardi[3,4]

Results: Studies using animal models of anxiety and involving healthy volunteers clearly suggest an anxiolytic-like effect of CBD. Moreover, CBD was shown to reduce anxiety in patients with social anxiety disorder.

Conclusion: Future clinical trials involving patients with different anxiety disorders are warranted, especially of panic disorder, obsessive-compulsive disorder, social anxiety disorder, and post-traumatic stress disorders. The adequate therapeutic window of CBD and the precise mechanisms involved in its anxiolytic action remain to be determined.

PHILOSOPHICAL TRANSACTIONS OF THE ROYAL SOCIETY B

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Phil. Trans. R. Soc. B (2012) **367**, 3364–3378
doi:10.1098/rstb.2011.0389

Review

Multiple mechanisms involved in the large-spectrum therapeutic potential of cannabidiol in psychiatric disorders

Alline Cristina Campos[1,2], Fabricio Araújo Moreira[3], Felipe Villela Gomes[4], Elaine Aparecida Del Bel[5] and Francisco Silveira Guimarães[4,*]

Possible mechanisms:

- CB1 receptor antagonist
- CB2 receptor inverse agonist
- FAAH (Fatty acid amide hydrolase) / anandamide transporter inhibition
- facilitation of 5-HT1Amediated neurotransmission in key brain areas
- potentiation of anandamide mediated neurotransmission (anti-compulsive, increased extinction, impaired reconsolidation of aversive memories, facilitation of adult hippocampal neurogenesis)
- activation of TRPV1 (transient receptor potential vanilloid 1) channels: antipsychotic effect

CBD & anxiety

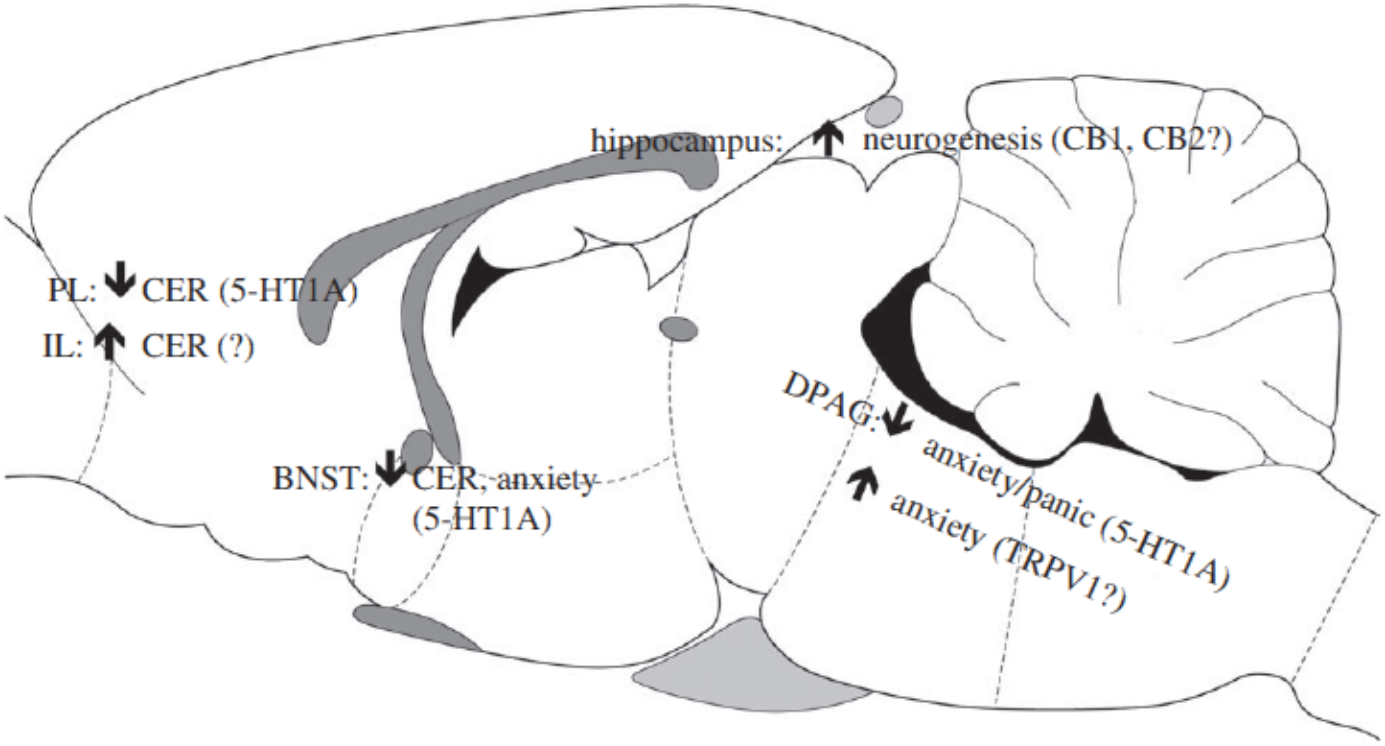

Figure 1. Possible brain sites and mechanisms of CBD effects on anxiety. BNST, bed nucleus of the stria terminalis; CeA, central nucleus of the amygdala; CER, conditioned emotional response; DPAG, dorsal periaqueductal grey; IL, infralimbic prefrontal cortex; PL, prelimbic prefrontal cortex.

Campos AC et al. Phil. Trans. R. Soc. B (2012) 367, 3364–3378.

Neuropsychopharmacology (2011) 36, 1219–1226

www.neuropsychopharmacology.org

Cannabidiol Reduces the Anxiety Induced by Simulated Public Speaking in Treatment-Naïve Social Phobia Patients

Mateus M Bergamaschi[1,2,3], Regina Helena Costa Queiroz[2,3], Marcos Hortes Nisihara Chagas[1,3], Danielle Chaves Gomes de Oliveira[1,3], Bruno Spinosa De Martinis[3,4], Flávio Kapczinski[3,5], João Quevedo[3,6], Rafael Roesler[3,7], Nadja Schröder[3,8], Antonio E Nardi[3,9], Rocio Martín-Santos[3,10], Jaime Eduardo Cecílio Hallak[1,3], Antonio Waldo Zuardi[1,3] and José Alexandre S Crippa*[,1,3]

PHILOSOPHICAL TRANSACTIONS OF THE ROYAL SOCIETY B BIOLOGICAL SCIENCES

Targeting the endocannabinoid system with cannabinoid receptor agonists: pharmacological strategies and therapeutic possibilities

Roger G. Pertwee

Phil. Trans. R. Soc. B 2012 **367**, doi: 10.1098/rstb.2011.0381

- Rimonabant: CB1 receptor antagonist / inverse agonist -> increased incidence of depression, anxiety and suicidality
- Development of medicines that inhibit cellular uptake and/or metabolism of endocannabinoids
- CB1 antagonists that pass not blood brain barrier
- Adjunctive strategies