Maconha e lesões cerebrais irreversíveis: mitos e fatos

Fórum sobre Maconha - CFM

Brasília, 28/03/ 2019

VGENTIL@USP.BR
www.psiquiatriafmusp.org.br
www.ipqhc.org.br

In This Issue

Biological Psychiatry

Volume 79, Number 7, April 1, 2016

A brief summary of the articles appearing in this issue of *Biological Psychiatry*.

Special Issue: Cannabinoids and Psychotic Disorders

The endocannabinoid system is complex and widespread, and it plays important roles throughout the central nervous system. In this review, **Lu and Mackie** (pages 516–525) introduce the endogenous cannabinoid system, detailing its receptors, endocannabinoids, and enzymes, with a particular focus on its role in synaptic plasticity. They also cover its relevance to and alterations in schizophrenia.

Controlled laboratory studies in humans provide compelling evidence to support an association between cannabinoids and psychosis. **Sherif *et al.*** (pages 526–538) review this evidence, focusing on psychosis-relevant outcomes. Data indicate that cannabinoids produce numerous symptoms in healthy humans that resemble schizophrenia and that individuals with schizophrenia appear more susceptible to these negative effects.

Purchased as marijuana-like drugs, synthetic cannabinoids are among the most commonly used new psychoactive substances, marketed as herbal blends and perceived as risk-free by inexperienced users. This review by **Fattore** (pages 539–548) describes the pharmacology and toxicology of these compounds, with particular reference to their psychoactive effects. She also summarizes evidence of psychotic episodes induced by ingestion of synthetic cannabinoids and highlights recent cases of intoxication and death.

This review by **Gage *et al.*** (pages 549–556) summarizes the epidemiologic evidence for the frequently observed association between cannabis use and psychosis. They posit that there is sufficient evidence to warrant a public health message that cannabis use may increase the risk of psychotic disorders. However, they also recommend complementary epidemiologic methods that can be used in further studies that are needed to address the outstanding questions of the size of this effect, the influence of particular strains of cannabis, and the groups most at risk.

Cannabis use has been associated with impaired cognition, but evidence has been mixed. In a systematic review of literature from the past decade, **Broyd *et al.*** (pages 557–567) found that acute and chronic cannabis use most consistently impairs verbal learning and memory and attention, followed by psychomotor function. Following abstinence, evidence suggests persistent cognitive impairment, but with some recovery of verbal learning and memory function. Overall, findings remain complex, and they conclude that further prospective studies are still needed.

Neuroanatomic alterations in cannabis users may be linked to the recent change in the composition of cannabis, with increases of Δ^9-tetrahydrocannabinol (Δ^9-THC) and decreases of the potentially therapeutic compound cannabidiol. **Lorenzetti *et al.*** (pages e17–e31) reviewed findings from structural neuroimaging investigations of human cannabis users and report consistent neuroanatomic alterations in regions that are high in cannabinoid receptors, including hippocampus, prefrontal cortex, amygdala, and cerebellum. This evidence suggests that THC may exacerbate, and cannabidiol protect from, the potentially harmful effects of cannabis.

Here, **Skosnik *et al.*** (pages 568–577) examine the relationship between neural oscillations, cannabinoids, and psychosis. They describe the different types of neural oscillations and discuss the role of neural oscillations in perception and cognition. They also review the preclinical literature on the relationship between cannabinoids and oscillations, and the effect of chronic and acute cannabis exposure. They conclude by presenting a hypothetical mechanism explaining the effect of cannabinoid agonists on neural oscillations.

Alpár *et al.* (pages e33–e45) review the organization, susceptibilities, and disease association of the endocannabinoid system in the fetal brain. They then use a combination of human longitudinal data and genetic and pharmacologic studies in experimental models to highlight the contributions of the endocannabinoid system and prenatal exposure to depression, schizophrenia, and epilepsy. Lastly, they discuss the medical relevance of plant-derived cannabinoids, contrasted with the potential harmful effects of THC.

Rubino and Parolaro (pages 578–585) review the animal model literature investigating the long-term effects of adolescent cannabinoid exposure. They discuss the development of the adolescent brain, the role of the endocannabinoid system in brain maturation during adolescence, and the impact of exogenous cannabinoid exposure during this specific developmental window, which includes impaired brain maturation, impaired cognition, dysregulated gamma-aminobutyric acidergic and glutamatergic systems, and increased risk for psychosis.

The increased use of cannabis in society, particularly in young individuals, has raised questions about its potential protracted neurobiological consequences. Epigenetic mechanisms are strong biological candidates that can be expected to contribute to the maintenance of long-term effects on brain and behavior. In this review, **Szutorisz and Hurd** (pages 586–594) describe reported epigenetic modifications associated with the use of cannabis and the potential relevance to psychiatric vulnerability.

The association between cannabis use and worse outcomes in schizophrenia may be related to the disruption by cannabis of the endogenous cannabinoid system's regulation of inhibitory neurons in the prefrontal cortex. Here, **Volk and Lewis** (pages 595–603) review evidence of endocannabinoid system abnormalities in the prefrontal cortex of individuals with schizophrenia and discuss how these alterations may interact with other impairments in inhibitory neurons to increase sensitivity to the deleterious effects of cannabis use in schizophrenia.

The endocannabinoid system plays an important role in the pathophysiology of psychosis and schizophrenia. **Leweke *et al.*** (pages 604–612) critically review the current approaches to target this neurotransmitter system for the treatment of psychotic symptoms and cognitive alterations in schizophrenia, including those using plant-derived and synthetic cannabinoids and modulators of the endocannabinoid system. Clinical trial data, however, are still limited.

ElSohly *et al.* (pages 613–619) examined the concentration of cannabinoids in cannabis products (marijuana, hashish and hash oil) seized by the United States over the last two decades. The data show that potency of the psychoactive compound Δ^9-THC has consistently risen over that time, from 4% in 1995 to 12% in 2014, whereas cannabidiol content has fallen. This increased shift in potency could pose a higher risk for recreational or medical marijuana users.

At the Tip of an Iceberg: Prenatal Marijuana and Its Possible Relation to Neuropsychiatric Outcome in the Offspring

2016

Alán Alpár, Vincenzo Di Marzo, and Tibor Harkany

Acute and Chronic Effects of Cannabinoids on Human Cognition—A Systematic Review

Samantha J. Broyd, Hendrika H. van Hell, Camilla Beale, Murat Yücel, and Nadia Solowij

Changes in Cannabis Potency Over the Last 2 Decades (1995–2014): Analysis of Current Data in the United States

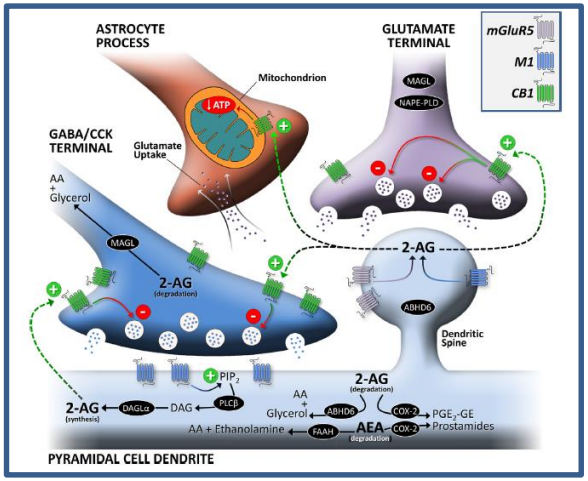
Mahmoud A. ElSohly, Zlatko Mehmedic, Susan Foster, Chandrani Gon, Suman Chandra, and James C. Church

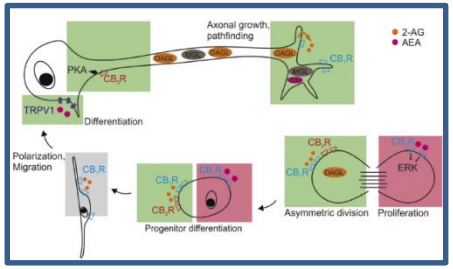
Cannabis and Psychosis: What Degree of Proof Do We Require?

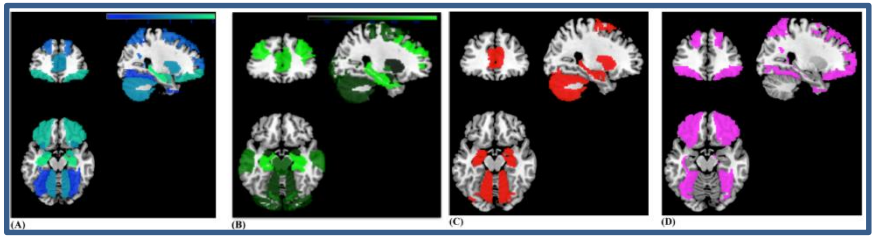
Robin M. Murray and Marta Di Forti

Synthetic Cannabinoids—Further Evidence Supporting the Relationship Between Cannabinoids and Psychosis

Liana Fattore







NEJM Journal Watch

2018

Barbara Geller, MD

Associate Editor

NEJM JOURNAL WATCH PSYCHIATRY

May 15, 2018

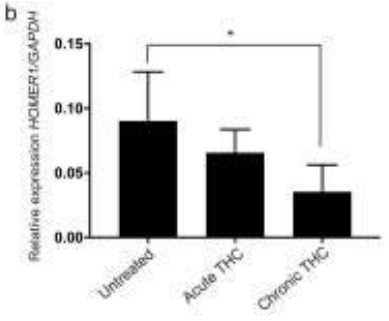
Effects of THC on Human Neurons

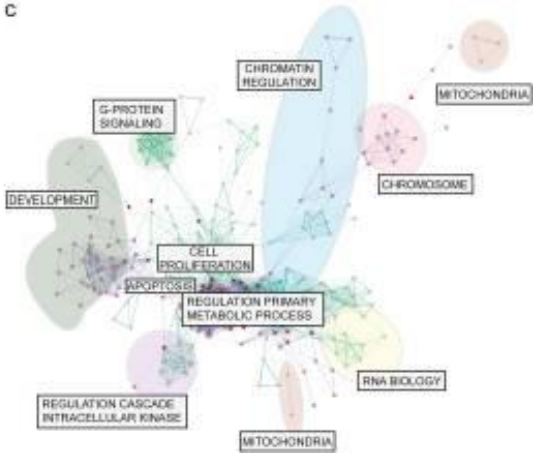
Barbara Geller, MD reviewing Guennewig B et al. Transl Psychiatry 2018 Apr 25.

THC exposure of human iPSC neurons impacts genes associated with neuropsychiatric disorders.

When exposed to tetrahydrocannabinol, neurons derived from human-induced pluripotent stem cells exhibited genetic and activation impairments similar to those in autism and schizophrenia.

Gene class	Acute THC		Chronic THC	
Postsynaptic density	Fold change	P-value	Fold change	P-value
GRID2	2.08	0.00013	2.26	3.22E-05
CAP2	1.73	8.91E-06	1.44	0.00020
GRIK1	1.41	4.76E-05	1.62	2.67E-06
SIPA1L1	1.27	5.59E-05	1.32	2.81E-05
HOMER1	-2.46	1.45E-07	-2.56	4.66E-08
SYNPO	-	n/a	2.34	0.00015
SYNGAP1	-	n/a	2.14	0.00027
PTCH1	-	n/a	2.14	0.00016
NTRK2	-	n/a	2.09	1.64E-05
SOS1	-	n/a	1.80	0.00032
RUSC1	-	n/a	1.56	0.00023
SRGAP2	-	n/a	1.30	0.00014
GSK3B	-	n/a	1.27	0.00015
EPHA4	-	n/a	-1.56	0.00028
SHANK1	-	n/a	-4.39	0.00026
Ion channel	**Fold change**	**P-value**	**Fold change**	**P-value**
TMEM38A	-2.04	3.14E-05	-	n/a
KCNF1	-2.87	7.98E-06	-	n/a
KCNK15	-8.86	8.45E-06	-	n/a
RYR3	2.58	5.09E-05	2.59	5.17E-05
GRID2	2.08	0.00013	2.26	3.22E-05
GRIK1	1.41	4.76E-05	1.62	2.67E-06
CACNG7	1.89	4.45E-05	2.10	4.55E-06
KCNJ10	1.74	1.05E-05	2.05	1.62E-07
KCNN3	2.48	1.15E-05	2.27	5.82E-05
ITPR2	1.18	4.24E-05	1.21	2.38E-05
LRRC8E	-2.92	7.83E-07	-2.40	2.39E-05
KCNA4	-3.99	9.22E-06	-3.59	5.23E-05
KCNE4	-5.42	5.31E-08	-4.56	2.83E-06
FXYD6	-	n/a	2.17	0.00025
ASIC1	-	n/a	1.82	0.00011
TMEM63A	-	n/a	1.45	0.00016
KCNT2	-	n/a	1.44	0.00019
KCNJ2	-	n/a	-1.87	0.00022
CHRNA9	-	n/a	-2.88	0.00026
KCNQ1	-	n/a	-6.47	0.00016
KCNK6	-	n/a	-6.81	9.78E-05



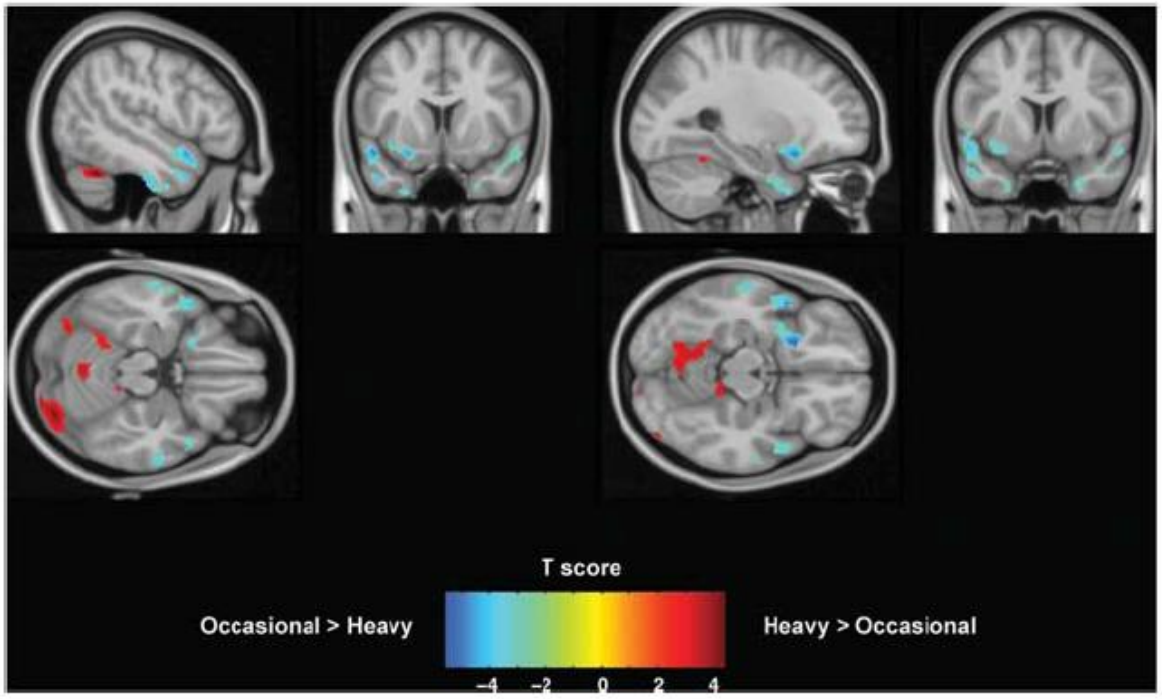


Network analysis combining all THC-related genes from acute and chronic THC treatment shows broad changes to fundamental cellular functions such as RNA biology, chromatin regulation and development

Long-Term Effects of Cannabis on Brain Structure

G Battistella *et al* **Neuropsychopharmacology (2014) 39,** 2041–2048

… regular cannabis use is associated with gray matter volume reduction in the medial temporal cortex, temporal pole, parahippocampal gyrus, insula, and orbitofrontal cortex;
… these regions are rich in cannabinoid CB1 receptors and functionally associated with motivational, emotional, and affective processing…
… these changes correlate with the frequency of cannabis use in the 3 months before inclusion in the study.
… the age of onset of drug use also influences the magnitude of these changes.



2014

Figure 1 Voxel-Based Morphometry results on gray matter. Cold color bar shows regions where gray matter volume is lower in regular smokers compared with occasional ones. Hot color bar represents the opposite contrast. Maps are thresholded at $P<0.005$ and $k>60$ and superposed on a standard brain in the MNI space. Figure shows results in planes centered at −26, 7, 14 mm and −48, 10, −19 mm. Color bars represent T score.

Effects of regular cannabis use on neurocognition, brain structure, and function: a systematic review of findings in adults

2018

Danilo A. Nader, MD and Zila M. Sanchez, PhD
Departmento de Medicina Preventiva, Universidade Federal de São Paulo

THE AMERICAN JOURNAL OF DRUG AND ALCOHOL ABUSE
2018, VOL. 44, NO. 1, 4–18

Review of recent studies - 56 of 898 records (9/2016) :

... whole brain volume is not affected by cannabis use

... regional alterations identified in CB1-rich areas.

... growing evidence of abnormalities in hippocampus volume and gray matter density of cannabis users relative to controls. *(Morphological changes in other brain regions are more controversial).*

... microstructural change in white matter integrity in specific brain regions - demyelination or axonal damage (?) - may result in impaired brain connectivity.

... may brain alterations resolve with continued abstinence?

Additional longitudinal studies in larger samples prior to the onset of cannabis use are needed to determine a causal pathway between heavy cannabis use and these alterations.

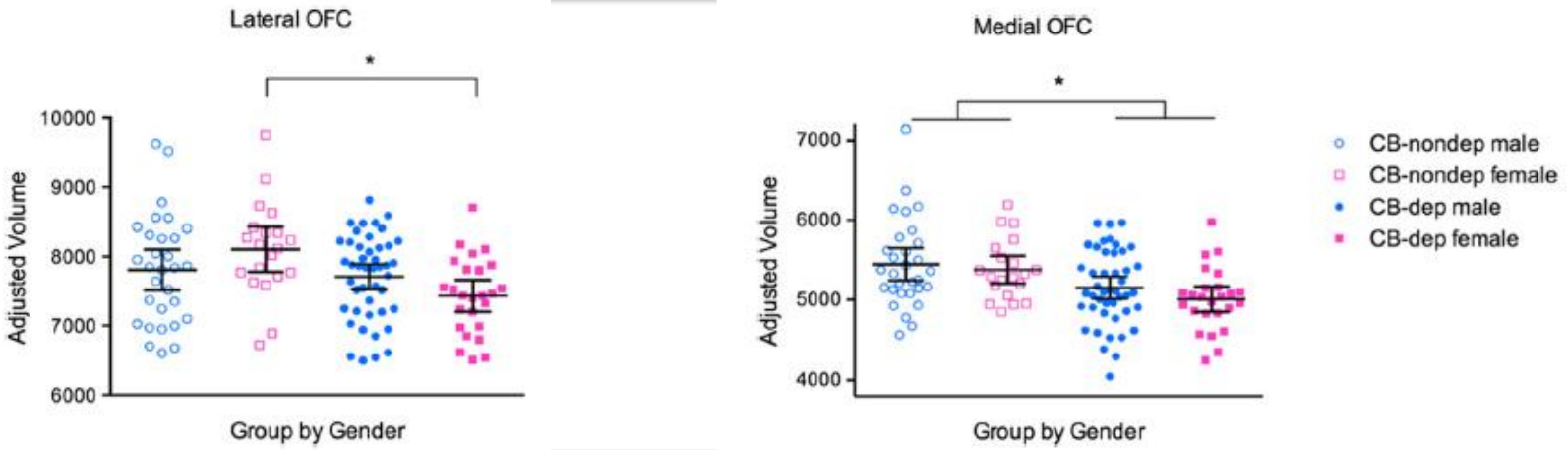
Orbitofrontal and caudate volumes in cannabis users: a multi-site mega-analysis comparing dependent versus non-dependent users

Psychopharmacology (2017) 234:1985–1995

Yann Chye[1] · Nadia Solowij[2] · Chao Suo[1] · Albert Batalla[3,4] · Janna Cousijn[5] · Anna E. Goudriaan[6,7] · Rocio Martin-Santos[4] · Sarah Whittle[8] · Valentina Lorenzetti[1,8,9] · Murat Yücel[1]

2017

… structural imaging study in 140 CB users and 121 controls. Differences in OFC and caudate volumes were investigated between 70 dependent (CB-dep) and 50 nondependent (CB-nondep) users.



- CB-dep users had significantly smaller volume in the medial and the lateral OFC than CB-nondep *(particularly in women)*.
- Reduced volume in the CB-dep group was associated with higher monthly cannabis dose.

INVITED REVIEW

2018

Cannabis Addiction and the Brain: a Review

Amna Zehra[1] · Jamie Burns[1] · Christopher Kure Liu[1] · Peter Manza[1] · Corinde E. Wiers[1] · Nora D. Volkow[1,2]
Gene-Jack Wang[1]

Journal of Neuroimmune Pharmacology (2018) 13:438–452

… findings on the effects of cannabis exposure during adolescence are controversial and require investigation with prospective designs…

The contribution of cannabis use to variation in the incidence of psychotic disorder across Europe (EU-GEI): a multicentre case-control study

Lancet Psychiatry 2019

Published Online March 19, 2019

2019

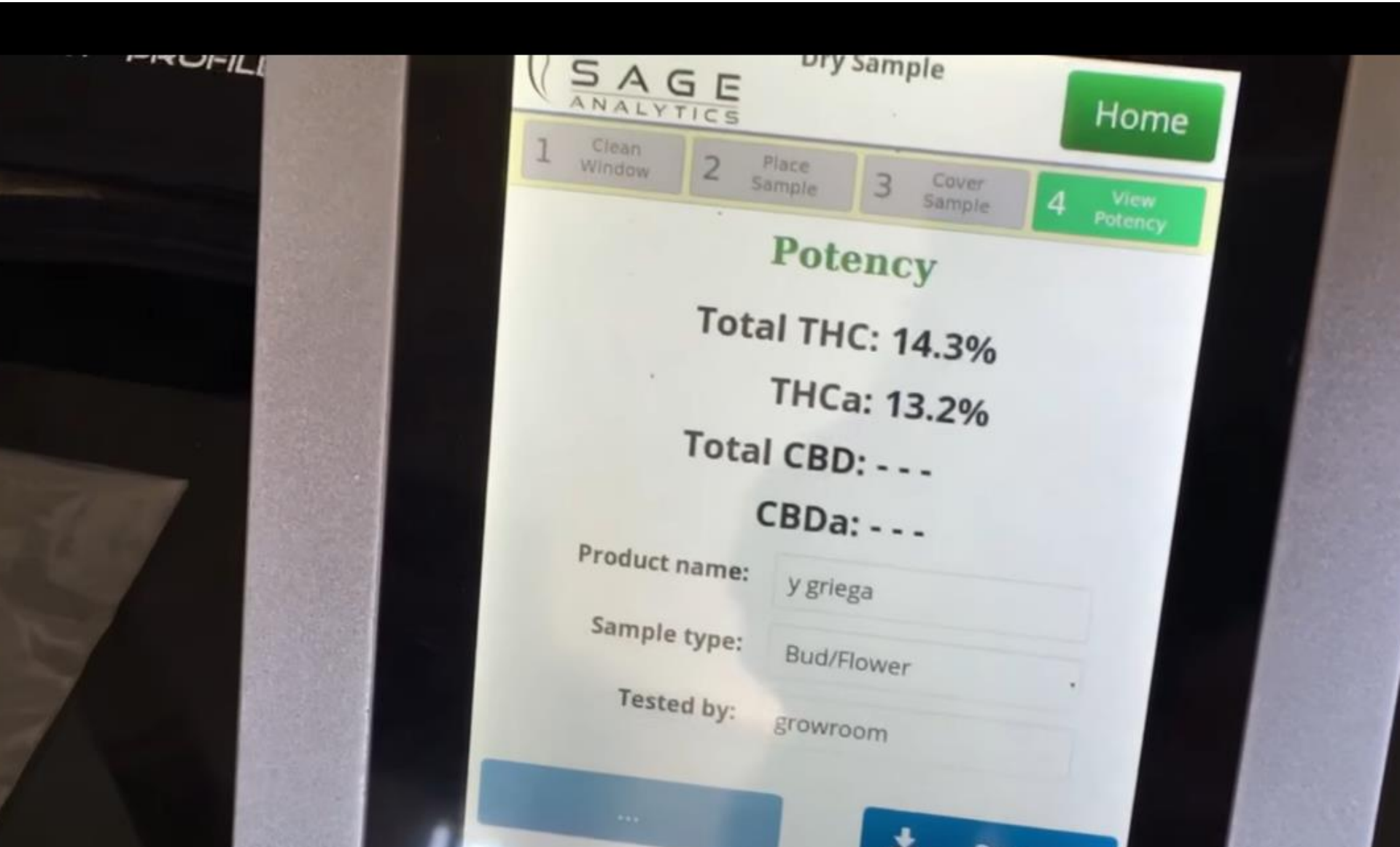
*Marta Di Forti, Diego Quattrone, Tom P Freeman, Giada Tripoli, Charlotte Gayer-Anderson, Harriet Quigley, Victoria Rodriguez, Hannah E Jongsma, Laura Ferraro, Caterina La Cascia, Daniele La Barbera, Ilaria Tarricone, Domenico Berardi, Andrei Szöke, Celso Arango, Andrea Tortelli, Eva Velthorst, Miguel Bernardo, Cristina Marta Del-Ben, Paulo Rossi Menezes, Jean-Paul Selten, Peter B Jones, James B Kirkbride, Bart PF Rutten, Lieuwe de Haan, Pak C Sham, Jim van Os, Cathryn M Lewis, Michael Lynskey, Craig Morgan, Robin M Murray, and the EU-GEI WP2 Group**

Findings Between May 1, 2010, and April 1, 2015, we obtained data from 901 patients with first-episode psychosis across 11 sites and 1237 population controls from those same sites. Daily cannabis use was associated with increased odds of psychotic disorder compared with never users (adjusted odds ratio [OR] 3·2, 95% CI 2·2–4·1), increasing to nearly five-times increased odds for daily use of high-potency types of cannabis (4·8, 2·5–6·3). The PAFs calculated indicated that if high-potency cannabis were no longer available, 12·2% (95% CI 3·0–16·1) of cases of first-episode psychosis could be prevented across the 11 sites, rising to 30·3% (15·2–40·0) in London and 50·3% (27·4–66·0) in Amsterdam. The adjusted incident rates for psychotic disorder were positively correlated with the prevalence in controls across the 11 sites of use of high-potency cannabis ($r = 0·7$; p=0·0286) and daily use ($r = 0·8$; p=0·0109).

USO DIÁRIO DE CANÁBIS (maconha, hashish, skunk) **= 3.2 vezes maior risco de psicose**

USO DE CANÁBIS DE ALTA POTÊNCIA (skunk) **= 4.8 vezes maior risco de psicose**

O Growroom visitou o escritório da Senses Biotech no Uruguai e testou uma amostra. Veja o resultado:



Review

Effects of Cannabis Use on Human Behavior, Including Cognition, Motivation, and Psychosis: A Review

Nora D. Volkow, MD; James M. Swanson, PhD; A. Eden Evins, MD; Lynn E. DeLisi, MD; Madeline H. Meier, PhD; Raul Gonzalez, PhD; Michael A. P. Bloomfield, MRCPsych; H. Valerie Curran, PhD; Ruben Baler, PhD

2016

JAMA Psychiatry. 2016;73(3):292-297

"A mudança nos padrões de uso da cannabis... na percepção do risco, e nas normas culturais, fazem com que os nossos conhecimentos atuais se apliquem apenas às condições em que essas drogas foram utilizadas no passado."

2003

"Como não há meio confiável para detectar vulnerabilidade específica e não existe tratamento eficaz para essa psicose, é melhor evitar o fogo."

Cannabis Psychosis: smoke and fire.
Gentil, V., Stress & Health, 2003.

vgentil@usp.br

Foto: A. Danila

www.psiquiatriafmusp.org.br
www.ipqhc.org.br

vgentil@usp.br