New Research on Psychedelics for Mood Disorders

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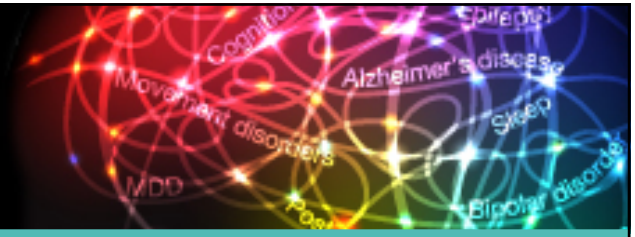
Learning Objective 1

Review the clinical data for the use of psychedelics in the management of mood disorders.

Faculty Name
Disclosures

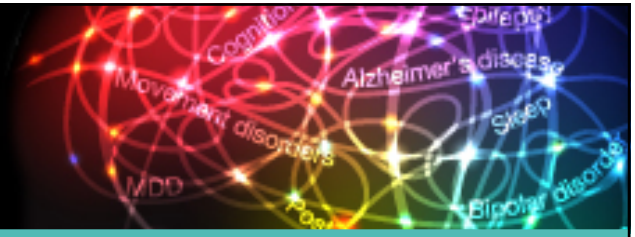
- ***Consultant:*** Mental Health Data Services, Inc. (MHDS); Quartet Health, Inc., Compass Pathways Ltd.
- ***Stock Shareholder or Stock Options:*** Mental Health Data Services, Inc. (MHDS), Quartet Health, Inc.

Agenda



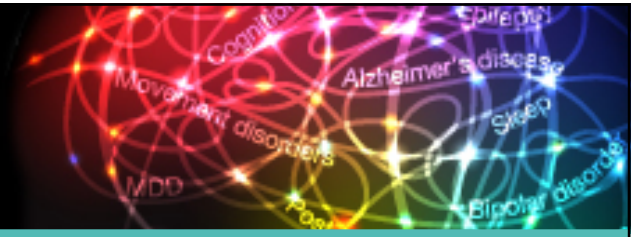
- Context of new research
- Prior issues and use
- Areas of Investigation
- Focus on psilocybin
- Cautionary Notes

Context of New Research



- Limits of current treatments for many common psychiatric disorders and reduced drug discovery by pharmaceutical houses
- Anxiety, alcoholism, depression, and PTSD
- Wave of interest by new generation of researchers and in entrepreneurial circles

Context of New Research



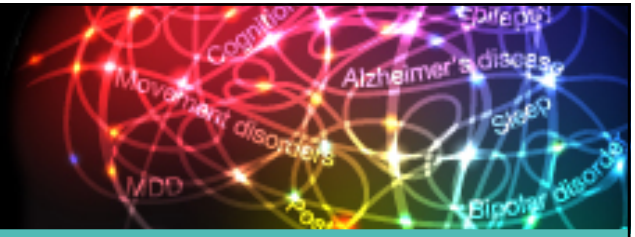
- A variety of agents have been studied often requiring complex approval processes due to restrictions
- Among these are LSD, MDMA, Ayahusca and Psilocybin
- Most studied for clinical purposed Psilocybin – Mood and anxiety disorders, MDMA - PTSD
- Imaging studies

MDMA: 3,4-methylenedioxy-methamphetamine; street name: Ecstasy/Molly

Prior Issues and Use

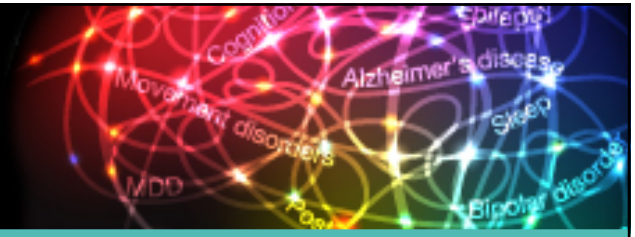
- Complex past history
- Use of many agents by tribes in different cultures
- Often used as part of established religious rituals
- Widespread non clinical use

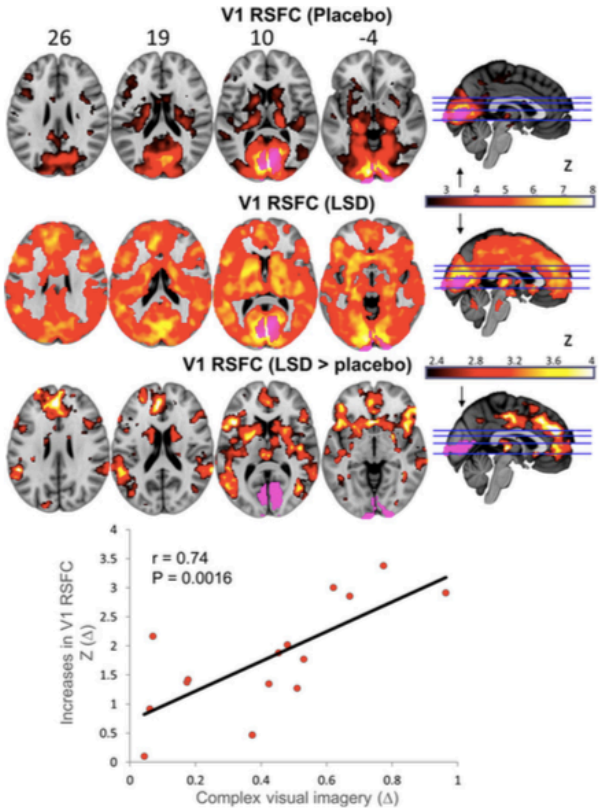
LSD and Psilocybin



- Both powerful 5HT2A agonists
- Evidence of change in cerebral blood flow and functional connectivity

LSD Neuroimaging

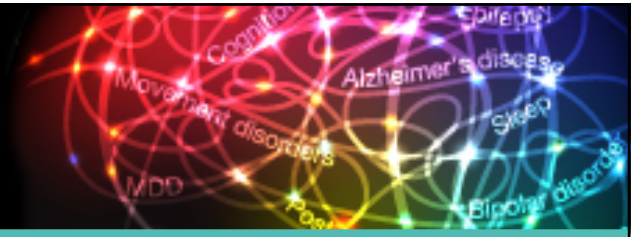




Significant between condition differences (orange = increases) in RSFC between the V1 seed region (purple) and the rest of the brain. (n = 15)

Carhart-Harris RL, et al. *Proc Natl Acad Sci U S A*. 2016;113(17):4853-4858.

LSD Neuroimaging



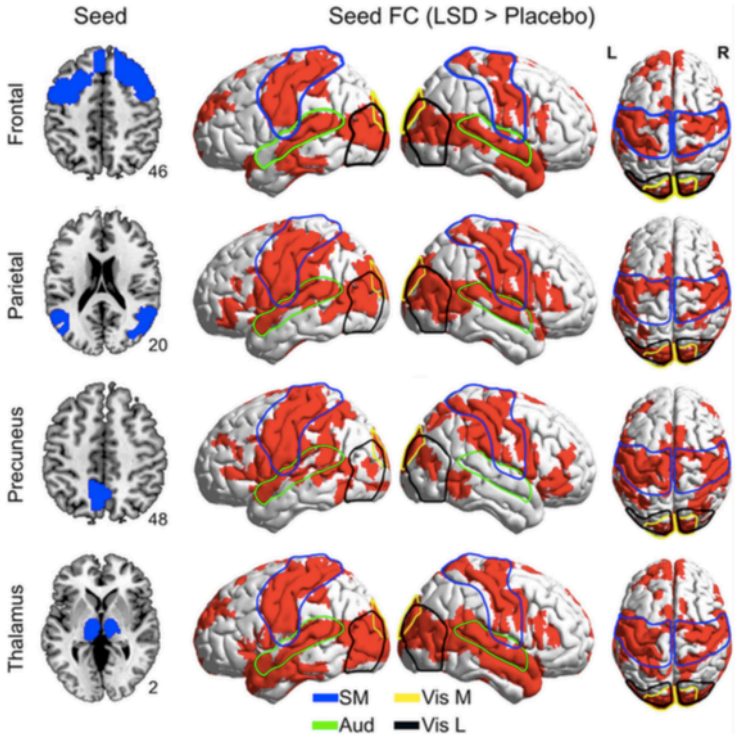


Figure 3. LSD Increases Between-System Functional Connectivity

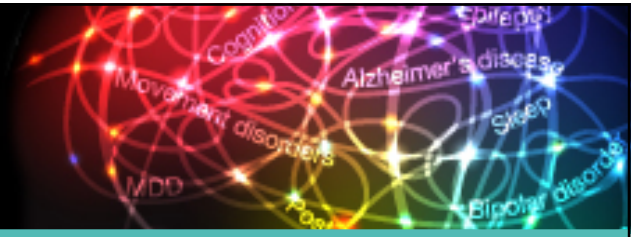
Results of seed correlation analyses based on four ROIs (leftmost column) defined from the map of significant FCD increases (Figure 1C). In the three columns at right, regions in red indicate significantly higher connectivity ($p < 0.05$, two-tailed t test, FDR-controlled for multiple comparisons) with the seed (leftmost column, in blue) under LSD relative to the placebo. A permutation test revealed that only four RSNs present a significant ($p < 0.05$, Bonferroni-corrected for multiple comparisons) overlap with the functional connectivity increases under LSD: the sensorimotor (SM), auditory (Aud), visual medial (Vis M), and visual lateral (Vis L) RSNs. The contour of these RSNs is jointly rendered with the maps of functional connectivity changes. See also Figures S1 and S3.

DISCUSSION

Taken together, the present results indicate that LSD enhances global and between-module communication while diminishing the integrity of individual modules, and that this effect is mediated by the brain's key integration centers such as those that are rich in 5-HT_{2A} receptors. These results invite comparisons with those of our previous functional im-

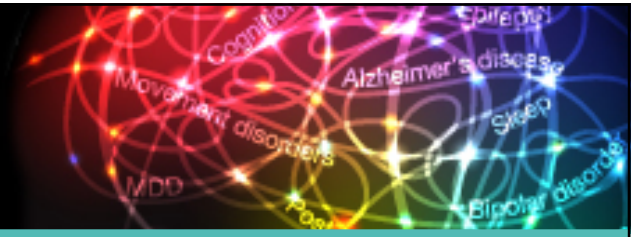
Tagliazucchi E, et al. *Curr Biol.* 2016;26(8):1043-1050.

Psilocybin



- Clinical studies
- Mood and anxiety studies in end of life care
- Treatment resistant depression

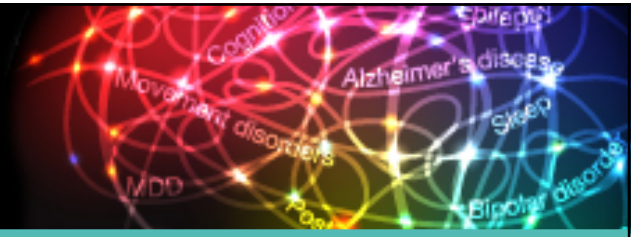
Psilocybin End of Life Care



- Ross et al. studied 29 cancer patients using a 2 session, double-blind, crossover (7 weeks after administration of dose 1) design employing psilocybin first then niacin second, or niacin first and psilocybin second
- Both groups had extensive orientation to the trial and psychotherapy with supportive, psychodynamic, and existential elements

Ross S, et al. *J Psychopharmacol.* 2016;30(12):1165-1180.

Psilocybin End of Life Care



- Psilocybin produced immediate and ongoing anxiolytic and antidepressant response
  - 83% in the psilocybin-first group (vs. 14% in the niacin-first group) meeting criteria for antidepressant response seven weeks after dose 1.
- Pre-crossover results were significant post initial drug administration, although Beck Depression Index between groups was significant at the $p < .05$ level, 1 day prior to initial drug administration but not at baseline.
- At follow-up at 6.5 months (after both groups received psilocybin), antidepressant or anxiolytic response rates were in the 60–80% range depending upon measure
- Subjects' mystical or spiritual experiences highly correlated with clinical response and mediated four out of six primary outcome measures

Ross S, et al. *J Psychopharmacol.* 2016;30(12):1165-1180.

Psilocybin End of Life Care

- 51 cancer patients using a 2 session, double-blind, crossover (5 weeks after administration of dose 1) design employing high-dose psilocybin 1st, then very low-dose (PBO-like) psilocybin second, or very low-dose (PBO-like) psilocybin first and high-dose psilocybin second
- Use of low-dose psilocybin as its own control, instructional language to subjects that aimed to minimize the PBO response, and extensive supportive meetings with study personnel (but not formalized psychotherapy) were distinctive element of the study design

Griffiths RR, et al. *J Psychopharmacol*. 2016:30(12):1181-1197.

Psilocybin End of Life Care

- High-dose psilocybin produced large decreases in clinician- and self-rated measures of depressed mood and anxiety.
  - 5 weeks after session 1, 92% in the high-dose psilocybin-first group (vs. 32% in the low dose-first group) showed clinically significant response and 60% vs. 16% symptom remission
- At 6 mon follow-up (after both groups received high-dose psilocybin), changes were sustained, with ~80% continuing to show clinically significant decreases in depressed mood and anxiety
- Subjects' mystical or spiritual experiences were highly correlated with clinical response and mediated seven of the primary outcome measures

Griffiths RR, et al. *J Psychopharmacol*. 2016:30(12):1181-1197.

Psilocybin Treatment Resistant Depression Proof of Concept Trial

- The inclusion criteria were major depression of a moderate to severe degree (17+ on the 21-item Hamilton Depression Rating scale [HAM-D]), and no improvement despite 2 adequate courses of antidepressant treatment of different pharmacological classes lasting at least 6 weeks within the current depressive episode.
- Subjects received two oral doses of psilocybin (10 mg and 25 mg, 7 days apart) in a supportive setting

Carhart-Harris RL, et al. *Lancet Psychiatry*. 2016;3(7):619-627.

Psilocybin Treatment Resistant Depression Proof of Concept Trial

- The adverse reactions we noted were transient anxiety during drug onset (all patients), transient confusion or thought disorder (nine patients), mild and transient nausea (four patients), and transient headache (four patients)
- Relative to baseline, depressive symptoms were markedly reduced 1 week (mean QIDS difference –11·8, 95% CI –9·15 to –14·35, p = .002, Hedges' g = 3·1) and 3 months (–9·2, 95% CI –5·69 to –12·71, p = .003, Hedges' g = 2) after high-dose treatment
- Marked and sustained improvements in anxiety and anhedonia were also noted

Carhart-Harris RL, et al. *Lancet Psychiatry*. 2016;3(7):619-627.

Psilocybin Treatment Resistant Depression Proof of Concept Trial

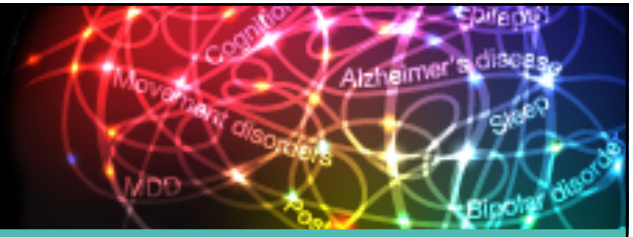
	QIDS						BDI			STAI-T			SHAPS			HAM-D		MADRS		GAF	
	Base-line	1 week	2 weeks	3 weeks	5 weeks	3 months	Base-line	1 week	3 months	Base-line	1 week	3 months	Base-line	1 week	3 months	Base-line	1 week	Base-line	1 week	Base-line	1 week
Mean (SD)	19·2 (2·0)	7·4 (4·9)	6·3 (4·6)	6·4 (5·1)	8·2 (5·4)	10·0 (6·0)	33·7 (7·1)	8·7 (8·4)	15·2 (11·0)	70·1 (5·8)	40·6 (14·2)	54·8 (14·5)	7·5 (3·7)	1·4 (2·7)	2·8 (3·7)	21·4 (4·5)	7·4 (6·9)	31·0 (5·0)	9·7 (9·8)	50·3 (9·2)	77·7 (13·0)
Difference versus baseline (95% CI)	..	−11·8 (−9·15 to −14·35)	−12·9 (−10·64 to −15·16)	−12·8 (−9·9 to −15·6)	−11·0 (−7·7 to −14·2)	−9·2 (−5·69 to −12·71)	..	−25·0 (−20·1 to −29·9)	−18·5 (−11·8 to −25·2)	..	−29·5 (−22·03 to −36·97)	−15·3 (−7·77 to −22·83)	..	−6·1 (−4·46 to −7·74)	−4·7 (−3·29 to −6·11)	..	−14·0 (−9·6 to −18·4)	..	−23·3 (−17·1 to −29·5)	..	27·3 (18·0 to 36·6)
Z	..	−3·1	−3·1	−3·06	−2·9	−3·0	..	−3·1	−3·1	..	−3·1	−2·9	..	−3·1	−3·1	..	−3·0	..	−3·1	..	3
Hedges' g*	..	3·1	3·2	3·2	2·7	2·0	..	3·2	2·0	..	2·7	1·4	..	1·9	1·3	..	2·4	..	2·7	..	2·4
p value*	..	0·002	0·002	0·002	0·003	0·003	..	0·002	0·002	..	0·002	0·004	..	0·002	0·002	..	0·003	..	0·002	..	0·003

Follow-up refers to the period starting after the second (high-dose) administration of psilocybin. Clinician-administered ratings (HAM-D, MADRS, and GAF) were completed only at baseline and 1 week after the high-dose session. QIDS=Quick Inventory of Depressive Symptoms. BDI=Beck Depression Inventory. STAI-T=State-Trait Anxiety Inventory. SHAPS=Snaith-Hamilton Pleasure Scale. HAM-D=Hamilton Depression Rating scale. MADRS=Montgomery-Åsberg Depression Rating Scale. GAF=Global Assessment of Functioning. *Compared with baseline.

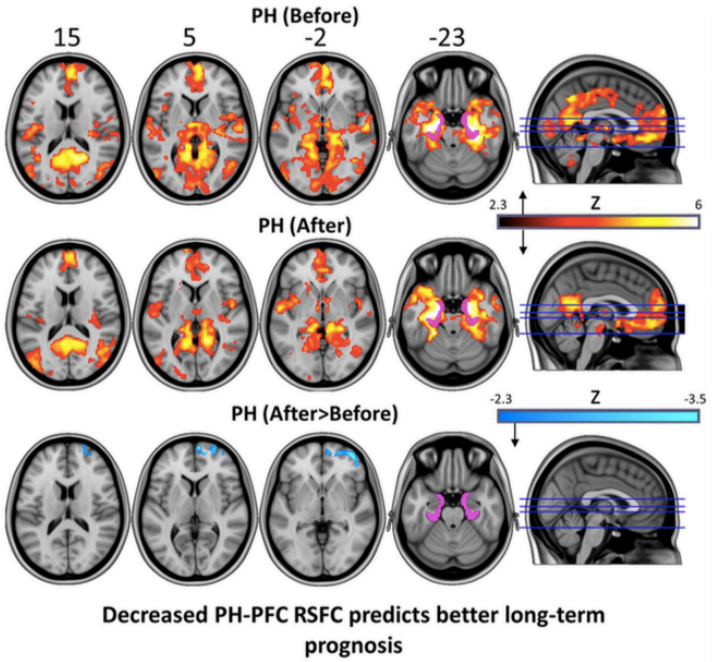
Table 3: **Clinical ratings at baseline and follow-up**

Carhart-Harris RL, et al. *Lancet Psychiatry*. 2016;3(7):619-627.

Psilocybin for Treatment Resistant Depression: Neuroimaging



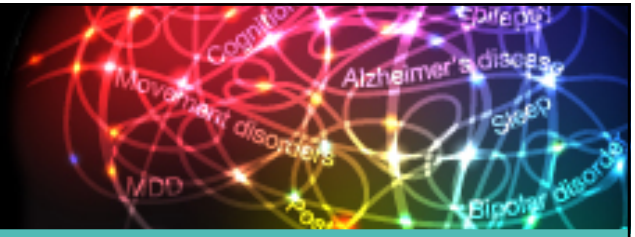
www.nature.com/scientificreports/



Decreased PH-PFC RSFC predicts better long-term prognosis

Carhart-Harris RL, et al. *Sci Rep* 2017;7(1):13187.

Psilocybin for Treatment Resistant Depression: Neuroimaging



- Quality pre and post treatment fMRI data were collected from 16 of 19 patients in open label trial one day after 25 mg dose.
- Decreased depressive symptoms were observed in all 19 patients at 1-week post-treatment and 47% met criteria for response at 5 weeks.
- Decreased parahippocampal-prefrontal cortex RSFC. was predictive of treatment response at 5-weeks
- Results revealed that patients scoring highest on ‘peak’ or ‘mystical’ experience had the greatest decreases in PH RSFC in limbic (e.g. bilateral amygdala) and DMN-related cortical regions (e.g. the PCC).

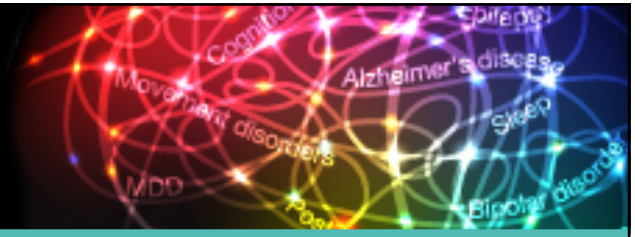
Carhart-Harris RL, et al. *Sci Rep* 2017;7(1):13187.

Cautionary Notes

- The history of psychedelics and their legal status as highly restricted compounds of course make this a more complex issue
- Use of psilocybin and related compounds in spiritual ceremonies has a very long history in many traditional and non-Western cultures
- More recent history of widespread non-clinical use, makes the status of these compounds more complex and suspect

Carhart-Harris RL, et al. *Lancet Psychiatry*. 2016;3(7):619-627.

Cautionary Notes



- Despite extensive evidence of the safety of these compounds in well-selected individuals under careful supervision, as in these studies, their prior history and the general history of expansion of indications for clinical agents, including their clinically questionable use after approval for specific indications, is an important cautionary tale.
- Beyond the clinical utility of these agents in individuals who are facing critical existential issues in end-of-life settings, it is likely that studies will expand into other important clinical populations such as those with treatment-resistant depression, where an initial proof of concept study showed similar responses to those reported in these studies.

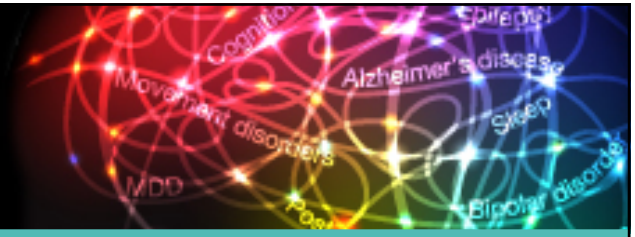
Carhart-Harris RL, et al. *Lancet Psychiatry*. 2016;3(7):619-627.

Cautionary Notes

- These compounds have important value in understanding the neural networks that support a well-delineated sense of self and other, and potentially in antidepressant or anxiolytic mechanisms of action.
- However, neuroimaging studies with psilocybin and other psychedelics agents are in their early stages.
- Many participants rated their psilocybin experience as among the most profound and meaningful of their lives. The benefit of these experiences on mood and anxiety seemingly continued to affect them months later, despite single administration of psilocybin and their serious medical conditions.

Carhart-Harris RL, et al. *Lancet Psychiatry*. 2016;3(7):619-627.

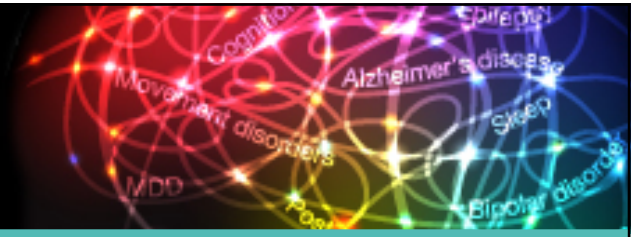
Cautionary Notes



- It is unclear at present to what degree this benefit is due to the power of these experiences, ongoing changes in neural mechanisms, or other causes.
- The experiences of salience, meaningfulness, and healing that accompanied these powerful spiritual experiences and that were found to be mediators of clinical response in both of these care fully performed studies are also important to understand in their own right and are worthy of further study and contemplation.

Carhart-Harris RL, et al. *Lancet Psychiatry*. 2016;3(7):619-627.

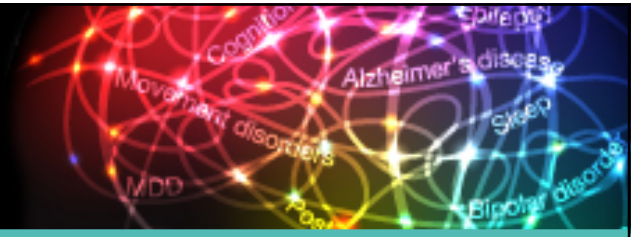
Cautionary Notes



- Given the strength of these findings, more extensive studies to replicate these outcomes are called for, as are studies in more diverse clinical populations
- It is difficult to blind these agents adequately, consideration should be given to including research groups that have had less prior involvement in this area to minimize placebo responsiveness
- The complex history and legal status of psilocybin and related agents suggests additional thought be given as to how to deal with the unique legal, ethical, and regulatory issues surrounding clinical use of these agents

Carhart-Harris RL, et al. *Lancet Psychiatry*. 2016;3(7):619-627.

Call to Action



- While very preliminary clinical data may support the use of psychedelics for the management of end of life mood and anxiety disorders and less so with treatment resistant depression
- Clinicians should proceed with caution, recognizing that more extensive studies are warranted

Questions & Answers

Don’t forget to fill out your evaluations to collect your credit.