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Psychedelic-Assisted Therapy for Anorexia Nervosa

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ABSTRACT

Anorexia Nervosa is a severe psychiatric disorder characterized by a distorted body image and an intense fear of weight gain, leading to self-imposed caloric restriction and excessive weight loss. Current treatments, including nutritional rehabilitation, psychotherapy, and pharmacological interventions, exhibit low long-term recovery rates. Psychedelic-assisted therapy (PAT) offers a promising avenue for treating anorexia by addressing the underlying psychological issues and comorbid disorders. Nine studies investigating the efficacy of psychedelic-assisted therapy in treating Anorexia Nervosa were systematically reviewed. The analysis indicates significant yet underexplored potential for PAT in the treatment of anorexia. The data overwhelmingly demonstrate a robust positive effect of the treatment across various psychedelic compounds. Common findings in the reviewed literature include a decrease in self-reported symptoms, weight gain, and a reduction in comorbidities. The reliance on self-reporting to measure clinical outcomes, small sample sizes, and the lack of blinding and placebo controls present significant challenges in interpreting the results and introduce the risk of biased reporting. The limited available data suggest that psychedelic-assisted therapy may be an effective treatment for eating disorders. However, caution is warranted in drawing definitive conclusions due to several significant limitations affecting data validity.

Introduction

Anorexia nervosa (AN) is a serious psychiatric disorder that deteriorates a patient's physical and mental well-being over time. This eating disorder is characterized by a disturbed body image and a fear of gaining weight, which results in behaviors that aim to control body weight. (Zipfel et al., 2015) Prevalent symptoms of anorexia nervosa are an abnormally low body weight (at least 15% below what would be expected, or a body mass index lower than 17.5), excessive exercise, and reduced dietary intake. (Diagnostic and statistical manual of mental disorders: DSM-5™ 2013). During a lifetime, 4% of females and 0.3% percent of males struggle with AN with very few achieving full remission. (van Eeden et al., 2021) It is estimated that only 46% of patients fully recover, 34% remain with partial symptoms, and 20% remain chronically ill in the long term. (Arcelus et al., 2011) The mortality rates of anorexia are higher than any other mental illness with approximately 4% of patients dying within 4 years of diagnosis. (Auger et al., 2021) At 5 years, the mortality rate increases 9 times. Anorexia nervosa can be classified into two subdivisions: a restrictive subdivision and a binge-purge subdivision. (Strauss, 1987) Patients diagnosed with the restrictive subtype lose body mass through caloric restriction or excessive exercise, while patients with the binge-purge classification intake large amounts of food and purge after that. (Balasundaram & Santhanam, 2021). The two principal differences between bulimia and the binge-purge subtype of anorexia are that patients with bulimia typically have a normal or higher than normal body weight, and their periods of restriction last shorter than the longer periods of restriction for AN. (Smith, 2016)

Anorexia Nervosa

Similarly to other conditions classified as eating disorders, the direct etiology of AN has proven to be notoriously difficult to derive. It is known that AN primarily affects the younger population, typically emerging in early to mid-adolescence. (Zipfel et al., 2015) This phase of human development is characterized by significant biological and psychological changes as well as alterations in social exposure. The combination of predisposing genetic and psychological characteristics and environmental cues may trigger the onset of AN during this vulnerable period. (Woerwag-Mehta & Treasure, 2008) Some common physical predispositions include 5-HT deficiency, prematurity, obstetric complications, low brain-derived neurotrophic factor (BDNF), and an altered hypothalamic-pituitary-adrenal axis. (Woerwag-Mehta & Treasure, 2008) Psychological predispositions of anorexia include perfectionism, rigidity, interpersonal distrust, low self-esteem, and avoidant coping style. (Grzelak et al., 2017). AN also has a strong correlation with social factors such as occupation (ex. ballet dancer, athlete, model), social isolation, abuse, and distorted family dynamics. (Woerwag-Mehta & Treasure, 2008)

Despite successful recovery in some patients, AN can result in longer-term effects. (Meczekalski et al., 2013) This may include consequences in fertility and pregnancy due to impairment of the gonadotropin-releasing hormone (GnRH) which results in hypoestrogenism and obstetric difficulties. AN also has been found to have a profound influence on bone metabolism which prevents patients from reaching normal peak bone mass, resulting in a higher risk of osteoporosis and bone fractures. Patients are also affected with cardiovascular complications such as sinus bradycardia that remain despite weight gain. (Meczekalski et al., 2013) It is crucial to note that in many patients despite AN remission, the comorbid disorders remain. (Fichter et al., 2017)

Neuroscience of Anorexia

The neuromodulator 5-HT has been found to be strongly involved in the development of AN, in particular, the 5-HT receptors 5-HT_{1A} and 5-HT_{2A} and the main metabolite of 5-HT, 5-hydroxyindoleacetic acid (5-HIAA).

Positron emission tomography (PET) and single photon emission computed tomography (SPECT) studies targeting the 5-HT_{1A}, 5-HT_{2A} receptors, and the 5-HT transporter 5-HTT in individuals with AN, demonstrate that patients with AN tend to have increased 5-HT_{1A} binding and decreased 5-HT_{2A} binding, pointing towards the neurochemical imbalance within the serotonergic system. (Gianni et al., 2020)

It is known that 5-HT is synthesized from an essential amino acid tryptophan that cannot be synthesized internally. Dietary tryptophan upon entering the blood circulation is taken up by the brain and hydroxylated, which results in the product of this process, 5-hydroxytryptophan. Later, the product is decarboxylated to form 5-hydroxyindoleacetic (5-HIAA). (Bailer & Kaye, 2011) Individuals with AN have been found to have reduced concentration levels of the 5-HT metabolite 5-HIAA in the cerebral spinal fluid (CSF), and reduced plasma prolactin response to drugs with 5-HT, due to being underweight. (Kaye, 1984) These findings suggest that during the acute phase of the illness, serotonergic activity is reduced premorbidly, and is further reduced due to the lack of dietary intake of tryptophan. When patients recover, concentrations of 5-HIAA are reported to be elevated in the CSF. Interestingly, it is known that in healthy patients, the direct activation of 5-HT receptors tends to reduce food consumption whereas interventions that block 5-HT receptor activation increase food consumption and promote weight gain. (Blundell, 1984) In addition, a restricted diet decreases the rate of serotonin receptors and the density of serotonin transporters which causes the oversensitivity to serotonin. (Higgins, 2018) However, individuals with AN premorbidly report rigidity, obsessionality and anxiety which are often associated with high levels of 5-HT. Therefore, due to calorie restriction, in the short term, individuals experience anxiolytic effects, which explains why patients with AN maintain restrictive behaviors that allow them to medicate their underlying anxiety. (Higgins, 2018)

Additionally, studies using positron emission tomography (PET) investigated women who recovered from AN. (Frankle et al., 2005) It was found that recovered AN patients had reduced 5-HT_{2A} activity, in the

amygdala and hippocampus as well as the anterior cingulate, sensorimotor, and occipital cortical regions. Another study using single photon emission computed tomography (SPECT) found that ill AN individuals had reduced binding of postsynaptic 5-HT_{2A} receptors in the left frontal and occipital cortex.

The reduction of 5-HT_{2A} activity in the anterior cingulate cortex has been influential in two core symptoms of AN: poor problem-solving and a distorted body image. The subcaudal cingulate regions play a crucial role in mediating the emotional aspect of the disease, as they have considerable connections with the amygdala, frontal lobes, and ventral striatum. They play a role in assigning emotional valence to internal and external stimuli, emotional learning, and expressing internal states. (Devinsky et al., 1995) The amygdala and other medial temporal regions play a role in regulating anxiety, fear, and the integration of cognition and mood. The amygdala allows us to initiate and change adaptive behaviors based on prior experience. (Cleare & Bond, 2000) This is reflected in the behavior of AN patients since due to their rigid and perfectionist personality type they have difficulties in incorporating feedback and altering behavior. Additionally, they fail to accurately recognize affective and social stimuli from the environment that would encourage them to problem-solve and change their behavior. (Kingston et al., 1996) Instead, they obsessively repeat maladaptive behaviors such as dietary intake avoidance and excessive exercise. As for distorted body image reduction of 5-HT_{2A} in the right parietal region can be associated with neglect and could be related to altered body image. (Bailer & Kaye, 2011; Higgins, 2018)

Dopamine (DA) functioning has also been found to be impaired in AN since individuals often portray anhedonic behaviors premorbidly. Normally, DA functioning modulates reward and effect and is central in processing reward in both primary and secondary reinforcers, for example, food. Studies have shown altered striatal dopamine function in individuals with AN and recovering from AN. (Bergen et al., 2005) In healthy patients the ingestion of, for instance, high-sugar foods may trigger dopamine release. This is a similar response as the ingestion of amphetamine. (Bailer et al., 2011) As expected in individuals with AN, high-sugar food triggers endogenous dopamine release, however, dopamine is experienced unpleasantly and anxiogenically. This could partially account for the desire for self-starvation in individuals with AN, as it down-regulates anxiety. (Higgins, 2018) Reward processing in individuals with AN is also altered in situations that do not involve food or weight. For instance, women who recovered from AN failed to differentiate between winning and losing money in a gambling task, demonstrating a failure to identify the positive or negative value of a stimulus. (Wagner et al., 2007) Moreover, DA metabolites such as dihydroxyphenylacetic acid in the CSF of patients with AN or recovered patients were depleted while in PET studies, to overcome DA metabolite depletion, subjects had increased binding of DA D2/D3.

Furthermore, the insula is another cortical region thought to be disrupted in patients with AN, and is characterized with the impairment within the circuit involving cortical (frontal, somatosensory and parietal) and subcortical structures (amygdala and striatum). The insula presents various functions and connections facilitating communication between regions. (Nunn et al., 2011) A major function includes the regulation of the autonomic nervous system, such as inhibiting activity from the amygdala to the sympathetic nervous system and stimulating activity of the parasympathetic nervous system. (Mesulam, 1983) The dysfunction of the insula leads to an imbalance of the sympathetic and parasympathetic nervous systems accounting for intense anxiety and fear which is experienced by patients in response to food stimuli. (Nunn et al., 2011) Additionally, in healthy patients activity of the insula increases before a meal and decreases after a meal, regulating appetite and satiety. (Shelley & Trimble, 2004) However, in individuals with AN insula activity decreased and remained constant before and after a meal, providing evidence for the insula involvement in the dysregulation of appetite in ill individuals. (Kerr et al., 2016) The abnormal and reduced activity of the insula was further provided using an fMRI to test primary and secondary cortical regions after sucrose and water administration. (Wagner, Aizenstein, Mazurkewicz, et al., 2007) Individuals recovered from AN showed significantly lower activation of the insula as well as the ventral and dorsal striatum, compared to controls. Due to differences in the activity of insula circuits, individuals might show altered appetite in response to food stimuli.

Lastly, the striatum has been thought to be impaired in AN. It is the largest component of the basal ganglia, composed of three nuclei, the caudate, putamen, and ventral striatum. (Báez-Mendoza & Schultz, 2013) It is known for its role in reinforcement learning, control, and action selections. (Graybiel, 2008) In a study, using the parametric analysis of fMRI activity during the choice of high-fat and low-fat food in AN individuals and controls, demonstrated that AN individuals have significantly increased activity in the dorsal striatum. (Foerde et al., 2015) This indicates that the striatum plays an important role in maladaptive food choices in AN by the lack of conscious food choices and instead slipping back to learned habits of lower food intake. However, when individuals with AN were shown images of thin bodies, they experienced increased activity in the ventral striatum in comparison to controls, which depicts the activation of the reward system, making unhealthy traits seem rewarding. (Scharner & Stengel, 2019)

Behavioral Treatments

The severity of AN has encouraged the development of behavioral and pharmacological treatments for the disorder. Common therapies include family-based treatment (FBT), cognitive-behavioral therapy (CBT), and third-wave acceptance-based treatments, which are all commonly assisted with pharmacotherapy. (Muratore & Attia, 2020) Family-based treatment is the first line, most promising therapy in adolescents. FBT is an outpatient program constructed in a way to restore an adolescent's health with the support of their parents. (Rienecke, 2017) It consists of three phases: phase 1 focuses on rapid restoration of physical health, which takes control over food intake and exercise away from the patient giving it to their parents, phase 2, which gradually returns responsibility to the adolescent, and the last phase, phase 3 which aims to review the development of the adolescent and establish a new identity and restore patients control over dietary intake. (Rienecke, 2017)

CBT is widely used in adult anorexia nervosa and is applied over more than 40 sessions, which focus on regularizing eating patterns, reducing or eliminating compensatory behaviors, and challenging previous beliefs of overvaluation of weight and body image. (Muratore & Attia, 2020) Stage 1 of CBT is considered to be crucial to the success of the overall treatment. It consists of getting the patient involved, allowing them to take ownership of the treatment, and establishing how they want to benefit from treatment. Establishing a self-monitoring 'in the moment' recording of eating and other relevant behavior is key in deriving the problem. The patient, throughout the week, describes their eating patterns and difficult moments, writing them in a journal to discuss during an upcoming session. In addition, weekly weigh-in sessions address the process of excessive body checking or its avoidance. (Murphy et al., 2010) The later stages of CBT differ from case to case as they discuss the individual problems of the patient which can include: overvaluation of weight and shape, dietary rules, event-related changes in eating, and clinical perfectionism. The last stage includes appointments that aim to discuss further steps to maximize the chance for continued recovery. (Frostad et al., 2018)

Third-wave treatments have been more widely implemented in the past two decades. They highlight the importance of acceptance and mindfulness in tolerating stressful triggers and reducing maladaptive behaviors, which are often not adequately addressed in currently established interventions. (Benfer et al., 2021) It combines successful strategies from CBT (exposure, self-monitoring) and adds focus to self-acceptance, mindfulness, awareness, dialectics, interpersonal relationships, and values. (Buerger et al., 2021) In other words, third-wave therapies target response-focused emotion regulation strategies, which change the expression or experience of emotion regulation after its occurrence. In contrast, CBT was rather focused on antecedent-focused emotion regulation strategies, which prevent the emotion response from being activated. (Linardon et al., 2017)

Pharmacotherapy

Pharmacotherapy is frequently paired with therapeutic interventions, due to AN's overlap with other psychiatric disorders. (Davis & Attia, 2017) Tricyclic antidepressants (TCAs) function by inhibiting norepinephrine and serotonin reuptake within presynaptic terminals, by blocking transporter sites of serotonin (SERT) and norepinephrine (NET), which causes a higher concentration of these neurotransmitters within the synaptic cleft. In response, serotonin type 1A autoreceptors (5- HT1A) sensitize. (Moraczewski et al., 2023) This contributes to an antidepressant effect. However, the neurotransmitters act as antagonists on postsynaptic cholinergic (alpha-1 and alpha-2), muscarinic, and histamine receptors (H1) (Hudspith et al., 2006) This causes various side effects such as dry mouth, drowsiness, dizziness, excessive sweating, constipation, and urinary retention. Therefore, despite first being thought to be a promising treatment, the side effects, and the discovery that when taken in overdose, or mixed with alcohol, they are lethal, SSRI use in AN treatment is being phased out.(Marvanova & Gramith, 2018) This demonstrated a major concern as patients with anorexia nervosa regularly exhibit suicidal thoughts.

Selective serotonin reuptake inhibitors (SSRIs), constitute a safer and more tolerable approach. SSRIs selectively inhibit the reuptake of serotonin, by blocking transporter sites of serotonin, increasing its effective concentration in the intra-synaptic space, therefore stimulating serotonergic neurons. However, SSRIs differ from TCAs as they selectively affect only serotonin without having an effect on other transporter proteins associated with dopamine or norepinephrine. (Lochmann & Richardson, 2018) In addition, SSRIs do not affect other receptors or sodium channels which are the cause of adverse effects for TCAs. However, there is a lack of evidence of the beneficial use of SSRIs during acute treatment of AN in underweight individuals. (Marvanova & Gramith, 2018) The use of 5-HT-increasing antidepressants under starvation leads to a decrease in SSRI efficiency caused by reduced CSF 5-HIAA which is the major 5-HT metabolite, suggesting minimized synaptic 5 -HT (Kaye et al., 1998) This could be caused by the lack of tryptophan, caused by reduced dietary intake, which is an essential amino acid and the sole precursor of serotonin reduction. (Shaw et al., 2002) However, after weight restoration SSRI antidepressant administration during the post-acute phase may provide some benefit in relapse prevention, weight maintenance, and mood improvement.

Antipsychotic medication has been investigated in clinical treatment, or more specifically second-generation antipsychotic drugs (SGAs), such as olanzapine, owing to the rigidity-held compulsions and anxiety of patients with AN. (Dold et al., 2015) Olanzapine provides moderate evidence of weight increase but shows limited utility as a stand-alone drug. Consequently, additional studies for AN are crucial, as minimal existing treatments show optimal improvements and there are no fully effective pharmacological treatments yet. In addition, new treatment methods should focus on targeting underlying mechanisms of AN and identifying core components allowing for a decrease in relapse rate.

Psychedelics

Psychedelic drugs are psychoactive substances that produce alterations in perception, cognition, and emotion. These include a wide range of drugs classified into several classes. The classic psychedelics include lysergic acid diethylamide (LSD), psilocybin (an active ingredient of magic mushrooms), and N, N-Dimethyltryptamine (DMT, a component of ayahuasca). (Nichols, 2016) Some other psychedelic substances include entactogens such as 3,4-Methylenedioxymethamphetamine (MDMA) and other substances like ketamine (a dissociative anesthetic) and scopolamine (Tupper et al., 2015). The renewed treatment of psychedelic-assisted therapy (PAT) has been used in clinical research settings around the world to treat illnesses such as depression, post-traumatic stress disorder (PTSD), and anxiety. (Breeksema et al., 2020) Natural psychedelics, such as ayahuasca and psilocybin, have a long history of use in sociocultural rituals. However, the first synthetic psy-

chedelic was discovered in 1943 when Albert Hofmann performed a self-experiment on lysergic acid diethylamide (LSD) to find its powerful effects to alter mood and cognition. This later sparked active clinical research in Europe and the United States. (Bastiaans et al., 1983) (Siegel, 1989) Despite the ever-growing body of clinical studies on the therapeutic use of substances, such as LSD, in the early 1960s, there was still no federal legal requirement in the Federal FD&C Act of 1938 that required drug manufacturers to show proof of drug efficiency in appropriate controlled clinical trials. (Belouin & Henningfield, 2018) In consequence, in October 1862, children were born with birth defects from mothers consuming the drug thalidomide for morning sickness. This caused the "Drug Amendments of 1962" to be signed into public law, strengthening regulatory controls on the experimentation of new chemical entities, such as psychedelics, causing research to decline. (Chhabra et al., 2005) However, now psychedelic treatment has been renewed (Breeksema et al., 2020. Recently preliminary clinical trials have been conducted to assess these drugs' pharmacological properties and efficiency, demonstrating a strong therapeutic potential for the treatment of several psychiatric disorders, including severe depression (Carhart-Harris et al., 2021), addiction (Johnson et al., 2016), anxiety (Griffiths et al., 2016), and obsessive-compulsive disorder (OCD) (Kelmendi et al., 2022).

Pharmacological Mechanism of Action

Classic psychedelics have a common mechanism of action consisting of the partial agonism for the serotonin 5-HT2A receptor. (Kim et al., 2020) This is hallmarked by animal studies on rats and mice using the so-called head twitch response, indicating a psychedelic state. (Halberstadt & Geyer, 2011) Mice that do not have a functioning 5-HT2A receptor due to a genetic knockout, do not exhibit the head-twitch response indicating this receptor is necessary for mediating a crucial mechanism of action for psychedelics. The 5-HT2A serotoninergic system is involved in learning, memory, cognition, pain perception, and the sleeping/waking cycle. (Raote et al., 2007) A high concentration of such receptors are located in the temporoparietal junction and the medial prefrontal cortex which are involved in cognitive and emotional functions. They can also be found in layer 5 of the neocortex (in the pyramidal neurons), in the reticular nucleus, and in the thalamus which is involved in visual perception and attention. (Vollenweider & Preller, 2020) This provides a cause for the increased sensory processing and decreased integrative processing in a psychedelic state. Additionally, classic psychedelics bind to other different subtypes of the 5-HT and DA receptors. (Halberstadt & Geyer, 2011) A treatment with a 5-HT1AR agonist resulted in reduced visual hallucinations suggesting the modulatory effect of the 5-HT1AR receptor on the 5-HT2A receptor. Also, blocking the D2 dopamine receptor reduces the effects on positive derealization. (Vollenweider et al., 1998) Moreover, a receptor that could potentially be involved in the effects of psychedelics is the trace amine-associated receptor (TAAR). By the use of psychedelics, the TAAR1 receptor is activated which inhibits dopaminergic activity, affecting an individual's sensitivity to stress and reward. (De Gregorio et al., 2016) The diverse binding profile and complex array of these interacting neurotransmismitter systems spanning cortical and subcortical regions, is partially responsible for the large variety of symptoms in a psychedelic state.

Apart from the altered binding of neurotransmitters, LSD and other classic psychedelics increase the complexity of dendrites and the number of synapses, which in turn increases the number of connections between neurons. (Olson, 2022) This mechanism can be found in the postsynaptic effects of psychedelics where they induce a release of glutamate and α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPAR) activation. Consequently, this triggers the release of brain-derived neurotrophic factor-tropomyosin receptor kinase B (BDNF-TrkB) and mammalian target of rapamycin (mTOR) signaling causing the upregulation of neuroplasticity-related genes. (Aleksandrova & Phillips, 2021) These effects of enhanced neuroplasticity could have a therapeutic impact by rewiring these neural circuits. For instance, in animal studies, psychedelic-induced neuroplasticity can reverse anxious behavior. (De Gregorio et al., 2022) This technique has been

implemented through microdosing, the regular use of small doses of psychedelics. (Ona & Bouso, 2020). However, there is still a lack of conclusive evidence to what extent the neuroplastic effects benefit humans.

Additionally, classic psychedelics and MDMA increase levels of oxytocin, which is a hormone that promotes strong feelings of sociability, empathy, and connectedness. (van Elk & Yaden, 2022) Consequently, this increases trust and willingness to cooperate during PAT. (Holze et al., 2021) Additionally re-opening the window for social reward learning during a psychedelic experience can offer long-term effects. This occurs in MDMA through binding to the serotonin transporter causing oxytocin release. (Nardou et al., 2019)

As a whole, many neuroscientific explanations have been proposed to account for the effects of psychedelics at a brain level. The three predominant models include the thalamocortical filter theory, the relaxed beliefs under psychedelics (REBUS) model, and claustro-cortical circuit (CCC) model. (van Elk & Yaden, 2022) The thalamo-cortical filter theory suggests that psychedelics work by disrupting the normal functioning of the thalamus leading to a breakdown of the usual communication patterns between the thalamus and the cortex. While the REBUS model focuses on the significant effect of altered activity of the 5-HT2A receptor as mentioned above, leading to an increased entropy in the brain, which allows the brain to explore a wider range of potential neural configurations, leading to altered perceptions and experiences. On the other hand, the CCC model suggests that psychedelics alter the balance of activity between the claustrum and the cortex. However, each model acknowledges that the effects of psychedelics are not merely a result of increased or decreased neural activity but involve a more complex rearrangement of neural networks. Yet, it is still difficult to predict the correct model, as the use of psychedelics has several effects on thought processing and behviour suggesting the combination of factors that account for it.(Doss, Madden, et al., 2021)

Psychological Mechanisms

A crucial psychological characteristic of psychedelics is to induce an altered state of consciousness, for instance, they allow an individual to undergo mystical experiences and an enhanced perception of emotions. A feeling of paradox, transcendence of space and time, joy, and awe often describe such mystical experiences. (Yaden et al., 2017) Individuals often describe these experiences as difficult to put into words because they escape from ordinary concepts and words. (Griffiths et al., 2006) Often people indicate that the experience allows them to learn something new about themselves or the world, as they often include the most important times of their lives. (Yaden et al., 2017) However these experiences are multidimensional constructs, and they occur due to multiple cognitive processes therefore, they cannot be described by a single mental state. (van Elk & Yaden, 2022) Additionally, psychedelics generate a feeling of awe, which includes a feeling of vastness, self-loss, connectedness, and physiological changes (chills, eyes widening), which could result in a change in a person's mental schemes allowing them to overcome personal obstacles. (Hendricks, 2018) In clinical settings, the extent of the psychedelic-induced mystical experiences has shown a positive correlation with improvements in subjective life quality, meaning in life, and mood in patients suffering from anxiety-related disorders, addiction and depression. (McCulloch et al., 2022)

Psychedelics also enhance cognitive and psychological flexibility. Psychological flexibility is the adaptive response to different stressors that promote an action-driven response. (Davis et al., 2020) Cognitive flexibility is the general ability to switch between different cognitive operations. In a psilocybin study, cognitive flexibility increases in individuals from baseline measured by the Penn Conditional Exclusion Test (PCET) which tests the participant's capacity to adapt to new criteria of a test with minimal errors. (Doss et al., 2021) Another study found that PAT increases cognitive flexibility (measured by using perseverative eros in a task-switching paradigm) and psychological flexibility for up to a month. (Davis et al., 2021) The presence of cognitive flexibility is crucial for PAT. It allows for enhanced adaptability to challenge existing mental frameworks, makes it easier to break down negative thought patterns and offers a heightened self-awareness, integrating new perspectives into the patient’s life. Increased cognitive flexibility and the combination of other

psychological factors can result in learning new habits and behavior change. (van Elk & Yaden, 2022) When combined with CBT they can allow the formation of new healthy habits enhancing lifestyle or terminating old unfavorable habits. (Teixeira et al., 2021) This review also provides evidence of a healthier lifestyle (healthier diet, less alcohol consumption) being associated with the use of psychedelics. Several clinical trials have reported positive lifestyle changes. (Griffiths et al., 2016; Griffiths et al., 2006; Griffiths et al., 2017)

Clinical Applications of Psychedelics

Psychedelic drugs and psychedelic-assisted therapy have been implicated in the treatment of addiction, post-traumatic stress disorder (PTSD), obsessive-compulsive disorder (OCD), anxiety, and depression. (Kurtz et al., 2022) Since OCD, addiction and anxiety share common mechanisms and symptoms with AN, they provide a rationale for the possible benefits from this alternative method of treatment for AN as well.

Obsessive-compulsive disorder is a psychiatric condition characterized by intrusive thoughts called obsessions, repetitive behaviors called compulsions, and avoidance behaviors. (American Psychiatric Association, 2022) Similarly to AN, the current treatment of OCD relies on CBT and pharmacological interventions such as SSRIs. However, it has been reported that the use of psychedelics, especially classic psychedelics, results in an improvement of OCD symptoms, however, the magnitude of improvement varies depending on the dose, mindset, and setting. (Buot et al., 2023) A relevant study was conducted at the University of Arizona, where patients were administered three psilocybin doses one week apart. They reported 23%-100% decreases in the Yale-Brown Obsessive Compulsive Scale (YBOCS) which measures the overall symptom severity of OCD. (Ehrmann et al., 2022) AN and OCD share a variety of symptoms including inflammation (increased levels of inflammatory cytokines TNF and IL), lowered binding of the 5-HT2a receptor, and reductions of DA in the nucleus accumbens. (Nagra, 2022) They also share psychological symptoms such as ritualistic patterns, perfectionism, and obsessive thoughts. Therefore, there is significant potential for psychedelics to have similar therapeutic properties useful in treating AN.

Moreover, addiction is a prevalent chronic relapsing medical condition with very limited effective treatment options. (Zafar et al., 2023) The current clinical treatment mostly relies on psychosocial intervention and pharmacotherapy; however, they provide limited success with 20% of individuals replacing within 1 month. However, in 6 randomized control trials, LSD has shown a beneficial effect on reducing alcohol misuse when compared to placebo. There were also significant reductions in alcohol misuse seen at 6-month follow-ups. (Krebs & Johansen, 2012) Similarly to AN, addiction often is associated with impairments in reward processing, and emotional regulation as well as DA and 5-HT deficits. Addiction also is characterized by deficits in cortical neuroplasticity. (Zafar et al., 2023) Despite first seeming as entirely separate disorders, AN and addiction share some psychological symptoms, such as loss of control, compulsive behaviors, and rituals. (Kranzler & Li, 2008) Therefore, yet again, due to the similarity of these disorders, psychedelics also have the potential to improve symptoms of AN.

Lastly, anxiety disorders are psychiatric disorders that usually are characterized by recurring intrusive thoughts or concerns, where people avoid certain situations out of worry. (Chand & Marwaha, 2022) Anxiety disorders are often comorbid with other psychiatric illnesses, therefore, it is difficult to derive their exact symptoms. Nonetheless, psychedelic therapeutic interventions for anxiety have demonstrated significant anti-depressive, anxiolytic, anti-addictive, and anti-suicidal properties. (dos Santos et al., 2016) Since anxiety is often comorbid with AN, these benefits may also be applied to patients with AN.

Psychedelic-Assisted Therapy

There are several methods proposed for psychedelic-assisted therapy (PAT), depending on the exact type of psychedelic used. The most common methods include MDMA-Assisted Psychotherapy, Ketamine Enhanced

Psychotherapy, the Preparation, Support, Integration (PSI) model, and Medication-Assisted Psychotherapy (MAP). Despite several differences, they share a similar structure. A preparation phase (varying in duration from 2 to 10 h) that is almost always described as a setting to discuss issues relevant to the individual and the therapeutic mechanism of the model. (Krupitsky & Grinenko, 1997) This phase also includes a treatment rationale and a focus on what aspects need to be worked on to achieve remission. In the next phase, the drug sessions usually last between 45 min (ketamine) and 8 hours (psilocybin) and are supervised by 1 - 2 clinicians in a living room-like environment. Therapists aim to support the participant in challenging moments and provide verbal and nonverbal interventions. (Carhart-Harris et al., 2016) Lastly, the intervention phase consists of patients discussing their experiences to consolidate their memories and promote integration into everyday life. (Jardim et al., 2020)

A common model utilized for AN is Medication-Assisted Psychotherapy (MAP) which is used in combination with LSD, DMT, and psilocybin. (Agin-Liebes et al., 2020) (Belser et al., 2017) It is the most unstructured and eclectic framework.

MAP first includes 6-12 hours of preparatory psychotherapy held over 2-3 weeks focusing on the personal history of the patient and their unresolved issues. Their sessions are aimed at working with family issues, addressing potential intrapsychic conflicts, and accepting diagnoses. After forming a good therapeutic relationship, patients are given more in-depth information concerning their psychedelic sessions and the altered state of consciousness that they will experience. (Grof et al., 1973) The sessions are held by two trained facilitators in an appropriately furnished room. During a psychedelic experience, patients lie down with eyeshades and are invited to direct their attention toward their internal thoughts, while therapists offer nonverbal, medical, and psychological support during the whole session. (Ross et al., 2016) During the final phase of the session, patients discuss their experiences in order to consolidate their memory.

Effects of Psychedelics on People with Anorexia Nervosa

Research on the effect of psychedelics on people with anorexia nervosa includes cross-sectional studies, small clinical trials, and case reports. A variety of psychedelics have been used such as ayahuasca, ketamine, MDMA, and psilocybin. The results are summarized in Table 1 and Table 2 below.

Table 1. Details of Studies: design, diagnosis, and measurement

Study (Country)	Treatment	Dosage	Control	Blinding	Target Condition/Inclusion Criteria	Measures (time horizon)
Peck et al., 2023 (United States)	Psilocybin	1 x 25mg (10)	SSRI medication (usual treatment)	Open-label study	In current episode of AN or in partial remission Female at birth BMI > 16 kg/m2	Eating Disorder Examination Questionnaire (EDE-Q) Body Image State Scales (BISS) State and trait anxiety (STAI-T)
Dechant et al., 2020 (United States)	Ketamine	500mcg/kg (1)	Inpatient eating disorder Therapy	Case Study	Diagnosed with AN since adolescence Comorbid MDD BMI 18.3 kg/m2	16-item Quick Inventory of Depressive Symptomatology (QIDS) 24-item Behavior and Symptom Identification Scale (Basis-24) (5 weeks)
Scolnick et al., 2020 (United States)	Ketamine	750 mcg/kg (1)	Outpatient Eating Disorder Therapy	Case Study	Diagnosed with AN since adolescence BMI 21.6 kg/m2	Patient Health Questionnaire-9 (PHQ9)
Spriggs et al., 2021 (United Kingdom)	Psilocybin	3 x 25mg	No placebo control	Open label	Primary Diagnoses of AN for more than 3 years Female at birth BMI ≥ 16 kg/m2	Eating Disorder Examination Questionnaire (EDE-Q) Magnetic Resonance Imaging (MRI) Electroencephalography (EEG)
Schwartz et al., 2021 (United States)	Ketamine	500mcg/kg	No placebo control	Open-label study	Patients chronically ill with AN for more than 7 years Female at birth	Eating Disorder Examination Questionnaire (EDE-Q) State-Trait Anxiety Inventory (STAI) Beck Depression Inventory (BDI)
Knatz Peck et al., 2022	Psilocybin	1 x 25mg (10)	No placebo control	Open-label study	Diagnosed with AN Mean BMI 19.7 Female at birth	Eating Disorder Examination Questionnaire (EDE-Q) Columbia Suicide Severity Scale (C-SSRS)
Brewerton et al., 2022 (United States)	MDMA	80-180 mg + supplemental half-dose of 40-60 mg (46)	No drug (43)	Double blind individual assessors	Diagnosed with AN without active purging Current criteria for PTSD (lasting >6 months)	Eating Attitudes Test (EAT-26)
Lafrance et al., 2017 (United States)	Ayahuasca	—	Usual Treatment	Cross Sectional Study	Participants diagnosed with AN (10) or with BN (6)	Self-report of symptoms with qualitative analysis

Renelli et al., 2018 (Canada)	Ayahuasca	–	Usual Inpatient and Outpatient treatment	Cross Sectional Study	Participants diagnosed with AN Participation in at least one ayahuasca ceremony in the past	Self-report on symptoms with qualitative analysis

Table 2. Details of studies: set, setting, and main findings

Study (Country)	Treatment Program	Pre-Treatment Session	Treatment Session	Setting	Post-Treatment Care	Main Findings
Dechant et al., 2020 (United States)	Ketamine Enhanced Psychotherapy Individual therapy (35 days)	Hospitalization to increase BMI Brief orientation	Racemic ketamine IV infusions (40 minutes) 2x weekly and 9th session after a week	Not described	Not described	Increase in weight. Reductions in suicidality thoughts and lower scores on the QIDS and BASIS-24 scale.
Scolnick et al., 2020 (United States)	Ketamine Enhanced Psychotherapy Individual therapy (14 days)	3 months of ketogenic diet Brief orientation	Racemic ketamine IV infusions (45 minutes)	Private room with dimmed lights Sound machine Using eye mask	KG diet continued Weekly therapist support for supportive psychotherapy Monitoring for a stable weight	PHQ-9 depression questionnaire scores reduction. Self-reported claim of being free of AN rules and behaviors.
Spriggs et al., 2021 (United Kingdom)	Psychedelic Assisted Psychotherapy	Two remote calls before an in-person session on the baseline day	3 oral doses of psilocybin (25mg) delivered over 6-week period	Semi-reclined position Eye mask and headphones	Monthly follow-ups after 6 months of treatment	Reductions in EDE-Q scores. Reductions in STAI anxiety symptoms.
Schwartz et al., 2021 (United States)	Ketamine Enhanced Psychotherapy	Lecture on possible drug side effects and limitations	IM Ketamine Doses and frequency were adjusted according to individuals' initial response	Room with Ketamine physician (DF) and RN to monitor health status	Follow-up psychiatrist's visits Weight monitoring consistently for a year post treatment	STAI state symptoms improvement. EDE-Q improvement for 2 patients. Increased weight.
Knatz Peck et al., 2022 (United States)	Psilocybin-Assisted Psychotherapy	Pre-Screening phone call Screening visit and dosing prep visit to check vital signs	Single dose of 25mg COMP360 psilocybin	Room with two psychologists to provide support and access for safety.	Participants required to stay in room for 8h Participants returned for assessment next morning and after 1 week, 1 month, and 3 months for post-treatment follow-ups.	Clinically significant reductions in EDE-Q (mean score from 2.7 to 1.1) STAI reductions for 2 patients. 2 patients experienced hypoglycemia

Brewerton et al., 2022 (United States)	MDMA-Assisted Psychotherapy	Brief orientation with Informed consent	MDMA-AT (8 hours) 3 times spaced 4 weeks apart Each session followed by a fast	Support from trained therapists to aid in processing difficult emotions	90 min follow-up session the next morning after an experimental session following 3-4 weeks. Follow-up sessions aimed to integrate lessons from experimental sessions into daily lives.	Reductions in EAT-26 scores 3-4 weeks post-treatment.
Peck et al., 2023 (United States)	Psilocybin-Assisted Psychotherapy	Two preparation sessions with informed consent of the therapeutic model	Single dose of drug COMP360 (synthetic psilocybin formulation)	Support from two psychologists for safety assessment	Participants in room for 8h, following 3 follow ups spaced 1 month apart	4 participants demonstrated clinically significant reductions in EDE-Q scores. Significant reductions in anxiety. No significant changes in BMI
Lafrance et al., 2017 (United States)	Ayahuasca Ceremony	Interviews (75-180 minutes) discussing suggestions for ways to improve therapeutic outcomes	Multi-day retreats that incorporated 2-3 ayahuasca ceremonies	Wide range of setting retreats, most rooted in Amazonian traditions (Shipibo, Ashaninka and other)	Not described	Self-reported reductions in ED thoughts and symptoms. Long-term improvements in emotion regulation and processing.
Renelli et al., 2018 (Canada)	Ayahuasca Ceremonies	Interviews discussing the patients' etiological backgrounds with AN and subjective evaluations of previous treatment effectiveness	Multi-day retreats rooted in Amazonian traditions.	Ammazonian retreats (Shipibo, Ashaninka)	Not described	Self-reported reductions in ED symptoms, improved emotional processing and self-love

Psychedelic Dosage, Method, and Safety Considerations

In the studies listed in Table 1, the doses of psychedelics depended on the specific substance and program. Ketamine doses ranged from 500-750 mcg/kg (Dechant et al., 2020; Scolnick et al., 2020; Schwartz et al., 2021), psilocybin was administered either 3x25 mg or a single dose of 25mg (Peck et al., 2023; Spriggs et al., 2021; Knatz Peck et al., 2022), and MDMA dosage ranged from 80-180 mg followed by a half-dose of 40-60mg (Brewerton et al., 2022). As for ayahuasca, no specific doses were given since the substance was administered in an infused form during ayahuasca retreats. (Lafrance et al., 2017; Renelli et al., 2018)

It is crucial to note that most studies were not controlled and only one used a double-blinding approach (Brewerton et al., 2022), while others were cross-sectional, open-label, or single-case studies. Additionally, the studies all shared an inclusion criteria of participants being diagnosed with AN according to DSM-5™ 2013 guidelines. Most also required a minimum BMI (ranging from a minimum of 16 to 18.5), which potentially excluded a large number of participants struggling with AN. Females were primarily taken under consideration due to the disorder being most predominant in females.

Treatment Program

Various treatment programs were utilized, ranging from ketamine-enhanced psychotherapy (Dechant et al., 2020; Scolnick et al., 2020; Schwartz et al., 2021), psychedelic-assisted psychotherapy (Spriggs et al., 2021), MDMA-assisted psychotherapy (Brewerton et al., 2022) and ayahuasca ceremonies. (Lafrance et al., 2017; Renelli et al., 2018)

The treatments began with either brief orientations discussing the drug effects or interviews to try to determine the patient's history and what they seek to accomplish throughout their treatment. In some cases, an inpatient or outpatient program was required to increase the participants' weights. (Dechant et al., 2020; Scolnick et al., 2020) During the treatment sessions, ketamine was either administered through IV or IM, psilocybin was administered orally, and ayahuasca was administered during multi day retreats. The setting commonly included a room with dimmed lights, using an eye mask and a sound machine. In some cases, psychologists or trained therapists assisted and guided the participants.

Efficiency

To measure efficiency, the Eating Disorder Examination Questionnaire (EDE-Q), state and trait anxiety (STAI-T), Eating Attitudes Test (EAT-26), and the Beck Depression Inventory (BDI) were used most commonly. However, all measurements were based on self-reported findings of participants making it difficult to draw precise conclusions.

In ketamine studies, participants generally reported immediate improvements in mood and energy. In two of the three studies, patients experienced a significant weight increase. In Dechant's case report (Dechant et al., 2020), the patient's weight increased from 54.3kg to 57kg after the end of the 8 ketamine infusions. As for psilocybin, despite reductions in EDE-Q and STAI scores, none of the participants sustained clinically significant increases in BMI. In Lafrance's study using ayahuasca participants had considerable self-reported results. One patient claimed that "There was an eating disorder before, there was some level of compulsivity but now there isn't" and "After done ayahuasca it's not like I could say "Oh, because I have done ayahuasca I'm not going to diet anymore" or "Because I have done ayahuasca I'm not going to compulsively exercise anymore." It wasn't that. I feel more capable of experiencing my emotions." (Lafrance et al., 2017) Additionally, one larger clinical trial using MDMA reported self-reported reductions in the Eating Attitudes Test (EAT-26) from mean scores of -3.04 to -0.68. The most significant change was reported around 3-4 weeks post-treatment.

Discussion

Among the 9 studies in this review, some positive results were observed, revealing the therapeutic potential of psychedelics for the treatment of anorexia nervosa. A vast majority of authors described the short-term and long-term improvements in self-report examination scores (Spriggs et al., 2021; Schwartz et al., 2021; Knatz Peck et al., 2022; Brewerton et al., 2022), as well as some authors described self-report improvements in comorbid disorders such as anxiety and depression (Peck et al., 2023; Knatz Peck et al., 2022; Schwartz et al., 2021; Spriggs et al., 2021). However, despite demonstrating symptom benefits, a study also noted a development of hypoglycemia after psilocybin ingestion in two patients (Knatz Peck et al., 2022). Moreover, a couple of studies mentioned the most profound benefits around 3-4 weeks after the beginning of treatment. (Brewerton et al., 2022; Knatz Peck et al., 2022).

The results of this review could conclude that patients with anorexia nervosa or patients in partial remission could benefit from psychedelic treatment. Reductions in EDE-Q scores were significant, from a mean of 2.7 to 1.1 in one study (Knatz Peck et al., 2022), and from a mean of 2.9 to 1.8 in another follow-up study (Peck et al., 2023). Similarly, some studies demonstrated reductions in EAT-26 scores from a reduction of 9.58 ($p=0.0007$) compared to placebo which reduced by 3.58 ($p=0.35$) (Brewerton et al., 2022). In a case report utilizing ketamine, the patient noted drastic improvements claiming “I know this sounds ridiculous, but I am no longer anorexic. I had so many rules I didn’t even know them. But they are gone. I can exercise because it feels good. It isn’t that I have to. I can stop when I want to.” (Dechant et al., 2020) During ayahuasca ceremonies, patients indicated similar drastic improvements mentioning “There was an eating disorder before, there was some level of compulsivity but now there isn’t.” (Lafrance et al., 2017), or “I feel like traditional therapy methods didn’t work very well on me. I just thought I’d have to suffer with it for the rest of my life and ayahuasca has definitely changed some huge, big chunks of it.” (Renelli et al., 2018). Similarly, reductions in comorbid disorders such as depression were significant from PHQ-9 score reductions from 13 to 6 in a ketamine case report. (Scolnick et al., 2020) Significant STAI reductions were also noted in a few studies (Schwartz et al., 2021; Knatz Peck et al., 2022; Peck et al., 2023) Yet heterogeneity was observed in terms of changes in weight and BMI. Some studies reported no clinically significant changes in BMI compared to placebo (Peck et al., 2023; Brewerton et al., 2022) while others reported an increase of weight (Dechant et al., 2020; Schwartz et al., 2021). Although it is crucial to mention that all studies only began when the patient's BMI was in a normal r $>18.5 kg/m^2$ therefore no increase in BMI was required.

Most studies did not apply adequate measures or assessments without a control or placebo. In early research Tomsovic and Edwards mentioned “the complexities and difficulties of achieving control over the placebo effect of a drug that has spectacular mind-altering properties, and where research is contaminated by expectations of benefit”. (Tomsovic & Edwards, 1970) Similarly, more modern clinical studies are experiencing similar difficulties because subjective and objective changes evoked by psychedelics, that are seen by the patient and the observer, make it extremely difficult to perform double-blind tests and placebo controls. Therefore, a reasonable approach would be to utilize an active placebo with lower doses of the drugs (Griffiths et al., 2006).

Moreover, results were primarily based on self-reported symptoms using various measures such as the Eating Disorder Examination Questionnaire (EDE-Q), Eating Attitudes Test (EAT-26), Patient Health Questionnaire (PHQ-9) and State Trait Anxiety Inventory (STAI). Such an approach may bring out bias and subjectivity, especially in a disorder like anorexia nervosa where lying and claims of not being “sick” anymore are common symptoms of the disorder. Thus, designing qualitative studies with pathology-oriented measures would be beneficial to demonstrate a more objective view of symptom improvements. This could be brought out by employing patients with a lower BMI and measuring its change after treatment. Nevertheless, the safety and tolerability of psychedelics still requires testing in underweight patients.

The present review has limitations. Firstly, only articles written in English were selected, excluding studies written in other languages that might have demonstrated other outcomes. Furthermore, as mentioned,

the studies selected were only carried out in patients with a normal BMI which excluded the vast majority of individuals in a current episode of anorexia nervosa. Also, the studies examined were mostly conducted with low numbers of patients making it difficult to draw universal beneficial conclusions for a large population. Lastly, due to most studies only employing self-report measures the results lack objective conclusions.

Despite this, preliminary results and plausible therapeutic mechanisms give a clear rationale for further research. Further research would benefit from larger, controlled trials with objective pathology measures investigating the safety and efficacy of psychedelics and PAT for patients with AN. In particular, it would be highly beneficial to explore this treatment for underweight and younger patients with AN which make up the majority of the individuals with this diagnosis. Additionally, it could be explored whether certain psychedelic substances could be better suited for patient groups with other comorbidities. Finally, trials comparing PAT to current AN treatment would be valuable to determine the relative efficacy and safety of the drugs.

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