Serotonergic psychedelic treatment for obesity and eating disorders: potential expectations and caveats for emerging studies

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There has been a substantial growth in private clinics and registered clinical trials employing serotonergic psychedelics for various psychiatric illnesses, including substance use disorder and major depressive disorder. Classical psychedelics include lysergic acid diethylamide (LSD), mescaline, psilocybin, and dimethyltryptamine (DMT), the latter 3 naturally occurring in some plant, fungal and animal species. Psychedelics are one of the oldest recreational drugs used ritually by ancient cultures, but the discovery in the 1940s of the psychoactive effects of LSD fueled a huge boom in clinical studies of psychedelics. Psychedelic-assisted psychotherapy showed apparent promise in the treatment of disorders including depression, anxiety, anorexia nervosa and alcoholism, and psychedelics were increasingly employed in psychiatry as late as 1970. However, following widespread recreational use and their subsequent classification as a Schedule I drug in 1967, open medicinal use screeched to a halt, and clinical studies of psychedelics were nearly absent until the mid 2000s. The recent resurgence in both animal and human psychedelic research, along with advancements in neuroimaging and pharmacology, have provided key insights into their physiologic action. Tryptamine-based psychedelics, LSD, mescaline, psilocybin and DMT all have agonist activity at serotonin (5-OH-tryptamine; 5-HT) receptors, notably 5-HT_1A, 5-HT_1B and 5-HT_1D. These receptors are densely expressed in the prefrontal cortex (PFC) and mesolimbic dopamine pathways, regions involved in emotion regulation and reward, and it is thought that activation of cortical 5-HT_3A and mesolimbic 5-HT_3C receptors mediate the effects of psychedelics on mood and addiction, respectively. In addition, classical psychedelics other than psilocybin may act as sympathomimetics via direct interactions with trace-amine associated receptors (TAARs), LSD has modest agonist activity at dopamine D2 receptors, and DMT can activate intracellular sigma-1 receptors. Hallucinogenic properties of these serotonergic agents are likely mediated through 5HT_2A receptors within the cortico–striato–thalamo–cortical feedback loop. Interestingly, psychedelics stimulate robust neural plasticity in the PFC, and these effects may be dissociable from their hallucinogenic properties. This likely occurs through brain-derived neurotrophic factor–mediated increases in spine density and synaptogenesis, mammalian target of rapamycin–mediated signalling and increased expression of synaptic proteins and functional synaptic strengthening.

There are various forms of “psycholytic” or “psychedelicy” psychotherapy that use a range of micro- and/or macro-doses of psychedelics across 1 or more treatment sessions, but a common goal of most psychedelic-assisted psychotherapies is to administer high doses to induce a mystical experience or “ego dissolution” in a clinical setting and facilitate subsequent behavioural change. Psychedelic-assisted therapy begins where a rapport is built with session facilitators before the experience (pretraining and baseline), and a relaxing environment is created with comforting music and eyeshades to block visual stimuli during the session. The psychedelic experience is followed by discussion with the facilitators to identify novel thoughts and feelings that arose during the session, termed “integration.” Some trials have used more intensive therapy, such as 11 hours of psychotherapy within 1 month after treatment. Small clinical studies investigating the effectiveness of psilocybin-assisted therapy in individuals with obsessive-compulsive disorder, depressive disorders, cancer anxiety, and alcohol and tobacco dependence have shown positive preliminary results. However, there are many considerations and limitations in psychedelic therapy trials (Box 1).

Two administrations of psilocybin (either with or without additional psychotherapy) appear to have rapid and enduring antidepressant effects, lasting weeks to months after the experience (see Doss and colleagues for a critique on these trials), and these experiences are associated with several changes in functional magnetic resonance imaging (fMRI) of brain regions. Psilocybin attenuates amygdala activity in response to neutral and negative images, and this has been proposed to underlie the associated increase in positive affect.

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**Box 1. Caveats and concerns with psychedelic therapy trials**

1. **Conflicts of interest:** Conflicts can be financial (there has been a growth of psychedelic drug companies testing compounds or paying consultation fees to psychedelic researchers), or they can result from conscious or unconscious bias of the researchers, leading to more subtle questionable research practices (e.g., P-hacking).

2. **Hawthorne or observer effects:** This refers to a condition in which study participants will modify their behaviour in response to their awareness of being observed. Given that participants are observed during the psychedelic experience, individuals may alter their behaviour in a manner that may be consistent with the expectations of the experimenter. Further, the participant’s behaviour can also change because of the interest, attention, or care received as part of the study.

3. **Expectancy:** Psychedelic trials are hard to blind owing to the nature of the psychoactive substance. Trials can employ inactive (placebo with therapy), or active (niacin, modafinil) placebo. However, while active placebo have psychoactive effects, none of these substances induce hallucinogenic effects. If the study participant suspects they are in the experimental group, they may be motivated to report stronger results on the questionnaires or to please the experimenters. Alternatively, if the participant is aware they are in the control group, their responses may reflect disappointment. Furthermore, participants who partake in psychedelic clinical trials are more likely to have experimented with psychedelic drugs previously and are more likely to know the difference between the control and active treatments, threatening the blinding of the trial.

4. **Regression toward the mean:** This is a statistical phenomenon that occurs when cases are selected for follow-up based on abnormally high or low scores at baseline and then in the follow-up the responses are likely to be closer to the mean, appearing as an apparent improvement. It is difficult to distinguish changes that are related to a true treatment effect and those that are related to regression to the mean, leading experimenters to conclude a treatment is effective when individuals may have improved over time without any intervention. Some have suggested multiple “stable” baseline assessments to limit variability and reduce regression to the mean or using alternative statistical designs, such as analysis of covariance modelling.

5. **Open-label designs:** In this type of study, the participant and the experimenter are aware of the specific treatment administered. While this mimics how the treatment might be delivered in a therapeutic, nonresearch setting, there are challenges with factors described above (Hawthorne effect, expectancies, regression to the mean) that can affect the clinical outcome. Furthermore, unblinding may lead to differences in how the psychotherapy component is administered and received once the therapist becomes aware of the treatment assignment. A double-blind randomized controlled trial is the gold standard for identifying treatment-specific effects; however, this is challenging with psychedelic therapy. Some possibilities to mitigate this problem may be to randomize the treatment and control groups to 1 of 4 or 5 different types of psychedelics specific effects; however, this is challenging with psychedelic therapy. It is difficult to distinguish changes that are related to a true treatment effect and those that are related to regression to the mean, leading experimenters to conclude a treatment is effective when individuals may have improved over time without any intervention. Some have suggested multiple “stable” baseline assessments to limit variability and reduce regression to the mean or using alternative statistical designs, such as analysis of covariance modelling.

6. **Harm:** Aside from the harm of increased risk of psychosis, which is rare and can be mitigated through exclusion of family history of psychosis in patient screening, an example of harm from a clinical trial employing psychedelic therapy is with the current Health Canada investigation of the Multidisciplinary Association for Psychedelic Studies employing 3,4-methylenedioxymethamphetamine (MDMA) for posttraumatic stress disorder (PTSD). While effect sizes in this highly touted trial were 0.91 of a standard deviation difference in score on a PTSD questionnaire between the MDMA and placebo group, 2 therapists were terminated for unethical therapy with a participant. The unique challenge is that employment of psychedelics in vulnerable populations can make participants more pliant to inappropriate therapy or therapists. A second harm is the current uncritical appraisal of the clinical trial community towards media coverage (through institution-driven press releases). This leads to an exaggeration of the reported effects and the proliferation of use in private clinics based on poor evidence. A third harm is a potential increased risk for substance use disorder. While psychedelics are not considered addictive and have been trialed for treatment of substance use disorder, care should be taken when administering psychedelics to vulnerable groups who are prone to substance use, such as individuals with eating disorders.
challenges in maintaining weight loss, some private companies are advocating for the use of psychedelic-assisted psychotherapy in the treatment of obesity.\(^3\) In addition, clinical trials to study the use of psychedelic therapy for obesity have been proposed, while those for anorexia nervosa (NCT04052568, NCT04505189, NCT04661514) and binge eating disorder (NCT05035927) are ongoing. For example, an ongoing trial for psilocybin-assisted therapy for anorexia nervosa will use 3 psilocybin doses, each separated by 2 weeks, with a monthly follow-up and a 12-month follow-up. They will perform MRI and electroencephalography at the first and third sessions. Each participant will be paired with 2 guides (therapist and/or psychiatrist) who will work with them for the duration of the trial in remote and in-person sessions on the baseline days and integration posttreatment.\(^3\) It has been proposed that psychedelic-assisted psychotherapy will help treat potential underlying disorders (anxiety or depression, substance abuse\(^1,2,19\)) that can precipitate unhealthy eating habits or hamper positive behavioural changes through therapy. Indeed an increase in depression and well-being scores were reported by individuals with eating disorders after a psychedelic experience.\(^32\)

There is some evidence that psychedelic treatment could have direct effects on food intake, in addition to inducing windows of plasticity\(^22,23\) and improving mood.\(^3,4,9\) Activation of 5-HT\(_2C\) receptors on proopiomelanocortin neurons in the hypothalamus produces satiety in rodents, and thus decreases meal size, whereas activation of 5-HT\(_2A\) receptors disrupts the continuity of feeding.\(^34\) Furthermore, activation of 5-HT\(_1A\) receptors on ventral tegmental area GABAergic neurones suppresses dopamine release and has been proposed to reduce the motivation to eat.\(^35\) While the acute effects of psychedelics on food intake via 5-HT receptors would be presumably short-lived, it is possible that the resulting increase in functional connectivity between 5-HT-associated networks would lead to greater activation of 5-HT receptors in regions that control food intake. Alternatively, a protocol could be developed for chronic low-dose psychedelics to acutely suppress appetite while augmenting behavioural therapy, similar to current or previously prescribed serotonergic weight-loss medications like locaserin. Notably, locaserin, a serotonin 5-HT\(_2C\) agonist, was originally approved in the US for weight loss, but was removed from the market in 2020 owing to an increased risk of cancer. It is conceivable that acute macro-dosing or chronic low-dose psychedelics could simultaneously reduce appetite/craving and facilitate healthy eating habits when paired with psychotherapy. However, emerging clinical studies will need to demonstrate the safety and feasibility of using such protocols in patients living with obesity or eating disorders.

Given the potential direct and indirect effects of psychedelic treatment on food intake, there is a lot of excitement for its use as a novel therapeutic. However, in addition to the challenges with psychedelic clinical trials outlined in Box 1, several considerations should be noted when designing clinical trials for the treatment of obesity. First, there is a strong need for completion of well-controlled clinical trials to determine efficacy of this potential treatment, given the paucity in current evidence. Second, it will be important to assess the potential for adverse events, such as serotonin syndrome, which may occur when psychedelics are taken alongside serotonergic medications used to treat comorbid depression. Third, given comorbid hypertension and cardiovascular disease in people living with obesity, particular caution should be taken with those taking high doses of serotonergic compounds. Finally, as with all individuals undergoing psychedelic therapy, there is a small risk of overwhelming distress during a drug reaction or a lasting psychotic reaction, which occurs more often in people with a family history of psychosis.\(^36\) Thus, carefully conducted research that considers the unique effects of psychedelics on brain and behavioural plasticity will inform the treatment of various disorders, including obesity.

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References

1. Bogenschutz MP, Forchheimer AA, Pommy JA, et al. Psilocybin-assisted treatment for alcohol dependence: a proof-of-concept study. J Psychopharmacol 2015;29:289-99.
2. Johnson MW, Garcia-Romeu A, Cosimano MP, et al. Pilot study of the 5-HT2AR agonist psilocybin in the treatment of tobacco addiction. J Psychopharmacol 2014;28:983-92.
3. Carhart-Harris RL, Roseman L, Bolstridge M, et al. Psilocybin for treatment-resistant depression: fMRI-measured brain mechanisms. Sci Rep 2017;7:13187.
4. Griffiths RR, Johnson MW, Carducci MA, et al. Psilocybin produces substantial and sustained decreases in depression and anxiety in patients with life-threatening cancer: a randomized double-blind trial. J Psychopharmacol 2016;30:1181-97.
5. Davis AK, Barrett FS, May DG, et al. Effects of psilocybin-assisted therapy on major depressive disorder. JAMA Psychiatry 2021;78:481-9.
6. Dawes RE, Timmermann C, Giribaldi B, et al. Increased global integration in the brain after psilocybin therapy for depression. Nat Med 2022;28:844-51.
7. Rucker JH, Iliff J, Nutt DJ. Psychiatry & the psychedelic drugs. Past, present & future. Neuropharmacology 2018;142:200-18.
8. Lowe H, Toyang N, Steele B, et al. Psychedelics: alternative and potential therapeutic options for treating mood and anxiety disorders. Molecules 2022;27:2520.
9. Canal CE, Murnane KS. The serotonin 5-HT2C receptor and the non-addictive nature of classic hallucinogens. J Psychopharmacol 2017;31:127-43.
10. Giacomelli S, Palmery M, Romanelli L, et al. Lysergic acid diethylamide (LSD) is a partial agonist of D2 dopaminergic receptors and it potentiates dopamine-mediated prolactin secretion in lactotrophs in vitro. Life Sci 1998;63:215-22.
11. Vollenweider FX. Brain mechanisms of hallucinogens and entactogens. Dialogues Clin Neurosci 2001;3:265-79.
12. Olson DE. Biochemical mechanisms underlying psychedelic-induced neuroplasticity. Biochemistry 2022;61:127-36.
13. Shao L-X, Liao C, Gregg I, et al. Psilocybin induces rapid and persistent growth of dendritic spines in frontal cortex in vivo. Neuron 2021;109:2535-2544.e4.
14. Ly C, Greb AC, Cameron LP, et al. Psychedelics promote structural and functional neural plasticity. Cell Rep 2018;23:3170-82.
15. Kyzar EJ, Nichols CD, Gainetdinov RR, et al. Psilocybin reversal learning in rats. Neuropsychopharmacology 2008;33:2007-19.
16. Doss M, Barrett FS, Corlett PR. Skepticism about recent evidence that psilocybin opens depressed minds. PsyArXiv 2022 [preprint].
17. Kraehenmann R, Preller KH, Scheidegger M, et al. Psilocybin-induced decrease in amygdala reactivity correlates with enhanced positive mood in healthy volunteers. Biol Psychiatry 2015;78:572-81.
18. Carhart-Harris RL, Mathukumaraswamy S, Roseman L, et al. Neural correlates of the LSD experience revealed by multimodal neuroimaging. Proc Natl Acad Sci U S A 2016;113:4853-8.
19. Silbersweig D. Default mode subnetworks, connectivity, depression and its treatment: toward brain-based biomarker development. Biol Psychiatry 2013;74:5-6.
20. Bluhm R, Williamson P, Lanius R, et al. Resting state default-mode network connectivity in early depression using a seed region-of-interest analysis: decreased connectivity with caudate nucleus. Psychiatry Clin Neurosci 2009;63:754-61.
21. Grandjean J, Buehlmann D, Buerge M, et al. Psilocybin exerts distinct effects on resting state networks associated with serotonin and dopamine in mice. NeuroImage 2021;225:117456.
22. Mulders PCR, van Eijndhoven PFP, Pluijmen J, et al. Default mode network coherence in treatment-resistant major depressive disorder during electroconvulsive therapy. J Affect Disord 2016;205:130-7.
23. Agin-Liebes GL, Malone T, Yalch MM, et al. Long-term follow-up of psilocybin-assisted psychotherapy for psychiatric and existential distress in patients with life-threatening cancer. J Psychopharmacol 2020;34:155-66.
24. Carhart-Harris RL, Bolstridge M, Rucker J, et al. Psilocybin with psychological support for treatment-resistant depression: an open-label feasibility study. Lancet Psychiatry 2016;3:619-27.
25. Boulougouris V, Glennon JC, Robbins TW. Dissociable effects of selective 5-HT2A and 5-HT2C receptor antagonists on serial spatial reversal learning in rats. Neuropsychopharmacology 2008;33:2007-19.
26. Doss MK, Považan M, Rosenberg MD, et al. Psilocybin therapy increases cognitive and neural flexibility in patients with major depressive disorder. Transl Psychiatry 2021;11:574.
27. Luppino FS, de Wit LM, Bouvy PF, et al. Overweight, obesity, and depression: a systematic review and meta-analysis of longitudinal studies. Arch Gen Psychiatry 2010;67:220-9.
28. Vainik U, Dagher A, Dubé L, et al. Neurobehavioral correlates of body mass index and eating behaviors in adults: a systematic review. Neurosci Biobehav Rev 2013;37:279-99.
29. Hall KD, Kahan S. Maintenance of lost weight and long-term management of obesity. Med Clin North Am 2018;102:183-97.
30. NeonMind Biosciences Inc. Mississauga: NeonMind Biosciences Inc.; 2022. Available: https://www.neonnmindbiosciences.com (accessed 2022 May 12).
31. Spriggs MJ, Douglass HM, Park RJ, et al. Study protocol for “Psilocybin as a treatment for anorexia nervosa: a pilot study.” Front Psychiatry 2021;12:735523.
32. Spriggs MJ, Kettner H, Carhart-Harris RL. Positive effects of psychedelics on depression and wellbeing scores in individuals reporting an eating disorder. Eat Weight Disord 2021;26:1265-70.
33. Aleksandrova LR, Phillips AG. Neuroplasticity as a convergent mechanism of ketamine and classical psychedelics. Trends Pharmacol Sci 2021;42:929-42.
34. Simansky KJ. Serotonergic control of the organization of feeding and satiety. Behav Brain Res 1996;73:37-42.
35. Valencia-Torres L, Olarte-Sánchez CM, Lyons DJ, et al. Activation of ventral tegmental area 5-HT2C receptors reduces incentive motivation. Neuropsychopharmacology 2017;42:1511-21.
36. Johnson M, Richards W, Griffiths R. Human hallucinogen research: guidelines for safety. J Psychopharmacol 2008;22:603-20.
37. Barnett AG, van der Pols JC, Dobson AJ. Regression to the mean: What it is and how to deal with it. Int J Epidemiol 2005;34:215-20.
38. Johansen P-O, Krebs TS. Psychedelics not linked to mental health problems or suicidal behavior: a population study. J Psychopharmacol 2015;29:270-9.
39. Lindsay B. Footage of therapists spooning and pinning down patient in B.C. trial for MDMA therapy prompts review. CBC News [Toronto]. Available: https://www.cbc.ca/news/canada/british-columbia/bc-mdma-therapy-videos-1.6400256 (accessed 2022 May 13).
40. Mitchell JM, Bogenschutz M, Lilienstein A, et al. MDMA-assisted therapy for severe PTSD: a randomized, double-blind, placebo-controlled phase 3 study. Nat Med 2021;27:1025-33.
41. Skot L, Mejdal A, Guala MM, et al. Eating disorders and subsequent risk of substance use disorders involving illicit drugs: a Danish nationwide register-based cohort study. Soc Psychiatry Psychiatr Epidemiol 2022;57:695-708.