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EMERGING TOPIC

Psychedelic treatment for anorexia nervosa: A first-hand view of how psilocybin treatment did and did not help

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Anorexia nervosa (AN) is a psychiatric illness with high mortality rates and limited treatment outcomes. Psilocybin treatment (PT) has shown promise for various mental health indications and there is significant interest in exploring its potential for AN; however, studies to date are preliminary. Given the probable surge in psychedelic studies for AN, more information is needed to understand how to successfully apply and optimize these treatments for this vulnerable population. In this Emerging Topics article, we present a nuanced exploration of the potential benefits and constraints of PT for AN, contextualized within the framework of our clinical findings from a modest phase 1 pilot study. We offer here a synthesis of first-hand experiences and comprehensive thematic insights gleaned from 10 individuals with lived experience, providing a rich tapestry of perspectives on this novel therapeutic approach.

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Psilocybin treatment (PT) is being evaluated for a broad range of mental health indications and there is significant interest in exploring its potential for anorexia nervosa (AN) (1). Adult AN is a notoriously treatment-resistant psychiatric illness with high mortality rates (2) and no treatments demonstrating clear superiority or strong outcomes, particularly for perceptions regarding body image and eating, or other mental psychopathology (3). Considerable evidence implicates altered serotonin function in AN (4, 5). Psilocybin acts on the serotonin system and may be able to alter perception (6). Although the role of the serotonin alterations in AN is not well understood and findings are somewhat mixed (7, 8), the documented role of 5-HT dysfunction raises the possibility that PT may have the potential to improve core psychopathology and perceptions not successfully targeted by existing behavioral and pharmacological treatments. There are few clinical trials to date and preliminary results are inconclusive. More studies are needed to explore its potential.

We published the first clinical trial evaluating PT for AN in a small, phase 1 pilot study of safety, tolerability, and preliminary outcomes for participants with AN and AN in partial remission (9). Results of this study were published by our group in 2023 (9). This was a very small feasibility study and therefore results must be interpreted with caution. However, in this commentary, we provide a granular view of findings based on qualitative data from semistructured interviews, extensive feedback and interviews from participants, and our subjective interpretations of data patterns. Providing an integrated perspective based on these findings and accrued experience ensures that we are utilizing feedback from key stakeholders to iterate treatment, and to ensure treatment acceptability and face validity in future studies for a treatment population that is notoriously difficult to treat.

Results from our study are highly preliminary; however, they suggest that PT is safe, tolerable, and highly acceptable. PT included a single 25 mg dose of psilocybin administered with specialized psychological support before (two sessions), during, and after (two sessions) the drug administration by trained psychologists (for additional details about the psychological support, see ref. 9). A total of 60% (6/10) of participants reported a reduction in the importance of physical appearance, 70% (7/10) reported feeling a quality-of-life improvement and shift in personal identity, and 90% endorsed the psilocybin dosing as one of their top five most meaningful life experiences. Within the context of the existing treatment landscape where treatment utilization rates are low and dropout rates are high (10), these personal reports are clinically significant and warrant further investigation. These endorsements suggest the potential for shifts in identity, the relative value of physical appearance, and quality-of-life improvements, all of which are behavioral markers of entrenchment and dysfunction within the illness.

Quantitatively, preliminary outcomes demonstrated a subset (4/10) of participants who experienced clinically significant reductions in eating disorder (ED) psychopathology to within community normative levels at 3-month follow-up after a single therapeutic dose of psilocybin offered in conjunction with psychological support by a specialized therapist. These score changes suggest remission from ED psychopathology, which we interpret to be noteworthy, as did the participants who experienced these effects. Importantly, many questions emerge from this study that can inform future research pathways. What was different about the 4/10 responders? What occurred that resulted in reductions in ED psychopathology scores? These questions speak to the importance of elucidating mechanisms of action and change (11). Other questions emerging pertain to the lack of effect on certain recovery markers traditionally defining full recovery (i.e., weight), and a lack of response by a subset of participants. What explains the discrepancy between participants endorsing the treatment as highly therapeutically meaningful, and yet not demonstrating changes in measured ED psychopathology? Last, in those who experienced significant and precipitous reductions in psychopathology, why did weight restoration not follow?

We cannot draw any systematic conclusions based on our limited data and sample. However, here we discuss important questions and raise hypotheses around psychological mechanisms that were engaged based on thematic responses from participants in the context of effects observed.

What Differentiated Responders?

Among those who demonstrated significant improvements in eating disorder symptoms, reductions were precipitous and sudden. Eating disorder examination (EDE) scores generally decreased sharply at Day 1 follow-up, with continuous decreases reported at the 1-month follow-up period and sustained at 3-month follow-up. Shape concerns and weight concerns were the most sensitive to change with significant effects at

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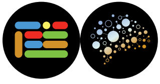

1-month follow-up, and sustained effects at 3-month follow-up for weight concerns. These constructs capture dissatisfaction and preoccupation and the relative importance of these features in relation to self-esteem/self-evaluation, which is a primary criterion of AN based on the DSM 5 (12). These effects align with participant-responder descriptions of how the treatment decreased eating disorder symptoms by resulting in a shift in their subjective importance.

It kind of just made me realize that I had wasted most of my life trying to manipulate my body when that's the least important thing about me. In reality, the least important thing about my life is my physical body.

I feel like I disconnected from my physical body, which was very liberating in a lot of ways too. I felt the whole soul death thing where I just felt like I was a soul, just kind of traveling through the universe and that made me sad to think that I had wasted so many years of my life just being so hyperfixated on this big chunk of me that just holds my being.

This suggests that, for responders, the treatment resulted in a reorganization in perception, values, and diminished significance of weight/shape in defining self-worth; that is, a reduction in the primary diagnostic criterion noted above. These participants tended to report diminished internal preoccupation and more mental capacity for renewing focus on other values and life experiences, which translated into less anguish and obsession about behavioral choices around food.

Before I participated, my anorexia was the most important relationship in my life that came before friends, family or partners and everything. I was valuing weight as the number one focus in my life. But during the psilocybin experience, I was able to see sort of the insignificance and it seemed so trivial after the experience. It just seemed trivial for me to focus my life around weight when there were so many other important factors.

What differentiated these participants from nonresponder participants? The small sample limited quantitative analyses; however, we did not find any significant correlations between demographic variables, psychedelic subscale scores and/or pretreatment scores with outcomes. In semistructured qualitative interviews, this group of participants reported experiencing a dissociation from their eating disorder as a core part of their identity along with a deeper connection to self. In these cases, this transformation in perspective appeared to motivate a decentralizing of weight and shape, which in some cases resulted in changes in eating behaviors.

On a neuropharmacological level, psilocybin's psychedelic effects are believed to emerge because of stimulation of the serotonin 2A receptor (13) as the intensity of psychedelic effects have been shown to be related to psilocybin's occupancy of the serotonin 2A receptor in the human brain. Brain imaging studies show that some individuals with AN have reduced activity of the serotonin 2A receptor (14). Studies show that some with AN have polymorphisms of the serotonin 2A receptor gene and this polymorphism could alter expression of this receptor (15). Two lines of evidence support this contention. First, PET brain imaging (5) shows some individuals with AN have reduced binding of the 5HT2A receptor. Second, a number of investigators (16) reported polymorphisms of the 5HT2A receptor in AN. Schmitz (17) reported that sequence variations of 5HT2A affect the efficacy and potency of psychedelics, including psilocybin. Thus, it is possible that altered function of the 5HT2A receptor may play a role in why some with AN fail to respond to psilocybin. To our knowledge, this hypothesis has not been tested in terms of psilocybin response in AN. We mention this potential confound as an issue that should be investigated in future studies using psilocybin to treat AN.

Future studies should focus on mechanisms of action and change (11) to elucidate psychological, demographic, and neurochemical features that may affect treatment response. It is possible, and indeed likely, that not all participants will respond, which mirrors the course of other pharmacology. Despite variable results, more evaluation is warranted given the striking response from a subset that included a highly treatment-resistant case, a female who refused traditional treatment, and two other treatment-refractory cases with illness durations of >5 years and significant distress conferred from ED psychopathology.

How and Why Did Participants Experience This Treatment as Therapeutically Meaningful?

Only a subset of participants was responders; however, the majority endorsed the treatment as therapeutically meaningful and significant. Understanding the subjective value of the treatment is important for future treatment iteration and to ensure feasibility and acceptability. Furthermore, it is also important to understand why subjective perceptions of benefit did not in all cases result in meaningful reductions in ED psychopathology. It is possible that assessment devices lacked sensitivity to capture granular behavioral changes that require more extended periods of time to translate into assessment markers such as weight. This suggests the need for a longer follow-up period and considerations for more sensitive assessment devices to track relevant behavioral changes, such as dietary recalls. In qualitative reports, which in most cases were at least 1 year out from study participation, participants noted some changes that they perceived to be personally significant for recovery but could be defined as subtle because they would be difficult or require prolonged sustained enactment to translate into meaningful symptom reduction.

It helps me to focus more on the joyful aspects of food. Just taste, textures, smells. Just kind of finding, rediscovering this kind of joy with food.

I would say I'm kind of generally more intuitive and kind of just looking to find more joyful experiences with food as opposed to just eating things out of obligation or, you know, following rules.

It made me like more appreciate my body. That has impacted what I choose to eat and when and how and not obsessing over it, but my habits have been the same.

Some also noted less preoccupation surrounding food and increased engagement in other life areas, even in the absence of significant or programmatic shifts in food intake.

It's just more of like something that was in my life or comes and goes, you know, I don't feel like it's my whole identity, which for a long time was really hard to separate. And then moving forward, I'm like, how do I be me without it? So, it's like I feel like I'm able to kind of create a whole life not having that as my identity, but still like validating it.

I do think that it has helped me to just continue trying, I think, and continue trying to keep on where I'm not going backwards, where I keep on either maintaining or trying to push forward because of that insight I gained into the bigger picture. And it helps me to kind of zoom out when I'm really stuck in my thoughts or behaviors.

It's impacted my ability to believe what I'm capable of and it has shown me that I don't have to live in the cycle of anorexia and how much anorexia has taken from, from me and my life. I can truly be a totally different person. And it gave me so much more brain space and brain capacity to either have a hobby or work in a different capacity, it's given me so much space to do other things.

This implies that these treatments may in the short term, improve quality of life and clinical impairment (1). Even in the absence of changes in the primary outcome, we believe that qualitative perceptions surrounding quality-of-life improvements are important to highlight and clinically meaningful. Patients with EDs have significant morbidity and mortality related to suicide, and thus these improvements should be a priority in treatment approaches.

What About Weight?

It is equally important to note that treatment effects did not generally translate into improvements in underweight status—a primary diagnostic marker and important physiological recovery metric. Of the four responders on the primary outcome of mental ED psychopathology, three gained weight at 3-month follow-up (0.4–1.2 body mass index [BMI] points) and one reported a 1.5 decrease in BMI, noting illness as the primary reason. When asked about this disparity, participants noted:

I thought that if I no longer worried about gaining weight it would be easy, but I am now realizing that restoring weight requires effort.

When you ask me questions about my weight and why it hasn't changed, it feels like you are only basing my recovery on weight and that feels bad since I feel like I no longer have an ED.

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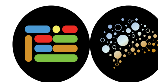

The irony is that now that I want to recover, I can eat intuitively, but that is not enough to support physical recovery.

Things might not look that different from the outside, but they feel completely different from the inside.

Furthermore, changes in BMI in the overall sample were highly variable. We cannot assume that any BMI changes were related to treatment effects; however, the results present a compelling hypothesis that behavioral changes necessary for full physical recovery (versus internal phenomenological belief systems related to AN) were not initiated from treatment, at least in its current design. The responder-participant with the most noteworthy weight restoration (1.2 BMI points at 3-month follow-up with a BMI shift from 16.9 to 18.1) stated that the necessary changes in eating were "not without effort" and required oversight from a dietician and a programmatic eating structure (versus intuitive eating). She noted that these changes were often difficult and required her to deliberately revisit the insights from the dosing experience.

You are able to act in a way that maybe had felt unachievable before if you set the right intention and so you still have to yourself implement it.

It gave me the push to be able to recover. I mean, it's still been a challenge and it's still been something that I actively have to work at.

AN is characterized by rigid and repetitive behaviors surrounding eating and exercise which are highly resistant to disruption and new learning. Some participants reported no change in ED behaviors postdosing, while others reported an improved desire to do so, but no significant structural changes. One participant appeared on Day 1 highly distraught that she had engaged in a compulsive exercise routine immediately upon discharge from her dosing experience. That is, even when insights were conferred and beliefs shifted, it may continue to be difficult to break rigid and repetitive ED behaviors. Participants may emerge with increased willingness, and yet still not know how to proceed with recovery systematically. Adjunctive behavioral treatments may be necessary to leverage potential neuroplasticity and provide more structured guidance for achieving meaningful behavior changes. Those with AN usually prefer high structure and certainty (18), and more directive models of behavioral treatment may be necessary to support this particular temperament signature.

I don't want it to go to waste. So I keep on trying to be like, no, I know better than this because I know it's not necessary. And so I use that to fuel my recovery. It didn't really feel like it changed my relationship with food, but it did make me feel like I don't need the anorexia.

Action is definitely the harder part. But mentally I'm able to see beyond that and know that's what I want. So I keep at it every day.

The lack of behavioral response overall may also be related to genetic variations. If some individuals with AN in our psilocybin trial had 5HT2A polymorphisms, as was discussed previously, this could alter their behavioral response to psilocybin and contribute to high variability and a lack of change in physical outcomes, including weight. To our knowledge, no studies have investigated the relationship of 5HT2A receptor polymorphisms in regard to psilocybin response in AN.

Nevertheless, the results suggest that psilocybin treatment may hold potential to occasion important attitudinal shifts that define AN. The lack of a clear signal in improving weight and behavior should not undermine the importance of this potential effect. Indeed, more treatments are needed to improve core psychopathology, as many existing treatment paradigms emphasize the inverse—behavioral shifts with no change in attitude or cognitive pathology.

Findings from this study based on quantitative and qualitative data suggest that psilocybin may be helpful in supporting meaningful psychological change in a subset of people with AN, and in some cases reductions in difficult-to-treat, core AN psychopathology such as shape and weight concerns. Our findings also suggest that psilocybin treatment may not be effective for all with AN, and may not serve as a stand-alone treatment in its current brief form due to a possible lack of effect on the full symptoms profile, and specifically important physical metrics such as weight restoration. However, these results and related hypotheses are highly preliminary and must be interpreted with caution due to the small, uncontrolled nature of this study. Ultimately, it will be important to better predict who is likely to benefit from this treatment and understand the possible benefits of this paradigm across the developmental spectrum given the prevalence rates of AN in youth. Based on our experience, larger, well-controlled future studies should include more thorough baseline assessments to understand the unique features predicting response including brain imaging studies and collection of genetic material to identify any biological factors associated with outcome. Given the discrepancy between qualitative self-reports of experience and quantified change, it is also possible that alternative measurement sources and assessments should be considered. Additionally, robust, specialized psychological support and/or behavioral treatment may be necessary for this population to leverage subtle shifts in attitudes due to AN's strong behavioral signature. Other variables that may impact outcome and warrant further investigation include dosage and number and frequency of administrations. Last, future studies should assess for and place serious value on quality-of-life improvements, including reductions in impairment necessary for reducing morbidity. Researchers should also be aware of the unique risks associated with those with AN (19). In conclusion, we hope these qualitative findings provide opportunities for other research teams to design studies where features can be evaluated, and treatments can be optimized based on these important clinical impressions from our team and participants with lived experience.

Data Availability

Clinical data referenced in this manuscript are publicly available in Dryad Data Repository (https://datadryad.org/stash/landing/show?id=doi%3A10.5061%2Fdryad.47d7wm3hq).

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Author Contributions

SKP, PHD acted as subinvestigator of the study. She was primary author of the manuscript and orchestrated and contributed to intellectual conceptualization of the perspective paper. She also participated in qualitative data collection. Hannah Fisher acted as research coordinator, conducted semistructured interviews on participants and edited the manuscript. Jessie Kim, BS acted as research coordinator. She collated relevant data and edited the manuscript. Samantha Shao, BA acted as research coordinator. She conducted all primary assessments and screening, oversaw clinical research coordination, organized and managed the database of results, and edited the manuscript. Julie Trim, PHD contributed to the intellectual conceptualization of the manuscript and and edited the manuscript. Walter H. Kaye, MD was investigator of this study and contributed to the writing and editing of this manuscript.

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Author Disclosures

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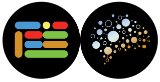

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