Supplements, Drugs & Substances

Huberman Lab Keypoints

Episodes in this pack: 9

Peptides: The Science, Uses & Safety | Dr. Abud Bakri

Guest: Dr. Abud Bakri
Date: 2026-06-01 · Duration: 2:48:23
URL: https://www.youtube.com/watch?v=_DfqnpSbMfE

KEYPOINTS

1. BPC-157 comes from a protein in gastric juice
Bakri, an internal medicine physician, explains that in 1991 a group in Croatia isolated a large protein, BPC, from gastric juice. BPC-157 is a 15-amino-acid fragment of it, and the body doesn't make that fragment on its own, despite what is often claimed online. The researchers were following two leads: Pavlov had sold dogs' gastric juice as a remedy for stomach complaints, and Hans Selye showed that stress damages the stomach lining, so they suspected the gut produced something protective.

2. BPC-157 seems to boost healing rather than suppress inflammation
In animal models it increases VEGF signaling and new blood vessel growth, helps cells move into wounds, adjusts nitric oxide production and, in one tendon model, increased growth hormone receptors on the tendon. Mice given corticosteroids, which normally slow wound healing, healed as well or better when BPC was added. Bakri finds its gut and brain effects more interesting than the muscle-and-joint hype. In mice it reduced intoxication from alcohol and blocked withdrawal symptoms.

3. The human evidence for BPC-157 is thin
Almost all the animal research comes from the single Croatian group. In humans there were only small phase 1 and phase 2 trials of BPC enemas in the early 2000s: no adverse events in phase 1 and a positive signal for ulcerative colitis in about 40 patients in phase 2. Nobody knows the right human dose. Most people inject 100–200 mcg a day based on what research websites sell, and Bakri suspects the effective dose is far higher.

4. The cancer question is still open
There is no sign of cancer in the animal research, and Bakri says there's no mechanism by which BPC would cause cancer the way smoking does. Because it promotes blood vessel growth, though, it could in theory feed an existing tumor. One melanoma cell study showed it reduced VEGF. Online users report worsening hematomas, and a physician friend of Huberman's noticed his facial spider veins getting worse.

5. In the US, the legal status is unsettled
BPC-157 was never FDA-approved. In late 2024 it and about 20 other peptides were moved to the FDA's 'category 2' list, which blocks compounding. That pushed people toward 'research use only' gray-market vials, which can vary from batch to batch. As of this conversation, BPC-157 had been taken off category 2 but not yet added to category 1, the list that would let doctors prescribe it through compounding pharmacies. Black-market powder from China costs about $5 a vial to make.

6. Khavinson's 'bioregulator' peptides are meant to keep working after you stop
Soviet researcher Vladimir Khavinson isolated short peptides from organs. Examples are pinealon (the tripeptide EDR, with no known receptor), epitalon from the pineal gland, and several thymus peptides. The idea is that short courses shift gene activity and the benefits continue afterward. Bakri repeatedly attaches a caveat: the evidence is largely Russian literature.

7. Thymosin alpha-1 stimulates T-cells
The thymus grows from birth until puberty and then shrinks. Thymosin alpha-1, a peptide of about 21 amino acids from Goldstein's lab, helps T-cells develop and multiply. It's approved in other countries as an add-on therapy for hepatitis B and C and some cancers, but results for sepsis and infection have been unimpressive. Bakri, speaking from personal use and not as a recommendation, injects 2.5 mg twice a week while traveling and on hospital rotations.

8. Restoring growth hormone with age is a double-edged choice
IGF-1 falls dramatically between 18 and 50 (sometimes called somatopause). Growth hormone benefits skin, sleep, recovery and the thymus, and no one thinks it causes cancer. However, it could speed up an existing cancer, it isn't good for heart and metabolic health, and growth hormone–deficient models live longer. Huberman's example is that large, high-IGF-1 dog breeds live shorter lives.

9. Some GLP-1 side effects may come from misuse
Bakri sees GLP-1 drugs as 'training wheels' for weight loss. He suspects that reported cognitive problems may stem from doses that are too high, too few electrolytes or nutrients, low blood sugar, or eating less socially, rather than from the drug acting on the brain. Women with obesity sometimes conceive unexpectedly on these drugs because weight loss changes leptin, a key fertility signal.

EXAMPLES

1. Bakri's torn triceps
With a grade 2 triceps tear (his arm bruised purple top to bottom), he injected BPC and other peptides locally at much higher doses than typical. His physical therapist was astonished by his progress at 3 weeks, and he was back in 3–4 weeks instead of the usual 3 months. He admits he can't know whether he would have healed that fast anyway.

2. Huberman's pinealon experiment
Taken at bedtime, pinealon cut Huberman's deep sleep. A small injection when he woke in the middle of the night instead roughly doubled his late-night REM, from about 1.5 to 3 hours, sometimes with grogginess the next morning. He does this about three times a month and reports more REM on the nights in between.

3. The 15-year nursing-home study
Khavinson gave nursing-home residents a pineal extract (epithalamin) plus a thymus peptide (thymalin) in 10–20-day courses

once or twice a year. He reported significantly lower deaths from heart disease, infection and cancer. Bakri calls it the most interesting longevity study he's seen 'if accurate', with the Russian-literature caveat.

4. The 'trinity stack' of the wealthy

Bakri describes people combining a GLP-1 drug, growth hormone or a secretagogue such as tesamorelin, and testosterone therapy for rapid fat loss and muscle gain, a mix behind some CEO and celebrity transformations. Asked whether it's healthy, he says, 'We'll find out.'

OTHER RELEVANT

1. Use peptides under a doctor's supervision

Find a physician who knows peptides and can monitor you. For example, check IGF-1 on tesamorelin and track weight loss on GLP-1s, since some celebrities clearly lost too much. Bakri expects telemedicine options and price competition to improve sourcing.

2. Be wary of 'research use only' vials

Quality varies widely between gray-market batches, and among compounding pharmacies too. Huberman, who has run a lab, jokes that nobody buying them is doing cell culture at home.

3. GHK-Cu is a collagen-related peptide

GHK-Cu is a glycine-histidine-lysine tripeptide bound to copper and found in type 1 collagen in skin, hair and connective tissue. That's why it's mostly used in topical creams and alongside red light therapy, though Bakri notes it has broader effects.

Health Effects & Risks of Kratom, Opioids & Other Natural Occurring Medicines | Dr. Chris McCurdy

Guest: Dr. Chris McCurdy
Date: 2025-07-21 · Duration: 2:42:52
URL: https://www.youtube.com/watch?v=gyE6Z4GLEeM

KEYPOINTS

1. Kratom is a Southeast Asian tree whose effects depend on dose

Kratom (Mitragyna speciosa) is native to the border region of peninsular Malaysia and Thailand. There, outdoor laborers chew fresh leaves or drink a decoction boiled for hours, using it much as people use coffee to get through heat and hard work. Traditionally it is also used for pain, mood and as a 'nature's Viagra.' McCurdy describes the paradox: small amounts act as a stimulant, while larger amounts produce a more euphoric, sedative, opioid-like effect, which men in the region used socially on weekend evenings in a mostly alcohol-free Muslim culture.

2. US kratom products are very different from the traditional leaf

Western products start as dried leaf, mostly from Indonesia (roughly 250,000 farmers), exposed to sun and air and shipped around the world. Ground leaf in capsules or as powder stirred into water is the closest thing to traditional use, and absorption is slow because the body has to extract the alkaloids itself. Extracts, concentrates and isolates made with ethanol, oil or juice deliver the compounds already pulled out, so they are absorbed much faster. McCurdy compares this range to light beer versus fortified spirits.

3. Read servings per bottle, not just the serving

McCurdy's lab has tested nearly every product on the market, and a single labeled serving is broadly similar to a traditional glass of tea. The danger is in the number of servings per container: a bottle may hold 2, 9 or 15. Someone used to downing a two-serving bottle can swallow a 15-serving shot in one go, in a form that is absorbed quickly. Some shots sit next to 5-hour Energy at gas stations.

4. 7-hydroxymitragynine products behave like pure opioids

The leaf contains roughly 20–40 alkaloids. The main one, mitragynine, is converted in the body into 7-hydroxymitragynine, which acts only on opioid receptors, and the plant itself has never been shown to make it. Manufacturers now synthesize it and sell semi-synthetic 'kratom-derived' products or isolates, under a dietary-ingredient loophole that treats metabolites as dietary ingredients. McCurdy's rat study (on bioRxiv, headed to the Journal of Pharmacology and Experimental Therapeutics) found these products cause respiratory depression equivalent to opioids.

5. Whole-leaf kratom acts on three pain systems at once

Mitragynine has only weak opioid-receptor affinity. Other alkaloids act strongly on serotonin, which affects mood and pain, and on adrenergic receptors, which drive stimulant activity. McCurdy calls the leaf a 'pharmaceutical shotgun' or 'symphony orchestra' that combines opioid, serotonergic and adrenergic pain relief in a way no single drug does. This may explain why some users call it the best pain relief they have had. He stresses that most of the roughly 1,000 papers on kratom, about 10% from his lab, study mitragynine alone, and 'mitragynine does not equal kratom.'

6. Physical dependence is real and tolerance builds for pain relief

A single use will not create dependence, but regular use can. Missing a morning dose brings headaches and misery similar to caffeine withdrawal, and with stronger products some users report restless legs, which looks more like opioid withdrawal. Pain-relieving effects seem to lose strength over time, pushing doses up. There are no chronic studies in humans or animals to say how quickly this happens.

7. Use is widespread and mostly not for getting high

Published estimates are 2–2.5 million US users, but sales and imports (1,950 metric tons a month in 2019) suggest over 20 million daily users. In McCurdy's ecological momentary assessment study, people logged each dose by smartphone. Most used it for energy, mood elevation and pain, including as a pre-workout or post-workout aid, and often within 30 minutes of waking. A smaller group used it to get high, probably with concentrates, and others used it to get off opioids.

8. Quitting kratom has no evidence-based protocol yet

Before COVID, addiction physicians in Gainesville saw patients improving after switching from opioids to kratom. After COVID, they saw people seeking treatment to get off kratom. Clinicians often use buprenorphine (Suboxone) or methadone, which seems to work, but McCurdy worries this addresses only the opioid component, ignores the serotonin and adrenergic effects, and may leave people dependent on a pure opioid that is harder to quit. Counseling and social support matter alongside medication.

9. Vein colors are mostly marketing

White, red, green, brown and yellow 'vein' products reflect how leaves were dried, plus sun or cold damage to trees normally grown in the shade. Alkaloid profiles across the colors are very similar in the lab's analyses, though other chemical differences cannot be ruled out. Huberman compares this to the indica-versus-sativa debate in cannabis.

EXAMPLES

1. The 'little blue bottle' habit

Huberman recounts a friend's assistant who went from one kratom-kava bottle to six a day and felt anxious and unwell with headaches when she cut back to three. That pattern resembles escalating nicotine pouch use.

2. The 2007 seizure case

In the first human case report (2008), with emergency physician Ed Boyer, a man who had switched from Dilaudid to leaf

kratom cold turkey took his wife's modafinil and had a full seizure. Afterward he quit kratom with only a runny nose and no cravings, a striking but single, caveated case that shows the risk of mixing drugs at home.

3. Coca leaf and Coca-Cola

Coca-Cola still imports Peruvian coca leaf through the Stepan Company in New Jersey. Alkaloids are removed for pharmaceutical cocaine, still the best local anesthetic for nasal and eye surgery, and the decocainized extract flavors the drink. The WHO is reviewing coca leaf, which is rich in calcium and vitamins, and McCurdy's lab plans to study it.

4. Theobromine in cacao

Theobromine, the main alkaloid in cacao, is a xanthine and close relative of caffeine with one fewer methyl group. It is a mild stimulant that may aid respiration, similar to theophylline, which was long used for asthma.

5. Medicines borrowed from nature

Morphine was the first alkaloid ever isolated and cocaine the second. Berberine from tree bark lowers blood glucose. GLP-1 drugs trace back to peptides in Gila monster saliva.

OTHER RELEVANT

1. Keep kratom away from anyone under 18 to 25

State limits are 18 or 21. McCurdy would prefer about 25 because the prefrontal cortex is still developing and the effects of kratom on young brains are unknown. Teens are drawn by 'you'll get high' claims and may take a second dose before the first hits.

2. Adults who use leaf products should go low and slow

Regular users commonly say 'less is more.' Never ratchet doses up, and treat dependence as a real possibility. Whether a few days off feel like caffeine withdrawal varies from person to person.

3. Avoid 7-OH, 'kratom-derived' and isolate products

Huberman's suggested framework: block young people's access, advise caution and the minimum effective dose for adults using leaf, and restrict the opioid-like derivatives. Many buyers do not realize they are not getting leaf.

4. Do not combine kratom with other drugs

No studies test kratom with alcohol. There are anecdotal reports that it reduces drinking, and NIAAA-funded groups are studying it for alcohol use disorder, but 7-OH products depress breathing like opioids. The modafinil seizure case shows the risk of combining substances at home. Tell clinicians exactly which product you used.

Supplements for Longevity & Their Efficacy | Dr. Peter Attia

Guest: Dr. Peter Attia
Date: 2024-07-29 · Duration: 2:30:41
URL: https://www.youtube.com/watch?v=79p1X_7rAMo

KEYPOINTS

1. Living longer today means delaying chronic disease
Attia notes that a century or more ago, living longer meant surviving childbirth, infection and trauma. Now it is mathematically equivalent to delaying cardiovascular, cerebrovascular, metabolic and neurodegenerative disease and cancer. He sorts tools into three groups: unavoidable behaviors done well or badly (eating, sleeping, moving); drugs that target specific diseases (statins, PCSK9 inhibitors, bempedoic acid, SGLT2 inhibitors, GLP-1 agonists, metformin); and 'geroprotective' molecules aimed at hallmarks of aging.

2. Attia takes rapamycin as his one purely geroprotective drug
He takes 8 mg once a week, pausing when he gets painful mouth ulcers (aphthous ulcers), which hit about 10% of users and are 'paradoxically the only biomarker' that it's working. Generic rapamycin costs about $5 per mg, roughly $40 a week. He also takes a PCSK9 inhibitor, bempedoic acid and an SGLT2 inhibitor, which he considers probably broadly geroprotective too.

3. Weekly pulsing changed his view of rapamycin's immune effects
Daily rapamycin is an immunosuppressant, approved in 1999 for transplant patients. A 2014 study by Joan Mannick and Lloyd Klickstein gave 65-year-olds the related drug everolimus on intermittent schedules and found better responses to flu vaccine. For Attia, that marked the shift from 'cool in mice' (the 2009 ITP result) to 'maybe we should take this', since the drug appears to modulate immunity in either direction.

4. The Interventions Testing Program is the strictest test of longevity molecules
The ITP tests compounds in genetically diverse (non-inbred) mice in triplicate at three institutions; of more than 50 molecules, very few extend life. Rapamycin worked even when started at about 21 months, roughly a 60-year-old human equivalent. Canagliflozin (an SGLT2 inhibitor), acarbose and 17-alpha estradiol also worked. Resveratrol did 'categorically nothing'.

5. Glucose control may matter independent of weight
Acarbose, which blocks glucose absorption in the gut, and canagliflozin, which makes you excrete glucose in urine, both extended mouse lifespan without lowering body weight. Attia reads this as evidence that tight glycemic control itself has longevity value.

6. NR failed the ITP at mega-doses
Nicotinamide riboside, an NAD precursor, was tested at roughly 500–1,000 mg per kg of body weight and produced no change in lifespan or healthspan. Mouse-equivalent doses for a 100-kg person would cost about $300 a day. Huberman says NR crosses cell membranes readily, while NMN's phosphate group is cleaved in the gut, which may favour NR at 300–600 mg over NMN at about 1,500 mg.

7. Human NR trials show statistical blips, not clinical benefit
In a roughly 100-person fatty-liver trial (MRI liver fat; above 5% counts as fatty liver), neither dose changed liver fat, weight, inflammation or glucose. Only a subgroup analysis (people under 27% liver fat) showed the lower dose dropping from 20% to 15%, while the higher dose did nothing. Attia warns never to confuse statistical with clinical significance, comparing it to lowering blood pressure from 160/100 to 157/97.

8. One intriguing signal: non-melanoma skin cancer
Attia found one study (NR or NMN — he considers them roughly equivalent) reporting 60–80% fewer basal and squamous cell carcinomas, with no effect on melanoma. He'd like to see it replicated. It might matter for people with heavy sun exposure, and he notes skin shows the largest age-related NAD decline.

9. Biological-age tests are mostly noise for now
Clocks that combine glucose, vitamin D and methylation markers are too variable to tell whether you measured the same 'state' a year apart. Attia says that, last he checked, companies weren't truly sequencing the epigenome base by base, just averaging methylation. He thinks the epigenetic piece may prove useful eventually.

EXAMPLES

1. The resveratrol mouse that couldn't breathe
The one positive resveratrol result used mice fed so much fat that their livers pushed into the chest cavity. Mega-doses rescued them, but humans would need to drink about their body weight in wine daily, which debunks the 'French paradox' explanation. The ITP's version found nothing.

2. Huberman's NAD infusion
He found an IV NAD drip (500 mg over roughly 30 minutes to 3 hours, often combined with glutathione and vitamin C) intensely unpleasant during the infusion, then felt good afterward. He felt similarly after plain saline drips. Sublingual NMN, 1,500 mg in the morning, makes his hair and nails grow fast. He takes it inconsistently.

3. Attia's over-the-counter list
Fish oil (EPA and DHA) in capsules for better compliance, thiamine (some evidence in mild cognitive impairment), vitamin D 5,000 IU (raises him from about 30 to 50 ng/mL), methylfolate and methyl-B12 to lower homocysteine (no B6, given nerve-damage risk), magnesium in three forms, ashwagandha for sleep, 5 g creatine, and Akkermansia-based probiotics.

4. Huberman's core list

Over 1 g of EPA a day from liquid fish oil, about 5,000 IU of D3 (adjusted by blood tests), methyl-B12, Tongkat Ali (which lowered his SHBG), green tea capsules, 10 g of creatine, and magnesium threonate, apigenin (50 mg) and sometimes inositol (900 mg) before sleep. He dropped nicotine gum because it felt too stimulating and had become a habit.

OTHER RELEVANT

1. The Titanic analogy

Attia's framing: exercise, sleep, nutrition and emotional health decide the Titanic's heading relative to the iceberg. Supplements are whether the dining room served lobster or steak. Both agree those four pillars dominate.

2. Don't take NAD-pathway supplements for longevity

Asked directly, both said no. Attia, citing an idea along the lines of 'show me your portfolio', says he passionately doesn't believe they do anything, so he takes none, but will change his mind if new data appear.

3. Experiment with exercise timing for energy

Huberman finds that finishing his workout before 9 a.m. gives him more energy all day than a late-morning session, and hypothesizes body-temperature rhythms are involved (untested). Track how timing affects your energy.

Ketamine: Benefits and Risks for Depression, PTSD & Neuroplasticity | Huberman Lab Podcast

Date: 2023-07-07 · Duration: 1:42:40
URL: https://www.youtube.com/watch?v=Rxmv7rT9leo

KEYPOINTS

1. Ketamine is a close cousin of PCP with real clinical value and real abuse potential
Both are dissociative anesthetics that block the NMDA receptor. Huberman says ketamine has proven 'miraculous' for some people, though not all, when used clinically for depression, suicidality and PTSD. It also has high abuse potential, and he notes that wider legal access, including take-home prescriptions, has brought more recreational use and some addiction.

2. Standard antidepressants leave a large gap
Drugs built on the monoamine hypothesis, such as SSRIs and bupropion, give true relief to only about 40% of depressed people. Benefits often take weeks or months to appear, and side effects (appetite and sleep changes, sharply reduced libido) make them intolerable for some. Huberman stresses these drugs have still helped many people and prevented suicides.

3. Ketamine works within hours, but the effect is short-lived
Relief can come the same day, even in people unresponsive to SSRIs, and can reduce suicidality, helplessness and worthlessness. Clinical studies also support uses in bipolar depression, PTSD, OCD, anxiety and substance addiction. The antidepressant effect often fades after about three days to a week, and weekly dissociative sessions aren't practical for many people.

4. It boosts plasticity by disinhibition
Ketamine blocks NMDA receptors on inhibitory neurons, which releases the brakes on excitatory neurons in mood and reward circuits. These neurons then fire in bursts, the pattern that best induces lasting changes. Bursting triggers BDNF release; BDNF binds TrkB receptors, adds glutamate (AMPA) receptors and grows new branches on neurons. Pre-clinical and clinical evidence suggests BDNF may actually be required for ketamine's antidepressant effect.

5. The opioid system appears necessary for the antidepressant effect
Ketamine binds mu and kappa opioid receptors, and its metabolite hydroxynorketamine (HNK) is highly selective for them. In a study by Stanford's Nolan Williams, Alan Schatzberg and colleagues, blocking opioid receptors with naltrexone left ketamine's euphoria and dissociation intact but abolished its antidepressant and anti-suicidal effects. Several studies support this.

6. The 'trip' and the therapeutic benefit may be separate
From the naltrexone result, Huberman draws a broader point for ketamine, psilocybin and MDMA. The acute subjective experience may not be what produces long-term relief. He doubts it's strictly either/or, but cautions against assuming the intensity of the experience predicts the benefit.

7. Ketamine quiets the brain's 'disappointment' circuit
The habenula inhibits the dopamine reward pathway (VTA and nucleus accumbens), reducing dopamine and raising cortisol; bright light in the middle of the night activates it. Ketamine therapy appears to lessen the habenula's inhibitory output, making the reward pathway more available.

8. Behavior determines whether the window of plasticity helps
Circuit changes do little unless daily life reinforces them. If someone keeps up pro-depressive patterns, ketamine provides little relief. Seeking stimulating work, social engagement and good physical and mental self-care are the 'anti-depressive behaviors' that make the opened window count.

EXAMPLES

1. The seven-patient trial that started it
In a small early study, seven people with major depression received IV ketamine at 0.5 mg/kg. Effects began within 10–15 minutes, peaked as a euphoric, dreamy, semi-dissociative state at 45–60 minutes, and the euphoria was over in about two hours. Depression relief came within minutes to hours and lasted at least three days, well beyond the drug's acute effects. This made ketamine especially attractive for depression that hadn't responded to other treatments.

2. Twice weekly for three weeks
Later clinical studies gave ketamine twice a week for three weeks. Patients had relief throughout, and many kept some benefit for months afterward before needing to repeat the course. Huberman attributes this durability to genuine circuit rewiring.

3. How dose translates by route
Oral ketamine delivers only about 25% active drug to the bloodstream, and sublingual or troche about 35%. Huberman uses himself as an example: at 100 kg, a 0.5 mg/kg clinical injection would be 50 mg. Matching it would take about 150 mg as a pill or about 200 mg as a troche. Doses of 1–2 mg/kg are in the anesthetic range.

4. What a 'K-hole' is
A K-hole is a pseudo-anesthetized state that happens when someone, usually recreationally, crosses from a sub-anesthetic into an anesthetic dose. Sensitivity varies a lot even at the same body weight, depending on metabolism. Very high doses carry risk of seizure and death, which is why clinical dosing is supervised.

5. R, S or racemic ketamine
After consulting clinicians, Huberman reports that trials so far suggest the combined R/S form is most potent for depression.

S-ketamine, the most commonly prescribed form including as a nasal spray, comes second, and R-ketamine is least effective. He acknowledges individual reports may differ.

6. Learned helplessness models

Much early antidepressant research measured how long a rat or mouse kept swimming before 'giving up' in water, a quantifiable stand-in for learned helplessness. Researchers then tested which drugs lengthened or shortened that time. Huberman notes the limits: you can't ask an animal whether it's depressed, so behavior is the only readout.

OTHER RELEVANT

1. Know where your dose sits

Clinical antidepressant studies use about 0.5 mg/kg by IV or intramuscular injection. Because oral and sublingual routes are less bioavailable, take-home doses are higher in milligrams, and confusion about conversions is a real risk. Ketamine can raise liver enzymes, which is why some frequent users choose routes that bypass the liver.

2. Microdosing has no published support for depression

According to Huberman and his clinician colleagues, there is no published clinical evidence that microdosing ketamine treats depression. The positive data come from 0.5 mg/kg doses or their oral or sublingual equivalents.

3. Use it inside a clinical structure

Most evidence comes from supervised settings. Ketamine can be habit-forming, and repeated home use outside a clinic is a different situation from the trials, so work with a clinician on frequency and setting.

4. Pair treatment with anti-depressive behaviors

In the days after a dose, deliberately engage with rewarding work, people and healthy routines, since these are the inputs the more plastic circuits are built to respond to. Avoid bright light in the middle of the night, which activates the habenula.

The Science of Psychedelics for Mental Health | Dr. Robin Carhart-Harris

Guest: Dr. Robin Carhart-Harris
Date: 2023-05-22 · Duration: 2:37:09
URL: https://www.youtube.com/watch?v=fcxjwA4C4Cw

KEYPOINTS

1. Classic psychedelics are 'psyche-revealing'
Carhart-Harris, a pioneer of psychedelic clinical research, notes that 'psychedelic' means mind- or psyche-revealing. He argues that what makes LSD and psilocybin uniquely interesting, compared with psychedelic-like drugs such as ketamine, MDMA or cannabis, is how they bring previously unconscious material into awareness. Explaining that biologically is, he says, a major gap to fill.

2. Microdosing evidence is thin so far
Definitions vary. A microdose of LSD is around the perceptual threshold of 10–12 micrograms, often taken on a schedule such as one day on and one or two days off. Popularizers like Jim Fadiman argue a true microdose should be sub-perceptible. Claims of better well-being and creativity lack compelling evidence, partly because placebo-controlled take-home dosing over weeks is hard and costly. A New Zealand study he thinks was well designed showed promising mood effects in presentations but was unpublished at the time.

3. Don't calibrate mushroom doses from clinical milligrams
Trials use 25 mg of synthetic psilocybin. Carhart-Harris estimates mushrooms contain roughly 1% psilocybin (plus psilocin), 'maybe a little higher,' but stresses this is guesswork. Proper potency studies hadn't been done, and he warns people not to use his answer to dose themselves.

4. Psychedelic therapy is very different from taking a psychedelic
Sessions use an eye mask, music throughout, settled conditions and ideally two mental-health professionals, at least one of them a psychiatrist, clinical psychologist, psychotherapist or psychiatric nurse. Protocols are similar across sites. Two dosing sessions spaced one to three weeks apart are the default at Hopkins, Imperial and NYU. His anorexia trial uses three.

5. 'Trust, let go, be open' predicts outcomes
Mentored by Johns Hopkins guides Bill Richards and Mary Cosimano, his team adopted this mantra, which he attributes to Richards. Trust in the therapist, measured even by a single rating on dosing morning, predicts the quality of the experience and outcomes weeks or months later. Readiness to surrender and to be open also predict response, but openness can be terrifying for people carrying significant trauma.

6. Psilocybin reduces brain modularity, and this tracks recovery
During a trip, communication across brain networks increases. In two separate depression cohorts this decrease in modularity was still present the next day in one and three weeks later in the other. The size of the change correlated with symptom improvement. He cautions not to over-read it, since sharper analytical cognition is associated with more modularity. Depression, he suggests, is like a rut in a landscape: easy to fall into, hard to climb out of.

7. The 'entropic brain' effect scales with trip intensity
EEG shows brain activity becomes more complex, harder to predict and more informationally rich on psilocybin. The effect reliably tracks the strength of the subjective experience: the bigger the trip, the bigger the effect.

8. Placebo doesn't explain psilocybin's antidepressant effect
In the psilocybin-versus-escitalopram trial, participants generally expected more from psilocybin. Yet pre-trial expectancy predicted response to escitalopram on virtually every one of about 12 scales and predicted response to psilocybin on none. He calls it 'a smash on the head' for the placebo critique, while granting skeptics have a point.

9. Psychedelics dissolve the ego; cocaine inflates it
In one of his studies, dose-dependent measures cleanly separated drugs: cocaine increased ego inflation without touching dissolution, while psychedelics did the opposite. His hypothesis is that 2A receptors are densely expressed in evolutionarily recent brain regions.

10. MDMA therapy is more interpersonal, and suggestion plays a role
MDMA sessions involve more talking and less use of eye shades. People often feel love for those around them, making the work closer to talk therapy. MDMA teams encourage patients to listen to their 'inner healer,' language Carhart-Harris notes has been criticized as suggestive. He concedes suggestion is probably one of the vehicles of the therapy, and that honesty about this matters.

11. Combining psilocybin and MDMA is an open question
Underground therapists already combine the two. Carhart-Harris is interested because traditions often learn by trial and error, and in some patients sequencing the drugs might help. Psilocybin can reach 'the kernel of your suffering' but sometimes aggressively, which can overwhelm people with PTSD, while MDMA softens the emotional edge. Huberman stresses that such use is illegal and that the science should come first.

EXAMPLES

1. The do-it-yourself blinded microdosing study
Led by Balázs Szigeti at Imperial, participants put their own LSD microdoses into opaque capsules alongside empty placebo capsules, shuffled them, and tracked them with QR codes. Mushrooms were dropped because burping revealed the taste. Microdosing didn't compellingly beat placebo: people who got placebo but thought they had microdosed did as well as those who actually microdosed.

2. NEJM 2022: psilocybin versus escitalopram

One arm received two 25 mg psilocybin sessions. The other took escitalopram (Lexapro) for six weeks plus a very low 1 mg psilocybin dose. That let all participants be told they were getting psilocybin and allowed identical psychotherapy. Huberman likens the low dose to microdosing; Carhart-Harris says it was simply a necessary placebo.

3. First-ever psilocybin in middle-aged healthy volunteers

Participants averaged about 40 years old, were about half women, and had never used a psychedelic. They received 1 mg placebo, then 25 mg. All changes came with 25 mg: better well-being, the entropic EEG effect, and diffusion tensor imaging showing decreased axial diffusivity in two prefrontal tracts to the thalamus and striatum. That is a pattern resembling brain maturation, and the reverse of what is seen in aging.

4. Ongoing anorexia and fibromyalgia trials

His three-session anorexia trial, then 19 patients in with two to go, showed improved weight at long follow-up but was unpublished. Huberman notes anorexia is the deadliest psychiatric illness. A single-dose 25 mg fibromyalgia study for generalized chronic pain, with EEG recording, doesn't ask people to focus on their pain. Carhart-Harris said it was 'going very well' and cautioned against over-promising.

OTHER RELEVANT

1. Be skeptical of microdosing claims

Expectancy appears to drive most reported benefits so far, so personal anecdotes are weak evidence.

2. Context is part of the treatment

Rapport, eyes-closed sessions, music, trained guides and integration afterwards are core components, not extras. Recreational use lacks them.

3. Clinical, not casual

The evidence comes from screened patients in supervised trials with fixed synthetic doses. Mushroom potency is uncertain and self-dosing can go badly wrong.

How Psilocybin Can Rewire Our Brain, Its Therapeutic Benefits & Its Risks

Date: 2023-05-08 · Duration: 2:09:01
URL: https://www.youtube.com/watch?v=eIxVfln02Ss

KEYPOINTS

1. Psilocybin is a tryptamine that mimics serotonin
Psilocybin is a tryptamine, like DMT and 5-MeO-DMT, and in its active form, psilocin, it closely resembles serotonin. Stomach acidity converts psilocybin to psilocin. Huberman notes that about 90% of the body's serotonin is made in the gut, but brain serotonin comes from separate neurons, not from gut stores.

2. The serotonin 2A receptor is the key
Psilocybin acts mainly at the 5-HT2A receptor, which sits in specific brain areas and parts of neurons, notably the apical dendrites of cortical pyramidal neurons that connect laterally across regions. That selectivity, rather than general serotonin boosting, is what Huberman says drives both the acute experience and the later circuit changes.

3. Visual hallucinations come from dense 2A receptors in visual cortex
The visual cortex has very high 2A expression, so at sufficient doses people hallucinate with eyes open or closed. With eyes open, much of the session gets absorbed in outside visuals like geometric fracturing or melting faces. Experts running trials told Huberman that therapeutic benefit depends on keeping the eyes covered for most of the session.

4. Rewiring alone is not the goal; adaptive rewiring is
Huberman repeats that plasticity is not automatically therapeutic: brain injury and methamphetamine also rewire the brain, maladaptively. The aim is changes that help someone function better afterwards. Set, setting, eyes-closed versus open, music and dose all shape whether the plasticity is beneficial.

5. Psilocybin increases connectivity across brain networks
Imaging studies show more lateral, less hierarchical communication between brain areas after psilocybin, including at rest. Despite this reduced modularity, Huberman notes that long-term memory problems are rarely reported in depression trials.

6. Plasticity mostly comes from new connections, not new neurons
Huberman estimates neurogenesis accounts for perhaps 1–2% of meaningful adult rewiring 'and I'm being generous.' Psilocybin's effects in animal models involve growth of dendrites and dendritic spines, which are new sites for excitatory input. He notes that depressed humans show fewer spines in frontal cortex.

7. Dose conversions and the 'heroic dose'
Mushrooms average about 1% psilocybin, so 1 g of mushrooms holds about 10 mg. A 'heroic dose' of about 5 g therefore equals roughly 50 mg. Potency ranges from about 0.5% to 2% across strains, batches, age and storage, so 1 g could deliver 20 mg, or 3 g only 10–15 mg. Research uses synthetic psilocybin given orally or intravenously. Microdosing in research terms means 1–3 mg daily; therapeutic doses are 10 mg or 25–30 mg, once or twice.

8. A typical session has a predictable arc
Participants fast for at least four hours, since food changes gut acidity. Effects begin 30–45 minutes after dosing, peak around two hours with intense emotion and often anxiety (part of 'ego dissolution'), and taper toward about six hours. Clinical playlists follow this arc: quiet, mostly instrumental music first, then 45–90 minutes of louder, percussive music at the peak, then softer, melodic or choral music.

9. Extreme anxiety at the peak predicts worse outcomes
Some anxiety is expected, but extreme anxiety is negatively correlated with relief from depression. That makes trained guides who can help people through it in real time essential.

10. Strict exclusions and cautions apply
People with psychotic or bipolar tendencies, or even a first-degree relative with bipolar disorder, schizophrenia or schizotypal traits, are typically excluded from trials. Most studies enroll adults aged 25 to about 70. Trials require participants to be off serotonergic antidepressants, but Huberman stresses never stopping medication without a physician or psychiatrist, which he calls potentially catastrophic. Psilocybin remained illegal outside research and some decriminalized areas at recording.

EXAMPLES

1. NEJM, November 2022: single-dose psilocybin for treatment-resistant depression
About 75–79 participants per group received 25 mg, 10 mg or 1 mg (control) of synthetic psilocybin with psychological support. At week three, 25 mg gave significantly more relief than 1 mg. 10 mg did not differ from 1 mg. Adverse events occurred in every group and were most frequent at 25 mg, including headache, anxiety and suicidal ideation.

2. Two-session trial: effect sizes beyond SSRIs
In a two-session protocol with about 11 hours of supportive psychotherapy, the authors reported large, rapid and sustained antidepressant effects. Effect sizes were roughly 2.5 times those typical of psychotherapy and more than 4 times those of antidepressant drug trials. Across such trials, 60–75% of people with major depression report good experiences and substantial relief.

3. 'Psilocybin Induces Rapid and Persistent Growth of Dendritic Spines in the Frontal Cortex In Vivo' (Neuron)
In mice, psilocybin rapidly grew mushroom-shaped dendritic spines in the prefrontal-equivalent cortex, and the new connections persisted after the drug cleared. That may help explain lasting effects in people.

4. Network connectivity in healthy volunteers
A study from Robin Carhart-Harris's group imaged healthy people at rest before and after psilocybin or MDMA and found

expanded connectivity between networks such as the default mode network.

5. Physiological sighs during sessions

Huberman says Matthew Johnson's Johns Hopkins team has begun teaching participants the physiological sigh before sessions so they can calm themselves at the peak. This builds on a Cell Reports Medicine paper from the Huberman and David Spiegel labs showing it is one of the fastest breathing tools for reducing arousal. He describes the in-session data as preliminary and unpublished.

OTHER RELEVANT

1. Setting must be physically safe and supervised

That means no open windows, nearby traffic, bodies of water or chance of getting lost, and at least one, ideally two or more, sober people present.

2. Know your dose, not just your grams

Because mushroom potency varies about fourfold, gram amounts are unreliable. The trial evidence centers on 25–30 mg under clinical supervision, with higher doses carrying more adverse events.

3. Plan for integration afterwards

Huberman highlights that combining psilocybin with talk therapy outperforms either alone. The weeks after a session, while plasticity persists, are when therapy and reflection can turn changes into adaptive ones.

Using Caffeine to Optimize Mental & Physical Performance

Date: 2022-12-05 · Duration: 2:22:35
URL: https://www.youtube.com/watch?v=iw97uvIge7c

KEYPOINTS

1. Caffeine acts mainly by blocking adenosine
Adenosine builds up the longer you are awake and drives sleepiness, and sleep clears it. Caffeine occupies adenosine receptors without activating them, so you feel less tired even though adenosine is still there. Huberman describes four main actions: blocking adenosine, raising dopamine and norepinephrine, boosting acetylcholine in the forebrain for flexible thinking, and increasing dopamine receptors in the brain's reward pathways.

2. Caffeine increases dopamine receptors in reward circuits, which is why it reinforces behavior
With more dopamine receptors ('parking spots') available, things that already feel good feel better. That is the evolutionary purpose of caffeine in plants. Huberman cites a study showing bees prefer nectar containing tiny amounts of caffeine, which strengthens their memory and preference for those flowers. Humans are conditioned the same way to the foods, places and activities paired with caffeine.

3. A useful single dose is 1–3 mg per kg of body weight
For a 100 kg (220 lb) person that is 100–300 mg per sitting; for 50 kg (110 lb) it is 50–150 mg. Huberman suggests starting at the low end if you are not a regular user. This is a per-dose figure, not a daily total. Two 200 mg doses an hour apart act like roughly 400 mg and are likely to cause jitters.

4. Being caffeine-adapted is different from tolerance
If caffeine raises your heart rate and makes you a bit anxious at a normal dose, you are probably not adapted. If it leaves you alert but relaxed, you probably are. Huberman counts you as a regular user if you have had caffeine daily for the past two weeks. Taking it two to four times a week makes you an intermittent user.

5. Delaying caffeine 90–120 minutes after waking is meant to prevent the afternoon crash
Huberman's reasoning: the natural morning cortisol rise helps clear leftover adenosine. Caffeine taken immediately only masks adenosine, which then hits once the caffeine wears off. Waiting, ideally after morning light and some movement, means caffeine arrives on top of a higher cortisol peak. A moderate dose then carries you into the afternoon without needing more.

6. Afternoon caffeine degrades deep sleep even if you fall asleep fine
Caffeine's 'quarter life' is about 12 hours: roughly 25% of a noon dose is still active at midnight. Huberman says that for about 95% of people, afternoon caffeine reduces slow-wave sleep, which then disrupts REM sleep and next-day emotional processing. Slow-wave sleep is also tied to growth hormone release and immune function. He recommends avoiding caffeine for 12 hours before bed, or at least 8–10.

7. Caffeine reliably improves mental and physical performance
Alertness rises within about five minutes on an empty stomach and peaks around 30 minutes. Improvements in reaction time, mood, focus, recall, dexterity, power and endurance are seen with 1–3 mg/kg taken beforehand. A 2020 European Journal of Nutrition study found caffeine boosted peak aerobic cycling power regardless of menstrual cycle phase.

8. Some of caffeine's 'boost' in regular users is relief from withdrawal
Habitual users who skip their usual dose perform worse, which inflates the apparent benefit when they take it. To maximize the effect, Huberman suggests taking caffeine on an empty stomach or abstaining for two to three days beforehand. A study he cites used a five-day abstinence and found cortisol responses to caffeine were reduced but not eliminated in daily users.

9. Several common fears about caffeine aren't supported
Large studies indicate caffeine does not cause or worsen osteoporosis as long as dietary calcium is adequate. At 1–3 mg/kg, or even double that, there are no consistent effects on testosterone or estrogen in men or women. Huberman cautions that about 90% of adults use caffeine, so good control groups are hard to find. Moderate intake is linked to lower depression risk and some protection against Parkinson's and possibly Alzheimer's, though these are associations.

EXAMPLES

1. Yerba maté and GLP-1
Yerba maté stimulates release of GLP-1, a satiety peptide first studied in Gila monsters, and may help blunt appetite. Huberman advises avoiding smoked varieties, which may be carcinogenic.

2. Theanine to take the edge off
Theanine, a nonprotein amino acid found in green tea, competes with excitatory glutamate signaling. Huberman cites 200–400 mg to offset caffeine jitters, with studies suggesting up to 900 mg/day is safe. One study found 17 days of 200–400 mg, one to three times daily, reduced depression and anxiety. He advises people prone to vivid dreams, night terrors or sleepwalking to avoid it at night.

3. Adrenaline after learning boosts memory
James McGaugh's review describes a medieval practice of throwing children into cold water after they witnessed something important, which made them remember it better. Lab studies confirm that spiking catecholamines after learning enhances memory. Huberman suggests caffeine, exercise or deliberate cold right after a learning session can work the same way.

4. Why Huberman doesn't endorse the 'nappuccino'
Drinking coffee right before a nap pushes caffeine into the afternoon. Caffeine also undermines the restorative effects of naps under 90 minutes and of NSDR, which on its own has been shown to raise dopamine.

5. Sugar paired with caffeine

Because caffeine reinforces whatever it accompanies, sweetened caffeinated drinks or coffee with dessert can strengthen sugar cravings. Separating the two can make cravings easier to break.

OTHER RELEVANT

1. Dose by body weight and per sitting

Calculate 1–3 mg/kg, start low if you're sensitive or new, and remember that closely spaced doses add up.

2. Exceptions to the morning delay

If you train hard soon after waking, take caffeine before the workout, but expect a bigger afternoon dip. To move to a later first dose, push it back about 15 minutes per day, or split it: half on waking and half an hour later.

3. Use caffeine to make exercise more rewarding

Caffeine before training, combined with the dopamine from exercise, gives a longer-lasting lift and makes exercise more reinforcing.

4. Replace fluid and a little sodium

Caffeine is a diuretic that also drives sodium loss. Huberman suggests hydrating with a small amount of sodium or electrolytes to sustain alertness, while staying mindful of blood pressure.

5. Protect sleep first

An occasional afternoon coffee won't ruin you, but making late caffeine a habit erodes deep sleep and leads to more caffeine the next day.

What Alcohol Does to Your Body, Brain & Health

Date: 2022-08-22 · Duration: 2:01:02
URL: https://www.youtube.com/watch?v=DkS1pkKpILY

KEYPOINTS

1. Even one to two drinks a day is linked to brain thinning
Heavy drinking (about 12–24 or more drinks a week) has long been known to degenerate the neocortex. A UK Biobank study of more than 35,000 healthy middle-aged and older adults found that an average of one to two drinks a day was also associated with thinning of the neocortex and other regions. Huberman stresses that 'chronic' refers to the pattern, so 14 drinks packed into a weekend counts too.

2. Alcohol is a toxin your liver converts into a worse toxin
Ethanol is both water- and fat-soluble, so it enters every cell directly. NAD-dependent steps convert it into acetaldehyde, which damages and kills cells indiscriminately, and then into acetate, which can be burned for fuel. The NAD-to-NADH step limits the rate, so when it falls behind, acetaldehyde builds up and liver cells take the hit. That is why alcohol counts as 'empty calories'.

3. Drinking removes top-down inhibition, and regular drinking rewires habit circuits
Alcohol suppresses the prefrontal brake on impulsive behavior while you are drunk. Even a once-a-week pattern of three or four drinks adds synapses in circuits for habitual behavior and removes them in circuits that control behavior, so people become more impulsive when sober too. Two to six months of abstinence generally reverses this, though years of heavy drinking leave lasting effects.

4. The serotonin lift is brief, and the next drinks can't bring it back
Acetaldehyde first makes serotonergic mood circuits hyperactive, which explains early talkativeness and well-being. Activity then drops, prompting another drink. By the third to fifth drink there is essentially no chance of recovering the high. Instead the forebrain and motor areas shut down, causing slurring, shuffling and eventually passing out.

5. Regular drinkers have higher cortisol even when sober
One drink a night, or two to four on weekends, shifts the hypothalamic–pituitary–adrenal axis toward more baseline cortisol, which lowers stress thresholds. This also explains 'hangxiety'. Huberman notes that people cutting back should expect a temporary rise in anxiety while the axis readjusts.

6. Genes and starting age shape the risk of alcoholism
Risk genes cluster in serotonin, GABA and HPA-axis pathways and interact with environment, trauma and social pressure. People with little alcohol dehydrogenase flush and feel sick, which tends to protect them. A warning sign is being able to drink all night with increasing energy, especially with blackouts. Starting young greatly raises dependence risk even without a family history.

7. Alcohol damages the gut–liver–brain axis in a way that drives more drinking
It kills beneficial gut bacteria and makes the gut leaky, so bacteria move into the bloodstream. Meanwhile the liver releases pro-inflammatory cytokines. These signals reach the brain and promote further drinking, a vicious cycle that is especially strong in alcohol use disorder.

8. Cancer risk rises with every daily drink, especially breast cancer
Each 10 g of alcohol a day, about one drink, raises cancer risk by roughly 4–13% depending on the study. A weekend total that averages to that counts the same. Alcohol both promotes tumor growth and suppresses anti-inflammatory and immune defenses. The association has been documented since a landmark 1987 paper.

9. Alcohol shifts testosterone toward estrogen
A 2000 review in the journal Alcohol describes alcohol's metabolites increasing aromatization of androgens to estrogens in the ovary, placenta, liver, testes and other tissues. In women this may be part of why estrogen-related cancers rise. Huberman notes that estrogen should never be driven too low in either sex, because it supports cognition and joints.

EXAMPLES

1. Hangover ranking by congeners
From least to most hangover-inducing in comfortable amounts: ethanol in orange juice, beer, vodka, gin, white wine, whiskey, rum, red wine, and brandy at the top. Because ethanol in orange juice ranks lowest, sugar is not the culprit. Congeners such as nitrites, which add flavor, track with severity.

2. Alcohol gives you pseudo-sleep, not real sleep
Citing Matt Walker, Huberman says even one glass of wine or one beer disrupts slow-wave and REM sleep. Drinking to fall asleep produces low-quality rest, which is part of why hangovers feel so bad.

3. Resveratrol doesn't rescue red wine
Even if resveratrol is beneficial, which is debated, you would need so much red wine to get a useful dose that the harms would outweigh any benefit. He notes David Sinclair confirmed this on an earlier episode.

4. Cold for clearance, but not while drunk
A small literature suggests raising epinephrine may speed parts of alcohol metabolism, lending some support to the old cold-shower lore. Because alcohol lowers core body temperature, getting into a pool or lake while inebriated is dangerous; only use cold exposure once sober.

OTHER RELEVANT

1. Rebuild your gut with low-sugar fermented foods

Justin Sonnenburg and Christopher Gardner's Stanford work found that 2–4 servings a day of kimchi, sauerkraut, natto, kefir or live-culture yogurt lowered inflammatory markers. This hasn't been tested specifically in alcohol use disorder, but Huberman considers it a logical repair step. Probiotics and prebiotics are an alternative with less human data.

2. Partially offset cancer risk with folate and B12, without relying on them

Folate and B vitamins, especially B12, have been shown to reduce, but not eliminate, alcohol-related cancer risk, probably because alcohol disrupts B-vitamin pathways. They are not a license to drink.

3. Manage a hangover with a few things that work

No single remedy works; Examine.com's review of purported cures, from Japanese pear juice to yohimbine, finds weak evidence. Electrolytes before bed and on waking, fermented foods and safe cold exposure address dehydration, gut disruption and depleted epinephrine and dopamine.

4. Quitting heavy use needs medical guidance

For people with serious alcohol use disorder, stopping cold turkey can be medically dangerous. The path to sobriety differs between people, so work with clinicians. Reward and pain systems reset after abstinence, with timing that depends on how much and how long you drank.

Psychedelics for Treating Mental Disorders | Dr. Matthew Johnson

Guest: Dr. Matthew Johnson
Date: 2021-09-20 · Duration: 2:52:05
URL: https://www.youtube.com/watch?v=GzvzWO0NU50

KEYPOINTS

1. Classic psychedelics act mainly on serotonin receptors, but chemistry doesn't predict the experience
Johnson groups LSD, psilocybin (found in more than 200 mushroom species), DMT and mescaline as classic psychedelics. Psilocybin resembles serotonin, yet mescaline structurally resembles dopamine and still produces a similar receptor-level effect. Huberman stresses that a molecule can trigger different parts of the same receptor's signaling pathway at different rates. That's why similar-looking compounds feel so different, and why people shouldn't try to 'cowboy their own chemistry.'

2. Hopkins-style sessions: screening, rapport, then a single high dose
Participants first undergo days of structured psychiatric interviews to exclude psychotic disorders and bipolar mania, plus cardiovascular screening. They then spend 4–8 hours of preparation building rapport with their guides. Early dose studies used placebo or 5, 10, 20 or 30 mg of psilocybin per 70 kg. Therapeutic work targets 20–30 mg (some people received 40–45 mg under weight adjustment), and the team has since dropped weight adjustment. The capsule takes effect in 15–60 minutes, and pulse and blood pressure are checked roughly every half hour.

3. Surrender, not control, seems to drive the benefit
Johnson tells participants that any emotion is welcome, even crying hysterically. That can be harder for experienced recreational users, whose party rule is to 'hold your shit.' He speculates that the reality-shattering phase, which can include losing one's sense of self, can be met by surrender, which tends toward transcendent experiences, or by clinging, which tends toward a bad trip.

4. Lasting change often looks like a shift in identity and agency
In his work with cancer patients who had cancer-related depression and anxiety, and with smokers who had repeatedly failed to quit, Johnson sees people step out of identities like 'I'm a smoker, I can't do it.' They report a supercharged sense of agency ('I'm just going to make a decision') and often say, 'I know this sounds like bullshit.' He contrasts this with ordinary advice to depressed people, which rarely sticks.

5. Ketamine works differently, and how it's delivered may matter
Spravato (esketamine nasal spray) is FDA-approved for treatment-resistant depression at fairly low, mildly psychedelic doses. Patients are told to ignore the altered state. Its antidepressant effect starts immediately but lasts about a week, whereas psilocybin effects have been seen a year or more later. Johnson points to Russian studies by Krupitsky in the 1990s–2000s that gave high-dose ketamine as psychedelic therapy and reported high success rates for heroin and alcohol addiction, and asks whether framing explains part of the gap.

6. The two big dangers: psychotic vulnerability and bad trips
People with schizophrenia, bipolar mania or a strong predisposition can be identified fairly reliably through a few hours of history-taking, and Johnson says psilocybin research in schizophrenia should be low on the list. The more common danger is a bad trip, which can happen to anyone at a high enough dose. Even in his lab, after the best preparation, about a third of people at roughly 30 mg report a stretch of intense fear, feeling trapped or 'losing their mind,' sometimes minutes before a beautiful experience.

7. Lasting perceptual effects exist but are rare and often confounded
Hallucinogen-persisting perceptual disorder is in the DSM: a very small percentage of users keep seeing halos or trails. Johnson notes that cases are clouded by unknown doses, purity and mixed drugs, and suspects a rare neurological susceptibility. He also argues the field historically blamed 'the weird other thing,' psychedelics, rather than alcohol or tobacco.

8. Microdosing is unproven and may carry its own risk
A microdose is roughly a tenth of an entry-level dose. For psilocybin that's about 1 mg. For LSD, whose psychedelic effects start around 100 micrograms, a common mistake is calling a 100-microgram dose a microdose. So far, studies haven't shown improved creativity, cognition or sustained mood, and none have tested the every-few-days schedules promoted by people like Paul Stamets. Johnson suspects there may be some real antidepressant effect, based only on anecdotes. He also flags that serotonin 2B activation (the mechanism behind fen-phen's heart-valve damage) is more worrying with repeated dosing over years than with a few therapeutic sessions.

9. Legal reform is moving, but approval isn't guaranteed
Johnson calls the assumption that everything will be legal in a few years premature. He distinguishes decriminalization from legalization and from regulated medical use, citing Oregon's state-level psilocybin therapy program, which must still work out how to coexist with federal law. If Phase 3 trials hold up, even at half the current effect sizes, he expected MDMA for PTSD and then psilocybin for depression to be approved within a few years.

EXAMPLES

1. The 'heroic dose' death in Oregon
Johnson keeps a growing file of people who panicked on psychedelics and were hurt or killed by running into traffic or falling. In one case, an 18-year-old in Oregon who wanted his 'biggest dose ever' ended up naked and disoriented in a neighbor's house and was killed by police, which Johnson calls an overuse of force.

2. Syd Barrett
Discussing psychosis risk, Johnson cites Pink Floyd's Syd Barrett, who heavily used LSD and showed a classic schizophrenia pattern. He adds that, as in many cases, there were hints of susceptibility beforehand. First psychotic breaks

and first drug use both peak in adolescence and early adulthood, which makes cause hard to untangle.

3. Survey reports of spontaneous change
Johnson's survey research includes people who took mushrooms recreationally and quit a 20-year smoking habit, or say it helped their depression or alcoholism. He notes efficacy rates are still higher with screening, preparation and support.

4. The Amsterdam truffle study
People who knew they were taking microdoses of psilocybin truffles showed small reaction-time shifts on cognitive tests. Johnson says these are just the effects you'd expect from being slightly high, which is why he insists on double-blind trials.

OTHER RELEVANT

1. Setting and support shape the outcome
Both men emphasize that the experience depends on the 'container': trusted guides, comfort, permission to let go and integration afterward. Johnson notes that the same high dose in a less-than-ideal environment raises the risk of a bad trip.

2. Screen honestly for personal and family psychiatric history
A personal or strong family history of psychosis or bipolar disorder is the main exclusion in trials. Heart disease is another, because psychedelics raise pulse and blood pressure.

3. Check dose units before taking anything
Micrograms versus milligrams is a common source of accidental full doses with LSD. Street products also vary in purity and may be mixed with other drugs.

4. To participate legally, look for clinical trials
Johnson points listeners to clinical trial registries (searching for psilocybin, MDMA or psychedelic turned up 40–50+ studies at the time) rather than unregulated use. Concussion and traumatic brain injury, which Huberman notes come largely from occupations like construction (jackhammers, for example) rather than from sports, is an emerging research target with a strong rationale but little data yet.