MAJOR DEPRESSIVE DISORDER: NEW TREATMENT TARGETS

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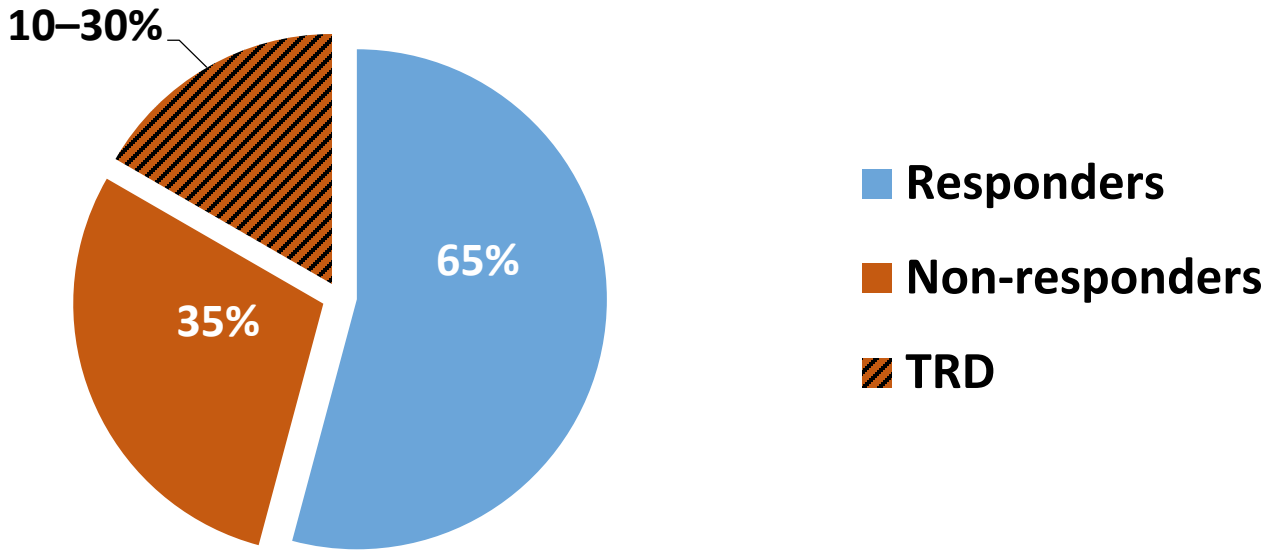
Disclosures

- Employed by King's College London
- Honorary Consultant Maudsley and Bethlem Hospitals (NHS)
- Paid lectures and advisory boards for all major pharmaceutical companies with drugs used in affective and related disorders
- No share holdings in pharmaceutical companies or related companies
- Lead Investigator for Embolden Study (AZ), BNC210 Study, and Aripiprazole Mania Study; Investigator-initiated studies from AZ, Eli Lilly and Company, Lundbeck, Wyeth
- Grant funding (past and present): NIMH (USA); CIHR (Canada); NARSAD (USA); Stanley Medical Research Institute (USA); MRC (UK); Wellcome Trust (UK); Royal College of Physicians (Edin); BMA (UK); UBC-VGH Foundation (Canada); WEDC (Canada); CCS Depression Research Fund (Canada); MSFHR (Canada); NIHR (UK)
- Formerly Chair of Special Committee for Psychopharmacology RCPsych; Immediate Past President of International Society for Affective Disorders; President of British Association for Psychopharmacology.

TRD: background and burden

MDD affects 10–15% of the population per year

Responses to current AD treatments:



Depression will be the **second leading cause of disease burden** by the year 2030

AD, antidepressant; MDD, major depressive disorder;
TRD, treatment-resistant depression.

Al-Harbi KS. Patient Pref Adherence. 2012;6:369-88.
Otte C. Dialogues Clin Neurosci. 2008;10:453-60.

There is a need for effective treatment after 2 treatment failures

1st LINE

MONOTHERAPY

- SSRI or SNRI

2nd LINE
(Adjunctive MDD or Switch)

SWITCH

ADD ON

TRD
(Treatment Resistant)

SWITCH

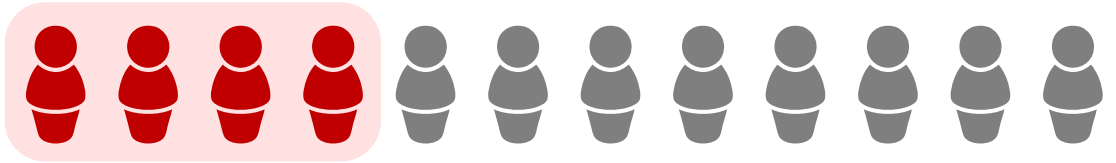
ADD ON

4th Line and >

New Combination

ECT or rTMS

1/3 OF MDD PATIENTS BECOME TREATMENT-RESISTANT

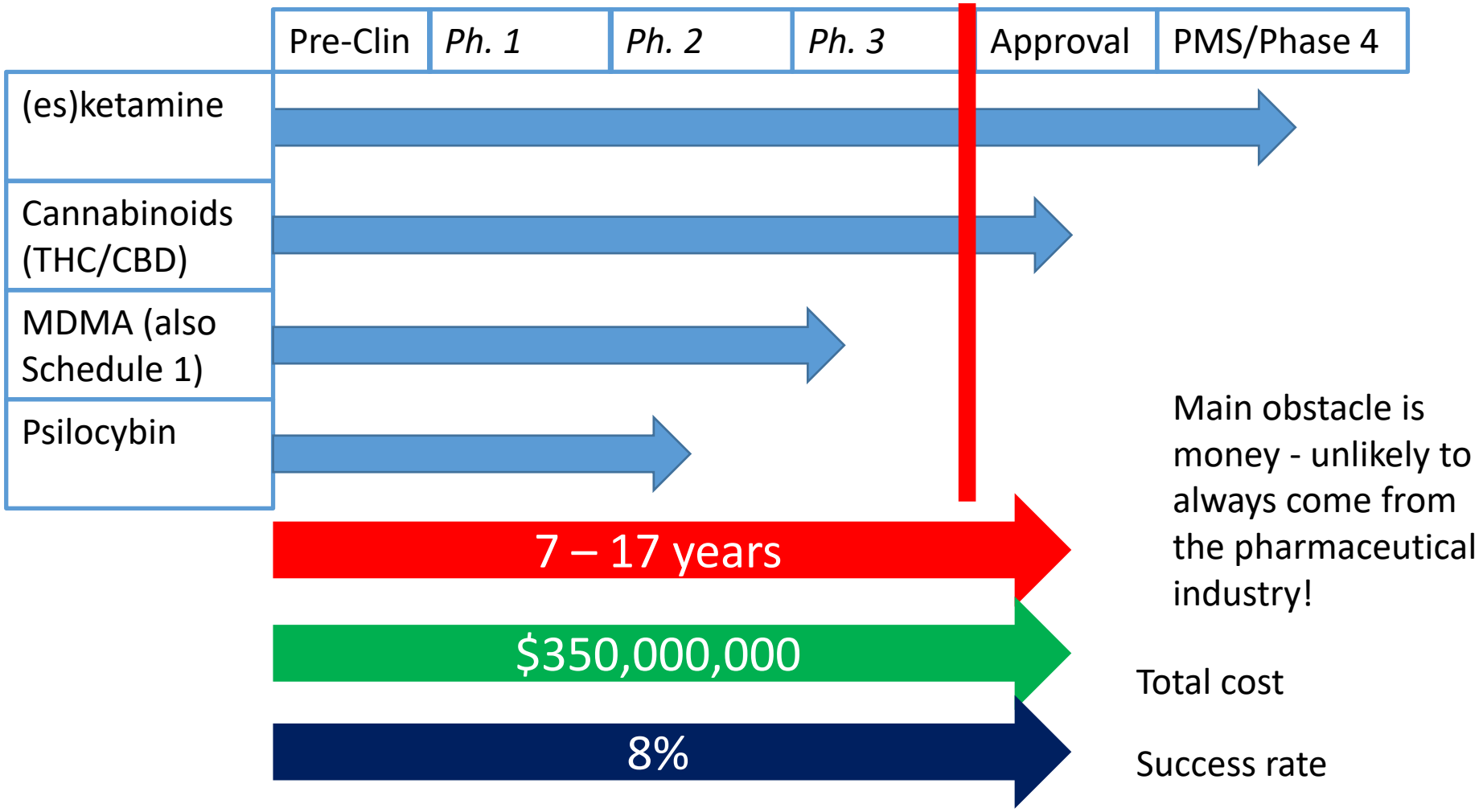


Current treatment strategies for patients with TRD

- Treatment strategies for patients who have not responded to therapy with a first-line AD:
  - **Optimization** of the current therapy to exclude “pseudo-resistance”
  - **Augmentation** with another agent
  - **Combination** therapy with another AD
  - **Dose escalation** of the currently prescribed AD
  - **Switching** to another AD monotherapy
- Although these strategies are common in clinical practice, evidence supporting their efficacy is limited
- New treatments are needed

Dold M, Kasper S. Int J Psychiatry Clin Pract. 2017;21:13-23.
Bauer M. et al. Int J Psychiatry Clin Pract. 2017;21:166-76.

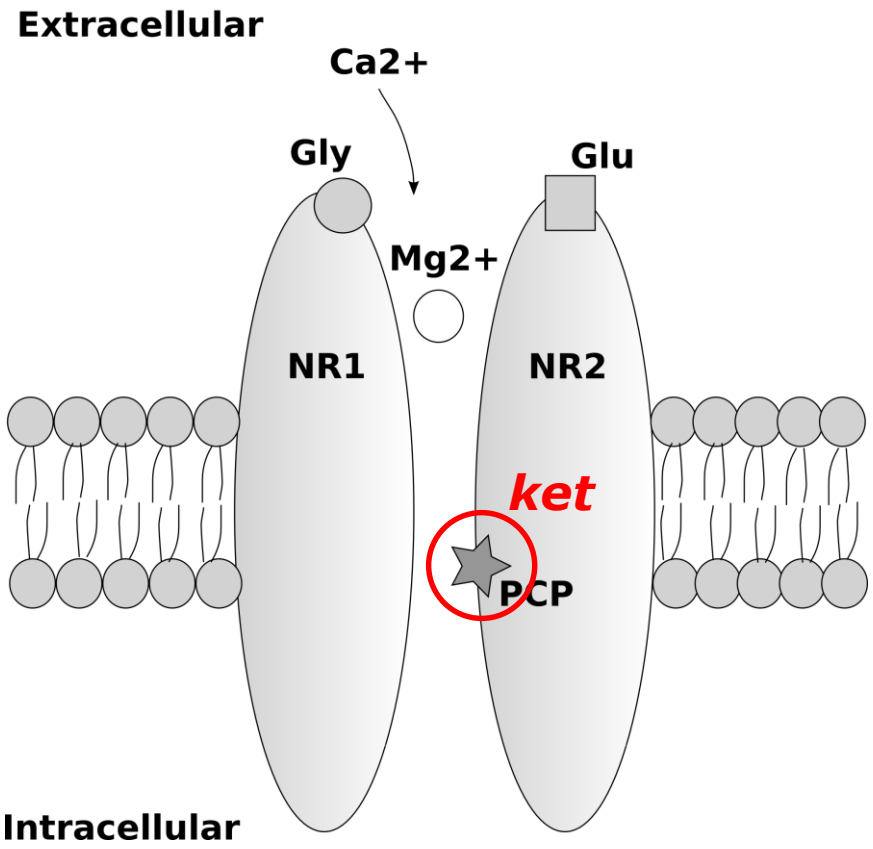
The journey from street to medicine



Main obstacle is money - unlikely to always come from the pharmaceutical industry!

Ketamine

- Uncompetitive NMDA receptor antagonist – binds to intrachannel site of activated NMDA receptor (same site as PCP and MK-801)
- Blocks passage of calcium regardless of depolarisation of the neuron, glutamate and glycine binding.



Effects of ketamine

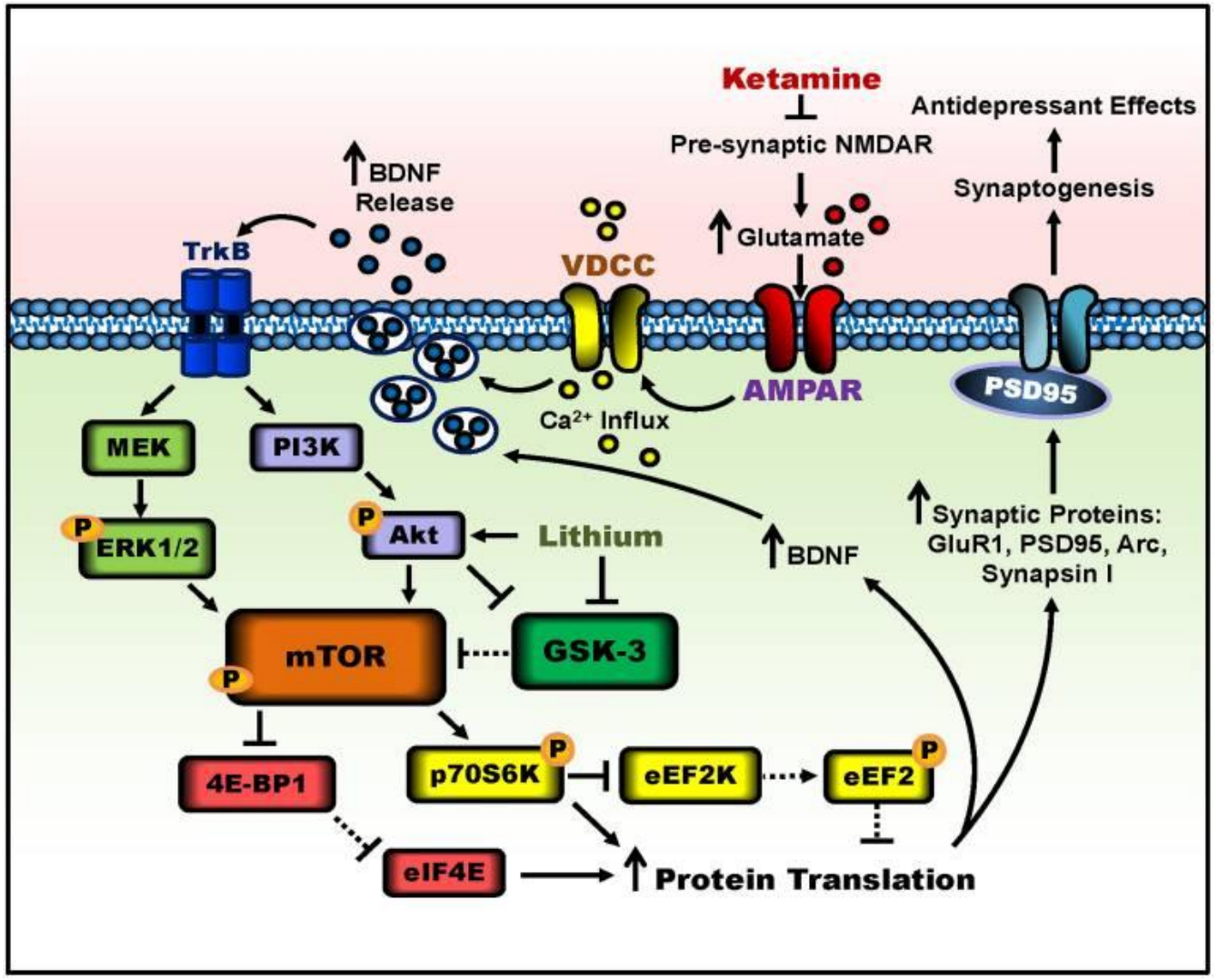
Dissociative anaesthetic:

At sub anaesthetic doses, it induces perceptual changes including perceptual distortions and delusion-like ideas, as well as inducing effects resembling the negative symptoms of schizophrenia.

At the same doses, ketamine has also been shown to have antidepressant properties, in people with treatment resistant depression, and bipolar depression.

What is the underlying mechanism?

Suggested Pathways

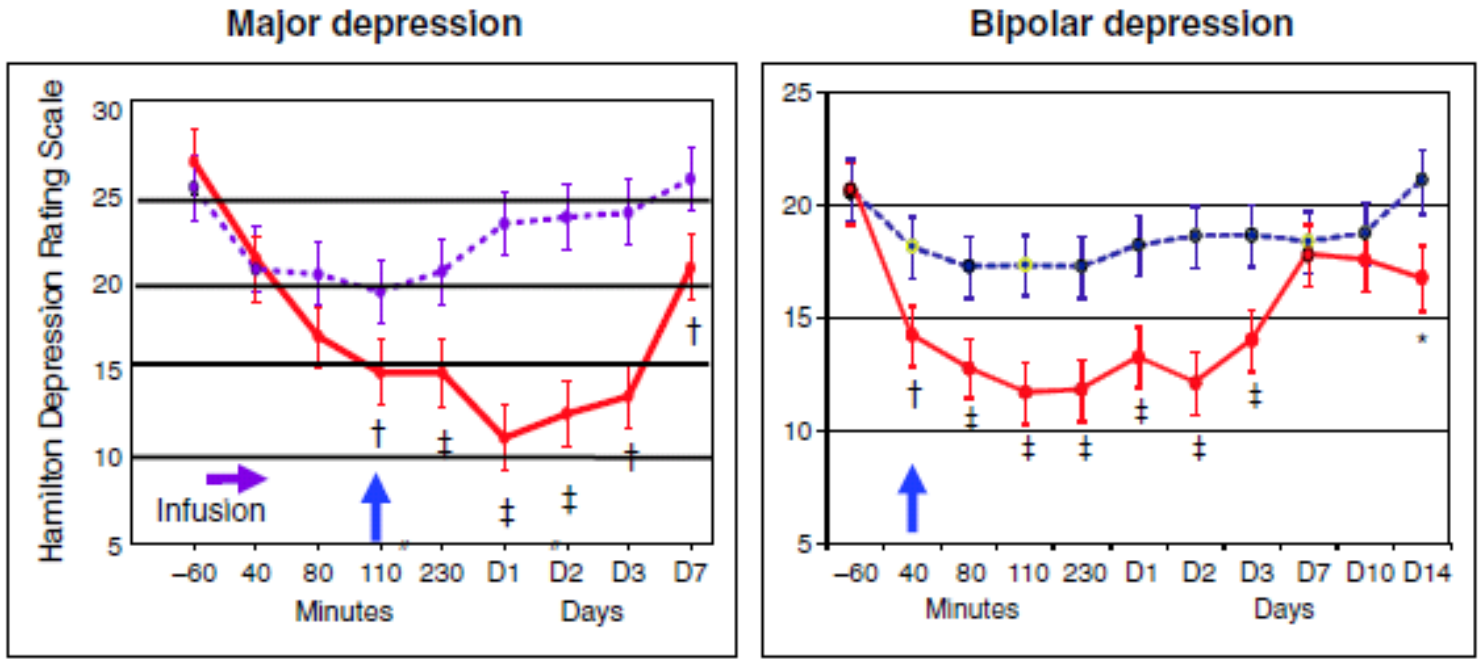


Sheung et al. Fron. Neuroscience Front. Neurosci., 21 July 2015

Ketamine as an Antidepressant

- Initial RCT by Zarate 1996 showed immediate effect of ketamine on treatment resistant depression.
- Antidepressant effect maintained for 7 days.
- Similar effect also seen in patients with bipolar depression (Diazgranados 2010).
- Dose – IV – 0.5mg/Kg over 40 mins. Racemic.
- Recent meta-analyses confirm these effects for unipolar and bipolar depression and show a robust effect size (Kishimoto et al. 2016).

Clearcut effect still apparent at 7 days



‡$P < 0.001$; †$P < 0.01$; and *$P < 0.05$.

Single intravenous infusion over 40 minutes
Treatment resistant depression

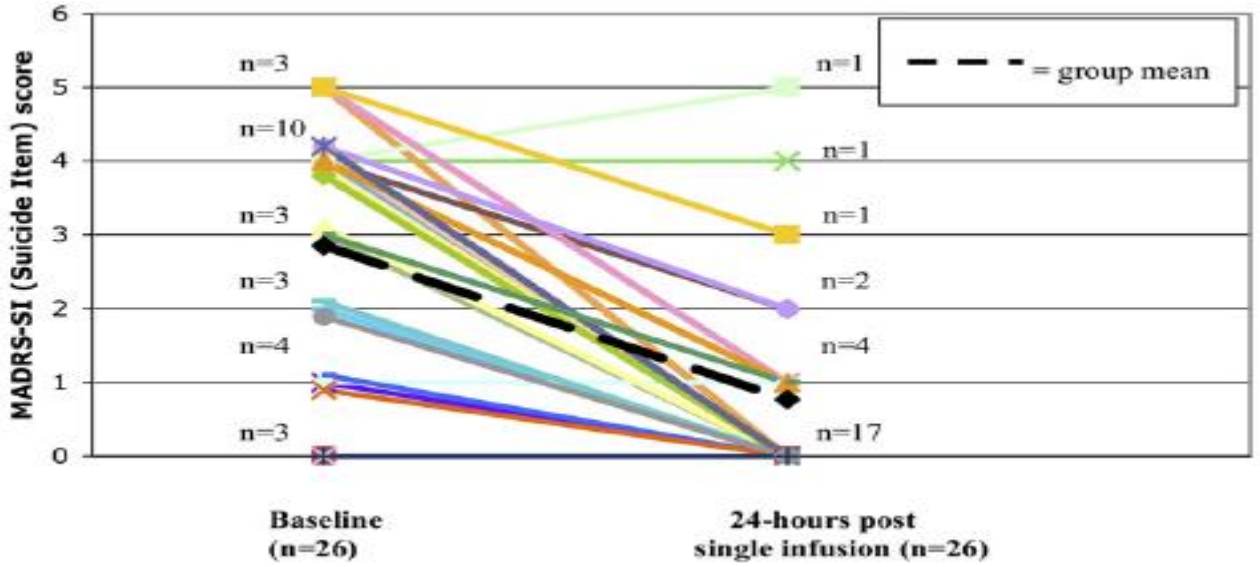
Adapted from Zarate 2006 and Diazgranados 2010

Ketamine and suicidal ideation

26 patients with TRD

Rated on MADRS

Price et al 2009



Acute bolus (0.2mg/Kg)
Larkin 2011

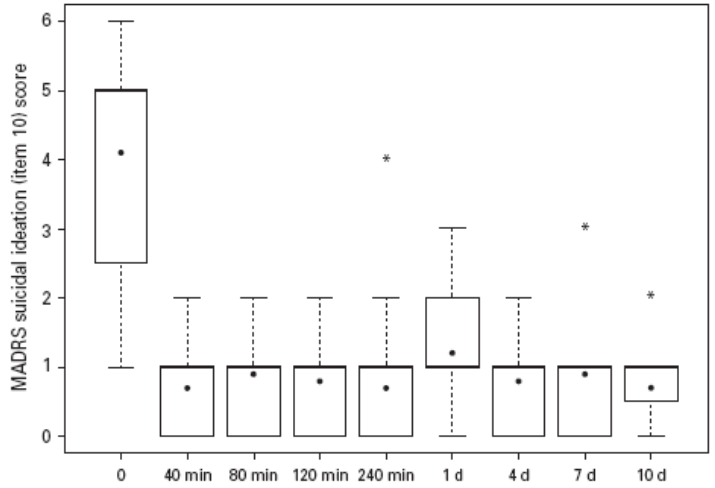


Fig. 3. Course of suicidal ideation, measured by Montgomery–Asberg Depression Rating Scale (MADRS) item 10, over 10 d in 14 patients who received ketamine.

Dissociative effects

- Experienced by almost all
  - Altered perception, sense of time
- Exact form varies
- Half find aversive
- Unrelated to mood response
- Unrelated to environmental noise

Other major side effects

- Psychiatric
  - 2 Suicidal behaviour
    - ‘woke up on bathroom floor surrounded by tablets’
    - Took overdose with intent – but then went to A/E
  - Increased distress about knives
    - Home visit required
    - Single extra dose of neuroleptic
  - Hypomanic relapse
    - Increased haloperidol after 2 weeks
    - Settled with no clear behaviour change
  - Mood instability
    - Similar to prior to infusion

J Psychopharmacol. 2014 Jun;28(6):536-44.

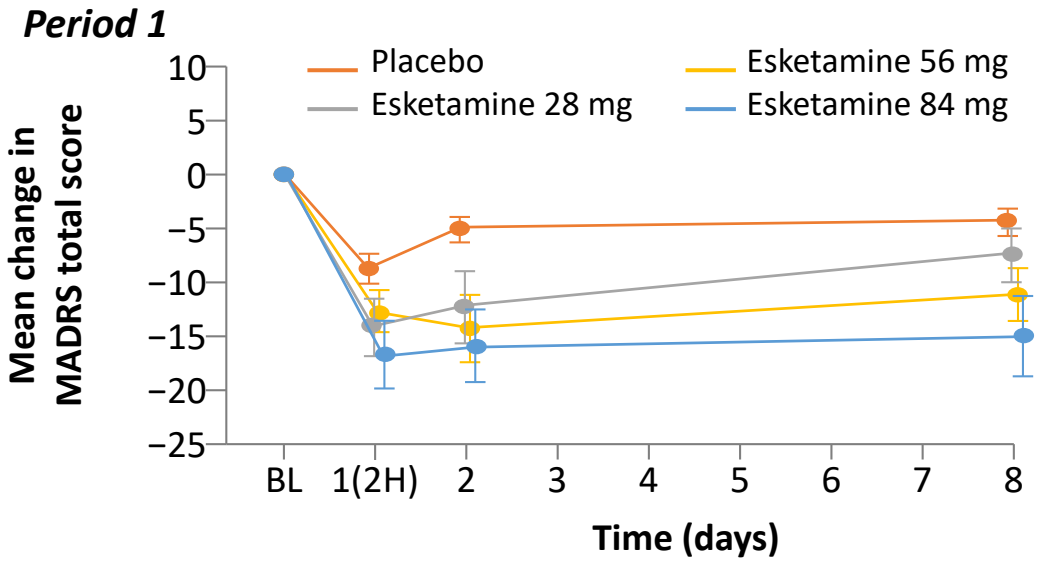
Is ketamine ready for the clinic?

- Now several placebo controlled clinical trials all demonstrating efficacy of ketamine treatment in otherwise treatment resistant depression.
- However, maintenance of response without repeated dosing is not always possible.
- Potential concerns about long-term safety of ketamine infusions.

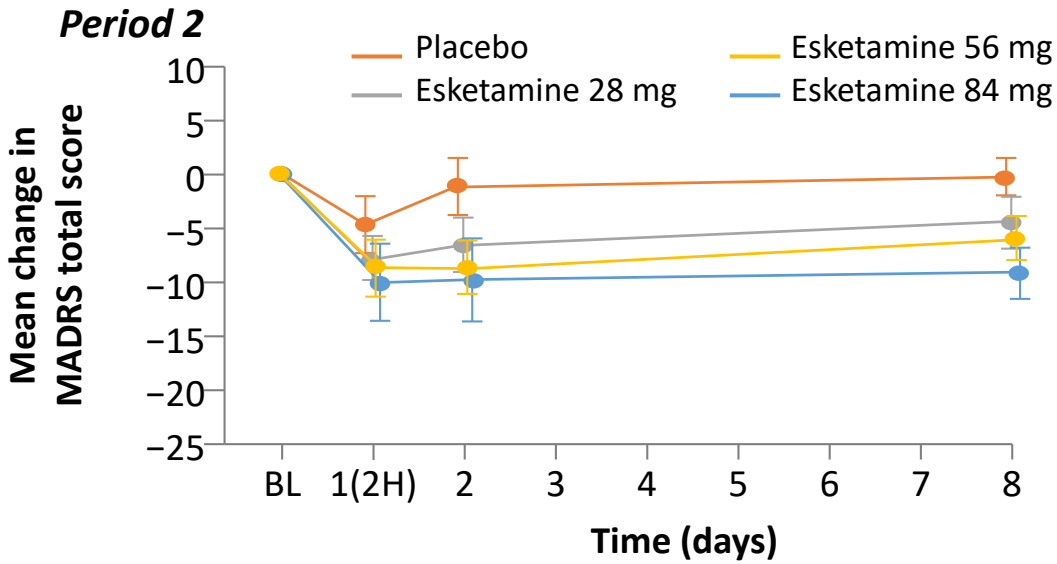
Future treatment options for patients with TRD: pharmacological options

Intranasal esketamine: a novel, NMDA receptor antagonist currently in a phase 3 trial, shows rapid onset of action, with sustained, dose-dependent efficacy in patients with TRD

Mean change in MADRS total score over time in double-blind phase



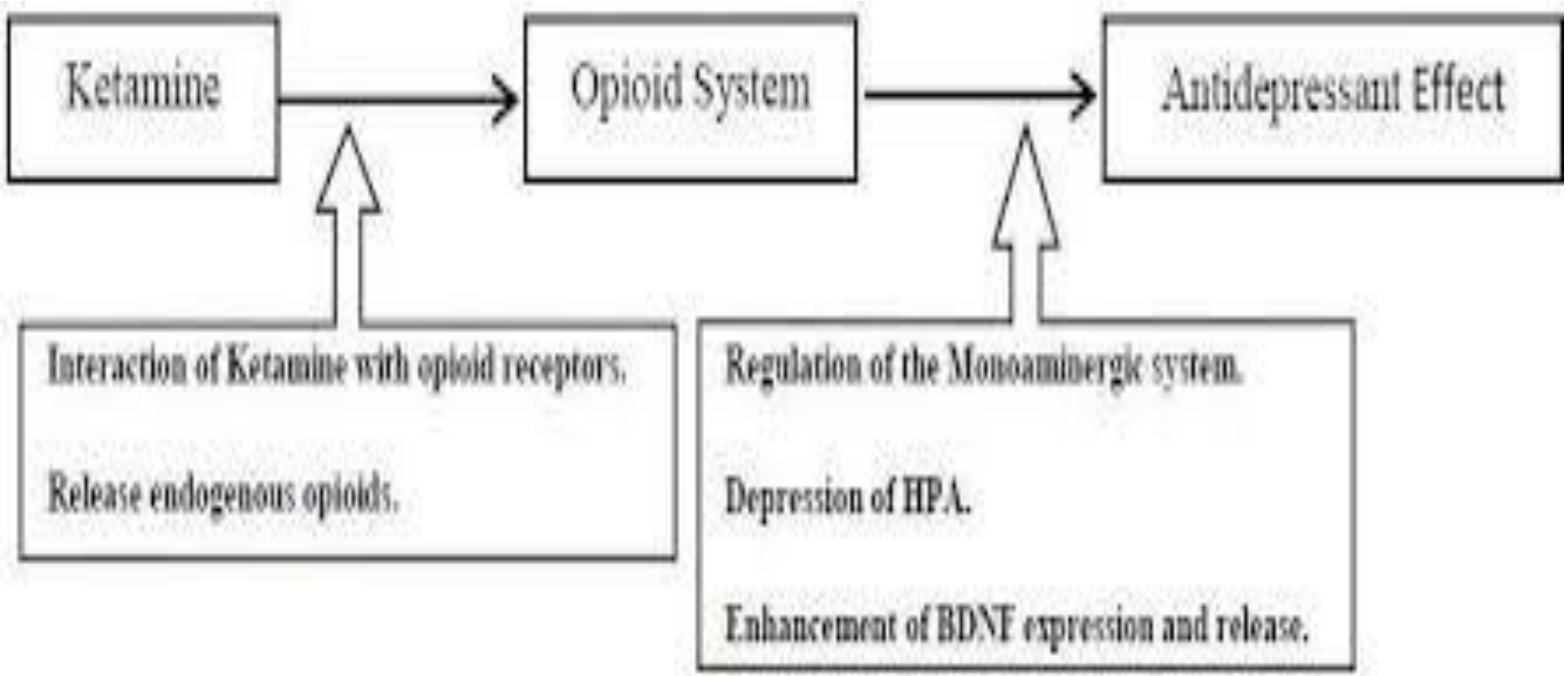
No. of participants				
Placebo	33	33		33
Esketamine 28 mg	11	11		11
Esketamine 56 mg	11	11		11
Esketamine 84 mg	12	12		12



No. of participants				
Placebo	6	6		6
Esketamine 28 mg	8	8		8
Esketamine 56 mg	9	9		9
Esketamine 84 mg	5	5		5

Daly EJ, et al. JAMA Psychiatry. 2018;75:139-48.

Changes shown in period 1 (days 1–8) and 2 (days 8–15);
period 2 consisted of participants who had received placebo in period 1 and had moderate-to-severe symptoms (n = 28).
BL, baseline; MADRS, Montgomery–Åsberg Depression Rating Scale; 2H, 2 hours post-dose.


Ketamine
Opioid System
Antidepressant Effect
Interaction of Ketamine with opioid receptors.
Release endogenous opioids.
Regulation of the Monoaminergic system.
Depression of HPA.
Enhancement of BDNF expression and release.

TRANSLATIONAL THERAPEUTICS

NHS National Institute for Health Research

Cannabidiol

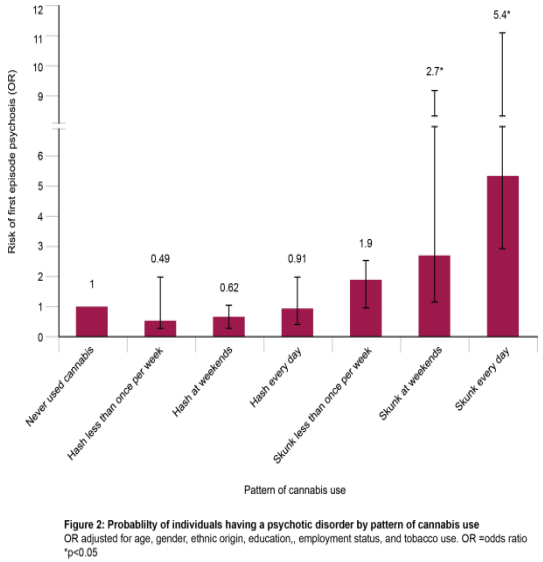
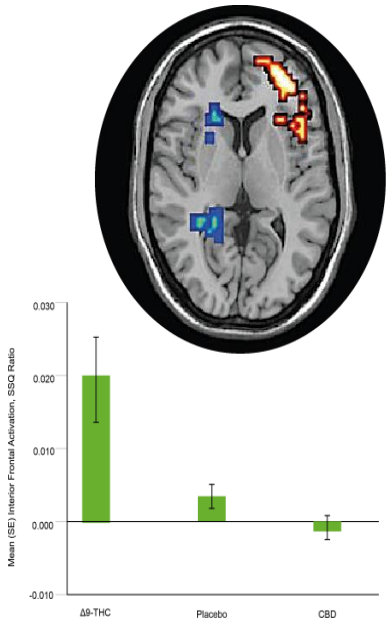
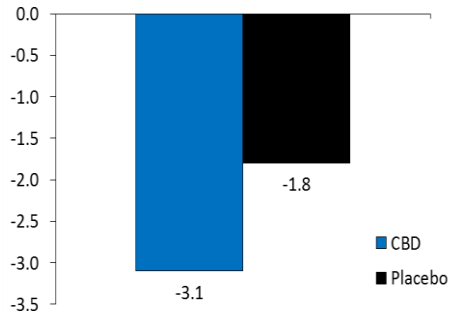


Figure 2: Probablilty of individuals having a psychotic disorder by pattern of cannabis use
OR adjusted for age, gender, ethnic origin, education,, employment status, and tobacco use. OR =odds ratio
*p<0.05





DISCOVERY SCIENCE

- Antipsychotic effects in animal models
- Cannabis less likely to cause psychotic symptoms when it has high CBD content

EXPERIMENTAL MEDICINE

- Blocks Induction of Psychosis by THC
- Opposite effects to THC on brain function

PHASE II TRIAL

- CBD Improves psychotic symptoms in patients with psychosis
- Distinct mechanism of action to conventional antipsychotic medication

HEALTH RESEARCH

Do LSD and Magic Mushrooms Have a Place In Medicine?

Alexandra Sifferlin @acsifferlin | May 26, 2015

Experts say it's hard to do research on the drugs under their current status

Getty Images

LSD and magic mushrooms are illegal for recreational use, but some medical experts see major benefits from the drugs. In a commentary published in the journal *The BMJ* on Tuesday, a London-based psychiatrist argues in favor of legally reclassifying the drugs so that they can more easily be used in medical research.

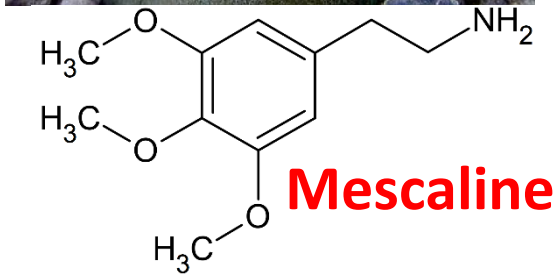
In his paper, James Rucker, a psychiatrist and honorary lecturer at the Institute of Psychiatry, Psychology and Neuroscience at King's College London, argues that psychedelic drugs like LSD are less harmful and addictive than other controlled drugs like cocaine or heroin. But strict restrictions on the drugs make it difficult to conduct medical trials, he says.

What are psychedelics?

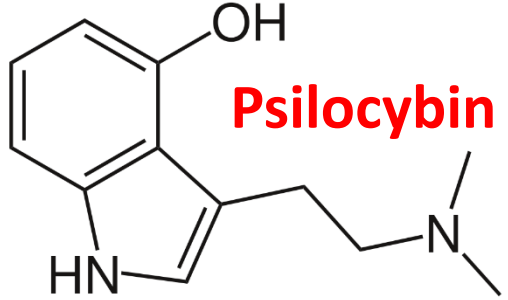
- Psychoactive drugs that produce mental state changes (*without disturbing consciousness)* summarised under 3 basic headings
  - 1. Perceptual
    - Misperceptions, illusions, eyes-closed hallucinations, synaesthesia
  - 2. Psychic
    - Mood alterations (ranging from panic through paranoia to euphoria), time distortion, disturbances in thought flow, blurring of conceptual and self/world boundaries (ego-dissolution), oneiric states, depersonalization/derealisation
  - 3. Somatic
    - Dizziness, tremor, nausea, blurred vision all reported. Any somatic experience, generally, is possible.
- ‘psychē’ – soul/mind & ‘dēloun’ – to reveal/manifest
  - Psychedelic = mind manifesting / soul revealing
  - Coined by psychiatrist, Humphry Osmond, in a letter he wrote to Aldous Huxley in 1956
    - “To fall in hell, or soar angelic, you need a pinch of psychedelic”
  - Other terms – hallucinogen/psychotomimetic – rarely used

CLASSICAL PSYCHEDELICS

Phenethylamine

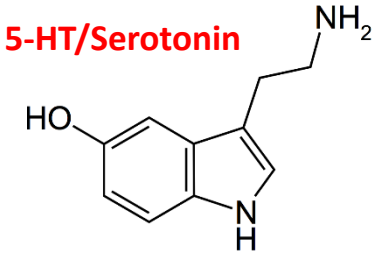


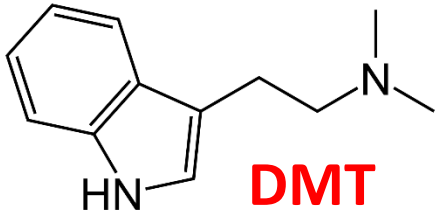
Mescaline



Psilocybin

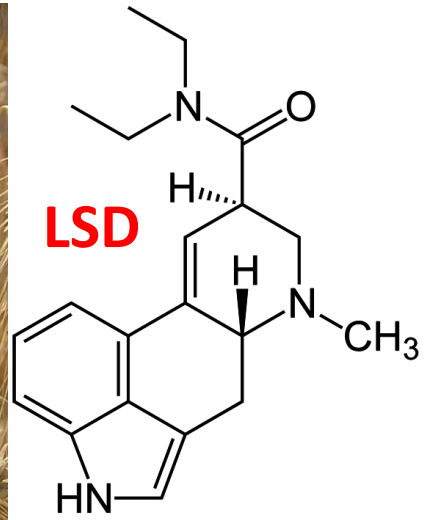
Tryptamines



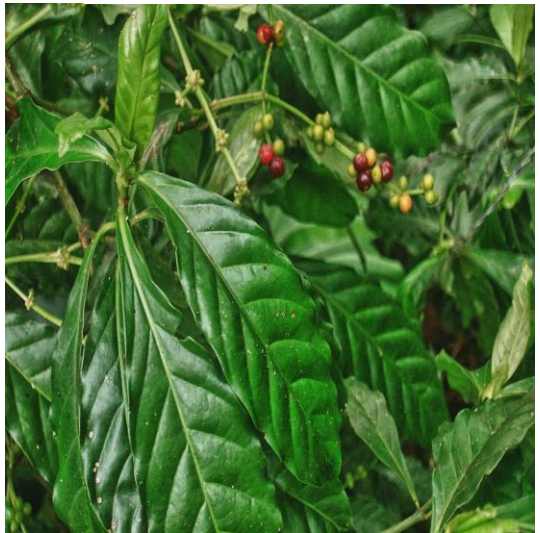


DMT

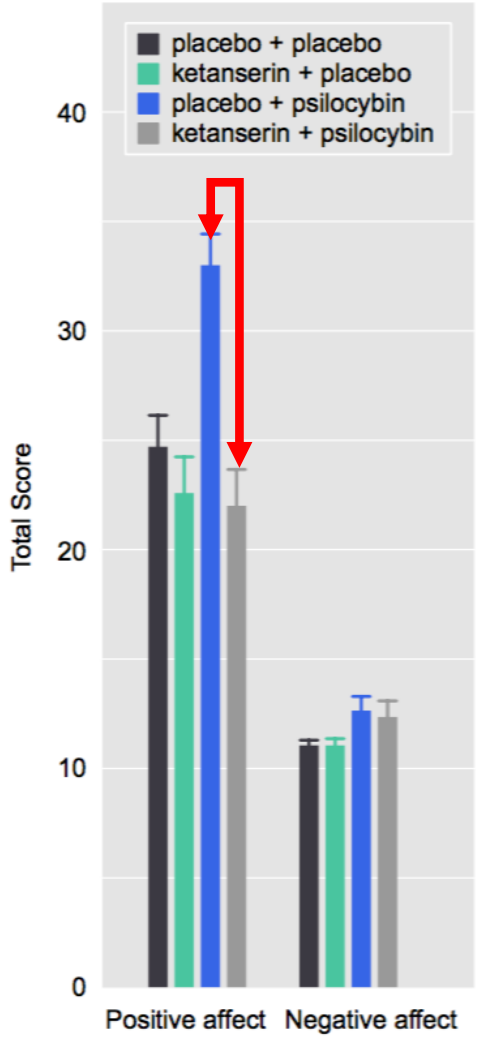
Ergolide

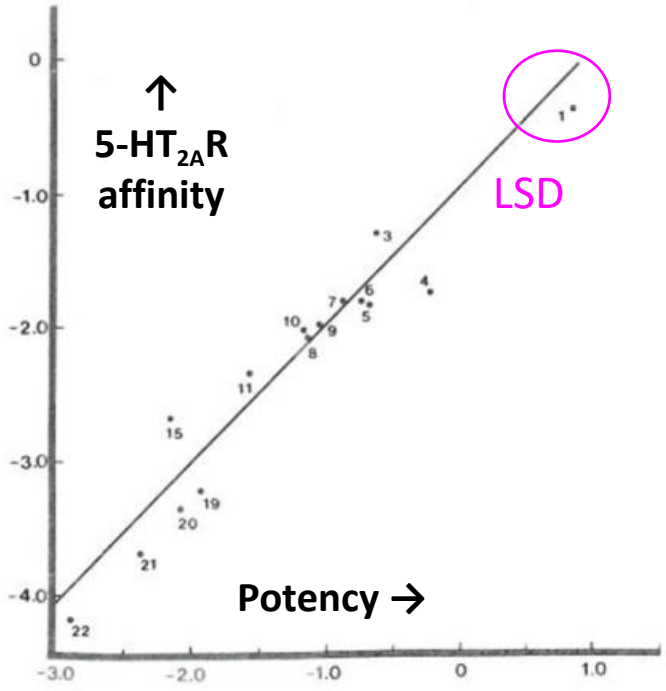


LSD



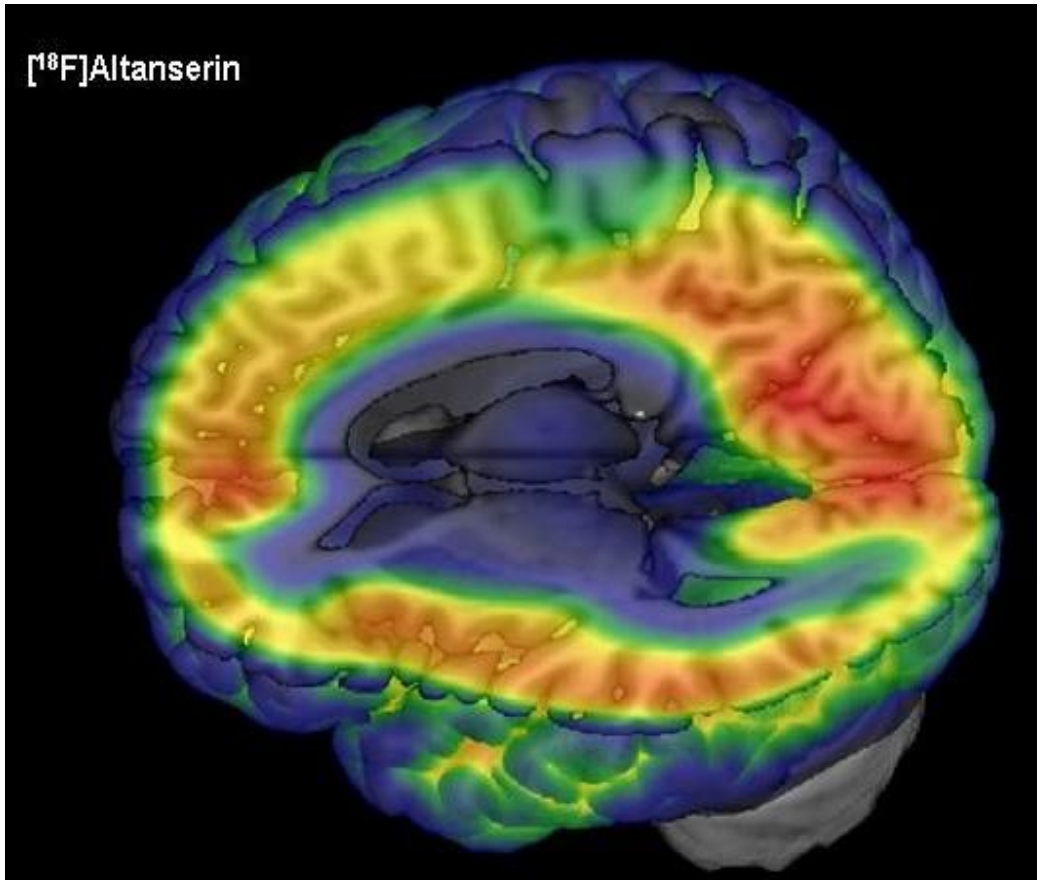
Type 2a Serotonin Receptors (5-HT_{2a}R) Mediate the Psychedelic Effect





Glennon, R. A., Titeler, M., & McKenney, J. D. (1984). Evidence for 5-HT2 involvement in the mechanism of action of hallucinogenic agents. *Life Sciences*, *35*(25), 2505–2511.

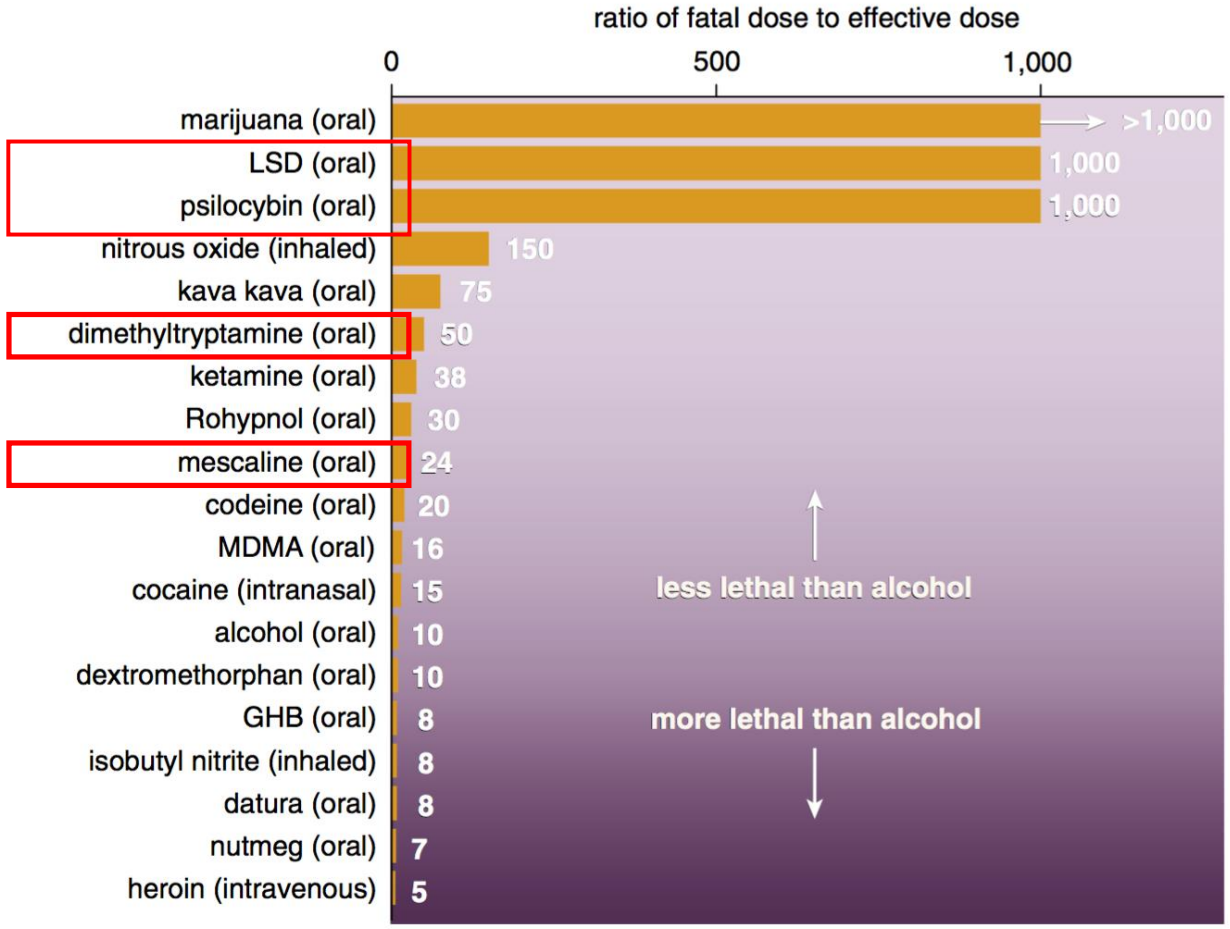
Where is the 5-HT_{2a} Receptor?



Hot colours =
5-HT_{2A} in cortex

Erritzoe, D., Frokjaer, V. G., Holst, K. K., Christoffersen, M., Johansen, S. S., Svarer, C., et al. (2011). In Vivo Imaging of Cerebral Serotonin Transporter and Serotonin2A Receptor Binding in 3,4-Methylenedioxymethamphetamine (MDMA or “Ecstasy”) and Hallucinogen Users. *Archives of General Psychiatry*, *68*(6), 562. http://doi.org/10.1001/archgenpsychiatry.2011.56

Physiological Harm – Toxic Ratios



Gable, R. S. (2004). Comparison of acute lethal toxicity of commonly abused psychoactive substances. *Addiction*, *99*(6), 686–696. http://doi.org/10.1111/j.1360-0443.2004.00744.x
Gable, R. (2006). The Toxicity of Recreational Drugs. *American Scientist*, *94*(3), 206. http://doi.org/10.1511/2006.3.206

Review

Psychedelics in the treatment of unipolar mood disorders: a systematic review

James JH Rucker[1,2*], Luke A Jelen[1,3*], Sarah Flynn[4], Kyle D Frowde[4] and Allan H Young[1,3]

Journal of Psychopharmacology
1–10

DOI: 10.1177/0269881116679368
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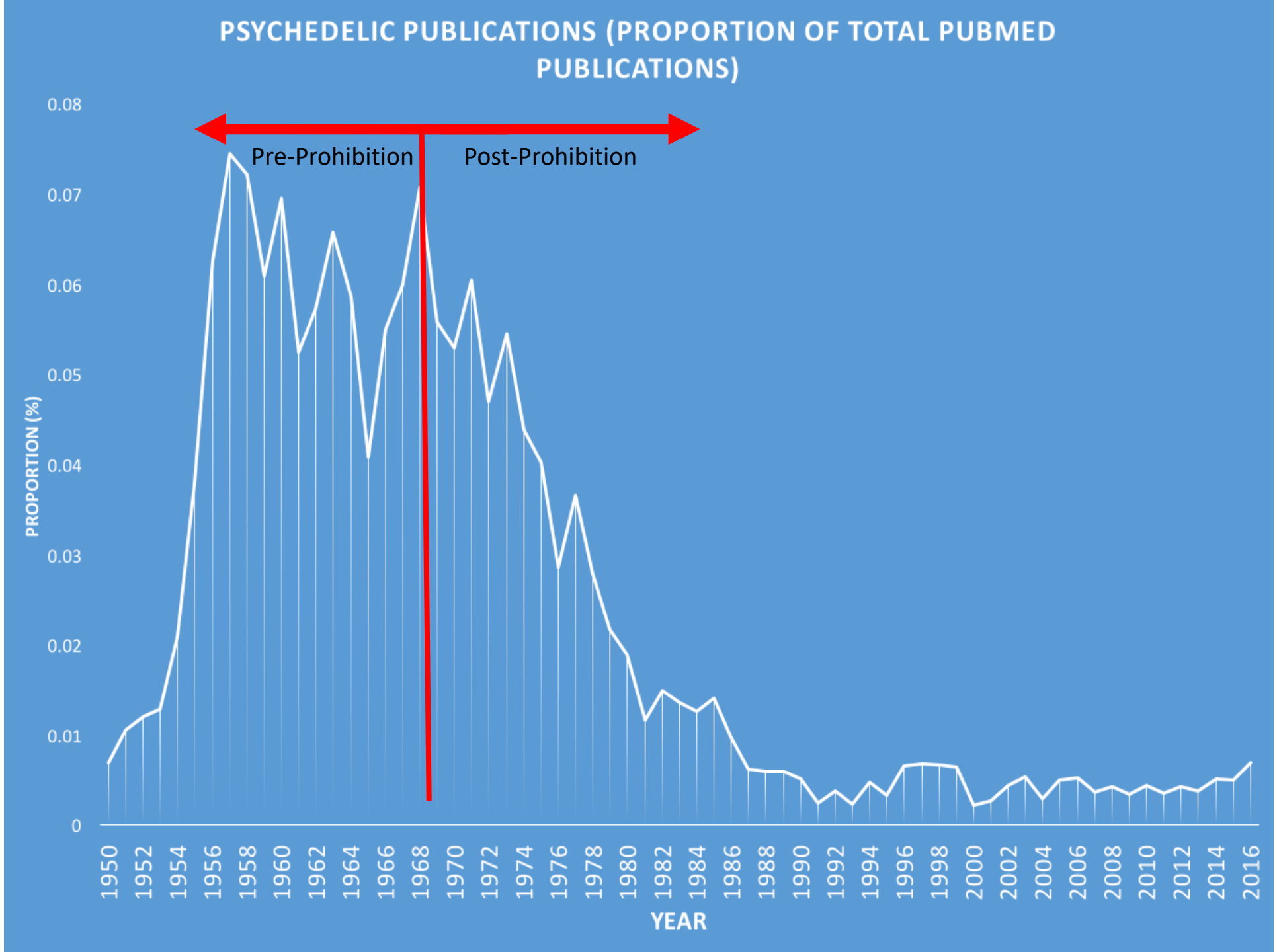
Abstract

Unipolar mood disorders, including major depressive disorder and persistent depressive disorder (dysthymia), confer high rates of disability and mortality and a very high socioeconomic burden. Current treatment is suboptimal in most cases and there is little of note in the pharmaceutical development pipeline. The psychedelic drugs, including lysergic acid diethylamide and psilocybin, were used extensively in the treatment of mood disorders, and other psychiatric conditions, before their prohibition in the late 1960s. They are relatively safe when used in medically controlled environments, with no reported risk of dependence. Here, we present a systematic review of published clinical treatment studies using psychedelics in patients with broadly defined UMD, and consider their place in psychiatry. Whilst all of the included studies have methodological shortcomings, of 423 individuals in 19 studies, 335 (79.2%) showed clinician-judged improvement after treatment with psychedelics. A recently completed pilot study in the UK favours the use of psilocybin with psychological support in treatment resistant depressive disorder. The evidence overall strongly suggests that psychedelics should be re-examined in modern clinical trials for their use in unipolar mood disorders and other non-psychotic mental health conditions.

Keywords

Depression, dysthymia, psychedelics, psilocybin, LSD


PSYCHEDELIC PUBLICATIONS (PROPORTION OF TOTAL PUBMED PUBLICATIONS)
Pre-Prohibition
Post-Prohibition
PROPORTION (%)
0.08
0.07
0.06
0.05
0.04
0.03
0.02
0.01
0
1950
1952
1954
1956
1958
1960
1962
1964
1966
1968
1970
1972
1974
1976
1978
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1982
1984
1986
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2002
2004
2006
2008
2010
2012
2014
2016
YEAR

PsiloDep Trial – Psilocybin in Treatment Resistant Depression

- Open label, feasibility trial of psilocybin with psychological support in resistant depression. PI - David Nutt.

- Patients seen at Imperial College London clinical research facility (the Hammersmith Hospital) between May 2015 and April 2016.

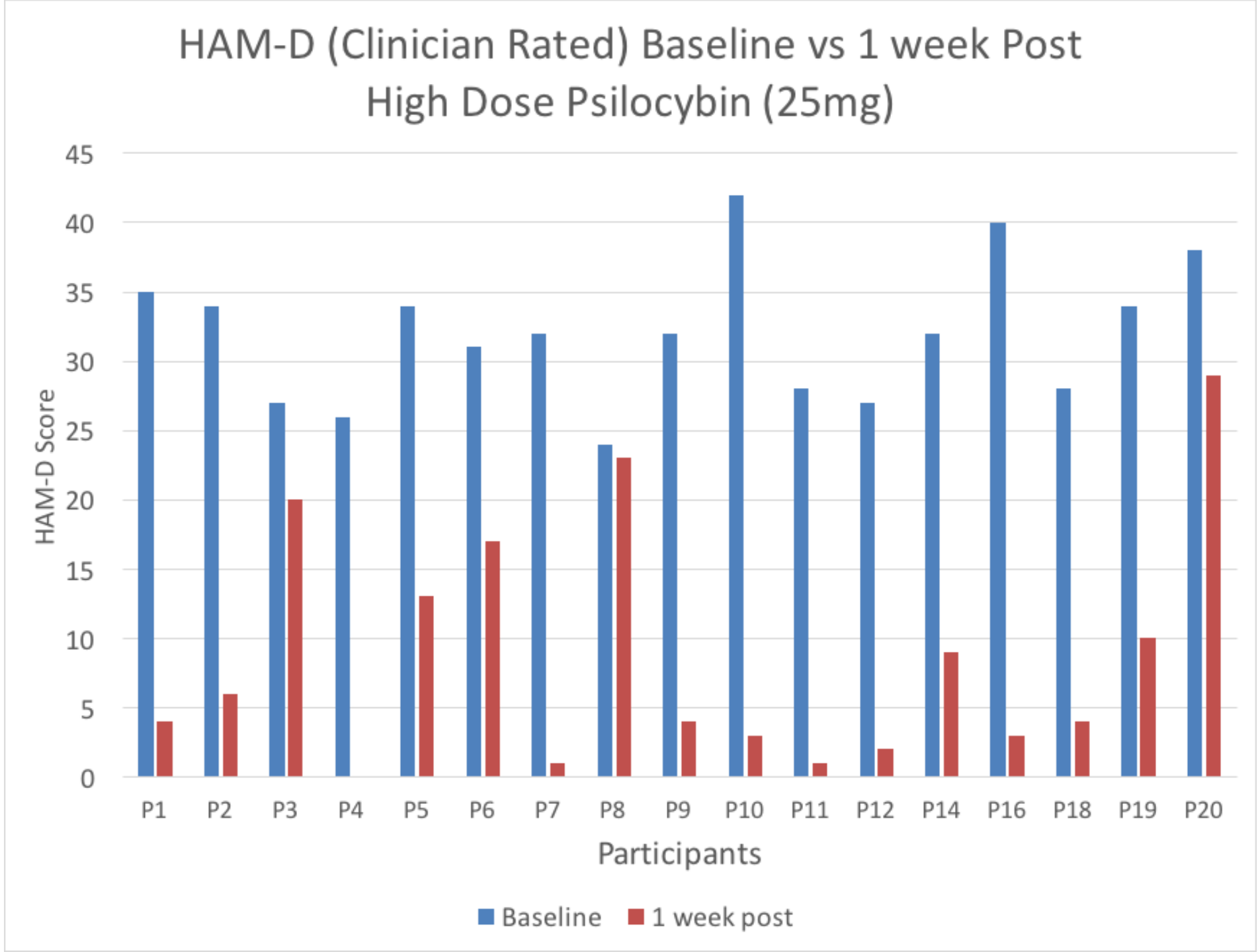
- N=20 (6 female), current moderate or severe depression (HAMD > 17). Failed at least two antidepressant treatments. Long histories of depression.

- Primary Outcome
  - Quick Inventory of Depressive Symptoms (QIDS) – self rated

Study Design/ Participant Journey

- Patients withdrawn from current meds
- Day patient design – no overnight hospital stays
- 2 people (at least one psychiatrist) with patient at all times
- Patients accompanied home
- During drug sessions – sequential measurements of HR and BP every 30mins-1hr
- Rescue medications (never used)
  - Oral lorazepam and risperidone

- No patient received additional antidepressant treatments in the 5 weeks after psilocybin treatment
- 6/20 patients started new courses of antidepressants between 5 weeks and 6 months


HAM-D (Clinician Rated) Baseline vs 1 week Post
High Dose Psilocybin (25mg)
HAM-D Score
45
40
35
30
25
20
15
10
5
0
P1
P2
P3
P4
P5
P6
P7
P8
P9
P10
P11
P12
P14
P16
P18
P19
P20
Participants
Baseline
1 week post

Details of adverse events

- No serious adverse events
- Transient adverse events (expected)
  - 15/20 reported mild anxiety (30-150 mins)
  - 8/20 reported post psilocybin headache (< 1 day)
  - 5/20 reported mild nausea (1-3 hours)
  - 3 instances of mild paranoia responsive to reassurance: subsided after 30-60 minutes
  - 1 prolonged experience (10 hours) - required us to stay with the participant until the early evening.

Trial criticisms…

- Pilot trial – feasibility & safety. Not a test of efficacy
- Unblinded, uncontrolled trial -> inflation of effect size
- How much improvement was attributable to drug vs. psychological support?
- Are they a self selecting group? Tend to believe strongly that psychedelics will help

Future Directions

- Phase 2: Feasibility RCTs
- Phase 3: Multi centre RCTs (Compass Pathways)
- Mechanism studies
- Money unlikely to come from pharma

Other Clinical Psychedelic Studies

Original Paper

Rapid and sustained symptom reduction following psilocybin treatment for anxiety and depression in patients with life-threatening cancer: a randomized controlled trial

Stephen Ross[1,2,3,4,5,6], Anthony Bossis[1,2,4], Jeffrey Guss[1,2,4], Gabrielle Agin-Liebes[10], Tara Malone[1], Barry Cohen[7], Sarah E Mennenga[1], Alexander Belser[8], Krystallia Kalliontzi[2], James Babb[9], Zhe Su[3], Patricia Corby[2] and Brian L Schmidt[2]

Psychopharm

Journal of Psychopharmacology
2016, Vol. 30(12) 1165–1180

DOI: 10.1177/0269881116675512
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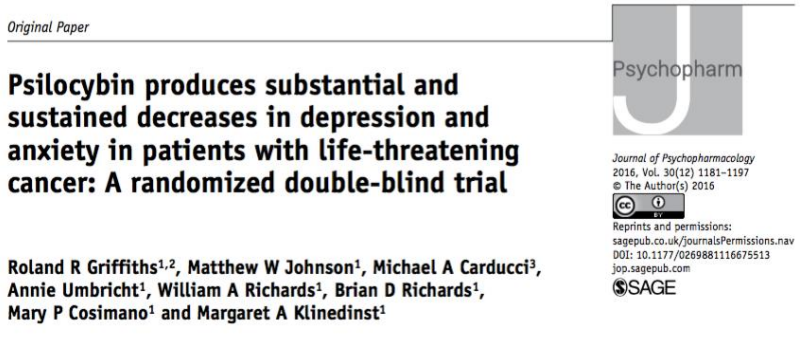

Original Paper

Psilocybin produces substantial and sustained decreases in depression and anxiety in patients with life-threatening cancer: A randomized double-blind trial

Roland R Griffiths[1,2], Matthew W Johnson[1], Michael A Carducci[3], Annie Umbricht[1], William A Richards[1], Brian D Richards[1], Mary P Cosimano[1] and Margaret A Klinedinst[1]

Psychopharm

Journal of Psychopharmacology
2016, Vol. 30(12) 1181–1197

DOI: 10.1177/0269881116675513
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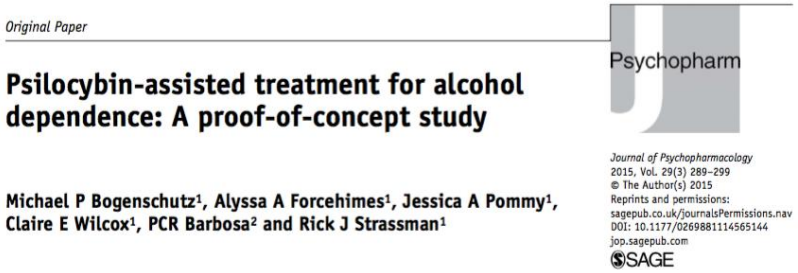

Original Paper

Psilocybin-assisted treatment for alcohol dependence: A proof-of-concept study

Michael P Bogenschutz[1], Alyssa A Forcehimes[1], Jessica A Pommy[1], Claire E Wilcox[1], PCR Barbosa[2] and Rick J Strassman[1]

Psychopharm

Journal of Psychopharmacology
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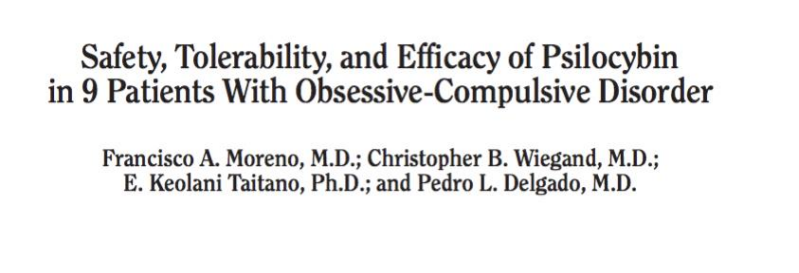

Safety, Tolerability, and Efficacy of Psilocybin in 9 Patients With Obsessive-Compulsive Disorder

Francisco A. Moreno, M.D.; Christopher B. Wiegand, M.D.; E. Keolani Taitano, Ph.D.; and Pedro L. Delgado, M.D.

Original Paper

Pilot study of the 5-HT_{2A}R agonist psilocybin in the treatment of tobacco addiction

Matthew W Johnson[1], Albert Garcia-Romeu[1], Mary P Cosimano[1] and Roland R Griffiths[1,2]

Psychopharm

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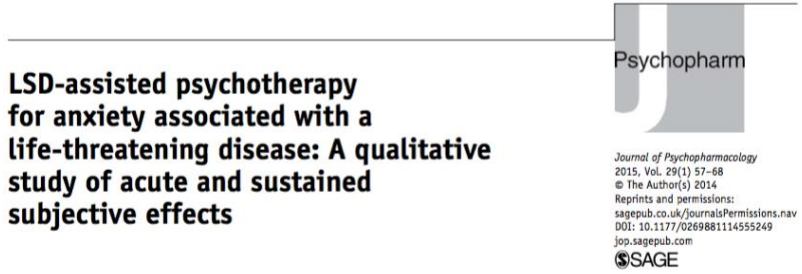

LSD-assisted psychotherapy for anxiety associated with a life-threatening disease: A qualitative study of acute and sustained subjective effects

Peter Gasser[1], Katharina Kirchner[2] and Torsten Passie[3]

Psychopharm

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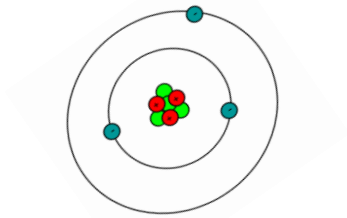
Delivering Psilocybin Therapy

- Delivered in dedicated centres, like day hospitals
  - Prescribing and overseeing psychiatrist
  - Each patient with their own therapist
- Day patient treatments
- Limited psychological support before, during and after.
  - Balance between cost and efficacy.
- Costs will be high relative to standard treatments
  - Limited to patients with treatment resistant illness (and those that can pay for it)
- Treatment probably no more frequently than 3 monthly
  - ?Risk of psychosis with repeated treatments
- Medication/side effect ‘sparing’ effect for most. Cure in the TRD group is rare.
- Whilst the drugs are not patentable, the therapeutic process may be.



Lithium

- Prevents manic recurrence; less effective against depression acutely.
- Effective probably in only a minority of patients in monotherapy.
- Narrow therapeutic index and long-term (renal) effects remain a concern.
- Clear benefits in Unipolar Disorder. (see Young AH. Lancet Psychiatry. 2017 Jul;4(7):511-512)
- MOA and time course of effects remain uncertain.
- Lithium probably reduces risk of suicide both in RCTs and possibly environmentally.
- Putative effects on Dementias.

Conclusion

- Many patients with depression do not respond to current therapy (TRD);
- Several treatment strategies for TRD are currently in use: augmentation, combination therapy, dose escalation and switching;
- “Street” drugs (Ketamine, cannabinoids, MDMA and psilocybin are being investigated for therapeutic benefits;
- Studies to date suggest ketamine is an effective antidepressant.
- Evidence suggests that molecular mechanism might occur through AMPA receptor agonism rather than NMDA receptor antagonism.
- Psilocybin RCTs are underway.
- Don’t forget lithium for unipolar depression!