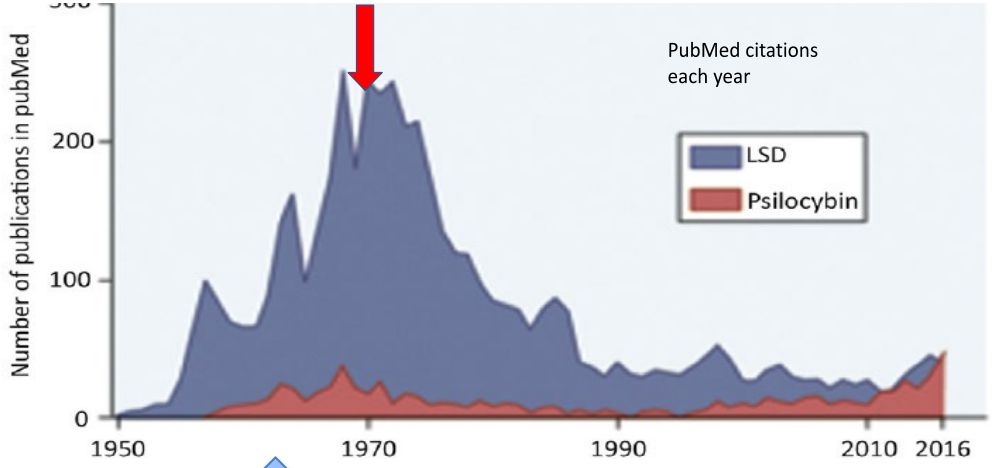
Psychedelic assisted therapies for mental illness

PAREA December 2022

David Nutt DM FRCP FRCPsych FBPhS FMedSci DLaws
Prof of Neuropsychopharmacology Imperial College London
d.nutt@imperial.ac.uk
david@awaknlifesciences.com
profdavidnutt@twitter.com

Psychedelics: history

Impact of the 1971 UN Psychotropics Convention on psychedelic research

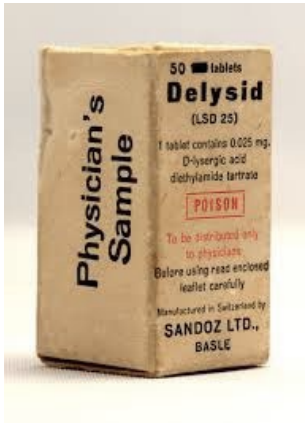


Kyzar et al 2017 TIPS

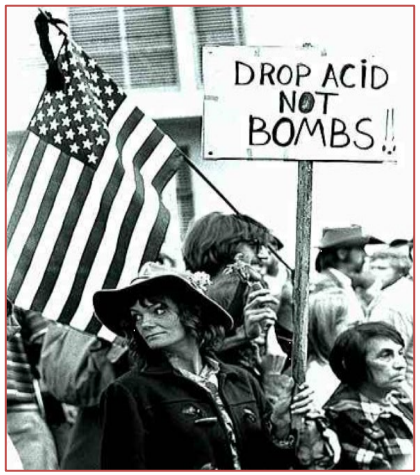
After fifteen years of successful research LSD Put into Schedule 1 – “highly dangerous and no medical use” despite massive medical value data

Psilocybin also banned as had similar pharmacology though no evidence of recreational use

➔ the worst censorship of ANY research in the history of the world



LSD banned as it was changing art, music and culture and was associated with the anti-Vietnam war movement



For over 50 years the ban has persisted based on the myth of serious harms despite overwhelming evidence to the contrary

Psychedelics and MDMA

UK experts

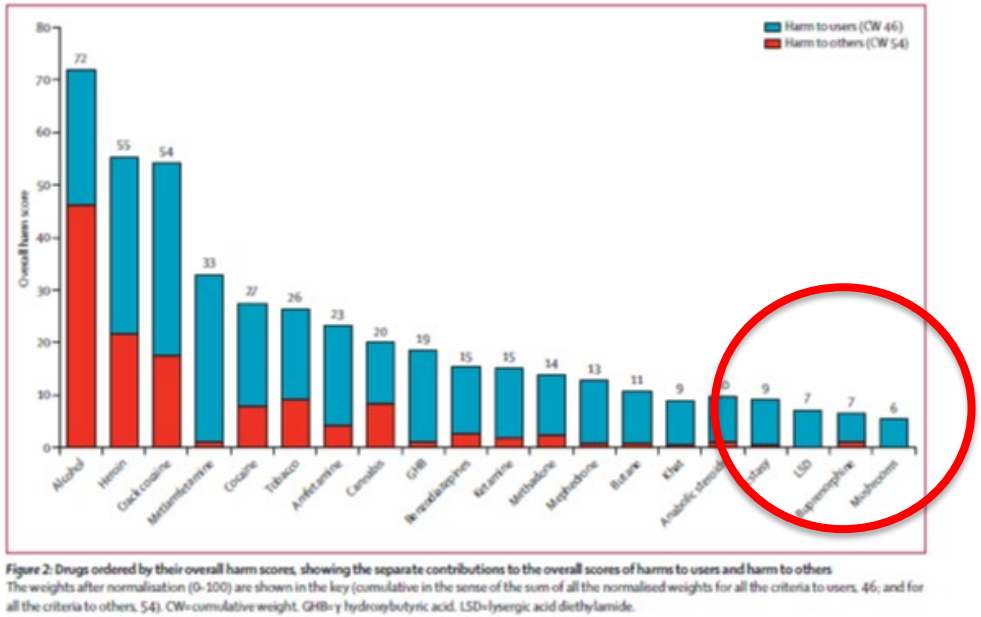
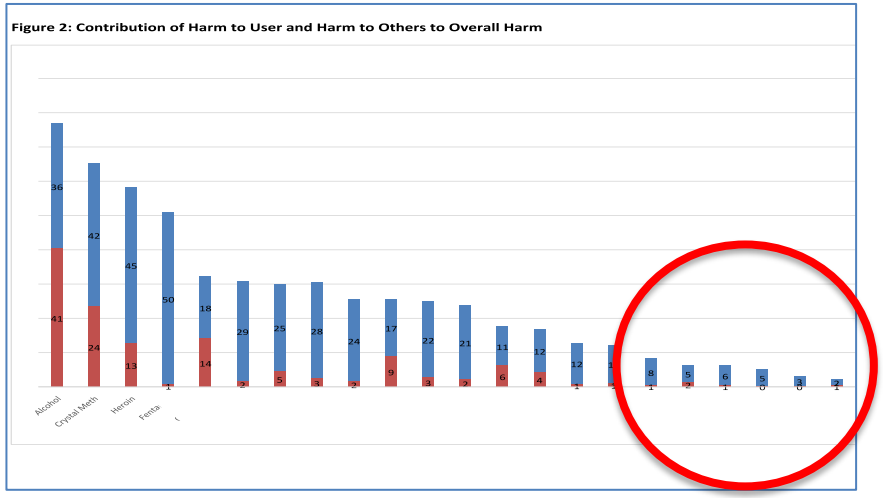


Figure 2: Drugs ordered by their overall harm scores, showing the separate contributions to the overall scores of harms to users and harm to others
The weights after normalisation (0-100) are shown in the key (cumulative in the sense of the sum of all the normalised weights for all the criteria to users, 46; and for all the criteria to others, 54). CW=cumulative weight. GHB=γ hydroxybutyric acid. LSD=lysergic acid diethylamide.

Nutt King & Phillips Lancet Nov 2010

van Amsterdam et al J Psychopharmacology 2014

EU experts



Bonomo et al J Psychopharmacology 2018

Australian experts

Resurrecting MDMA (ecstasy)

Invented 1904 – never tested in humans

1970s - Sasha Shulgin synthesized MDMA & gave it to himself, his wife and friends who were psychotherapists.

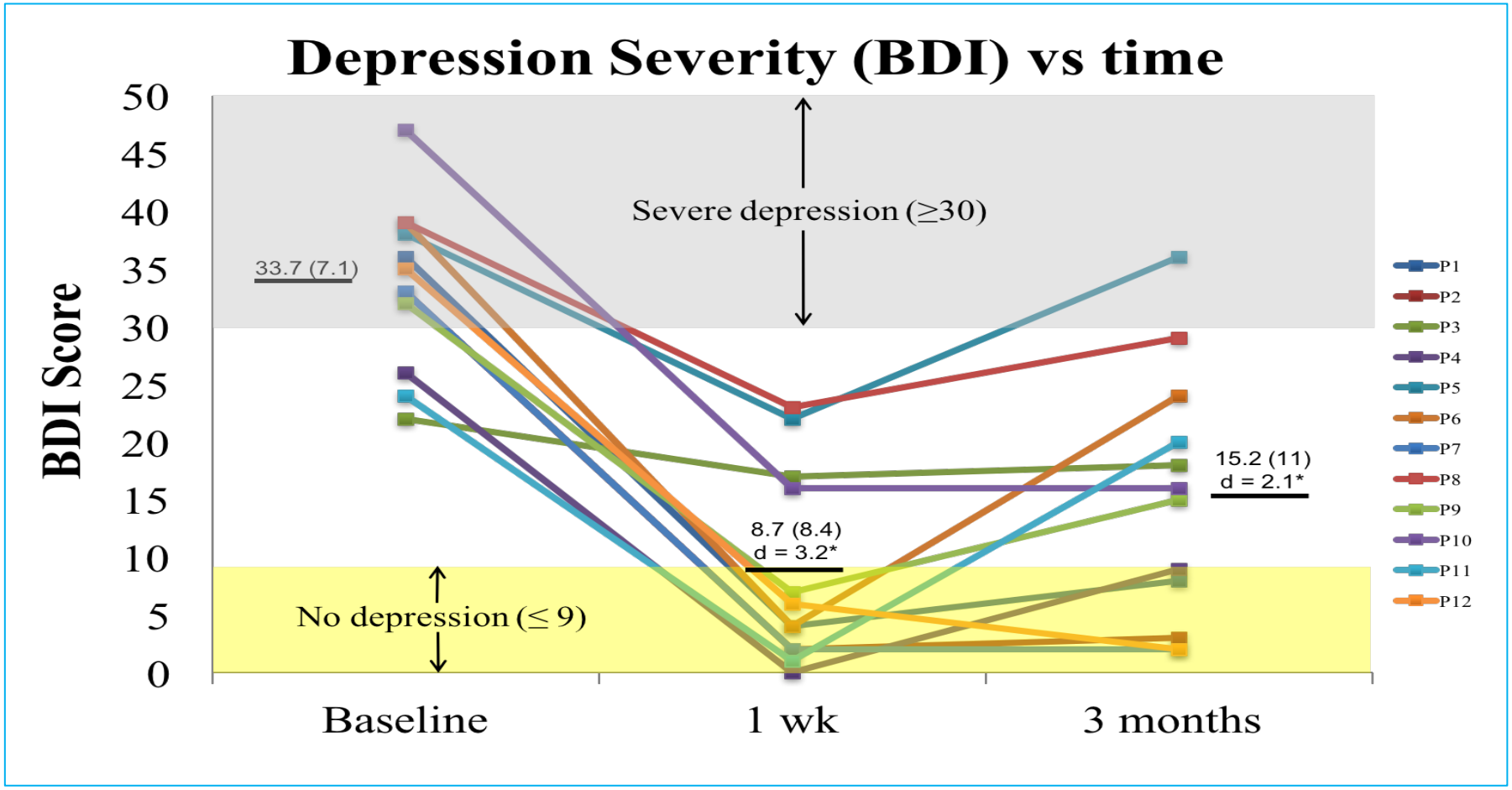
Positive reports of MDMA as adjunct to psychotherapy; no controlled trials.

Recreational use – MDMA (‘ecstasy’) made illicit in US 1985

Now back in clinical trials by MAPS

Latest clinical data on psilocybin and MDMA

One 25mg psilocybin treatment
→ remarkable efficacy in treatment resistant depression (TRD)



All failed >2 antidepressants and CBT

Most efficacious single dose treatment for TRD ever reported

Carhart-Harris et al Lancet Psychiatry 2016

Replication study
COMPASS Pathways new trial just published

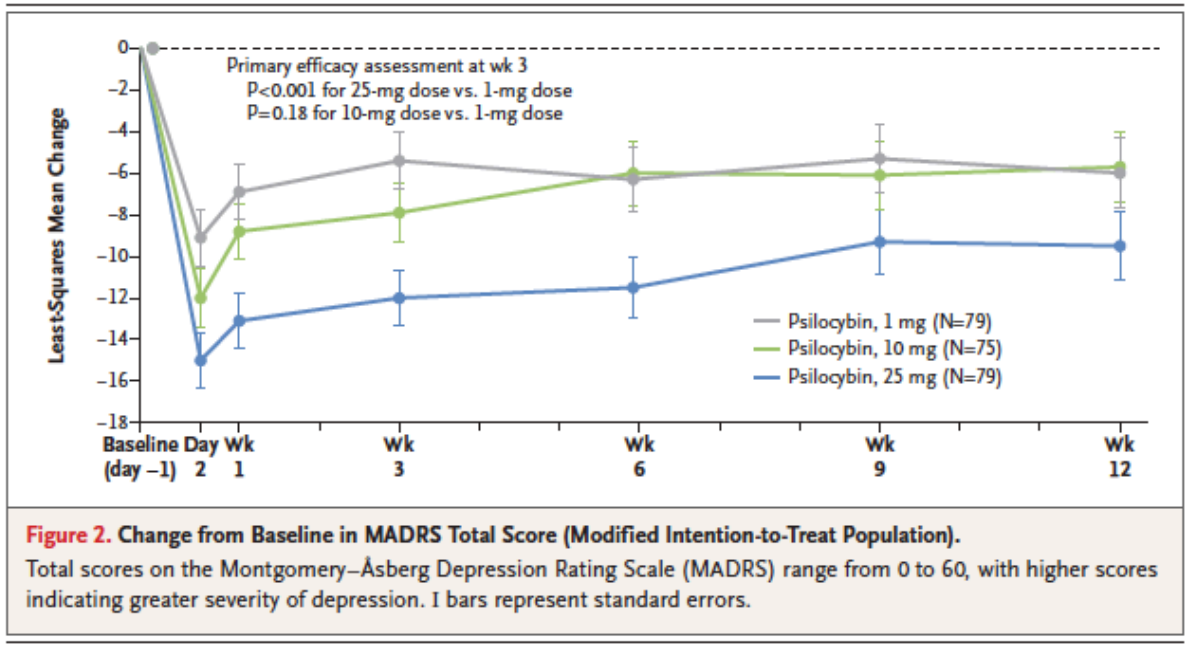
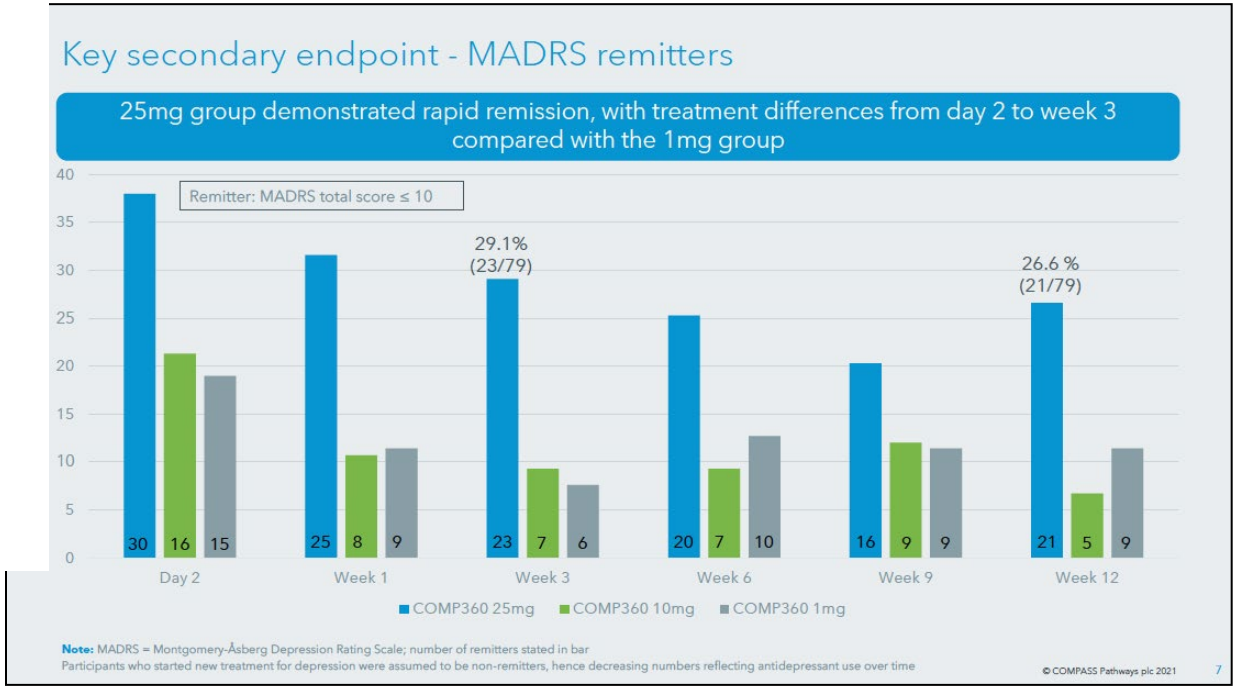


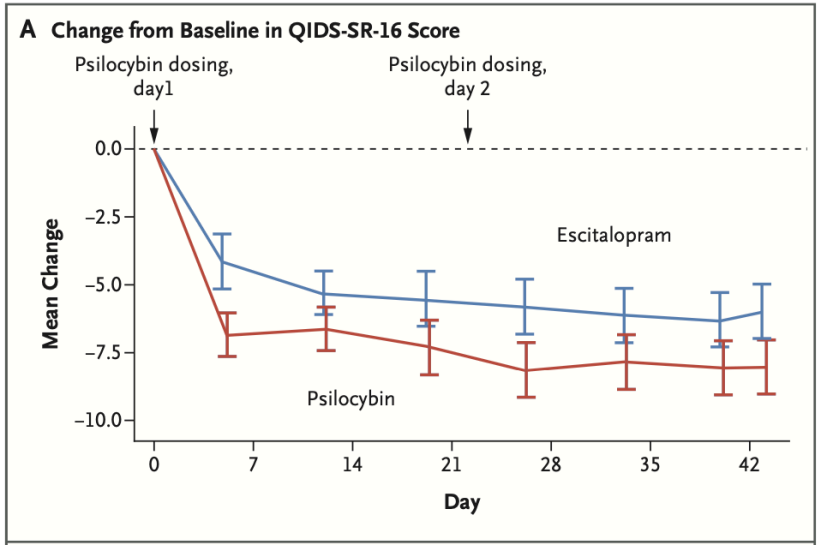
Figure 2. Change from Baseline in MADRS Total Score (Modified Intention-to-Treat Population).
Total scores on the Montgomery–Åsberg Depression Rating Scale (MADRS) range from 0 to 60, with higher scores indicating greater severity of depression. I bars represent standard errors.



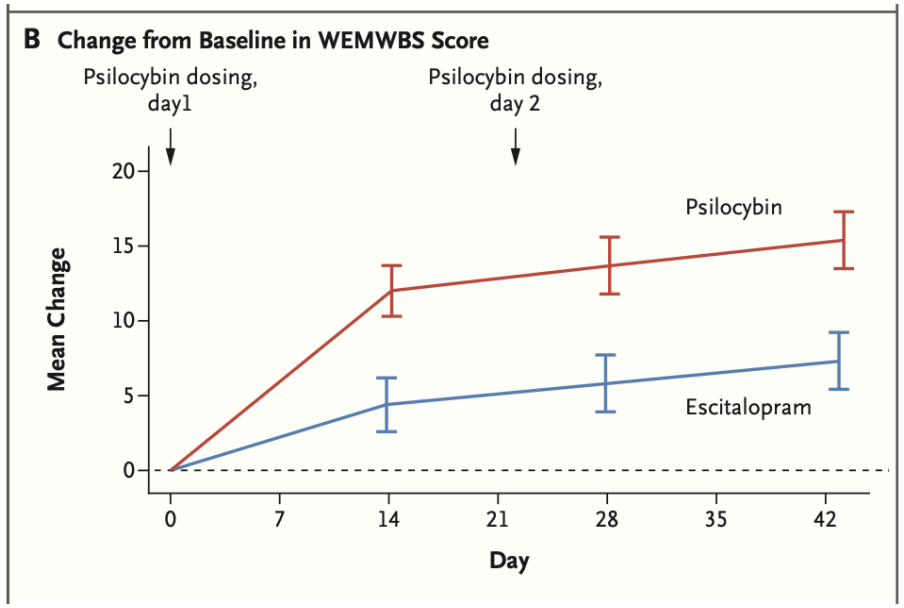
Goodwin et al 2022 NEJM

Our psilocybin –v-escitalopram trial

Reductions in depression scores



Improvements in wellbeing



Remission rates % patients

Scale	Psilocybin	Escitalopram
QIDS	57	29
BDI	58	18
HAMD	49	10
MADRS	29	7

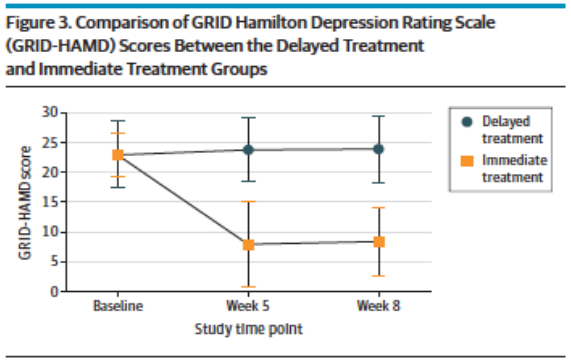
Carhart-Harris et al NEJM 2021

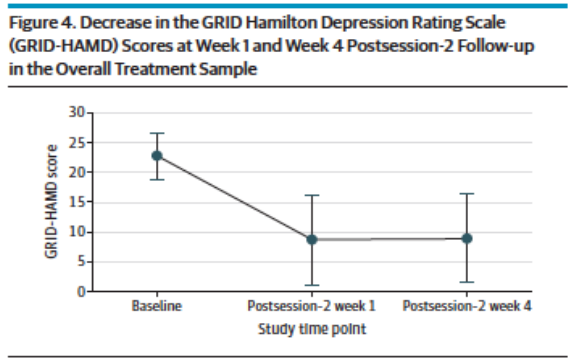
Other trials with psilocybin - all positive

End of life anxiety and depression –
2 double-blind RCTs:

- Griffiths - Johns Hopkins and
- Ross - NYU

Depression – Griffiths - Johns Hopkins – comparison with no-treatment ➔





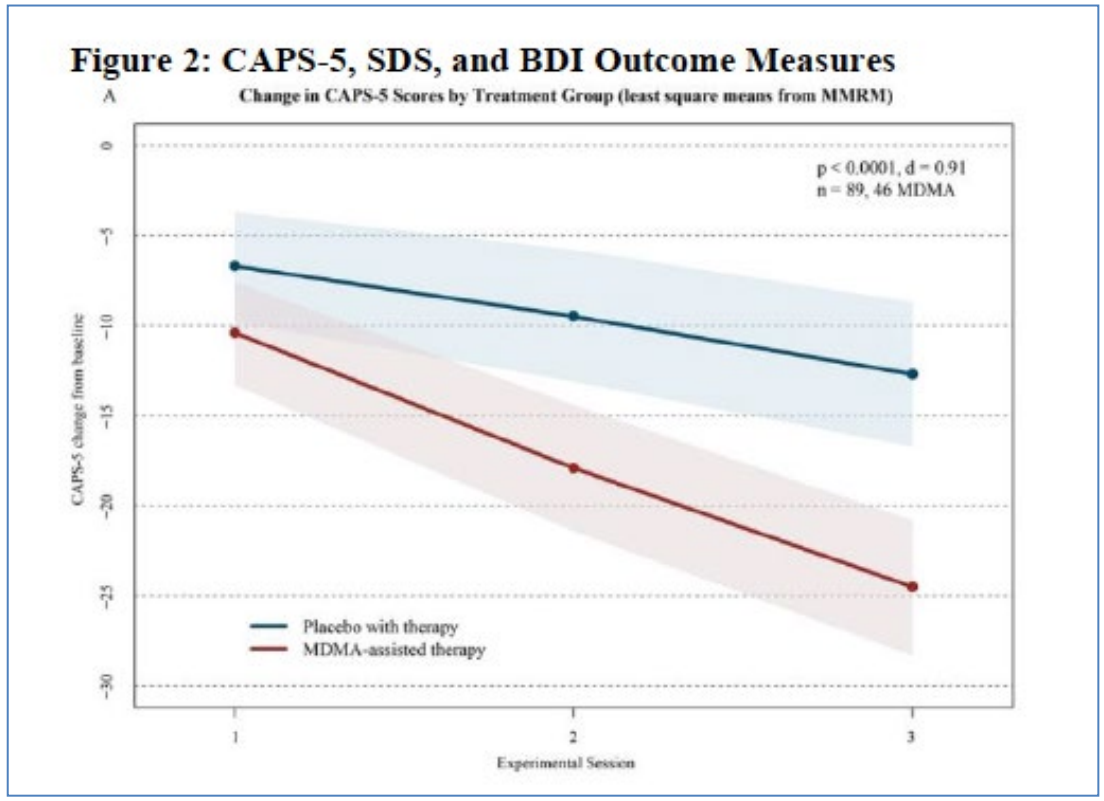
Davis et al 2021

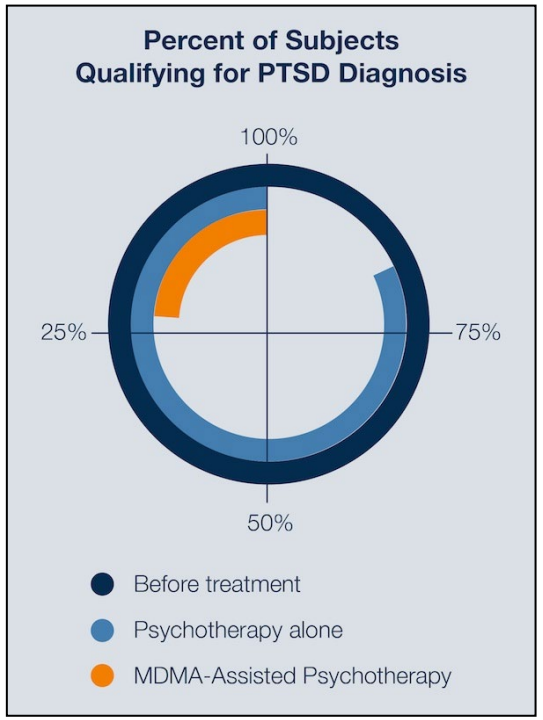
Many others now underway including in anorexia, OCD, pain syndromes
Note Australian government programme as well

Smoking quitting - Johnson - Johns Hopkins
Alcohol dependence – Bogenschutz - New Mexico

These are all internalizing disorders – cognitions are self-referential and ruminative

MDMA-Assisted Psychotherapy for PTSD trials: Phase 3 first study

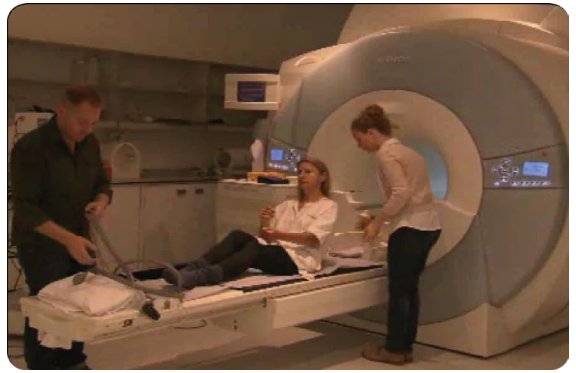




Mitchell et al Nature Medicine 2021

MAPS 2nd phase 3 study just completed – data in new year - if positive then likely to get FDA approval

How MDMA works in PTSD



Check for updates

news & views

PSYCHIATRY

Putting the MD back into MDMA

A phase 3 study shows that MDMA may be a promising treatment for PTSD, which will require a shift in how this drug is perceived.

David J. Nutt and Harriet de Wit

MDMA—colloquially known in its unregulated form as 'E' or 'ecstasy' in Europe and as 'molly' in the USA—is a small, amphetamine-like molecule that has had a rollercoaster reputational ride, from being positioned as a promising new therapeutic tool to being branded a brain-damaging recreational drug. Most of those historic fears were overstated, and recent empirical research, especially into the treatment of post-traumatic stress disorder (PTSD) and related conditions, is now bringing MDMA back into the medical fold. In this issue of *Nature Medicine*, Mitchell et al. report the first phase 3 study of MDMA, which reveals significant efficacy and an excellent safety profile in people with severe PTSD[1]. It now seems likely that it will be an approved medication in a few years.

MDMA was invented by Merck in 1912 as a precursor in a new synthesis for hemostatic substances[2]; Merck tested MDMA in animal models in 1927 and in 1959 but found nothing of interest. It was then resurrected by Alexander Shulgin other drugs such as alcohol or stimulants. The rave scene was less troublesome than traditional drunken gatherings from a policing point of view; however, the use of MDMA in public contexts attracted the attention of politicians while US President Reagan and his wife Nancy were ramping up the war on drugs.

The Reagans fueled a moral panic about this new drug with calls to ban it. The US therapists resisted, but, encouraged by misleading claims of brain damage, the US Drug Enforcement Administration criminalized MDMA in 1985. Recreational use continued, although clinical research effectively stopped. In 1986, a group of therapists established the Multidisciplinary Association for Psychedelic Studies (MAPS) to continue to explore the therapeutic utility of MDMA. By the end of the 1980s, MDMA was banned in most Western countries.

Despite the vast extra costs and bureaucratic constraints that the illegal status of MDMA introduced, clinical research by MAPS progressed. The first clinical study of MDMA, undertaken by

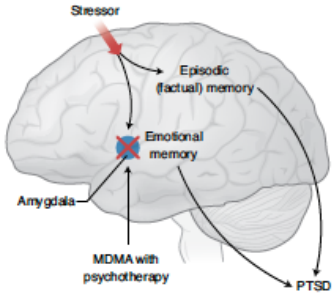
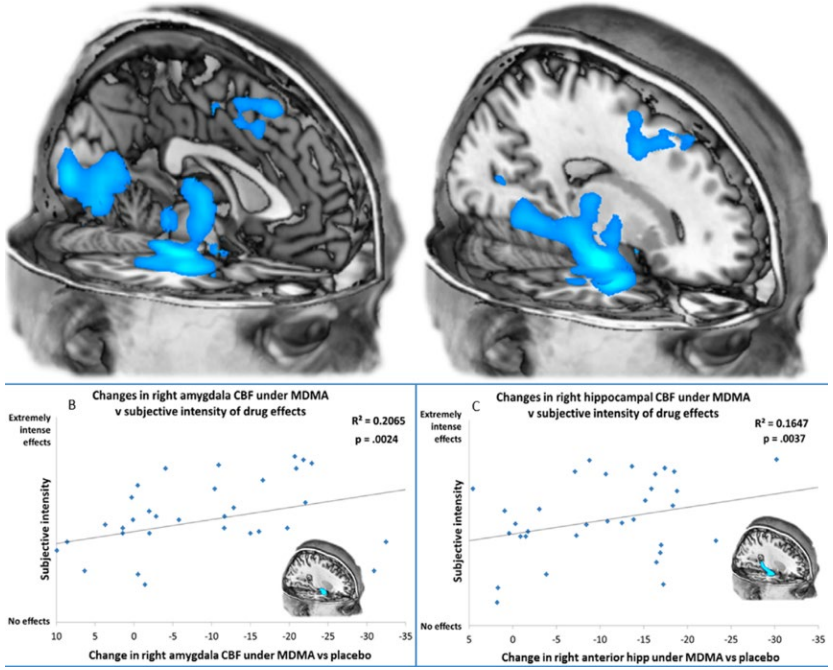


Fig. 1 | The brain pathways of PTSD and site of action of MDMA in therapy. A severe, life-threating stressor (trauma) leaves an emotional trace as well as a factual trace in different parts of the brain. Negative emotions are reactivated by remembering the trauma or as part of a conditioned fear reflex—for example, a car backfiring activates the memory and emotions of experiencing a gunshot. MDMA treatment facilitates the extinction of these emotional resurgences.

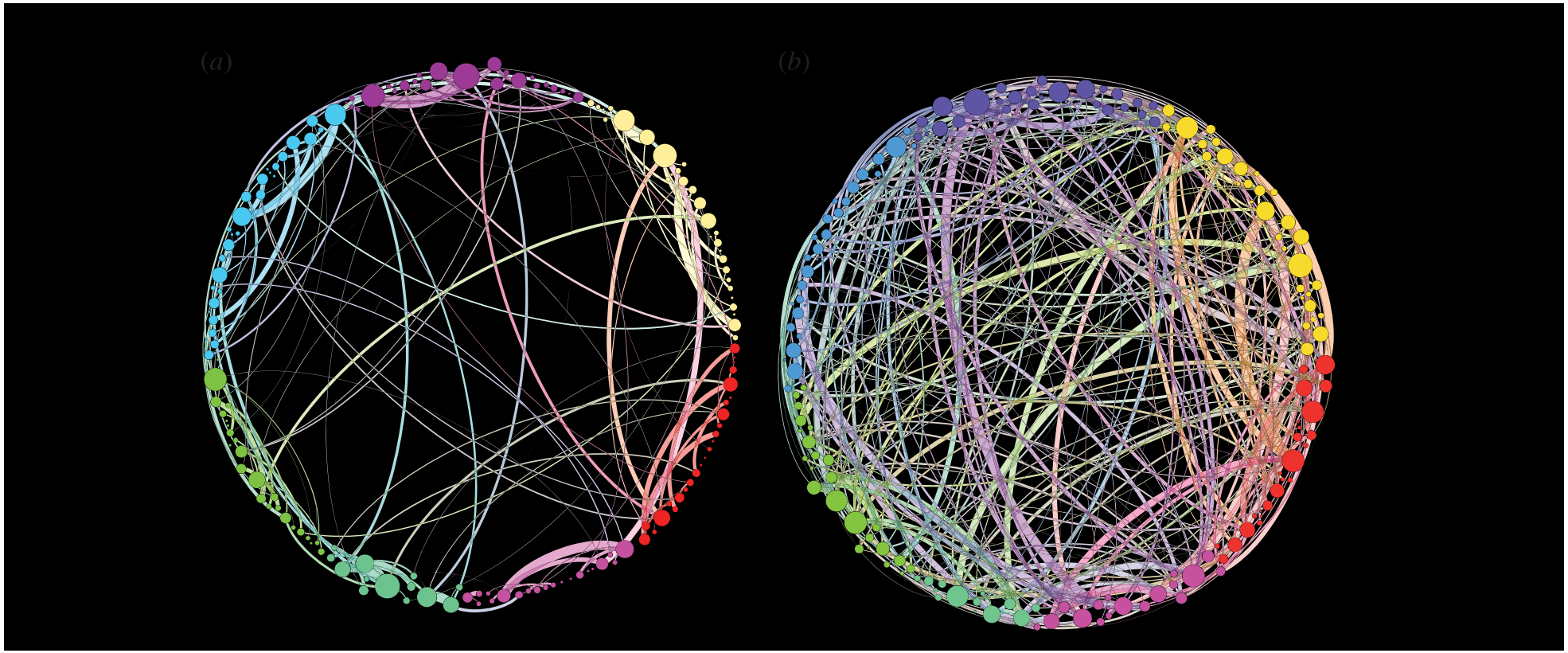
Nutt and de Wit
Nature Medicine June 2021



Carhart-Harris, R. L., Kevin, M., Robert, L., David, E., Wall, M. B., Bart, F., … Nutt, D. J. (2015). *Biological Psychiatry*, *78*(8), 554–562.

How psychedelics work

By switching of the “control centres” psilocybin increases brain connectivity → new solutions to old problems?

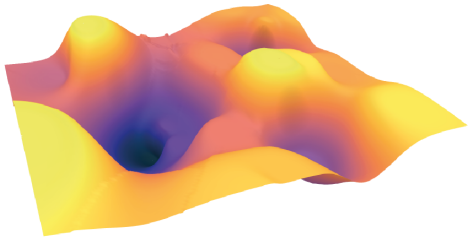


Normal **Psilocybin**

Petri et al J. R. Soc. Interface 11: 20140873. http://dx.doi.org/10.1098/rsif.2014.0873

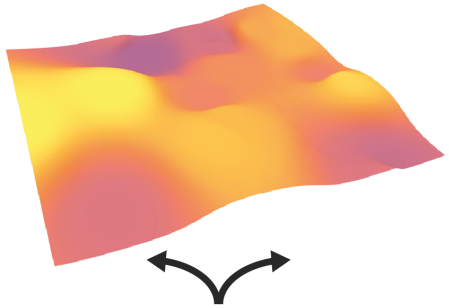
Brain imaging results
Psilocybin increases brain flexibility in depression

Depression



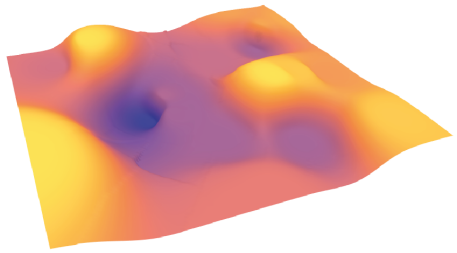
The depressed brain encourages rigid thought patterns that impact well-being. This can be viewed as a 'landscape' with deep wells that make it difficult for patients to 'move between' different thoughts & perspectives.

Psilocybin



Psilocybin therapy 'flattens' the brain's landscape & 'opens-up' the rigidity of the depressed to allow new thoughts, insight & perspectives to emerge.

Post-treatment



Post-treatment, a flatter landscape makes it easier for patients to experience healthier flexibility & diversity in their thought patterns.

Note – escitalopram doesn't do this

nature medicine

ARTICLES

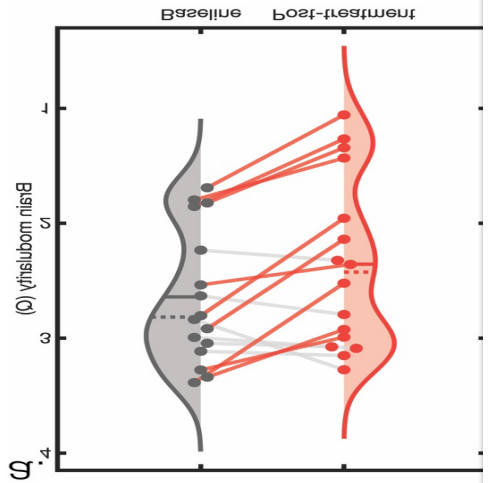
https://doi.org/10.1038/s41591-022-01744-z

Check for updates

Increased global integration in the brain after psilocybin therapy for depression

Richard E. Daws[1,2], Christopher Timmermann[1,3], Bruna Giribaldi[3], James D. Sexton[3], Matthew B. Wall[4,5,6], David Erritzoe[3], Leor Roseman[3], David Nutt[3] and Robin Carhart-Harris[3,7]

April 2022



Patients' experience of the benefits of psilocybin

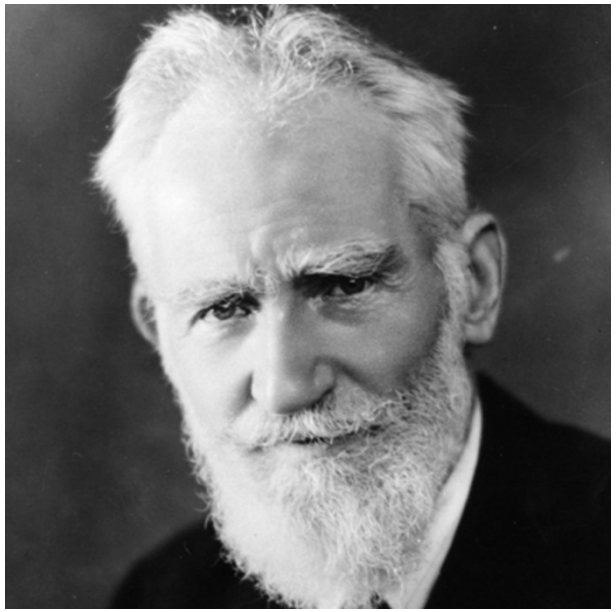
"My outlook has changed significantly. I'm more aware now that it's pointless to get wrapped up in endless negativity. I feel as if I've seen a much clearer picture."

My mind works differently. I ruminate much less, and my thoughts feel ordered, contextualized. Rumination was like thoughts out of context, out of time; now my thoughts feel like they make sense, with context and logical flow.

Watts et al Journal of Humanistic Psychology 2017, Vol. 57(5) 520

“Those who cannot change their minds cannot change anything”

George Bernard Shaw (1856-1950)



Psychedelic treatment has changed the minds of our patients through changing their brains

What we need to do now is change the minds of health care professionals and politicians about these therapies and bring them back into medical practice