s22 [redacted]

From: s22 [redacted]
Sent: Monday, 21 November 2022 3:53 PM
To: SKERRITT, John; s22 [redacted]
Cc: s22 [redacted]
Subject: Prof Nutt's Presentation from today to share with all your teams and guests as promised
Attachments: TGA talk minus video .pdf

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Psilocybin and MDMA therapy Update for the TGA

Nov 2022

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Declaration of interests – 2019-2022

- Advisor - British National Formulary
- Past President - British Neuroscience Association - European Brain Council
- Past President - European College of Neuropsychopharmacology
- **Chair – DrugScience [UK] and PAREA Europe**
- Member International Centre for Science in Drug Policy
- **CRO Awaknlifesciences**
- Editor of the Journal: Drug Science policy and law

- Advisory Boards - Opiant, COMPASSPathways, Psyched Wellness, Neural Therapeutics, Alvarius

- Speaking honoraria (in addition to above) Lundbeck, BMS/Otsuka, Janssen, Takeda

- Member of the Lundbeck Foundation Neurotorium programme and Chair of the editorial board

- Grants or clinical trial payments: Wellcome Trust, MRC

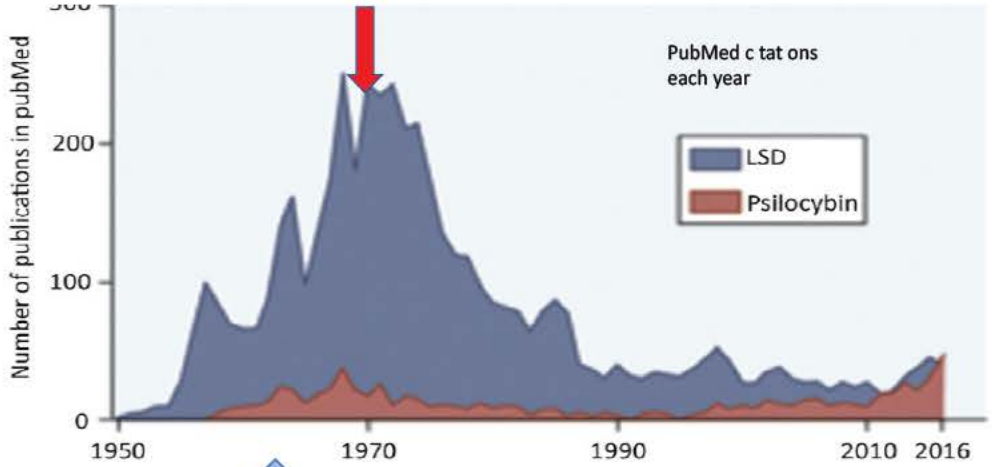
- Share options – P1vital, Awakn, Psyched Wellness Director Equasy Enterprises and GABA Labs

- Expert witness in a number of legal cases relating to psychotropic drugs

- Edited/written 35 books - some purchased by pharma companies

Psilocybin – introduced into medicine in 1958

Impact of the 1971 UN Psychotropics Convention on psychedelic research

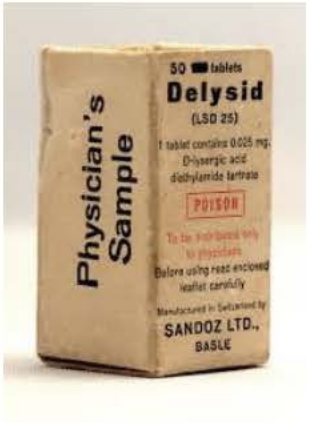


Kyzar et a 2017 T PS

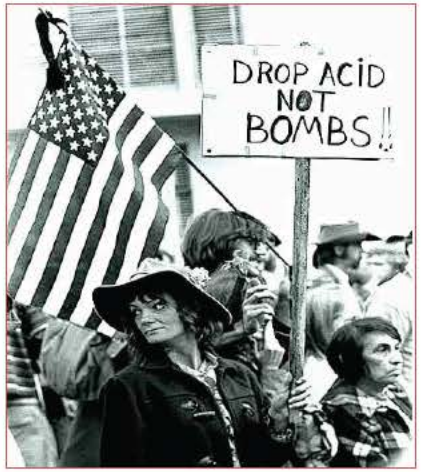
After fifteen years of successful research LSD Put into Schedule 1 – “highly dangerous and no medical use” despite massive medical value data

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

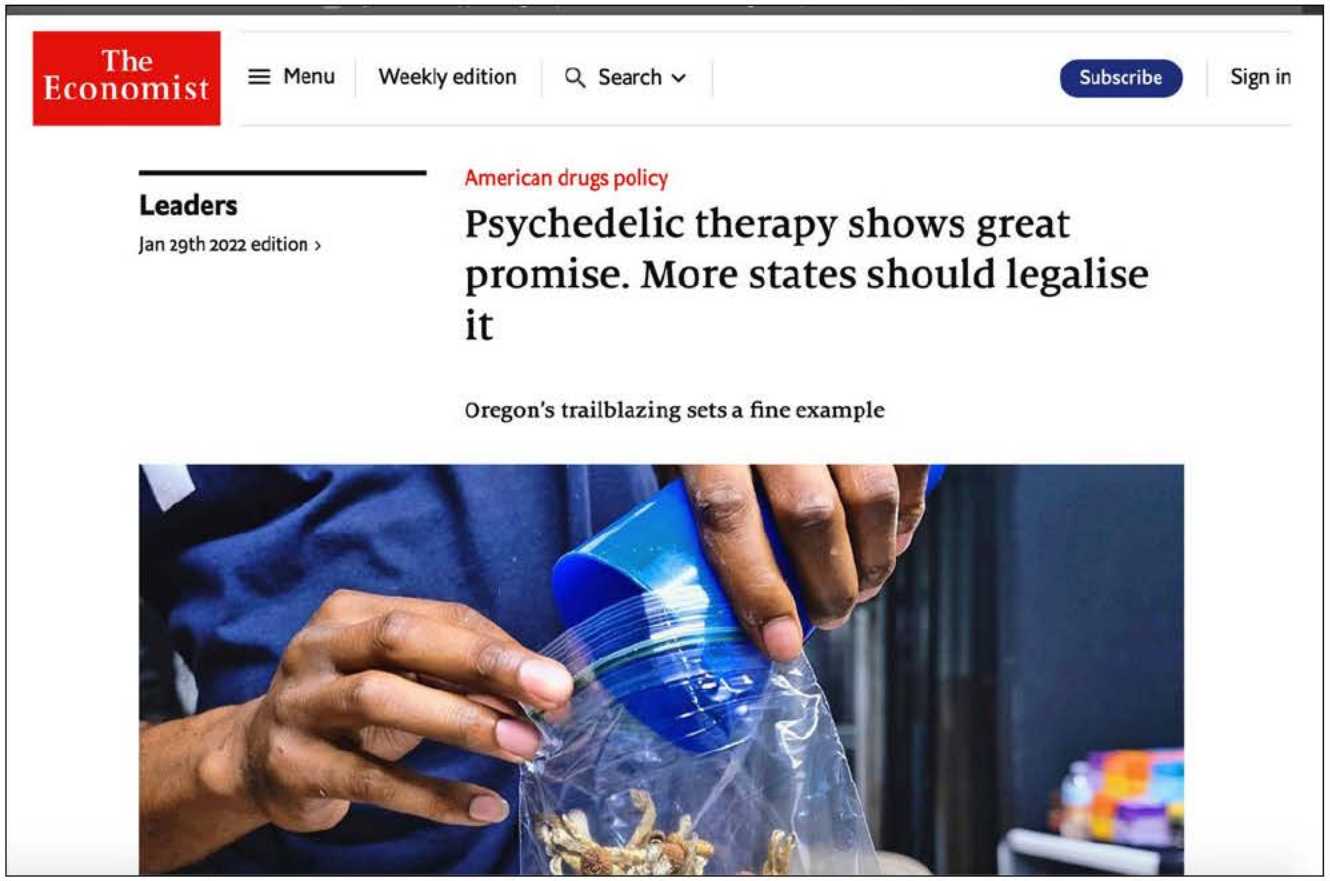
➔ the worst censorship of ANY research in the history of the world



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



Now back in the USA



Biden says psilocybin and MDMA will be registered medicines in 2 years

What is driving this renaissance?

Back to the future - Pooled analyses in the 1960s

- **44 psychiatrists, 5000 subjects and 25,000 drug sessions:**
  Rate of psychosis: 0.2%
  Rate of suicide of 0.04%
  (Cohen S. (1960) LSD: side e

"Treatment with LSD is not without acute adverse reactions, but given adequate psychiatric supervision and proper conditions for its administration, the incidence of such reactions is not great,"

- **700 psych**
  One case of pro
  (Chandler Al. & Hartman M

- **350 patients**
  One attempted suicide
  (Ling TM, Buckman J (1963) The Treatment of Anxiety with Lysergic Acid and Methylphenidate. Practitioner 191: 201-4)

- **Review of 20 years of psychedelic therapy in the UK, 4000 patients and 50,000 psychedelic drug-assisted sessions.**
  Two completed suicides
  Thirty-seven patients with a prolonged psychosis
  (Malleson, N. (1971) 'Acute Adverse Reactions to LSD in clinical and experimental use in the UK.' Br J Psychiatry. 18(543): 229-30)

They worked in addictions too
Six LSD trials in alcoholism

1970	problems and treatment intentions	quiet room	group therapy

Since the 1971 ban I estimate over 100 million excess deaths globally from alcohol dependence

Suppose LSD had successfully treated 10% = 10 million lives saved

How many lives saved by LSD ban – probably none but say 1000

Benefit – risk ratio = 1000x – ? Any medicine has a comparable ratio?

Effect size ... all current therapies

Journal of Psychopharmacology 2012 Krebs and Johanssen

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

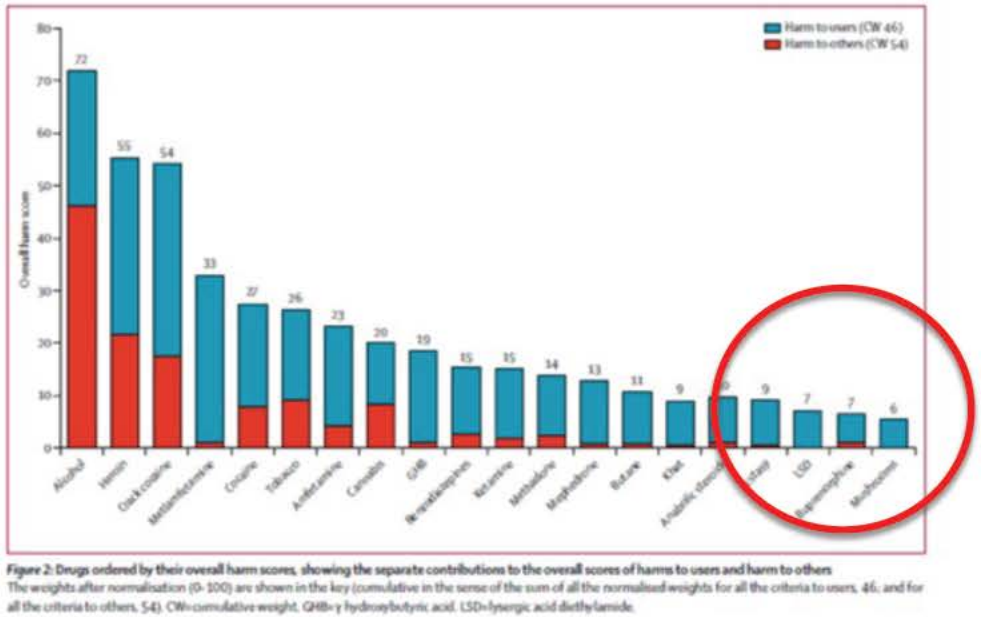
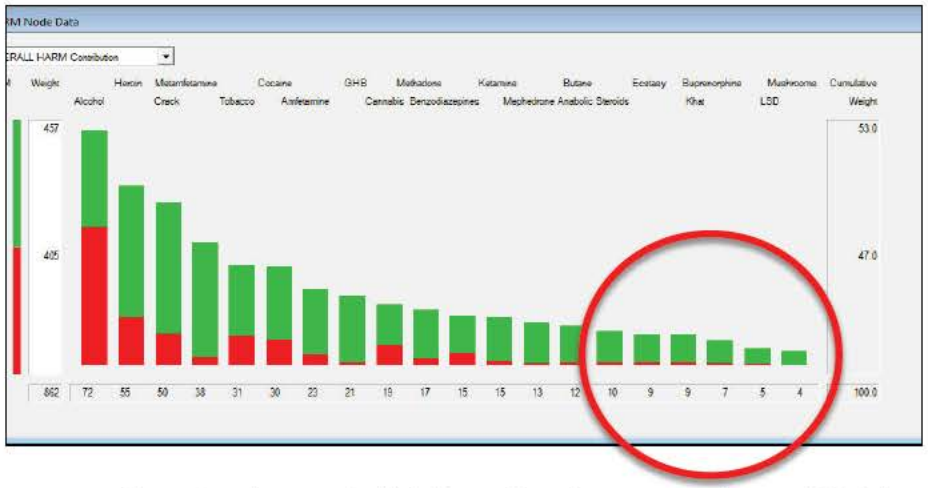


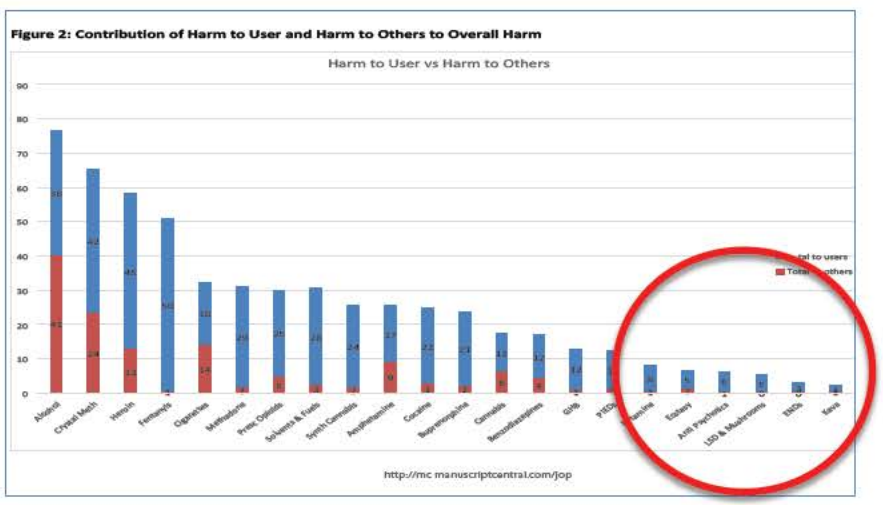
Figure 2: Drugs ordered by their overall harm scores, showing the separate contributions to the overall scores of harms to users and harm to others
The weights after normalisation (0-100) are shown in the key (cumulative in the sense of the sum of all the normalised weights for all the criteria to users, 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

MDMA - How attitudes have changed in twenty years

Then → ecstasy causes brain damage – fabrication of evidence to justify ban
Now → MDMA can heal the brain

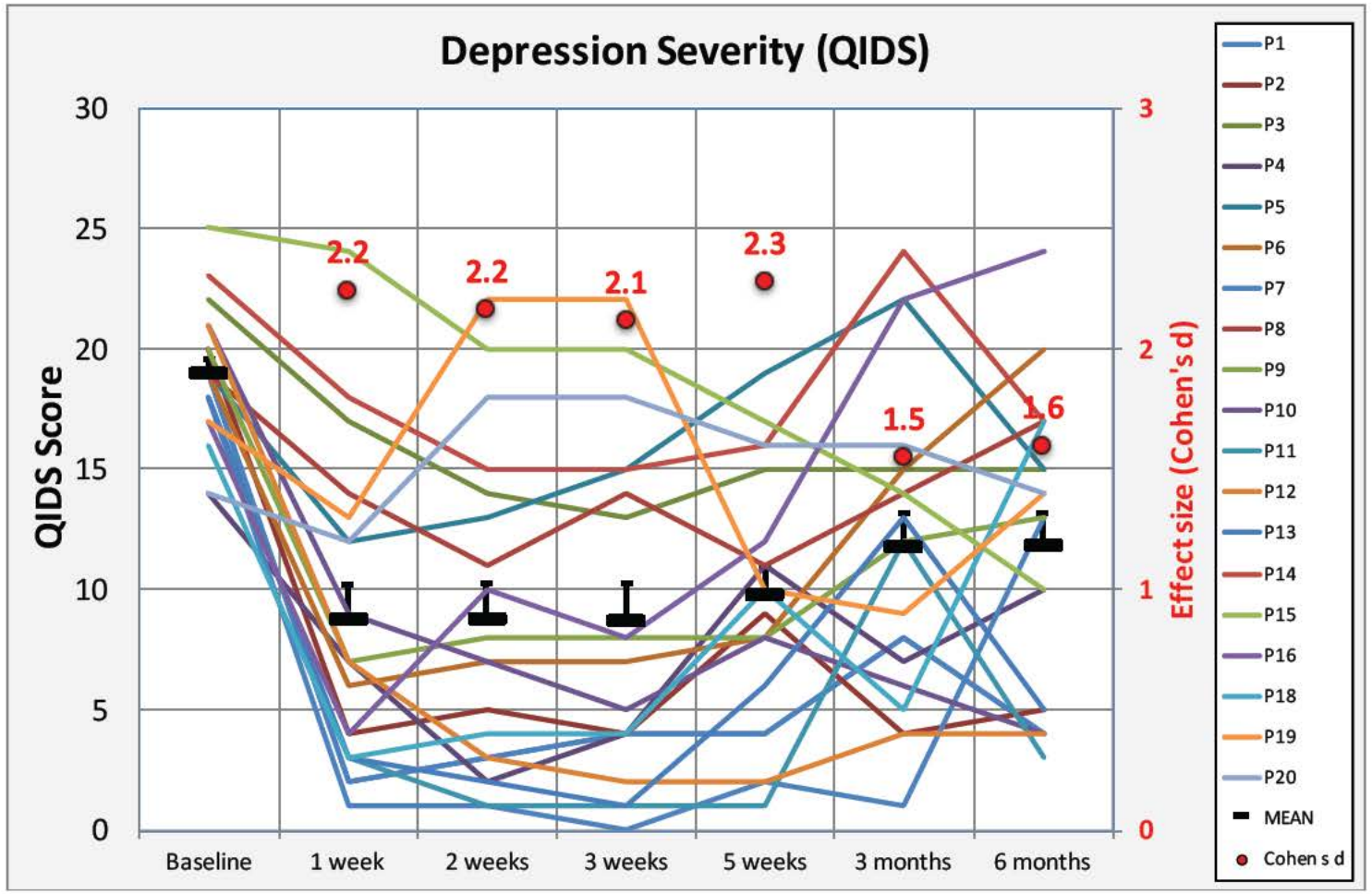
War-induced PTSD has been the driver

More US and Australian soldiers kill themselves than are killed by enemy

Aleppo 2016

Latest clinical data on psilocybin and MDMA

Single 25mg dose of Psilocybin ➔ most powerful single intervention for resistant depression



All failed on at least 2 antidepressant medicines and CBT

Carhart-Harris et al Psychopharmacology 2017

Replication study
COMPASS Pathways new trial just published

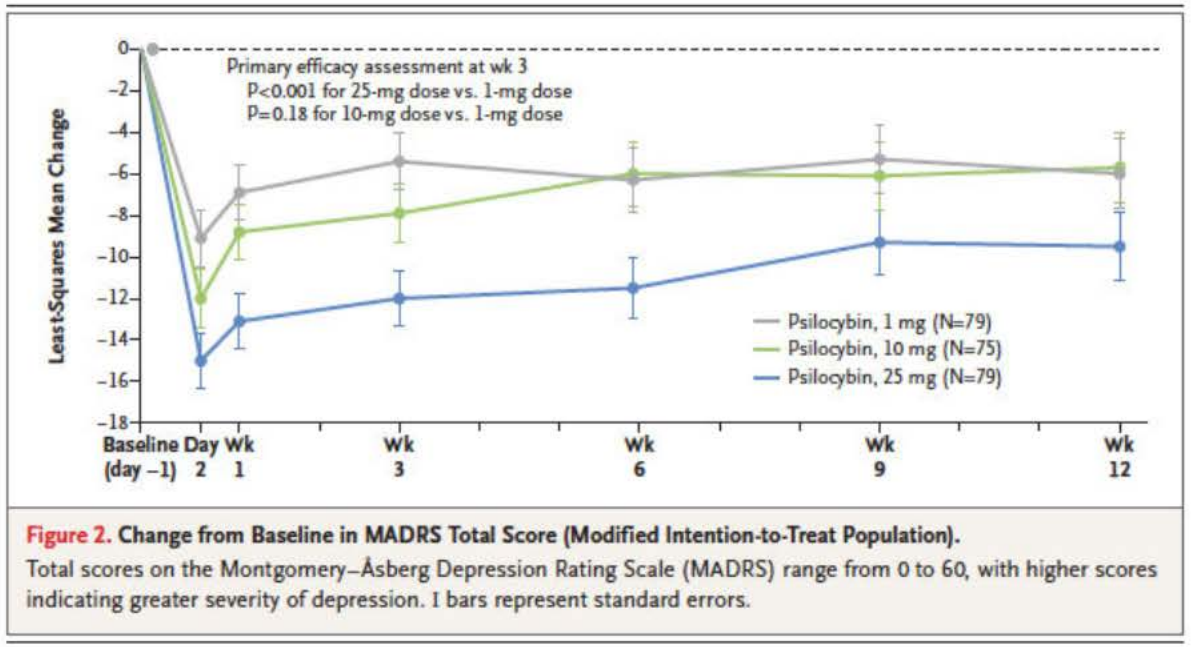
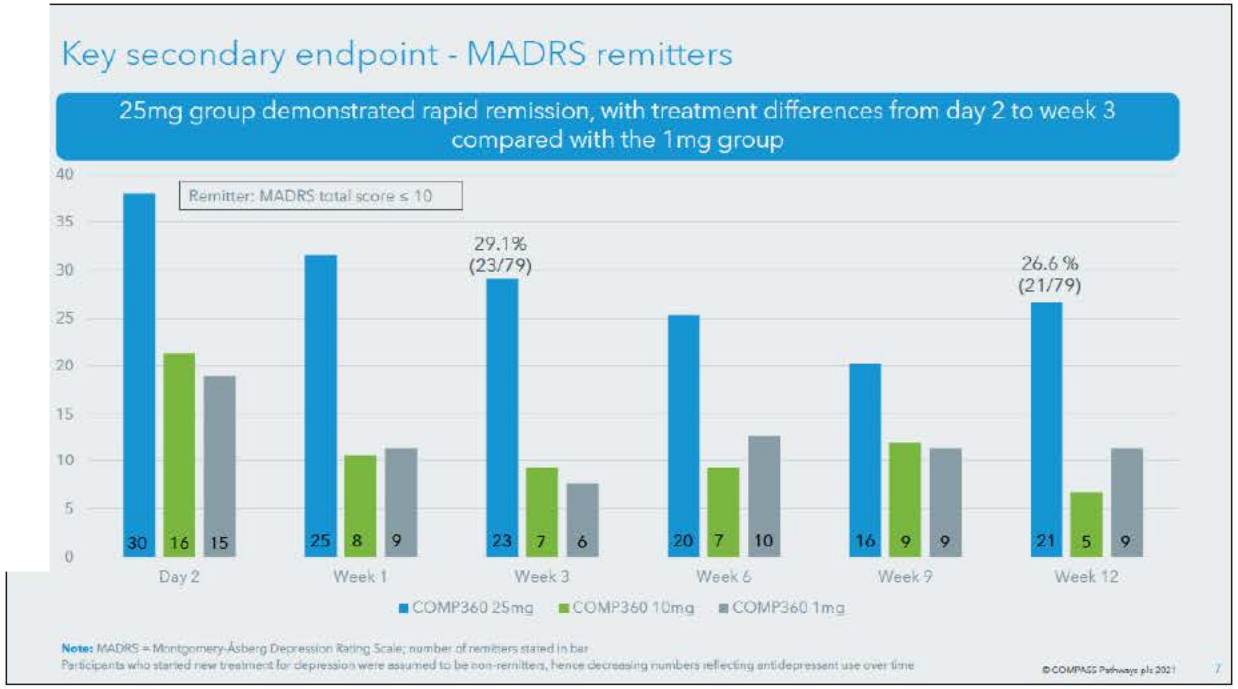


Figure 2. Change from Baseline in MADRS Total Score (Modified Intention-to-Treat Population).
Total scores on the Montgomery–Åsberg Depression Rating Scale (MADRS) range from 0 to 60, with higher scores indicating greater severity of depression. I bars represent standard errors.

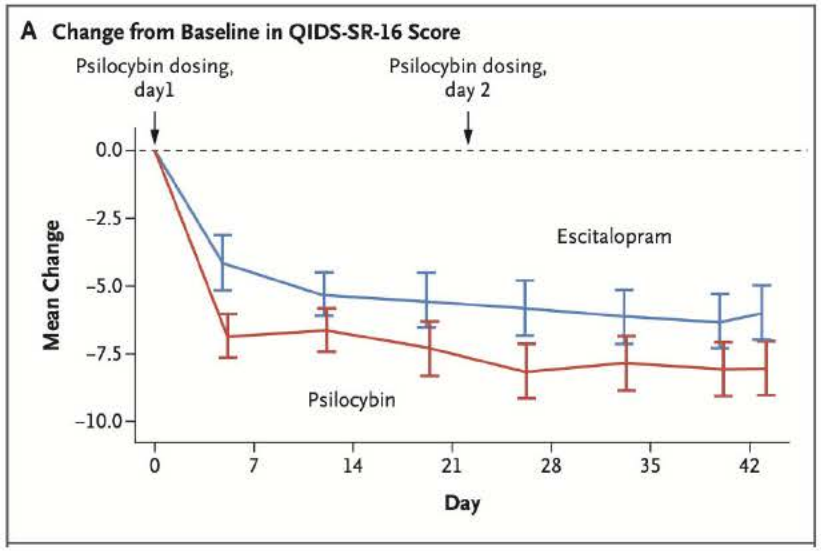


Goodwin et al 2022 NEJM

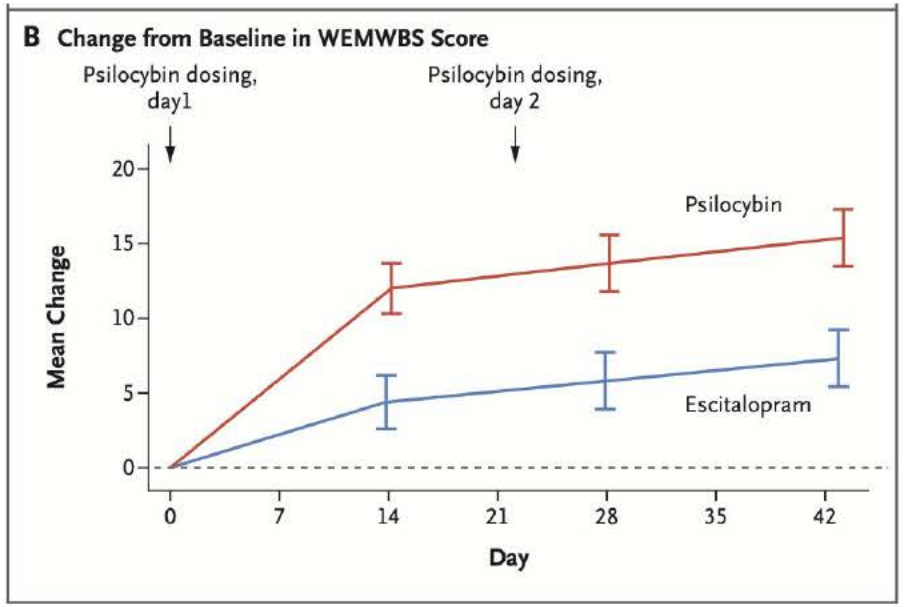
Our psilocybin –v-escitalopram trial

Carhart-Harris et al NEJM 2021

Reductions in depression scores



Improvements in wellbeing

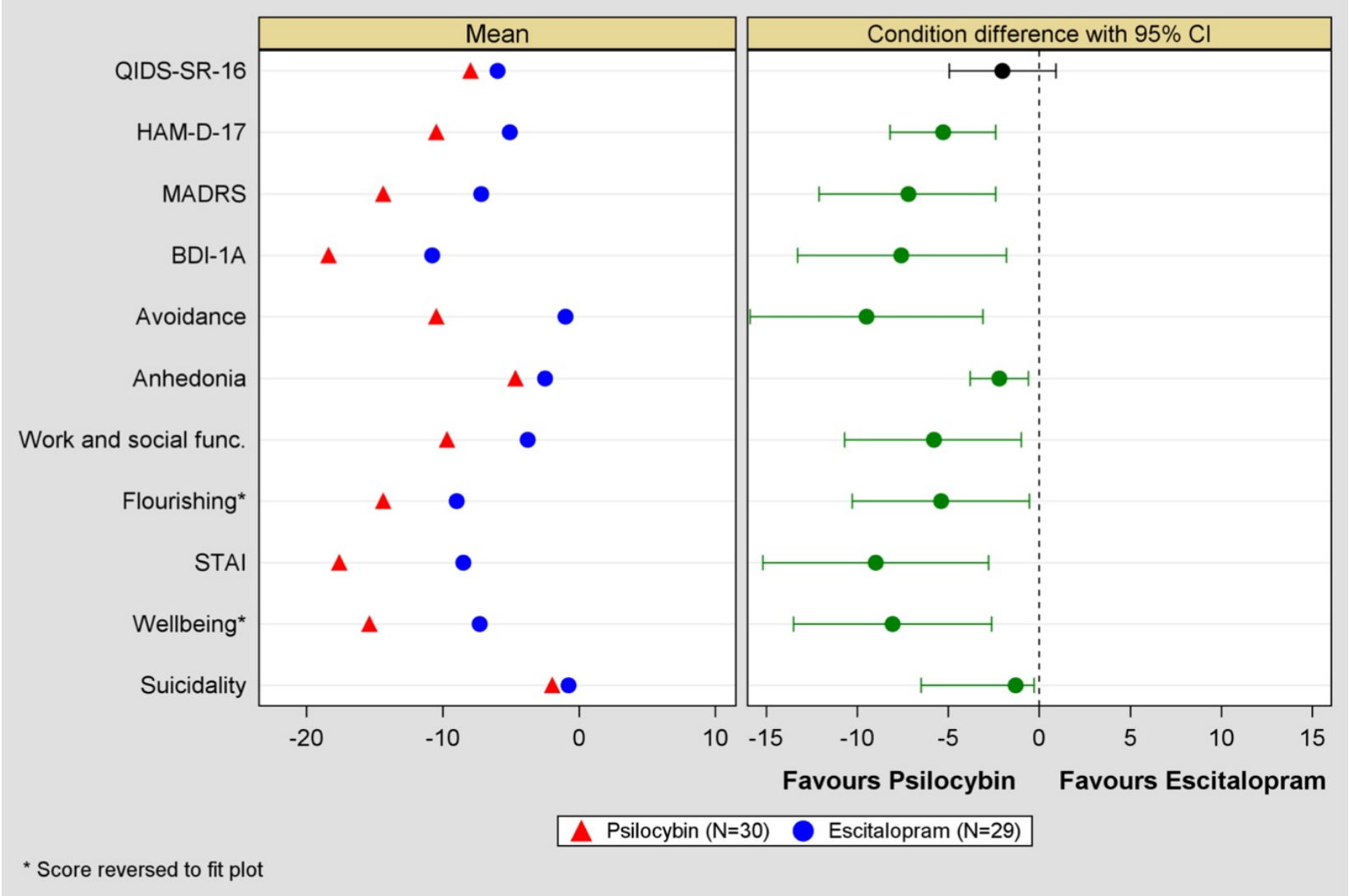


Remission rates % patients

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

Note the analysis in the TGA expert review paper is incorrect

Efficacy: psilocybin beats escitalopram on most measures



And much higher remission rates

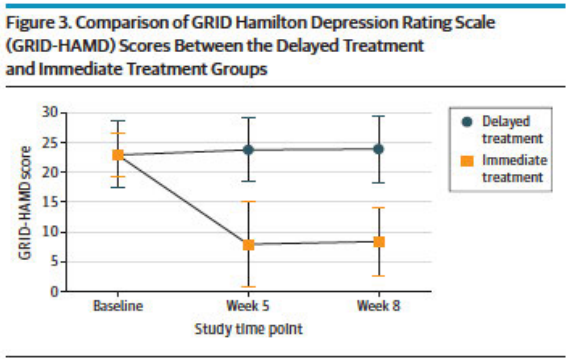
Carhart-Harris et al NEJM 2021

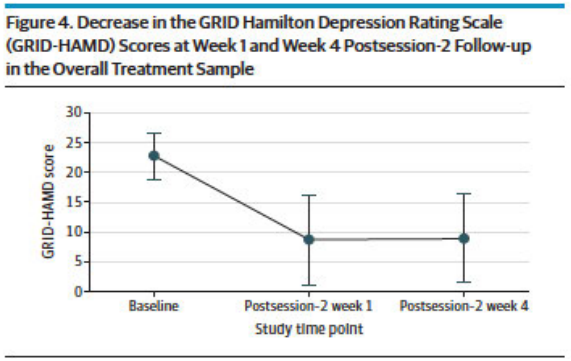
Other trials with psilocybin - all positive

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

- Griffiths - Johns Hopkins and
- Ross - NYU

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





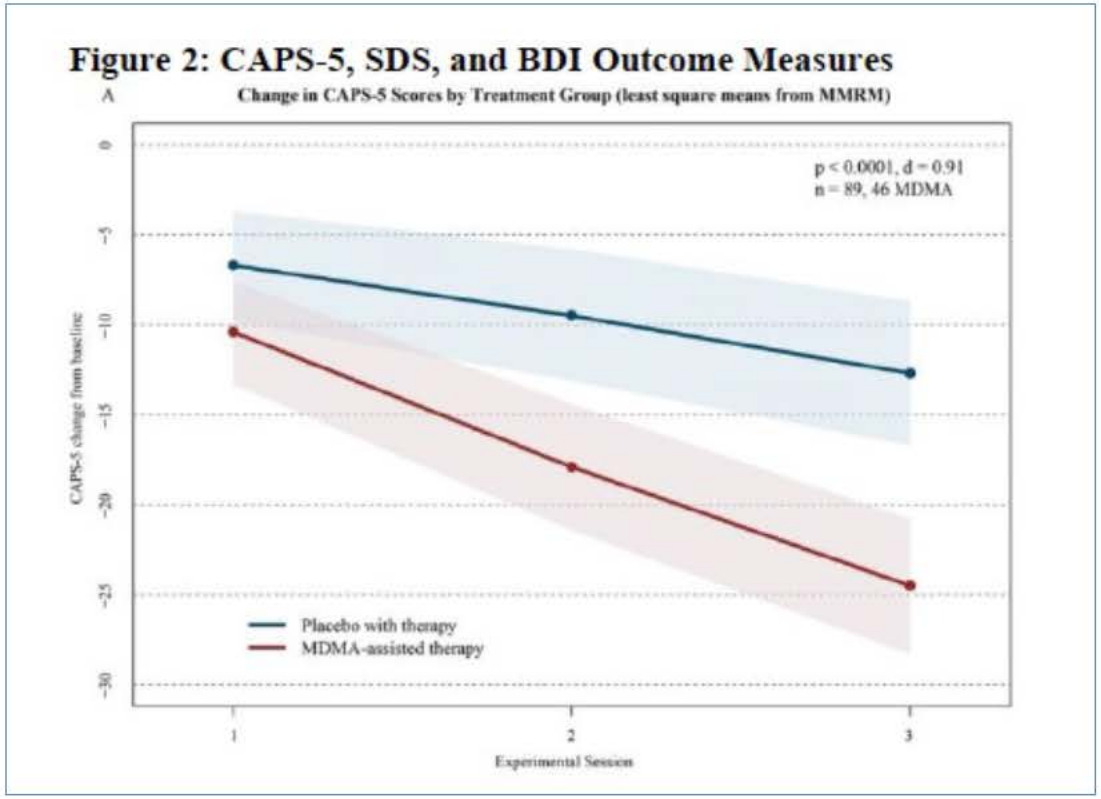
Davis et al 2021

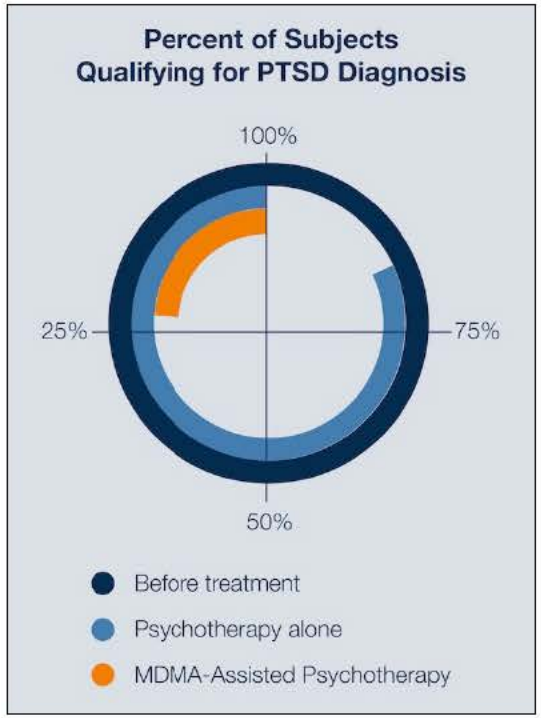
Many others now underway including in anorexia, OCD, pain syndromes
Note Australian government programme as well

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

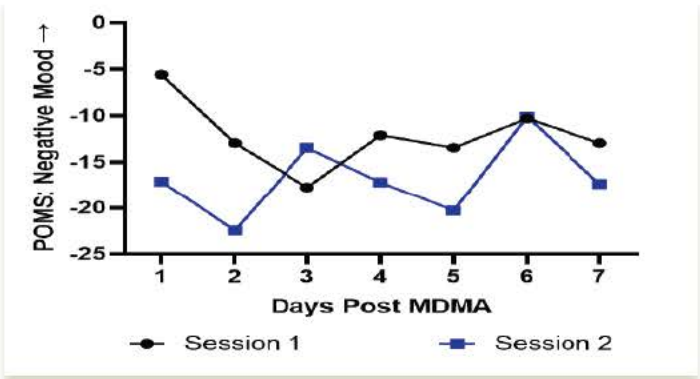
MAPS 2nd phase 3 study just completed – data in new year - if positive then likely to get FDA approval

The Bristol-Imperial MDMA-Alcoholism ('BIMA') Study

Much alcohol use is to deaden memories of trauma

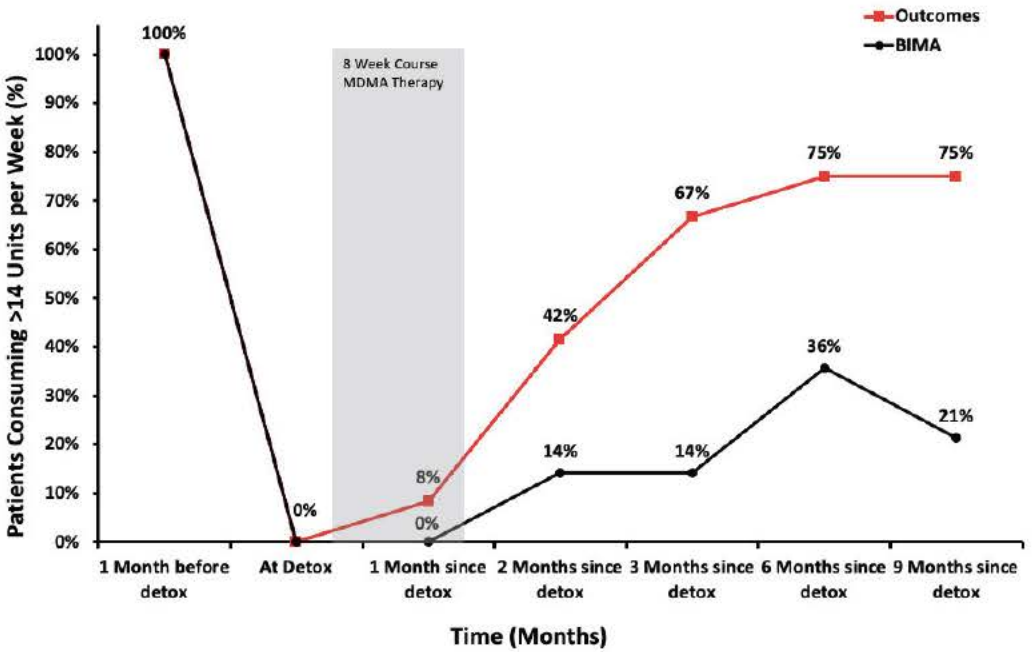
Very high levels in veterans

No mood reduction after the MDMA sessions



Profile of Mood States (POMS) carried out by daily telephone calls for 7-days after each MDMA session (Average scores across 26 MDMA sessions)

MDMA → reduced drinking and increased abstinence rate



Comparison of MDMA Therapy against Treatment As Usual for Alcohol Use Disorder

Sessa et al 2021 Journal of Psychopharmacology

What about harms?

Harms of psilocybin and other psychedelics
A recent review by Drug Science UK

Review

Adverse effects of psychedelics: From anecdotes and misinformation to systematic science

Anne K Schlag[1,2,3], Jacob Aday[1,4,5], Iram Salam[1], Jo C Neill[1,6] and David J Nutt[1,2]

Psychopharm

Journal of Psychopharmacology
2022, Vol. 36(3) 258–272

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Potential psychiatric adverse effects of PSILOCYBIN in clinical treatment trials

Hallucinogen use disorder (addiction)	NONE REPORTED
Abuse liability and dependence	NONE REPORTED
Harms to self or others	NONE REPORTED
Challenging experiences	PART OF THERAPY
HPPD Hallucinogen persistent perceptual disorder	NONE REPORTED
Psychosis	NONE REPORTED BECAUSE AT RISK PATIENTS ARE EXCLUDED

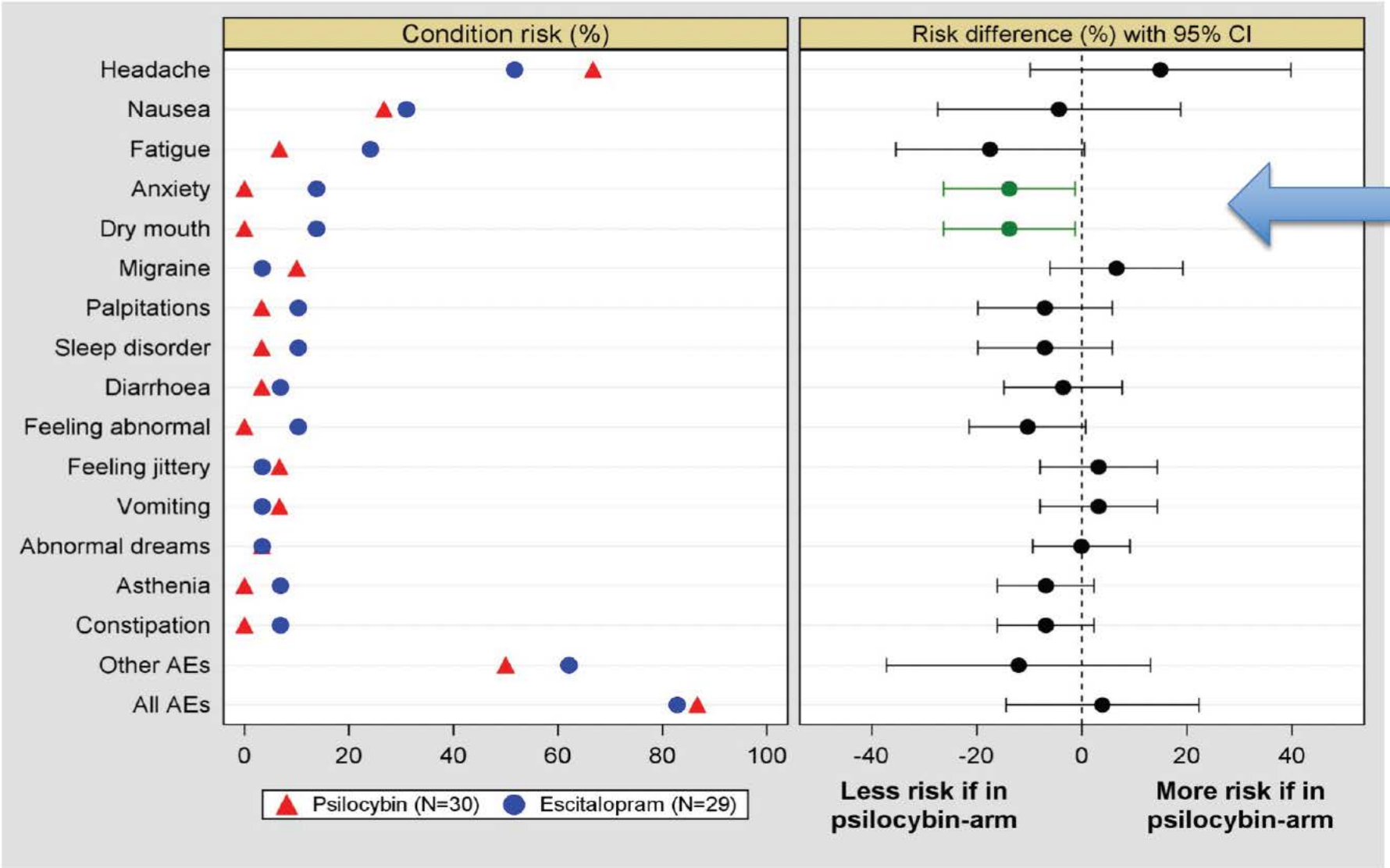
Nothing surprising as only one or two doses given
And drug only in the body for a few hours

Potential neurologic adverse effects of PSILOCYBIN in clinical practice

Toxicity and overdose risk	NONE REPORTED
Neurotoxicity	NONE REPORTED
Cardiovascular harms	MILD ELEVATIONS IN BLOOD PRESSURE NOT REQUIRING INTERVENTIONS
Emergency medical assistance	NONE REPORTED

Nothing surprising as treatment given in medical settings

Side effects in psilocybin-v-escitalopram trial



Psilocybin better

Figure S6. Supplementary appendix

Carhart-Harris et al 2021 NEJM

COMPASS Pathways trial – adverse effects

Table 3. Adverse Events Reported on Day 1, from Day 2 up to Week 3, and after Week 3 up to Week 12 (Safety Population).*

Adverse Event	Psilocybin, 25 mg (N=79)	Psilocybin, 10 mg (N=75)	Psilocybin, 1 mg (N=79)
		number (percent)	
Day 1			
Any adverse event	48 (61)	35 (47)	30 (38)
Any severe adverse event	3 (4)	6 (8)	1 (1)
Adverse events occurring in ≥5% of participants in any group			
Headache	19 (24)	11 (15)	13 (16)
Nausea	17 (22)	5 (7)	1 (1)
Euphoric mood	4 (5)	5 (7)	3 (4)
Fatigue	5 (6)	2 (3)	4 (5)
Insomnia	2 (3)	3 (4)	5 (6)
Anxiety	3 (4)	6 (8)	0
Mood altered	4 (5)	3 (4)	0
Dizziness	5 (6)	1 (1)	0
Paresthesia	2 (3)	4 (5)	0
Abnormal thinking	0	4 (5)	0
Any serious adverse event	0	0	0
Day 2 up to wk 3			
Any adverse event	44 (56)	36 (48)	35 (44)
Any severe adverse event	7 (9)	5 (7)	1 (1)
Adverse events occurring in ≥5% of participants in any group			
Headache	9 (11)	5 (7)	9 (11)
Insomnia	4 (5)	5 (7)	8 (10)
Anxiety	4 (5)	6 (8)	3 (4)
Fatigue	6 (8)	2 (3)	3 (4)
Suicidal ideation	5 (6)	4 (5)	2 (3)
Depression	3 (4)	3 (4)	4 (5)
Mood altered	4 (5)	0	1 (1)
Any serious adverse event	4 (5)	4 (5)	0
Suicidal ideation	2 (3)	2 (3)	0
Intentional self-injury	2 (3)	1 (1)	0
Hospitalization	0	1 (1)	0
After wk 3 up to wk 12			
Any adverse event	23 (29)	24 (32)	24 (30)
Any severe adverse event	2 (3)	3 (4)	0
Adverse events occurring in ≥5% of participants in any group			
Headache	3 (4)	2 (3)	6 (8)
Any serious adverse event	4 (5)	3 (4)	1 (1)
Suicidal behavior	3 (4)	0	0

Goodwin et al 2022 NEJM

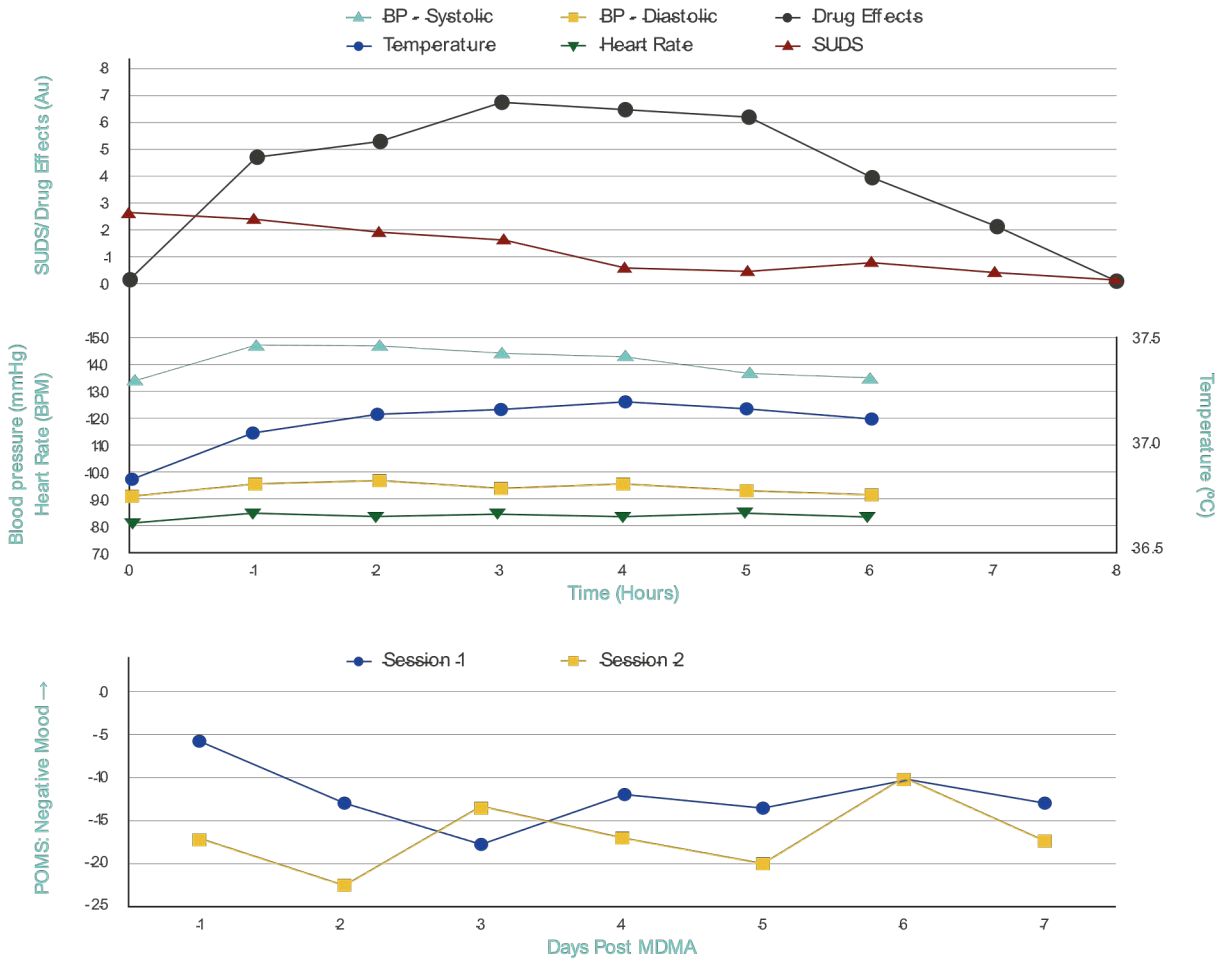
Treatment-emergent adverse events related to MDMA

Adverse Drug Reaction (>7%)	MDMA (N=46)	Placebo (N=44)	Adverse Drug Reaction (>7%)	MDMA (N=46)	Placebo (N=44)
Muscle tightness	65%	11%	BP increased	13%	-
Decreased appetite	52%	11%	Feeling jittery	13%	-
Nausea	30%	11%	Chest pain (non-cardiac)	11%	2%
Hyperhidrosis	21%	2%	Dry Mouth	11%	4%
Feeling cold	20%	7%	Vision Blurred	9%	2%
Restlessness	15%	-	Pollakiuria	9%	2%
Mydriasis	15%	-	Intrusive Thoughts	9%	-
Dizziness (postural)	13%	4%	Vomiting	9%	-
Bruxism	13%	2%	Stress	9%	-
Nystagmus	13%	-	Musculoskeletal Pain	9%	-

*Phase 3 PTSD Study

From the first phase 3 MAPS trial – largely predicted by acute pharmacology

MDMA Safety and Tolerability (from the BIMA study)

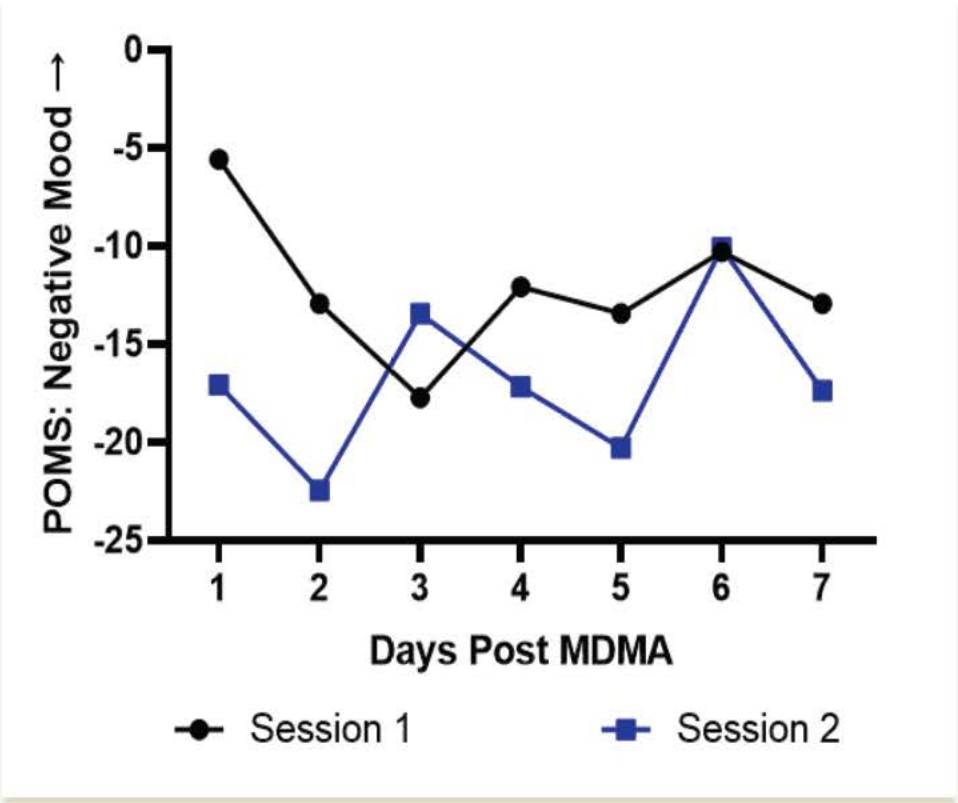


Participant number:	Abnormal physiological changes in MDMA sessions observed:	Serious adverse events recorded:	Post-MDMA affect drop in the week after the session	Suicide risk (as measured by C-SSRS):	Subjective report of participants' tolerability of MDMA therapy course:	Abnormal changes in blood test results and ECG between baseline and the end of the MDMA course:
B01	None	None	None	Nil	Positive	Nil
B02	None	None	None	Nil	Positive	Nil
B04	None	None	None	Nil	Positive	Nil
B05	None	None	None	Nil	Positive	Nil
B09	None	None	None	Nil	Positive	Nil
B11	None	None	None	Nil	Positive	Nil
B15	None	None	None	Nil	Positive	Nil
B16	None	None	None	Nil	Positive	Nil
B17	None	None	None	Nil	Positive	Nil
B20	None	None	None	Nil	Positive	Nil
B21	None	None	None	Nil	Positive	Nil
B25	None	None	None	Nil	Positive	Nil
B26	None	None	None	Nil	Positive	Nil
B28	None	None	None	Nil	Positive	Nil

Sessa et al 2021

Does MDMA lower mood after treatment?

No mood reduction after the MDMA sessions in BIMA



Profile of Mood States (POMS) carried out by daily telephone calls for 7-days after each MDMA session (Average scores across 26 MDMA sessions)

Modern neuroimaging research reveals how these drugs work

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

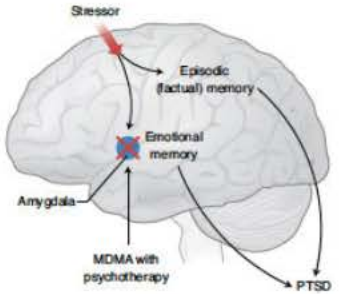
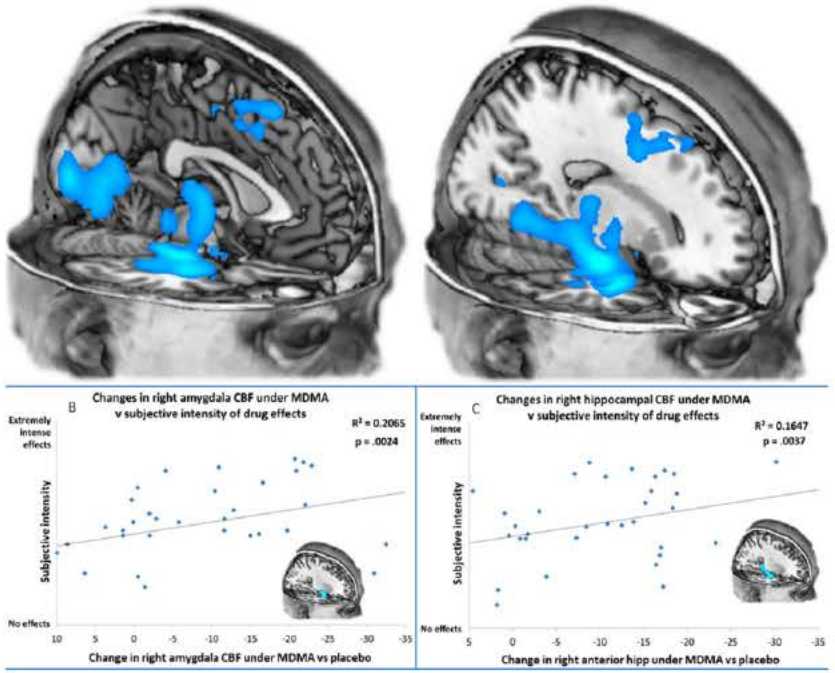


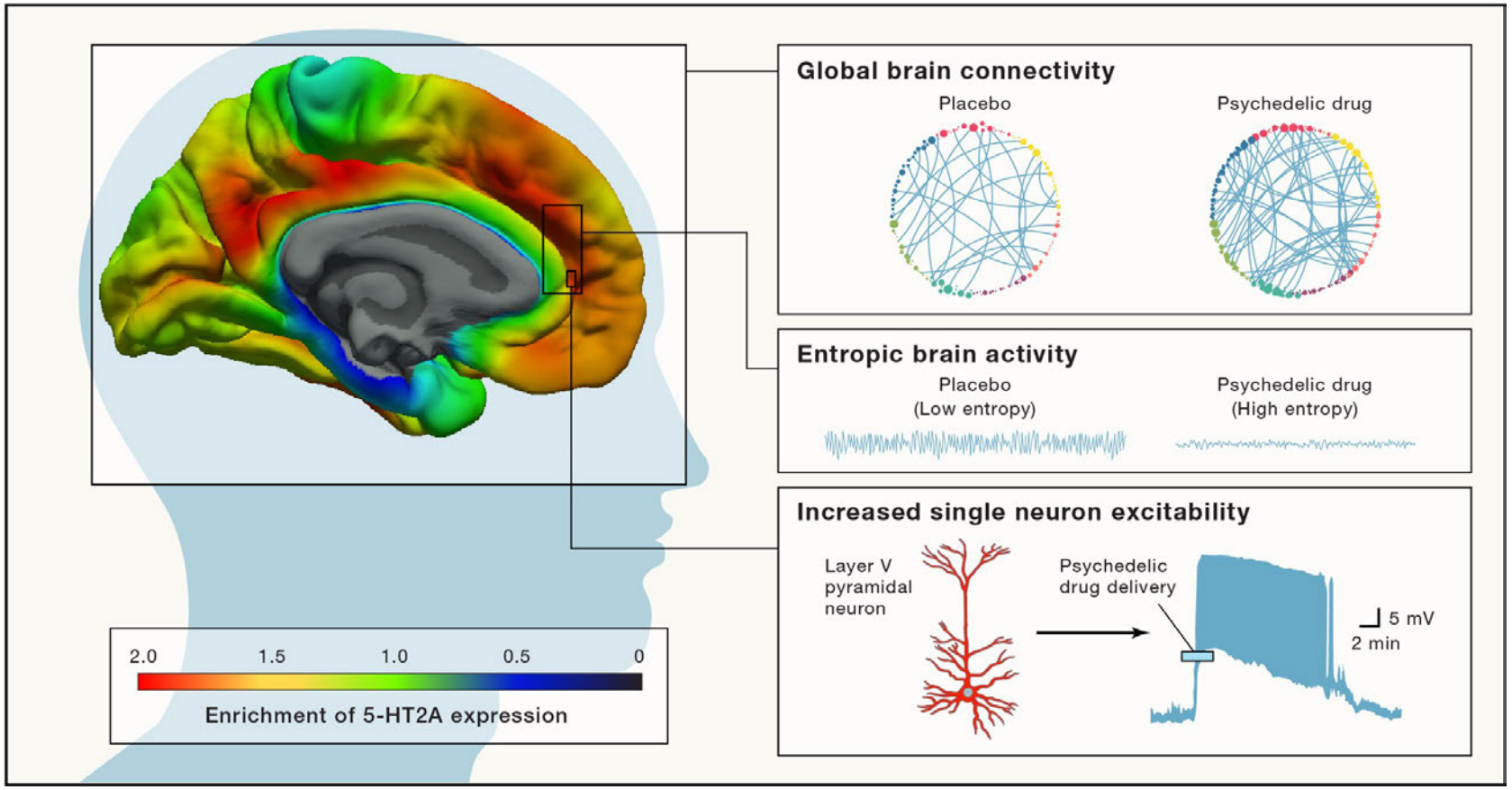
Fig. 1 | The brain pathways of PTSD and site of action of MDMA in therapy. A severe, life-threating stressor (trauma) leaves an emotional trace as well as a factual trace in different parts of the brain. Negative emotions are reactivated by remembering the trauma or as part of a conditioned fear reflex—for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



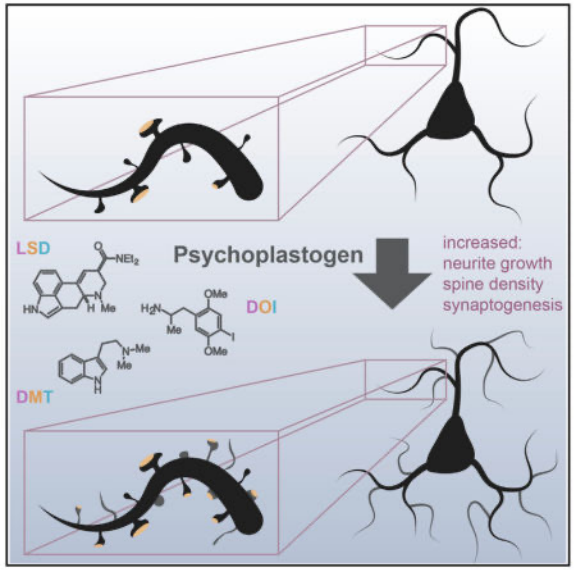
Carhart-Harr s, R. L., Kev n, M., Robert, L., Dav d, E., Wa , M. B., Bart, F., … Nutt, D. J. (2015). *Biological Psychiatry*, *78*(8), 554–562.

Brain mechanisms of psilocybin



Nutt et al Cell 2020

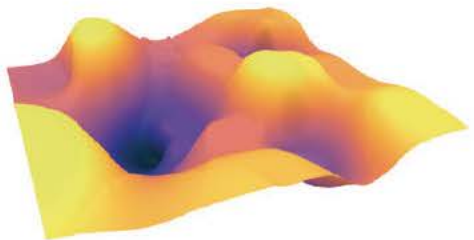
+ neuroplasticity



Ly et al Cell Reports 2018

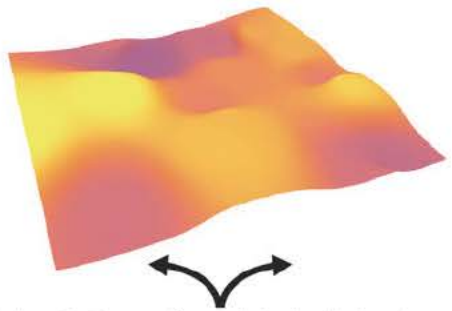
Brain imaging results
Psilocybin increases brain connectivity in depression

Depression



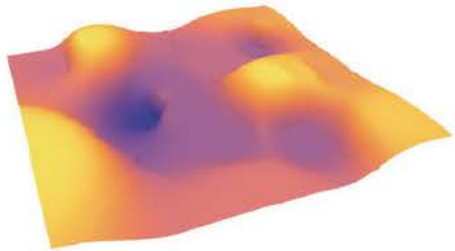
The depressed brain encourages rigid thought patterns that impact well-being. This can be viewed as a 'landscape' with deep wells that make it difficult for patients to 'move between' different thoughts & perspectives.

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

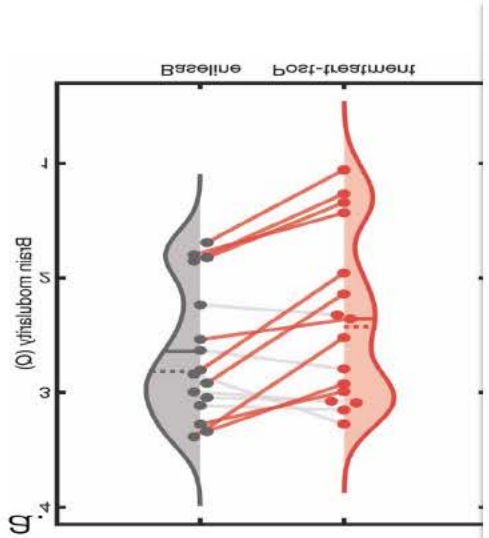
https://doi.org/10.1038/s41591-022-01744-z

Check for updates

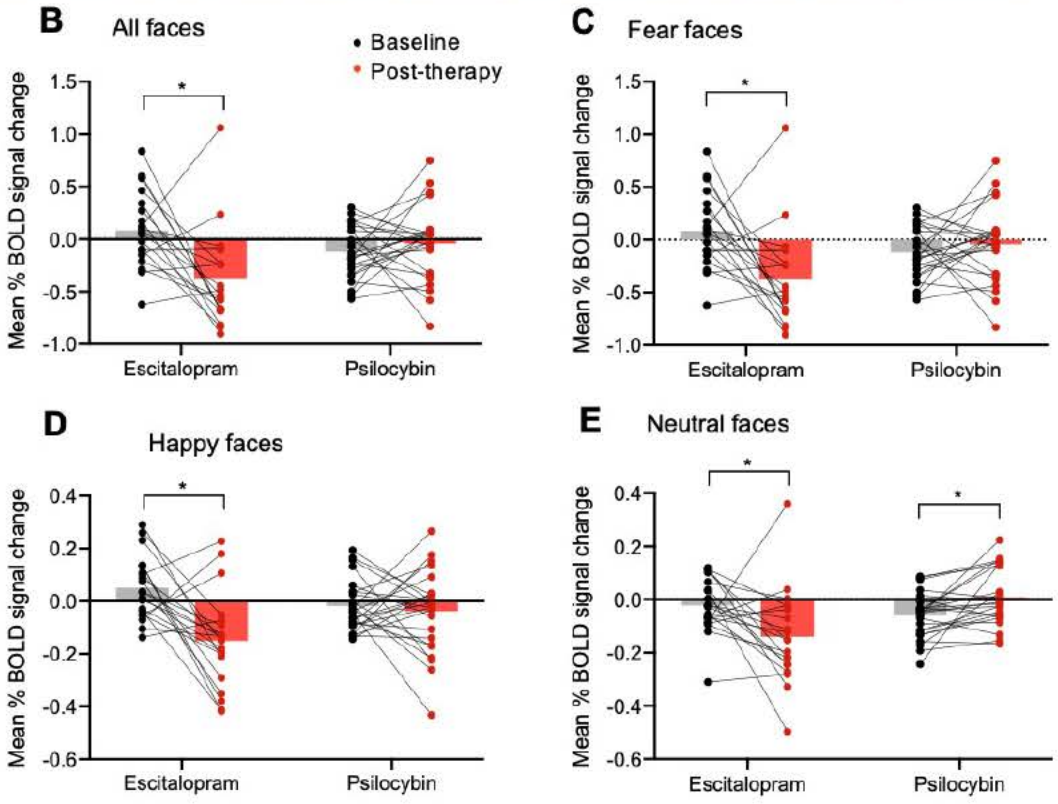
Increased global integration in the brain after psilocybin therapy for depression

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



In contrast escitalopram blunts emotional centres of the brain - fMRI

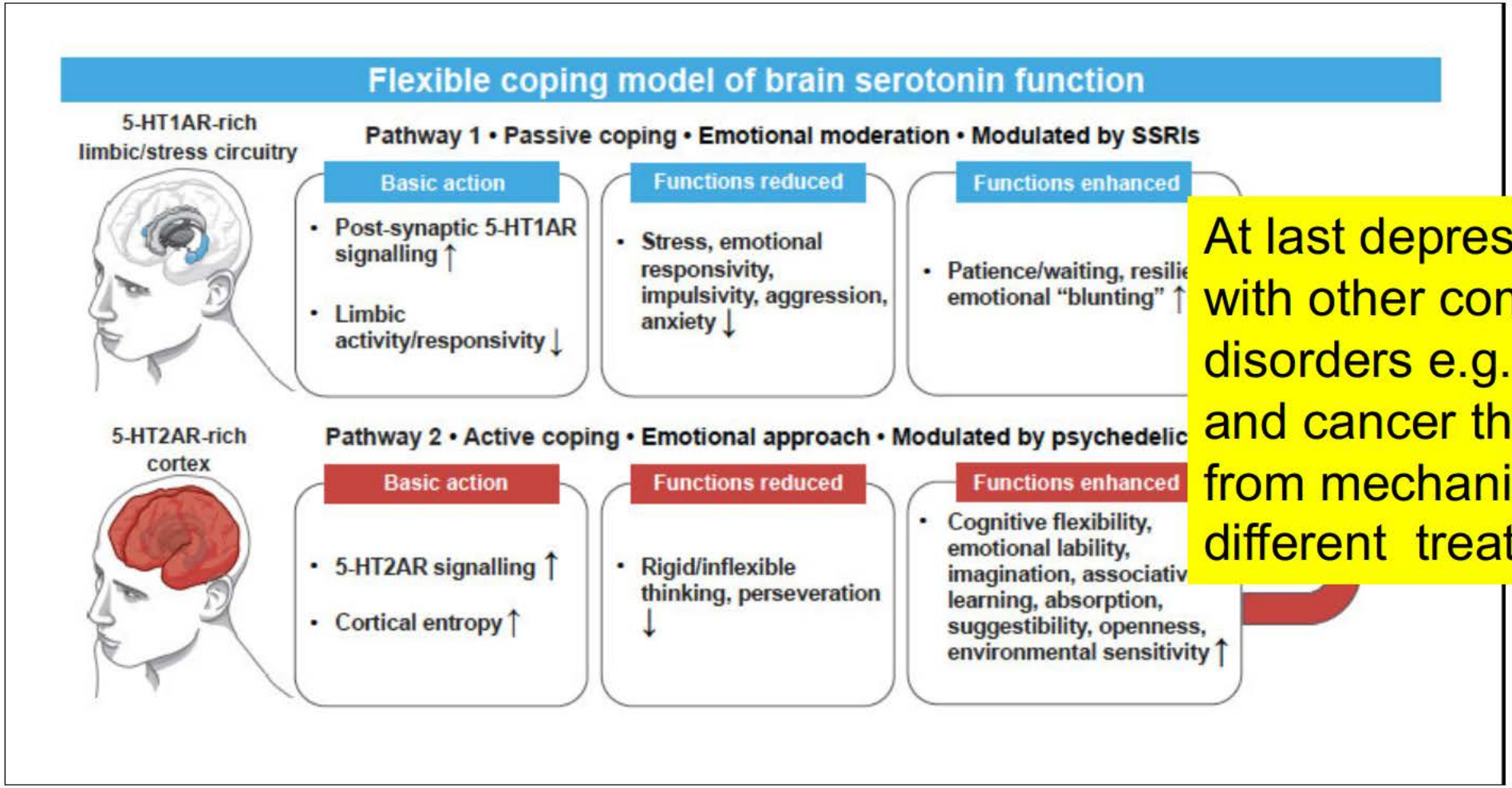


Escitalopram blunts brain response to all emotions

Psilocybin does not blunt and may enhance neutral

Wall et al submitted

There are now two ways to lift depression
Different brain regions and different 5-HT receptors



At last depression on par with other common disorders e.g. hypertension and cancer that benefit from mechanistically-different treatment options

Carhart-Harris and Nutt – Journal of Psychopharmacology 2017 – free download

Thanks and questions

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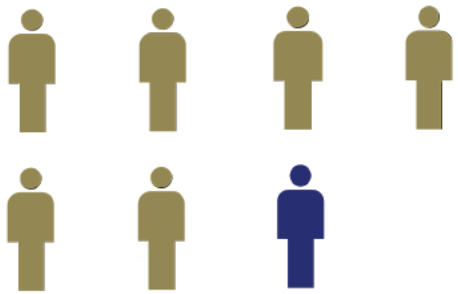
TGA Rescheduling Interim Decision

Important Information

- 1 in 5 Australian adults **(4.8 million people)** had a chronic mental illness pre-COVID-19*
- As a result of the COVID-19 pandemic, 4 in 5 Australians now report poor mental health and 34% of Australians said their mental health had declined in the pandemic**



- 1 in 7 Australians are now on anti-depressants (18% increase in last 5 years, 95% increase in last 15 years)^
- 1 in 30 children on antidepressants as young as 4 years of age
- Prescriptions have doubled over the past 10 years^^
- Australia has the second-highest per capita usage of antidepressants of all OECD countries^^^

- Over 45% of Australians will experience mental illness in their lifetime
- Globally, there has been an estimated increase of more than 129 million cases of major depression (53.2mn) and anxiety (76.2mn) disorders during the pandemic due to the combined effects of the pandemic and lockdown measures***

- The most common mental illnesses are:

Post-Traumatic Stress Disorder (PTSD), Other Anxiety Disorders, Depression and Substance use Disorders

*Impact before recent bushfires and current COVID-19 pandemic **Smiling Mind state of mind report 2021
*** The Lancet (2021) Global prevalence and burden of depressive and anxiety disorders in 204 countries and territories in 2020 due to the COVID-19 pandemic.
Australian Bureau of Statistics 2018, National Health Survey First Results, cat. no. 4364.0.55.001, ABS, Canberra
PsychWatch Australia, April 2019 with information from Department of Human Services, Canberra
Australian Bureau of Statistics 2009, National Survey of Mental Health and Wellbeing: Summary of Results, 4326.0, 2007. ABS: Canberra.
^Cochrane antidepressants discontinuation review 2021 – infographic
^^McCarthy M. Antidepressant use has doubled in rich nations in past 10 years BMJ 2013; 347 :f7261 doi:10.1136/bmj.f7261
^^^Australian Journal of General Practice (2021)

	General Population*	ADF Veterans
Criteria (over 12 month period) for:	%	%
Mental Disorders	20	46
PTSD	6.4	17.7
Depression Episodes	4.1	11.2
Alcohol Disorder	4.3	12.9
Suicidal Ideation (Plans or Attempts)	2.2	21.7
Co-Morbidity	8.5	55.2

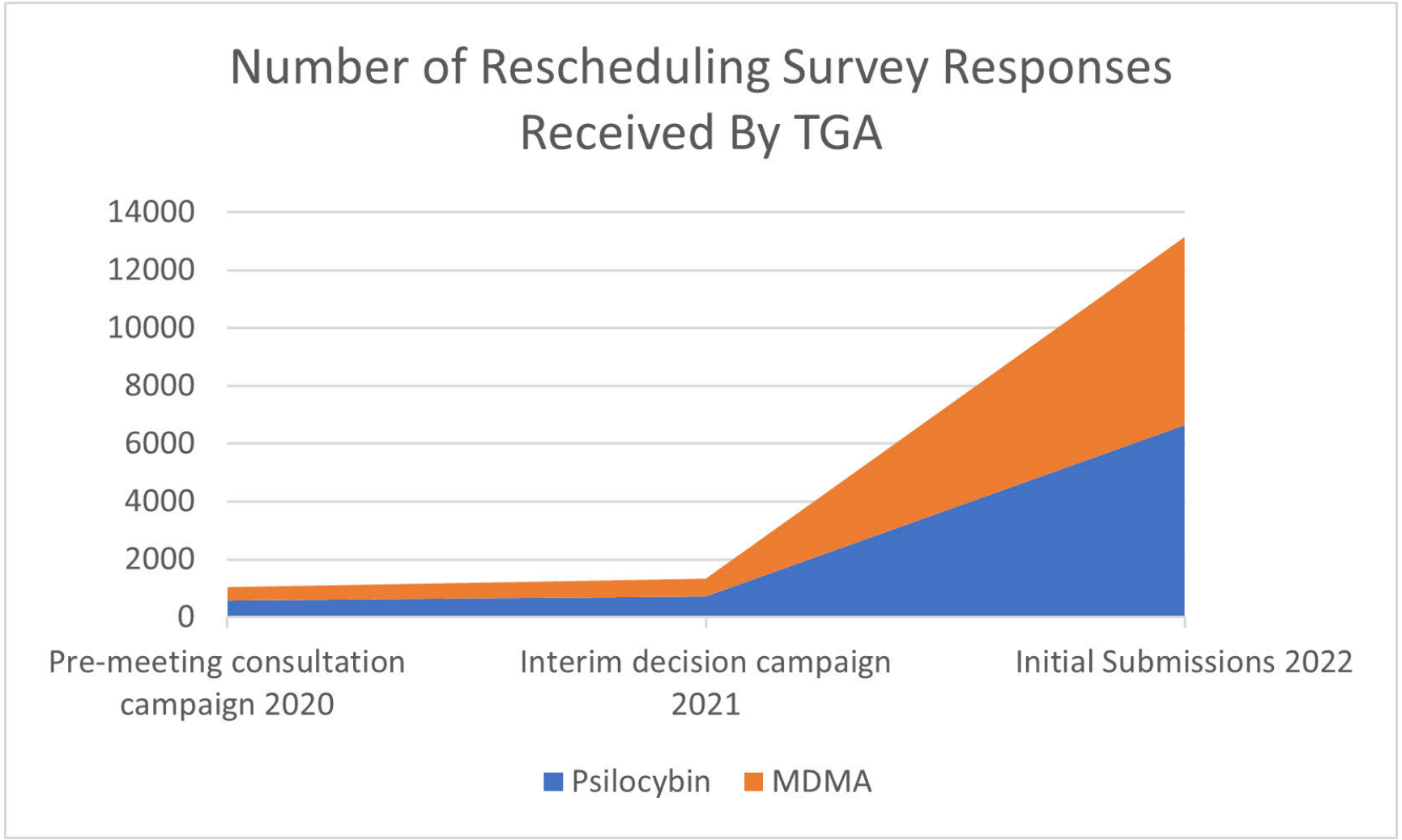
- 10% of **First Responders** have PTSD and 1 in 3 suffer from high psychological distress. They have suicidal thoughts at two times the rate of adults in the general population and one First Responder takes his or her own life every 6 weeks (Beyond Blue).

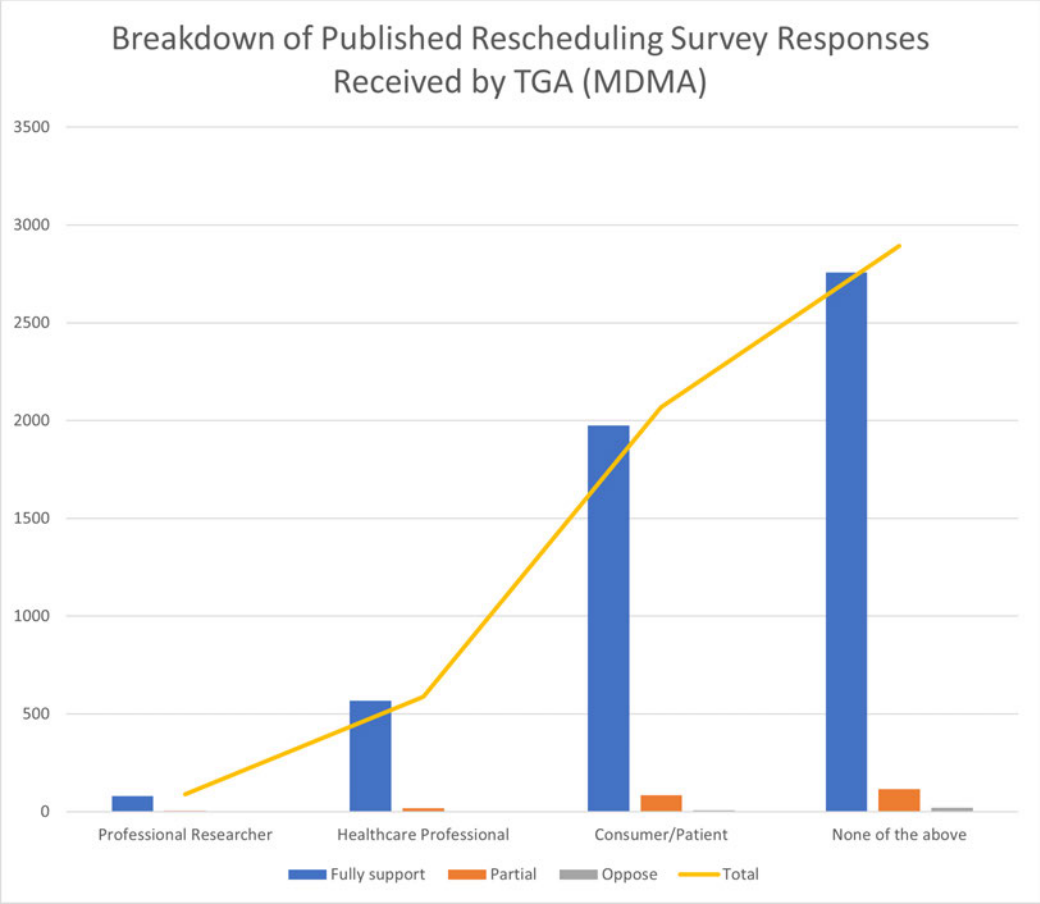
*above 16 years of age

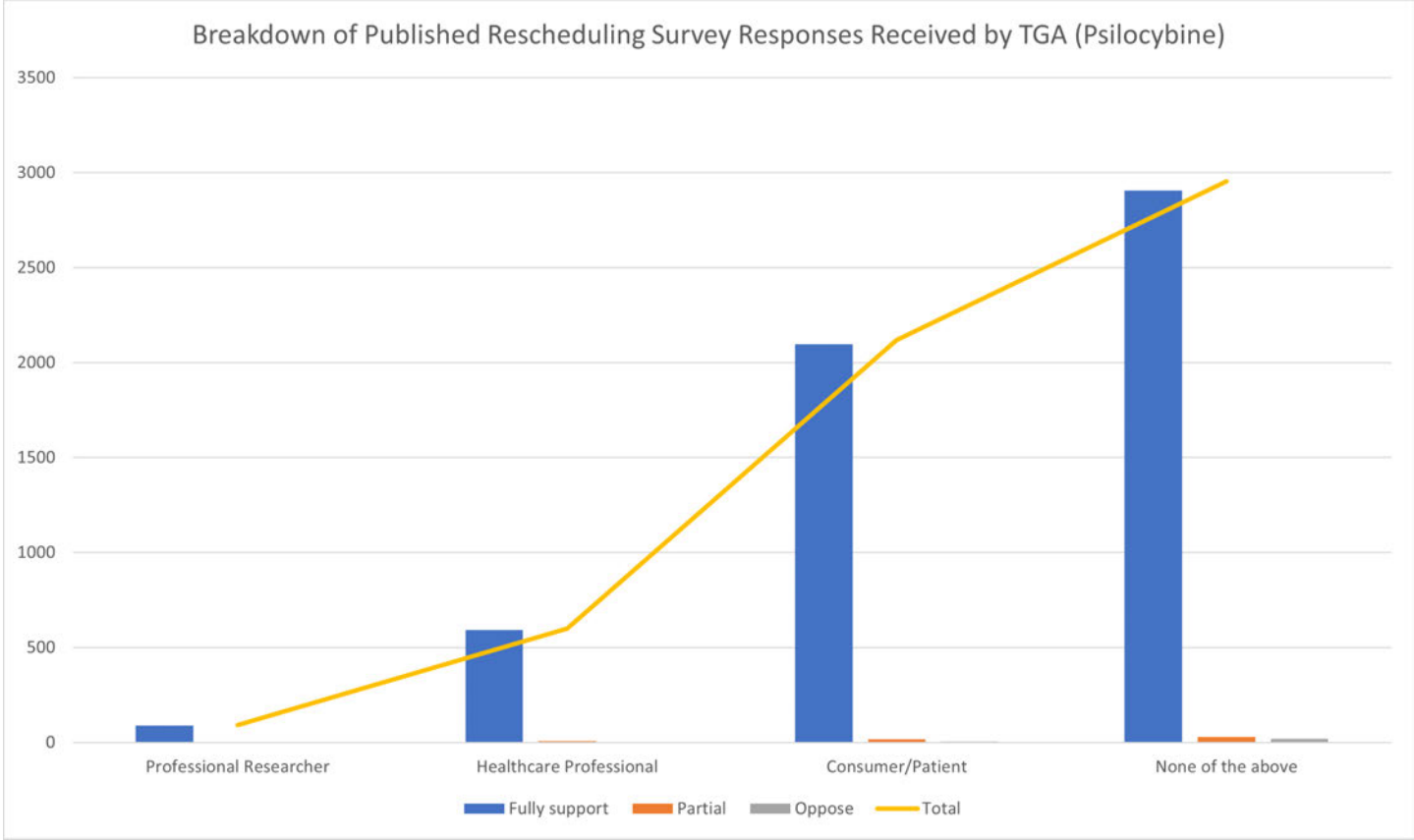
Veterans Information- Mental Health Prevalence: Department of Veterans Affair 2018

General Population- 2007 National Survey of Mental Health & Wellbeing (ABS)

Substance	Pre-meeting consultation campaign 2020	Interim decision campaign 2021	Initial Submissions 2022
Psilocybin	575	728	6650
MDMA	478	605	6505




Breakdown of Published Rescheduling Survey Responses Received by TGA (MDMA)
3500
3000
2500
2000
1500
1000
500
0
Professional Researcher
Healthcare Professional
Consumer/Patient
None of the above
Fully support
Partial
Oppose
Total


Breakdown of Published Rescheduling Survey Responses Received by TGA (Psilocybine)
3500
3000
2500
2000
1500
1000
500
0
Professional Researcher
Healthcare Professional
Consumer/Patient
None of the above
Fully support
Partial
Oppose
Total

1. There was insufficient evidence that MDMA or Psilocybin when used as part of psychotherapy has an established therapeutic value as required by the Schedule 8 policy guidelines

2. Risks and Benefits

3. The Optimal Dose has not been established

4. Risk of Dependence

5. There are significant benefits to waiting for more clinical trial results

6. Training Regime

7. States and Territories don’t have established mechanisms to give effect to the controls proposed in our applications

8. Risk of Diversion for Misuse in the Supply Chain

9. Current regulation of these substances for therapeutic use abroad is consistent with the controls associated with Schedule 9 of the Poisons Standard in Australia.

10. Scheduling is not an appropriate mechanism for establishing clinical governance and in the case of Psilocybin rescheduling would bypass the processes for clinical trials

11. Reliance on the Views of the Royal Australian and New Zealand College of Psychiatrists (RANZCP) and the Australian Psychological Society (APS)