Cannabis & Mental Health Primer Webinar
Zach Walsh

1

Disclosure

- My research has received financial support from Tilray and Doja in the form of funding to sponsor a clinical trial for which I am principal investigator.
- Former director of clinical research for Indigenous Bloom as an advisory board member.
- Potential for conflict(s) of interest:
  - Zach Walsh has received research support from Tilray & Doja.
  - Tilray & Doja are licensed producers of cannabis for medical purposes.
  - I hold shares in Indigenous Bloom.
  - Indigenous Bloom is an Indigenous operated cannabis company.
- Other [illegible]

CIHR IRSC SSHRC CRSH

2

Overview - Me

- Clinical psychologists (#2011)
- Trained in addictions treatment
  - University of Chicago
  - Brown University - Center for Alcohol and Addiction Treatment
- Professor - UBC
- Lead - Therapeutic Recreational & Problematic Substance Use lab
- Published and presented widely on cannabis use and mental health
  - HOC
  - Senate
  - BC Supreme Court
  - Uruguay and Costa Rica
- PI - Canada's 1st clinical trial of cannabis to treat mental health d/o
- Advisory boards of MAPS Canada & Clinical team for MDMA for PTSD trials
- CIHR & SSHRC funded studies of cannabis use in young adults

3

Overview - Today

PART 1

- History
  - 3000 BCE to C-45
- The plant
  - Cannabinoids
    - THC-CBD…
  - Terpenes
    - Entourage effect
  - Strains/Chemovars
    - Indica / Sativa
  - Modes of Administration

4

Overview - Today

PART 2

- Cannabinoids in humans
  - The Endocannabinoid System
    - Endocannabinoid deficits
    - Endocannabinoid care
  - Cannabinoid pharmacology
- Medical Cannabis use
  - Patient reports
  - Cannabis for pain and anxiety
  - Substitution
    - Benzodiazapines
    - Opioids
    - Alcohol

5

Overview - Today

PART 3

- Cannabinoids and Mental Health
  - Anxiety
  - Depression
  - Psychosis
  - Risk
  - PTSD

6

Overview - Today

PART 4

- Problems
  - Withdrawal
  - Disorder
  - Assessment
  - Treatment
  - Safe use
  - Driving
- Special populations
  - Youth
  - Older adults

7

Cannabinoids

- Endocannabinoids
  - Naturally occurring in animals
  - Anandamide
  - 2-AG
- Phytocannabinoids
  - From plants
  - THC, CBD and many others
- Synthetic
  - K9, Spice

8

9

History - China

Shen-Nung (c.2700 B.C.)

10

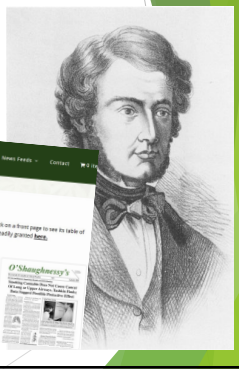
History - India

- Ganja
- Bhang
- Holi
- The Vedas call cannabis a source of happiness, joy-giver, liberator that was compassionately given to humans to help us attain delight and lose fear (Abel, 1980).

11

History - Europe

- William Brooke O'Shaughnessy
  - Introduced medical use of cannabis to Europe
  - From India - 1841



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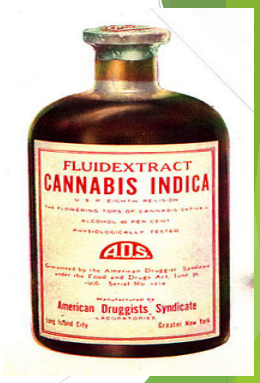


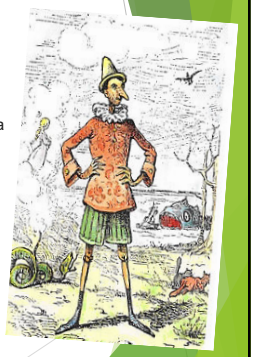
13

History - Prohibition

"Marihuana is a short cut to the insane asylum. Smoke marihuana cigarettes for a month and what was once your brain will be nothing but a storehouse of horrid specters. Hasheesh makes a murderer who kills for the love of killing out of the mildest mannered man who ever laughed at the idea that any habit could ever get him…"

Harry Aslinger, 1937

1st Commissioner of the Federal Bureau of Narcotics



14

History - Canada

- Canada - Janey Canuck - The Black Candle (1922)

15

Canada - Recent

16

Background – Medical Cannabis in Canada

- *Parker* (2000) - constitutional right to choose cannabis as medicine without fear of criminal sanction
- In 2001, the *Marihuana Medical Access Regulations* (MMAR)
  - Access
    - Health Canada - Prairie PPS
    - Private production license
    - Designated grower (1:1…2:1)

17

CANADIAN MEDICAL MARIHUANA SYSTEM

MMAR	MMPR
ENDED MARCH 31, 2014	STARTED APRIL 1, 2014

Health Canada Santé Canada

18

MMPR

MARIHUANA FOR MEDICAL PURPOSES REGULATIONS

- Simplified/decentralized application process
- Multiple Licensed Producers
  - Increased quality & strain choice
- Research funding & materials
- No self-production or storefronts

  - Allard
- 2016 ACCESS TO CANNABIS FOR MEDICINAL PURPOSES REGULATIONS (ACMPR)

19

C-45: THE CANNABIS ACT

- Sale -provincial gov't
  - online (mail) and retail stores;
  - public/private models
- Minimum age of 18 (provinces can adjust)
- Adults –
  - up to 30 grams –
  - 4 plants per household
- Youth (12-17) –
  - decriminalized for 5 grams or less
  - Providing cannabis to minors – 14 year max
- Limits on advertising and branding
- Outside of regulated framework
  - 45+ new penalties
- UP FOR REVIEW 2023 (THOUGHTS?)

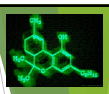
20

Cannabinoids

- The Cannabinoids
  - Delta-9-tetrahydrocannabinol (Δ^9-THC)
    - 5-25% "superweed?"
  - Cannabinoids
    - Over 100 Cannabinoids
      - Cannabinol and Cannabidiol (CBD)
  - THCA, THC, CBDA, CBD, CBGA, CBG, CBN
  - Some on plant ratios of 2:1, >20:1,
    - Terpenes
    - Entourage effect of herbal cannabis
    - Whole plant – coevolution with humans?
  - Synthetic Cannabinoids
    - Sativex - extract
    - Dronabinol (Marinol)-Levonantradol (30x THC)
    - Spice / K2
  - Rimonabant – antagonist

21

Pharmacology of THC



- THC functions by binding to the Cannabinoid Receptor (CB_1).
  - The presence of this receptor indicates that there is a naturally occur (endogenous) ligand, Anandimide, as well as other related compounds.
- The response can affect the hippocampus and hypothalamus
  - Hippocampus -involved in ***motivation*** and ***emotion*** as part of the limbic system; has a central role in the ***formation of memories***.
  - Hypothalamus -regulating ***sleep cycles***, ***body temperature***, ***appetite***, etc., and that acts as an endocrine gland by ***producing hormones***, including the releasing factors that control the hormonal secretions of the pituitary gland.

22

CBD

- **Well Documented:**
  - Anti-epileptic
- **Potential**:
  - Analgesic (acute and chronic pain)
  - Antipsychotic
  - Anxiolytic
  - Anti-cancer
  - Anti-inflammatory

23

23

CBD

- **CBD does not activate CB1 or CB2 receptors**
- **Does not mimic endocannabinoids.**
- **Interacts indirectly with the endocannabinoid system**
- **Agonist**
  - **5 HT 1A** (anxiolytic; antidepressant)
  - **Adenosine** (anxiolytic)
  - **TRPV1** - (analgesic)
  - **Mu and delta opiate** – (analgesic)

24

Terpenes

- Biologically active cannabis constituents with pharmacologic effects.
- > 200 in the cannabis plant.
- Most are "Generally Recognized as Safe" as food additives.
- How to optimize terpene absorption?

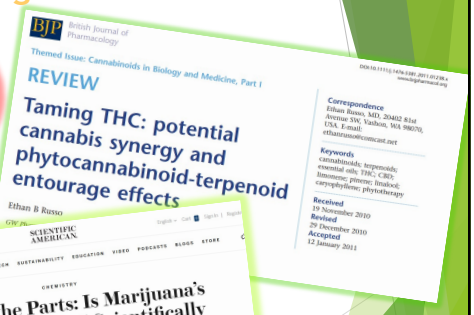
25

Cannabis Terpenoid Activity Table

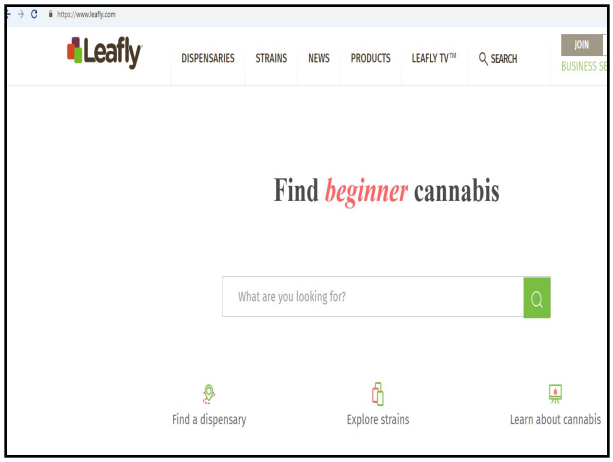
Terpenoid	Structure	Commonly encountered in	Pharmacological activity (Reference)	Synergistic cannabinoid
Limonene		 Lemon	Potent AD/immunostimulant via inhalation (Komori *et al.*, 1995)	CBD
			Anxiolytic (Carvalho-Freitas and Costa, 2002; Pultrini Ade *et al.*, 2006) via 5-HT$_{1A}$ (Komiya *et al.*, 2006)	CBD
			Apoptosis of breast cancer cells (Vigushin *et al.*, 1998)	CBD, CBG
			Active against acne bacteria (Kim *et al.*, 2008)	CBD
			Dermatophytes (Sanguinetti *et al.*, 2007; Singh *et al.*, 2010)	CBG
			Gastro-oesophageal reflux (Harris, 2010)	THC
α-Pinene		 Pine	Anti-inflammatory via PGE-1 (Gil *et al.*, 1989)	CBD
			Bronchodilatory in humans (Falk *et al.*, 1990)	THC
			Acetylcholinesterase inhibitor, aiding memory (Perry *et al.*, 2000)	THC?, CBD
β-Myrcene		 Hops	Blocks inflammation via PGE-2 (Lorenzetti *et al.*, 1991)	CBD
			Analgesic, antagonized by naloxone (Rao *et al.*, 1990)	CBD, THC
			Sedating, muscle relaxant, hypnotic (do Vale *et al.*, 2002)	THC
			Blocks hepatic carcinogenesis by aflatoxin (de Oliveira *et al.*, 1997)	CBD, CBG
Linalool		 Lavender	Anti-anxiety (Russo, 2001)	CBD, CBG?
			Sedative on inhalation in mice (Buchbauer *et al.*, 1993)	THC
			Local anesthetic (Re *et al.*, 2000)	THC
			Analgesic via adenosine A$_{2A}$ (Peana *et al.*, 2006)	CBD
			Anticonvulsant/anti-glutamate (Elisabetsky *et al.*, 1995)	CBD, THCV, CBDV
			Potent anti-leishmanial (do Socorro *et al.*, 2003)	?
β-Caryophyllene		 Pepper	AI via PGE-1 comparable phenylbutazone (Basile *et al.*, 1988)	CBD
			Gastric cytoprotective (Tambe *et al.*, 1996)	THC
			Anti-malarial (Campbell *et al.*, 1997)	?
			Selective CB$_2$ agonist (100 nM) (Gertsch *et al.*, 2008)	THC
			Treatment of pruritus? (Karsak *et al.*, 2007)	THC
			Treatment of addiction? (Xi *et al.*, 2010)	CBD

26

Entourage?



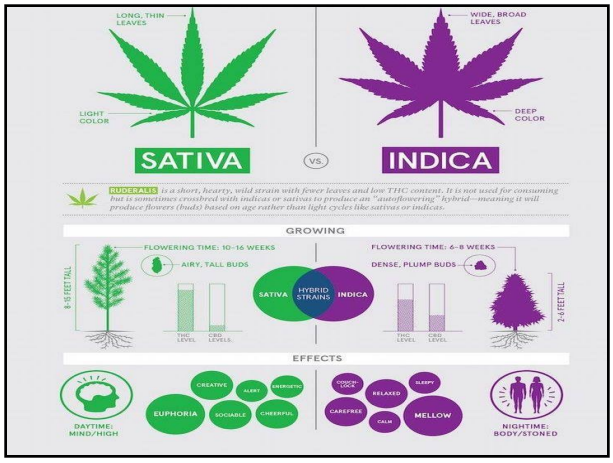
27


Leafly
DISPENSARIES
STRAINS
NEWS
PRODUCTS
LEAFLY TV™
SEARCH
JOIN
Find beginner cannabis
What are you looking for?
Find a dispensary
Explore strains
Learn about cannabis

28

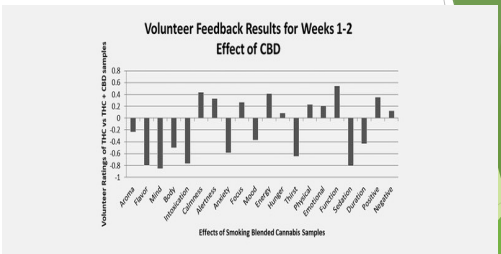

Hybrid Gg4 Original Glue
Sativa Jh Jack Herer
Hybrid Ww White Widow
Indica Bk Bubba Kush
Hybrid Pex Pineapple Express
Sativa Dp Durban Poison
Indica Nl Northern Lights
Hybrid Tw Trainwreck
Hybrid Ak AK-47
Hybrid Hb Headband
Indica Chz Blue Cheese
Sativa Lh Lemon Haze
Indica Pk Purple Kush
Sativa Sc Strawberry Cough
Indica Bry Blueberry
Hybrid Cd Chemdawg
Sativa Ss Super Silver Haze
Indica Ga Grape Ape
Sativa Atf Alaskan Thunder Fuck
Indica Bbk Blackberry Kush
Sativa Slh Super Lemon Haze
Indica Mks Master Kush
Hybrid Cp Cherry Pie
Hybrid Mzo Mazar X Blueberry OG

29


LONG, THIN LEAVES
LIGHT COLOR
WIDE, BROAD LEAVES
DEEP COLOR
SATIVA
VS.
INDICA
RUDERALIS is a short, hearty, wild strain with fewer leaves and low THC content. It is not used for consuming but is sometimes crossbred with indicas or sativas to produce an "autoflowering" hybrid—meaning it will produce flowers (buds) based on age rather than light cycles like sativas or indicas.
GROWING
FLOWERING TIME: 10-16 WEEKS
AIRY, TALL BUDS
FLOWERING TIME: 6-8 WEEKS
DENSE, PLUMP BUDS
6-15 FEET TALL
2-6 FEET TALL
SATIVA
HYBRID STRAINS
INDICA
EFFECTS
DAYTIME: MIND/HIGH
CREATIVE
ENERGETIC
ALERT
EUPHORIA
SOCIABLE
CHEERFUL
FOCUSED
RELAXED
SLEEPY
CAREFREE
CALM
MELLOW
NIGHTIME: BODY/STONED

30

CBD vs



Lewis, Russo & Smith, 2018

31

EDIBLES DOSING CHART

THC CONTENT PER DOSE	WHAT TO EXPECT	WHO'S IT FOR?
1 - 2.5 mg THC	• Mild relief of pain, stress, anxiety, and other symptoms • Improved focus and creativity	• First-time consumers • Microdosers
2.5 - 15 mg THC	• Stronger symptom relief • Euphoria • May impair coordination and alter perception	• Patients with persistent problems • Restless sleepers • Social butterflies
15 - 30 mg THC	• Strong euphoria or unwanted effects in unaccustomed consumers • May impair coordination and alter perception	• Well-seasoned consumers • Medical patients with developed tolerances • Experienced consumers seeking to sustain sleep
30 - 50 mg THC	• Very strong euphoria in unaccustomed consumers • Likely to impair coordination and alter perception	• Consumers who have poor GI absorption of cannabinoids • People with significant tolerance to THC
50 - 100 mg THC	• Can cause extreme side effects such as rapid heart rate, nausea, and pain • Highly likely to impair coordination and alter perception	• For experienced THC individuals only • Patients with cancer, inflammatory disorders, or conditions that necessitate high doses

Always begin at the lowest recommended dose. Gradually increase by 1 or 2mg per dose, if necessary, to find your optimal dose. For more information go to Healer programs: **www.healer.com/programs**

HEALER Leafly

32

Concentrates

33

Concentrates

CRUMBLE
Dried oil with a honey-comb like consistency

BADDER/BUDDER
Concentrates whipped under heat to create a cake-batter like texture

SHATTER
A translucent, brittle, & often golden to amber colored concentrate made with a solvent

DISTILLATE
Refined cannabinoid oil that is typically free of taste, smell & flavor. It is the base of most edibles and vape cartridges

CRYSTALLINE
Isolated cannabinoids in their pure crystal structure

DRY SIFT
Ground cannabis filtered with screens leaving behind complete trichome glands. The end-product is also referred to as kief

ROSIN
End product of cannabis flower being squeezed under heat and pressure

BUBBLE HASH
Uses water, ice, and mesh screens to pull out whole trichomes into a paste-like consistency

34

Concentrates

35

Modes of use

- Absorption
  - Oral Administration
    - Highly Lipid Soluble
      - Will hardly dissolve in water
      - Bake in food
        - First pass metabolism
      - Oral dose must be doubled or tripled to have same effect as inhalation
        - Peak effects: 1 to 3 hrs after ingestion
  - Inhalation
    - Depth of Inhalation

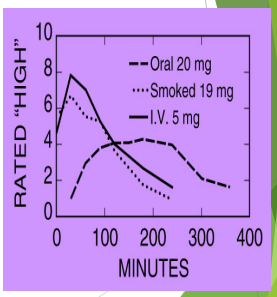
Vs duration
10-25% cannabinoids
Peak effects: 15 to 60 minutes

36

Modes

Distribution

- The time course for intensity of a subjective "high" after consuming various doses of THC via different routes of administration



37

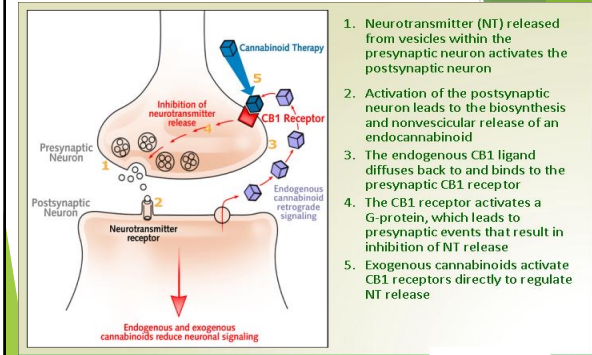
Part 2 - Cannabis, the Brain & Mental Health

38

Neurological Effects of THC

- Endocannabinoid Synaptic Transmission
  1. Transmission of neurotransmitter into the post-synaptic neuron.
  2. Production of endocannabinoids in the post-synaptic neuron.
  3. The endocannabinoid (e.g. anadamide, 2AG) is released into the synaptic cleft.
  4. In the synaptic cleft the endocannabinoid binds to the cannabinoid receptor of the pre-synaptic neuron.
     - This in turn modulates neurotransmission pre-synapticly
     - Post-Synaptic Neuron → Pre-Synaptic Neuron (Retrograde Transmission)
- This mechanism is reverse of what is typically seen
  - Pre-Synaptic Neuron → Post-Synaptic Neuron (Normal Transmission)

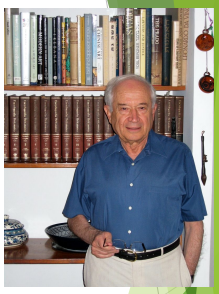
39



1. Neurotransmitter (NT) released from vesicles within the presynaptic neuron activates the postsynaptic neuron
2. Activation of the postsynaptic neuron leads to the biosynthesis and nonvesicular release of an endocannabinoid
3. The endogenous CB1 ligand diffuses back to and binds to the presynaptic CB1 receptor
4. The CB1 receptor activates a G-protein, which leads to presynaptic events that result in inhibition of NT release
5. Exogenous cannabinoids activate CB1 receptors directly to regulate NT release

40

Neuropharmacology



- Receptors - 2 discovered 1990
  - Likely many more
  - Second Messenger System
- Endocannabinoids
  - Anandamide
  - 2-arachidonylglycerol (2-AG)
  - THC > duration & effect
- Presynaptic Neuromodulators
  - From post to pre synaptic
  - Effects depend on nature of pre
    - Depolarization-induced **suppression of inhibition**
    - Depolarization-induced **suppression of excitation**
- Stress Recovery
  - Relax, eat, sleep,forget & protect

41

Effects on Behavior of Humans

- Subjective Effects
  - Bipolar / contradictory
- Mood Changes and Getting High
  - Mood swings
  - Social effects
- Perception
  - Loss of sensitivity to pain
  - Time distortion

McKim, 2017

42

Effects on Behavior of Humans

- Memory
  - No effect on the ability to recall material already well learned or on recognition memory
  - Does disrupt the ability to recall words or narrative material
    - Short term memory
    - Temporal disintegration
- Attention
  - Easily distracted
- Creativity
  - Appreciation
  - No evidence that creativity is enhanced
- Setting? (NCAP)

McKim, 2017

43

Effects on Behavior of Humans

- Performance
  - Varied results
    - Level of use
    - Features of task
    - Ability vs attention/ motivation
- Performance Screening Tests
  - Standardized Field Sobriety Tests
    - Gaze nystagmus, Walk and turn test, One-leg stand
    - 56% of high THC group identified vs 2.5% placebo

McKim, 2017

44

Cannabis for Therapeutic Purposes

- Risks and benefits
- Cannabis is:
  - **"…one of the safest therapeutically active substances known to man"**

US Drug Enforcement Administration

Judge Francis Young -1988

45

Conditions in Clinical Practice
Rank order - Hergenrather 2016

- Pain (acute pain, chronic inflammatory, neuropathic)
- Mental disorders (all kinds)
- Cancers
- Gastrointestinal disorders
- Insomnia
- Migraine headaches
- Harm reduction, alternative to opioids . . .
- Spastic disorders
- Autoimmune disorders
- Neurodegenerative disorders
- Glaucoma
- Skin diseases
- Epilepsy, Autism, Tourettes, ADD, Dystonia, Dementia
- AIDS and other infections

46

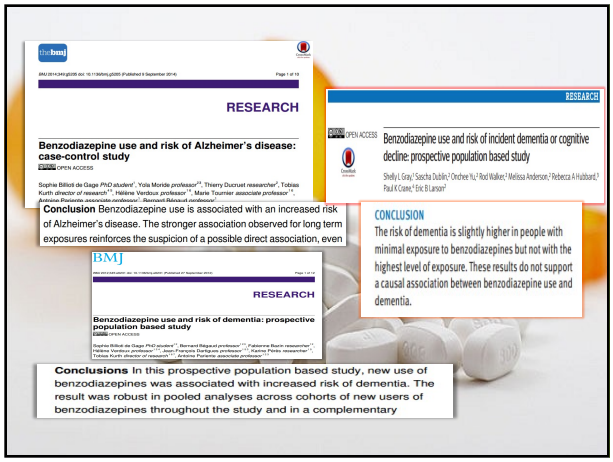
Cannabis for Therapeutic Purposes

47

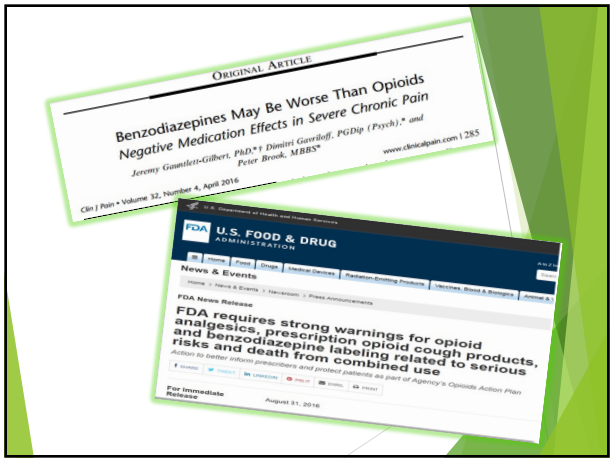
Cannabis & Mental Health

Cannabis Access for Medical Purposes Study (CAMPS)	N=628
Sleep	85%
Pain	82%
Anxiety	78%
Depression	66%
Appetite/ Weight	56%
Nausea	49%

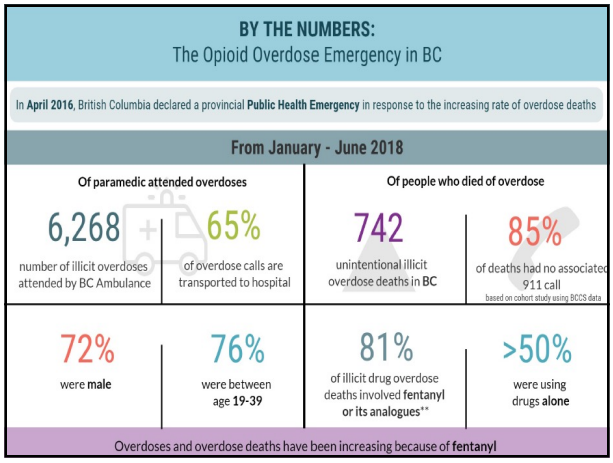
48


RESEARCH
Benzodiazepine use and risk of Alzheimer's disease: case-control study
Conclusion Benzodiazepine use is associated with an increased risk of Alzheimer's disease. The stronger association observed for long term exposures reinforces the suspicion of a possible direct association, even
RESEARCH
Benzodiazepine use and risk of incident dementia or cognitive decline: prospective population based study
CONCLUSION
The risk of dementia is slightly higher in people with minimal exposure to benzodiazepines but not with the highest level of exposure. These results do not support a causal association between benzodiazepine use and dementia.
BMJ
RESEARCH
Benzodiazepine use and risk of dementia: prospective population based study
Conclusions In this prospective population based study, new use of benzodiazepines was associated with increased risk of dementia. The result was robust in pooled analyses across cohorts of new users of benzodiazepines throughout the study and in a complementary

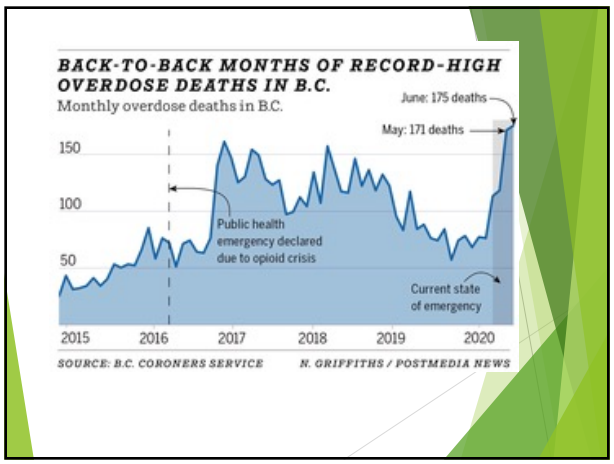
49


ORIGINAL ARTICLE
Benzodiazepines May Be Worse Than Opioids
Negative Medication Effects in Severe Chronic Pain
Jeremy Gauntlett-Gilbert, PhD,*† Dimitri Gavriloff, PGDip (Psych),* and Peter Brook, MBBS*
Clin J Pain • Volume 32, Number 4, April 2016
U.S. FOOD & DRUG ADMINISTRATION
News & Events
FDA News Release
FDA requires strong warnings for opioid analgesics, prescription opioid cough products, and benzodiazepine labeling related to serious risks and death from combined use
Action to better inform prescribers and protect patients as part of Agency's Opioids Action Plan
For Immediate Release
August 31, 2016

50


BY THE NUMBERS:
The Opioid Overdose Emergency in BC
In April 2016, British Columbia declared a provincial Public Health Emergency in response to the increasing rate of overdose deaths
From January - June 2018
Of paramedic attended overdoses
6,268
number of illicit overdoses attended by BC Ambulance
65%
of overdose calls are transported to hospital
Of people who died of overdose
742
unintentional illicit overdose deaths in BC
85%
of deaths had no associated 911 call
based on cohort study using BCCS data
72%
were male
76%
were between age 19-39
81%
of illicit drug overdose deaths involved fentanyl or its analogues**
>50%
were using drugs alone
Overdoses and overdose deaths have been increasing because of fentanyl

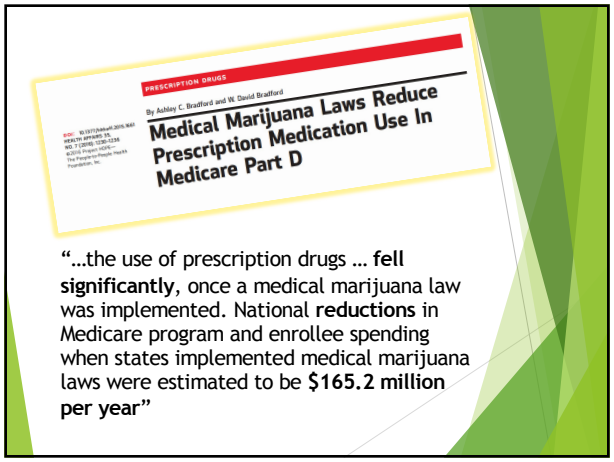
51


BACK-TO-BACK MONTHS OF RECORD-HIGH OVERDOSE DEATHS IN B.C.
Monthly overdose deaths in B.C.
June: 175 deaths
May: 171 deaths
150
100
50
Public health emergency declared due to opioid crisis
Current state of emergency
2015
2016
2017
2018
2019
2020
SOURCE: B.C. CORONERS SERVICE
N. GRIFFITHS / POSTMEDIA NEWS

52


Global NEWS
Okanagan
TV News Programs
More people using pot as substitute for pills and booze
Drug and Alcohol REVIEW
Drug and Alcohol Review (2015)
DOI: 10.1111/dar.12323
Substituting cannabis for prescription drugs, alcohol and other substances among medical cannabis patients: The impact of contextual factors
PHILIPPE LUCAS[1], ZACH WALSH[2], KIM CROSBY[3], ROBERT CALLAWAY[4], LYNNE BELLE-ISLE[1,5], ROBERT KAY[6], RIELLE CAPLER[7] & SUSAN HOLTZMAN[8]

53


PRESCRIPTION DRUGS
By Ashley C. Bradford and W. David Bradford
Medical Marijuana Laws Reduce Prescription Medication Use In Medicare Part D
"…the use of prescription drugs … **fell significantly**, once a medical marijuana law was implemented. National **reductions** in Medicare program and enrollee spending when states implemented medical marijuana laws were estimated to be **$165.2 million per year**"

54

Substituting Cannabis

55

Cannabis, Pain, & Anxiety

"I saw in it (cannabis)a means of effectively combating the fixed ideas of depressives, disruptin the chain of their ideas, of unfocusing their attention …

Jacques-Joseph Moreau (1845)

56

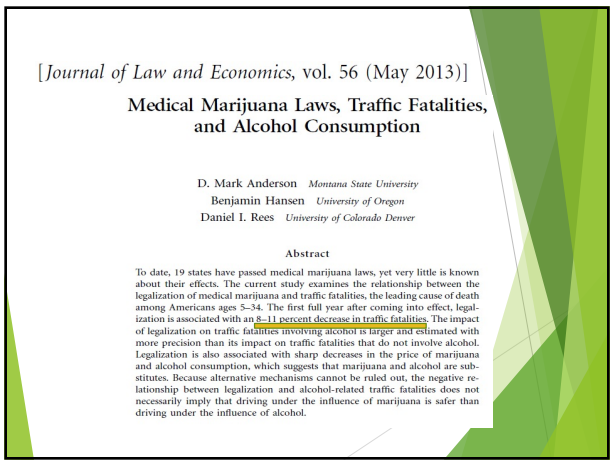
Substituting cannabis for alcohol

UBC students (n=253)

When using cannabis	
Don't drink as quickly	71%
Don't drink as much	53%
Don't desire alcohol	34%
Crave alcohol	0%

Walsh, Crosby & Lucas, *in prep*

57



[*Journal of Law and Economics*, vol. 56 (May 2013)]

Medical Marijuana Laws, Traffic Fatalities, and Alcohol Consumption

D. Mark Anderson *Montana State University*
Benjamin Hansen *University of Oregon*
Daniel I. Rees *University of Colorado Denver*

Abstract

To date, 19 states have passed medical marijuana laws, yet very little is known about their effects. The current study examines the relationship between the legalization of medical marijuana and traffic fatalities, the leading cause of death among Americans ages 5–34. The first full year after coming into effect, legalization is associated with an 8–11 percent decrease in traffic fatalities. The impact of legalization on traffic fatalities involving alcohol is larger and estimated with more precision than its impact on traffic fatalities that do not involve alcohol. Legalization is also associated with sharp decreases in the price of marijuana and alcohol consumption, which suggests that marijuana and alcohol are substitutes. Because alternative mechanisms cannot be ruled out, the negative relationship between legalization and alcohol-related traffic fatalities does not necessarily imply that driving under the influence of marijuana is safer than driving under the influence of alcohol.

58

Addictive Behaviors

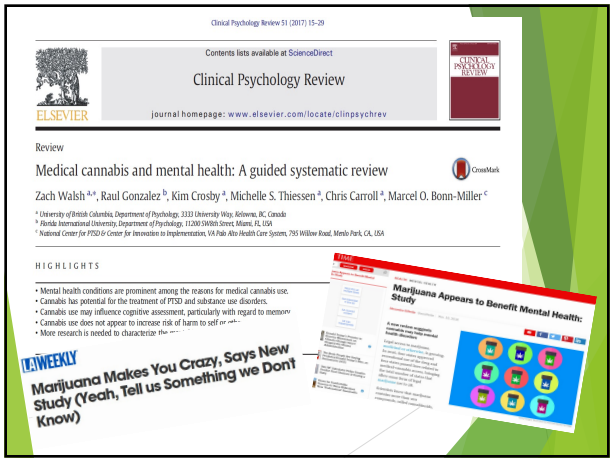
Intentional cannabis use to reduce crack cocaine use in a Canadian setting: A longitudinal analysis

Drug and Alcohol Review

Cannabis use is associated with lower rates of initiation of injection drug use among street-involved youth: A longitudinal analysis

HUDSON REDDON, KORA DEBECK, MARIA EUGENIA SOCIAS, HUIRU DONG, EVAN WOOD, JULIO MONTANER, THOMAS KERR & MICHAEL-JOHN MILLOY

59



Clinical Psychology Review

Review

Medical cannabis and mental health: A guided systematic review

Zach Walsh, Raul Gonzalez, Kim Crosby, Michelle S. Thiessen, Chris Carroll, Marcel O. Bonn-Miller

HIGHLIGHTS

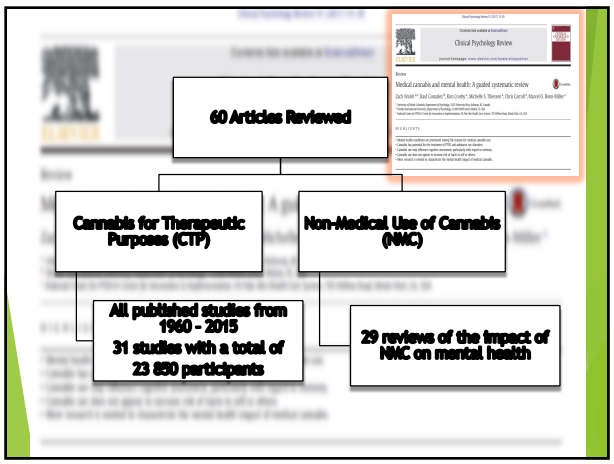
- Mental health conditions are prominent among the reasons for medical cannabis use.
- Cannabis has potential for the treatment of PTSD and substance use disorders.
- Cannabis use may influence cognitive assessment, particularly with regard to memory
- Cannabis use does not appear to increase risk of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

Marijuana Appears to Benefit Mental Health: Study

LA WEEKLY

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

60



61

Overview - Anxiety

- Anxiety disorders - Overview
- Cannabis and general anxiety
- Cannabis and social anxiety disorder
- Cannabis substitution for benzodiazepines
- CBD
- Summary / conclusions

62

Generalized Anxiety Disorder

Associated with three (or more) of the following six symptoms (with at least some symptoms having been present for more days than not for the past 6 months);

1. Restlessness or feeling keyed up or on edge.
2. Being easily fatigued.
3. Difficulty concentrating or mind going blank.
4. Irritability.
5. Muscle tension.
6. Sleep disturbance.

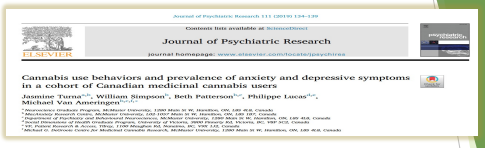
(American Psychiatric Association, 2013)

63

Human studies – Medical

- **Anxiety**
  - 8 Cross-sectional studies of medical
    - 5 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

64



Cannabis use behaviors and prevalence of anxiety and depressive symptoms in a cohort of Canadian medicinal cannabis users

888/2032 (43.7%) reported authorization to treat anxiety symptoms

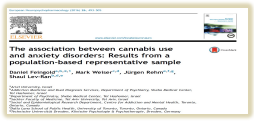
46% Generalized Anxiety Disorder
42% Social Anxiety Disorder
26% Panic Disorder/Agoraphobia
26% Major Depressive Disorder

63% met screening criteria for ≥1 disorder

92% – Cannabis improved symptoms	
1	Anxiety
2	Irritability
3	Sleep onset
4	Anxiety attack
5	Low mood
6	Muscle tension
7	Restlessness
8	Sleep interruption

65

Human studies – Harms?



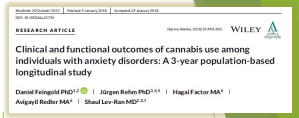
The association between cannabis use and anxiety disorders: Results from a population-based representative sample

Large longitudinal epidemiological study National Epidemiological Study of Alcohol and Related Conditions(NESARC)

3yrs & >30, 000 participants

Cannabis use was not associated with development of any anxiety disorder

Individuals with baseline panic disorder were more prone to initiate cannabis use at follow-up – medical?



Clinical and functional outcomes of cannabis use among individuals with anxiety disorders: A 3-year population-based longitudinal study

NESARC focusing on social anxiety, panic disorder, generalized anxiety disorder, and specific phobias (N = 3,723).

Compared cannabis users and non users in rates of remission, suicidality, general functioning, and quality of life

With control factors in analyses - no differences in outcome.

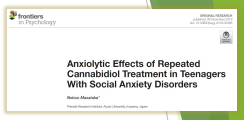
"poorer outcome of anxiety disorders among cannabis users may be attributed, mainly to differences in baseline factors and not cannabis use."

66

Human studies – SAD


Clinical Psychology Review

Medical cannabis and mental health: A guided systematic review


Anxiolytic Effects of Repeated Cannabidiol Treatment in Teenagers With Social Anxiety Disorders

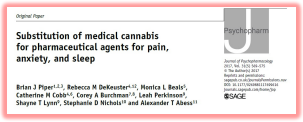
- Socially anxious > cannabis use to relieve symptoms than individuals with other anxiety d/o
- Nonmedical cannabis use among the socially anxious may be associated with cannabis-related problems
  - SAD typically precedes the development of problematic cannabis use
- CBD use is associated with:
  - decreased subjective anxiety among SAD patients
  - decreased cognitive impairment and anxiety in a simulated public speaking task

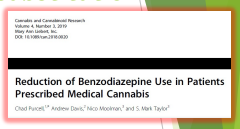
- 300mg CBD/ day – 4 weeks
- 18-19 y/o w/ SAD and Avoidant PD
  - (N= 17 CBD v 20 placebo)
- Significant reductions in anxiety in the CBD group

"many of the participants treated with CBD became positive in their attitude toward seeking treatment."

67

Cannabis – benzodiazepine substitution


Substitution of medical cannabis for pharmaceutical agents for pain, anxiety, and sleep


Reduction of Benzodiazepine Use in Patients Prescribed Medical Cannabis

- Dispensary members (n = 1513) survey
- 72% decreased use of benzodiazepines
  - Over half decreased "a lot"
- 77% reduced opioids
- 38% antidepressants

- Benzodiazepines using patients (n = 146) from a cannabis clinic
- 30% discontinued benzodiazepines after 2-month
- 45% after 4 & 6 months

68

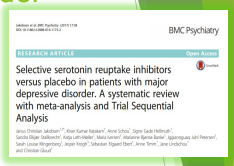
Cannabis & Anxiety – Summary

- Anxiety is among the most frequently cited reasons for using medical cannabis
- Patients report relief of symptoms including irritability, agitation, sleep
- Cannabis use does not appear to lead to development of anxiety d/o
- Cannabis use does not appear to worsen outcomes among those with anxiety d/o
  - BUT anxiety can be a symptom of cannabis overdose and withdrawal
- Cannabis is being used as a substitute for benzodiazepines
  - Comparative efficacy trials required
- Preliminary evidence suggests that CBD isolate has anxiolytic effects independent of THC or herbal cannabis
- No RCT has examined the effectiveness of cannabis versus placebo

69

Major Depressive Disorder

- 7% - prevalence
- Negative Affect is a well-established risk factor -
  - Traits/ personality
  - Refractory?
- Among largest contributors to non-fatal health loss
- Annual cost >200B$ in US
- High comorbidity
  - Anxiety
  - Substance use - including cannabis
- Extant treatments - behavioral therapy and pharmacotherapy
- High proportion of US adults prescribed antidepressants
  - adverse effects
  - questionable effectiveness


BMC Psychiatry

RESEARCH ARTICLE Open Access

Selective serotonin reuptake inhibitors versus placebo in patients with major depressive disorder. A systematic review with meta-analysis and Trial Sequential Analysis

"Our results show that the harmful effects of SSRIs versus placebo for major depressive disorder seem to outweigh any potentially small beneficial effects."

70

Major Depression

- 1. Depressed mood most of the day, nearly every day*
- 2. Diminished interest or pleasure in all, or almost all, activities*
- 3. Significant weight loss when not dieting or weight gain
- 4. Insomnia or hypersomnia nearly every day.
- 5. Psychomotor agitation or retardation
- 6. Fatigue or loss of energy
- 7. Feelings of worthlessness or excessive or inappropriate guilt
- 8. Diminished ability to think or concentrate, or indecisiveness
- 9. Recurrent thoughts of death / suicidal ideation

(American Psychiatric Association, 2013)

71

Cannabis & Depression - Mood


Pharmacology, Biochemistry and Behavior

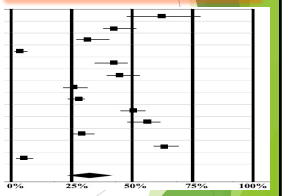
Acute and residual mood and cognitive performance of young adults following smoked cannabis

- Healthy adults (n=91) – pre, 1h, 24h, 48h
  - smoked 12.5% THC cannabis vs placebo
- 1h - Increased Arousal and Positive Mood, Friendliness, Elation, Confusion
- 24h - Increases in Friendliness and Elation for 24 h.
- No evidence of residual cognitive impairment.

72

Cannabis & Depression

Cannabis Access for Medical Purposes Study (CAMPS)	N=628
Sleep	85%
Pain	82%
Anxiety	78%
Depression	66%
Appetite/ Weight	56%
Nausea	49%



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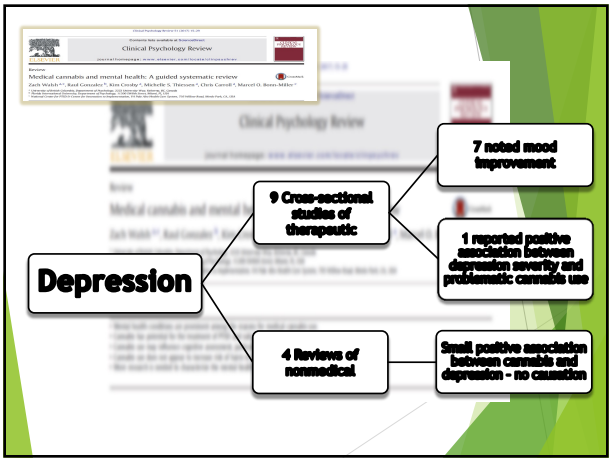


74

Cannabis & Bipolar Disorder

- Anecdotal reports suggest that some individuals use cannabis to effectively treat symptoms of bipolar disorder (BD)
- Narrative review suggested potential for managing manic and depressive symptoms
- Evidence of improved neurocognitive functioning in BD patients who use cannabis
- Reviews concluded that non-medical cannabis use among those with BD may:
  - prolong or worsen manic states
  - increased odds of suicide attempts
  - earlier age of BD onset
  - psychosis
  - more severe course of illness

75

Cannabis & Bipolar Disorder

- 35 studies (n=51,756; female: 60%),
- 24% cannabis use among Bipolar D/O
- Cannabis users were younger at first episode
- More lifetime suicide attempts
- More lifetime psychotic symptoms
- No differences in:
  - rapid cycling
  - comorbid anxiety disorders

- Compared Bipolar to Major Depression
- BPD > frequency and quantity cannabis
- BPD> criteria for CUDs
- No differences in associations:
  - rates of other co-morbid psychiatric d/o
  - treatment utilization
  - suicidality

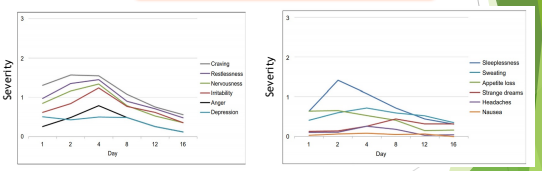
76

Cannabis and Depression - Summary

- Endocannabinoid system implicated in depression
- Mood improvement is a frequently cited motive among medical cannabis users
- Cannabis produces short term improvements in mood
- Evidence is mixed with regard to reduction in motivation
- Cannabis use is prevalent among those with bipolar depression
  - Similar outcomes to major depression
  - Some additional cautions regarding psychosis risk
- Cannabis may be particularly helpful for relieving negative mood in the context of chronic pain

77

Withdrawal



78

Cannabis Anxiolytics & Antidepressants

REVIEW

WILEY

Is cannabis treatment for anxiety, mood, and related disorders ready for prime time?

Jasmine Turna BSc, PhD(c)[1,2] | Beth Patterson BScN, MSc[1,3] | Michael Van Ameringen MD, FRCPC[1,3,4]

- Extant treatment evidence is a few small, primarily single-dose studies.
- Not whole plant

"...it may be difficult to objectively place cannabis in the armamentarium of psychopharmacological treatments until further research is conducted and treatment guidelines developed"

79

Cannabis and sleep - preclinical

frontiers in Molecular Neuroscience

Cannabinoids, Endocannabinoids and Sleep

- Endocannabinoids are important in sleep and sleep neurophysiology
- Sleep patterns clearly altered by cannabinoid drugs
- Cannabis /THC
  - decreased sleep onset latency,
  - decreased waking after sleep onset
  - increased slow-wave sleep and decreased REM sleep

80

Cannabis and sleep

International Journal of Drug Policy

Editors' choice

Cannabis for therapeutic purposes: Patient characteristics, access, and reasons for use

International Journal of Drug Policy

Research paper

Medical cannabis access, use, and substitution for prescription opioids and other substances: A survey of authorized medical cannabis patients

Cannabis Access for Medical Purposes Study (CAMPS)	N=628
Sleep	85%
Pain	82%
Anxiety	78%
Depression	66%
Appetite/ Weight	56%
Nausea	49%

Licensed producer survey	N=271
Pain	73%
Stress	60%
Insomnia	57%
Depression	46%
Headache	32%

81

Cannabis and sleep

- Patients may decrease their use of pharmaceutical sleep medication
- Relatively rapid tolerance with regular use
- Withdrawal/ cessation associated with:
  - Decreases in total sleep time
  - Decreased sleep efficiency
  - Increased Latency to sleep onset
  - Increased wake after sleep

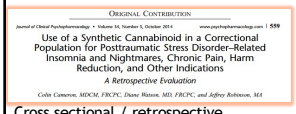
82

Cannabis and sleep

- Studies are flawed
- Cannabis use associated with decrease in slow wave sleep & increase in stage 2
- No effect on total sleep time.
- Reduced disturbance & better sleep quality with a medical condition (e.g. pain, spasticity, PTSD)
  - Secondary effects of cannabinoids
- More research needed on dose

83

Cannabis & nightmares

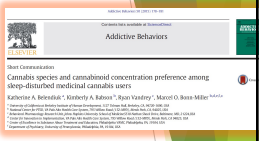


Cross sectional / retrospective

Reduced PTSD symptoms

Improved sleep & nightmares

Discontinuation of meds (e.g. opioids, benzos)



Dispensary sample

n = 163 – 81 insomnia & 14 nightmare

Reported "sativa" preference for reduced nightmares

Higher CBD preference for insomnia

Small trial from PTSD clinic (n=10)

Reduced nightmares

General clinical improvement

84

Cannabis and sleep – Summary

- Clear role for endocannabinoid system in sleep
- Use for sleep disturbance is common among medical users
- May be most effective for sleep in the context of other symptoms
  - Pain, PTSD
- Cannabis withdrawal involves sleep disturbance
- Nabilone reduces nightmares
- Preliminary evidence of high-CBD cannabis preference for insomnia
- More research needed

85

Cannabis and madness

"The deleterious, even vicious, qualities of the drug render it highly dangerous to the mind and body upon which it operates to destroy the will, cause one to lose the power of connected thought, producing imaginary delectable situations and gradually weakening the physical powers.

Its use frequently leads to insanity."
Harry Anslinger, 1937
1st Commissioner of the Federal Bureau of Narcotics

86

Cannabis and madness

FEBRUARY 14, 2019

RESOURCE

We are the Drug Policy Alliance.

Letter from Scholars and Clinicians who Oppose Junk Science about Marijuana

When research is misrepresented to uphold and perpetuate the worst myths about people of color and people with mental illness, we are required to speak up.

We urge policymakers and the public to rely on scientific evidence, not flawed pop science and ideological polemics, in formulating their opinions about marijuana legalization.

https://www.drugpolicy.org/resource/letter-scholars-and-clinicians-who-oppose-junk-science-about-marijuana

87

Clinical


European Archives of Psychiatry and Clinical Neuroscience (2020) 270:403–412
https://doi.org/10.1007/s00406-019-01068-z

ORIGINAL PAPER

Cannabis use and psychosis: a review of reviews

Alkomiet Hasan[1] · Rupert von Keller[1] · Chris Maria Friemel[1] · Wayne Hall[2] · Miriam Schneider[3] · Dagmar Koethe[4,5] · F. Markus Leweke[4,6] · Wolfgang Strube[1] · Eva Hoch[1,7]

Received: 26 September 2018 / Accepted: 18 September 2019 / Published online: 28 September 2019
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1 - Does the prevalence of psychotic disorders differ according to cannabis use?

2- Do cannabis users have earlier onsets of psychotic illnesses?

3- Differences between cannabis users and non-users with psychotic illnesses?

4- Biological link between cannabis use of and the development of psychosis?

Largest meta-analyses n = 90,818 participants & and the largest systematic review 113,802 participants

(American Psychiatric Association, 2013)

88

Clinical


European Archives of Psychiatry and Clinical Neuroscience (2020) 270:403–412
https://doi.org/10.1007/s00406-019-01068-z

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Received: 26 September 2018 / Accepted: 18 September 2019 / Published online: 28 September 2019
© Springer-Verlag GmbH Germany, part of Springer Nature 2019

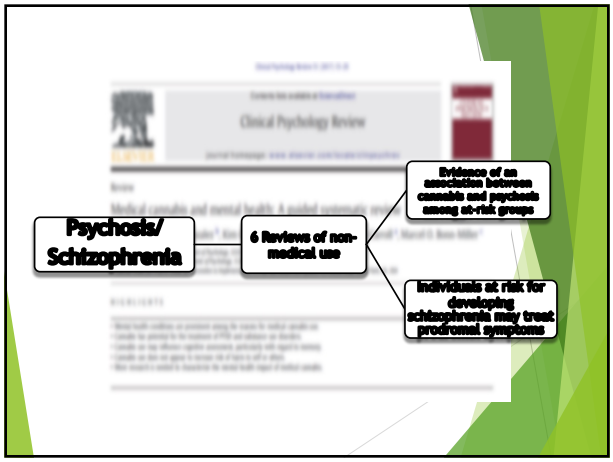
1 - Does the prevalence of psychotic disorders differ according to cannabis use?
YES - Dose-dependent

2- Do cannabis users have earlier onsets of psychotic illnesses?
YES - 2-3 years earlier

3- Differences between cannabis users and non-users with psychotic illnesses?
MIXED – may worsen positive symptoms, relapse, hospitalizations – NOT duration, suicidality

4- Biological link between cannabis use of and the development of psychosis?
NO clear relationship

89



90

91

Clinical

ORIGINAL ARTICLE

Association between alcohol, cannabis, and other illicit substance abuse and risk of developing schizophrenia: a nationwide population based register study

S. M. Nielsen[1,2], N. G. Toftdahl[1,2], M. Nordentoft[1,2] and C. Hjorthøj[1,2]*

- Danish survey >3m ; 200k SUD, 20k Schz
- Any SUD increased risk of developing schizophrenia [hazard ratio (HR) 6.04 (CI) 5.84-6.26].
  - Cannabis (HR 5.20, 95% CI 4.86-5.57)
  - Alcohol (HR 3.38, 95% CI 3.24-3.53)
  - Hallucinogens (HR 1.86, 95% CI 1.43-2.41),
  - Sedatives (HR 1.68, 95% CI 1.49-1.90)
  - Other substances (HR 2.85, 95% CI 2.58-3.15)
- Associations between "almost any type" of SUD and schizophrenia

92

Clinical – Causal versus co-occuring

SUBSTANCE USE AND RELATED DISORDERS (F LEVIN AND E DAKWAR, SECTION EDITORS)

Cannabis and Psychosis: a Critical Overview of the Relationship

- > 100 papers/ year 2012-2015 versus < 10/yr 1990s

- Current /prior cannabis associated with 1st episode psychosis/ schizophrenia
- Cannabis use is part of a cluster of "general deviant behavior"
- Schizophrenia is linked to diverse array of variables

"Future research studies that focus exclusively on the cannabis-psychosis association will therefore be of little value in our quest to better understand psychosis and how and why it occurs."

93

CBD & Psychosis

Cannabidiol (CBD) as an Adjunctive Therapy in Schizophrenia: A Multicenter Randomized Controlled Trial

Philip McGuire, F.R.C.Psych., F.Med.Sci., Philip Robson, M.R.C.P., F.R.C.Psych., Wesslee Jerzy Cubala, M.D., Ph.D., Daniel Vasile, M.D., Ph.D., Paul Dugald Morrison, Ph.D., M.R.C.Psych., Rachel Barron, B.Vet.Med., M.R.C.V.S., Adam Taylor, Ph.D., Stephen Wright, F.R.C.P.(Edin), F.F.P.M.

- Large dose of single molecule isolate
  - CBD 1000 mg/day (N=43) /placebo (N=45)
- At 6 weeks the CBD group had:
  - Lower positive symptoms
  - Higher rate of improvement
- Well tolerated / no difference in adverse events

Psychological Medicine

cambridge.org/psm

Normalization of mediotemporal and prefrontal activity, and mediotemporal-striatal connectivity, may underlie antipsychotic effects of cannabidiol in psychosis

Original Article

Aisling O'Neill[1], Robin Wilson[1], Grace Blest-Hopley[1], Luciano Annibale[1], Marco Colizzi[2,3], Mick Brammer[1], Vincent Giampietro[1] and Sagnik Bhattacharyya[1]

- One time/ single dose of CBD (600 mg)
- FMRI indicated CBD attenuated acute dysfunction in mediotemporal and prefrontal activation & mediotemporal-striatal function during experimental task
- Psychosis patients w/ CBD (13) were intermediate between controls (19) and placebo
- Trend-level symptom reduction in psychosis patients at 5.5hrs.

94

Schizophrenia – Summary

- Exaggerated and lurid depictions of the association between cannabis and psychosis are an enduring aspect of cannabis related-stigma from the early days of prohibition to the current backlash against progressive cannabis policy
- The etiology of both psychotic disorders and substance use is complex and multidetermined
  - The ECS likely has a role
- Individuals with psychotic disorders are more likely to use cannabis
  - This use often precedes formal diagnosis of psychosis
- Individuals with psychotic disorders who use cannabis demonstrate earlier onset and worse course of treatment
- The preponderance of evidence suggests shared vulnerabilities rather than a casual relationship
- CBD may have anti-psychotic effects

95

Psychology of Addictive Behaviors

Couples' Marijuana Use Is Inversely Related to Their Intimate Partner Violence Over the First 9 Years of Marriage

Philip H. Smith
University at Buffalo, SUNY and Yale University

Gregory G. Homish, R. Lorraine Collins, and Gary A. Giovino
University at Buffalo, SUNY

Helene R. White
Rutgers University

Kenneth E. Leonard
University at Buffalo, SUNY

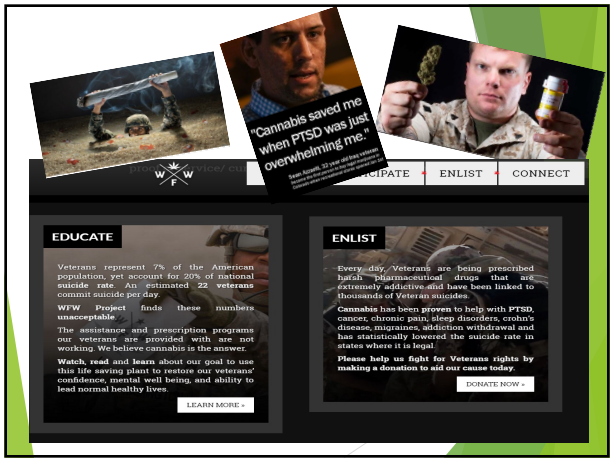
more frequent marijuana use by husbands and wives predicted less frequent IPV perpetration by husbands. Husbands' marijuana use also predicted less frequent IPV perpetration by wives. Moderation analyses demonstrated that couples in which both spouses used marijuana frequently reported the least frequent IPV perpetration. There was a significant positive association between wives' marijuana use and

96

History – PTSD & Cannabis

- Patient/combat veterans have taken a leading role in advocacy
- CNN WEEDS 3 Documentary – 2015
- US VA – will not recommend
- Canada – Vets only group to get federal coverage for cannabis
- Advocacy continues – several groups e.g Veterans for Medical Cannabis Access

97



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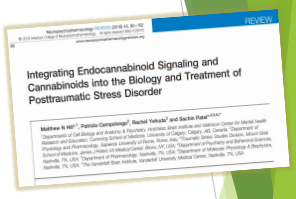
99

Preclinical - summary



"…deficiencies in eCB signaling can result in:

- hyperactivity of the amygdala
- hypoactivity of the mPFC
- impaired regulation of the stress response
- elevated levels of basal and stress-induced anxiety
- increased retrieval and impaired extinction of emotionally aversive memories
- increased propensity to develop a state of inflammation."

100

PTSD Symptoms I

CRITERION A - Experience traumatic event

CRITERION B - Intrusion

Presence of one (or more) of the following intrusion symptoms associated with the traumatic event(s), beginning after the event(s) occurred:

1. Recurrent, involuntary, and intrusive distressing memories of the traumatic event(s)
2. Recurrent distressing dreams in which the content and/or affect of the dream are related to the traumatic event.
3. Dissociative reactions (e.g., flashbacks) in which the individual feels or acts as if the event(s) were recurring.
4. Intense or prolonged psychological distress at exposure to internal or external cues that symbolize or resemble an aspect of the traumatic event(s).
5. Marked physiological reaction to external or internal cues that symbolize or resemble an aspect of the traumatic event(s).

CRITERION C - Avoidance

Persistent avoidance of stimuli associated with the traumatic event(s), beginning after the traumatic event(s) occurred, as evidenced by one or both of the following:

1. Avoidance of or efforts to avoid distressing memories, thoughts, or feelings about or closely associated with the traumatic event(s).
2. Avoidance of or efforts to avoid external reminders (people, places, conversations, activities, objects, situations) that arouse distressing memories, thoughts, or feelings about or closely associated with the traumatic event(s).

(American Psychiatric Association, 2013)

101

PTSD Symptoms - II

D -Negative Alterations in Cognition & Mood

1. Inability to remember an important aspect of the traumatic event
2. Persistent and exaggerated negative beliefs or expectations about oneself, others, or the world
3. Persistent, distorted cognitions about the cause or consequences of the traumatic event(s) that leads the individual to blame self or others.
4. Persistent negative emotional state .
5. Marked diminished interest or participation in significant activities.
6. Feelings of detachment or estrangement from others.
7. Persistent inability to experience positive emotions (e.g., happiness, satisfaction, or loving feelings).

E - Arousal & Reactivity

1. Irritable behavior and angry outbursts (with little or no provocation) typically expressed as verbal or physical aggression toward people or objects.
2. Reckless or self-destructive behavior.
3. Hypervigilance.
4. Exaggerated startle response.
5. Problems with concentration.
6. Sleep disturbance (e.g. problems falling or staying asleep or restless sleep).

(American Psychiatric Association, 2013)

102

Posttraumatic Stress Disorder

4 studies of CTP

Substantial portion treat PTSD symptoms with cannabis

Self-report of good outcomes

Effective for improving sleep and reducing nightmares

103

Human studies -II

Preliminary, Open-Label, Pilot Study of Add-On Oral Δ⁹-Tetrahydrocannabinol in Chronic Post-Traumatic Stress Disorder

- Small open label trial from PTSD clinic (n=10)
- Reduced symptom severity
- Improved sleep & nightmares
- Reduced hyperarousal

PTSD Symptom Reports of Patients Evaluated for the New Mexico Medical Cannabis Program

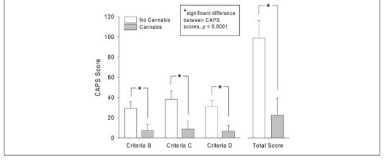
- Cross sectional / retrospective
- Recruited from cannabis clinic
- Notable reductions in:
  - re-experiencing
  - avoidance
  - hyperarousal

104

PTSD Symptom Reports of Patients Evaluated for the New Mexico Medical Cannabis Program

Greer et al., 2014	80 (20)	New Mexico, US	Medical evaluations of patients seeking CTP	PTSD	Cross-sectional (5)	Patients who used CTP reported reductions of 75% in symptoms of trauma related re-experiencing, avoidance, and hyperarousal.

FIGURE 1
CAPS Scores for the No-Cannabis and Cannabis Conditions. Data Are Expressed as Group Means ± S.D.
*Significant Difference Between CAPS Scores, $p < 0.0001$.



105

106

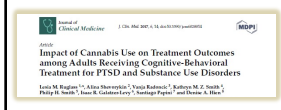
Recent updates I

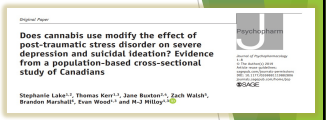
- Elevated hyperarousal symptoms are associated with anxiety-related cannabis use
- Higher hyperarousal patients reported greater anxiolytic effects relative to those with more avoidance and reexperiencing symptoms
- Consistent with a negative reinforcements model of PTSD and cannabis use

- Large prospective study in VA
- PTSD associated with later development of problematic cannabis use
- Cannabis use associated with greater intrusion symptoms at 6 months
- "Coping-oriented pattern of heightened avoidance of negative emotional states via cannabis use"
- Limitations -
  - No query of medical use
  - No reporting of other symptom groups

107

Recent updates II





- Baseline cannabis use was unrelated to endpoint (12-wk) PTSD or SUD.
- Higher cannabis use was associated with higher PTSD symptom severity early in treatment, but lower PTSD symptom severity later in treatment.
  - Cannabis use may be synergistic with CBT to reduce PTSD symptoms.
- As cannabis use increased primary substance use decreased and vice versa.
  - Substitution?

- Higher levels of cannabis use among those with PTSD.
- PTSD was associated with depression and suicidality among non-cannabis users
- PTSD was not associated with these outcomes among cannabis users

108

Recent updates III


Journal of Affective Disorders

Research paper

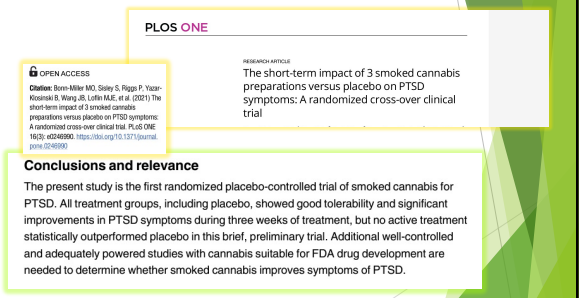
Short and Long-Term Effects of Cannabis on Symptoms of Post-Traumatic Stress Disorder

Emily M. LaFrance[a], Nicholas C. Glodosky[a], Marcel Bonn-Miller[b], Carrie Cuttler[b,c]

- 404 medical cannabis self-identified with PTSD were tracked with app
- >90% session resulted in acute reductions of over 50% in:
  - Intrusive thoughts
  - Flashbacks
  - Irritability
  - Anxiety
- PTSD symptoms did not change over time
- Doses increased over time
  - Tolerance?

109

Recent updates IV


PLOS ONE

RESEARCH ARTICLE

The short-term impact of 3 smoked cannabis preparations versus placebo on PTSD symptoms: A randomized cross-over clinical trial

OPEN ACCESS

Citation: Bonn-Miller MO, Sisley S, Riggs P, Yazar-Klosinski B, Wang JB, Loflin MJE, et al. (2021) The short-term impact of 3 smoked cannabis preparations versus placebo on PTSD symptoms: A randomized cross-over clinical trial. PLoS ONE 16(3): e0246990. https://doi.org/10.1371/journal.pone.0246990

Conclusions and relevance

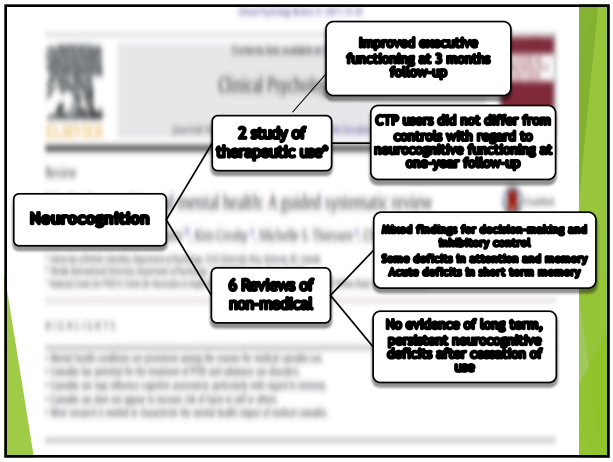
The present study is the first randomized placebo-controlled trial of smoked cannabis for PTSD. All treatment groups, including placebo, showed good tolerability and significant improvements in PTSD symptoms during three weeks of treatment, but no active treatment statistically outperformed placebo in this brief, preliminary trial. Additional well-controlled and adequately powered studies with cannabis suitable for FDA drug development are needed to determine whether smoked cannabis improves symptoms of PTSD.

110

PTSD SUMMARY

- Extant treatments are inadequate for many and consequences are severe
- Preclinical research has identified an etiological role for the ECS
- Substantial anecdote, advocacy and cross-sectional evidence in favour
- Nabilone reduced nightmares and improves sleep
- Longitudinal evidence is mixed - and methodologically limited
  - Some evidence for negative reinforcement/ exacerbation of avoidance
  - Some evidence for reduced anxiety, depression and suicidal ideation
- Evidence for acute symptom improvement with no long term gains

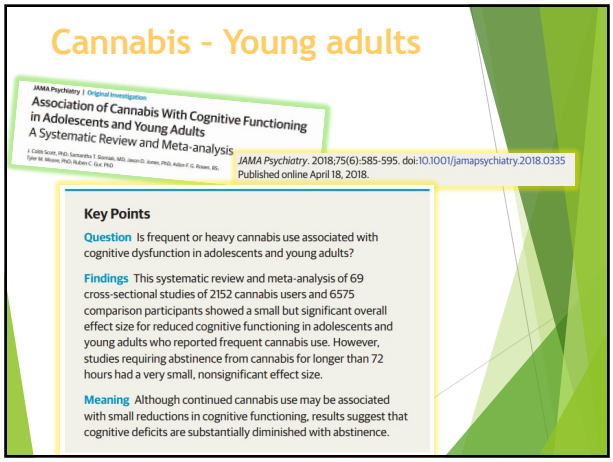
111


Neurocognition
2 study of therapeutic use⁶
Improved executive functioning at 3 months follow-up
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

112


Splendor in the Grass? A Pilot Study Assessing the Impact of Medical Marijuana on Executive Function
Results suggest that in general, MMJ patients experienced some improvement on measures of executive functioning, including the Stroop Color Word Test and Trail Making Test, mostly reflected as increased speed in completing tasks without a loss of accuracy. On self-report questionnaires, patients also indicated moderate improvements in clinical state, including reduced sleep disturbance, decreased symptoms of depression, attenuated impulsivity, and positive changes in some aspects of quality of life. Additionally, patients reported a notable decrease in their use of conventional pharmaceutical agents from baseline, with opiate use declining more than 42%. While intriguing, these findings are preliminary and warrant further investigation
Structural neuroimaging correlates of alcohol and cannabis use in adolescents and adults
Drug and Alcohol Dependence
A longitudinal examination of the relationship between cannabis use and cognitive function in mid-life adults
Findings
Conclusions: Mid-life cannabis users had poorer verbal recall than non-users, but this was not related to their current level of cannabis use, and cannabis use was not associated with accelerated cognitive decline.

113


Cannabis - Young adults
JAMA Psychiatry | Original Investigation
Association of Cannabis With Cognitive Functioning in Adolescents and Young Adults
A Systematic Review and Meta-analysis
JAMA Psychiatry. 2018;75(6):585-595. doi:10.1001/jamapsychiatry.2018.0335
Published online April 18, 2018.
Key Points
Question Is frequent or heavy cannabis use associated with cognitive dysfunction in adolescents and young adults?
Findings This systematic review and meta-analysis of 69 cross-sectional studies of 2152 cannabis users and 6575 comparison participants showed a small but significant overall effect size for reduced cognitive functioning in adolescents and young adults who reported frequent cannabis use. However, studies requiring abstinence from cannabis for longer than 72 hours had a very small, nonsignificant effect size.
Meaning Although continued cannabis use may be associated with small reductions in cognitive functioning, results suggest that cognitive deficits are substantially diminished with abstinence.

114

Cannabis - Older adults

Literature Review

Marijuana Use Among Adults 50 Years or Older in the 21st Century

Gerontology & Geriatric Medicine
Volume 4: 1–14
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sagepub.com/journalsPermissions.nav
DOI: 10.1177/2333721418781668
journals.sagepub.com/home/ggm
SAGE

Shawnta L. Lloyd, MPH[1] and Catherine W. Striley, PhD, MSW, MPE[1]

Abstract

Background: Marijuana is the most commonly used illicit drug among older adults. As an older population grows in the United States that has a tolerant attitude toward marijuana use, the dynamics of marijuana use and the effects of marijuana on personal, social, and health outcomes among older adults require attention. **Objectives:** This review summarizes epidemiological literature on marijuana use among older adults. **Method:** A literature search was conducted using PubMed, AgeLine, and an online search engine from January 2000 to December 2017, resulting in 18 articles. **Results:** The greatest increase in marijuana use was observed among those in the older adult population 50 years or older, and those 65 years or older had the greatest increase in marijuana use in the older adult population. Common correlates of marijuana use among those in the older population included being male, being unmarried, having multiple chronic diseases, having psychological stress, and using other substances such as alcohol, tobacco, other illicit drugs, and prescription drugs. **Conclusion:** The increased use of marijuana in older populations requires surveillance and additional research to understand the use and effects of marijuana in older populations to avoid negative health outcomes.

115

Problems - Respiratory

Marijuana Use and the Risk of Lung and Upper Aerodigestive Tract Cancers: Results of a Population-Based Case-Control Study

SPECIAL ARTICLE

Effects of Marijuana Smoking on the Lung

116

Problems- Withdrawal

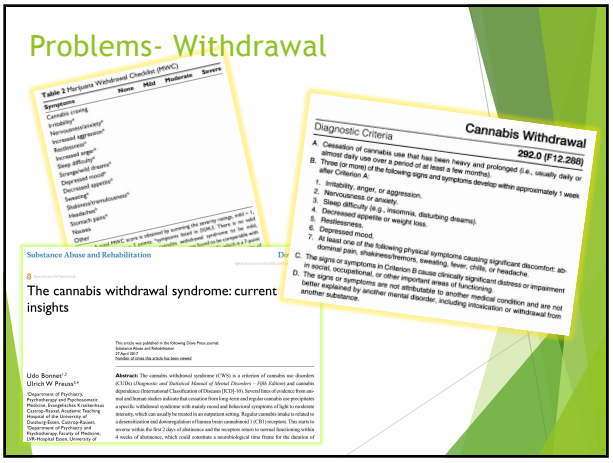


Table 2 Marijuana Withdrawal Checklist (MWC)

Symptoms	None	Mild	Moderate	Severe
Cannabis craving				
Irritability*				
Nervousness/anxiety*				
Increased aggression*				
Restlessness*				
Increased anger*				
Sleep difficulty*				
Strange/vivid dreams*				
Depressed mood*				
Decreased appetite*				
Sweating*				
Shakiness/tremulousness*				
Headaches*				
Stomach pains*				
Nausea				
Other				

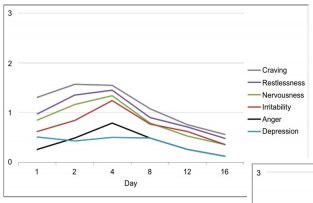
Substance Abuse and Rehabilitation

The cannabis withdrawal syndrome: current insights

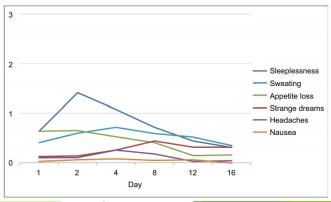
Diagnostic Criteria — Cannabis Withdrawal 292.0 (F12.288)

117

Problems- Withdrawal



The cannabis withdrawal syndrome: curr
insights



118

Treatment considerations

- Harm reduction
  - Edibles
- Use of CBD to reduce withdrawal

IMCJ Integrative Medicine: A Clinician's Journal

Cannabidiol Oil for Decreasing Addictive Use of Marijuana: A Case Report

UK Research and Innovation

Cannabidiol: a novel treatment for cannabis dependence?

119

Overdose

Green out

- *Canadian Institute of Health Information*
- 2017-2018 -2,266 ER visits (>25, 000 for other substances)
- Mostly from edibles
  - Dabbing
- Symptoms:
  - Paranoia
  - Anxiety
  - Lethargy
  - Extreme dry mouth
  - Burning eyes
  - Shortness of breath
  - Increased heart rate
  - Shaking / trembling
  - Chills / sweats
  - Disorientation / lack of focus
  - Nausea

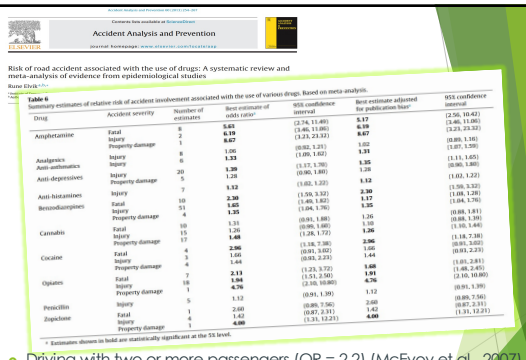
https://www.theleafnews.com/news/leaflet-Cannabis-overdoses-in-emergency-rooms-492201931.html

120

Cannabis & Driving

- Influence upon performance is short-lived
  - **Peak acute effects … obtained within 10 to 30 minutes** (NHTSA. 2004. *Drugs and Human Performance Facts Sheets*)
  - "impairment from cannabis **typically clears 3-4 hours after use**, a minimum wait period before driving." (Fischer et al., 2011. *Lower risk cannabis use guidelines for Canada*)
- Experienced users become tolerant
  - "Experienced smokers who drive on a set course show **almost no functional impairment** under the influence of marijuana."(Sewell et al., 2009. *The effect of cannabis compared with alcohol on driving*)
  - "Patients … develop tolerance to the impairment of psychomotor performance, **so that they can drive vehicles safely.**" (Grotenhermen and Mueller Vahl. 2012. *The therapeutic potential of cannabis and cannabinoids*)

121


Accident Analysis and Prevention

Risk of road accident associated with the use of drugs: A systematic review and meta-analysis of evidence from epidemiological studies

Rune Elvik

Table 6
Summary estimates of relative risk of accident involvement associated with the use of various drugs. Based on meta-analysis.

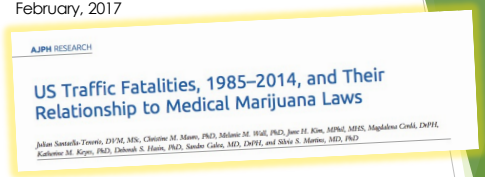
Drug	Accident severity	Number of estimates	Best estimate of odds ratio*	95% confidence interval	Best estimate adjusted for publication bias*	95% confidence interval
Amphetamine	Fatal	8	**5.83**	(2.74, 11.49)	**5.17**	(2.56, 10.42)
	Injury	2	**6.19**	(3.46, 11.06)	**6.19**	(3.46, 11.06)
	Property damage	1	**8.67**	(3.23, 23.32)	**8.67**	(3.23, 23.32)
Analgesics	Injury	8	1.06	(0.82, 1.21)	1.02	(0.80, 1.16)
Anti-asthmatics	Injury	6	**1.33**	(1.09, 1.62)	**1.31**	(1.07, 1.59)
Anti-depressives	Injury	20	**1.39**	(1.17, 1.78)	**1.35**	(1.11, 1.65)
	Property damage	5	1.28	(0.80, 1.80)	1.28	(0.80, 1.80)
Anti-histamines	Injury	7	**1.12**	(1.02, 1.23)	**1.12**	(1.02, 1.22)
Benzodiazepines	Fatal	10	**2.30**	(1.59, 3.32)	**2.30**	(1.59, 3.32)
	Injury	51	**1.65**	(1.49, 1.82)	**1.17**	(1.08, 1.28)
	Property damage	4	**1.35**	(1.04, 1.76)	**1.35**	(1.04, 1.76)
Cannabis	Fatal	10	1.31	(0.91, 1.88)	1.26	(0.88, 1.81)
	Injury	15	1.26	(0.99, 1.60)	1.10	(1.10, 1.44)
	Property damage	17	**1.48**	(1.28, 1.72)	**1.26**	(1.18, 7.18)
Cocaine	Fatal	4	**2.96**	(1.38, 7.38)	**2.96**	(0.93, 3.02)
	Injury	3	1.66	(0.91, 3.02)	1.66	(0.93, 2.23)
	Property damage	4	1.44	(0.93, 2.23)	1.44	(1.01, 2.81)
Opiates	Fatal	7	**2.13**	(1.23, 3.72)	**1.60**	(1.48, 2.45)
	Injury	18	**1.94**	(1.51, 2.50)	**1.91**	(2.10, 10.80)
	Property damage	1	**4.76**	(2.10, 10.80)	**4.76**	(0.91, 1.39)
Penicillin	Injury	5	1.12	(0.91, 1.39)	1.12	(0.89, 7.56)
Zopiclone	Fatal	1	2.60	(0.89, 7.56)	2.60	(0.87, 2.31)
	Injury	4	1.42	(0.87, 2.31)	1.42	(1.31, 12.21)
	Property damage	1	**4.00**	(1.31, 12.21)	**4.00**	

* Estimates shown in bold are statistically significant at the 5% level.

- Driving with two or more passengers (OR = 2.2) (McEvoy et al., 2007)
- Exceeding the speed limit by 3+ mph (OR = 1.89) (Kloeden et al., 2002)
- Using a mobile phone (OR = 4.1) (Redelmeier and Tibshirani, 1997)

122

February, 2017


AJPH RESEARCH

US Traffic Fatalities, 1985–2014, and Their Relationship to Medical Marijuana Laws

Julian Santaella-Tenorio, DVM, MSc, Christine M. Mauro, PhD, Melanie M. Wall, PhD, Jane H. Kim, MPhil, MHS, Magdalena Cerdá, DrPH, Katherine M. Keyes, PhD, Deborah S. Hasin, PhD, Sandro Galea, MD, DrPH, and Silvia S. Martins, MD, PhD

"Medical marijuana laws were associated with immediate reductions in traffic fatalities in those aged 15 to 44 years …Dispensaries were also associated with traffic fatality reductions in those aged 25 to 44 years."

123

Cannabis - Young adults

CSSDP CANADIAN STUDENTS FOR SENSIBLE DRUG POLICY

Sensible Cannabis Education
A Toolkit for Educating Youth

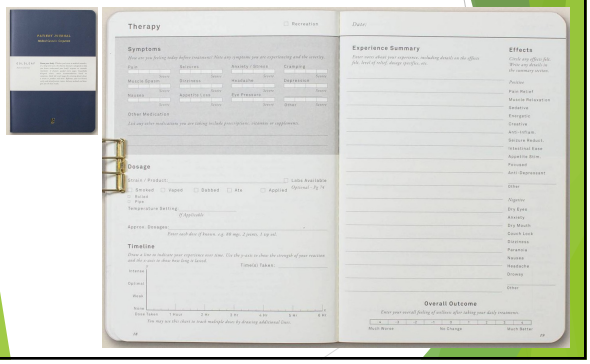
www.cssdp.org/youthtoolkit

1. 10 Principles for Approaching Cannabis Education with Young People

2. Pull Away Curriculum
   a. Cannabis 101
   b. Why Youth Use and Don't Use Cannabis
   c. Harm Reduction
   d. Legislative Overview
   e. Literature Review of Health Harms (as of Dec 2017

124

Mindful Cannabis Use



125

Jeffrey Y. Hergenrather, MD
General practice physician
Solo private practice
Cannabis consultations since 1997
Sebastopol, California

SOCIETY of CANNABIS CLINICIANS

President and founding member of
The Society of Cannabis Clinicians

126

Treatment plan

Dosing range: Titrate for desired effect (low and slow)

- Micro-dosing 1 ug/kg/day
- Average dosing:
- "High dose" 1-20 mg/kg/day

Frequency of dosing

- Episodic or as needed
- Daily administration: morning, evening or bedtime
- Multiple or frequent administrations daily
- Holidays

127

Treatment Plan

Method of Admininistration (MOA):

- ☐ Oral tincture, infusion, or spray, alcohol or oil based
- ☐ Full extract cannabis oil, FECO
- ☐ Other ingested flowers, products, or concentrates
- ☐ Vapor or smoke
- ☐ Suppositories
- ☐ Topical

Cannabinoid ratio: Preferred ratio of principle cannabinoids, THC:CBD.

- ☐ **High CBD** strain: CBD:THC (30:1 <-> 10:1) , (ACDC, Charlotte's Web, and others)
- ☐ **Balanced**: 6:1<-> **1:1** <-> 1:2 THC:CBD, nominally 1:1
- ☐ **High THC** strain: (THC:CBD ~ 100:1 <-> 50:1)
- ☐ **Other:** e.g. consider a High CBD tincture in the AM before breakfast and a balanced THC:CBD tincture at bedtime

Frequency: Frequency varies depending therapeutic goal, variations in the rate of hepatic metabolism, and MOA.

- ☐ Once daily
- ☐ Twice daily, AM before breakfast or PM, and bedtime
- ☐ Three times daily, every 8 hours ~ AM before breakfast, PM, and bedtime
- ☐ Other _____

128

Developing the Treatment Plan

Suggested Dose: Wide range in dosing depending on tolerance and individual differences.

Generally dosing is increased by slow titration to effective dose.

- ☐ 2 1/2 mg to 5 mg per dose
- ☐ 5 - 10 mg per dose
- ☐ 10 - 20 mg per dose
- ☐ 20 - 40 mg per dose
- ☐ ~ 50 mg per dose
- ☐ Other: e.g. Increase dose gradually and speadily..

Target dose: (SPECIAL CONDITIONS)

- ☐ Minimum target dose: _____ mg / day, (or mg/dose)
- ☐ Maximum target dose: _____mg / day, (or mg/dose)

Tolerance (a reminder): Develops with a steady, at least daily, dosing with induction of auto-regulation of cannabinoid CB1 receptor population (internalization of CB1 receptors). From onset tolerance develops in ~ 1-2 weeks,

Footnotes:

1. All products are considered to be organically grown and produced.
2. Products have accurately measured cannabinoid content and terpenes when available.
3. Hold dose if too sleepy
4. Drug-Drug interactions: For nearly all conventional pharmaceuticals there is no significant drug-drug interactions with cannabis/cannabinoids. Clobazam and other anti-epileptics drugs metabolized by the hepatic CYP 2C19 and CYP 3A4 families, with concurrent high doses of cannabis concentrates (> 1 mg/kg/day) should be monitored for safe and effective blood levels of these anti-epileptic medications.

129

Treatment Plan - Precautions

- Anxiety and panic in the neophyte or THC sensitive
- Syncope and/or fall risk especially with high dose "dabs"
- Smoking > bronchitis ~ No COPD, emphysema, or cancers
- Habit Forming ~ Not addictive, minor withdrawal
- Drug Drug interaction: CYP450 2C and 3A families
- Association with schizophrenia and psychosis
- Association with the hyperemesis syndrome

130

THANKS

http://blogs.ubc.ca/walshlab/ ZACHARY.WALSH@UBC.CA

131

Psychedelics & Psychedelic-Assisted Psychotherapy Primer

11-15-2023 – Richmond 12:45-4:00

Zach Walsh, PhD., R.Psych.

1

Disclosure

- Have conducted paid clinical work for MAPS.
- Member of advisory boards for Numinus, Mycomedica Life Sciences, EntheoTech and MAPS Canada. All of which are developing psychedelic psychotherapy options in Canada.
- Advisor to Quantified Citizen
- Funders of my research:

CIHR IRSC SSHRC CRSH Mitacs

2

Overview - Me

- Clinical psychologists (#2011)
- Trained in addictions treatment
  - University of Chicago
  - Brown University – Center for Alcohol and Addiction Treatment
- Professor– UBC
- Lead - Therapeutic Recreational & Therapeutic Substance Use lab
- Published and presented widely on psychedelic use and mental health
- Clinical team for MDMA for PTSD trials
- PI – Canada's 1st clinical trial of cannabis to treat mental health d/o
- Advisory boards of MAPS Canada
- CIHR & SSHRC funded studies of substance use

3

OVERVIEW – TODAY

12:45 -1:15

- Introduction to the psychedelic "renaissance"
  - Current regulatory status
  - The past 5 years
  - The next 5 years
- Psychedelic History
  - Indigenous technologies
  - Mainstream psychiatry
  - Criminalization
  - Renaissance

4

OVERVIEW - TODAY

1:15 - 1:45

- Categories and terminology
- Classic psychedelics
  - Psilocybin
    - LSD, Ayahuasca, DMT, Mescaline, Peyote
- MDMA – Empathogen
  - Neurophysiological effects
- Ketamine – Dissociative
  - Effects & mechanisms

5

OVERVIEW - TODAY

1:45 – 2:30

- Mechanisms
  - Neurophysiology
  - Mystical
  - Behavioral
- Conditions and evidence
  - Psilocybin
    - End of life anxiety
    - Depression
    - Substance use
  - MDMA
    - PTSD
    - Relationships
  - Ketamine
    - Treatment Resistant Depression
    - Suicidality
    - Substance use

6

OVERVIEW - TODAY

2:45 – 3:30

- Special topic
  - Psychedelics and antisocial behavior
  - Mindfulness-based intervention
- Approaches to psychedelic psychotherapy
  - Psycholytic/ dynamic
  - Non-directive/ humanistic
  - Third wave behaviorist/ mindfulness
  - Ketamine assisted psychotherapy
- Sample protocol
  - Preparation
    - Psychoeducation, grounding & intention.
  - Creating Optimal Set and Setting
    - Role of Ritual & Ceremony
  - Integration

7

OVERVIEW - TODAY

3:30 – 4:00 PM

- Microdosing
- Risks
  - Safety
  - Misuse
  - Acute phase
  - Equity & culturally safe care
  - Trauma and violence informed care
  - Ethical Considerations

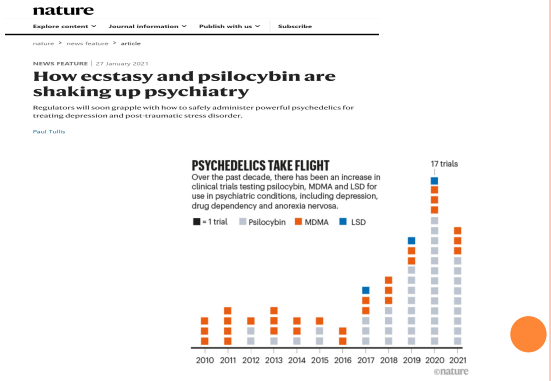
8

OVERVIEW - TODAY

This is not a training in psychedelic psychotherapy – Its an introduction to the field

9

INTRO PSYCHEDELIC RENAISSANCE



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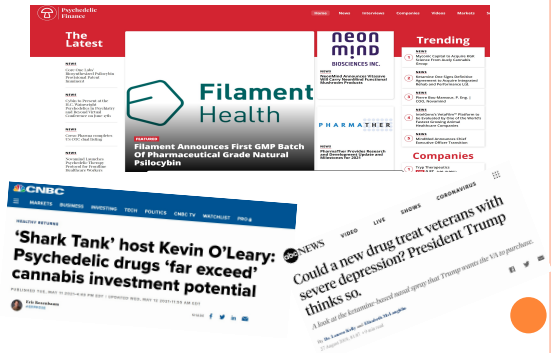
INTRO PSYCHEDELIC RENAISSANCE



11

INTRO PSYCHEDELIC RENAISSANCE

12

Intro Psychedelic Renaissance

TheraPsil
THERAPEUTIC PSILOCYBIN

TheraPsil's 4 Pillar Mission

- **COMPASSIONATE ACCESS:** Expanding safe, equitable and legal access to psilocybin-assisted therapy for those in medical need.
- **PUBLIC EDUCATION:** Increasing awareness of TheraPsil's governance and the merits and limitations of psilocybin-assisted therapy.
- **PROFESSIONAL TRAINING:** Develop and deliver safe, simple and effective protocols for credentialed health professionals to provide psilocybin-assisted therapy, in collaboration with other active organizations.
- **RESEARCH:** Facilitate research and evaluation in collaboration with Canadian and international partners.

Why We Exist.. Our Vision

- Canadians in medical need deserve access to effective therapies, in consultation with a physician, which can improve their quality of life/death.
- When effective therapy involves a prohibited/controlled substance, we challenge the laws that are in conflict with science and compassionate care.
- Care providers must collaborate with patients, government and health authorities toward healing psychological trauma, addiction, illness, and pain.

"I have been able to be happy and anxiety-free and not worry about what's going to happen tomorrow. I'm able to live in the day and in the moment".

- Laurie Brooks, British Columbia

"Psilocybin has been a gentle teacher for me. It expands my ability to BE WITH whatever shows up: the vast range of emotions and challenges that arise when one is dying."

- Andrea Bird, Ontario
Photo credit: Andreea Muscurel

13

Intro Psychedelic Renaissance

"Canadians have now acknowledged patients' "Right To Die" when faced with serious suffering at end-of-life. Surely, Canadians have a "Right To Try" a medicine that may help them want to live."

Bruce Tobin Ph.D.

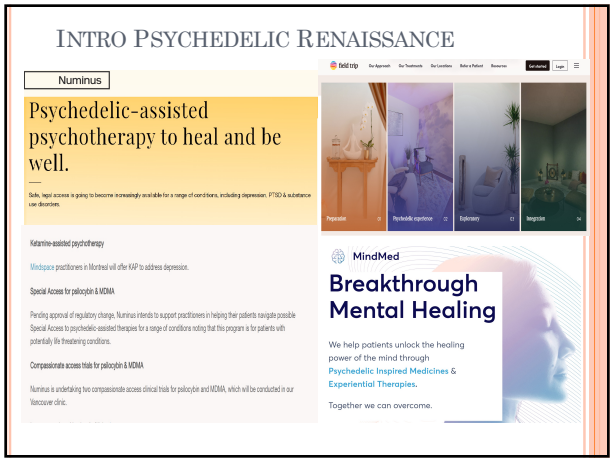
Our Legal Argument

1. The Canadian *Charter of Rights and Freedoms* (section 7) states that everyone has the right to "life, liberty, and security of person".
2. Canadian courts have ruled in three landmark cannabis cases (*R v. Parker* (Ontario Court of Appeal 2000), *R v. Smith* (Supreme Court Canada 2015) and *Allard v. Canada* (Canada Federal Court 2016)) that the absolute prohibition of cannabis by the *Controlled Drugs and Substances Act (CDSA)* contravenes section 7 because it "limits the liberty of medical users by foreclosing **reasonable medical choices** through the threat of criminal prosecution. Similarly, by forcing a person to choose between a legal but inadequate treatment and an illegal but **more effective** one, the law also infringes on security of person". (SCC: *v. Smith*, 2015) These rulings have led to amendment of the *CDSA* to allow for the medical use of cannabis.
3. Psilocybin, like cannabis, represents a "reasonable medical choice", and a "more effective" treatment for some cancer patients suffering from end-of-life distress, and for whom other treatments have failed. (See scientific argument above)
4. Therefore, the absolute prohibition of psilocybin limits the liberty of medical users by foreclosing a reasonable medical choice through the threat of criminal prosecution. Similarly, by forcing a person to choose between a legal but inadequate treatment and an illegal but more effective one, the law also infringes on security of person for the medical psilocybin user.
5. Therefore, an exemption should be issued to allow for medical use of psilocybin for patients as described above.

14

Intro Psychedelic Renaissance

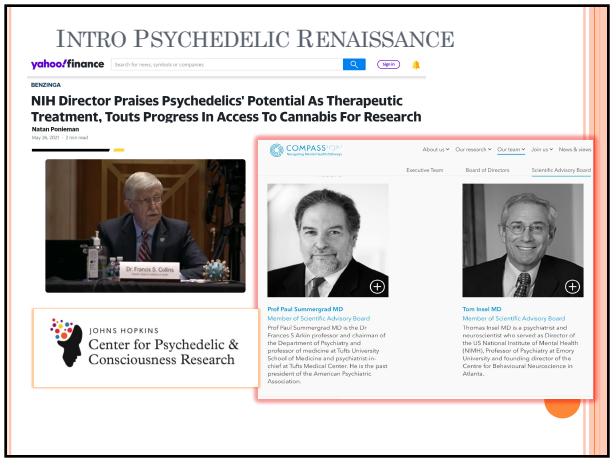
15


INTRO PSYCHEDELIC RENAISSANCE
Numinus
Psychedelic-assisted psychotherapy to heal and be well.
Ketamine-assisted psychotherapy
Special Access for psilocybin & MDMA
Compassionate access trials for psilocybin & MDMA
MindMed
Breakthrough Mental Healing
We help patients unlock the healing power of the mind through Psychedelic Inspired Medicines & Experiential Therapies.
Together we can overcome.

16

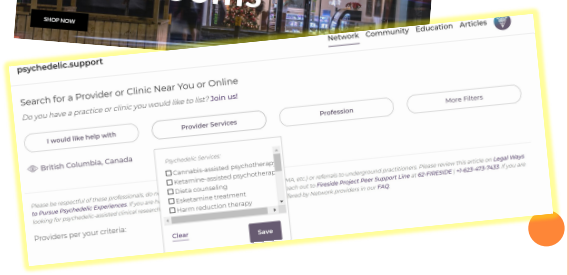

INTRO PSYCHEDELIC RENAISSANCE
Forbes
Oregon Legalizes Psilocybin Mushrooms and Decriminalizes All Drugs
Los Angeles
California Is One Step Closer to Decriminalizing Mushrooms, LSD, and Ecstasy
CBC | MENU
British Columbia
Motion to prevent sale of magic mushrooms defeated by Vancouver council
Coun. Pete Fry referred to motion as 'anti-drug hysteria'
CBC News - Posted: Sep 12, 2019 10:13 AM PT | Last Updated: September 12, 2019

17


INTRO PSYCHEDELIC RENAISSANCE
yahoo/finance
BENZINGA
NIH Director Praises Psychedelics' Potential As Therapeutic Treatment, Touts Progress In Access To Cannabis For Research
Natan Poniman
JOHNS HOPKINS
Center for Psychedelic & Consciousness Research
COMPASS
Prof Paul Summergrad MD
Member of Scientific Advisory Board
Tom Insel MD
Member of Scientific Advisory Board

18

Intro Psychedelic Renaissance



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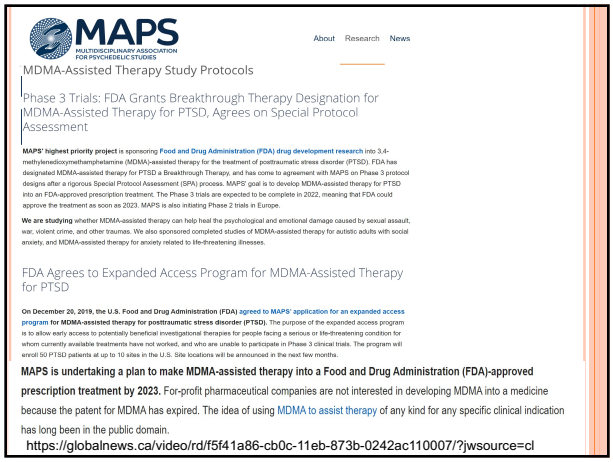


20

Psychedelic History – Indigenous Technology

21

Psychedelic History – Indigenous Technology

- Mazatec people in what is now Mexico have a long tradition of use of psilocybin mushrooms

María Sabina died in 1985, at the age of 91 in extreme poverty because she only received things that her patients brought her in exchange for services.

He (Bernardino García Martínez) asked:

"that the name of my great-grandmother be given the attention it deserves, a true museum worthy of her; the paving of the road that leads to her house which is now totally abandoned "

22

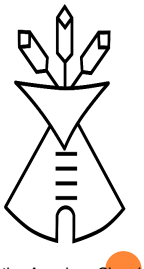
"The first ever documented recreational use of psilocybin mushrooms growing outside Mexico occurred in Vancouver. In 1965 RCMP confiscated Psilocybe semilanceata or Liberty Cap mushrooms from students at UBC. Evidently this mushroom had been recognized as being related to species encountered by magic mushroom tourists in Mexico."

a place of mind

23

Peyote

Quanah Parker



Native American Church

24

25

- History of LSD
  - Ergot Fungus
    - Ergotism
    - St. Anthony's Fire (Middle Ages)
  - Albert Hoffman
    - Synthesized lysergic acid compounds
    - Tested LSD-25 (1943)
  - Studied for Potential Use
    - Mental disorders, alcoholism, psychotic behavior, personal insight
  - Timothy Leary (1960s)
    - Turn on, Tune in, Drop out

26

Categories and Terminology

- Psychedelics
  - Hallucinogens
  - Empathogenics
  - Psychotomimetrics
  - Entheogens
  - Club drugs

- The word "hallucinate" comes from Latin words meaning "to wander in the mind."
- Psychedelic means "mind manifesting".

27

Categories and terminology

- The following is a list of some organisms known to contain hallucinogens
- Plant Psychedelics
  - Ayahuasca (combination of plants containing DMT & harmaline)
  - Morning Glory (seeds contain LSA)
- Dissociatives
  - Iboga (*Tabernanthe iboga)* (contains ibogaine)
  - *Salvia divinorum* (contains salvinorin A)
  - Datura (contains scopolamine)
- Cacti psychedelics
  - Peyote (*Lophophora williamsii*) (contains mescaline)
  - San Pedro (*Trichocereus pachanoi*) (contains mescaline)

28

Categories and terminology

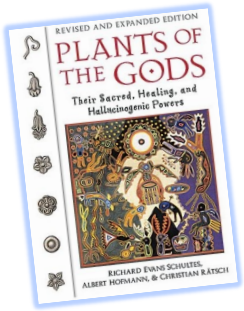
- Fungi Psychedelics
  - Psilocybe mushrooms (contain psilocybin and psilocin)
  - Ergot fungus
- Dissociatives
  - Fly Agaric mushroom (*Amanita muscaria*) (contains muscimol)
- Animals
  - Psychoactive psychedelic toads (*Bufo alvarius*) (contain 5-MeO-DMT and bufotenine)

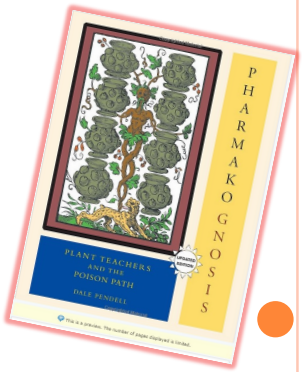
29

Categories and terminology

30

Categories and terminology





31

Categories and terminology

Indolamine/Serotonin Psychedelics

- LSD, psilocybin, DMT
- Actions on serotonin receptors is unclear – 5HT2a
- Likely a "mixed bag" of serotonin actions.
- Visual distortions and psychic effects predominate
  - changes in mood
  - thought disruption
  - altered time perception
  - depersonalization
  - hallucinations
  - suggestibility

32

Categories and terminology

- DMT: Short-acting, LSD-like, binds to serotonin-2 receptors.
  - Must be smoked or sniffed (inactive orally).
  - Metabolized by MAO enzyme.
- Primary active ingredient in Ayahuasca
  - Mixed with MAO 'I'(inhibitor)
  - Harmaline?

33

Categories and Terminology

LSD

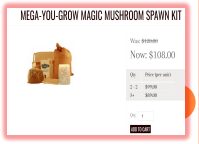
- Dosage and Sources
  - Hits
    - 1970s: 100 micrograms
    - Gel tab
    - Window pane
    - Microdots
- Pharmacokinetics
  - Usually taken orally
    - Effects begin between 30-90 min. after ingestion
      - Half-life: 110 minutes in humans
      - Metabolized in the liver

34

Categories and Terminology

Psilocybin

- 1/200 as potent as LSD; lasts 6–10 hours
- Well absorbed orally (eaten raw).
- Found in several mushroom species, which differ greatly in the concentration of the active ingredient.
- Most varieties found in southern U.S., Mexico, Central America.
- Mostly Cubenses – self produced



35

- Discriminative Stimulus Properties
  - Nonhumans readily learn to discriminate from saline.
  - Blocked by seratonin agonists.
- Tolerance
  - Tolerance develops rapidly
    - If taken repeatedly, its effects disappear within 2 or 3 days.
      - No amount of the drug will be effective
      - Tolerance dissipates quickly
      - Cross tolerance with other serotonin hallucinogens

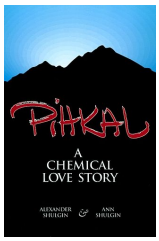
36

MDMA

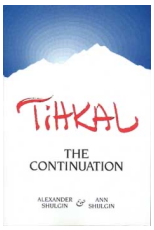
- Ecstasy and Synthetic Mescaline-Like Drugs
  - Combo of catecholamine-like & stimulants
  - MDMA
    - 3,4-Methylenedioxymethamphetamine
    - White or colored tablets (100 mg)
  - Originally synthesized by the Merck drug company
    - Patented in 1914
  - No use until the 1960s
    - Given to patients to enhance intimacy and communication
    - Designer drugs
      - Minor molecular changes evade laws
      - Most dissapeared (DMA, DOM, DOET)
  - Reclassified in 1985

37

MDMA



phenethylamines

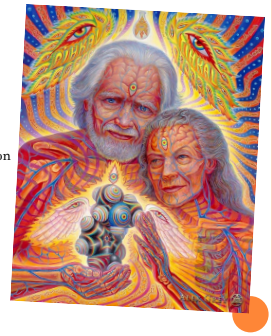


tryptamines

38

MDMA

- Pharmacokinetics
  - Orally
    - Peak level in 2 hrs
    - Metabolized to MDA
      - Half-life: about 8 hrs
        - 40 hours for full elimination
  - Used socially
    - Wakefulness
    - Endurance
    - Energy
    - Euphoria
    - Sensory perception
    - Extroversion



39

MDMA

- Neurophysiology
  - Increase transmission at synapses that use serotonin, norepinephrine, and dopamine
    - Causes the release and blocks reuptake
- Discriminative Stimulus Properties
  - Increased serotonin activity
  - Enhances stimulus properties of LSD

40

MDMA

- Behavior and Performance
  - A dose of 75 to 100 mg induces a non-hallucinogenic empathogenic state
    - Increased muscular tension
      - Bruxism – teeth grinding
    - Increase in body temperature, stiffness, loss of appetite, headache, nausea, blurred vision, and insomnia,
      - Dehydration?
    - Days after –
      - difficulty in concentration, fatigue, and depression

41

MDMA

- Self-Administration
  - Nonhumans
    - Readily self-administered by primates
    - Blocked by blocking 5-HT(2a) receptors
      - Unlike stimulants
  - Human Epidemiology
    - Increase in the number of users throughout the 1990s
    - Increase in number of mentions in emergency room admissions between 1994 and 1999
    - Use began to drop around 2000

42

Dissociatives

- Dissociative Anesthetics
  - Phencyclidine (PCP)
    - Synthetic drug developed in 1963
      - Dissociative anesthetic
      - Withdrawn from the marked due to delirium, disorientation, agitation (emergence delirium)
        - Sernylan
        - Crystal, angel dust, hob, horse tanks
  - Ketamine
    - Developed to replace PCP
    - Veterinary use
    - Liquid is colorless and tasteless
      - Swallowed or injected
        - Converted to powder, snorted

43

Ketamine

- Pharmacokinetics and Dose
  - Ketamine can be snorted, injected, or taken orally.
    - Oral administration is slowly absorbed.
      - Typically used intranasally in recreational context
      - IV or IM medical
      - Effects last from 35 to 40 minutes
      - Typical oral dose is 175 mg; intranasal dose is 50 mg

44

Ketamine

- Neurophysiology
  - Block NMDA receptors for glutamate
  - Act as reinforcers
  - Endogenous analog unknown
- Behavior and Performance
  - Amnesia
    - NMDA
  - Relaxation, warmth, numbness
  - Euphoric feeling, distortions in body image, floating in space
  - Mood changes

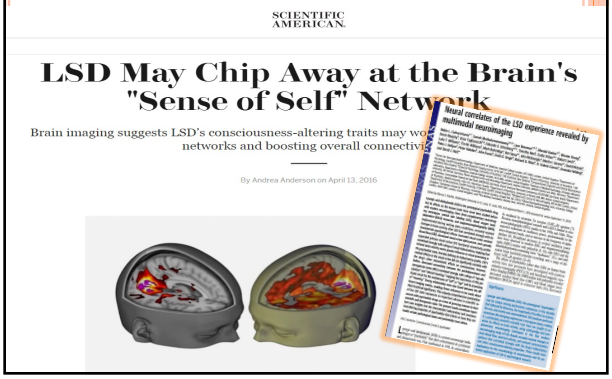
45

KETAMINE

- Self-Administration
  - Nonhumans
    - PCP: monkeys, dogs, baboons, and rats
      - Reinforcement not blocked by DA receptors
    - Ketamine: rats and monkeys
  - Human Epidemiology
    - Patterns of use are similar to LSD.
      - But, unlike LSD, some occasional users may become chronic users.
        - Popular in select areas

46

MECHANISMS



47

MYSTICAL EXPERIENCE

- Marsh Chapel Experiment / Good Friday Experiment
- "the most powerful cosmic homecoming I have ever experienced"
  - Huston Smith
- In a 25-year follow-up to the experiment in 1986, all of the subjects given psilocybin except for one described their experience as having elements of "a genuine mystical nature and characterized it as one of the high points of their spiritual life"
- "[psychedelic] mushroom use may constitute one technology for evoking revelatory experiences that are similar, if not identical, to those that occur through so-called spontaneous alterations of brain chemistry."[1]
  - William A. Richards

48

Original Papers

Psychopharm

Mystical-type experiences occasioned by psilocybin mediate the attribution of personal meaning and spiritual significance 14 months later

RR Griffiths *Department of Psychiatry and Behavioral Sciences and Department of Neuroscience, Johns Hopkins University School of Medicine, Baltimore, Maryland, USA.*
WA Richards *Johns Hopkins Bayview Medical Center, Baltimore, Maryland, USA.*
MW Johnson *Department of Psychiatry and Behavioral Sciences, Johns Hopkins University School of Medicine, Baltimore, Maryland, USA.*
UD McCann *Department of Psychiatry and Behavioral Sciences, Johns Hopkins University School of Medicine, Baltimore, Maryland, USA.*

- Participants were 36 hallucinogen-naïve adults reporting regular participation in religious/ spiritual activities.
- At the 14-month follow-up,
  - 58% and 67%, respectively, of volunteers rated the psilocybin-occasioned experience as being among the five most personally meaningful and among the five most spiritually significant experiences of their lives;
  - 64% indicated that the experience increased well-being or life satisfaction;
  - a central role of the mystical experience assessed on the session day in the high ratings of personal meaning and spiritual significance at follow-up.

49

50

Original Paper

Psychopharm

Hallucinogen use and intimate partner violence: Prospective evidence consistent with protective effects among men with histories of problematic substance use

Zach Walsh[1], Peter S Hendricks[2], Stephanie Smith[3], David S Kosson[3], Michelle S Thiessen[1], Philippe Lucas[4] and Marc T Swogger[5]

Journal of Psychopharmacology
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DOI: 10.1177/0269881116642538
jop.sagepub.com
SAGE

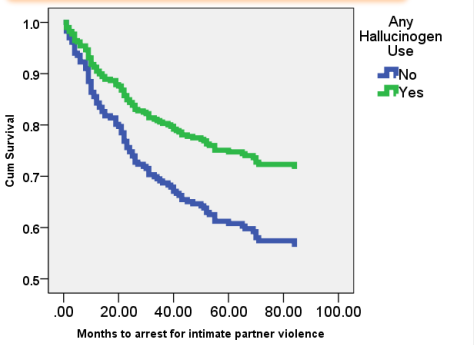
- Arrest for intimate partner violence
- 302 male inmates – Illinois County Jail
- With substance use disorders
- Any hallucinogen use/ hallucinogen d/o
- Prevalence 44%/ 7%

51

Original Paper

Hallucinogen use and intimate partner violence: Prospective evidence consistent with protective effects among men with histories of problematic substance use

Zach Walsh[1], Peter S Hendricks[2], Stephanie Smith[1], David S Kosson[1], Michelle S Thiessen[1], Philippe Lucas[2] and Marc T Swogger[3]

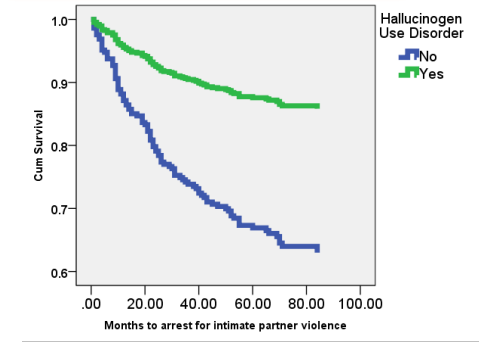


52

Original Paper

Hallucinogen use and intimate partner violence: Prospective evidence consistent with protective effects among men with histories of problematic substance use

Zach Walsh[1], Peter S Hendricks[2], Stephanie Smith[1], David S Kosson[1], Michelle S Thiessen[1], Philippe Lucas[2] and Marc T Swogger[3]



53

Original Article

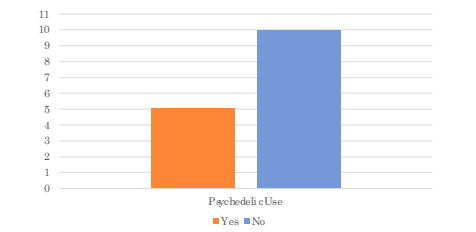
Psychedelic use and intimate partner violence: The role of emotion regulation

Michelle S Thiessen[1], Zach Walsh[1], Brian M Bird[2] and Adele Lafrance[3]

Journal of Psychopharmacology
1–7

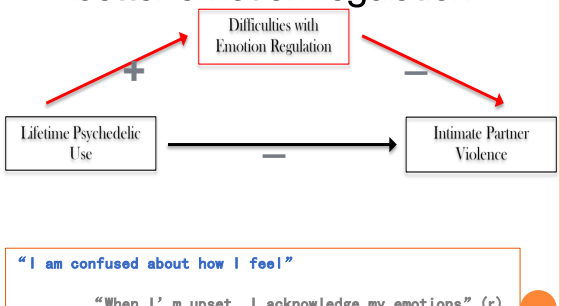
DOI: 10.1177/0269881118771782

- Psychedelic associated with reduced partner violence perpetration among men



54

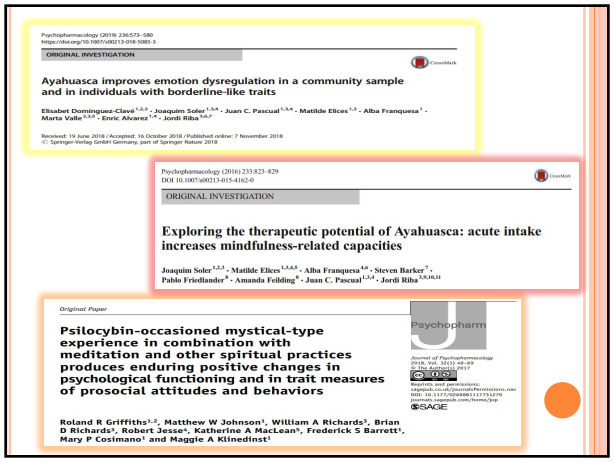
Protective effect mediated by better emotion regulation



"I am confused about how I feel!"

"When I' m upset, I acknowledge my emotions" (r)

55

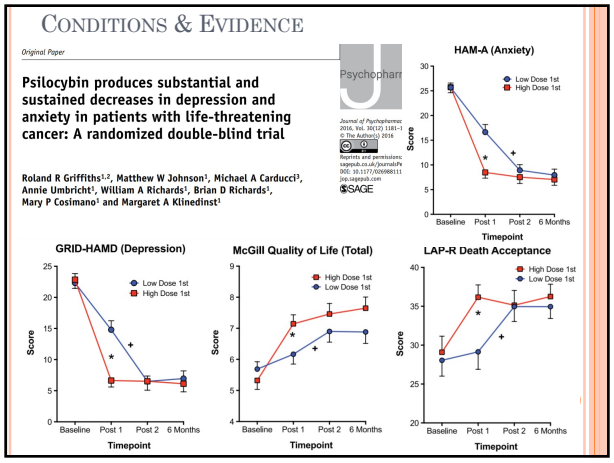


Ayahuasca improves emotion dysregulation in a community sample and in individuals with borderline-like traits

Exploring the therapeutic potential of Ayahuasca: acute intake increases mindfulness-related capacities

Psilocybin-occasioned mystical-type experience in combination with meditation and other spiritual practices produces enduring positive changes in psychological functioning and in trait measures of prosocial attitudes and behaviors

56



CONDITIONS & EVIDENCE

Psilocybin produces substantial and sustained decreases in depression and anxiety in patients with life-threatening cancer: A randomized double-blind trial

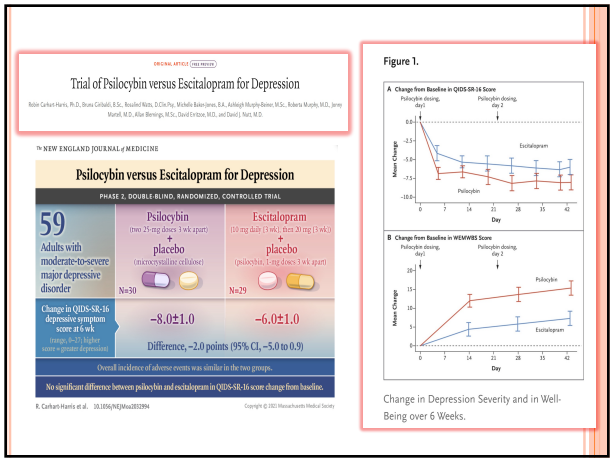
HAM-A (Anxiety)

GRID-HAMD (Depression)

McGill Quality of Life (Total)

LAP-R Death Acceptance

57



Trial of Psilocybin versus Escitalopram for Depression

The NEW ENGLAND JOURNAL of MEDICINE

Psilocybin versus Escitalopram for Depression

PHASE 2, DOUBLE-BLIND, RANDOMIZED, CONTROLLED TRIAL

59 Adults with moderate-to-severe major depressive disorder

Psilocybin (two 25-mg doses 3 wk apart) + placebo (microcrystalline cellulose) N=30

Escitalopram (10 mg daily [3 wk], then 20 mg [3 wk]) + placebo (psilocybin, 1 mg doses 3 wk apart) N=29

Change in QIDS-SR-16 depressive symptom score at 6 wk (range, 0–27; higher score = greater depression): −8.0±1.0 vs −6.0±1.0

Difference, −2.0 points (95% CI, −5.0 to 0.9)

Overall incidence of adverse events was similar in the two groups.

No significant difference between psilocybin and escitalopram in QIDS-SR-16 score change from baseline.

R. Carhart-Harris et al. 10.1056/NEJMoa2032994 Copyright © 2021 Massachusetts Medical Society

Figure 1.

A Change from Baseline in QIDS-SR-16 Score

B Change from Baseline in WEMWBS Score

Mean Change

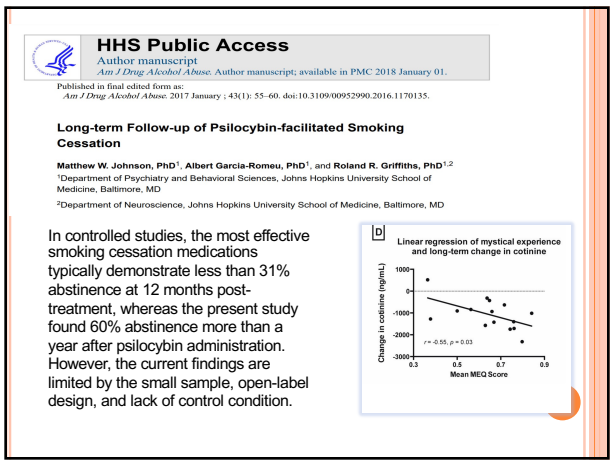
Day

Psilocybin

Escitalopram

Change in Depression Severity and in Well-Being over 6 Weeks.

58



HHS Public Access

Author manuscript

Am J Drug Alcohol Abuse. Author manuscript; available in PMC 2018 January 01.

Published in final edited form as:

Am J Drug Alcohol Abuse. 2017 January ; 43(1): 55–60. doi:10.3109/00952990.2016.1170135.

Long-term Follow-up of Psilocybin-facilitated Smoking Cessation

Matthew W. Johnson, PhD[1], **Albert Garcia-Romeu, PhD**[1], and **Roland R. Griffiths, PhD**[1,2]

[1]Department of Psychiatry and Behavioral Sciences, Johns Hopkins University School of Medicine, Baltimore, MD

[2]Department of Neuroscience, Johns Hopkins University School of Medicine, Baltimore, MD

In controlled studies, the most effective smoking cessation medications typically demonstrate less than 31% abstinence at 12 months post-treatment, whereas the present study found 60% abstinence more than a year after psilocybin administration. However, the current findings are limited by the small sample, open-label design, and lack of control condition.

D

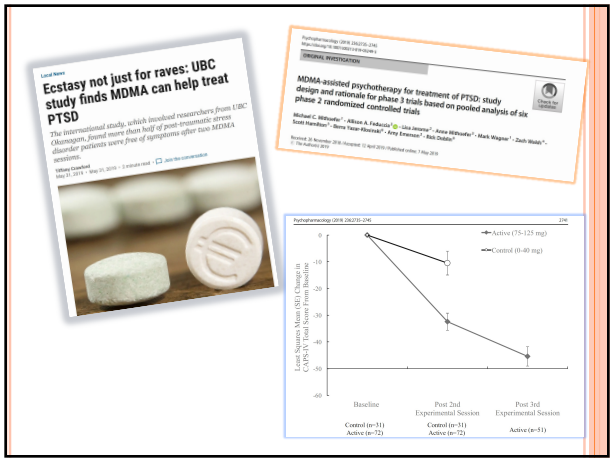
Linear regression of mystical experience and long-term change in cotinine

Change in cotinine (ng/mL)

Mean MEQ Score

$r = -0.55$, $p = 0.03$

59



Ecstasy not just for raves: UBC study finds MDMA can help treat PTSD

The international study, which involved researchers from UBC Okanagan, found more than half of post-traumatic stress disorder patients were free of symptoms after two MDMA sessions.

Johnny Crawford

May 31, 2019

ORIGINAL INVESTIGATION

MDMA-assisted psychotherapy for treatment of PTSD: study design and rationale for phase 3 trials based on pooled analysis of six phase 2 randomized controlled trials

Psychopharmacology (2019) 236:735–746

Active (75-125 mg)

Control (0-40 mg)

Least Squares Mean (SE) Change in CAPS-5 Total Score From Baseline

Baseline

Post 2nd Experimental Session

Post 3rd Experimental Session

Control (n=31)

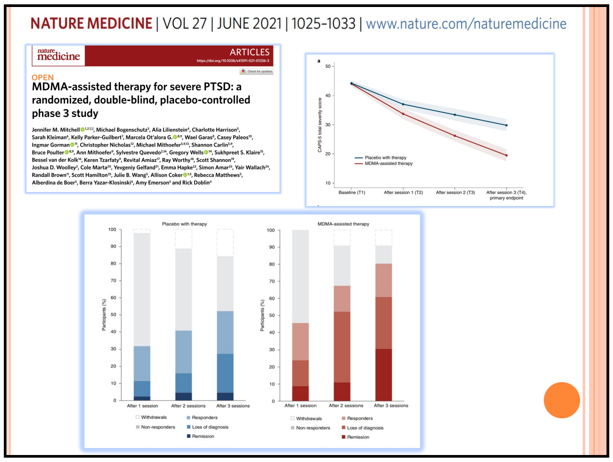
Active (n=72)

Control (n=31)

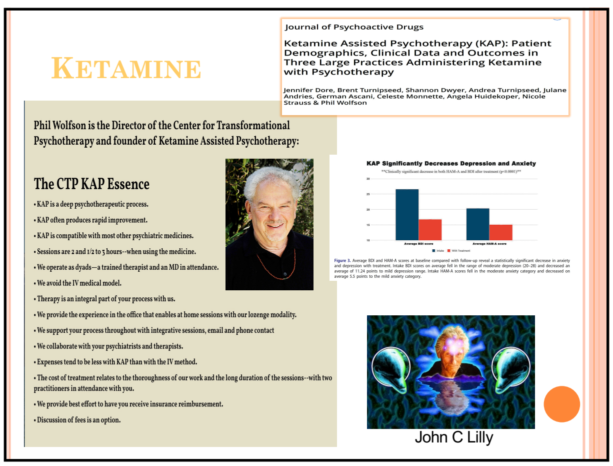
Active (n=72)

Active (n=51)

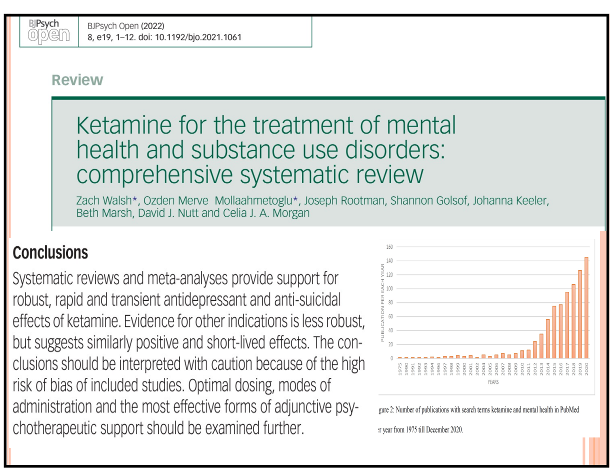
60


NATURE MEDICINE | VOL 27 | JUNE 2021 | 1025–1033 | www.nature.com/naturemedicine
nature medicine
ARTICLES
https://doi.org/10.1038/s41591-021-01336-3
OPEN
MDMA-assisted therapy for severe PTSD: a randomized, double-blind, placebo-controlled phase 3 study
Jennifer M. Mitchell, Michael Bogenschutz, Alia Lilienstein, Charlotte Harrison, Sarah Kleiman, Kelly Parker-Guilbert, Marcela Ot'alora G., Wael Garas, Casey Paleos, Ingmar Gorman, Christopher Nicholas, Michael Mithoefer, Shannon Carlin, Bruce Poulter, Ann Mithoefer, Sylvestre Quevedo, Gregory Wells, Sukhpreet S. Klaire, Bessel van der Kolk, Keren Tzarfaty, Revital Amiaz, Ray Worthy, Scott Shannon, Joshua D. Woolley, Cole Marta, Yevgeniy Gelfand, Emma Hapke, Simon Amar, Yair Wallach, Randall Brown, Scott Hamilton, Julie B. Wang, Allison Coker, Rebecca Matthews, Alberdina de Boer, Berra Yazar-Klosinski, Amy Emerson and Rick Doblin
CAPS-5 total severity score
Placebo with therapy
MDMA-assisted therapy
Baseline (T1)
After session 1 (T2)
After session 2 (T3)
After session 3 (T4), primary endpoint
Placebo with therapy
MDMA-assisted therapy
Participants (%)
After 1 session
After 2 sessions
After 3 sessions
Withdrawals
Responders
Non-responders
Loss of diagnosis
Remission

61


KETAMINE
Journal of Psychoactive Drugs
Ketamine Assisted Psychotherapy (KAP): Patient Demographics, Clinical Data and Outcomes in Three Large Practices Administering Ketamine with Psychotherapy
Jennifer Dore, Brent Turnipseed, Shannon Dwyer, Andrea Turnipseed, Julane Andries, German Ascani, Celeste Monnette, Angela Huidekoper, Nicole Strauss & Phil Wolfson
Phil Wolfson is the Director of the Center for Transformational Psychotherapy and founder of Ketamine Assisted Psychotherapy:
The CTP KAP Essence
• KAP is a deep psychotherapeutic process.
• KAP often produces rapid improvement.
• KAP is compatible with most other psychiatric medicines.
• Sessions are 2 and 1/2 to 3 hours--when using the medicine.
• We operate as dyads—a trained therapist and an MD in attendance.
• We avoid the IV medical model.
• Therapy is an integral part of your process with us.
• We provide the experience in the office that enables at home sessions with our lozenge modality.
• We support your process throughout with integrative sessions, email and phone contact
• We collaborate with your psychiatrists and therapists.
• Expenses tend to be less with KAP than with the IV method.
• The cost of treatment relates to the thoroughness of our work and the long duration of the sessions--with two practitioners in attendance with you.
• We provide best effort to have you receive insurance reimbursement.
• Discussion of fees is an option.
KAP Significantly Decreases Depression and Anxiety
Clinically significant decrease in both HAM-A and BDI after treatment (p<0.0001)
Average BDI score
Average HAM-A score
Intake
With Treatment
Figure 3. Average BDI and HAM-A scores at baseline compared with follow-up reveal a statistically significant decrease in anxiety and depression with treatment. Intake BDI scores on average fell in the range of moderate depression (20–28) and decreased an average of 11.24 points to mild depression range. Intake HAM-A scores fell in the moderate anxiety category and decreased on average 5.5 points to the mild anxiety category.
John C Lilly

62


BJPsych open
BJPsych Open (2022)
8, e19, 1–12. doi: 10.1192/bjo.2021.1061
Review
Ketamine for the treatment of mental health and substance use disorders: comprehensive systematic review
Zach Walsh*, Ozden Merve Mollaahmetoglu*, Joseph Rootman, Shannon Golsof, Johanna Keeler, Beth Marsh, David J. Nutt and Celia J. A. Morgan
Conclusions
Systematic reviews and meta-analyses provide support for robust, rapid and transient antidepressant and anti-suicidal effects of ketamine. Evidence for other indications is less robust, but suggests similarly positive and short-lived effects. The conclusions should be interpreted with caution because of the high risk of bias of included studies. Optimal dosing, modes of administration and the most effective forms of adjunctive psychotherapeutic support should be examined further.
PUBLICATION PER EACH YEAR
YEARS
gure 2: Number of publications with search terms ketamine and mental health in PubMed
r year from 1975 till December 2020.

63

"This Is Something That Changed My Life": A Qualitative Study of Patients' Experiences in a Clinical Trial of Ketamine Treatment for Alcohol Use Disorders

O. Merve Mollaahmetoglu[1*], Johanna Keeler[1], Katherine J. Ashbullby[1], Eirini Ketzitzidou-Argyri[1], Meryem Grabski[1,2] and Celia J. A. Morgan[1]

[1] Psychology Department, Psychopharmacology and Addiction Research Centre, University of Exeter, Exeter, United Kingdom, [2] Department of Clinical, Educational and Health Psychology, Clinical Psychopharmacology Unit, University College London, London, United Kingdom

OPEN ACCESS

Edited by:
Giovanni Martinotti

"It was peaceful. It was calming and I just sat back and... you know, I didn't lose sense of who I was. I always knew who I was, and I had confidence that this would be temporary."

"So it was a sort of mixture of extreme comfort for want of a better word with a sort of paranoia where one's brain is saying, if you guys in the room will leave the room, I'm stuck here for the rest of my life, sort of thing."

"It was a sense of completeness sense of, I suppose in a way finality, a source of finish. But also, a sense of enormous growth and a feeling of oneness with other entities, other living beings in particular, but also the world and universe as a whole."

"It helped family wise, relationship wise in every, every single avenue of my life. It's changed it...doing the ketamine and seeing this other dimension enforced my belief of another life and I now live every single day to the max. When I go for a walk, I'm very observant of my world around me. I take pleasures in life rather than pleasures of...drink...So...it's still with me and I hope it'll stay with me for forever."

64

A Single Ketamine Infusion Combined With Motivational Enhancement Therapy for Alcohol Use Disorder: A Randomized Midazolam-Controlled Pilot Trial

Elias Dakwar, M.D., Frances Levin, M.D., Carl L. Hart, Ph.D., Cale Basaraba, M.P.H., Jean Choi, M.S., Martina Pavlicova, Ph.D., Edward V. Nunes, M.D.

Objective: Pharmacotherapy and behavioral treatments for alcohol use disorder are limited in their effectiveness, and new treatments with innovative mechanisms would be valuable. In this pilot study, the authors tested whether a single subanesthetic infusion of ketamine administered to adults with alcohol dependence and engaged in motivational enhancement therapy affects drinking outcomes.

Methods: Participants were randomly assigned to a 52-minute intravenous administration of ketamine (0.71 mg/kg, N=17) or the active control midazolam (0.025 mg/kg, N=23), provided during the second week of a 5-week outpatient regimen of motivational enhancement therapy. Alcohol use following the infusion was assessed with timeline followback method, with abstinence confirmed by urine ethyl glucuronide testing. A longitudinal logistic mixed-effects model was used to model daily abstinence from alcohol over the 21 days after ketamine infusion.

Results: Participants (N=40) were mostly middle-aged (mean age=53 years [SD=9.8]), predominantly white (70.3%), and largely employed (71.8%) and consumed an average of five drinks per day prior to entering the study. Ketamine significantly increased the likelihood of abstinence, delayed the time to relapse, and reduced the likelihood of heavy drinking days compared with midazolam. Infusions were well tolerated, with no participants removed from the study as a result of adverse events.

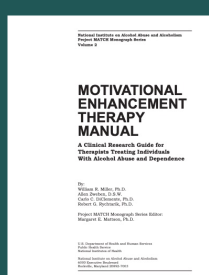
Conclusions: A single ketamine infusion was found to improve measures of drinking in persons with alcohol dependence engaged in motivational enhancement therapy. These preliminary data suggest new directions in integrated pharmacotherapy-behavioral treatments for alcohol use disorder. Further research is needed to replicate these promising results in a larger sample.

Am J Psychiatry 2020; 177:125–133; doi: 10.1176/appi.ajp.2019.19070684

65

Rationale for this approach

- Ketamine has been shown to reduce cravings and act on psychological mechanisms to increase motivation to quit
- Therapy aimed at enhancing motivation may take advantage of these shifts induced by ketamine to deepen commitment and strengthen motivation for change
- Mirrors other psychedelic work in which psychoactive effects facilitate re-evaluation of meaning and personal values while also restructuring commitments and behaviours
- Session timing takes advantage of window of heightened neuroplasticity as a potent period for the initiation and reinforcement of new behaviour


National Institute on Alcohol Abuse and Alcoholism
Project MATCH Monograph Series
Volume 2

MOTIVATIONAL ENHANCEMENT THERAPY MANUAL

A Clinical Research Guide for Therapists Treating Individuals With Alcohol Abuse and Dependence

By:
William R. Miller, Ph.D.
Allen Zweben, D.S.W.
Carlo C. DiClemente, Ph.D.
Robert G. Rychtarik, Ph.D.

Project MATCH Monograph Series Editor:
Margaret E. Mattson, Ph.D.

U.S. Department of Health and Human Services
Public Health Service
National Institutes of Health

National Institute on Alcohol Abuse and Alcoholism
6000 Executive Boulevard
Rockville, Maryland 20892-7003

66

(Dakwar et al., 2014; Dakwar et al., 2020)

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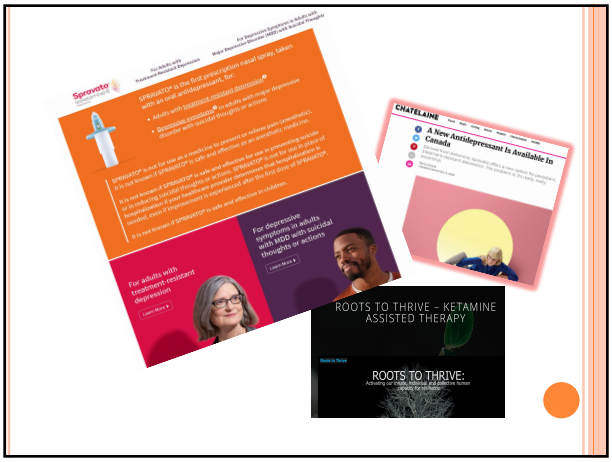
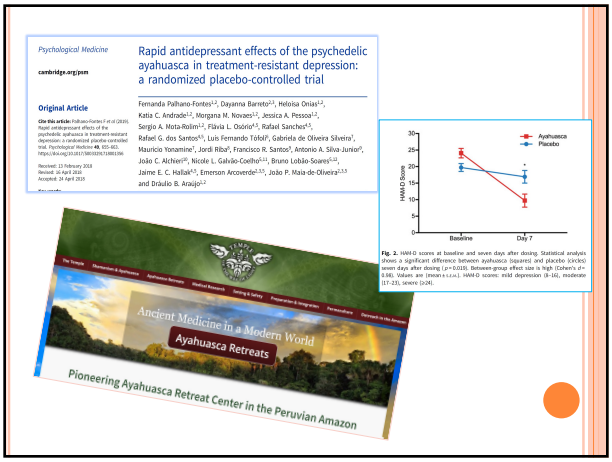

Spravato
SPRAVATO® is the first prescription nasal spray, taken with an oral antidepressant, for:
For adults with treatment-resistant depression
For depressive symptoms in adults with MDD with suicidal thoughts or actions
CHATELAINE
A New Antidepressant Is Available in Canada
ROOTS TO THRIVE – KETAMINE ASSISTED THERAPY
ROOTS TO THRIVE:

67


The New York Times
OPINION
Why Are Ketamine Ads Following Me Around the Internet?
March 1, 2023
Gmail
Jennifer, Ketamine Therapy co
Dear Jennifer,
KETAMINE THERAPY
MIRACLE CURE
The New York Times
Ketamine can be mind-altering, and getting it has become much easier.

68


Psychological Medicine
cambridge.org/psm
Original Article
Rapid antidepressant effects of the psychedelic ayahuasca in treatment-resistant depression: a randomized placebo-controlled trial
Fernanda Palhano-Fontes[1,2], Dayanna Barreto[2,3], Heloisa Onias[1,2], Katia C. Andrade[1,2], Morgana M. Novaes[1,2], Jessica A. Pessoa[1,2], Sergio A. Mota-Rolim[1,2], Flávia L. Osório[4,5], Rafael Sanches[4,5], Rafael G. dos Santos[4,5], Luis Fernando Tófoli[6], Gabriela de Oliveira Silveira[1], Mauricio Yonamine[7], Jordi Riba[8], Francisco R. Santos[9], Antonio A. Silva-Junior[9], João C. Alchieri[10], Nicole L. Galvão-Coelho[2,11], Bruno Lobão-Soares[2,12], Jaime E. C. Hallak[4,5], Emerson Arcoverde[2,13], João P. Maia-de-Oliveira[2,3,5] and Dráulio B. Araújo[1,2]
Ayahuasca
Placebo
HAM-D Score
Baseline
Day 7
Ancient Medicine in a Modern World
Ayahuasca Retreats
Pioneering Ayahuasca Retreat Center in the Peruvian Amazon

69

INTERNATIONAL REVIEW OF PSYCHIATRY
2018, VOL. 30, NO. 4, 291–316
https://doi.org/10.1080/09540261.2018.1486289

Taylor & Francis

REVIEW ARTICLE

Current perspectives on psychedelic therapy: use of serotonergic hallucinogens in clinical interventions

Albert Garcia-Romeu and William A. Richards

Department of Psychiatry & Behavioral Sciences, Johns Hopkins University School of Medicine, Baltimore, MD, USA

- Psychoanalytic/Psycholytic - talk therapy w/ low to moderate dose
  - **access to unconscious**
  - **ego-loosening**
  - **regression to earlier developmental stages**
  - **lowered defense mechanisms**
- Humanistic/existential
  - psychedelic therapy
  - higher dose
  - non-directive
  - preparation / integration
- Current model - psychedelic with
  - motivational enhancement
  - CBT
- Behaviorist?

70

INTERNATIONAL REVIEW OF PSYCHIATRY
https://doi.org/10.1080/09540261.2018.1474088

Taylor & Francis

REVIEW ARTICLE

Psychedelics and the new behaviourism: considering the integration of third-wave behaviour therapies with psychedelic-assisted therapy

Zach Walsh and Michelle S. Thiessen

Department of Psychology, University of British Columbia, Kelowna, BC, Canada

- Accentuated mindfulness and emotional regulation might underlie some of the beneficial effects of psychedelic experiences
- The practice and development of mindfulness and emotion regulation are key components of Third Wave Behavior Therapies.
- Do adjunctive Third Wave therapies have potential to enhance the positive effects of psychedelic therapy?

71

Cross Cutting Issues – Set & Setting

- Set and setting important across approaches
  - Music
  - Atmosphere
  - Rapport
  - Preparation
  - Integration

72

Yale Manual for Psilocybin-Assisted Therapy of Depression

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Journal of Contextual Behavioral Science 15 (2020) 92–102
Contents lists available at ScienceDirect
Journal of Contextual Behavioral Science
journal homepage: www.elsevier.com/locate/jcbs

The use of the psychological flexibility model to support psychedelic assisted therapy☆

Rosalind Watts[a,*], Jason B Luoma[b]
[a] Imperial College London Psychedelic Research Group, United Kingdom
[b] Portland Psychotherapy Clinic, Research, & Training Center, United States

Session Name	Session Overview and Ways ACT is Employed
Preparatory Psychoeducation Session #1 (2 hours)	Therapist aims to establish therapeutic alliance through: • Listening to participant's narrative of depression and treatment history to understand patterns of psychological inflexibility that are most prominent; • Psychoeducation regarding the psilocybin experience, therapeutic boundaries (e.g., touch) and safety measures; • Teaching grounding techniques including diaphragmatic breathing; • Assisting the participant in setting an intention for medication session #1.
Medication Session #1 (at 1 week)	• In line with supportive stance during medication sessions, the therapist does not provide significant ACT interventions or feedback. • ACT-based clinical formulation continues as therapist listens to emergent narratives and notes instances of psychological flexibility and inflexibility, especially present moment awareness, self-as-context, and experiential avoidance.
Debriefing Session #1 (1-2 hours, day after medication session)	• Therapist elicits complete narrative of participant's experience during medication session. • Identify and explore aspects of the participant's narrative that engage with ACT principles, as well as instances when they moved toward or away from psychological flexibility.
Debriefing Session #2 (1-2 hours, 1 week after medication session)	Therapist and participant continue to review and reflect on the participant's: • Psilocybin experience, including any emotional, mental, or lifestyle changes that followed the dosing session. • Values, by discussing the participant's completed Valued Living Questionnaire, and relative importance of valued domains of living. • Experiences living in accordance with or not living in alignment with their values.

Preparatory Psychoeducation Session #2 (2 hours, at 4 weeks)	• Conduct psychoeducation regarding: ○ The cognitive processes and behaviors that contribute to depression from an ACT perspective (i.e. cognitive fusion, experiential avoidance, reason-giving etc.); ○ How depressive patterns can be changed through an interactive process between the principles of ACT and the experience with psilocybin; and
	○ Mindfulness practice. • Through this process, the therapist aims to induce "creative hopelessness." • Assisting the participant in setting an intention for medication session #2.
Medication Session #2 (at 5 weeks)	Same as medication session #1
Debriefing Session #3 (1-2 hours, day after medication session)	Therapist elicits complete narrative of participant's experience during medication session, exploring: • Aspects of the experience in relation to ACT principles discussed previously. • Metaphors derived from psilocybin experience or from ACT (i.e. house and furniture metaphor) to aid in understanding of the principles, such as self-as-context.
Debriefing Session #4 (1-2 hours, 1 week after medication session)	Using the ACT Matrix if helpful, therapist and participant continue to review and reflect on the participant's medication experience and changes that have taken place, to explore: • What the participant values most; • How to put their values into action. Therapist may shift towards a more directive behavioral approach to help the participant to define precise actions they can take to start living in accordance with their values.
Follow-up Sessions #1 and #2 (2 and 4 weeks after medication session #2)	Therapist continues to explore and reinforce; • Insights gained from the psilocybin experience while assessing for changes in psychological flexibility; • How the dosing and therapy sessions brought each ACT process to light, using the ACT hexaflex; • Relevant ACT concepts • Successful behavioral changes and committed actions taken; • Mindfulness practices and other concrete ways the study experience can be translated into lasting changes. Therapist leads termination discussions and plans for post-study follow up care for the participant.

73

MAPS Public Benefit Corporation
IND #063384

MAPP1 Protocol Synopsis
Amendment 4 Version 1: 22 May 2020

MAPS Public Benefit Corporation

Protocol MAPP1
IND #063384

Original Protocol Version 1: 16 January 2017
Original Protocol Version 2: 07 June 2017
Amendment 1 Version 1: 26 February 2018
Amendment 2 Version 1: 12 September 2019
Amendment 3 Version 1: 13 November 2019
Amendment 4 Version 1: 22 May 2020

A Randomized, Double-Blind, Placebo-Controlled, Multi-Site Phase 3 Study of the Efficacy and Safety of Manualized MDMA-Assisted Psychotherapy for the Treatment of Severe Posttraumatic Stress Disorder

Preparatory Period with Enrollment Confirmation ~6 weeks (+5/-5 weeks)			
Study Visit		**Visit Duration/ Visit Timing**	**Brief Description of Events**
Preparatory Period	Preparatory Session 1	1.5 hours/ 0 to 12 days after Enrollment	90-minute Preparatory Session. Target visit timing on tapering needs. If needed, schedule calls between Visits if indicated for tapering, safety, or further questions about medical history.
Preparatory Period	Preparatory Session 2	1.5 hours/ 2 to 21 days after Prep Session 1	90-minute Preparatory Session/ongoing assessment. If tapering is complete or not needed, check eligibility and schedule upcoming visits. If tapering is ongoing, schedule post taper call for ongoing assessment.
	Preparatory Session 3 & Enrollment Confirmation	3 hours (90-minute measures, 90-minute therapy)/ 3 to 6 days after Baseline CAPS-5	Complete Baseline self-report measures. Complete 3-hour Preparatory Session (~90-minute measures, 90-minute therapy) and schedule Exp. Session 1. If enrollment is not confirmed, do not randomize; complete Study Termination.

74

Treatment Period From Randomization to Integrative Session 3.3 12 weeks (-3/+4)			
Study Visit		**Visit Duration/ Visit Timing**	**Brief Description of Events**
Treatment 1	Randomization	.5 hours/ Within 2 week of Baseline CAPS-5/ 24 to 48 hours before Exp. Session 1	Complete after enrollment and scheduling Exp. Session 1. Enter demographics in Medrio for use in randomization. The participant does not need to be present for this.
Treatment 1	Experimental Session 1	8 hours + overnight/ Within 2 weeks of Baseline CAPS-5	8 hours with overnight stay. Dose is 80 mg with supplemental half-dose of 40 mg unless contraindicated.
Treatment 1	Integrative Session 1.1	1.5 hours/ Morning after Experimental Session 1	90-minute Integrative Session, followed by phone check-ins that includes Since Last Visit C-SSRS assessment on Days 2, 4, 6, 7, 8, 10, 12, 14 post Experimental Session.
Treatment 1	Integrative Session 1.2	1.5 hours/ 3 to 14 days after Experimental Session 1 at least 2 days after Integrative Session 1.1	Between 3 and 14 days after Experimental Session, a 90-minute Integrative Session is completed.
Treatment 1	Integrative Session 1.3	1.5 hours/ 20 to 34 days after Experimental Session 1; at least 2 days after Integrative Session 1.2; 1 to 7 days before Experimental Session 2	90-minute Integrative Session. Measures include LEC-5 and C-SSRS.
Treatment 2	Experimental Session 2	8 hours + overnight/ 21 to 35 days after Experimental Session 1	The second Experimental Session lasts 8 hours with an overnight stay. Dose is 80 or 120 mg plus supplemental half-dose unless contraindicated.
Treatment 2	Integrative Session 2.1	1.5 hours/ Morning after Experimental Session 2	90-minute Integrative Session. Followed by phone check-ins that includes Since Last Visit C-SSRS assessment on Days 2, 4, 6, 7, 8, 10, 12, 14 post Experimental Session.
Treatment 2	Integrative Session 2.2	1.5 hours/ 3 to 14 days after Experimental Session 2; at least 2 days after Integrative Session 2.1	90-minute Integrative Session.
Treatment 2	Integrative Session 2.3	1.5 hours/ 20 to 34 days after Experimental Session 2; at least 2 days after Integrative Session 2.2 1 to 7 days before Experimental Session 3	90-minute Integrative Session . Measures include LEC-5 and C-SSRS.

75

Psychedelic Microdosing

- What is microdosing?
  - Successive self-administration
  - Within a limited time window
  - Doses that do not impair normal functioning and are predominantly sub-sensorium
- What is being microdosed?
  - Predominantly psilocybin and LSD, but others have been noted in observational research
- How much?
  - Typical: 5 - 20 µg of LSD /0.1 to 0.3g of dried psilocybin
  - Several times a week with microdose days alternating with non-microdose days.

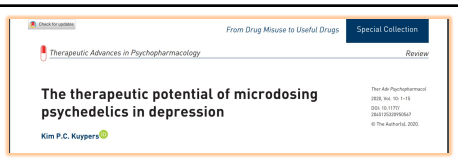
(Cameron et al., 2020;; Hutten et al., 2019a; Hutten et al., 2019b; Lea et al., 2020a; Lea et al., 2020b; Polito & Stevenson, 2019; Rosenbaum et al., 2020; Kuypers et al., 2019)

76

Stacking

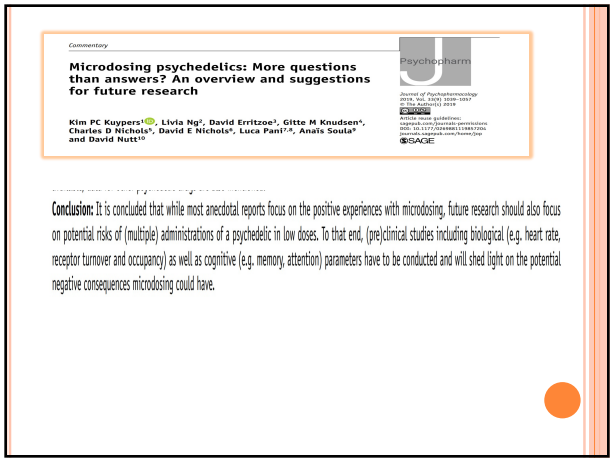
- Growing interest has focused on combining microdoses of primarily psilocybin-containing mushrooms with other substances such as:
  - Lions Mane mushrooms (*Hericium erinaceus*)
  - Niacin
  - Cacao
  - Chocolate
  - Syrian rue (*Peganum harmala*)

77



- Reviewed 14 experimental studies of LSD and psilocybin microdosing
- Findings show subtle positive effects on cognitive processes
  - time perception,
  - convergent and divergent thinking
  - brain regions involved in affective processes

78



Commentary

Microdosing psychedelics: More questions than answers? An overview and suggestions for future research

Kim PC Kuypers[1], Livia Ng[2], David Erritzoe[3], Gitte M Knudsen[4], Charles D Nichols[5], David E Nichols[6], Luca Passie[7,8], Anaïs Soula[9] and David Nutt[10]

Psychopharm
Journal of Psychopharmacology 2019, Vol. 33(9) 1039–1057
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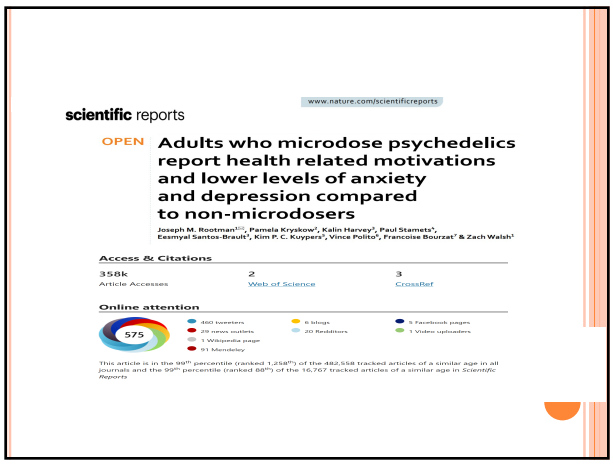
DOI: 10.1177/0269881119857204
journals.sagepub.com/home/jop
SAGE

Conclusion: It is concluded that while most anecdotal reports focus on the positive experiences with microdosing, future research should also focus on potential risks of (multiple) administrations of a psychedelic in low doses. To that end, (pre)clinical studies including biological (e.g. heart rate, receptor turnover and occupancy) as well as cognitive (e.g. memory, attention) parameters have to be conducted and will shed light on the potential negative consequences microdosing could have.

79



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scientific reports

OPEN

Adults who microdose psychedelics report health related motivations and lower levels of anxiety and depression compared to non-microdosers

Joseph M. Rootman[1,2], Pamela Kryskow[2], Kalin Harvey[2], Paul Stamets[3], Esamyal Santos-Brault[3], Kim P. C. Kuypers[4], Vince Polito[5], Francoise Bourzat[2] & Zach Walsh[1]

Access & Citations

358k	2	3
Article Accesses	Web of Science	CrossRef

Online attention

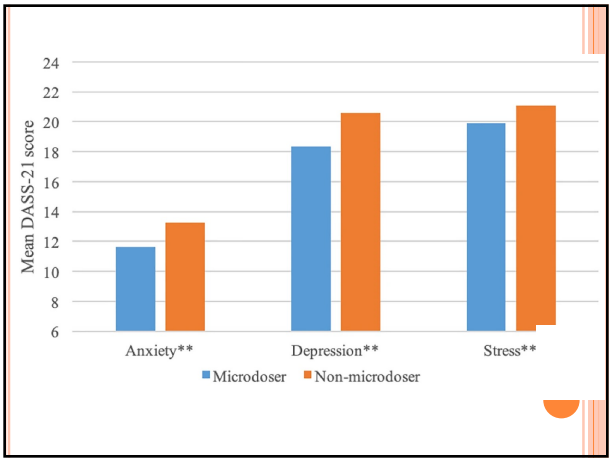
This article is in the 99th percentile (ranked 1,258th) of the 482,558 tracked articles of a similar age in all journals and the 99th percentile (ranked 68th) of the 16,767 tracked articles of a similar age in *Scientific Reports*

80

Psilocybin (n = 3486)	
Frequency	
5 or more times per week**	23.0% (800)
1-4 times per week**	72.4% (2520)
Combination/ stacking*	**54.7% (1890)**

	No concerns (2665)	Mental health concerns (1261)
Enhance mindfulness	82.0% (2184)	84.9% (1070)
Improve mood**	70.6% (1882)	87.3% (1104)
Enhance creativity	75.3% (2006)	72.2% (911)
Enhance learning**	60.0% (1599)	54.6% (688)
Decrease anxiety**	47.0% (1252)	78.0% (984)
Improve sleep**	25.4% (678)	33.1% (418)
Decrease substance use**	18.3% (489)	41.5% (523)

81



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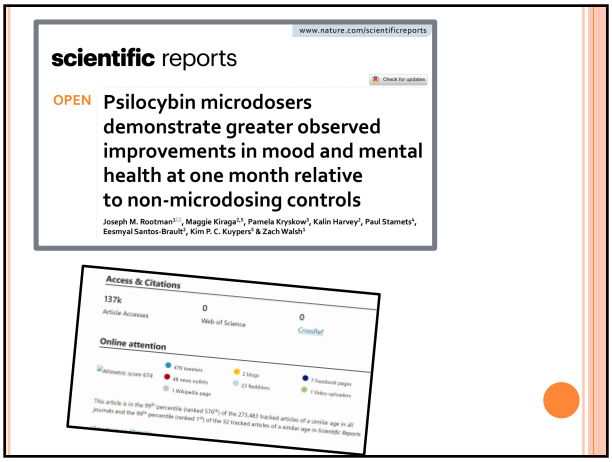
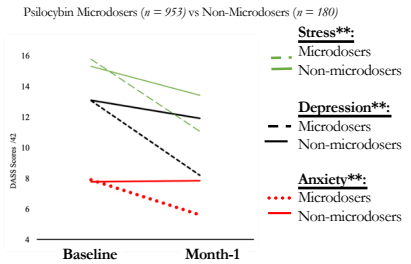


83

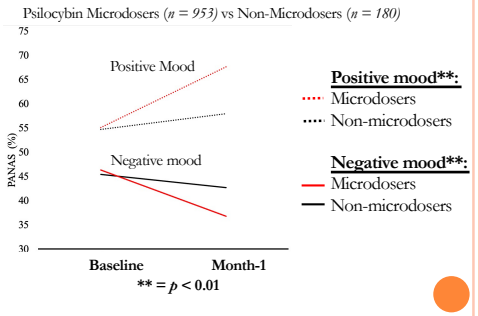
Mental health (DASS) – Longitudinal



** = $p < 0.01$

84

Mood (PANAS) - Longitudinal



85

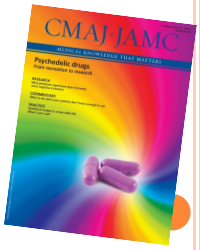
Harms & Risks

- Withdrawal
  - No withdrawal symptoms
- Self-Administration
  - Nonhumans
    - Not self-administered by nonhumans
      - Adverse effects
      - Work to avoid
        - Exception is
        - **Hawaiian dogs eat shrooms** & mongoose eat trippy toads
        - DMT with monkeys with a history of administering MDMA
  - Humans
    - Ancient - No continuous consumption

86

Harms & Risks

- Harmful Effects
  - Acute psychotic reaction or "freak out"
  - Flashbacks & trailing phenomena ?
  - No recorded death from overdose
- Bad Trips?
  - Difficult – In & Through
  - Re-traumatization?
- Importance of Set & Setting



87

MDMA

- Withdrawal
  - Hangover effects
- Harmful Effects of Ecstasy
  - Depletion in serotonin (reversible?)
    - Sleep disorders, depression, persistent anxiety, impulsiveness, hostility, and selective impairment of memory and attention
      - Most effects dissipate after about 6 months once drug is stopped
    - Heat regulation: increase in body temperature may lead to heatstroke, muscle tissue damage, kidney failure, seizures
    - Electrolyte imbalances
  - Quality control
    - Impure

88

HALLUCINOGENS - DISSOCIATIVES

- Harmful Effects
  - Disorientation, agitation, hyperactivity
  - Long term heave use – severe bladder problems

89

ETHICAL CONSIDERATIONS

ORIGINAL ARTICLE

Journal of Psychedelic Studies
DOI: 10.1556/2054.2019.032

Diversity, equity, and access in psychedelic medicine

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[2]Department of Psychology, University of Connecticut, Storrs, CT, USA
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(Received: October 29, 2019; accepted: November 12, 2019)

Although it is exciting to witness the culmination of decades of drug policy advocacy and clinical research, the psychedelic science movement struggles with many of the same social issues that plague healthcare in general. The healing properties of plant medicines and their derivatives were originally brought to Western consciousness by indigenous cultures from all over the world. These practices are now being adapted to Western models of healthcare, in part, to achieve governmental approval as medical treatments. The current models of psychedelic psychotherapy being utilized in clinical trials are resource-intensive and therefore likely to remain out of reach for the socioeconomically disadvantaged if approved as medical treatments. Moreover, people of color and women are uncommon in leadership positions in the psychedelic research community, and few people of color are included as research participants in psychedelic studies. This piece introduces a special issue with a focus on issues of diversity, equity, and accessibility in psychedelic medicine.

Keywords: psychedelics, diversity, race, culture, therapy

90

Ethical Considerations

ORIGINAL ARTICLE

Journal of Psychedelic Studies 4(1), pp. 69–71 (2020)
DOI: 10.1556/2054.2019.030
First published online December 5, 2019

Considerations for psychedelic therapists when working with Native American people and communities

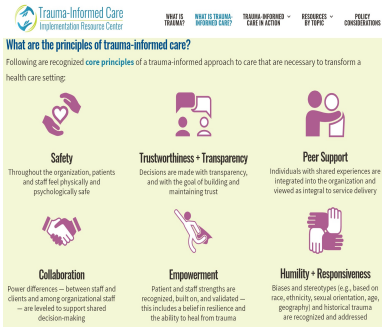
BELINDA ERIACHO*

Kaalogii, LLC, Tempe, AZ, USA

- Trust and respect are the keys to building a strong rapport. It is important to understand throughout our history with non-native people that our relationships were typically fraught with deceit and mistrust. As a result, our natural tendency and response to someone offering to help us is skepticism. Therapist and practitioners will need to exercise patience and over time for the relationship will flourish.
- Native American individuals are private by nature and do not typically disclose their personal lives. Growing up in a small community on the reservation where everyone knows each other and should not be taken too lightly. There is often reluctance for a native individual living in a small community to share their personal lives openly, especially with a stranger. There may be fear from the native client's perspective that others in the community will know their business. Therefore, it is important that precautionary measures are taken to ensure each individual's privacy outside of the clinical and therapeutic settings is maintained.
- Therapeutic models that allow for Native American traditional practitioners to be a part of treatment plan processes have proven to be beneficial (e.g., Pouchly, 2012). In addition, allowing native clients to use health practices (such as sweat lodge or talking circles) can improve the treatment outcomes.
- The concepts of mental illness and associated disorders have a different causation and remedies in Native American cultures, and this understanding should be included in the treatment plan as much as possible (Duran, Duran, Heart, & Horse-Davis, 1998).
- Spirituality is not separated from our physical, emotional, and mental bodies. Hence, the treatment plan should be culturally specific(Bassett, 2012).
- Educating ourselves about the Native American culture(s) for which we will be providing care is fundamental to establishing rapport with clients and cos, and languages (Bureau of Indian Affairs, 2019).

91

Ethical Considerations



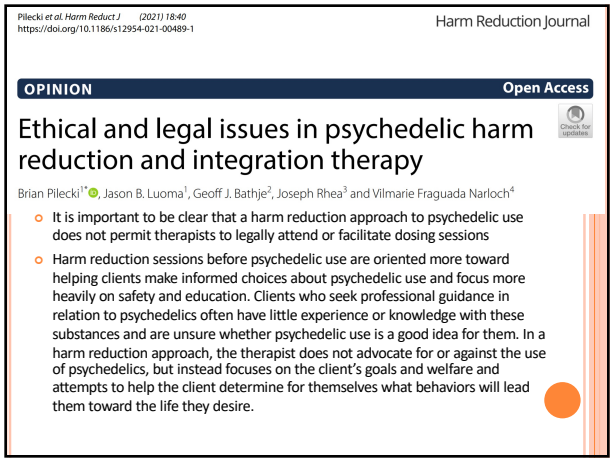
https://youtu.be/8wxnzVib2p4

- Trauma-informed care seeks to:
  - Realize the widespread impact of trauma and understand paths for recovery;
  - Recognize the signs and symptoms of trauma in patients, families, and staff;
  - Integrate knowledge about trauma into policies, procedures, and practices; and
  - Actively avoid re-traumatization.

92

- Start Within
  - I pledge to ground my work in the field with work on myself, and to treat personal growth as a lifelong process.
- Study the Traditions
  - I pledge to grow my knowledge of the history of psychedelics and their many traditions of use, in a good-faith effort to appreciate both the potential of these substances and the conflict and complexity surrounding them.
- Build Trust
  - I pledge to invest in building trust in my relationships across the psychedelic field, and repair trust where possible.
- Consider the Gravity
  - I pledge to consider the implications of the choices that I make, understanding the potential consequences of unethical behavior to individuals, communities, and the psychedelic field at large.
- Focus on Process
  - I pledge to make the process as important as the outcome, letting the future I hope to see guide the approach I take in getting there.
- Create Equality & Justice
  - I pledge to actively take steps to make the world more equitable and just.
- Pay it Forward
  - I pledge to support the flourishing of the psychedelic field and the communities in which I work, and to give back should my work lead to personal gain.

93

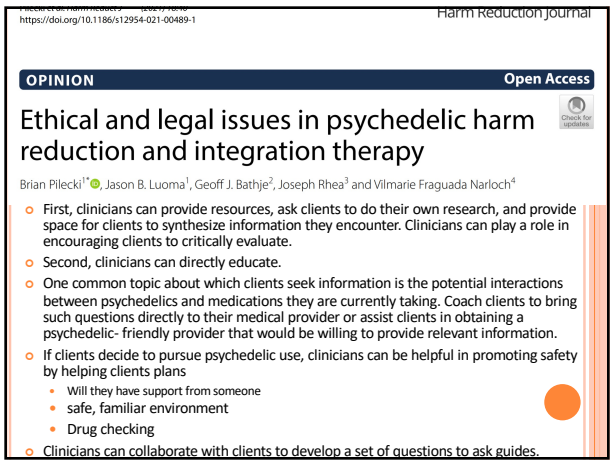

Pilecki et al. Harm Reduct J (2021) 18:40
https://doi.org/10.1186/s12954-021-00489-1
Harm Reduction Journal
OPINION
Open Access

Ethical and legal issues in psychedelic harm reduction and integration therapy

Brian Pilecki[1*], Jason B. Luoma[1], Geoff J. Bathje[2], Joseph Rhea[3] and Vilmarie Fraguada Narloch[4]

- It is important to be clear that a harm reduction approach to psychedelic use does not permit therapists to legally attend or facilitate dosing sessions
- Harm reduction sessions before psychedelic use are oriented more toward helping clients make informed choices about psychedelic use and focus more heavily on safety and education. Clients who seek professional guidance in relation to psychedelics often have little experience or knowledge with these substances and are unsure whether psychedelic use is a good idea for them. In a harm reduction approach, the therapist does not advocate for or against the use of psychedelics, but instead focuses on the client's goals and welfare and attempts to help the client determine for themselves what behaviors will lead them toward the life they desire.

94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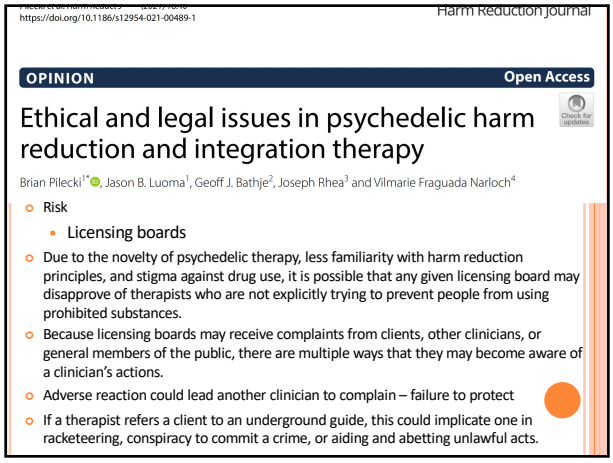
- First, clinicians can provide resources, ask clients to do their own research, and provide space for clients to synthesize information they encounter. Clinicians can play a role in encouraging clients to critically evaluate.
- Second, clinicians can directly educate.
- One common topic about which clients seek information is the potential interactions between psychedelics and medications they are currently taking. Coach clients to bring such questions directly to their medical provider or assist clients in obtaining a psychedelic- friendly provider that would be willing to provide relevant information.
- If clients decide to pursue psychedelic use, clinicians can be helpful in promoting safety by helping clients plans
  - Will they have support from someone
  - safe, familiar environment
  - Drug checking
- Clinicians can collaborate with clients to develop a set of questions to ask guides.

95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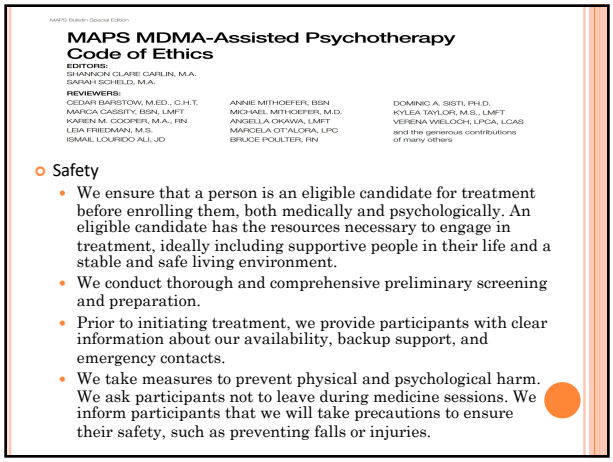
- Risk
  - Licensing boards
- Due to the novelty of psychedelic therapy, less familiarity with harm reduction principles, and stigma against drug use, it is possible that any given licensing board may disapprove of therapists who are not explicitly trying to prevent people from using prohibited substances.
- Because licensing boards may receive complaints from clients, other clinicians, or general members of the public, there are multiple ways that they may become aware of a clinician's actions.
- Adverse reaction could lead another clinician to complain – failure to protect
- If a therapist refers a client to an underground guide, this could implicate one in racketeering, conspiracy to commit a crime, or aiding and abetting unlawful acts.

96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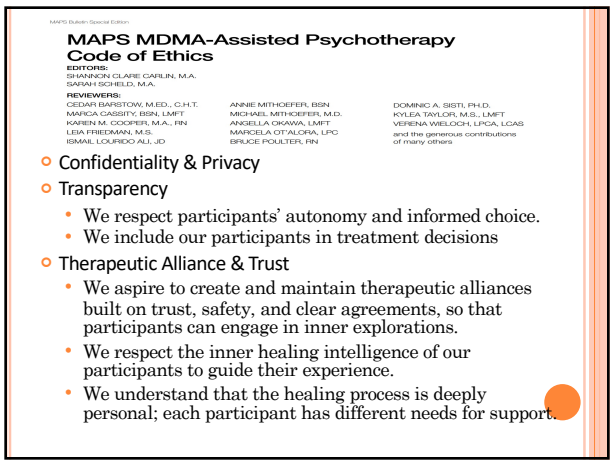
VERENA WIELOCH, LPCA, LCAS
and the generous contributions of many others
Safety
We ensure that a person is an eligible candidate for treatment before enrolling them, both medically and psychologically. An eligible candidate has the resources necessary to engage in treatment, ideally including supportive people in their life and a stable and safe living environment.
We conduct thorough and comprehensive preliminary screening and preparation.
Prior to initiating treatment, we provide participants with clear information about our availability, backup support, and emergency contacts.
We take measures to prevent physical and psychological harm. We ask participants not to leave during medicine sessions. We inform participants that we will take precautions to ensure their safety, such as preventing falls or injuries.

97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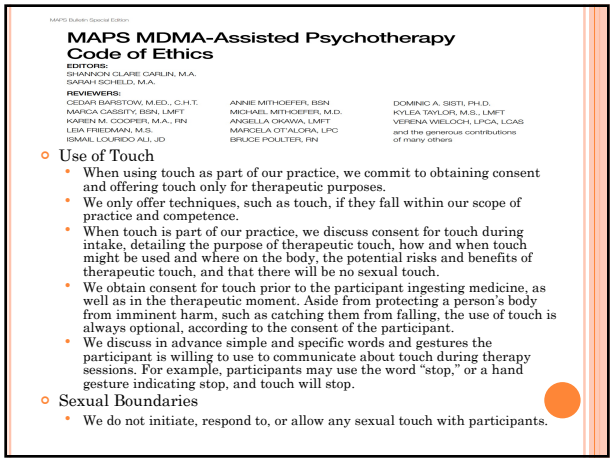
Confidentiality & Privacy
Transparency
We respect participants' autonomy and informed choice.
We include our participants in treatment decisions
Therapeutic Alliance & Trust
We aspire to create and maintain therapeutic alliances built on trust, safety, and clear agreements, so that participants can engage in inner explorations.
We respect the inner healing intelligence of our participants to guide their experience.
We understand that the healing process is deeply personal; each participant has different needs for support.

98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Use of Touch
When using touch as part of our practice, we commit to obtaining consent and offering touch only for therapeutic purposes.
We only offer techniques, such as touch, if they fall within our scope of practice and competence.
When touch is part of our practice, we discuss consent for touch during intake, detailing the purpose of therapeutic touch, how and when touch might be used and where on the body, the potential risks and benefits of therapeutic touch, and that there will be no sexual touch.
We obtain consent for touch prior to the participant ingesting medicine, as well as in the therapeutic moment. Aside from protecting a person's body from imminent harm, such as catching them from falling, the use of touch is always optional, according to the consent of the participant.
We discuss in advance simple and specific words and gestures the participant is willing to use to communicate about touch during therapy sessions. For example, participants may use the word "stop," or a hand gesture indicating stop, and touch will stop.
Sexual Boundaries
We do not initiate, respond to, or allow any sexual touch with participants.

99

- Diversity
  - We respect the value of diversity, as it is expressed in the various identities and experiences of our participants
- Special Considerations for Non-Ordinary States of Consciousness
  - Participants in non-ordinary states of consciousness may be especially open to suggestion, manipulation, and exploitation; therefore, we acknowledge the need for increased attention to safety and issues of consent.
  - We examine our own actions and do not engage in coercive behavior.
  - In working with non-ordinary states that can evoke unconscious material for both the participant and therapy provider, we acknowledge the potential for stronger, more subtle, and more complicated transference and countertransference, and, with that in mind, we practice self-awareness and self-examination, and seek supervision as needed.
  - We respect the spiritual autonomy of our participants. We practice vigilance in not letting our own attitudes or beliefs discount or pathologize our participants' unique experiences. We hold and cultivate an expanded paradigm, which includes the experiences people have in extraordinary states.
  - We protect our participants' health and safety through careful preparation and orientation to the therapy, as well as thorough integration.
  - We support participants who may experience crisis or spiritual emergency related to psychedelic experiences with appropriate medical and psychological care, engaging the support of outside resources as needed.

100

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- Finance
- Competence
- Relationship to Colleagues and the Profession
- Relationship to Self
  - We subscribe to the value of humility, out of respect for the transformative power of the experiences we have the privilege to witness and support, and out of respect for human dignity

101

THANKS

Therapeutic, Recreational, & Problematic Substance Use Lab

http://blogs.ubc.ca/walshlab/ ZACHARY.WALSH@UBC.CA

102