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[1,2] and major depressive disorder.[3–6] 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.[7] 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.[7] 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.[7]

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_{2C}, 5-HT_{2A}, and 5-HT_{1A}.[8] 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_{2A} and mesolimbic 5-HT_{2C} receptors mediate the effects of psychedelics on mood and addiction, respectively.[8,9] 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.[8,10] Hallucinogenic properties of these serotonergic agents are likely mediated through 5-HT_{2A} receptors within the cortico–striato–thalamo–cortical feedback loop.[11] Interestingly, psychedelics stimulate robust neural plasticity in the PFC, and these effects may be dissociable from their hallucinogenic properties.[12] 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.[12–14]

There are various forms of "psycholytic" or "psychedelytic" 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,[4] termed "integration." Some trials have used more intensive therapy, such as 11 hours of psychotherapy within 1 month after treatment.[5] 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.[15] However, there are many considerations and limitations in psychedelic therapy trials (Box 1).

Two administrations of psilocybin (either with[5] or without[3,6] additional psychotherapy) appear to have rapid and enduring antidepressant effects, lasting weeks to months after the experience[3,5,6] (see Doss and colleagues[16] 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) placebos. However, while active placebos 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.[37]
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 to parse out if there are effects specific to the psychedelic under study. It would also be important to report the experimental group to which the participants thought they were assigned.
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,[36,38] an example of harm from a clinical trial employing psychedelic therapy is with the current Health Canada investigation of the Multidiciplinary Association for Psychedelic Studies employing 3,4-methylenedioxymethamphetamine (MDMA) for posttraumatic stress disorder (PTSD).[39] 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,[40] 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 trials in study previews and 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[9] and have been trialed for treatment of substance use disorder,[1,2] care should be taken when administering psychedelics to vulnerable groups who are prone to substance use, such as individuals with eating disorders.[41]

state.[17] Notably, brain activity observed 1 day after a high-dose psychedelic experience is different than during the acute psychedelic state, whereby a decrease in default mode network (DMN) function occurs during the psilocybin[3] or LSD[18] acute experience but an increase in DMN strength is observed 1 day after psychedelic exposure.[3] Previous studies have associated an increase in DMN integrity as a marker of depressed mood;[19,20] thus, it is unclear what the delayed increase in DMN integrity represents given that there is a reported increase in mood following the experience.[3] It is possible that delayed strengthening of 5-HT–DMN connectivity is paired with a reduction in functional connectivity of dopamine-associated striatal networks, as seen in mice,[21] creating synergistic positive effects on mood or craving. Some have additionally proposed that, like electroconvulsive therapy, which also increases integrity of the DMN associated with its antidepressant effect,[22] psychedelic experience opens up a window of plasticity. Indeed, animal studies have shown that activation of serotonin 5-HT_{2C} receptors induce synaptic, structural and functional changes of the major output neurons of the PFC.[12–14] The sustained antidepressant effects of psilocybin detectable 6 months after administration[23,24] may be due to synergistic effects of drug-induced neuroplasticity and experience-dependent neuroplasticity through psychotherapeutic interventions.

Cognitive flexibility, the ability to change behaviour when environmental conditions change, is impaired in substance use disorder, obsessive–compulsive disorder, and major depressive disorder, which many be amenable to psychedelic therapies. Animal studies have found that drugs targeting 5-HT_{2A} and 5-HT_{2C} receptors can bidirectionally modulate cognitive flexibility.[25] In humans, psilocybin-assisted therapy increased cognitive flexibility in patients with major depressive disorder.[26] This increase in cognitive flexibility was associated with a nonlinear increase in dynamic functional connectivity, detected with a timeseries of fMRI images, across the brain, a marker of increased neural flexibility.[26] The investigators speculated that this window of neuroplasticity could allow for an increased capacity to shift between different mental states, allowing for an improved response to psychotherapy.[26]

Obesity has a high association with major depressive disorder[27] and impairments in cognitive flexibility,[28] both of which could contribute to the modest effectiveness of behavioural interventions and poor adherence to traditional weight-loss strategies. Despite the incentives for losing weight and the wide availability of traditional weight-loss methods, average long-term adherence to dieting and exercise is low, and many individuals living with obesity are unsuccessful in their attempts to lose weight.[29] Furthermore, approximately 80% of excess weight is regained within 5 years of most weight-loss attempts, barring long-term counselling, sustained behavioural changes, medication, or more invasive interventions like bariatric surgery.[29] Individuals living with obesity may be eligible for supplemental pharmacotherapy or surgical intervention in cases where diet, exercise and behavioural modification are repeatedly unsuccessful, but these approaches still vary in long-term effectiveness and pose their own physical, psychosomatic and financial challenges. In response to these

challenges in maintaining weight loss, some private companies are advocating for the use of psychedelic-assisted psychotherapy in the treatment of obesity.[30] 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.[31] It has been proposed that psychedelic-assisted psychotherapy will help treat potential underlying disorders (anxiety or depression,[3,4,8,15,17,23,26] substance abuse[1,2,15]) 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[12,33] and improving mood.[8,32] 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_{2C} receptors on ventral tegmental area GABAergic neurons 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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