



BIOLOGIC AND CLINICAL RATIONALE FOR THE USE OF PSILOCYBIN IN HYPERPHAGIA

Overeating disorders such as hypothalamic obesity (HO), binge eating disorder (BED) and Prader-Willi Syndrome (PWS) are serious medical illnesses marked by severe disturbance to a person's control over their eating behaviors and high anxiety around food. All three of these conditions are characterized by abnormal neural responses to food, especially highly palatable foods ([Vlaardingerbroek 2021](#); [Citrome 2019](#)). Additionally, individuals affected by these conditions suffer from severe anxiety and can have significant compulsive and impulsive behaviors, particularly around eating ([Samodien 2021](#); [Kayadjanian 2021](#); [Guerdjikova 2019](#)). Self-mutilatory behaviors, such as skin picking can be seen in all of these conditions, presumably associated with abnormal neuronal connectivity ([Bull 2021](#); [Houazene 2021](#)). Because psilocybin alters neuronal connections the potential opportunities of this therapy include treatment of overall anxiety, anxiety around food, compulsive and impulsive behaviors, self-mutilatory behaviors, and repetitive and intrusive thoughts, especially about food in people with overeating disorders like HO, BED and PWS.

Variations on psilocybin paired with psychotherapy have shown some evidence of effect in treating cancer-related psychiatric stress, depression and anxiety, and nicotine and alcohol addiction. Clinical trials are ongoing to evaluate the efficacy of psychedelics for anorexia nervosa (NCT04052568, NCT04661514, NCT04505189), a condition where intrusive thoughts drive maladaptive and life-threatening behavior and in which treatment resistance is common ([Foldi 2020](#)). There are parallels between intrusive thoughts in people with addiction, anorexia nervosa/binge eating and OCD, where affected individuals ruminate on the potential relief afforded by food, often devising elaborate plans to get food ([Lutter 2009](#)). Positive effects of psychedelics have been seen on depression and wellbeing scores in individuals reporting an eating disorder ([Spriggs 2021](#)).

The action of psilocybin has been primarily associated with activation of the 5-HT_{2A} receptor. The 5-HT_{2A} receptor has been associated with hyperphagia in animal studies and in some human studies. Stimulation of 5-HT_{2A} receptors in the paraventricular

hypothalamus attenuates neuropeptide Y-induced hyperphagia through activation of corticotropin releasing factor (Grignaschi 1996). The 5-HT_{2C/2B} receptor agonist m-chlorophenylpiperazine inhibits 2deoxyD-glucose-induced hyperphagia in rats (Sugimoto 2001). Association of 5-HT_{2A} receptor gene polymorphism with eating disorders has shown some conflicting results (Serretti 2007). Studies using positron emission tomography and single photon emission computed tomography with 5-HT-specific radioligands have consistently shown 5-HT_{1A} and 5HT_{2A} receptor and 5-HT transporter alterations in anorexia nervosa and bulimia in cortical and limbic structures, which may be related to anxiety, behavioral inhibition, and body image distortions (Bailer 2011). Overweight was found to be associated with increased 5-HT_{2A} binding in most cortical regions in humans (Erritzoe 2006). Ayahuasca, which contains the psychoactive component N,N-dimethyltryptamine and is a 5-HT_{2A} agonist, has shown some positive effects on eating disorder related thoughts and symptoms (Renelli 2020; LaFrance 2017).

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