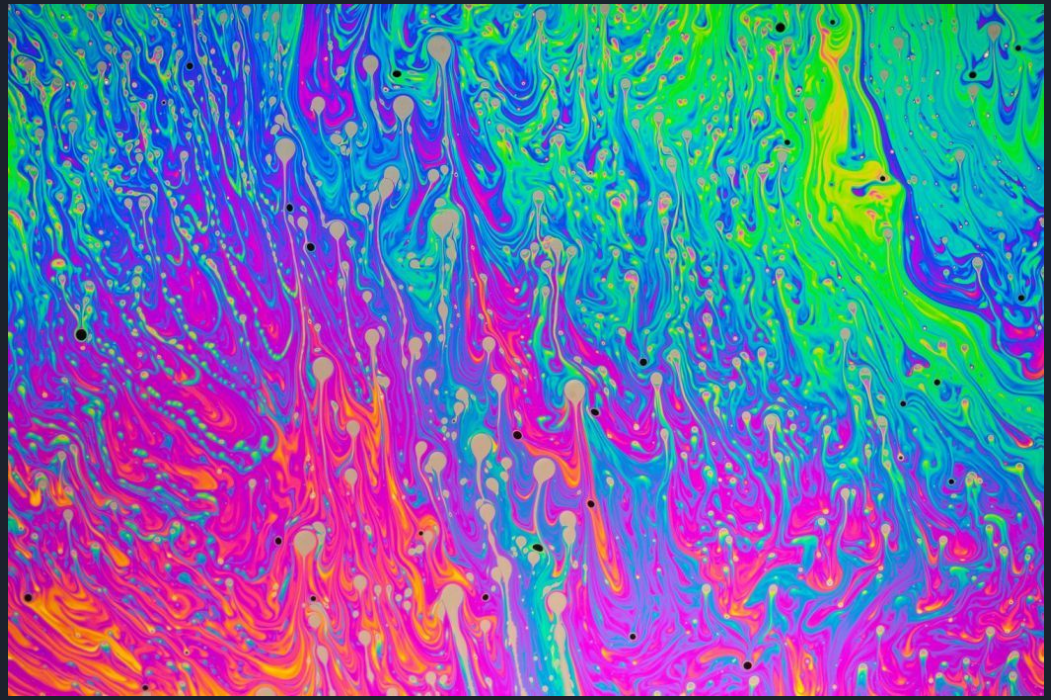


Psychedelic Drugs and its therapeutic uses

Zane Dax, BHSc

Psychedelic chemistry

Tryptamine derivatives are simple indole alkaloids, derived biosynthetically from tryptophan, an essential amino acid that is universally distributed in all plants and animals (humans are not able to naturally produce it)

Decarboxylation of tryptophan by aromatic amino acid decarboxylase, an enzyme fundamental to basic metabolic processes in plants and animals, yields tryptamine

Hydroxylation of tryptamine at position 5 on the indole ring yields 5-hydroxytryptamine (5-HT), also known as serotonin.
Serotonin is also a major central nervous system neurotransmitter, and most hallucinogenic drugs are thought to be agonists at 5HT2a receptors, one of about fourteen subtypes of serotonin receptors.

A trivial chemical modification of tryptamine, viz. the addition of two methyl groups (CH_3) groups to the side-chain nitrogen, yields the simplest of the hallucinogenic tryptamines, N,N-dimethyltryptamine or DMT.

related compound, bufotenine or 5-hydroxy-N,N-dimethyltryptamine (5-OH-DMT), can be derived from serotonin by a similar methylation reaction; bufotenine is so named because it is found in the skins of certain toads belonging to the genus Bufo.

The O-methylation of the hydroxy group of bufotenine yields 5-methoxy- N,N-dimethyltryptamine (5-MeO-DMT), a compound similar to DMT in that it is a short-acting hallucinogen, but approximately 10 times more potent, on a per weight basis.

The 4-hydroxy analog of bufotenine is psilocin (4-hydroxy-N,N-dimethyltryptamine), which is the active principle in the hallucinogenic “magic” mushrooms

(McKenna & Riba, 2018)

The simple hallucinogenic tryptamine derivatives, by which is meant here DMT and its derivatives, 5-MeO-DMT, psilocin, psilocybin, and bufotenine are widely distributed in nature, occurring in animals as well as plants and fungi
Tryptamine derivatives have been reported from over 26 higher plant families; those including hallucinogenic derivatives such as DMT, 5-MeO-DMT, and bufotenine are the *Aizoaceae, Apocynaceae, Poaceae, Fabaceae, Malpighiaceae, Myristicaceae, Pandanaceae, Rubiaceae, Rutaceae, and Urticaceae*

Psilocybin and psilocin are apparently restricted to higher fungi and are found primarily in mushrooms of the genera Psilocybe, Stropharia, and Panaeolus

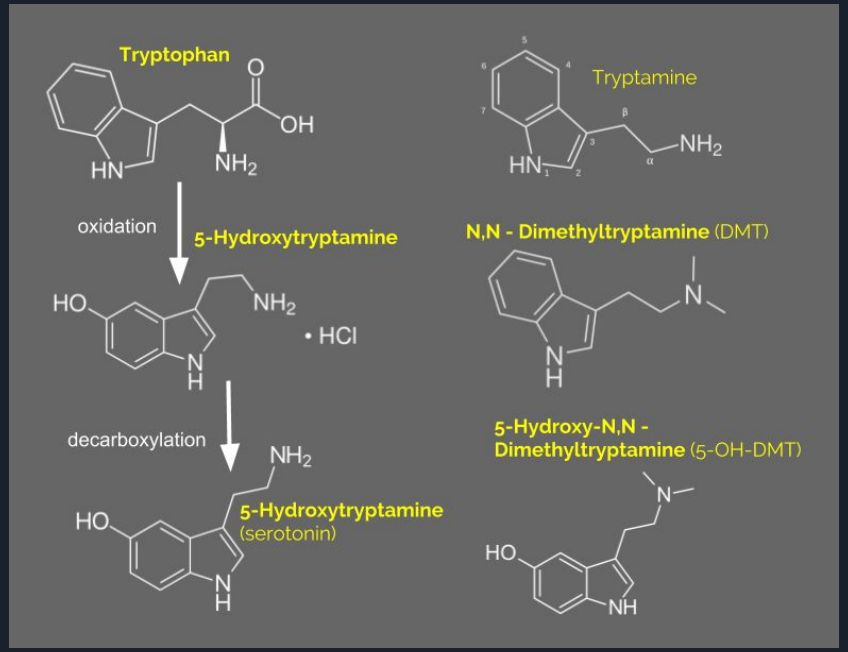
DMT and 5-MeO-DMT are both potent, extremely short-acting hallucinogens whose total duration of action is less than 30 min from “baseline” to "baseline". Neither of these derivatives is orally active, due to degradation by the enzyme monoamine oxidase (MAO), which is present in the liver and gut, as well as the brain, of humans and other mammals.
Psilocin is orally active by itself and does not require an MAOI (monoamine oxidase inhibitor which protects from degradation) for activation; as a result, no special preparation is required to experience the effects of the magic mushrooms.

(McKenna & Riba, 2018)

This compound is derived from psilocybin, which is simply the 4-phosphoryl ester of psilocin; psilocybin is converted to psilocin in the body and it is psilocin that is thought to be the active form of psilocybin.

tryptamine derivatives ß-carbolines, which, like tryptamines, are structurally simple and widely distributed in the plant kingdom

less potent but definitely psychoactive lysergic acid derivatives are found in plants, notably the sacred morning glories of Mexico and Central America (members of the genera Ipomoea, Rivea, and Turbina) as well as in the well-known ergot fungus (Claviceps purpurea and other Claviceps spp.). Other than ergot fungi and the morning glory family (Convolvulaceae), however, lysergic acid derivatives are rare in nature



(McKenna & Riba, 2018)

Psilocybin mushrooms

The Spanish conquistadores encountered a flourishing mycolatrous religion among the Aztecs at the time of the arrival of Cortés in the court of Moctezuma in 1519. Based on linguistic analyses of lexicons compiled by the Spanish missionaries, Wasson has presented convincing evidence that the inebriating mushrooms were known, not only to the Aztecs and Maya, but also to the Nahua, Otomi, Matlatzinca, Mazahua, Tarascan, Huastecan, Totomac, Mixe, Zoque, Mazatec, Zapotec, Chatino, Mixtec, and Chinantla linguistic groups.

The Spanish missionaries, regarded the Aztec's ritual and religious use of *teonanácatl*, a name erroneously translated as "god's flesh" as a particularly odious and blasphemous parody of the Christian Eucharist. the considerable intimidatory powers of the Spanish Inquisition, succeeded in driving the practice underground for the next 400 years. it was rediscovered and made known to the world by the famous team of R. Gordon and Valentina Wasson, in an article published in Life magazine in May, 1957

The majority of the known species belong to the genus Psilocybe, but other genera reported to contain psilocybin include *Agrocybe, Conocybe, Copelandia, Paneolina, Paneolus, Galerina, Gymnopilus, Inocybe, Pluteus, Hypholoma, Gerronema, and Mycena.*

(McKenna & Riba, 2018)

Medicinal plants in South America

medicinal plants that Columbus encountered in his earliest visits to the New World, the intoxicating snuff prepared from the seeds of the *Fabaceoustree, Anadenanthera peregrina.* Commissioned Friar Ramon Pane to undertake an ethnographic documentation of the use of cohoba (or cogioba), as it was known to the Taino people, the indigenous inhabitants of what is now Haiti.

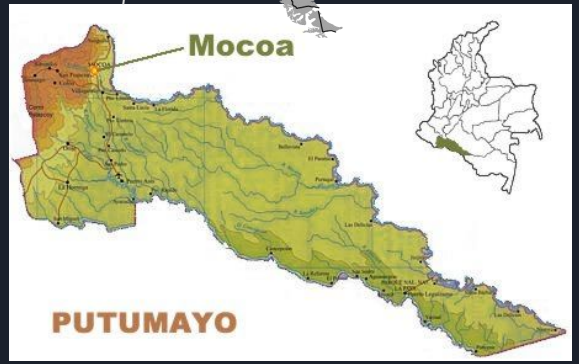
in the Atacama desert, another snuff, known as vilca or huilca in Peru and Bolivia and cébil in Northern Argentina, was similarly prepared from a different Anadenanthera species native to this region, A. colubrina. Many well-preserved grave sites containing snuffing implements, including carved snuff trays, snuffing tubes, and woven bags containing snuff powders, have been excavated in this area and dated to as early as 570 AD. established the presence of tryptamine alkaloids in the snuff powders, thus confirming their identity as derived from Anadenanthera species

of Anadenanthera species The most abundant alkaloids reported from A. peregrina and A. colubrina are bufotenine, DMT, and 5-methoxy- DMT.

(McKenna & Riba, 2018)

Medicinal plants in South America

In the Colombian Putumayo, the Bora, Witoto, and Muinane prepare an orally active hallucinogen from the resin of *Virola theiodora, V. elongata, and V. pavonis.*
the drug, which is known as *oo-koo-he* among the Witoto and *kú-ru-ku* among the Bora, is prepared by stripping the bark, collecting the resin, and concentrating it to a thick, syrupy consistency. This is then mixed with the ashes of other plants (usually *Gustavia peoppigiana or Theobroma* spp.) and rolled into pellets, these pellets is said to induce a rapid and violent intoxication



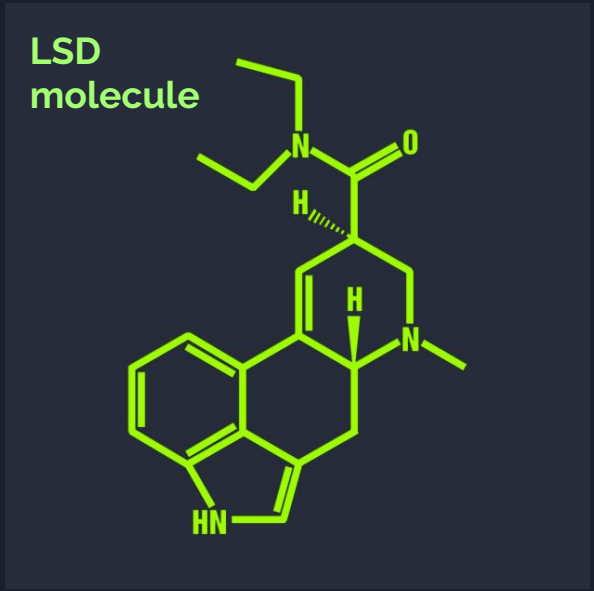
(McKenna & Riba, 2018)

Short history of psychedelics in research

LSD was used in psychotherapy for treatment of mood disorders and alcohol dependence, drugs such as LSD showed initial therapeutic promise before prohibitive legislature in the mid-1960s

Psychedelic drugs (Psychedelic is a neologism that combines the words psychē (ψυχή, 'soul') and dēloun (δηλοῦν, 'to make visible, to reveal'), to denote 'mind-revealing' in reference to the category of drugs

lysergic acid diethylamide (LSD) in the early 1950s, psychedelics, and particularly LSD, became widely used by psychologists and psychiatrists



(Carhart-Harris & Goodwin, 2017)

(Carhart-Harris & Goodwin, 2017)

Table I Notable Landmarks of Mid-Twentieth Century Psychedelic Research Plus Events of Cultural Significance

Year	Landmark	References
1943	LSD's psychoactive effects discovered by Albert Hofmann (16th and 19th April)	Hofmann, 1980
1947	Werner Stoll publishes first paper on psychological effects of LSD in humans	Stoll, 1947
1950	First English language publication on LSD	Busch and Johnson, 1950
c. 1953	ACNP Founding president Joel Elkes (President in 1961) publishes on LSD after openly self-experimenting with it	Bradley *et al*, 1953; Roberts, 2008
1954	Aldous Huxley's 'The Doors of Perception' published: documents mescaline self-experiment	Huxley, 1954
1956	Term 'psychedelic' coined by Humphrey Osmond in communication with Aldous Huxley	Huxley, 1980
1957	Term 'magic mushrooms' coined by LIFE magazine	Wasson, 1957
1958	Identification of psilocybin in magic mushrooms by Albert Hofmann	Hofmann *et al*, 1958
1959	Closed conference held in Princeton on 'the use of LSD in psychotherapy', Jonathan Cole attends, an early ACNP president	Abramson, 1959
1960	First major European conference on psychedelics; Sidney Cohen publishes positive meta-analysis on LSD safety	Passie, 1996; Cohen, 1960
1961	Jonathan Cole (ACNP president 1965-66) expresses 'very mixed feelings on psychedelic research' as critical commentaries emerge	Mangini, 1998
1962	The Marsh Chapel or 'Good Friday' experiment conducted at Harvard under Timothy Leary's supervision but without institutional approval	Pahnke, 1966; Mangini, 1998
1963	Leary dismissed from Harvard; Aldous Huxley and JFK die (both on 22nd November)	Stevens, 1987
1964	Cole takes 'sober look' at psychedelics in JAMA; discussions on LSD take center stage at 1964 APA meeting; Ken Kesey travels across US taking LSD with 'Merry Pranksters'	Mangini, 1998; Cole and Katz, 1964; Stevens, 1987; Wolfe, 1968
1965	Sandoz stop manufacture of LSD and psilocybin	Stevens, 1987
1966	Prohibition of psychedelics and curtailment of research begins in US; Senator Robert Kennedy formally questions this move	Stevens, 1987; Lee and Shlain, 1992
1967	Timothy Leary declares 'turn on, tune in and drop out' at festival in Golden Gate Park	Stevens, 1987
1970	President Nixon signs Controlled Substances Act, LSD and psilocybin made Schedule I	Stevens, 1987; Lee and Shlain, 1992

Abbreviations: ACNP, American College of Neuropsychopharmacology; JAMA, *Journal of the American Medical Association*; NIMH, National Institute of Mental Health.

Historical timeline of psychedelic drugs used in medical research up to prohibition

Psychedelics for mental illness

Note that plant based psychedelics is far from recent and is part of the ancient holistic healing approach to mental health.

Psychologists and psychiatrists in the 1950s got interested in psychedelics for their effects on their patient subjects.

In a recent meta-analysis of **19 studies** of psychedelics for mood disorders published **between 1949 and 1973** found that 79% of patients showed 'clinically judged improvement' **post** treatment

Three Double Blind-Random Controlled trials have assessed the impact of a single dose of **psilocybin** on depressive symptoms in patients with life-threatening cancer and for treatment-resistant depression (TRD). All four studies found rapid, marked, and enduring anti-anxiety and depression effects post psilocybin.

Other studies have found improvements with obsessive compulsive disorder symptoms, alcohol dependence with psilocybin, anxiety with LSD, and depression with ayahuasca

(Carhart-Harris & Goodwin, 2017)

(Carhart-Harris & Goodwin, 2017)

Table 2 Clinical Trials Involving Psychedelics Published During the Present 'Second Wave' of Psychedelic Research

Study	Population/indication and sample size	Drug and design	Main efficacy outcome
Moreno *et al* (2006)	Obsessive compulsive disorder, $n=9$	Psilocybin: single-arm, within subjects, variable doses. Up to four doses of psilocybin	All patients showed improvements within 24 h of a treatment but no effect of dose
Grob *et al* (2011)	Anxiety and depression in end-stage cancer, $n=12$	Psilocybin: DB-RCT, crossover, inert placebo. Single dose of psilocybin	Significant reductions in trait anxiety at 3 months and depression at 6 months
Johnson *et al* (2014)	Long-term chronic tobacco smoking, $n=15$	Psilocybin: open-label. Up to three doses of psilocybin after four CBT sessions	80% of sample abstinent at 6 month follow-up
Gasser *et al* (2014)	Anxiety related to life-threatening disease, $n=12$	LSD: DB-RCT, crossover, very low dose (VLD) LSD = control. Single dose of LSD	Significant decreases in state and trait anxiety *vs* VLD at 2 months and sustained for 12 months
Bogenschutz *et al* (2015)	Alcohol dependence, $n=10$	Psilocybin: open-label. Up to two doses after seven motivational therapy sessions	Significant decrease in drinking behaviors for up to 9 months
Osorio Fde *et al* (2015) and Sanches *et al* (2016)	Major depressive disorder (MDD), $n=6$+study extension to $n=17$	Ayahuasca: open-label. Single dose of ayahuasca	Significant decreases in depressive symptoms for up to 21 days
Carhart-Harris *et al* (2016a,b)	Treatment-resistant MDD, $n=12$ +study extension to $n=20$	Psilocybin: open-label. Two doses of psilocybin	Significant decreases in depressive symptoms for up to 6 months
Ross *et al* (2016)	Anxiety and depression related to life-threatening cancer, $n=29$	Psilocybin: DB-RCT, crossover, niacin = active placebo. Single dose of psilocybin	Significant decreases in anxiety and depression *vs* niacin at 7 weeks (pre crossover) and sustained for 6.5 months
Griffiths *et al* (2016)	Anxiety and depression related to life-threatening cancer, $n=51$	Psilocybin: DB-RCT, crossover, VLD psilocybin = control. Single dose of psilocybin	Significant decreases in anxiety and depression *vs* VLD at 5 weeks (pre crossover). Effects sustained for 6 months

Abbreviations: DB-RCT, double-blind randomised controlled trial; VLD, very low dose; MDD, major depressive disorder; TRD, treatment-resistant depression.

Psychedelics vs Pharmaceuticals

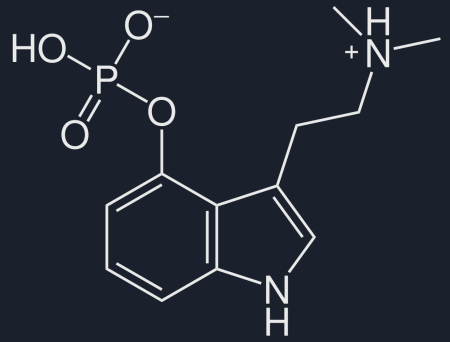
For specific antidepressant usage, psilocybin, and psychedelics more generally, share some similarities with conventional antidepressants (ie, serotonergic modulation)

But the difference is the chronic antidepressant action of SSRIs includes reduced limbic responsiveness and emotional moderation by receptor signaling. This contrasts of psychedelics emphasis on emotional release

(Carhart-Harris & Goodwin, 2017)

Serotonin

Psilocybin



Arthur Heffter isolated mescaline, the principal psychoactive constituent of the peyote cactus, in 1897

Over 100 species of mushrooms have been found to contain psilocybin, many falling within the genus Psilocybe. Psilocybin is a relatively small compound based on the structure of tryptamine.

Humphry Osmond, to coin the term "psychedelic", meaning "mind-manifesting" as a descriptor of this class of drugs

Consistent with medical and observational studies, the founder of Alcoholic Anonymous, Bill Wilson, was a proponent of the theoretic potential of classic psychedelics to facilitate treatment of addiction. Wilson concluded this after receiving medically supervised LSD sessions, and likening the effects to the spiritual experience that had prompted his sobriety decades beforehand

therapeutic laboratory studies of psilocybin :

- cancer related depression
- treatment-resistant depression
- addiction
- obsessive-compulsive disorder
- cluster headaches

(Johnson & Griffiths, 2017)

Psychedelics and smoking cessation

A retrospective cross-sectional anonymous online survey characterized 358 individuals (52 females) who reported having quit or reduced smoking after ingesting a psychedelic in a non-laboratory setting ⩾1 year ago.

On average, participants smoked 14 cigarettes/ day for 8 years, and had five previous quit attempts before their psychedelic experience.

This study does suggest that psilocybin and other serotonergic psychedelics may hold considerable potential in the treatment of tobacco, and possibly other substance use disorders, and should therefore continue to be examined as a pharmacological aid in the treatment of addiction

Results:

- 38% reported continuous smoking cessation after psychedelic use (quitters).
- 28% reported a persisting reduction in smoking (reducers)
- 34% of the 358 participants (relapsers) reported a temporary smoking reduction before returning to baseline smoking levels, with a mode time range to relapse of 3–6 months. *Relapsers rated their psychedelic experience significantly lower in personal meaning and spiritual significance than both other groups*

(Johnson, Garcia-Romeu, Johnson & Griffiths, 2017)

Mycology: mushrooms

(Jo, Hossain & Park, 2014)

The worldwide diversity of mushroom species is roughly accounted as 0.14 million. Of these, 14,000 are known and 7,000 are considered to have varying levels of edibility. More than 2,000 species are safe and 700 are documented to have considerable pharmacological properties

Toxic substances are also found in some mushroom species with beneficial properties. The ingestion of mushrooms containing toxins is accidental and often occurs through the misidentification of species

It is critical to characterize the toxicological profile of mushroom species before using them for human consumption.

Mushroom toxins (toxidromes classification) have been divided into seven main categories: amatoxins (cyclopeptides), orellanus (Cortinarius species), gyromitrin (monomethylhydrazine), muscarine, ibotenic acid, psilocybin, and coprine

Mycology: medicinal mushrooms

All amatoxin-containing fungi are found within the families Amanitaceae (genus Amanita), Agaricaceae (genus Lepiota), and Cortinariaceae (genus Galerina). species of Amanita such as Amanita virosa, A. phalloides, A. ocreata, A. verna, A. suballiacea, A. bisporigera, A. hygroscopica, and A. tenuifolia are abundant in amatoxins. Amatoxins are bicyclic octapeptides and powerful thermostable poisons

The most potent amatoxin is α-amanitine, and is among the nine amatoxins that have been recognized. Ataxia, motor depression, euphoria, dizziness, gastrointestinal disturbances, drowsiness, muscle twitches and mood are common symptoms associated with amatoxin poisoning

Gyromitrin is an oxidizable volatile liquid at room temperature, making it an unstable chemical. The toxin gyromitrin is present in some species of Gyromitra. Ingestion of Gyromitra, and even the inhalation of vapors produced during the cooking of this mushroom, can cause toxicity. Diarrhea, vomiting, fatigue, vertigo, ataxia, tremor, and nystagmus are the most common symptoms of this intoxication. Development of hemolysis and hepatic diseases of moderate severity may develop in some patents. Symptoms of intoxication start 8~12 hr after ingestion. The antidote is pyridoxine.

(Jo, Hossain & Park, 2014)

Mycology: medicinal mushrooms

Muscarine is abundant in C. rivulosa, C. dealbata, C. cerussata, C. phyllophila, and C. candicans. It is also present in Amanita muscaria and the Inocybe genus. Symptoms of muscarinic syndrome include increased pulse rate, headache, nausea, vomiting, dizziness, and rapid breathing.
The symptoms of muscarinic poisoning caused by ingestion of mushrooms are sweating, tearing, drooling, vomiting, diarrhea, blood pressure, and shortness of breath due to effects on the parasympathetic nervous system. Administration of atropine is recommended to neutralize the muscarinic effects. It causes paralysis 20~22 min after ingestion by acting on the central nervous system. Muscimol can serve as an insecticide and can kill flies. The mushrooms containing muscimol are Amanita muscaria and Tricholoma muscarium. The antidote is physostigmine.

Psilocybin is found abundantly in the genus Psilocybe, Common mushrooms that contain psylocibin include P. bohemica, P. mexicana, P. semilanceata, P. baeocystis, and P. cubensis.
Frequently reported symptoms of this intoxication include hypertension, tachycardia, visual problems, nausea, anxiety, asthenia, vertigo, mydriasis, motor incoordination, and disorientation.
Indole derivative-containing psilocin mushrooms are usually blue in color. Symptoms of psilocin toxicity include curly limbs, tongue anxiety, poor comprehension, colorful hallucinations, and auditory hallucinations. The mushrooms containing psilocin are Panaeolus papilionaceus, Panaeolus sphinctrinus, and Panaeolus subbalteatus. The antidote is chlorpromazine.

(Jo, Hossain & Park, 2014)

Mycology: toxic mushrooms

Table 2. Molecular properties and mechanism of toxicity of different toxins found in various mushroom species

Toxin name	Sources	Molecular properties	Mechanism of toxicity	Reference
Ostreolysin	*Pleurotus ostreatus*	A 16-kDa acidic protein, is a member of the aegerolysin protein family. It contains 137 residues of amino acids 13 positively and 16 negatively charged residues.	Transient increase in arterial blood pressure and then a progressive fall to mid-circulatory pressure accompanied by bradycardia, myocardial ischemia, and ventricular extrasystoles. The hyperkalemia resulting from the hemolytic activity probably plays an important role in its toxicity.	[29, 30]
Amatoxin	Different species of *Amanita*	Thermostable bicyclic octapeptide. Nine amatoxins have been identified and α-amanitine is the most active.	Inhibit RNA polymerase-II and thus transcription of DNA occurs by protein synthesis and cell necrosis.	[16, 31]
Phallotoxin	*Amanita phalloides*	Peptides containing bicyclic-skeleton with a transannular thioether bridge.	Specific binding of the toxin to F-actin in liver cells, which consequently inhibits the depolymerization of F-actin into G-actin.	[32]
Agaritin	*Agaricus bisporus*	Is an L-glutamic acid (b-N-(g-L(+) glutamyl)-4-hydroxymethyl) phenylhydrazine).	Agaritine can be enzymatically activated to a mutagenic metabolite and can bind with DNA and form adducts.	[33, 34]
Orellanine	*Pleurotus ostreatus* and *Cortinarius orellanus*	Is a heat-stable bipyridine N-oxide. Orellanine chemically resembles the pyridine herbicides paraquat and diquat and is deoxidized to orelline that is non-toxic.	*In vitro* data strongly suggest that orellanine generates oxygen radicals at the target site through redox cycling and/or redox activation of iron. Further data from cellular systems indicate that a metabolite of the toxin can inhibit protein synthesis.	[35]
Gyromitrin	*Gyromitra esculenta*	Gyromitrin is a volatile liquid, which is quite unstable, oxidizes at room temperature, and exists free or bonded with glucosides.	The hydrazines are convulsants, and they react with pyridoxal phosphate to form a hydrazine, which results in the decreased activity of glutamic acid decarboxylase and diminished formation of GABA.	[36]
Acromelic acid	*Clitocybe acromelalga*	Is a member of kainoid family, a group of non-proteinogenic pyrolidine dicarboxylic acids.	Acromelic acid A exhibits neuroexcitatory activity, can bind glutamate receptors, mimics glutamic acid, causes characteristic behavior changes, and induced selective damage to the interneurons in the lower spinal cord when tested in an animal model.	[37]
Ibotenic acid	*Amanita muscaria* and *A. pantherina*	Is an α-amino-3-hydroxy-5-isoxazole acetic acid.	An NMDA receptor agonist. Because of the acidic property of the isoxazole moiety, it is similar to glutamic acid and mimics its effects in animals.	[14, 15]
Muscimol	*Amanita muscaria* and *A. pantherina*	It is a decarboxylated product of ibotenic acid.	This substance shows structural resemblance to GABA and imitates the action of this inhibitory neurotransmitter in the CNS.	[14, 15]
Muscarine	*C. serussata*, *C. dealbata*, *C. phyllophilla*, *C. rivulosa* and *A. muscaria*	It is tetrahydro-4-hydroxy-*N,N,N*-5-tetramethyl-2-furanmethanaminium.	Muscarine's structure is very similar to that of acetylcholine and it binds to the same receptors. It is not hydrolyzed by cholinesterase causing a parasympathomimetic symptomatology.	[31]
Psilocybin and psilocin	-	Component of the tyramine type, 4-phosphoryloxy-*N,N*-dimethyltryptamine	Cleavage of the phosphoric ester group by alkaline phosphatase and unspecific esterases indicates that psilocybin acts as a prodrug and that its hydroxyl metabolite psilocin the active agent. Activity of psilocybin is due to the activation of serotonin 2-A receptor.	[38, 39]

GABA, gamma-aminobutyric acid; NMDA, *N*-methyl-D-aspartate; CNS, central nervous system.

Table 1. Clinical manifestations, sites of toxicity, and toxicity potential of various mushroom species

Toxic syndrome	Toxins	Sites of toxicity	Species	Mortality rate	Reference
Acute gastroenteritis without liver failure	GI irritants	GIT	*Chlorophyllum molybdites*, *Clitocybe nebularis*, *Omphalotus illudens*	Rare	[19]
Hallucinogenic	Psilocybin, psilocin	CNS (hallucinogenic effects)	*Psilocybe cubensis*, *P. mexicana*, *Conocybe cyanopus*, *G. aeruginosa*	Rare	[20, 21]
CNS excitation and depression (stupor, coma, delirium, agitation, hallucinations and seizures)	Ibotenic acid, muscimol	CNS (depressant and excitatory effects)	*Amanita muscaria*, *A. pantherina*, *A. gemmata*	Rare	[22]
Cholinergic excess (vomiting, diarrhea, bradycardia, bronchorrhea, tearing, bronchospasm, salivation)	Muscarine	Autonomic nervous system (muscarinic receptors)	*Clitocybe dealbata*, *C. illudens*, *I. fastigiata*, *Boletus calopus*	Rare	[20, 21]
Flushing, headache, tachycardia, chest pain, anxiety	Coprine	-	*Coprinus atramentarius*	Rare	[20, 21]
Gastroenteritis and delayed onset renal failure	Allenic norleucine	Kidney, GIT	*Amanita smithiana*	Rare	[20, 21]
Delayed liver toxicity and delayed gastroenteritis	Amatoxins, phallotoxins	GIT, liver, kidney	*Amanita phalloides*, *A. virosa*, *A. verna*, *A. bisporigera*, *Galerina autumnalis*, *G. marginata*, *G. venenata*, *Lepiota helveola*	2–30%	[23, 24]
Seizures, delayed gastroenteritis, and liver toxicity	Gyromitrin	GIT, CNS, liver and blood	*Gyromitra esculenta*, *G. infula*, *Sarcosphaera coronaria*, *Chrysina macropus*	0–10%	[20, 21]
Delayed renal failure, cellular and oedematous intestinal fibrosis	Orellanine, orellinine, cortinarin	Kidney, GIT	*Cortinarius orellanus*, *C. speciosissinus*, *Mycena pura*, *O. orarius*	Rare	[25]
Delayed rhabdomyolysis	Unknown	Muscle	*Tricholoma equestre*	25%	[26]
Erythromelalgia	Acromelic acid	Peripheral nerves, skin	*Clitocybe acromelalga*	Rare	[27]
Delayed encephalopathy (patients with renal failure)	Unknown	Encephalopathy	*Pleurocybella porrigens*	27%	
Abdominal pain, diarrhea, and intense sweating	-	-	*Clitocybe rivulosa*	-	[28]

GI, gastrointestinal; GIT, gastrointestinal tract; CNS, central nervous system.

(Jo, Hossain & Park, 2014)

Psilocybin

Psilocybin & depression

Psilocybin is a naturally occurring plant alkaloid found in the Psilocybe genus of mushrooms, Psilocybin is a prodrug of psilocin (4-hydroxy-dimethyltryptamine).

Psilocybin is a serotonin receptor agonist and classic psychedelic drug whose principal psychoactive effects are mediated by serotonin 2A (5-HT) receptor agonism

agonist *is a chemical that binds to a receptor and activates the receptor to produce a biological response.*

Psilocybin has shown enhanced cognitive flexibility, associative learning, cortical neural plasticity, and antidepressant responses increased and sustained improvements in wellbeing and optimism

Antidepressant medications and cognitive behavioural therapy can be effective for some patients, but around 20% do not respond to any intervention, and many of those who do respond, eventually relapse

(Carhart-Harris, et al, 2016)

Psilocybin & depression

Psilocybin's acute psychedelic effects typically became detectable between 30 min and 60 min after dosing, peaked between 2 hrs and 3 hrs after dosing, and subsided to negligible levels at which the patient could be assessed for discharge at least 6 h after dosing

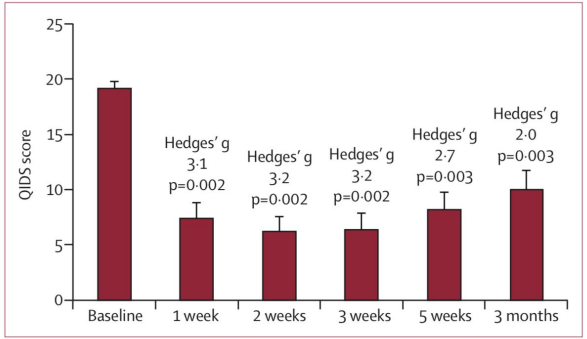


Figure 3: **Mean depression severity (QIDS) over time**
Depression severity determined by self-rated 16-item QIDS. QIDS scores of 16–20 are considered to reflect severe depression, scores of 11–15 are considered moderate depression, scores of 6–10 are considered mild depression, and scores of 5 and less are considered absent depression. All post-treatment assessments were obtained after the high-dose session (ie, 1 week post-treatment refers to 1 week after the high-dose session). Hedges' g values versus baseline are shown. QIDS=Quick Inventory of Depressive Symptoms.

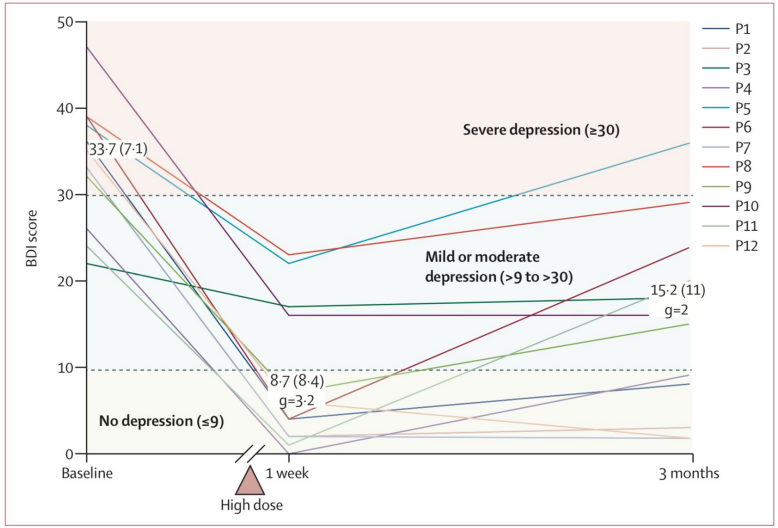


Figure 4: **Depression severity (BDI) over time, by patient**
Figure shows depression severity (BDI) over time plotted for each of the 12 patients. Mean values (SD) are shown as well as the relevant effect sizes (Hedges' g) versus baseline. BDI=Beck Depression Inventory.

The most common adverse events were transient anxiety (mostly mild) during drug onset (n=12), transient confusion or thought disorder (n=9), mild and transient nausea (n=4), and transient headache (n=4).

No prolonged psychotic symptoms were observed in any of the patients.

(Carhart-Harris, et al, 2016)

Psilocybin & Cancer + depression

Depression is an independent risk factor of early death in cancer patients

Antidepressants and, less frequently, benzodiazepines are used to treat depressed mood and anxiety in cancer patients, although evidence suggesting efficacy is limited and conflicting, and benzodiazepines are generally only recommended for short-term use because of side effects and withdrawal

Symptoms:

- Nausea or vomiting occurred in 15% of participants in the high-dose session and none in the low-dose session.
- physical discomfort (any type) occurred in 21% of participants in the high-dose session and 8% in the low-dose ses- sion.
- Psychological discomfort (any type) occurred in 32% of participants in the high-dose session and 12% in the low-dose session.
- anxiety occurred in 26% of participants in the high-dose session and 15% in the low-dose session.

(Griffiths, et al, 2016)

Psilocybin & Cancer + depression

The depression scales show a high baseline for both types of doses but decreases as the weeks progress

Table 4. Effects of psilocybin on the 11 therapeutically relevant outcome measures assessed at Baseline, Post-session 1 (5 weeks after Session 1), Post-session 2 (5 weeks after Session 2), and 6 months follow-up that fulfilled conservative criteria for demonstrating an effect of psilocybin*.

Measure	Group	Assessment time-point			
		Baseline[a]	Post-session 1[b]	Post-session 2[c]	6 months[d]
GRID-HAMD-17 (Depression)	Low-Dose-1st (High-Dose-2nd)	22.32 (0.88)	*14.80 (1.45)*	6.50 (0.86)***	6.95 (1.24)
	High-Dose-1st (Low-Dose-2nd)	22.84 (0.97)	*6.64 (1.04)****	6.52 (1.44)	6.23 (1.30)
Beck Depression Inventory (BDI)	Low-Dose-1st (High-Dose-2nd)	18.40 (1.09)	*12.92 (1.58)*	8.17 (1.24)***	8.00 (1.50)
	High-Dose-1st (Low-Dose-2nd)	17.77 (1.61)	*7.00 (1.39)***	5.80 (1.41)	6.17 (1.26)
HADS Depression	Low-Dose-1st (High-Dose-2nd)	9.48 (0.71)	*6.04 (0.79)*	4.57 (0.73)*	4.64 (0.72)
	High-Dose-1st (Low-Dose-2nd)	9.81 (0.69)	*3.92 (0.74)**	4.28 (0.89)	3.46 (0.66)
HAM-A (Anxiety)	Low-Dose-1st (High-Dose-2nd)	25.68 (0.89)	*16.64 (1.53)*	8.92 (1.14)***	7.95 (1.19)
	High-Dose-1st (Low-Dose-2nd)	25.73 (1.11)	*8.48 (1.16)****	7.52 (1.27)	7.04 (1.17)
STAI-Trait Anxiety	Low-Dose-1st (High-Dose-2nd)	47.46 (1.62)	*40.48 (2.11)*	35.48 (2.05)**	36.83 (2.08)
	High-Dose-1st (Low-Dose-2nd)	47.73 (1.91)	*34.64 (1.84)**	34.28 (2.25)	35.32 (2.18)
POMS Total Mood Disturbance	Low-Dose-1st (High-Dose-2nd)	51.72 (6.35)	42.48 (7.72)	21.09 (5.81)***	23.50 (6.57)
	High-Dose-1st (Low-Dose-2nd)	56.93 (5.33)	*18.96 (5.78)***	17.14 (6.35)	12.52 (5.36)
Brief Symptom Inventory (BSI)	Low-Dose-1st (High-Dose-2nd)	41.76 (4.40)	*33.74 (4.47)*	26.08 (4.53)*	23.50 (3.85)
	High-Dose-1st (Low-Dose-2nd)	40.19 (3.71)	*18.08 (3.62)***	16.48 (3.77)	14.35 (3.35)
MQOL (Overall Quality of Life)	Low-Dose-1st (High-Dose-2nd)	5.69 (0.24)	6.17 (0.32)	6.90 (0.34)**	6.88 (0.37)
	High-Dose-1st (Low-Dose-2nd)	5.32 (0.29)	*7.14 (0.29)**	7.46 (0.34)	7.65 (0.36)
MQOL (Meaningful Existence)	Low-Dose-1st (High-Dose-2nd)	6.03 (0.30)	6.10 (0.39)	7.30 (0.35)***	7.29 (0.31)
	High-Dose-1st (Low-Dose-2nd)	5.43 (0.29)	*7.23 (0.33)**	7.30 (0.38)	7.62 (0.35)
LAP-R Death Acceptance	Low-Dose-1st (High-Dose-2nd)	28.05 (2.04)	29.14 (2.25)	34.95 (1.92)***	34.95 (1.52)
	High-Dose-1st (Low-Dose-2nd)	29.09 (2.07)	*36.17 (1.59)**	35.13 (1.90)	36.25 (1.59)
LOT-R (Optimism)	Low-Dose-1st (High-Dose-2nd)	13.56 (0.97)	13.60 (1.23)	15.96 (1.12)**	16.68 (1.14)
	High-Dose-1st (Low-Dose-2nd)	14.15 (0.97)	*17.23 (0.67)**	17.16 (0.99)	17.43 (0.92)

Table 6. Percentage of participants with clinically significant response rate and symptom remission rate as assessed with the clinician-rated measures of depression and anxiety*[a].

Measure	Group	Assessment time-point					
		Post-session 1		Post-session 2		6 months[b]	
		Clinical response	Symptom remission	Clinical response	Symptom remission	Clinical response	Symptom remission
GRID-HAMD-17 (Depression)	Low-Dose-1st (High-Dose-2nd)	32%	16%	75%	58%	77%	59%
	High-Dose-1st (Low-Dose-2nd)	92%***	60%**	84%	68%	79%	71%
HAM-A (Anxiety)	Low-Dose-1st (High-Dose-2nd)	24%	12%	83%	42%	82%	50%
	High-Dose-1st (Low-Dose-2nd)	76%***	52%**	80%	60%	83%	63%

* Data are percentage of participants fulfilling criteria at Post-session 1 (5 weeks after Session 1), Post-session 2 (5 weeks after Session 2), and 6 months. Clinical response was defined as ⩾50% decrease in measure relative to Baseline; Symptom remission was defined as ⩾50% decrease in measure relative to Baseline and a score of ⩽7 on GRID-HAMD-17 or HAM-A. For the Post-session 1, Post-session 2, and 6-month time-points, respectively, the number of participants was 25, 24, and 22 in the Low-Dose-1st (High-Dose-2nd) Group, and 25, 25, and 24 in the High-Dose-1st (Low-Dose-2nd) Group.

(Griffiths, et al, 2016)

Psilocybin & Cancer + depression

Participant ratings greatly increase regarding attitudes about life, mood, social effects, behavior and spirituality. Life satisfaction jumps from 52% to 82-86% weeks after treatment

Table 8. Participant ratings of persisting effects attributed to the session on ratings completed 5 weeks after the low-dose and high-dose psilocybin sessions, and, again, retrospectively for the high-dose session 6 months after the second session[+].

Questionnaire and subscale description	Assessment time-point		
	Low dose (5 weeks)	High dose (5 weeks)	High dose 6-month follow-up
Persisting Effects Questionnaire (% of maximum score)			
Positive attitudes about life	39.57 (3.91)	57.78 (3.10)***	61.17 (3.51)***
Negative attitudes about life	3.82 (0.99)	5.08 (1.54)	3.18 (0.96)
Positive attitudes about self	35.16 (3.80)	50.70 (3.46)***	54.78 (3.37)***
Negative attitudes about self	3.89 (0.86)	4.80 (1.43)	3.52 (1.16)
Positive mood changes	36.85 (3.99)	49.06 (3.45)***	55.32 (3.58)***
Negative mood changes	3.42 (1.18)	5.42 (1.57)	3.00 (1.18)
Altruistic/positive social effects	35.60 (3.79)	47.42 (3.49)***	51.11 (3.69)***
Antisocial/negative social effects	3.55 (1.11)	3.73 (1.06)	2.51 (0.90)
Positive behavior changes	48.40 (4.66)	59.60 (4.02)***	64.78 (4.03)***
Negative behavior changes	1.60 (1.27)	3.60 (1.97)	0.87 (0.61)
Increased spirituality	37.07 (4.31)	52.48 (3.88)***	57.43 (4.17)***
Decreased spirituality	1.68 (0.63)	1.88 (0.68)	1.27 (0.39)
How personally meaningful was the experience? (maximum score=8)	4.62 (0.31)	6.38 (0.20)***	6.65 (0.18)***
Top 5 most meaningful of life, including single most (% of participants)	24%	62%***	67.4%***
How spiritually significant was the experience? (maximum score=6)	3.16 (0.24)	4.46 (0.19)***	4.78 (0.17)***
Top 5 most spiritually significant of life, including single most (% of participants)	24%	66%***	69.6%***
Did the experience change your sense of well-being or life satisfaction? (maximum score=3)	1.50 (0.19)	2.20 (0.16)***	2.33 (0.14)***
Increased well-being or life satisfaction moderately or very much (% of participants)	52%	86%***	82.6%***

[+]Except where noted, numerical data show means (1 SEM) for persisting effects ratings 5 weeks after the low-dose session (n = 50), 5 weeks after the high-dose session (n = 50), and, again, retrospectively for the high-dose session 6 months after the second session (n = 46). There were no significant differences between ratings of the high dose at 5 weeks after the session vs. the 6-month follow-up. Asterisks indicate significant differences from ratings obtained 5 weeks after the low dose session (*p<0.05, **p<0.01, ***p<0.001, planned comparisons).

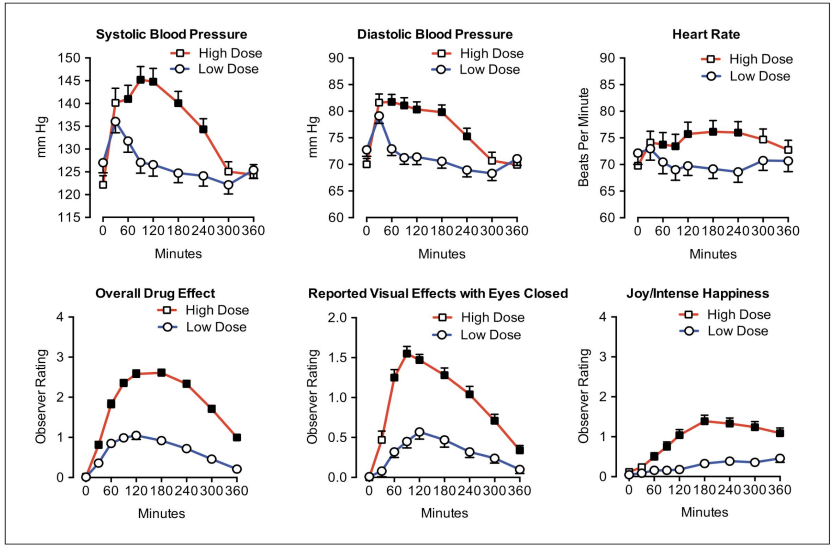


Figure 2. Within-session time-course of psilocybin effects on cardiovascular and observer-rated measures.
Cardiovascular (systolic and diastolic blood pressure, and heart rate) and observer (i.e. monitor)-rated overall drug effect, visual effects with eyes closed (as described by the participant), and joy/intense happiness. Data points show means; brackets indicate 1 SEM; circles show data after the low dose (n = 50); squares show data after the high dose (n = 50). Filled squares indicate the dose conditions were significantly different at the indicated time-point (p<0.05, planned comparisons). Y-axes for observer ratings show maximum possible scores.

(Griffiths, et al, 2016)

Psilocybin & Cancer + depression

Figure 5 shows a strong effect relationship for anxiety and depression experiences of study participants

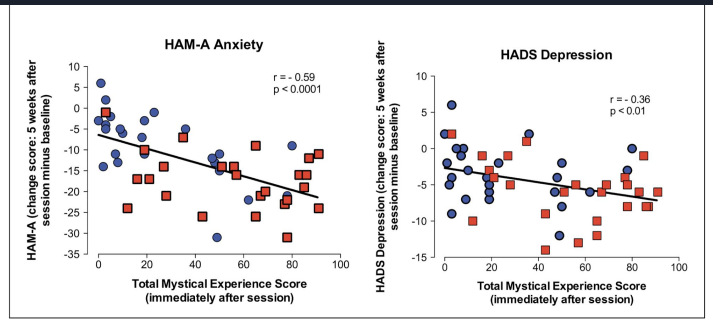
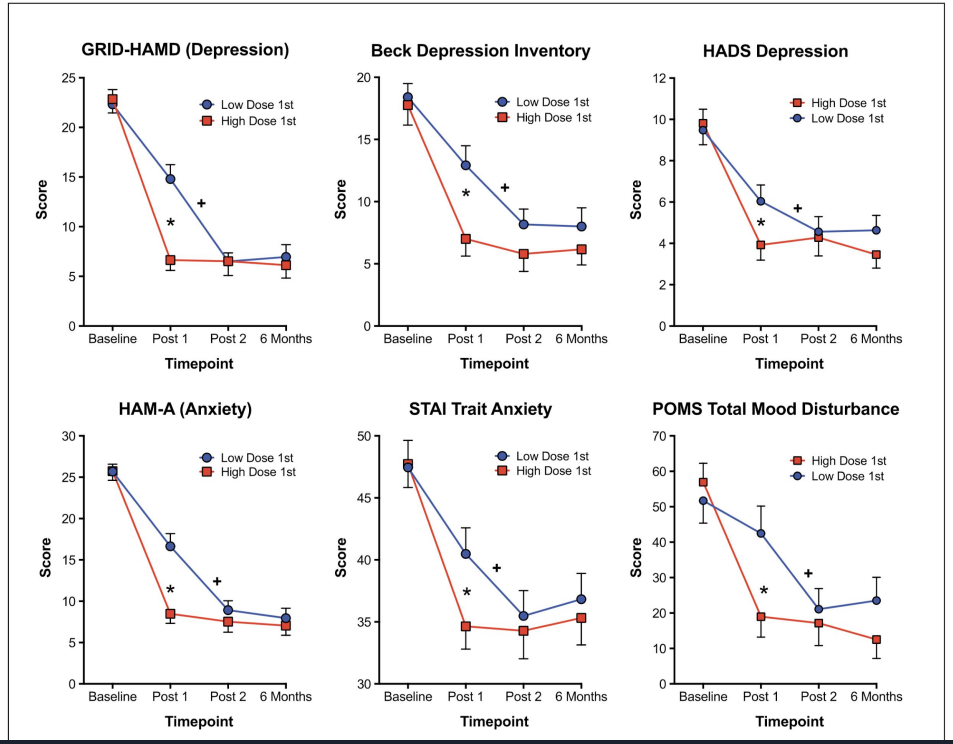


Figure 5. Relationship between the Mystical Experience Questionnaire (MEQ30) total score assessed at end of Session 1 and several illustrative outcome measures assessed 5 weeks after Session 1.

Each panel shows scores on an outcome measure assessed 5 weeks after Session 1 as a function of the total MEQ30 score obtained 7 h after psilocybin administration on Session 1. MEQ30 scores are expressed as a percentage of maximum possible score. Data points represent individual participants (n = 50 or 51); blue circles represent the group that received the low dose on the 1st session; red squares represent the group that received the high dose on the 1st session. Correlation coefficients and p-values are shown.

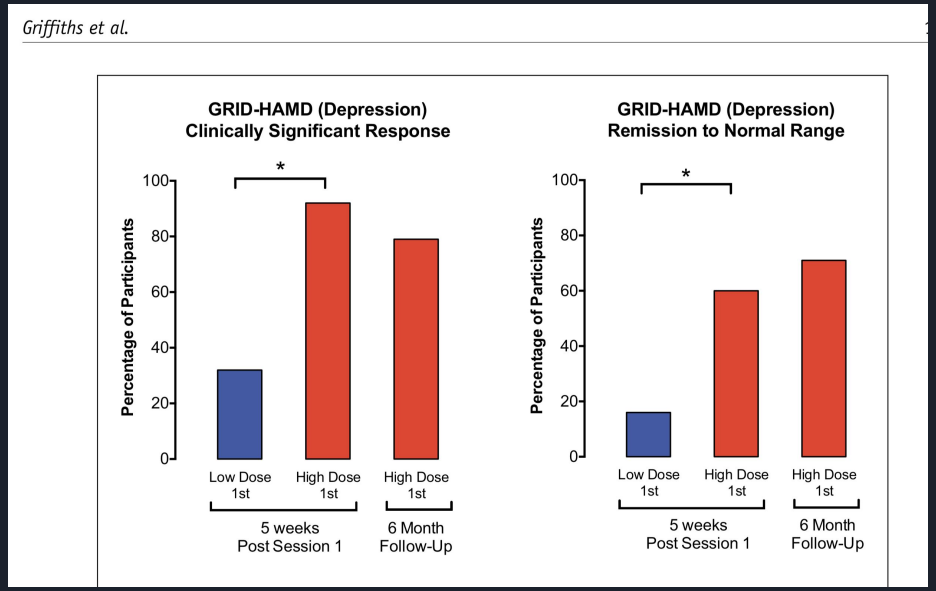


(Griffiths, et al, 2016)

Psilocybin & Cancer + depression

Patients given psilocybin show a strong positive treatment effect on lowering depressive symptoms

Ratings by patients themselves, clinicians, and community observers suggested these effects endured at least 6 months. The overall rate of clinical response at 6 months on clinician-rated depression and anxiety was 78% and 83%, respectively.



(Griffiths, et al, 2016)

Psilocybin & spirituality

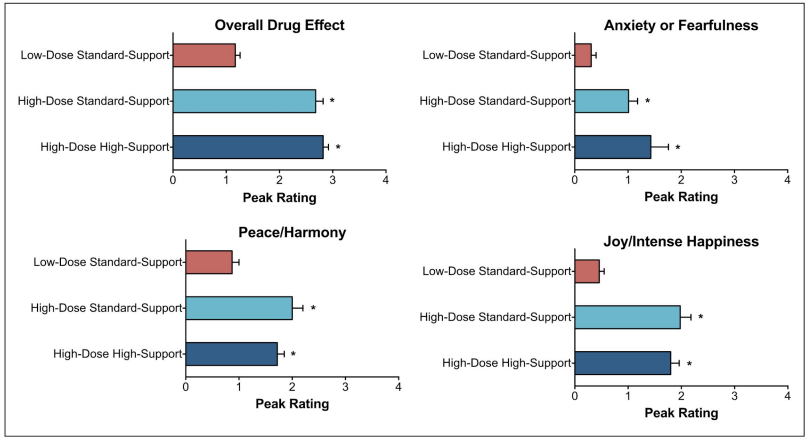


Figure 2. Guide ratings of volunteer behavior and mood assessed throughout the psilocybin sessions (Illustrative results from Table 2).
Data are means of the peak response in each of the two psilocybin sessions in each participant. Bars show group means; brackets show 1 SEM; * indicates a significant difference from Low-Dose Standard-Support (Planned comparisons, $p<.05$); there were no significant differences between the High-Dose High-Support and High-Dose Standard-Support groups.

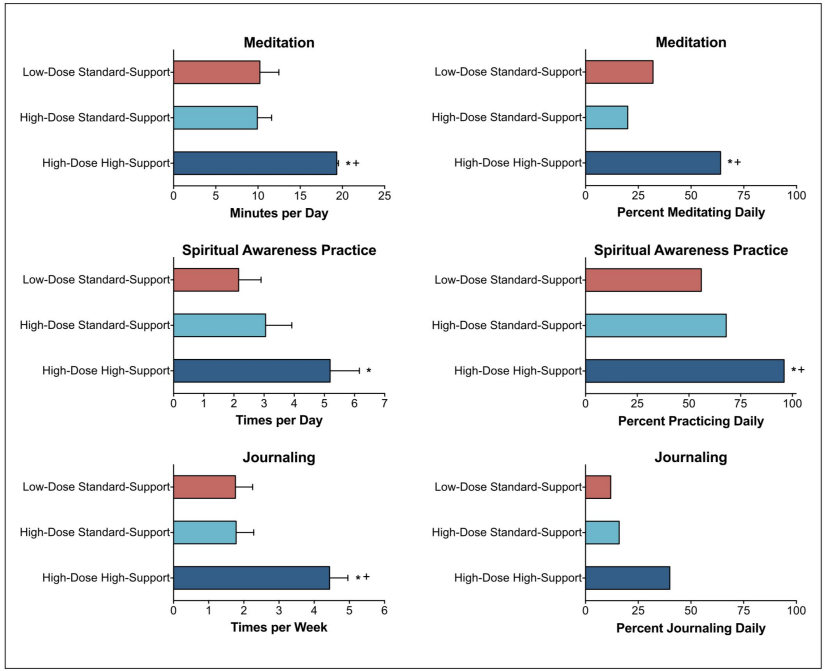


Figure 4. Spiritual practices at 6 months (from Table 4).
Data, which were obtained at the 6-month follow-up, show retrospective ratings for the past 4 months. Bars displaying rate data show means; brackets show 1 SEM (n=25). Meditation rate data are minutes per day for all days. Bars displaying proportion data show the percentage of the group (n=25) reporting the practice during the indicated time interval. * indicates a significant difference from the Low-Dose Standard-Support group; + indicates a significant difference between the High-Dose High-Support group and the High-Dose Standard-Support group (Planned comparisons, $p<0.05$).

25 study participants experienced psilocybin and had made positive changes to their life 6 months after the study. Participants had significant changes in attitudes, moods, behavior, spirituality and well-being

(Griffiths, et al, 2018)

Psilocybin & spirituality

Table 5. Participant ratings of effects attributed to psilocybin session experiences at 6 month assessment.

Measure	Low-Dose Standard-Support	High-Dose Standard-Support	High-Dose High-Support
Attitudes, Moods, Behavior, & Spirituality			
Positive attitudes about life	22.71 (5.11)	61.66 (6.18)***	73.11 (4.14)***
Negative attitudes about life	0.98 (0.37)	1.66 (0.63)	3.02 (1.17)
Positive attitudes about self	23.85 (4.92)	55.35 (6.01)***	68.73 (4.22)***
Negative attitudes about self	0.44 (0.27)	2.04 (0.65)	4.00 (1.54)*
Positive mood changes	21.42 (4.42)	51.47 (5.96)***	65.42 (4.73)***
Negative mood changes	1.07 (0.60)	0.71 (0.28)	1.69 (1.30)
Altruistic/positive social effects	21.24 (4.44)	53.24 (5.85)***	67.02 (4.22)***+
Antisocial/negative social effects	0.8 (0.49)	0.36 (0.36)	1.16 (0.60)
Positive behavior changes	27.20 (4.98)	61.60 (6.76)***	78.40 (5.26)***+
Negative behavior changes	0.8 (0.82)	0.00 (0)	0.00 (0)
Increased spirituality	20.76 (4.95)	58.69 (6.36)***	73.62 (4.00)***+
Decreased spirituality	1.14 (0.44)	0.84 (0.36)	1.26 (0.94)
How personally meaningful was experience?			
Mean (max score=8)	3.80 (0.35)	6.76 (0.31)***	7.20 (0.14)***
% rating top 5 most personally meaningful	12%	84% ***	84% ***
% rating the single most personally meaningful	0%	28%*	36%**
How spiritually significant was the experience?			
Mean (max score=8)	2.60 (0.26)	4.68 (0.34)***	5.52 (0.12)***+
% rating top 5 most spiritually significant	12%	76% ***	96%***+
% rating the single most spiritually significant	0%	40% **	56% ***
Did the experience change your sense of of well-being or life satisfaction?			
Mean (max/min score= -3 to +3)	1.08 (0.23)	2.20 (0.23)***	2.60 (0.13)***
% rating moderately or very much (+2 or +3)	20%	72% ***	92%***

Data on attitudes, mood, altruistic/social effects, behavior, and spirituality are means expressed as percentage of maximum possible score, with 1 SEM shown in parentheses (n=25); data for the final three questions are either mean raw scores with 1 SEM shown in parentheses or percentages of group (n=25).
Within a row, asterisks indicate a significant difference from the Low-Dose Standard-Support group (*p<.05, **p<.01, ***p<.001), and + indicates a significant difference between the High-Dose High-Support group and the High-Dose Standard-Support group (+p<.05). Significance levels were determined with z-tests for proportions for percentile data and with Planned comparisons for other numerical ratings.

Table 6. Longitudinal measures assessed at 6 months that showed significant between group differences.

Measure	Low-Dose Standard-Support	High-Dose Standard-Support	High-Dose High-Support
Mysticism Scale: (Lifetime)			
Interpretation (max score=108)	75.64 (3.25)	**87.58 (5.10)***	**99.96 (2.05)***+**
Introvertive (max score=108)	60.72 (3.83)	**86.96 (5.75)*****	**95.08 (2.31)*****
Extrovertive (max score=172)	40.12 (3.26)	**49.22 (4.53)**	**59.80 (2.90)***+**
Total Score (max score=288)	176.48 (9.65)	**223.76 (14.78)****	**254.84 (5.82)***+**
Faith Maturity Scale (FMS)			
Total Score (max score=84)	43.96 (2.36)	**52.60 (3.24)***	**58.52 (2.15)*****
Religious Coping (Brief RCope)			
Positive Religious Coping (max score=21)	2.89 (0.89)	7.28 (1.19)**	**7.88 (1.44)****
Daily Spiritual Experience Scale (DSES)			
Total (questions 1-14; max score=70)	28.04 (3.32)	**37.88 (3.66)***	**41.56 (2.80)****
How close do you feel to God (max score=4)	1.63 (0.16)	**2.12 (0.15)***	**2.36 (0.15)****
Death Transcendence Scale (26 items)			
Mysticism scale (max score=35)	20.76 (1.83)	**26.16 (2.12)***	**30.96 (1.25)***
Religious scale (max score=35)	20.72 (1.67)	**26.36 (1.86)***	**27.67 (1.17)***
Total Score (max score=182)	113.92 (3.33)	**125.68 (4.61)***	**131.25 (3.53)***
Gratitude Questionnaire (GQ-6)			
Total Score (max score=43)	37.4 (0.82)	**39.16 (0.66)**	**39.52 (0.58)***
Life Attitude Profile (LAP-R)			
Coherence (Life meaning)(max=56)	36.08 (1.74)	**38.60 (1.85)**	**43.40 (1.60)*+**
Trait Forgiveness Scale			
Total Score (max score=50)	37.88 (1.32)	37.36 (1.43)	**41.08 (0.83)+**
Forgiveness of Transgression (TRIM-18)			
Benevolence Motivation (max score=30)	18.63 (1.11)	**22.88 (1.36)***	**23.80 (0.89)***
Avoidance Motivation (max score=35)[1]	**22.38 (1.41)**	**16.50 (1.67)***	**17.20 (1.50)***
Sanctification of Strivings			
Life strivings as sacred/spiritual (max score=5)	2.43 (0.25)	2.76 (0.26)	**3.47 (0.20)*+**
Schwartz Value Scale			
Tradition (mean centered score)	−1.58 (0.22)	−1.17 (0.24)	**−0.79 (0.19)***
Interpersonal Closeness (IOS)			
Mean rating (max score=7)	2.82 (0.20)	**3.37 (0.29)**	**3.70 (0.29)***
Observer-rated spiritual/religious sentiments (ASPIRES)			
Prayer Fulfillment (max score=50)	32.35 (1.51)	**39.58 (1.24)*****	**40.72 (0.94)****
Universality (max score=35)	24.17 (0.96)	27.04 (1.19)	28.08 (0.68)**
Total (max score=115)	76.30 (2.65)	**88.42 (2.51)****	89.60 (1.69)**
Observer-rated positive changes in behavior & attitudes			
Total change score	3.24 (0.75)	5.39 (0.93)	9.20 (1.40)***+

Participants had strong increase in spirituality, faith and religious attitudes

(Griffiths, et al, 2018)

LSD

LSD

D-Lysergic Acid Diethylamide (LSD)

was first synthesized in 1937 by Albert Hoffman

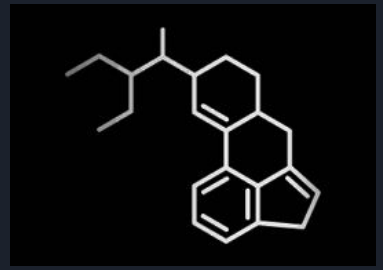
LSD stimulates the sympathetic system, causing hyperthermia, sweating, palpitation, the elevation of blood pressure, convulsions, an increase in muscle tension, tremors, and muscular incoordination

vulnerable subjects (people with a pre-existent risk of mental disease), LSD may induce a real psychosis, described as panic, paranoia and distrust, suspicious feelings or delusions of grandeur, confusion, impairment of reasoning, regret, depression, loneliness and/or somatic discomfort, all of which can be of monumental proportions

LSD administration decreased signalling between the parahippocampus and the retrosplenial cortex (RSC); the magnitude of the decrease correlated with ratings of "ego-dissolution" and "altered meaning", both of which are considered hallmarks of psychosis.

LSD produces changes in body perception, synaesthesia, thought disorders, and time distortion. Some potent psychotropic effects :

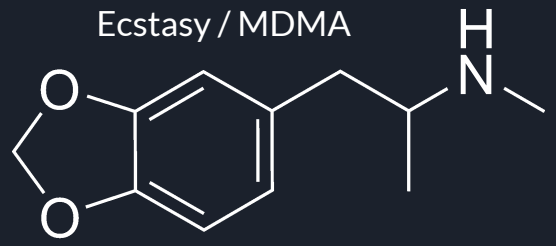
- "mystical experiences"
- altered state of consciousness
- Euphoria
- enhanced capacity for introspection
- a sense of unity
- transcendence of time and space
- positive mood & attitude towards others
- feelings of joy, blessedness and peace and the self



(De Gregorio, Comai, Posa & Gobbi, 2016)

MDMA / Ecstasy

Ecstasy/ MDMA & depression



3,4-Methyldioxymethamphetamine (MDMA), or "ecstasy", has been shown to cause reductions in serotonin axons and receptors in rats and human studies.

A number of studies have reported that MDMA users report higher levels of depression than controls days post use of MDMA. These studies do fail from study design such as controlling for other drug use which confounds the results.

The failure to find a difference between the current MDMA-using group and the poly-drug control group indicates that the increased depression rating scale scores reported by MDMA users may not necessarily be due to MDMA use.

In the data from Roiser & Sahakian's study tests are concordant with the hypothesis that MDMA causes long-term reductions in serotonin system function

(Roiser & Sahakian, 2004)

MDMA and psychiatric symptoms

±3,4-Methylenedioxymethamphetamine (MDMA, 'ecstasy') damages serotonergic neurons in rodents and non-human primates

Findings in this area are mixed, appearing to be even more variable than evidence regarding other functional domains such as cognition

studies using the Hospital Anxiety and Depression Scale (HADS), a self-report measure that is not confounded by somatic effects, do not report ecstasy users to have elevated anxiety or depression scores

The hypothesis that ecstasy use would be associated with anxiety and depression was not supported, high prevalence psychiatric symptomatology is more closely related to other drug use than to use of ecstasy

(Bedi, Van Dam, & Redman, 2010)

MDMA history & use

MDMA was first synthesized by the pharmaceutical company Merck in 1912 as a precursor of a haemostatic drug called methylhydrastinin, but it was not tested at that time either in humans or animals

1950s, the U.S. army assayed a number of phenethylamines, including MDMA, in toxicological animal studies. Until its prohibition in the U.S. in 1985, MDMA was widely used as an adjunct to the psychotherapeutic process

MDMA were administered in psychotherapeutic settings, therapeutic use of MDMA just by Leo Zeff, Ph.D., the “Secret Chief” and leader of the underground therapeutic use of MDMA

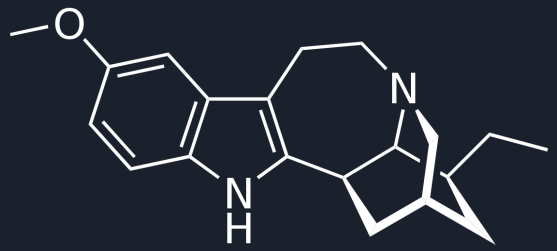
Before the prohibition of MDMA in 1985, it was used by a wide range of psychotherapists to treat diverse psychological disorders, including psychosis and anxiety, in individuals and couple therapy as well in group therapy. It is also useful in reducing physical pain secondary to some kinds of cancer

The therapeutic potential of MDMA consists in temporarily reducing or eliminating anxiety and fear, thus helping subjects gain access to their emotions and internal conflicts without the overwhelming fear normally associated with these emotions and memories

Study results show low doses of MDMA administered as an adjunct to psychotherapy were found to be safe for the six subjects with chronic PTSD treated in this clinical trial and there were promising signs of efficacy and reduced PTSD symptomatology.

(Bouso, et al, 2008)

Ibogaine



Ayahuasca

Ayahuasca

Ayahuasca is a psychotropic tea obtained from *Banisteripsis caapi* and Psychotria viridis, two plant species native to the Amazon Basin

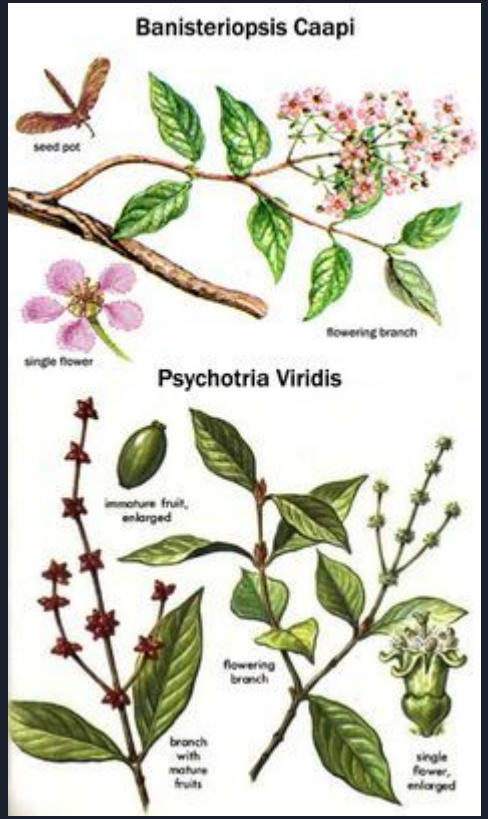
In the US, Canada, Holland, and Brazil, federal laws protect the religious use of ayahuasca and in Peru it has recently been declared part of the National Cultural Heritage

Effects start between 30 and 45 minutes, peak between 90 and 120 minutes and are resolved by 240 minutes

Ayahuasca induces a modified state of awareness that includes dream-like imagery with eyes closed, increased insight and intense emotions

P. viridis contains the hallucinogen N,N-dimethyltryptamine (DMT)
DMT is thought to elicit its psychotropic effect through stimulation of the 5-HT2A receptors. DMT is not active when administered orally, as it is readily metabolized to 3- indoleacetic acid by monoamine oxidase. However, B. caapi contains harmala alkaloids that reversibly block the metabolic breakdown of DMT, leading to psychoactivity

Study results of ayahuasca users showed a lower presence of psychopathological symptoms compared to controls. They performed better in neuropsychological tests, scored higher in spirituality and showed better psychosocial adaptation as reflected by some attitudinal traits such as Purpose in Life and Subjective Well-Being.



(Bouso, et al, 2012)

Ayahuasca

Recent evidence from a randomized controlled trial (RCT) supports the rapid antidepressant effects of the psychedelic ayahuasca in treatment-resistant depression.

Major depressive disorder has been closely associated with deregulations of the hypothalamic-pituitary-adrenal (HPA) axis, both at rest and in response to stress

cortisol awakening response is increased in patients with major depression, suggesting hyperactivity of the HPA axis

open label trial in treatment-resistant depression observed a reduction of up to 87% in depression severity, already at 24 h after a single dosing session with ayahuasca

Ayahuasca is a decoction of two plants: Psychotria viridis and Banisteriopses caapi
P. viridis contains the psychedelic tryptamine N,N-dimethyltryptamine (N,N-DMT), whose action is mediated by serotonin (5-HT2A) and sigma-1 receptors
B. caapi contains β-carbolines (harmaline, harmine and tetrahydroharmine), which work as indirect monoaminergic agonist due to the inhibition of monoamine oxidase isoenzyme (MAO)

this brew does not exhibit dose tolerance, i.e., the decrease of the effect of a drug or medication by excessive or frequent exposure of the patient to its active principle, and is not addictive

(Galvão, et al, 2018)

Ayahuasca

key physiological systems altered in major depression, i.e., was observed that ayahuasca increased cortisol levels 2h after its ingestion in healthy subjects
Depression severity diminished significantly 1 day after dosing, and between- group differences increased from D1 to D7

Cortisol is a steroid hormone that triggers stress response in an adaptive way: it increases cardiovascular and respiratory activity, mobilizes glucose to provide enough fuel to remove the stressor and limit acute inflammation processes (45). Not only the excess, but also the reduction of cortisol is believed to be harmful. Major depression has been traditionally associated with hypercortisolism, but an increasing number of studies have found evidence of hypocortisolism in depression

Ayahuasca was originally used for medicinal purposes by indigenous populations from Brazil, Ecuador, Peru, and Colombia

(Galvão, et al, 2018)

Cannabis

Cannabis & sleep

Evidence suggests that cannabis is likely beneficial for sleep initiation, sleep disturbances have been reported as a primary symptom of withdrawal.

The primary psychoactive constituent being Δ9-tetrahydrocannabinol (Δ9-THC), which has neural implications that are mediated through cannabinoid (i.e., CB1) receptors located in the brain primary neural effects of Δ9-THC is sedation

- Endogenous cannabinoids have been shown to increase the level of adenosine, a sleep-promoting agent
- Neurons in the lateral hypothalamus involved in regulation of arousal systems express CB1 receptors, resulting in inhibition of the arousal system

The prefrontal cortex has been shown to play a primary role in normal sleep, and reductions in activity in the prefrontal cortex have been observed among individuals with insomnia or sleep deprivation, and among heavy cannabis users abstinent for 30 days

Cannabis-based medicine extract (2.7 mg Δ9-THC, 2.5 mg CBD) improves short-term sleep problems among individuals with insomnia and chronic pain

(Babson & Bonn-Miller, 2014)

Cannabis & sleep

Cannabis and two of its major components, Δ-9-tetrahydrocannabinol (THC) and cannabidiol (CBD)

THC exerts its effects on the brain and body by binding to CB1 and CB2 receptors in the endocannabinoid system, which modulates the sleep-wake cycle

CB1 receptor antagonists increase wakefulness and reduce rapid eye movement (REM) time in animal studies

The relationship between CB1 receptor inactivation and wakefulness is likely related to anandamide (AEA), an endogenous cannabinoid that, like THC, binds to the CB1 receptor and promotes sleep, including increased slow wave sleep (SWS) and REM time
AEA is degraded by the enzyme, fatty acid amide hydrolase (FAAH). FAAH and its associated gene have also been linked with aspects of sleep.

The literature regarding the effects of THC and CBD on sleep is mixed.

- THC administration has been shown to promote sleep onset and increase REM sleep, which is important for memory consolidation
- Other studies have demonstrated a reduction in REM sleep following THC administration chronic cannabis users exhibit decreased SWS compared to controls immediately following termination of use, with recovery after fours weeks of abstinence

(Maple, McDaniel, Shollenbarger & Lisdahl, 2016)

Cannabis & sleep

The endocannabinoid system regulates mood CNR1 (which codes for the human CB1 receptor) and FAAH genes have been associated with risk for mood disorders in humans

Findings from Maple et al (2016) study:

- FAAH genotype was significantly associated with depressive and greater sleep problems symptoms
- CNR1 genotype did not significantly predict depressive or sleep problem symptoms
- Greater depressive symptoms were significantly related to poorer sleep quality
- FAAH and depression found a marginally higher frequency of rs324420 A carrying adults in those with major depressive disorder and bipolar disorder compared to controls

Heavy cannabis use is associated with CB1 receptor downregulation, which decreases endocannabinoid signaling. Reduced endogenous cannabinoid activity is related to poorer sleep

THC and CBD impact sleep differently, and their effects depend upon dose
Since our data are cross-sectional and dose-dependent, the direction of causality between cannabis use and sleep problems cannot be determined. this study relied on measures of self-report, which are less ideal than objective measures.

(Maple, McDaniel, Shollenbarger & Lisdahl, 2016)

Halberstadt, A. L., & Geyer, M. A. (2011). Multiple receptors contribute to the behavioral effects of indoleamine hallucinogens. Neuropharmacology, 61(3), 364-381. doi:10.1016/j.neuropharm.2011.01.017

Hallucinogens are a class of pharmacological agents that increase the intensity and lability of affective responses and produce profound distortions of perceptual processes encompassing the visual, auditory and tactile modalities

peyote cactus (Lophophora williamsii), which contains mescaline; teonanácatl mushrooms containing psilocin and psilocybin; and ayahuasca, a decoction prepared from the bark of β- carboline-containing Banisteriopsis species in combination with plants containing N,N-dimethyltryptamine (DMT)

classical hallucinogens belong to two classes of chemicals:

(1) indoleamines, including the ergoline LSD and indolealkylamines such as DMT, 5-methoxy- DMT (5-MeO-DMT), psilocin, and 4-phosphoryloxy-DMT (psilocybin)

(2) phenylalkylamines, such as the phenethylamines mescaline and 2,5-dimethoxy-4-bromophenethylamine (2C-B), and the phenylisopropylamines 2,5-dimethoxy-4-iodoamphetamine (DOI), 2,5-dimethoxy-4-methylamphetamine (DOM), and 2,5-

phenylalkylamine hallucinogens are highly selective for 5-HT2 sites (5-HT2A, 5-HT2B, and 5-HT2C receptors)

intoxicating effects of LSD are likely to result from interactions with serotonin (5-hydroxytryptamine, 5-HT) in the brain, the hallucinogenic effects of LSD result from effects on central serotonergic systems. There is extensive evidence that LSD and other indoleamine hallucinogens inhibit the firing of serotonergic DRN neurons by activating 5-HT1A receptors.

LSD, psilocin, DMT, and 5-MeO- DMT inhibit cells downstream from the raphe nuclei by stimulating postsynaptic 5-HT1A receptors. These agents are approximately 4 to 5 times more potent at presynaptic than postsynaptic sites

hallucinogen discriminative stimulus is blocked to varying degrees by a variety of non-selective 5-HT antagonists, including methysergide, metergoline, mianserin, methiothepin, and cyproheptadine

phenylalkylamines and the indoleamines act via a common 5-HT2A mechanism, the former agents have high affinity only for 5-HT2 receptors and therefore produce a discriminative stimulus which is less complex

LSD binds to DA D1, D2, D3, D4, and D5 receptors with high affinity and acts as a partial agonist at DA D1 and D2 receptors and as a full agonist at DA D4 receptors. the stimulus effects of LSD occur in two temporal phases, the first phase involving 5-HT2A receptors and the second involving DA receptors.

Indoleamine hallucinogens, including 5-MeO-DMT, LSD, and DPT

References

Babson, K. A., & Bonn-Miller, M. O. (2014). Sleep disturbances: Implications for cannabis use, cannabis use cessation, and cannabis use treatment. *Current Addiction Reports, 1*(2), 109-114. doi:10.1007/s40429-014-0016-9

Bedi, G., Van Dam, N., & Redman, J. (2010). Ecstasy (MDMA) and high prevalence psychiatric symptomatology: Somatic anxiety symptoms are associated with polydrug, not ecstasy, use. *Journal of Psychopharmacology, 24*(2), 233-240. doi:10.1177/0269881108097631

Bouso, J. C., Doblin, R., Farré, M., Alcázar, M. Á., & Gómez-Jarabo, G. (2008). MDMA-assisted psychotherapy using low doses in a small sample of women with chronic posttraumatic stress disorder. *Journal of Psychoactive Drugs, 40*(3), 225-236. doi:10.1080/02791072.2008.10400637

Bouso, J., González, D., Fondevila, S., Cutchet, M., Fernández, X., Ribeiro Barbosa, P., . . . Riba, J. (2012). Personality, psychopathology, life attitudes and neuropsychological performance among ritual users of ayahuasca: A longitudinal study. *PLoS One, 7*(8) doi:10.1371/journal.pone.0042421

Carhart-Harris, R. L., Bolstridge, M., Rucker, J., Day, C. M. J., Erritzoe, D., Kaelen, M., . . . Nutt, D. J. (2016). Psilocybin with psychological support for treatment-resistant depression: An open-label feasibility study. *The Lancet. Psychiatry, 3*(7), 619.

Carhart-Harris, R. L., & Goodwin, G. M. (2017). The therapeutic potential of psychedelic drugs: Past, present, and future. Neuropsychopharmacology : *Official Publication of the American College of Neuropsychopharmacology, 42*(11), 2105-2113. doi:10.1038/npp.2017.84

References

De Gregorio, D., Comai, S., Posa, L., & Gobbi, G. (2016). d-lysergic acid diethylamide (LSD) as a model of psychosis: Mechanism of action and pharmacology. *International Journal of Molecular Sciences, 17*(11), 1953. doi:10.3390/ijms17111953

Galvão, Ana C de Menezes, de Almeida, R. N., Silva, Erick A Dos Santos, Freire, F. A. M., Palhano-Fontes, F., Onias, H., . . . Galvão-Coelho, N. L. (2018). Cortisol modulation by ayahuasca in patients with treatment resistant depression and healthy controls. *Frontiers in Psychiatry, 9*, 185.

Griffiths, R. R., Johnson, M. W., Carducci, M. A., Umbricht, A., Richards, W. A., Richards, B. D., . . . Klinedinst, M. A. (2016). Psilocybin produces substantial and sustained decreases in depression and anxiety in patients with life-threatening cancer: A randomized double-blind trial. *Journal of Psychopharmacology, 30*(12), 1181-1197. doi:10.1177/0269881116675513

Griffiths, R. R., Johnson, M. W., Richards, W. A., Richards, B. D., Jesse, R., MacLean, K. A., . . . Klinedinst, M. A. (2018). 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. *Journal of Psychopharmacology, 32*(1), 49-69. doi:10.1177/0269881117731279

Jo, W., Hossain, M. A., & Park, S. (2014). Toxicological profiles of poisonous, edible, and medicinal mushrooms. Mycobiology, 42(3), 215-220. doi:10.5941/MYCO.2014.42.3.215

Johnson, M. W., & Griffiths, R. R. (2017). Potential therapeutic effects of psilocybin. *Neurotherapeutics, 14*(3), 734-740. doi:10.1007/s13311-017-0542-y

References

Johnson, M. W., Garcia-Romeu, A., Johnson, P. S., & Griffiths, R. R. (2017). An online survey of tobacco smoking cessation associated with naturalistic psychedelic use. *Journal of Psychopharmacology, 31*(7), 841-850. doi:10.1177/0269881116684335

Maple, K. E., McDaniel, K. A., Shollenbarger, S. G., & Lisdahl, K. M. (2016). Dose-dependent cannabis use, depressive symptoms, and FAAH genotype predict sleep quality in emerging adults: A pilot study. The American Journal of Drug and Alcohol Abuse, 42(4), 431.

Roiser, J. P., & Sahakian, B. J. (2004). Relationship between ecstasy use and depression: A study controlling for poly-drug use. *Psychopharmacology, 173*(3), 411-417. doi:10.1007/s00213-003-1705-6