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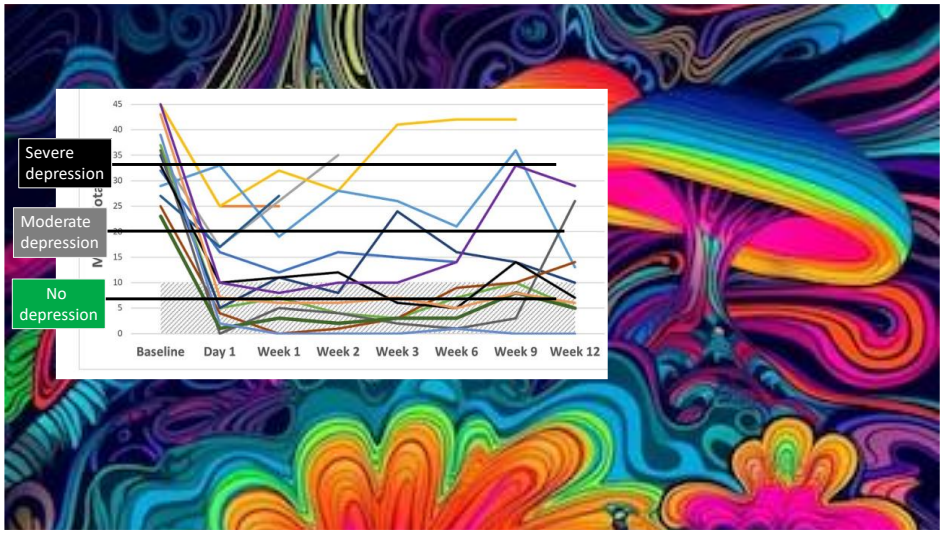
4:00 P.M.

Are Psychedelic Drugs Ushering in a New Paradigm in Depression Treatment?



By George Christison MD

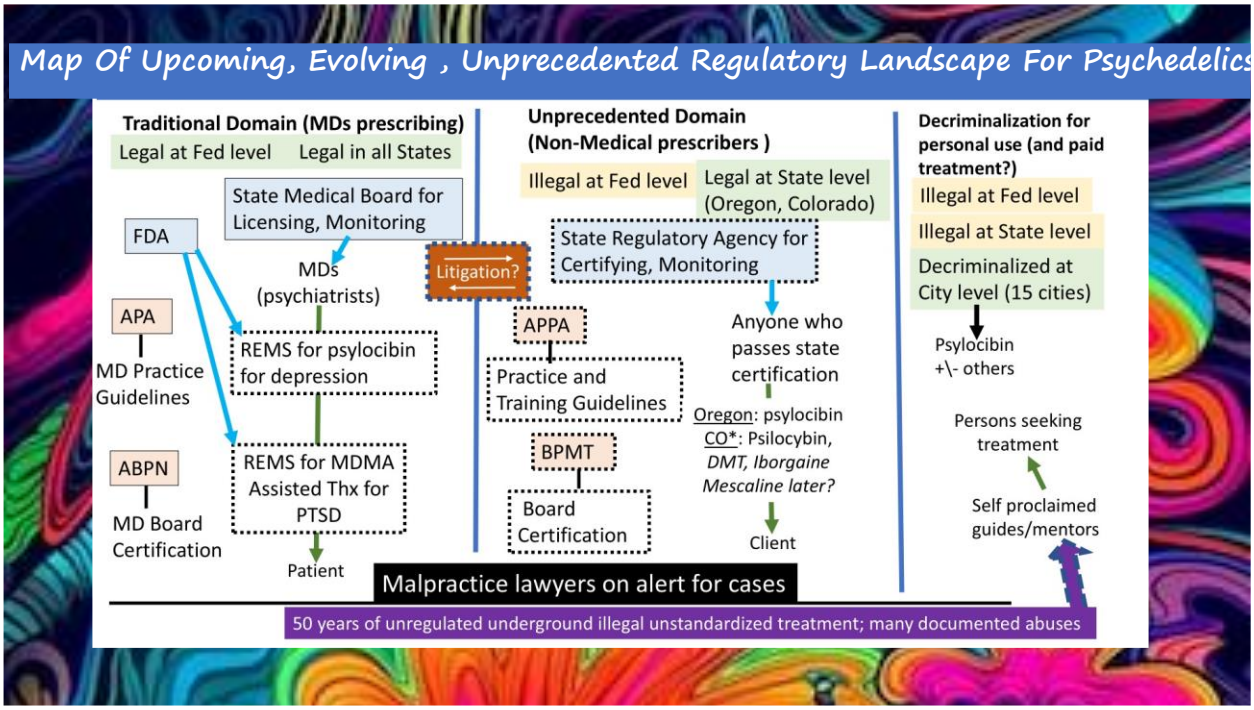
Assembly Room, A.K. Smiley Public Library

Summary:
Very well-respected experts in the field of Psychiatry are expressing hope that, based on accumulating evidence, the psychedelic drug psilocybin can provide very rapid and lasting relief for the often disabling condition of major depression. Since 2018, fifteen clinical trials have been published. Remarkably, these trials gave only one or two doses and produced dramatic reductions in depression symptoms within a week or less, reductions shown to last 6-12 months. Also, patients with years of depression unresponsive to multiple treatments have shown marked benefit within days after a single dose. This paper explores the effects of psilocybin in the brain and discusses the challenges of conducting a clinical trial of a psychedelic drug. Finally, the growing list of other conditions for which psilocybin is being tried is summarized and it is noted that in 2023 the editors of the respected journal Neuropharmacology called psychedelics a “therapeutic revolution”.

Background of the author:
Dr. Christison did his medical training at UC San Diego followed by a psychiatry residency at Duke University and then a schizophrenia research fellowship at the National Institutes of Mental Health. He joined the Psychiatry faculty at Loma Linda Medical School in 1988. He has received over a dozen teaching awards, including School of Medicine Teacher of the Year. His clinical work centered on the care of persons with serious mental illness and those with substance addiction. Now retired from patient care, he teaches psychiatry residents and advises the psychiatry department on research development.

First, what we won't be talking about

The psychoactive ingredient in "magic mushrooms" is psilocybin, which is in the category of drugs called psychedelics. There is currently a controversial and highly energized confluence of social, economic, political, regulatory and even spiritual issues swirling around the use and manufacture of psychedelics in the US (and elsewhere). This is a slide illustrating some of those issues that I made for a different presentation (it is just for illustration; don't worry about the acronyms).



These issues could fill two or three Fortnightly talks, but I am going to place them all in a big box and shove it up into the attic for now.

The primary goal of this talk is to enable all of you to be able to give a careful answer this question, should a loved one ask for your advice on this matter: "I am so depressed and nothing is working. I read on line that people are going to places where they can take magic mushrooms and it is really helping their depression. I know it sounds like something out of the 1960s fringe, but I am getting desperate. Should I try it?"

Serious depression is very serious

Major Depressive Disorder produces markedly reduced energy, motivation and ability to concentrate or focus. It can be disabling and, in fact, has been found to be the leading worldwide cause of disability (1).

Major depressive disorder can be lethal. It causes pessimism and negative ruminations about oneself and the future, with a serious risk of suicide. While not all suicides are directly due to depression, it is a serious contributor to a total age-adjusted rate of suicide increase of 35.2% from 1999 to 2018 (2,3). Suicide is the second leading cause of death for ages 10-34. (2,3)

Sadly, although they are very widely used, current antidepressant medications leave a lot to be desired. 30-50% of patients do not have remission of their depression on their first antidepressant trial (4).

Again, setting aside all of the questions about legality, manufacture, cost, etc, this talk is going to narrowly focus on: **does psilocybin (the active ingredient of magic mushrooms) actually seem to work for serious depression?**

I'll start with the bottom line: yes.

"An entirely new paradigm of care"

If asked to name the top two most respected medical journals in the US, most doctors and researchers would say the New England Journal of Medicine and the Journal of the American Medical Association (JAMA). In the Sept 5, 2023 issue of JAMA is an editorial by Dr. Rachel Yehuda, Endowed Professor of Psychiatry and Neuroscience of Trauma at Mount Sinai Medical School in New York, titled, "Psychedelic Therapy – A New Paradigm of Care for Mental Health" (5)

This is not some Timothy Leary-loving paranormal psychology priestess writing in a backwater fringe journal.

Dr. Yehuda's concluding paragraph reads,

> *"The social, economic, and public health impacts of untreated mental disorders demand solutions. If psychedelic therapies do prove to have enduring effects after just a single or a few administrations in the context of a few sessions for preparation and integration, they have the potential to offer not just a new approach to mental health care, but an entirely new paradigm of care."*

The article in that issue of the journal that prompted the editorial is titled, "Single-Dose Psilocybin Treatment for Major Depressive Disorder: A Randomized Clinical Trial" (6). We will be taking a closer look at that study a little later.

The neurochemical neighborhood within which psilocybin lives.

I want to go over this, because many of you will likely have heard of one or more of these and it helps to know how they group – or don't group - together.

First, meet the family

Psilocybin belongs to the class of drugs called psychedelics. This includes LSD, peyote (active ingredient is mescaline) and ayahuasca (active ingredient is DMT, dimethyltryptamine). These are the "classic psychedelics". What makes these drugs all relatives of each other is that they all bind to a particular serotonin receptor called the 2A receptor. A bit more on this in a minute. Other important characteristics of this family: these drugs can produce vivid hallucinations and unusual experiences of altered consciousness.

Very importantly, all have very low, if any, risk of addiction (7). There is a particular brain pathway/system in the brain (the mesolimbic dopamine pathway) that is tied to the experience of pleasure and to

wanting to something again. All known addictive chemicals, from nicotine to heroin, activate and hijack this system, causing people to keep using the substance over and over despite it clearly being harmful for them in multiple ways – the definition of addiction.

Psychedelics do not activate this pathway. They may be overused in some contexts, they may have side effects, but they do not cause an addictive disorder.

Next, meet the neighbors

This is more of a mixed group. I clump them together because they are also being closely studied for possible mental health benefits. They include ketamine (which can be addictive), dextromethorphan, and ecstasy (3,4 methylenedioxymethamphetamine or MDMA). Whether or not these are called psychedelics depends on who you talk to. They act differently in the brain than the classic psychedelics and can produce qualitatively different subjective experiences.

Finally, meet the bad boys who live across the tracks (bad pun)

These are all addictive and all are serious problems (drug cartels don't make psilocybin – they make these). They include the opiates (like fentanyl), methamphetamine (speed), Spice (synthetic cannabinoids), barbiturates (downers), and a growing list of newly synthesized dangerous drugs.

What is the evidence for psilocybin being effective for major depressive disorder?

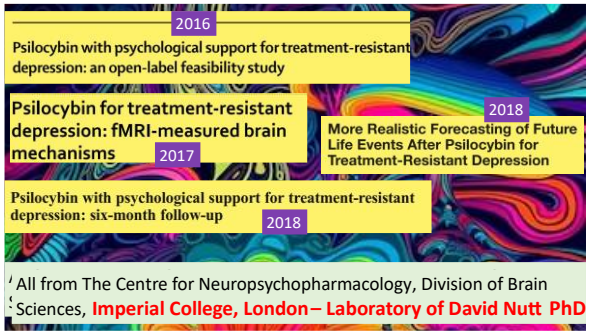
This is a new field with the first trial of psilocybin for depression being published in 2016 (8). Since then there have been 14 additional clinical trials (6, 9-23), all of which have shown rapid significant reductions in depression with psilocybin, using either one dose or two doses 1-2 weeks apart. Two studies followed these patients longer term and found the effects were maintained up to 12 months (10, 15)

Before we dive into these, a word about funding.

This study by Barnett and co workers (24) found that no funding for psychedelic assisted therapy trials was granted by the NIH from 2006-2020. All 14 of the clinical trials to date were either done in Britain or were funded privately. This does not negate the findings, but it can raise concerns of bias if a private funding agency is hoping to obtain a positive result. On the other hand, this is no different from the hundreds of clinical trials conducted by "Big Pharma" with the obvious hope of obtaining return on investment.

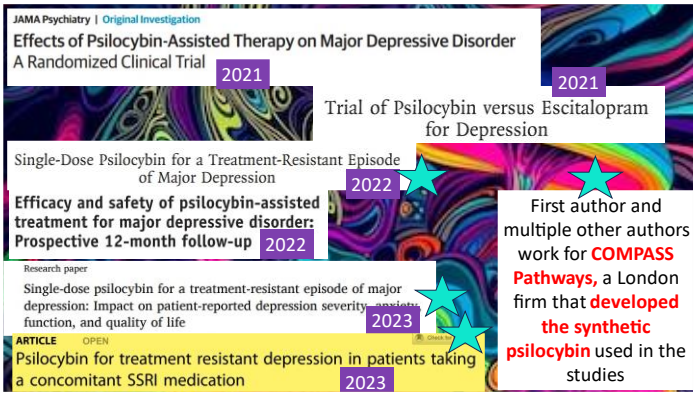
Clinical drug trials are broadly divided into two types. The first type is uncontrolled (or "open") trials. These give the experimental medication to a group of persons with the diagnosis of interest just to see what happens – benefits and side effects – with no control group. The second type are randomized controlled trials (RCTs). In these, one group of participants gets the medication and another, control, group gets something else for comparison (placebo, a low dose of the medication or a different

medication). Both the participants and those evaluating them for the effects of the drugs are "blind" to who is getting which type of pill.



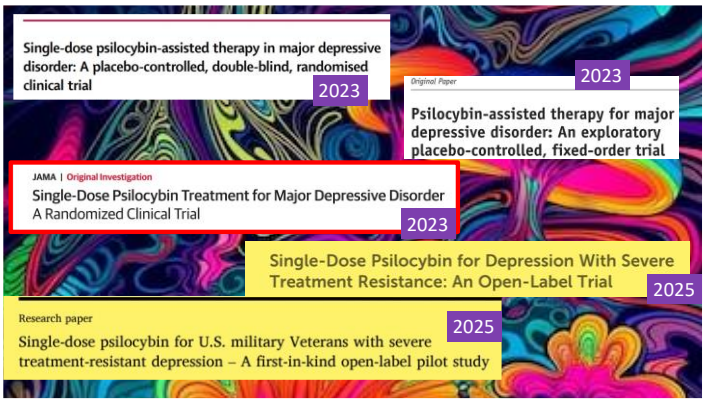
Between 2016 and 2018, Dr David Nutt, then at Imperial College London published the first three open studies of psilocybin (8-10). His group gave persons with major depression two doses of psilocybin, 1 week apart and found impressive benefit.

Prior to pivoting to focus on psychedelics, Dr. Nutt had a long and distinguished career in neuropsychopharmacology research, studying many different kinds of medications and (despite his unfortunate name) is highly respected.



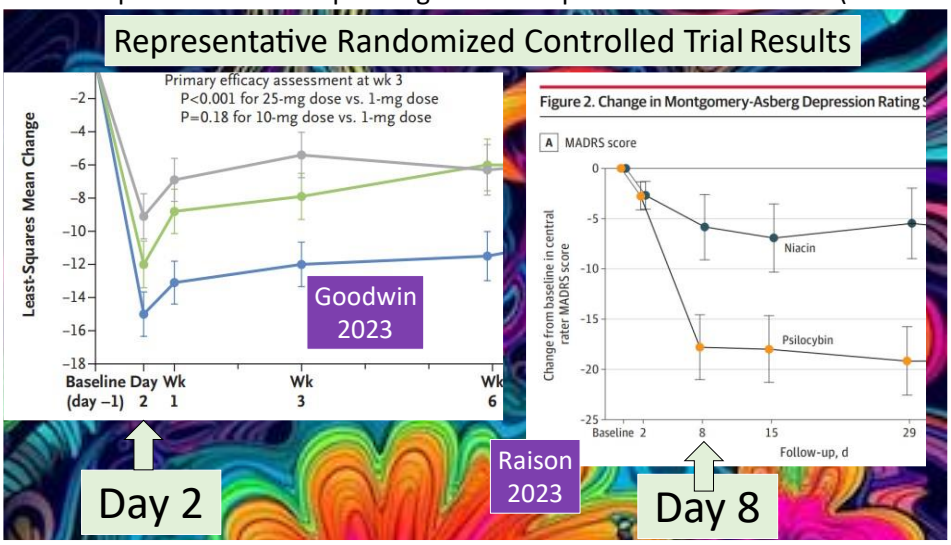
After these pioneering promising open studies, the first randomized controlled trial came out in 2021 (13) (white boxes indicate controlled trials, yellow boxes open trials, in the slide to the left). That same year Dr Nutt's group published the first (and, so far only) head-to-head study of psilocybin versus a standard antidepressant, escitalopram (12). Both drugs did well. Psilocybin's improvement numbers were numerically better, but this difference did not reach statistical significance.

Interest was clearly increasing, with 2 studies published in 2022 (14-15) and three more in 2023 (16-18). The three studies marked by blue stars in the above slide (14, 16, 17) were all done by the same research group who used a proprietary synthetic (lab-made) form of psilocybin; many of the authors were employed by the firm that developed this. Given the prevalence of depression, if psilocybin becomes FDA approved for treatment, a company with a track record in developing and testing a pure synthetic compound could be in a very profitable position. Again, this in no way negates their data, but is a factor to keep in mind.



The slide above shows the most recently published studies (18-23); we will dive into the red-bordered one toward the end of the paper.

The two published just this year (22-23) (yellow boxes) were open studies testing the drug in persons whose depression is not responding after multiple current treatments (more on one of these in a minute). Both studies found large and rapid reductions in depression.

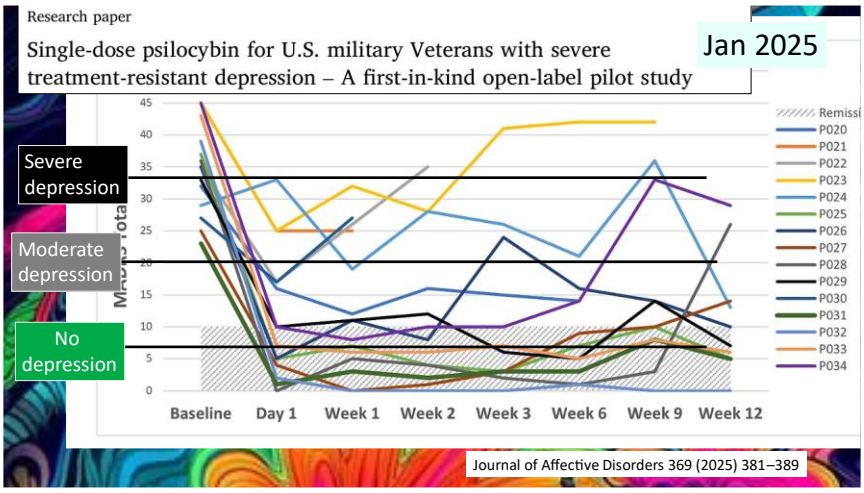


The slide to the left shows results that are representative of recent randomized controlled trials (6, 17). In each graph, the psilocybin group is the lower line, indicating greater reduction in depression scores.

What is especially noteworthy in these and other trials of psilocybin for depression is the very rapid and sustained response.

This is shown even more dramatically in a paper just published 2 months ago, sponsored by the VA (23). The researchers sought to put psilocybin to the ultimate test – treating depression in persons with severe depression for whom nothing seems to work. They screened more than 200 veterans and chose 14 for the trial. The participants had a mean depression duration of 13.5 years, a mean of 6.7 failed medication treatment trials and a mean baseline depression score of 35.3 on a scale where scores of 35 or greater indicate severe depression.

The lines in the slide below are the results for each of the 14 veterans after one 25mg dose of psilocybin. It didn't work for all fourteen, but to have so many having the kind of responses depicted in the graph must have been for them and their families something close to a miracle.



How can one or two psilocybin doses produce rapid-onset, lasting improvement?

If you are prescribed a medication treatment for depression currently, it typically takes 4-6 weeks to reach full benefit and you have to keep taking it daily for up to a year to avoid relapse. How

can it be that just one or two doses of psilocybin can produce a large reduction in depressive symptoms within days, and last months? Is this something that is just too good to be true or might there be a neurobiological (i.e. brain) reason that could explain why the results are so different?

What happens when psilocybin enters the brain?

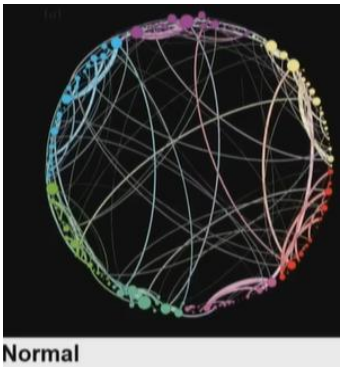
Serotonin is one of the most well known brain chemicals. Current antidepressants (almost) all also modify the brain serotonin system, but not in the same way that the psychedelics do. Psychedelics all hone in on the serotonin 2A receptor, which is one of 15 serotonin receptors in the brain (25). What is critical about this set of receptors is where they are localized – and how this is the starting point of an explanation for why the effects are so much different than current antidepressants.

Bear with me, first a little brain anatomy. A fairly good way to imagine how the brain is structured is to picture a bicycle helmet perched atop your fist. The helmet is what is called cortex (or cerebral cortex) which handles complex brain functions. Remove it, and you see your fist. Your fist is where subcortical structures sit; these are involved in emotions, coordination of movement, motivation and memory consolidation, among many other things. Now look at your arm. This represents the nerves that run down your spinal columns to carry out the orders given by the brain and then to carry messages back.

Hold up that helmet again and marvel at it. The cerebral cortex in humans is a gorgeous six-layer cake, with different layers talking to each other in a carefully orchestrated dance. There is one layer – layer 5 – that acts a bit like a hall monitor to keep the other parts of the cortex walking in nice straight lines and only going into those rooms where they are needed.

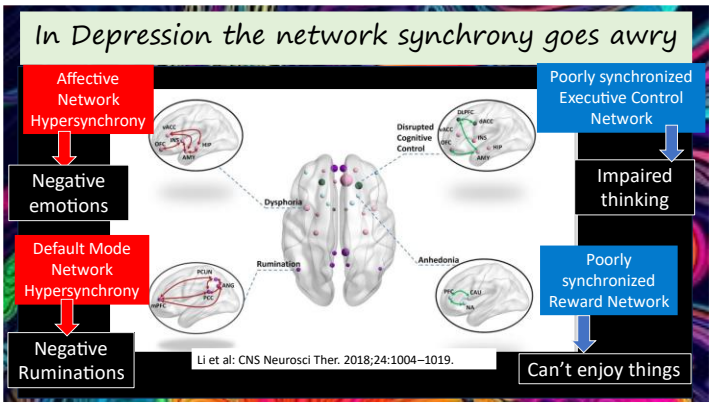
Almost the only brain area where these peculiar 2A receptors are found is in layer 5 of the cerebral cortex, (25). So, it appears that when psychedelic drugs like psilocybin enter the brain, the go to the 2A receptors in layer 5 and tie up and gag the hall monitors. Suddenly, now all the kids can go into whatever room they want and talk to whomever they want.

This is shown most dramatically in two diagrams from a 2014 paper (26), again from Dr. Nutts research group. The first is shown to the left. It is a schematic of actual data collected from normal human volunteers. The areas around the rim of the circle show the different areas of the cerebral cortex (color coded).


Normal

The lines connect areas that are in synchrony with each other – when one activates, so does the other. Intermingled in this data are 20 or more intrinsic large-scale networks whose nodes co-activate with each other in synchrony. (The discovery of these large intrinsic functional brain networks is one of the most significant advances in brain science in the last 20 years).

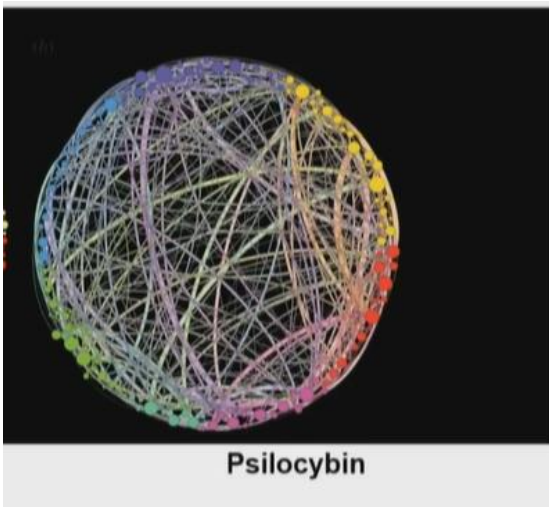
A single network's nodes are often dispersed across large areas of the brain and the network is in good health when the nodes are co-activating in optimal synchrony.



Unfortunately, that optimal synchrony is not present in persons with major depressive disorder. Many studies have documented abnormal synchrony (the term used is functional connectivity) in four key networks.

This is illustrated in the slide to the left (from ref 27). The two networks on the left have hypersynchrony, posited to lead to entrenchment of negative emotions and of pessimistic negative ruminations. On the right are two networks whose synchrony is abnormally loose, causing the network to dysfunction. The network on the upper right serves important aspects of thinking and cognition while the network on the lower right nurtures heathy desires for pleasure and enjoyment. Dysfunction in these networks is thought to produce impaired thinking and concentration and the loss of ability to enjoy things, all characteristics of depression (27).

The key element here is: these network changes stay stuck. Major depressive disorder is difficult to come out of, and as many as a third of persons with this disorder are "non-responders" to multiple trials of our current treatments.



The slide to the left shows what happened to these neat and tidy networks after the volunteers were given a dose of psilocybin. The head of the lab that produced these data, Dr. David Nutt, compares this to an orchestra abruptly losing its conductor, "…with no central control, the different parts of the brain begin free-styling. The brain becomes chaotic and disorganized…**I**nstead of Bach, the orchestra plays free jazz" (25).

The title of a 2024 paper describes this with scientific bluntness: "Psilocybin desynchronizes the brain" (28). These researchers describe finding, "Psilocybin massively disrupted functional connectivity (FC) in cortex and subcortex…These FC changes were driven by brain desynchronization across spatial scales (areal, global), which dissolved network distinctions." This is how you say, "free jazz" in neuroscience-speak.

How does massive disruption and desynchronization of brain networks cause depression to abruptly improve?

Obviously, the brain does not stay desynchronized with "massively disrupted functional connectivity". The acute effects of the drug wear off. The question is, what state is the person in following this?

A very common feature of depression is negative pessimistic ruminations ("I'm worthless", "Things will never work out", "I'll never find anyone who could stand to be in relationship with me", etc). Neurobiologically, these are a type of rut or stuck pattern of cortical connection/communication that is

strong and hard to break out of. Our thoughts just keep sliding down into those ruts and ways of thinking.

By releasing the brakes of layer 5, the ruts or overly strong patterns of communication are broken up and the person is now free to think more freely in many other ways that combat negative pessimistic thoughts. Also, the networks that had become out of optimal synchrony – too loosely connected – abruptly have a chance to reset and reconnect more properly.

Dr. Nutt's answer is that these networks have experienced a type of "reset". He puts it this way, "This process might be likened to a 'reset' mechanism in which acute modular disintegration…enables a subsequent re-integration and resumption of normal functioning" (9).

A final aspect might be a possible consequence of "all the new connections". A person becomes able to see things in profound new ways and gains new perspectives at a high level of philosophical, metaphysical or spiritual understanding. This is the aspect of the drugs that have, for centuries, led to their incorporation into spiritual ceremonies of many indigenous peoples.

The above explanations are all still speculative, but to the degree they have merit, one can see how one dose could have lasting effects.

What actually happens in a clinical trial?

Doing a clinical trial with a psychedelic is no easy feat. To see the strengths and weaknesses of how this is done, let's take a close look at the randomized controlled trial published in JAMA in 2023 which led to the editorial suggesting that psychiatric treatment may well be on the verge of a major paradigm shift.

First, we must look at funding since, as noted above (24) NIH has yet to fund such research (despite impressive results published in top journals).

This study was funded by Usona Institute. Part of their stated mission is to "further the scientific understanding and therapeutic application of consciousness-expanding medicines" (29).

All non-governmental funding sources have hoped-for results, whether it is Pfizer hoping to make billions or this institute's desire to advance psychedelics into mainstream medicine. As noted earlier, this does not negate findings, it just means the methods need to be carefully scrutinized.

The first thing one notes is that this paper has 34 (count 'em-34!) authors (see below). Why? It is a bit easier to understand when one learns this was done across 11 clinical sites, 1,529 potential participants were screened and 1425 were excluded for not meeting study criteria, leaving 104 to enter the study. That is very labor intensive – and they haven't even started the study yet!

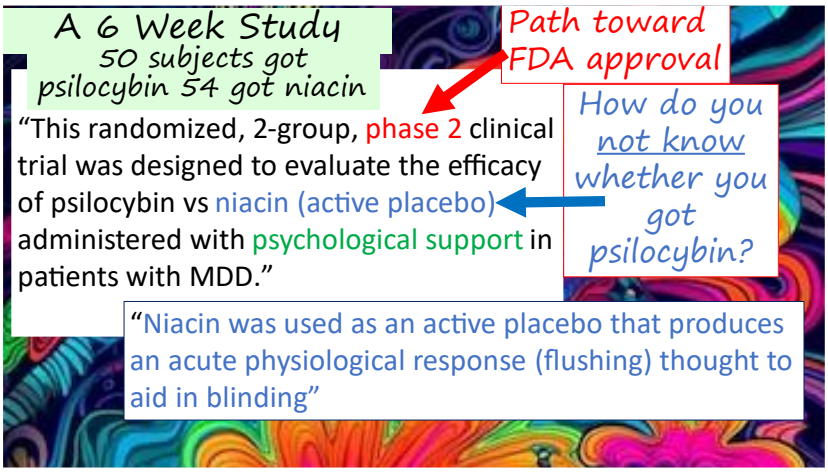
JAMA | Original Investigation

Single-Dose Psilocybin Treatment for Major Depressive Disorder
A Randomized Clinical Trial

Charles L. Raison, MD; Gerard Sanacora, MD, PhD; Joshua Woolley, MD, PhD; Keith Heinzerling, MD; Boadie W. Dunlop, MD, MS; Randall T. Brown, MD, PhD; Rishi Kakar, MD; Michael Hassman, DO; Rupal P. Trivedi, MD; Reid Robison, MD; Natalie Gukasyan, MD; Sandeep M. Nayak, MD; Xiaojue Hu, MD; Kelley C. O'Donnell, MD, PhD; Benjamin Kelmendi, MD; Jordan Sloshower, MD, MSc; Andrew D. Penn, RN, MS, NP; Ellen Bradley, MD; Daniel F. Kelly, MD; Tanja Mletzko, MA; Christopher R. Nicholas, PhD; Paul R. Hutson, PharmD; Gary Tarpley, PhD; Malynn Utzinger, MD; Kelsey Lenoch, BS; Kasia Warchol, BS; Theraysa Gapasin, MS, aMFT; Mike C. Davis, MD, PhD; Courtney Nelson-Douthit, BS; Steffanie Wilson, PhD; Carrie Brown, MA; William Linton, BS; Stephen Ross, MD; Roland R. Griffiths, PhD

Limited generalizability?

Persons included in this study, although carefully screened to have major depressive disorder, may not be not your typical group of 104 persons with major depression. This is because studies of psychedelics attract people interested in psychedelics. The authors note, "Ten participants (19.6%) in the psilocybin group and 13 (24.5%) in the niacin group reported previous lifetime use of a psilocybin." (Have 20-25% of your friends and relatives tried psilocybin at some point?) The good news is that these prior users were evenly balanced between the two study groups.



The slide to the left begins to get into the nuts and bolts of study design. Things to note: The participants were followed for 6 weeks after they received their single dose of either psilocybin or niacin.

Depressive symptoms were measured by a well-established, commonly used rating scale called the Montgomery-Asberg Depression Rating Scale (MADRS) prior to getting the study medications (baseline) and on days 2, 8, 15, 29, and 43 after getting the medication.

The authors note this is a "phase 2 clinical trial". The path to FDA approval has three phases. Phase 1 is mostly about seeing if the drug is safe to continue testing. Phase 2 involves testing the new medication against some type of control group to assess effectiveness and further assess safety. Three other phase 2 studies have been published (12-14).

A phase 3 study is designed to confirm efficacy/ effectiveness, compare it with standard or similar interventions, and collect further information about safety. Clinicaltrials.gov lists two phase 3 studies currently underway: one sponsored by the Usona Institute (30) and one sponsored by COMPASS Pathways (31); both are still actively recruiting participants.

Psilocybin vs Niacin

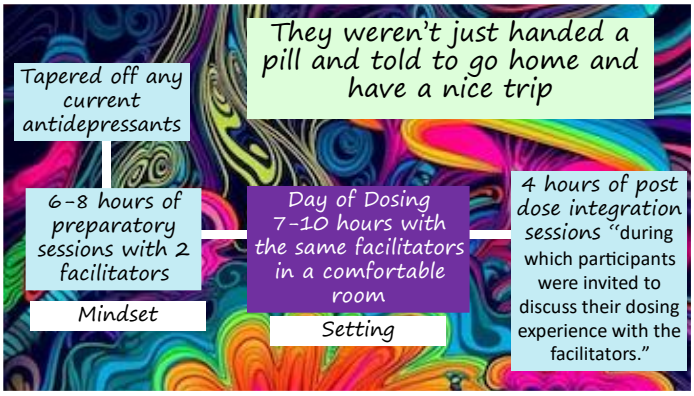
A serious difficulty in clinical trials of mind-altering substances (others being MDMA, Ketamine and LSD) is effective blinding. This trial is a randomized double blind control trial. Randomized means that participants are assigned to one of the two groups by a reliable method of random assignment. Double

blind means neither the participants nor those who are rating their symptoms know what drug they received.

Blinding is not hard to achieve for the raters. But for the ones who get a drug – the effects of psilocybin are so powerful, how can you NOT know whether you received it or not? Niacin causes uncomfortable flushing, but this is unlikely to fool most people. This is compounded by the fact (noted above) that 20-25% of participants have prior experience with psychedelic use.

Many studies ask the participants, at the end of the study, to guess what drug they received. For reasons not given, this (surprisingly) was not done in this study.

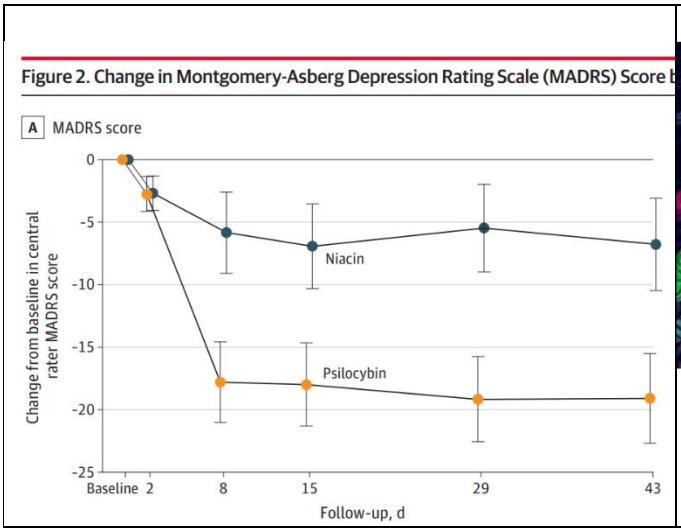
Treatment protocol

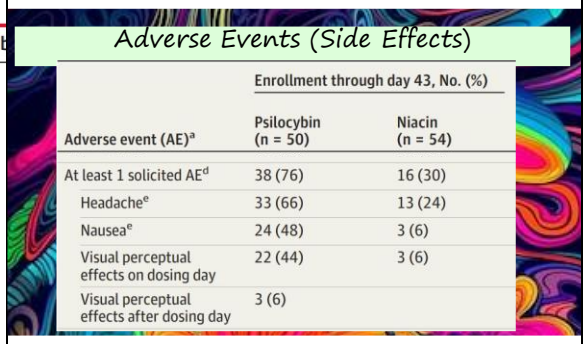


The treatment protocol used in this study is fairly standard in psilocybin studies. In the days prior, the participant is given preparatory sessions to aid in having an optimal mindset toward the experience. In the days following the day of dosing, "integration sessions" are given to aid in processing the experience.

During the dosing session, participants were encouraged to wear eyeshades and listen to a curated playlist on headphones.

Results





Adverse event (AE)[a]	Enrollment through day 43, No. (%) Psilocybin (n = 50)	Niacin (n = 54)
At least 1 solicited AE[d]	38 (76)	16 (30)
Headache[e]	33 (66)	13 (24)
Nausea[e]	24 (48)	3 (6)
Visual perceptual effects on dosing day	22 (44)	3 (6)
Visual perceptual effects after dosing day	3 (6)	

The mean change in depression score and 95% confidence intervals for each group is shown above. By Day 8, the psilocybin group had clearly separated from the niacin group and the difference between the two groups was statistically significant from that point on.

Safety

Treatment-related side effects were not severe, except for one psilocybin patient who experienced paranoia and a panic attack. The rate of other side effects is shown in the table above, with headache, nausea and visual perceptual changes all being more common in the psilocybin treated participants.

Where Are Things Going From Here?

Crawling toward hoped-for FDA approval

The website ClinicalTrials.gov lists all registered clinical trials that are planned or initiated. Scanning those related to psilocybin and depression, one sees multiple proposed or active phase 2 trials, many in special patient populations or using some newly developed proprietary form of psilocybin.

There are two very large phase 3 trials mentioned earlier in this paper (30,31) that are actively recruiting for participants at this time. These may take years to complete.

Getting psilocybin outside of a doctor's office

The regulatory map regarding psilocybin and other psychedelics is rapidly changing. Although illegal federally, it is currently legal in some states or municipalities. Interestingly, in San Francisco, where it is legal to use but not sell psilocybin, there is a "concierge service" that seeks to match persons with one of their network of carefully vetted guides to help one through an experience with psilocybin (and other drugs) (32).

Using psilocybin to treat other conditions

Finally, it must be noted that promising results have also been reported in clinical trials using psilocybin to treat many other conditions (references listed are simply representative, not comprehensive):

- Alcohol Use Disorder (alcoholism) (33)
- Nicotine dependence (quitting smoking) (34)
- End of life anxiety and/or demoralization (35)
- Trauma related disorders such as PTSD (36)
- Anorexia Nervosa (37)
- Chronic pain (38)

It is too early to say if psychedelics will come to have an important role in helping those suffering from any of these conditions. However, the growing momentum of interest in the potential of psychedelics is reflected in the prestigious journal Neuropharmacology devoting its entire May 2023 issue to these drugs, and to lead off with an editorial titled: "Psychedelics: Threshold of a Therapeutic Revolution" (39)

References

Please forgive some heterogeneity in formatting

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