Complexities of psychedelics for therapeutic use in obesity and eating disorders

In an interesting and timely editorial, Borgland and Neyens provide a snapshot of preclinical research that could support the development of psychedelic drugs as part of a therapeutic regimen in individuals with obesity or eating disorders (EDs), including anorexia nervosa (AN) and binge eating disorder (BED).[1] The role of the serotonergic system in appetite was key in the development of the 5-HT_{2C} receptor agonist lorcaserin as a treatment for obesity.

The editorial highlights studies in rodents showing that 5-HT_{2A} receptor agonism augments neuroplasticity in the prefrontal cortex — a critical brain region for inhibitory control and decision-making, which has been shown to be functionally altered in individuals with obesity and may instigate maladaptive eating behaviours. However, recent rodent obesity-model studies have shown conflicting results regarding weight loss following psilocybin treatment.[2,3] The high comorbidity of EDs and obesity with mood disorders may contribute to the etiology of these conditions at the psychological and neurobiological levels,[4] often leading to the prescription of selective serotonin reuptake inhibitor antidepressants.

However, the caveats and concerns associated with psychedelic therapy trials described in the editorial are less representative of the complexities of contemporary psychedelic drug development under stringent clinical/laboratory practice guidelines. Moreover, as therapeutic indications, obesity and EDs have complex neuropsychiatric and physiologic components.

A central concern in the development of novel, or third-generation, psychedelic drugs for therapeutic use or prolonged microdosing paradigms (if shown to be therapeutically efficacious) is the potential for cardiac valvulopathy and toxicity due to off-target 5-HT_{2B} receptor agonism.[5–7] While this is of less concern for physically healthy individuals who may undergo 1 or 2 psychedelic treatment sessions, underlying cardiac issues may contraindicate the use of chronic "microdoses" of psychedelics in individuals with EDs and obesity. Cardiovascular issues in these populations may be caused by the chronic use of appetite suppressants, electrolyte abnormalities from purging can cause arrhythmias, and high adiposity can precipitate heart disease. Cardiac failure has been observed with the recreational use of 3,4-methylenedioxy-methamphetamine (MDMA),[8] currently in phase 2 trials for AN-restrictive subtype and BED (where participants were ineligible if they were classified as AN-purging subtype). During the development of next-generation psychedelics, the progression of compounds with lower agonist affinity at the 5-HT_{2B} receptor is a key workflow element to reduce cardiac risks, and rigorous cardiac screening, monitoring and reporting of adverse events is a requirement in clinical trials.

Determining the appropriate dosage of psychedelic compounds may also be complicated in individuals with high and low body weights. Weight-adjusted dosing of psilocybin has been reported in individuals with a body mass index between 17.5 and 35.6,[9] but may be less appropriate for individuals with severe obesity or EDs, as complex interactions between serotonergic function, drug effects and body weight have been reported.[10] Moreover, psychotherapy is a critical component of psychedelic treatment programs to support the patient with integration into meaningful behavioural and psychological changes to facilitate long-term recovery. It is likely that specialized psychotherapy programs focusing on eating behaviours will be required for people with obesity or EDs as therapeutic indications.

Psychedelic drug development is an exciting field with potential to provide vital pharmaceutical tools. Furthermore, the development of next-generation psychedelic compounds with lower 5-HT_{2B} affinity than classic psychedelics presents enhanced safety for individuals with EDs and obesity.

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