Psychiatric disorders

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Psilocybin for the treatment of anorexia nervosa

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In individuals with anorexia nervosa, psilocybin therapy comes with specific risks and concerns; but an encouraging phase 1 trial underscores the necessity for more research into classic psychedelics to address the urgent need for effective treatments.

Anorexia nervosa (AN) is a serious psychiatric disorder characterized by low body weight, body image distortions, and strict limitations on eating, affecting up to 1.4% of women (but about 8–10 times fewer men) worldwide. Individuals with AN exhibit a notably increased risk of dying from medical complications or suicide and only about one-third of patients achieve stable long-term recovery. Importantly, AN is an under-researched disorder and no approved medications are available specifically for its treatment[1]. In this issue of *Nature Medicine*, Knatz Peck et al.[2] present a feasibility study investigating psilocybin treatment for AN. Psilocybin is the main psychoactive component of 'magic' mushrooms, a classic psychedelic similar to lysergic acid diethylamide (LSD) and ayahuasca. Psychedelics have recently been re-evaluated as potential tools for the treatment of psychiatric disorders, including internalizing disorders that often co-occur with AN — such as major depression[3] and obsessive–compulsive disorder (OCD)[4] — with promising results.

In the study from Knatz Peck et al.[2], ten participants with AN (current AN or in partial remission, mean body mass index (BMI) of 19.7) received one dose (25 mg) of psilocybin together with psychological support. The treatment was shown to be safe, well tolerated, and acceptable to patients. Adverse effects were mild and mirrored typical psilocybin-associated symptoms such as transient headache, nausea and fatigue; no serious medical or psychiatric adverse events were reported. Shape concerns significantly decreased at the 1 month follow-up, and four patients had decreases in eating disorder scores at 3 months that qualified them for remission from eating disorder psychopathology.

These findings corroborate existing knowledge about the safety and tolerability of psilocybin when administered within a controlled clinical setting. Psilocybin has been reported to facilitate beneficial psychological effects that outlast their acute effects in the human body, manifesting as acute psychedelic experiences, subacute 'afterglow' effects and long-term effects[5]. Therefore, psychedelics are not administered on a daily basis, but once or a few times only — embedded in a psychotherapeutic process. Accordingly, in the study by Knatz Peck et al.[2], patients received two preparatory psychotherapy sessions before, and two integration sessions after their psilocybin experience. Psychotherapy is thought to help maximize therapeutic benefits of the treatment, at the same time minimizing risks that might result from overwhelming acute drug effects.

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Different mechanisms have been proposed for the therapeutic effects of psilocybin, some of which appear to be consistent with current models of the pathophysiology of AN. On a molecular level, psychedelics share an agonism at the serotonin receptor 5-hydroxytryptamine (5-HT_{2a}), which is essential for psychedelic effects. As in major depression[3] and OCD[4], alterations of serotonin homeostasis have also been discussed in AN — more precisely, a hyperserotonergic state as a trait marker and an undernutrition-related hyposerotonergic state in the acutely underweight phase of AN — even if mechanisms are not yet fully understood[6]. Psychedelics have also been associated with increased brain-derived neurotrophic factor (BDNF)-related neuroplasticity, including enhanced synaptic complexity[7]. In this way, psilocybin could potentially help to ameliorate the severe undernutrition-related reduction in brain grey matter that has been consistently reported in individuals with AN, thereby exerting neuroprotective effects[8].

On a network level, psychedelics have been suggested to modulate thalamocortical circuits, tuning functional connectivity towards decreased sensory filtering of internal and external stimuli. In addition, there is converging evidence that psychedelics affect the activity of the default mode network (DMN), a group of interconnected brain areas that are coherently activated at rest. DMN activity has been reported to be altered in AN[9] and associated with rumination and rigid thinking in mental health disorders that can be positively influenced by psychedelics (such as depression)[10]. Similarly, rumination (about food and weight) is a symptom that many individuals with AN experience as excruciating[11], presenting another promising target for psilocybin.

From a phenomenological perspective, individuals experience states of ego dissolution under the influence of psilocybin, followed

by increased cognitive and emotional flexibility and changes in views on life, self and others[5]. Consistent with this, in the study by Knatz Peck et al.[2], most patients reported feeling more positive about life endeavours and having improved quality of life after psilocybin. Of note, as in major depression and OCD, there is robust evidence of reduced cognitive flexibility in AN, a circumstance that may also warrant investigation of the use of psilocybin in this setting.

Besides these potential beneficial mechanisms of psilocybin in AN, however, there are also potential risks to be considered when planning future randomized controlled trials. The medical abnormalities associated with AN, such as low body weight and electrolyte abnormalities, could be associated with an increased susceptibility to potent central nervous system drugs. Comparable doses to those used by Knatz-Peck et al.[2] have shown good tolerability in trials in investigating psilocybin for patients experiencing existential distress during palliative care. However, the mixed sample in the current study (including currently ill and partially recovered patients, with a relatively high mean BMI) limits the generalizability of findings to patients with severe and enduring AN — which at the same time might be the group of patients that most desparately awaits new treatments.

Another potential risk to be considered are the body image distortions that are a core symptom of AN. Patients percieve their bodies as larger than they are, which, at times, might seem delusional. As psychedelics have previously been associated with pro-psychotic effects, they might represent a risk in patients with AN. However, the delusion-like symptoms in AN are usually restricted to a limited set of body features such as the waist or thighs and are closely related to the fear of being overweight or obese. Furthermore, modern molecular psychiatry approaches that captialize on genetic correlation did not show a close association of AN with psychotic disorders[12], which suggests that the risk of triggering psychotic episodes may be limited.

In conclusion, the preliminary findings by Knatz Peck et al.[2] suggest that psilocybin therapy could be well tolerated by patients with mild to moderate AN, possibly reducing eating disorder psychopathology in a subset of individuals. Given the unmet need for effective and acceptable treatments for this disorder, psilocybin therapy may represent a promising avenue for further clinical evaluation, with randomized controlled trials being needed to definitively assess the efficacy of of psilocybin in this setting.

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Competing interests

The authors declare no competing financial or non-financial interests related to the topic.