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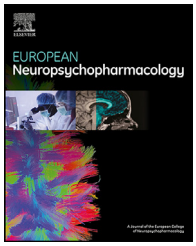

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REVIEW

Psychedelics in the treatment of eating disorders: Rationale and potential mechanisms

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Abstract
Eating disorders are serious illnesses showing high rates of mortality and comorbidity with other mental health problems. Psychedelic-assisted therapy has recently shown potential in the treatment of several common comorbidities of eating disorders, including mood disorders, post-traumatic stress disorder, and substance use disorders. The theorized therapeutic mechanisms of psychedelic-assisted therapy suggest that it could be beneficial in the treatment of eating disorders as well. In this review, we summarize preliminary data on the efficacy of psychedelic-assisted therapy in people with anorexia nervosa, bulimia nervosa, and binge eating disorder, which include studies and case reports of psychedelic-assisted therapy with ketamine, MDMA, psilocybin, and ayahuasca. We then discuss the potential therapeutic mechanisms of psychedelic-assisted therapy in these three eating disorders, including both general therapeutic mechanisms and those which are relatively specific to eating disorders. We find preliminary evidence that psychedelic-assisted therapy may be effective in the treatment of anorexia nervosa and bulimia nervosa, with very little data available on binge eating disor-

Glossary of abbreviations: 5-HT, Serotonin; AN, Anorexia nervosa; BED, Binge eating disorder; BN, Bulimia nervosa; DMT, N,N-Dimethyltryptamine; ED, Eating disorder; LSD, Lysergic acid diethylamide; MDD, Major depressive disorder; MDMA, 3,4-Methyl enedioxy methamphetamine; MAOI, Monoamine oxidase inhibitor; OCD, Obsessive-compulsive disorder; PAT, Psychedelic-assisted therapy; PTSD, Post-traumatic stress disorder; SSRI, Selective serotonin reuptake inhibitor.

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der. Regarding mechanisms, psychedelic-assisted therapy may be able to improve beliefs about body image, normalize reward processing, promote cognitive flexibility, and facilitate trauma processing. Just as importantly, it appears to promote general therapeutic factors relevant to both eating disorders and many of their common comorbidities. Lastly, we discuss potential safety concerns which may be associated with these treatments and present recommendations for future research.

1. Introduction

1.1. Eating disorders

Eating disorders (EDs) are a group of serious conditions characterized by abnormal eating behavior which negatively affects physical and mental health. The most prevalent EDs in adults include anorexia nervosa (AN), bulimia nervosa (BN), and binge eating disorder (BED). (Diagnostic and statistical manual of mental disorders: DSM-5™ 2013; Udo and Grilo, 2018) Common symptoms of these three EDs are shown in Table 1. EDs are associated with chronic illness and disability, reduced quality of life, and increased suicide risk, with AN having the highest mortality rate of any psychiatric disorder. (Diagnostic and statistical manual of mental disorders: DSM-5™ 2013; J Arcelus et al., 2011) EDs additionally show a high degree of comorbidity with other psychological disorders, particularly mood disorders, substance abuse disorders, post-traumatic stress disorder (PTSD), and obsessive-compulsive disorder (OCD). (Diagnostic and statistical manual of mental disorders: DSM-5™ 2013; Brewerton, 2007)

The pathogenesis of EDs is not completely understood, and it may share etiology with other psychiatric disorders. Girls and young women are particularly at risk, although EDs can affect anyone. (Zipfel et al., 2015) Other likely contributing factors include genetic predisposition, hormonal dysregulation, anxious or obsessive temperament, stress, traumatic experiences in childhood, and environmental factors, such as an environment that highly values thinness. (Zipfel et al., 2015; Brewerton, 2018) Some studies have also noted cognitive and neurological abnormalities which may constitute risk or maintenance factors for EDs. (Zipfel et al., 2015; Kaye, 2008; Kessler et al., 2016)

Therapy for EDs most commonly involves behavior-centered strategies, sometimes combined with pharmacological treatment. (Davis and Attia, 2017; Davis and Attia, 2019) Antidepressants, particularly selective serotonin reuptake inhibitors (SSRIs), have shown some efficacy in people with BN or BED. (Davis and Attia, 2017; Leombruni et al., 2006) Less commonly, BN may be treated with other classes of antidepressants or antiepileptic medications, and BED with appetite-suppressing stimulants. (Davis and Attia, 2017) AN has proven more difficult to treat with medication, and drugs which improve BN or BED symptoms appear to have little efficacy in AN. (Davis and Attia, 2017) Some studies show that the antipsychotic olanzapine may help people with AN gain weight, but it does not appear to improve psychological symptoms. (Davis and Attia, 2017; Attia et al., 2019) Regarding psychotherapy, cognitive behavioral therapy has the most robust evidence base. (Hay, 2020) Family-based therapy, interpersonal therapy, motivational interviewing, psychoanalytic therapy, and some disorder-specific therapies are also sometimes used, with varying degrees of efficacy. (Zipfel et al., 2015; van den Berg et al., 2019; Startup et al., 2021)

Overall, the efficacy of ED treatments is limited, particularly for AN. Therapy may primarily be effective in the management of co-morbid diseases or weight, and the core symptoms of EDs are not always addressed by current therapies. (van den Berg et al., 2019; de Vos et al., 2014) While up to two thirds of people with AN and BN recover eventually, some remain ill for years or even decades. (Zipfel et al., 2015; Keel and Brown, 2010) There is a need for treatments which can accelerate recovery, and which are effective in treatment-resistant cases.

1.2. Psychedelic-assisted therapy

Psychedelic-assisted therapy (PAT) shows some efficacy in the treatment of mood disorders, addiction, and PTSD. (Breeksema et al., 2020) Several different classes of psychedelics are commonly used in PAT. The classic psychedelics include lysergic acid diethylamide (LSD), psilocybin (the principal psychoactive component in magic mushrooms), and N,N-Dimethyltryptamine (DMT, the principal psychoactive component in ayahuasca). (Nichols, 2016) Additionally, the rapid-acting antidepressant ketamine and the empathogen 3,4-Methyl enedioxy methamphetamine (MDMA) have some psychedelic properties and are combined with psychotherapy in a similar manner. (Smith et al., 2022; Drozdz et al., 2022) Classic psychedelics have a long history of use in sociocultural rituals and were first investigated as possible therapeutic agents in the 1950s, though political regulations brought this research to a halt by the 1970s. (Nichols, 2016) Research into the clinical use of psychedelics cautiously recommenced in the 1990s and has rapidly accelerated in the last decade. (Nichols, 2016)

When used in a safe setting, psychedelics can evoke profound psychological experiences which often have personally meaningful content. (Yaden et al., 2022; Roseman and Nutt, 2018) In PAT, these experiences are embedded in a therapeutic context in order to maximize safety and clinical benefits. (Garcia-Romeu and Richards, 2018) PAT may have some degree of trans-diagnostic efficacy in that it addresses underlying psychological and neurobiological pathologies that could contribute to various psychiatric di-

Table 1 Key symptoms of EDs according to the DSM-V. (Diagnostic and statistical manual of mental disorders: DSM-5™ 2013) OCD = obsessive compulsive disorder, PTSD = post-traumatic stress disorder.

	Anorexia Nervosa	Bulimia Nervosa	Binge Eating Disorder
Body weight	Significantly low body weight	Typically normal or overweight	Typically overweight
Eating behavior	Restriction of energy intake despite low weight	Episodes of binge eating (consuming extremely large amounts of food) Inappropriate compensatory behaviors to prevent weight gain (e.g. vomiting)	Episodes of binge eating (consuming extremely large amounts of food)
Self-image	Disturbance in experience of body weight or shape; undue influence of body weight or shape on self-evaluation	Undue influence of body weight and shape on self-evaluation	Feelings of depression, guilt, or disgust with oneself after binge eating
Other psychological symptoms	Intense fear of weight gain and/or behavior interfering with weight gain	A sense of a lack of control over binge eating episodes	A sense of a lack of control over binge eating episodes Marked distress regarding binge eating
Common comorbidities	Bipolar disorder, depression, anxiety disorders, OCD, substance use disorders, PTSD	Depression, bipolar disorder, anxiety disorders, substance abuse disorders, personality disorders, PTSD	Bipolar disorder, depression, anxiety disorders, substance use disorders

agnoses, including EDs. (Kočárová et al., 2021) Previous authors have named serotonergic mechanisms, changes in functional connectivity, and enhanced cognitive flexibility as potential mechanisms by which PAT may treat AN in particular. (Gukasyan et al., 2022) Some have also seen potential for serotonergic psychedelics to treat BN, BED, and obesity, and also name cognitive flexibility as a potential mechanism. (Borgland and Neyens, 2022)

For this review, we searched the PubMed database for studies which included people with EDs using the following search terms: (Hallucinogen OR Psychedelic OR Ketamine OR Psilocybin OR Mescaline OR Ayahuasca OR "Lysergic Acid Diethylamide") AND ("Anorexia Nervosa" OR “Bulimia Nervosa” OR “Binge Eating Disorder” OR "Eating Disorder"). The search was first performed in February 2022, and updated in May 2023. Further records were identified via citation searching. Based on the results of this search, we extracted data from 13 records. We first discuss their findings on how psychedelics affect people with EDs, including both improvements in ED symptoms and comorbid disorders. We then propose therapeutic mechanisms by which PAT may be helpful in the treatment of AN, BN, and BED, including both psychological mechanisms and associated neurobiological changes. Finally, we discuss important safety considerations for future trials with psychedelics in people with EDs. We believe these findings provide a clear rationale for more extensive research into PAT for the treatment of AN, BN, and BED.

2. Effects of psychedelics in people with eating disorders

Research on the effects of psychedelics in people with EDs has included case reports, cross-sectional research, and small clinical studies, mostly focusing on AN and BN (Table 2). One 1959 case report describes a patient with AN who was treated with two doses of psilocybin and showed strong therapeutic effects, including improved mood and weight gain. (Verroust et al., 2021) Other case reports describe therapeutic benefits in people with EDs undergoing ketamine-assisted therapy. (Dechant et al., 2020; Ragnhildstveit et al., 2021; Scolnick et al., 2020; Robison et al., 2022; Schwartz et al., 2021) One experienced lasting remission from BN after ketamine treatment, (Ragnhildstveit et al., 2021) while another recovered from AN after ketamine combined with a ketogenic diet. (Scolnick et al., 2020) Another patient with AN experienced reductions in comorbid suicidality and depression after ketamine treatment, though she did not achieve remission. (Dechant et al., 2020) A case series of ketamine treatment in four people with EDs with comorbid treatment-resistant depression reported improvement in both depression and ED symptoms in 3 out of 4 patients. (Schwartz et al., 2021) Finally, a separate series of five people with EDs treated for anxiety and depression reported improvements in both of these comorbid disorders, in addition to some improvements in ED symptoms. (Robison et al., 2022)

Four cross-sectional studies have also investigated self-reported effects of psychedelic use in people with EDs. In a prospective survey, 28 participants with a lifetime ED diagnosis reported significant improvements in depression and well-being after taking a classic psychedelic. (MJ Spriggs et al., 2021) The study also reported moderate evidence for an association between symptom improvement and emotional breakthrough, indicating that emotional breakthrough may mediate positive outcomes in EDs after psychedelic experiences. A second survey study investigated the impact of psychedelic use on symptoms of disordered eating in people with a history of using psychedelics. (Lafrance et al., 2021) They reported that more frequent psychedelic use was associated with reductions in disor-

Table 2 Summary of studies describing the effects of psychedelics on eating disorder symptoms, organized by type. AN = anorexia nervosa, BED = binge eating disorder, BN = bulimia nervosa, MDD = major depressive disorder, MDMA = 3,4-Methyl enedioxy methamphetamine, OSFED= other specified feeding and eating disorder.

Study	Type	Eating Disorders	Treatment	Results
Dechant et al., 2020	Case report	AN	Ketamine	Transient improvement in suicidality, depression
Ragnhildstveit et al., 2021	Case report	BN	Ketamine	Sustained remission >1 year post-treatment
Scolnick et al., 2020	Case report	AN	Ketamine	Sustained remission from AN, MDD >6 months post-treatment
Verroust et al., 2021	Case report	AN	Psilocybin	Improved mood, weight gain at 1 month post-treatment
Robison et al., 2022	Case series	AN, BN	Ketamine	Immediate improvement in ED, mood disorder symptoms; no long-term follow-up
Schwartz et al., 2021	Case series	AN, BN	Ketamine	Improvements in ED, mood disorder symptoms
Lafrance et al., 2017	Cross-sectional	AN, BN	Ayahuasca	Self-reported improvement in ED symptoms
Lafrance et al., 2021	Cross-sectional	Not specified	Various classic psychedelics	Psychedelic use negatively related to disordered eating
Renelli et al., 2018	Cross-sectional	AN, BN	Ayahuasca	Self-reported improvement in ED symptoms
MJ Spriggs et al., 2021	Cross-sectional	Any ED	Various classic psychedelics	Self-reported improvements in depression, well-being
Brewerton et al., 2022	Clinical trial	AN, BN, BED, OSFED	MDMA	Improvement in ED symptoms 3–4 weeks post-treatment
S Knatz Peck et al., 2022	Clinical trial	AN	Psilocybin	Improvement in ED symptoms 1 month post-treatment
Mills et al., 1998	Clinical trial	AN, BN	Ketamine	Sustained reductions in depressive symptoms, compulsive behaviors for several months

dered eating, with spirituality and emotional regulation as mediating factors. Finally, two exploratory studies interviewed people with EDs who partook in ayahuasca ceremonies as a treatment for ED symptoms. These individuals reported subjective improvements in symptoms, particularly improvements in negative body perception, and they contrasted ayahuasca positively with typical ED therapies, reporting that ayahuasca led to greater improvements and helped them better understand the roots of their disorder. (Lafrance et al., 2017; Renelli et al., 2018)

Most importantly, some clinical studies with psychedelics have included people with EDs. An early trial suggested that ketamine infusions could treat compulsive eating behavior in patients with AN, though the concomitant use of opioids makes the results difficult to interpret. (Mills et al., 1998) More recently, a trial of MDMA-assisted therapy for PTSD included 13 patients with clinical ED symptoms, which significantly improved after MDMA compared to placebo. (Brewerton et al., 2022) Lastly, preliminary data from a pilot study of psilocybin treatment for AN found that 4 out of 5 patients had significant and persistent reductions in ED symptoms one month post-treatment. (S Knatz Peck et al., 2022) More trials with psilocybin are underway. (S Knatz Peck et al., 2022; MJ Spriggs et al., 2021)

Many of these studies are limited by open-label designs and the biases inherent in self-reported symptoms, and the heterogenous methods make results difficult to evaluate. Nevertheless, there are plausible reasons to hypothesize that psychedelics could be a particularly effective treatment for EDs. As we will discuss next, psychedelics may both activate general therapeutic factors and address symptoms that are relatively specific to EDs.

3. Potential mechanisms of psychedelic-assisted therapy in the treatment of eating disorders

3.1. Improved body image

Both AN and BN are associated with a distorted body image, defined as a disturbance in the perception of weight or body shape. (Smolak and Levine, 2015) Several mechanisms have been proposed to explain the association between body image disturbances and these EDs. Firstly, those with AN or BN frequently evaluate themselves based on their shape, weight, and perceived control over their bodies, while neglecting other characteristics. (Diagnostic and statistical manual of mental disorders: DSM-5™ 2013) Concerns about weight and shape have been shown to predict ED onset, and over-valuing weight and shape, as well as attempting to control them, may be an underlying core psychopathol-

ogy in AN and BN. (Smolak and Levine, 2015; McLean and Paxton, 2019; A Kearney-Cooke and Tieger, 2015) Secondly, many people with EDs internalize culturally promoted body objectification, such as body shape and weight ideals or the sexualization of certain body types. (Davenport et al., 2015; A Kearney-Cooke and Tieger, 2015) Finally, people with EDs struggle with emotional regulation, and behaviors such as bingeing, over-exercising, or starving oneself provide temporary relief from negative feelings about physical appearance. (A Kearney-Cooke and Tieger, 2015)

PAT is thought to help people break down maladaptive beliefs and thought patterns, which could include negative beliefs about one's own body and shape. (Carhart-Harris and Friston, 2019; Ho et al., 2020) Ordinarily, the brain continuously constructs a first-person concept of the body and its environment (the 'bodily self') by predictive coding. (Apps and Tsakiris, 2014) This involves dynamic optimization of beliefs about the self via bottom-up updating, which results from the comparison between existing beliefs, or priors, and new sensory inputs. (Ho et al., 2020) Within this framework, distorted body image could result from distorted high-level priors which are resistant to bottom-up updating (for example, "My body is not thin enough"). (Ho et al., 2020) As psychedelics disrupt top-down predictive networks, prior beliefs about the body can weaken, allowing sensory input to influence them once more. (Ho et al., 2020) In line with this, people often report alterations in how they perceive themselves and their bodies while under the influence of psychedelics. (Breeksema et al., 2020; Preller and Vollenweider, 2018; Girn and Kalina, 2018) In an appropriate therapeutic setting, enabling bottom-up signals to disrupt maladaptive priors could help people with EDs reinstate healthier beliefs about their body and its shape. (Carhart-Harris and Friston, 2019; Ho et al., 2020) This is also in line with the finding that providing bottom-up information about a healthy body size via virtual reality can improve body image distortions in people with AN. (Keizer et al., 2016)

Neurobiologically, psychedelic effects on the bodily self may particularly involve the insula, a key region for interoceptive awareness, self-referential processing, and self-recognition. (Craig, 2009; Damasio et al., 2000) Insula function is known to be disrupted in EDs. (Zipfel et al., 2015; Bulik et al., 2022; Frank et al., 2019) Psilocybin generally appears to increase activity in the insula, (Lewis et al., 2017) and its acute effects in this region are also correlated with reduced self-referential processing. (Smigielski et al., 2020) Reduced self-referential processing is a typical phenomenon in PAT, culminating in the complete dissolution of the self in the most extreme cases. (Mason et al., 2020; Nour et al., 2016; Lebedev et al., 2016)

Participants with EDs in previous studies have reported effects on self-referential processing and body image while under the influence of psychedelics. For example, one individual with AN saw herself first as a "rotting, decaying skeleton" and later as a "full-bodied, just beautiful woman" under the influence of ayahuasca, which motivated her to "start gaining some weight." (Lafrance et al., 2017) A second person reported that she "experienced [her] body as a gift", motivating her to nourish it more properly. (Lafrance et al., 2017) Other participants had similar experiences, in which they reported improved self-image, including body image, and a greater motivation to treat themselves and their bodies with more care. (Lafrance et al., 2017; Renelli et al., 2018) In people with EDs, temporary dissolution of the self – and its associated beliefs about the body – could allow for more flexibility in these beliefs.

3.2. Normalized reward processing

People with EDs show dysfunctional reward processing which can be observed in both behavior and brain activity. BN and BED are characterized by a bias towards food rewards over other types of rewards, as well as steeper discounting of monetary rewards and altered reinforcement learning. (Leenaerts et al., 2022) People with EDs also show altered activity in the striatum, insula, and anterior cingulate cortex (ACC) in response to food images. (Zipfel et al., 2015; Leenaerts et al., 2022; Bohon and Stice, 2011; Foldi et al., 2020; Haynos et al., 2021; Keating et al., 2012) This may also extend to social stimuli, such as feedback from others. (El-Deredy et al., 2015; Wagner et al., 2010) In BN and BED, reduced structural and functional connectivity between frontal regions and the striatum is associated with binge frequency and compulsive reward seeking. (Leenaerts et al., 2022; Haynos et al., 2021) AN is also sometimes characterized by anhedonia, a state in which response to rewards is globally reduced. (Keating et al., 2012)

AN in particular can be viewed as a disease of "reward contamination," in which maladaptive conditioning causes normally punishing stimuli to be rewarding (e.g. starvation) and normally rewarding stimuli to be punishing (e.g. high-calorie foods). (Keating et al., 2012) This contamination is relatively specific to disease-related stimuli, such as food, exercise, and body shape. (Keating et al., 2012; O'Hara et al., 2015; Kogel et al., 2021) Consistent with this theory, people with AN show increased activity in reward regions when viewing moldy food and reduced activity after eating or consuming sugar. (Keating et al., 2012; O'Hara et al., 2015) They also show reductions in gray matter in the striatum and somatosensory cortex, which may underlie their abnormal responses to food. (Titova et al., 2013)

People with AN also often have a favorable view of their disorder, believing that it helps them feel safe, communicate distress, and deal with strong emotions. (Schmidt and Treasure, 2006) One maladaptive "reward" obtained from disordered eating is control over negative emotions and other undesirable experiences. People with EDs show high levels of experiential avoidance, defined as the unwillingness to have particular private experiences, including difficult emotions, memories, and thoughts. (Rawal et al., 2010; Frank et al., 2018) Many people with AN report using control over food to help cope with emotions they find overwhelming. (Startup et al., 2021; Schmidt and Treasure, 2006) Binge eating is also mediated by experiential avoidance, and targeting avoidance with therapy can reduce the frequency of episodes. (Lillis et al., 2011)

PAT may help normalize reward processing. As discussed above, psychedelics are thought to weaken the influence of high-level priors and allow bottom-up information to update beliefs. (Carhart-Harris and Friston, 2019) This may also apply to beliefs about what is rewarding and what is not. In

the right therapeutic context, psychedelics may help people to reevaluate their beliefs about their own bodies, food, and the utility of their unhealthy behaviors. Furthermore, psychedelics may restore responses to naturally rewarding stimuli and counteract anhedonia. (Hesselgrave et al., 2021) In people with depression, psilocybin therapy increased scores on the Snaith-Hamilton Pleasure Scale, which measures one's self-reported ability to feel pleasure. (Carhart-Harris et al., 2016) LSD has also been shown to increase reward responses and reward-based reinforcement learning, without also increasing responses to negative feedback. (Glazer et al., 2022; Kanen et al., 2022) Additionally, psychedelics may be able to adjust reward responses to social stimuli by re-opening a critical period of social reward learning. (Nardou et al., 2019) MDMA, LSD and psilocybin have all been shown to increase oxytocin, which evokes a period of synaptic plasticity necessary for social reward learning. (Nardou et al., 2019; Holze et al., 2019; F Holze et al., 2021; Schmid et al., 2015; F Holze et al., 2022) People with EDs often struggle in social situations and show maladaptive emotional responses to social events, which then feed into their avoidant coping behavior. (Startup et al., 2021) PAT may present an opportunity for re-learning positive interactions with other people.

PAT has also been shown to reduce experiential avoidance, thought to be an underlying factor in maladaptive reward processing. (Zeifman et al., 2020; Watts et al., 2017) Under normal circumstances, avoidant coping strategies can "work" in the short-term via negative reinforcement. In the psychedelic state, however, this is no longer the case: attempts to avoid unpleasant experiences often only intensify those experiences. (Wolff et al., 2020) By contrast, accepting difficult emotions can make them seem less frightening and ultimately lead to relief; acceptance is thus negatively reinforced in a type of operant conditioning. (Wolff et al., 2020; Wolff et al., 2022) People thus learn that they can withstand even very intense negative emotions, and that accepting these emotions is more rewarding than avoiding them. Moreover, the brain may be particularly receptive to learning experiences at this time because psychedelics promote neuroplasticity in cortical regions, including regions important for emotional regulation. (Calder and Hasler, 2022; Barrett et al., 2020) In the abovementioned study of people with EDs who consumed ayahuasca, several individuals describe shifts away from unhealthy coping mechanisms, as well as greater ability to accept negative emotions. (Lafrance et al., 2017)

3.3. Reduced behavioral and cognitive rigidity

AN in particular is characterized by a rigid style of thinking and behaving, including but not limited to rigidity in eating behavior, which may also be a risk factor that appears before the disease itself. (Startup et al., 2021; Wollburg et al., 2013) Rigid thinking styles are also associated with a greater need for control and fear of losing self-control. (Froreich et al., 2016; Palmieri et al., 2021) OCD, which is characterized by rigid, uncontrollable patterns of thought and behavior, is comorbid in 15–29% of people with AN, and up to 79% of people with AN will experience compulsions or obsessions in their lifetime. (Zipfel et al., 2015) AN is also associated with reduced self-reported cognitive flexibility, as well as impaired perceptual flexibility, both of which may constitute risk or maintenance factors for the disorder. (Miles et al., 2020)

Like other maladaptive priors, rigid ways of thinking and behaving could become loosened in the psychedelic state, allowing for revision. (Gukasyan et al., 2022; Carhart-Harris and Friston, 2019) Relatedly, the psychedelic state often requires people to give up some degree of control over what is happening, and therapists commonly advise clients to "trust, let go, and be open." (Wolff et al., 2020) Voluntary surrender of control under psychedelics may serve as a useful foil for people with a high need for control, as often seen in AN. When properly handled in a safe and supportive therapeutic context, these individuals may be able to experience a positively valenced loss of control that does not come with expected negative consequences. (Wolff et al., 2020) In this vein, previous research suggests that psilocybin might be able to improve symptoms of OCD, which is often comorbid with EDs and shares control-related symptoms. (Palmieri et al., 2021; Moreno et al., 2006)

People with BN and BED may not benefit from this aspect of PAT as much, because they show a different kind of behavioral rigidity. Rather than excessive control, lack of control over binge episodes is a central feature. (Diagnostic and statistical manual of mental disorders: DSM-5™ 2013) Binge eating is a compulsive behavior that shows some similarities with addiction: people feel compelled to persist in unhealthy behaviors despite severe consequences. (O'Hara et al., 2015) Because of this commonality, people with BN and BED may instead benefit from the anti-addictive properties of psychedelics. Participants in trials of psilocybin for alcohol use disorder reported greater control over their choices and behaviors, including but not limited to their drinking, and many remained abstinent from alcohol for years after treatment. (Bogenschutz et al., 2018; Bogenschutz et al., 2015; Bogenschutz et al., 2022) If this effect generalizes to people with BN and BED, it is possible that PAT could help them resist the impulse to binge.

3.4. Trauma processing

Traumatic experiences, particularly in childhood, are common in people with EDs and are considered a risk factor for developing an ED. (Solmi et al., 2021; Brewerton, 2019; Molendijk et al., 2017; Tagay et al., 2010; Dansky et al., 1997; Brewerton et al., 2021) EDs have been linked to many types of potentially traumatic events, including a history of sexual, physical, or emotional abuse, as well as neglect and bullying. (Brewerton, 2007) Consequently, EDs are frequently accompanied by trauma-related symptoms, including a lower tolerance to distress and trauma, heightened threat perception, and heightened emotional reactivity and avoidance, all of which may drive maladaptive eating behaviors. (Brewerton, 2007; Brewerton, 2019; Brewerton et al., 2021; Rijkers et al., 2019; Holzer et al., 2008) Between 9.4% and 24.3% of people with an ED also fulfill clinical criteria for PTSD at some point in their lives. (Brewerton, 2007) More specifically, some studies report that up to 47% of people with AN and 62% in people with BN fulfill clinical criteria for PTSD. (Rijkers et al., 2019) Trauma

exposure and PTSD may also be associated with more severe ED symptoms, (Molendijk et al., 2017; Rijkers et al., 2019; Backholm et al., 2013) and there is some evidence that the relationship between trauma and EDs may partly be mediated by PTSD symptoms. (Dansky et al., 1997; Holzer et al., 2008; Dubosc et al., 2012; Mitchell et al., 2016; KS Mitchell et al., 2021) Consequently, integrating trauma therapy into the treatment of EDs is essential in people with previous exposure to trauma. (Brewerton, 2007; Brewerton, 2019; Molendijk et al., 2017; Brewerton et al., 2021; Holzer et al., 2008)

Most psychotherapies applied in those with PTSD are exposure-based and aim to extinguish conditioned fear to trauma-related cues, which can be aversive enough that clients terminate therapy. (Krediet et al., 2020) Psychedelics have an advantage in that they may provide some protection against re-traumatization in psychotherapy, and MDMA may provide the best protection. (Hasler, 2022) During PAT, people may re-experience painful memories, but they are often able to face and work through these difficult experiences rather than being simply overwhelmed. (Sessa, 2017) This has been dubbed the "helioscope" effect. (Hasler, 2022) Neurobiologically, this effect may arise from the fact that MDMA, LSD, and psilocybin acutely reduce the activity and responsiveness of the amygdala. (Bedi et al., 2009; Gamma et al., 2000; Mueller et al., 2017; Kraehenmann et al., 2015) They also have strong prosocial and anxiolytic effects, which may counteract trauma-related avoidance and hyperarousal in psychotherapy sessions. (Brewerton et al., 2021; Krediet et al., 2020; Dolder et al., 2016; Preller et al., 2016)

MDMA-assisted psychotherapy has been shown to be particularly effective in the treatment of PTSD, (JM Mitchell et al., 2021; Mithoefer et al., 2018) and though there are no controlled studies on EDs specifically, preliminary results from people with comorbid EDs show promising results. (Brewerton et al., 2022; Brewerton et al., 2021) Ketamine and classic psychedelics may also act as "helioscopes" and show some potential in the treatment of trauma-related psychopathology. (Feder et al., 2021; Anderson et al., 2020) Relatedly, people with EDs who attended ayahuasca ceremonies have reported positive effects on trauma-related symptomatology. Several participants reported more insight into the root causes of their psychological problems, including previous traumatic experiences. (Lafrance et al., 2017; Renelli et al., 2018) They also reported that ayahuasca helped them to deal with difficult emotions. (Renelli et al., 2018)

3.5. Improvements in co-morbid disorders and general therapeutic factors

Comorbid disorders are more common than not in people with EDs, and they are strong predictors of mortality. (J Arcelus et al., 2011; Hambleton et al., 2022) Apart from trauma history and PTSD, discussed above, EDs are often comorbid with depression and anxiety, and PAT may be able to address these disorders in addition to specific ED symptoms. (Gukasyan et al., 2022; Borgland and Neyens, 2022) Several clinical trials with psilocybin and LSD have shown promising results in the treatment of depression and anxiety disorders, including in treatment-resistant cases. (Gasser et al., 2014; F Holze et al., 2022; Carhart-Harris et al., 2021; Griffiths et al., 2016; Ross et al., 2016; Davis et al., 2021) In a small pilot study of psilocybin for the treatment of AN, two individuals showed meaningful reductions in comorbid anxiety symptoms. (S Knatz Peck et al., 2022) Additionally, ketamine is an effective antidepressant and may be particularly useful in reducing suicidality, one of the main causes of death in people with EDs. (Reinstatler and Youssef, 2015; Surjan et al., 2022) In people with EDs, ketamine has already been seen to reduce anxiety and depression, (Scolnick et al., 2020; Robison et al., 2022; Schwartz et al., 2021) as well as suicidality. (Dechant et al., 2020)

Interestingly, both EDs and mood disorders are often comorbid with gastrointestinal symptoms and reduced diversity of the gut microbiome. (Lam et al., 2017) A dysregulated microbiome may constitute a development or maintenance factor for AN in particular. (Butler et al., 2021) It has been suggested that psychedelics exert some of their long-term effects via the microbiome. (Kuypers, 2019) Psilocybin has been shown to diversify the intestinal microbiome in mice, and this diversification appeared to be responsible for lasting antidepressant-like behavioral effects. (Cordner et al., 2022) Normalization of the gut microbiome may thus assist with recovery from both EDs and comorbid mood disorders, and presents an intriguing avenue for future research. (Kleiman et al., 2015)

EDs are also commonly comorbid with substance use disorders, and they may share some underlying neurobiology. EDs are associated with abnormalities in the dopamine system, including altered dopamine receptor binding in reward regions, D2 receptor polymorphisms, and abnormal dopaminergic reactions to food, starvation, and exercise. (Leenaerts et al., 2022; Keating et al., 2012; O'Hara et al., 2015) Particularly for BN and BED, these changes are similar to those seen in addiction. (Avena and Bocarsly, 2012) Psychedelics have thus far shown promising results in trials focused on alcoholism and smoking cessation, and they are theorized to help with addiction recovery in general. (Bogenschutz et al., 2015; Bogenschutz et al., 2022; Johnson et al., 2017; Sessa et al., 2021)

One small trial suggested that psilocybin might be useful in the treatment of OCD, (Moreno et al., 2006) another common comorbidity with EDs. There is also some evidence for ketamine's efficacy in OCD. (Sharma et al., 2020; Rodriguez et al., 2013) One case report of ketamine treatment for BN also described resolution of compulsory symptoms. (Ragnhildstveit et al., 2021) However, these results are very preliminary and it remains to be seen whether psychedelics truly have the potential to treat OCD symptoms.

The potential for treating multiple co-morbid disorders suggests that psychedelics have some degree of transdiagnostic efficacy, similar to psychotherapy. (Kočárová et al., 2021) It is thus plausible that they facilitate general processes of therapeutic change, in addition to mechanisms specific to EDs. Based on data from in-person psychotherapy, Klaus Grawe proposed five general mechanisms of therapeutic change which have been widely influential and map particularly well onto PAT. (Grawe, 1997) Grawe concluded that the *therapeutic alliance, resource activation,*

Table 3 Typical aspects of three categories of eating disorders which may cause safety concerns or contraindicate psychedelic-assisted therapy.

Average age of onset	Anorexia Nervosa Under 18	Bulimia Nervosa Under 18	Binge Eating Disorder -
Body weight	Low body weight or refeeding syndrome may be present	-	Obesity-related hypertension, cardiovascular disease may be present
Common comorbidities (Diagnostic and statistical manual of mental disorders: DSM-5™ 2013)	Bipolar disorder	Bipolar disorder, personality disorders	Bipolar disorder
Medication interactions	Serotonergic medications	Serotonergic medications	Serotonergic medications
Common psychedelic side effects	-	Nausea and vomiting	-

clarification (understanding the root of one's psychological problems), *problem actuation* (emotional experience of one's problems), and *mastery* (reinforcement of appropriate coping methods) were important drivers of therapeutic change. Their importance has been supported by studies with diverse patient groups, including those which included people with EDs. (Mander et al., 2013)

Introducing psychedelics into therapy may both promote these general mechanisms of change and solidify their impact via effects on neuroplasticity. The first mechanism, the therapeutic alliance, can be strengthened by psychedelics via positive effects on empathy, trust, and sociality. (Dolder et al., 2016; Oehen and Gasser, 2022) Regarding resource activation, people have often described discovering new personal strengths and motivations after psychedelic experiences, (Mander et al., 2013; Oehen and Gasser, 2022) and this theme has appeared in interviews with people with EDs as well. (Lafrance et al., 2017) Reflecting Grawe's concept of clarification, many people describe an improved understanding of their problems following psychedelic experiences, and this is thought to be a key mechanism of PAT. (Peill et al., 2022) Additionally, people commonly report extremely emotional experiences of their problems during PAT, often accompanied by the release of suppressed or "forbidden" emotions; this is akin to Grawe's idea of problem actuation. (Roseman et al., 2019; Gasser et al., 2015) Finally, PAT may be able to reinforce appropriate coping strategies by promoting acceptance of difficult experiences over avoidance. (Wolff et al., 2020) It may thus be particularly suited to disorders characterized by avoidance-related behaviors, which would include EDs and many of their common comorbidities.

4. Safety considerations

Psychedelics have a favorable safety profile when used in controlled settings, and toxicity is rare even in uncontrolled settings. (Nichols and Grob, 2018; AC. Parrott, 2012; AC. Parrott, 2012; Thomas et al., 2017; Mithoefer et al., 2019) Nevertheless, there may be specific safety considerations relevant to treating people with EDs (Table 3), in addition to general safety guidelines for clinical use of psychedelics (see Johnson et al., 2008 for a review (Johnson et al., 2008)).

One of these considerations is the typical age of people with EDs. ED prevalence increases by the age of 14, with a median age of onset of 17 for AN, 16 for BN, and 21 for BED, and early intervention is critical. (Udo and Grilo, 2018) According to preliminary data from a survey of naturalistic psychedelic use, younger age may be a risk factor for persisting perceptual symptoms in the weeks after a psychedelic experience. (Zhou et al.) Though psychedelics may be no more harmful than alternative psychiatric medications given to younger age groups, the lack of data on their long-term effects on cognitive development should warrant caution.

Additionally, dangerously low or high body weight may increase the risk for certain adverse effects. People with AN in particular may have a dangerously low body weight, raising concerns about medical stability and dosing. Medical instability can result from low body weight or from refeeding syndrome, comprising abnormal electrolyte concentrations and cardiac, hepatic, or renal dysfunction. (Zipfel et al., 2015) Recent, rapid weight loss can also be a sign of instability. Medical stability should be closely monitored due to the risk that psychedelics could exacerbate some of these problems, with some substances perhaps riskier than others. On the other hand, people with BED are 3-6 times more likely to suffer from obesity than the general population, and this brings other challenges. (McCuen-Wurst et al., 2018) Obesity raises the risk for hypertension and other cardiovascular problems, which are often an exclusion criterion in clinical trials with psychedelics due to concerns about increased heart rate and blood pressure. (Borgland and Neyens, 2022; Johnston et al., 2022) Additionally, while classic psychedelics do not need to be dosed according to body weight, MDMA effects do depend on weight. (Studerus et al., 2021; Spriggs et al., 2022) Many studies with MDMA have thus far used a standard dose without accounting for body weight, which could result in unexpectedly intense effects for those who are underweight or relatively weak effects for those who are overweight. (JM Mitchell et al., 2021; Mithoefer et al., 2018)

Certain comorbidities of EDs also present challenges and may make PAT unwise, or at least justify extreme caution. There is some concern that psychedelics could exacerbate mania in bipolar disorder due to its partially shared etiology with psychosis. (Bosch et al., 2022) Additionally, people with comorbid personality disorders may not be able to benefit from PAT without specialist care because of difficulty maintaining trust and a stable therapeutic alliance. (Bender, 2005)

Medication interactions must also be considered. Though clinical trials often exclude people who are taking additional medications, real-world clinical practice (currently limited to restricted medical use programs (Oehen and Gasser, 2022)) must consider the risks and benefits of continuing or stopping medications. The risk of serotonin toxicity, in particular, may be substantial and has not yet been fully explored. Classic psychedelics share activation of 5-HT2A receptors, and MDMA also has serotonergic activity. (Nichols, 2016) EDs and many of their common comorbidities are often managed with psychotropics that affect serotonergic neurotransmission, including SSRIs, serotonin norepinephrine reuptake inhibitors, tricyclic antidepressants, monoamine oxidase inhibitors (MAOIs), buspirone, trazodone, mirtazapine and atypical antipsychotics. (Davis and Attia, 2017) While SSRIs appear to be safe when combined with classic psychedelics, (Becker et al., 2021) many other drug combinations have not been adequately tested. In general, serotonin agonists such as classic psychedelics, appear to have a lower risk for development of serotonin toxicity. (Malcolm and Thomas, 2021) However, serotonin releasing agents such as MDMA can precipitate serotonin toxicity when combined with other drugs, for example MAOIs. (Pilgrim et al., 2012)

Because of this potential risk, careful monitoring of diagnostic criteria for serotonin toxicity should be considered with people with EDs on serotonergic medications. Serotonin-related adverse reactions occur along a spectrum from mild symptoms to a severe and life-threatening reaction encompassing neuroexcitation, changes in mental status, and instability in the cardiovascular system. (Buckley et al., 2014; Ellahi, 2018) Typical psychedelic drug effects may overlap with signs of mild serotonin toxicity, including altered mental status, mydriasis, mild hyperthermia, changes in temperature sensation, mild tremors or shaking, and gastrointestinal distress. (Nichols and Grob, 2018; AC. Parrott, 2012; Mithoefer et al., 2011; F Holze et al., 2021) Transient signs of serotonergic drug ingestion which follow the psychological trajectory of the psychedelic experience are to be expected, but these somatic symptoms are more persistent and intense with serotonin toxicity.

Finally, common side effects of psychedelics should be considered in light of ED symptoms. Vomiting is a common effect of ayahuasca in particular, though it can also occur with other psychedelics. (Rossi et al., 2022) Though people with BN in ayahuasca studies thus far have not found this problematic, (Lafrance et al., 2017) samples have been small and other psychedelics with lower rates of nausea and vomiting may be more suitable for those with bingeing and purging behavior.

5. Conclusion and outlook

Preliminary evidence suggests that PAT could be beneficial in the treatment of AN and BN, as well as several common comorbidities, presenting a clear rationale for future research. Specifically, preliminary studies support more research into therapy with psilocybin, ketamine, and ayahuasca for AN, ketamine and ayahuasca for BN, and MDMA for EDs associated with trauma-related pathology.

PAT may improve symptoms of EDs by both addressing specific ED symptoms and promoting general therapeutic factors. Previous accounts of psychedelic use in people with EDs suggest that psychedelics may improve distorted body image, normalize maladaptive reward processing, reduce behavioral and cognitive rigidity, and aid in trauma processing. Furthermore, psychedelics may promote general therapeutic factors that are helpful in recovering from avoidance-related psychological disorders, including both EDs and common comorbidities. Psychedelics' ability to relax higher order beliefs may account for some of this, as may their ability to promote acceptance of difficult thoughts and emotions. Changes arising during or shortly after a psychedelic experience may additionally have a lasting impact on the brain via psychedelics' effects on cortical neuroplasticity.

Given preliminary results and plausible therapeutic mechanisms, there is a clear rationale for future studies into PAT for EDs. Future research would benefit from larger, controlled trials investigating the safety and efficacy of PAT with different substances for different ED diagnoses. In particular, it is still unclear whether specific psychedelic substances are better suited to certain patient groups. It is possible, for example, that MDMA may be particularly suitable for those with a history of trauma. There is also a rationale for better inclusion of people with BED, because despite commonalities with BN, BED has been far less researched in connection with PAT. Future trials should also make a point to record safety-related outcomes, taking into consideration that safety concerns may vary with different ED diagnoses. Specifically, it would be useful to record data on the presence and impact of gastrointestinal side effects (e.g. vomiting), weight-related side effects, and any lasting perceptual abnormalities, particularly in younger patients. Finally, trials comparing PAT to other ED treatments would be valuable in order to determine the relative safety and efficacy of psychedelic treatments.

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Interpretation of the data: AC, SM, NF, PP, GH

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GH does not have a conflict of interest regarding the content of the paper.

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