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REVIEW

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Pharmacotherapeutic strategies for the treatment of anorexia nervosa – novel targets to break a vicious cycle

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ABSTRACT

Introduction: Anorexia nervosa (AN) has one of the highest mortality rates of all mental illnesses. No approved pharmacological treatments exist for AN, but novel neurobiological targets show promise.

Areas covered: Studies show that in individuals with AN, there are alterations in brain neurotransmitter signaling, alongside associated mental rigidity and comorbid anxiety and depression. Available and new therapies could be used to improve alterations in neurobiology and behavior. This narrative review serves as a review of previously published literature assessing the efficacy of traditional pharmacotherapy in treating AN while also exploring novel treatments, including dissociative anesthetics, psychedelics, cannabinoids, hormones, neurosteroids, and ketogenic nutrition.

Expert opinion: If best practice psychotherapeutic interventions have failed, we recommend a neuroscience and brain research-based medication approach that targets dopamine neurotransmitter receptors to enhance cognitive flexibility and illness insight while reducing dread and avoidance toward food. It is furthermore essential to recognize and treat comorbid conditions such as anxiety, depression, or obsessive-compulsive disorder as they interfere with recovery, and typically do not resolve even with successful AN treatment. Novel strategies have the promise to show efficacy in improving mood and reducing specific AN psychopathology with hopes to be used in clinical practice soon.

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Anorexia nervosa; anxiety; depression; eating disorder; ketamine; psychedelics; ketogenic; nutrition

1. Introduction

Anorexia nervosa (AN) is a severe psychiatric illness characterized by food avoidance, severe emaciation, and a perception of being overweight despite a very low body weight [1]. AN is a chronic disorder with frequent relapse, high disease burden, and treatment cost [2–6], and treatment effectiveness is limited [7,8]. AN has a mortality rate 12 times higher than the death rate from all causes of death for females 15–24 years old [5,6,9]. AN demonstrates a complex interaction between environmental, psychological, and neurobiological factors. No medication to date has been approved for AN and developing pharmacological interventions for AN to support behavioral interventions is an important research priority [10].

Neurobiological research is increasingly providing more insight into neurotransmitter systems that may underly or contribute to its pathophysiology, while significant knowledge gaps still exist [11,12]. Studies using animal models of eating disorders (EDs) have highlighted the role of monoamine neurotransmitters, specifically dopamine and serotonin, in behaviors related to food restriction and excessive consumption. The most commonly used such animal model is the activity-based anorexia (ABA) model, where rodents have restricted food but continuous access to a running wheel, which leads to hyperactivity, self-starvation, and frequently death [13,14]. The ABA model has been linked to altered dopaminergic activity and heightened expression of the dopamine D2 receptor, which were both associated with weight loss [15,16]. Environmental factors that trigger stress responses can lead to changes in dopamine and serotonin pathways, which may be long-lasting and play an important role in the persistence of alterations in eating behavior [17–21]. Research involving humans has shown dynamic adaptions wherein there is increased binding of serotonin 1A receptors in individuals with acute anorexia nervosa (AN). In contrast, serotonin 2A receptor expression is lower compared to normal levels after recovery [22]. Ill AN demonstrated normal levels of dopamine D2 receptor availability. However, the post-recovery AN showed elevations in receptor expression levels in the striatum that were related to anxiety [23,24]. These data provide potential evidence for a framework where modifications in dopamine and serotonin neurocircuitry may depend on AN illness state, although premorbid trait vulnerabilities have also been hypothesized [25]. Furthermore, the available human brain imaging and basic research studies support the following model for AN development and maintenance. Elevated anxious traits predispose individuals with AN to experience environmental stimuli as threatening, which facilitates negative conditioning to eating, shape, and weight triggered by environmental circumstances. This conditioned fear utilizes dopaminergic fronto-striatal-hypothalamic circuits to drive

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Article highlights

- Anorexia nervosa is a severe psychiatric illness, and while no medications have been approved for its treatment, progress on its neurobiology promises the development of novel pharmacological targets and interventions.
- The integration of animal models for anorexia nervosa with human neurobiological research provides an opportunity to build more refined disease models.
- Research on existing psychoactive mediations shows either limited impact on the anorexia nervosa-specific psychopathology or no randomized controlled trials have yet been conducted.
- Novel targets and medications such as psychedelics, recombinant leptin, cannabinoids, or neuroactive steroids are very promising agents to directly target the pathophysiology and associated psychopathology of anorexia nervosa.
- Nutrition interventions in anorexia nervosa that affect metabolism, and a wide array of neurotransmitter systems may also have a role in the future to normalize neurotransmission and behavior.

dread and avoidance toward food and override appetitive signals via combined dopamine D1 and D2 receptor activation in the caudal nucleus accumbens [26]. Combined blockage of these receptors could alleviate this dreaded response. AN has also been associated with behavioral rigidity interfering with behavior change [27]. Dopamine receptor D2 receptor agonists may be particularly effective in improving cognitive flexibility and decision-making and could therefore have a role in treating AN [28]. Furthermore, an adaptation of dopaminergic circuits to food restriction promotes the disorder-specific vicious cycle of weight loss and more food restriction [29].

While no medication has been approved for AN to date, yet individuals with AN are frequently treated with psychoactive medications [30]. In this narrative review and update article, we briefly discuss past research, which is described in more detail in our previous publication, and then focus on novel developments over the past 5 years [31]. In the expert opinion, we aim to provide practical suggestions to clinicians seeking medication treatments for patients with AN and guide directions toward new research targets for further AN treatment development.

2. Methods

The review portion of this article provides a narrative review of pharmacological treatments in AN. The narrative review was chosen to integrate a broad range of issues in AN treatment relating to pharmacological intervention because of the relative lack of randomized controlled studies [32]. A comprehensive literature search was conducted using the UCSD Library Database, PubMed, and Google Scholar to identify studies related to novel treatments or updates for traditional treatments within the last 5 years for anorexia nervosa [31]. The search included general terms such as 'anorexia nervosa treatments' and 'novel anorexia nervosa treatments,' as well as more specific terms targeting potential therapeutic interventions, such as 'anorexia nervosa recombinant leptin' and 'anorexia nervosa ketamine.' This study serves as a brief review and an update to our previous article on pharmacological interventions in anorexia nervosa (AN), expanding on recent developments in the field. While studies published before 2019 are referenced in the main text to provide background and context, drawing on data summarized from existing literature reviews or providing brief updates on existing treatments, this narrative review primarily focuses on studies published between 2019 and 2024 to highlight novel treatments for AN. Therefore, the search criteria were specifically filtered to include articles published within this timeframe.

3. Summary and update on Previously discussed pharmacological agents

Our previous publication reviewed the then-up-to-date literature on pharmacological intervention studies in AN [31]. We briefly summarize and update the main findings and agents, and their biological targets are summarized in Table 1. We then describe novel treatments that are listed in Table 2.

3.1. Appetite stimulating medications

To target the hallmark signs of AN, food avoidance, and low weight, the appetite-stimulating medication cyproheptadine, the opiate naltrexone, the cannabinoid dronabinol, and the alpha-2 adrenergic agent clonidine have been studied, and some of those studies included active controls such as individuals on antidepressants or antianxiety medication [31]. No more recent literature on the use of those agents in the treatment of AN could be identified except for an experimental protocol for the use of naltrexone in eating disorders [34]. Surprisingly, none of those agents showed strong efficacy in promoting weight gain or reversing AN psychopathology, which warranted recommendation as a treatment agent for AN. Why these medications have been ineffective in the AN population while stimulating weight gain in others remains elusive. The above-described research and model for developing and maintaining AN implicates primarily fear and dopamine brain circuits [29]. We suspect that the mechanisms that drive food restriction in AN are too strong, and the appetite-stimulating agents are too nonspecific for them to be therapeutically effective.

3.2. Antidepressant medication

Early studies tested the tricyclic antidepressants clomipramine and amitriptyline. Double-blind studies in small samples did not indicate medication benefits, while a larger retrospective chart review that compared clomipramine and the selective serotonin reuptake inhibitor (SSRI) paroxetine in addition to psychotherapy suggested faster weight gain in the paroxetine group. However, no control group was included, making the distinction from the effects of intensive psychotherapy difficult. SSRIs are commonly indicated for the treatment of depression, anxiety, and obsessive-compulsive disorder, which are frequent comorbidities of AN, and multiple formulations in this class have been tested, including fluoxetine, fluvoxamine, paroxetine, and sertraline. None of the larger or controlled studies showed benefit over placebo with respect to weight gain in AN. This outcome was surprising since it had been speculated that improving mood and anxiety would improve AN treatment [31]. These results further highlight that the pathophysiology of AN is not primarily based on serotonin neurotransmission but may be

Table 1. Previously discussed pharmacological agents and their neurobiological targets. https://go.drugbank.com [33].

Medication Class	Active Human Neurobiological Targets
Appetite Stimulants	
Clonidine	Agonist on Alpha-2A, 2B and 2C Receptor; Inhibitor of Amine Oxidase 3
Cyproheptadine	Antagonist on Histamine H1, Serotonin 2A, 2C Receptor
Dronabinol	Agonist on Cannabinoid 1 and 2 Receptor
Naltrexone	Antagonist on Opioid Mu, Kappa and Delta Receptor
Antidepressants	
Amitriptyline	Inhibitor of Serotonin and Noradrenaline Transporter; Antagonist on Serotonin 2A Receptor
Clomipramine	Inhibitor of Serotonin Transporter; Antagonist on Serotonin 2A, 2B, 2C Receptor
Fluoxetine	Inhibitor of Serotonin Transporter
Fluvoxamine	Inhibitor of Serotonin Transporter
Paroxetine	Inhibitor of Serotonin Transporter
Sertraline	Inhibitor of Serotonin Transporter
Anxiolytics	
Alprazolam	GABA A Receptor Ligand and Positive Allosteric Modulator
Antipsychotics	
Aripiprazole	Partial Agonist on Dopamine D2 Receptor; Antagonist on Serotonin 2A Receptor
Haloperidol	Antagonist on Dopamine D2 Receptor; Biologically Active on Serotonin 2C Receptor
Olanzapine	Antagonist on Dopamine D2 and Serotonin 2A Receptor
Pimozide	Antagonist on Dopamine D2 and D3 Receptor; Inhibitor of Potassium Voltage-gated Channel
Quetiapine	Antagonist on Dopamine D2 and Serotonin 2A Receptor
Risperidone	Antagonist on Dopamine D2 and Serotonin 2A Receptor
Sulpiride	Antagonist on Dopamine D2 Receptor
Mood Stabilizers	
Carbamazepine	Inhibitor of Voltage-gated Sodium Channel Alpha Subunit
Lithium	Exact Mechanism of Action Unknown, Likely Inhibitor of Inositol Monophosphatase
Lamotrigine	Inhibitor of Voltage-dependent R-type Calcium Channel Subunit Alpha-1E and Voltage-gated Sodium Channel Alpha Subunit; Blocker of Voltage-gated Sodium Channel Alpha Subunit
Oxcarbazepine	Blocker of Sodium Channel Protein Type 11 Subunit Alpha
Topiramate	Antagonist on Glutamate Receptor Ionotropic, Kainate Receptor and Voltage Gated L-type Calcium Channel; Agonist on GABA Receptor Subunit Alpha; Inhibitor of Voltage-gated sodium channel alpha subunit and Carbonic anhydrase 2 and 4
Valproate	Inhibitor of Mitochondrial Aminobutyrate Amionotransferase, Glycogen Synthase Kinase-3 Alpha and Histone Deacetylase 9
Hormones	
Dehydroepiandrosterone (DHEA)	Inhibitor of Glucose-6-phosphate 1-dehydrogenase
Estrogen	Agonist on Estrogen Receptors Alpha and Beta
Ghrelin	Ghrelin Receptors, Vagus Nerve Stimulation
Oxytocin	Agonist on Oxytocin Receptor and Vasopressin V1A, V1b and V2 Resceptors
Testosterone	Agonist on Androgen Receptor
Other Treatments	
Acetylcysteine	Stimulator for Glutathione Synthetase; Activator of Cystine/Glutamate Transporter
D-cycloserine	Inhibitor of Glutamate Receptor Ionotropic, NMDA 1 Receptor, D-alanine – D-alanine Ligase A and Alanine Racemase
Zinc	Catalyst for Multiple Enzyme Functions

caused by other factors, such as dopamine-related circuits. It is important to note that studies that tested SSRIs in AN did not comprehensively assess changes in AN-unrelated psychopathology, such as generalized anxiety, major depression, or obsessive-compulsive behaviors. This is a weakness of those studies as more recent research indicates that comorbidity has an impact on mortality and long-term outcomes of AN and needs to be addressed in the treatment plan [35,36]. These data are supported by a recent retrospective study over up to 1 year on the use of psychoactive medication in youth and young adults with AN [37]. That study showed greater improvements in BMI in individuals treated with antidepressants or antipsychotics compared to those without medication intervention. How those medications may have supported BMI increases in AN are unclear, but we suspect that improved mood regulation and anxiety may be the mechanisms involved. In support of this model is a recent study that indicated that fearful expectation and associated orbitofrontal brain response are predictive of long-term weight outcomes and that depression and anxiety were related to long-lasting psychopathology [38]. In summary, it appears that the pathophysiology that underlies depression or anxiety is not similar to or simply driving AN's pathophysiology but that untreated comorbidities, including depression, anxiety, or obsessive-compulsive disorder, clearly impede the recovery from AN.

3.3. Anxiolytic medication

The only benzodiazepine studied, alprazolam, was not superior to placebo in a laboratory study. Benzodiazepines bind to the gamma-aminobutyric acid (GABA) A receptor to enhance neurotransmitter action. Genetic research suggested that polymorphisms of GABAergic receptor neurotransmission genes may contribute to AN [39], and animal studies that tested resilience to developing AN implicated hippocampal GABA activity [40]. Human functional imaging studies on GABA brain activity are inconclusive, and larger studies should investigate this neurotransmitter system in AN [41]. Novel neurosteroids that alter GABA receptor function, as discussed in detail below, may be helpful in the future by enhancing GABA action on the receptor level in AN.

3.4. Typical and atypical antipsychotic medications

Early studies in small samples compared pimozide or sulpride with placebo, indicating limited weight gain benefits [42,43].

Table 2. Novel treatments to target anorexia nervosa core and associated behaviors.

Novel Agents for Further Study	Active Human Neurobiological Targets	Preliminary AN Psychopathology Treatment Effect	Weight Gain Effect	General Psychopathology Treatment Effect
Dissociative Anesthetics				
Ketamine	Antagonist on the Ionotropic Glutamate Receptor NMDA 3A and Neuronal Acetylcholine Receptor Subunit alpha-7; Potentiatior of the Serotonin 3A Receptor; Inhibitor of Cholinesterase and Nitric Oxide Synthase	TBD	TBD	↓ Depression ↓ Suicidality
Psychedelics				
Psilocybin	Metabolized to Active Metabolite Psilocin, and Agonist on Serotonin 2A Receptor	↓ Shape Concern ↓ Weight Concern ↓ Eating Concern	←→	↓ Depression ↑ Cognitive Flexibility
Hormones				
Metreleptin	Leptin Receptor but the Exact Central Pharmacodynamics and Mechanisms Remain Unclear	↓ Thoughts of Food ↓ Fear of Weight Gain ↓ Feeling Fat ↓ Drive for Activity	↑ or ↓	↓ Depression ↑ Concentration ↑ Social Contacts
Neuroactive Steroids				
Brexanolone	Positive Allosteric Modulator of the GABA A Receptor; Inhibitor of GABA Subunit Alpha 1, Beta 2, Delta and Gamma 2; Modulator of the GABA Subunit Gamma 3	TBD	TBD	↓ Anxiety ↓ Depression
Nutrition				
Nutritional Ketosis	Elevated Ketone Levels in Ketosis from a Ketogenic Diet Enter Brain Mitochondria for Energy Prodiuction and affect Glutamate and GABA Production, but Mechanims of Action Remain Largely Unknown	↓ Shape Concern ↓ Weight Concern ↓ Eating Concern ↓ Restraint ↑Acceptance Self & Body	←→	↓ Anxiety ↓ Depression
Cannabinoids				
Cannabidiol	Antagonist and Modulator of the Cannabinoid 1 Receptor	TBD	TBD	TBD

A retrospective chart review on haloperidol suggested that the medication was associated with less intense body image disturbance and drive for thinness [44]. Most studies in this group were conducted with the atypical antipsychotic olanzapine. The results were somewhat mixed, but a larger, controlled study in the outpatient level of care indicated a small but significant weight gain that was likely related to metabolic factors [45]. A few studies have researched olanzapine since then. Pruccoli, Pettenuzzo & Parmeggiani conducted an observational naturalistic case-control study with retrospective data extraction from patients hospitalized at the same treatment center [46]. Any patients, including within the control group, that received antipsychotic medication other than, or in addition to, olanzapine were excluded. A total of 118 patients were enrolled (mean age = 15.4 ± 1.7 years), including 52 controls, 37 treated with low-dose olanzapine, defined as ≤5 mg/day, and 29 with full-dose olanzapine, set at >5 mg/day. The study reported increased body weight in the olanzapine-treated groups without improving cognitive AN symptoms or body image attitudes. Most notably, they reported that depressive symptoms, as measured by the Beck Depression Inventory (BDI-II), were significantly improved in the low-dose olanzapine and control groups, as compared to no significant improvement in the high-dose olanzapine group. This suggests that low-dose olanzapine, defined as a maximum reached dosage of ≤5 mg/day, may be more effective in the treatment of depressive symptoms in AN over high-dose olanzapine, or on the other hand that higher doses of olanzapine may interfere with mood improvement. In another study, Karwautz et al. conducted an open-observational prospective study design to test the safety of olanzapine use in youth with AN and whether olanzapine serum dose would be related to clinical improvement [47]. Changes in weight gain and scores on the Clinical Global Impression (CGI) scale were defined as primary outcomes. Olanzapine serum concentration was not related to CGI clinical improvement ratings. Furthermore, there was no statistically significant correlation between weekly weight change and olanzapine serum concentration. Altogether, those studies indicate that olanzapine is a well-tolerated drug in youth with AN, but clinical effectiveness for illness-specific signs and symptoms has not been shown. The atypical antipsychotics risperidone or quetiapine had not shown weight improvements over placebo in earlier studies. A more recent observational study on risperidone in youth with AN similarly found no significant improvements in BMI or psychopathology from admission to discharge and no difference in one-year rehospitalization rates [48]. The atypical antipsychotic and dopamine modulator aripiprazole was associated with increased weight in a retrospective chart review of a high-level of care setting when compared with patients who were not on the medication. Aripiprazole's partial dopamine D2 receptor agonism has shown effects on cognitive flexibility and decision-making in the animal model. In contrast, dopamine D2 receptor stimulation in the brain stem may facilitate food intake in the AN animal model [28,49]. Altogether, the data on the antipsychotic agents that act as dopamine and serotonin receptor antagonists do not seem effective in improving specific AN pathophysiology but could be helpful in reducing acute distress and dread response described above in the animal model. The dopamine D2 receptor partial agonist aripiprazole and its more recent analog cariprazine hold potential in attenuating cognitive rigidity and facilitating food intake and should be studied further. Randomized controlled studies on those agents are lacking. A limitation of most previous studies that should be remedied in future studies is the lack of

information on aspects such as illness insight, mood, emotion regulation, or anxiety, which is not reflected in the primary outcome measure of weight gain.

3.5. Mood stabilizers

A small early study indicated improvements from lithium versus placebo in weight gain in AN. A recent small case series suggested improved mood regulation in youth with AN treated with lithium [50]. While lithium may contribute to better emotion regulation and subsequent treatment compliance, its potential effects on kidney function are concerning as AN by itself is often associated with acute kidney injury, and the use of lithium in this population cannot be recommended without the need for other psychopathology such as bipolar mood disorder [51]. A recent case series reported on the use of valproate in youth with AN to treat mood instability, aggression, and noncompliance [52]. The intervention was reported as effective in stabilizing mood but not for eating disorder-specific symptoms. Another recent larger observational study followed 234 children and adolescents with AN and compared the effects of mood stabilizers, including lithium, valproate, lamotrigine, topiramate, carbamazepine, and oxcarbazepine [53]. No significant difference was reported between mood stabilizer-treated and not-treated patients regarding changes in BMI, AN-specific or general psychopathology, or one-year rehospitalization. In summary, mood stabilizers do not show promise to target the core symptoms of AN.

3.6. Hormone treatments

AN is associated with low sex hormone levels, which affect not only bone density but also psychopathology. Prescriptions of the sex hormone estrogen or testosterone was not beneficial to improve body weight. The steroid hormone dehydroepiandrosterone indicated a beneficial effect on BMI but no bone density effect. Another hormone, the hypothalamic peptide hormone oxytocin, can affect appetite, mood, and anxiety, thus affecting the core and associated behaviors of AN. However, oxytocin did not improve weight gain across several studies in the past, and the effects on emotion regulation were inconclusive. Recently, a controlled multisite trial was conducted comparing intranasal oxytocin and placebo in 61 individuals with AN [54]. Participants were treated with 18 IU of oxytocin or placebo twice a day. The study did not find significant benefits of oxytocin over placebo on symptom measures over time or in relation to a food-exposure paradigm. Another hormone, the stomach-derived ghrelin, stimulates food intake, among other functions. It showed improved gastric emptying but little effect on weight gain, and no additional studies were identified in the literature since [55]. Altogether, while sex hormone levels are especially disturbed in AN, the application of these agents has not been proven successful. This is surprising because low body weight in AN and associated low sex hormone levels have been associated with poor cognitive flexibility, and hormone supplementation was hypothesized to normalize cognitive function [56–59]. Like appetite-stimulating agents, low hormone levels may not be central but secondary to the underlying pathophysiology of AN and other factors directly driving AN behavior [60].

3.7. Other agents

Low zinc levels led to a few small nutritional supplementation studies and showed benefits in weight restoration [61,62]. Zinc inhibits the glutamate-sensitive brain N-Methyl-D-Aspartate (NMDA) receptor system and regulates arousal, mood, and anxiety, behaviors that are part of the AN syndrome [63], but no new studies on zinc in AN have been published. Supplementation of the essential amino acid and dopamine precursor tyrosine or omega-3 fatty acid was not superior over placebo for core AN behaviors, but tyrosine supplementation showed some benefits to enhance mood [64]. In another study, the NMDA partial agonist d-cycloserine was used to augment food exposure treatment in AN and was reported to lead to improved weight gain over placebo [65]. However, the lack of follow-up studies raises the question of whether negative outcomes were not published or whether the intervention did not prove feasible.

4. Novel treatments to target anorexia nervosa core behaviors

4.1. Dissociative anesthetics

The dissociative anesthetic ketamine is a noncompetitive NMDA receptor antagonist that has been used off-label intravenously for treatment-resistant depression. The intranasal formulation esketamine, the S(+) enantiomer of ketamine, has received FDA approval for the condition. Ketamine has been in use since the 1960s as an anesthetic [66]. Studies have shown that the antagonism of NMDA receptors can contribute to neuroplasticity, thus allowing for the formation of new patterns of thought and neural connections [67]. Aside from NMDA receptors, ketamine has also been found to interact with a multitude of other receptors, including choline, serotonin, opioid, GABA, and dopamine receptors [68]. Of particular interest is the influence of ketamine on the dopamine circuitry, given that dopamine dysregulation appears to be closely linked to the pathophysiology of AN [15,29]. In addition to its potential benefits to improve mood, ketamine has been shown to decrease stress-induced inflammation and increase neurogenesis, which could be beneficial in the treatment of AN [69]. Work in animal models using the ABA model supported this possibility, indicating that low-dose ketamine could enhance resilience to AN by moderating brain GABA function [70].

Human studies assessing the use of ketamine in AN or other EDs have been small but raised the possibility that ketamine could have efficacy in improving symptoms such as rigid thinking, compulsions, depression, and suicidality in AN [49]. A case series done by Keeler et al. studied four patients with weight-restored AN and comorbid major depressive disorder (MDD) who were treated with either intranasal esketamine or intramuscular ketamine [71]. The duration and quantity of doses applied were variable between patients and determined individually by the patient and clinician. The study found that all patients anecdotally endorsed improvement in their depression symptoms. However, Patient Health Questionnaire (PHQ-9) scores, an assessment that measures the severity of depression across different symptom domains, only improved in those treated with intranasal esketamine, and there was no significant effect of ketamine on BMI in the studied patients. Two case reports in individuals with AN with comorbid

severe mood and personality psychopathology suggested improvements in general psychopathology, including suicidality, in this population in response to ketamine [72,73]. These findings support the notion that ketamine has efficacy in treating mood problems frequently seen in AN, but maybe less so for AN-specific psychopathology. This notion is supported by a case series of four individuals with different eating disorders who were treated with ketamine, which resulted in improved depression but only minor changes in eating disorder psychopathology [74]. One study augmented a nutritional intervention, which is described in detail below, with ketamine, but the added effect of the ketamine intervention was difficult to disentangle [75]. In summary, at this point, the extent to which ketamine helps AN-specific symptomatology is unclear, but ketamine may significantly improve depression symptoms in this population.

4.2. Psychedelics

Psilocybin is a hallucinogenic monoamine that occurs naturally in certain species of mushrooms with strong agonistic effects on serotonin 2A and less strong effects on serotonin 2B, 2C, and 1A receptors. Serotonin is a neurotransmitter that contributes to various aspects of normal brain function, including appetite, reward, mood, impulse control, and motor activity. Psilocybin is currently being studied for the treatment of a variety of psychiatric disorders and mainly shows promise in major depression [76]. Research has repeatedly demonstrated altered serotonin function in AN, and psilocybin is another agent that could potentially treat those with AN [77]. Human neuroreceptor brain imaging studies have shown that in those with AN, there are increases in serotonin 1A receptor binding, while the serotonin 2A receptor showed decreased binding in the frontal cortex [22]. An animal model using the ABA model and psilocybin application indicated improved cognitive flexibility, adaptation to changes in reinforcement contingencies, and better body weight maintenance [78]. In this study, antagonism at the serotonin 1A receptor interfered with the therapeutic effects, suggesting that it is psilocybin's serotonin 1A agonistic effect that was mechanistically involved in improving AN behaviors.

One study, an open-label trial reported by Peck et al., investigated the use of psilocybin in AN [79]. Ten participants received a single 25-mg dose of synthetic psilocybin together with psychological support. Two of the 10 study participants had already been remitted from AN psychopathology prior to the trial. Three participants decreased in symptoms and were remitted after the psilocybin treatment based on the Eating Disorder Examination Questionnaire (EDE-Q) symptom scores at the one-month follow-up and four at the three-month follow-up. However, changes in BMI were not found to be statistically significant. Most participants endorsed that they found the treatment beneficial and noticed positive changes within 3 months of psilocybin treatment. However, the results from the study were highly variable among participants, and it is too early to tell whether psilocybin could be an effective treatment for AN. Of note, Johns Hopkins University (NCT04052568) and Imperial College London (NCT04505189) have completed clinical trials assessing the use of psilocybin in AN treatment. However, their findings have yet to be published. One additional study through COMPASS Pathways (NCT05481736, https://clinicaltrials.gov/study/NCT05481736) examining the safety and efficacy of 25 mg compared to 1 mg of psilocybin alongside traditional psychological support is currently underway, with a projected end date of December 2024.

A few additional studies have been reported assessing the use of other psychedelics in AN treatment. In one study, prospective online data were collected from 28 individuals with a lifetime ED diagnosis and who were planning to take a psychedelic drug [80]. They were then assessed for psychiatric symptoms both at 1 to 2 weeks before a psychedelic experience and at 2 weeks later. The psychedelics taken varied, including psilocybin, lysergic acid diethylamide (LSD), ayahuasca, N-dimethyltryptamine (DMT), mescaline, and ibogaine. The results showed significant improvements in psychological wellbeing and depression when participants were assessed 2 weeks after taking psychedelics. While at the start of the study, 32% of the participants reported moderate-to-severe depression, 2 weeks after taking psychedelics, none of the participants fell within the moderate-to-severe range for depression, and the group mean fell below the threshold to qualify for depression on the Quick Inventory of Depressive Symptomology; QIDS-SR16. However, the study did not disclose the types of eating disorders participants had and, therefore, did not assess AN-specific psychopathology. In another study, Renelli et al. investigated the impact of ayahuasca compared to typical treatments for ED psychopathology in 13 individuals diagnosed with either AN ($n = 8$) or BN ($n = 5$) [81]. Ayahuasca is a plant-based psychedelic that has historically been used in indigenous and religious ceremonies to elicit strong emotional reactions. In a semi-structured interview format, the 13 participants, all of whom had participated in at least one ayahuasca ceremony since being diagnosed with and treated for an ED, reported reduced ED symptoms and thoughts, increased acceptance and love of oneself, healing related to the root cause of the ED, and better processing of difficult memories and emotions when compared to conventional ED treatments. Thus, ayahuasca could benefit AN symptomatology and comorbid psychiatric conditions. Limitations of the study included that it did not assess weight changes among participants or quantitative assessments of mood or anxiety. In summary, psychedelic medication could have promise to aid in AN treatment, but more evidence is needed before this intervention can be judged for its use in AN.

4.3. Novel hormone treatments

Leptin is an amino acid hormone naturally produced by adipocytes, and leptin receptors are distributed throughout the brain. Leptin plays a critical role in regulating energy balance and body weight. Leptin regulates appetite via the hypothalamus and affects food reward by targeting dopaminergic terminals in the ventral tegmental area [82]. While leptin is commonly associated with overriding hunger signals and promoting satiety, Hebebrand et al. have hypothesized a mechanism through which leptin could normalize brain function and behavior in patients with AN [83]. They hypothesize that in AN, there is a flawed adaptation to starvation through hyperleptinemia-induced dopamine release in the hypothalamus, which may reinforce eating disorder-specific cognitions and behaviors in a similar way dopamine release

also reinforces specific cognitions and behaviors in other forms of addiction [83]. By administering recombinant leptin, they hypothesized that the brain would be 'tricked' into perceiving that the body has adequate energy reserves, which would result in reducing the hyperactivity and obsessive behaviors associated with AN and potentially restoring cognitive functions linked to decision-making and emotional regulation. Such effects may facilitate the early stages of psychological recovery and reduce resistance to treatment.

A set of recent case studies added evidence for the use of recombinant leptin in the treatment of AN. Milos et al. administered recombinant leptin, metreleptin, in three underweight patients diagnosed with AN who presented with significantly elevated levels of hyperactivity as part of their clinical presentation [84]. Number of days for dosing differed by patient and were 6 days, 9 days, and 14 days. Two of the three patients reported fast and significant decreases in repetitive thoughts of food, drive for activity, feeling fat, fear of weight gain, inner tension, and depressed mood on visual analog scales. However, the third patient did not report any cognitive or emotional changes. At the conclusion of the study, 2 of the 3 patients had slightly gained weight, and the third patient slightly lost weight while on metreleptin. A recent case report from the same investigators by Gradl-Dietsch et al. on a 15-year-old adolescent with AN who received metreleptin for 9 days showed a similar reduction in AN-related thoughts and improved depression ratings [85], as did an adolescent patient with atypical AN reported by Hebebrand et al. [86]. Importantly, all these reports showed that symptoms quickly reemerged with the cessation of metreleptin treatment. Recombinant leptin is, at this time, cost-prohibitive, costing approximately $1,600 for a single middle dose of 5.8 mg. Nevertheless, while case reports must be viewed with caution, and it is unclear whether the neurobiological model holds, the dramatic improvements during medication dosing are impressive and deserve further study.

4.4. Neuroactive steroids

Neuroactive steroids bind to membrane receptors and alter the excitability of excitatory or inhibitory neurons. Allopregnanolone, a major metabolite of progesterone, is a potent, endogenous neuroactive steroid that modulates neuronal excitability through positive allosteric modulation on the synaptic and extrasynaptic gamma-aminobutyric acid (GABA) type A receptors [87,88]. The extrasynaptic GABA A receptors mediate tonic inhibition, which makes allopregnanolone's mechanism unique compared to benzodiazepines, which mediate the phasic inhibition at GABA A receptors [89]. Brexanolone is a medication that is effective in rapidly reducing depressive and anxiety symptoms in postpartum depression [90]. Individuals with AN have elevated anxious traits, experience negative emotions, including fears, worries, and anxiety, across many situations, and tend to perceive environmental stimuli as threatening [91–93]. Trait anxiety has been associated with AN psychopathology previously [94–96]. For instance, anxiety moderated the relationship between body dissatisfaction and disordered eating, suggesting that nonspecific anxiety contributes to AN behaviors and severity [97]. Brain research that focused on trait anxiety irrespective of EDs found this temperament trait to be associated with amygdala activation and areas of high GABA A receptor distribution [98–100]. Several studies have found altered amygdala response in groups with EDs in response to body image, taste, or emotional conflict tasks [101–103]. It is possible that normalizing anxiety and depressive symptoms in AN will reduce the expression of AN behaviors, especially drive for thinness and body dissatisfaction. Commonly used antianxiety or antidepressive medication has not been able to target AN-specific anxiety and fears, suggesting that those medications cannot target the specific pathophysiology underlying AN [31,104]. As stated above, AN has been associated with polymorphisms of GABAergic receptors which may make them less susceptible to traditional anxiolytic medication [39]. Neuroactive steroids such as allopregnanolone may be able to reverse or ameliorate a functional deficit on the GABA A receptor in AN. Of note, no studies to date have assessed the use of neuroactive steroids in AN.

4.5. Nutrition interventions

It has previously been hypothesized that the pathophysiology of AN may include metabolic abnormalities, or AN may be a 'metabolic disorder of psychological origin' [105]. As described above, negative affect, deficits in regulating emotions, and elevated anxious traits are considered important for AN etiology [106–108]. Stress and anxiety affect glucose metabolism, altering blood sugar levels [109]. Animal studies found that 40% of mice had a stress-susceptible phenotype associated with elevated blood glucose but reduced brain glucose metabolism, suggesting a specific mechanism in susceptible individuals [110]. It was subsequently hypothesized that stress-related disorders could be associated with altered glucose metabolism [111]. For instance, research in humans indicated altered brain glucose metabolism after acute stress using the Trier Social Stress Test [112]. In individuals with a chronic stress condition, posttraumatic stress disorder, they showed lower brain glucose metabolism after administration of the stress hormone hydrocortisone [113]. We have recently developed a model for how stress and anxiety interfere with energy metabolism and contribute to self-starvation [114]. We hypothesize that high state and trait anxiety levels create ongoing interference with brain glucose utilization in AN as a risk factor before, during, or after weight loss. If a person with that disposition loses weight and enters a ketosis state, the brain will use ketones as an alternative energy source that may be less affected by anxiety. Thus, the individual learns that starvation paradoxically provides a better subjective feeling of having sufficient energy, and food restriction becomes self-reinforcing. However, this state also depletes the body's resources and eventually leads to death. We propose that providing a person with that disposition with ketone bodies while ensuring normal weight will remove the desire to self-starve and support weight maintenance [114]. We propose that ketogenic therapy, which provides a food composition of 70% fat, 20% protein, and 10% carbohydrates, could be an effective intervention for AN. A single case study suggested that ketogenic therapy, followed by ketamine infusion, could

help a patient with long-standing weight-normalized AN to recover [115]. In a follow-up open-label trial to test whether the case report response could be replicated, five weight-normalized adults with AN and persistent eating disorder thoughts and behaviors adopted ketogenic nutrition therapy. In addition, participants received six ketamine infusions after four to eight weeks of stable ketosis and were followed over six months [75]. All participants completed the study protocol without significant adverse effects and significantly improved on AN-specific behaviors while maintaining a normal weight range. These studies support the benefit of further examining the ketogenic diet as a treatment intervention for AN. Currently, a trial is underway that provides this nutrition to a partially recovered weight normalized group with AN (NCT06000774, clinicaltrials.gov). Implementing such a nutritional intervention requires motivation by the patient just as with the treatment as usual food approach in the outpatient level of care, and additional strict behavioral management that supports eating is typically needed in a higher level of care program [116]. Key is a provider team that conveys a strong rationale for the intervention together with motivational strategies and provides close follow-up and support. Of note, in the case report and the case series [75,115], ketamine infusions were added once the subjects had been on the ketogenic intervention for at least four weeks. The choice was clinically driven and based on a small positive report of decreased obsessions/compulsions in a pilot study of 12 patients with AN [117]. Whether ketamine is helpful or necessary as an adjunct to the ketogenic dietary intervention or whether there are subgroups who will benefit will be important research questions to answer.

4.6. Cannabinoids

Cannabinoids occur naturally in the human body as endocannabinoids or can be derived from plants. Commercial cannabis products have recently been legalized in many states of the U.S.A. and can be legally purchased in several countries around the world for recreational use. They are typically harvested from marijuana or hemp plants but can also be made synthetically. The endocannabinoid system comprised cannabinoid 1 and 2 receptors (CB1R and CB2R, respectively), endogenous ligands (e.g. N-arachidonoylethanolamide [AEA], also known as anandamide, and 2-arachidonoyl glycerol [2-AG]), and enzymes for ligand biosynthesis and inactivation. Endocannabinoids are involved in the regulation of appetite, food intake, and energy balance [118]. A few medications in that class have been FDA-approved for medicinal purposes. The synthetic cannabis tetrahydrocannabinol (THC) dronabinol approved for AIDS-related weight loss and chemotherapy-related nausea and vomiting, discussed previously in the previous review [31], has not shown a strong effect size for weight gain in AN that would have warranted further study. Cannabidiol (CBD), which can be derived from marijuana or hemp plants, is non-addictive and is approved for seizure disorders, including Dravet and Lennox-Gastaut syndrome. CBD is a CB1R antagonist, facilitating endocannabinoid signaling by inhibiting the cellular uptake and enzymatic hydrolysis of endocannabinoids [119,120] while also binding to serotonergic (5HT1A) receptors. CBD has shown anxiolytic effects, both in rodent models and in healthy and anxious humans [121], and the anxiolytic action of CBD appears to be mediated, in part, by brain 5-HT1A serotonin receptors [122]. Clinically, CBD has been alleged to be helpful for depression, anxiety, or posttraumatic stress disorder, but the literature is inconclusive [123]. In AN, clinical research found elevated blood levels of the anandamide AEA, as well as elevated levels of CB1R, but not CB2R, mRNA, and an association between a polymorphism of the FAAH gene, has been reported in AN in the Japanese population [124]. However, other research in AN associated genetic differences in cannabinoid receptor nucleotide frequency with comorbid psychiatric conditions but not the eating disorder diagnosis [125]. Currently, a study on CBD in AN is underway, but no results have been published yet (NCT04878627, clinicaltrials.gov).

5. Conclusion

This report serves as a brief review of and update to our previous article covering pharmacological intervention studies in AN [23]. Previously examined pharmacological interventions included appetite stimulators, antidepressants, anxiolytics, typical or atypical antipsychotics, mood stabilizers, hormonal treatments, and other agents such as zinc or tyrosine. There have been only very few updates on these interventions in recent years. This may highlight that AN's pathophysiology may not primarily involve one neurotransmitter system or may not be able to be targeted with one specific medication class. While we are still waiting for FDA approval of a medication for AN, exploring novel treatments centered around a range of pharmacological agents and therapeutic strategies, each targeting distinct pathways involved in the disorder's pathophysiology, is very promising. While current pharmacological treatments for AN show limited effectiveness in addressing core symptoms, emerging therapies offer promising avenues for future exploration. These novel interventions, ranging from psychedelics to neuroactive steroids and nutritional strategies, highlight the need for an approach to AN treatment that targets different neurobiological systems and that may need to be tailored to the individual. Continued research is crucial to understand the underlying mechanisms better and optimize therapeutic outcomes for individuals with AN. Animal models, such as the ABA model, can be useful in this work to better understand mechanisms of, for instance, neurotransmitter adaptations in response to underweight and weight normalization and can help explain, for instance, human functional imaging research findings. However, they cannot model emotional or behavioral factors such as fear of weight gain or body image distortion.

6. Expert opinion

Since our last review, no medications have been available that have received FDA approval for the treatment of AN. This is truly detrimental for a disorder with one of the highest mortality rates among psychiatric illnesses. Brain research

indicates the involvement of fear-based learning and dopamine-associated circuits utilized or highjacked by exaggerated fear toward food, eating, and weight gain. The described neuroscience-based model for AN supports using low-dose of the dopamine D2 receptor partial agonist aripiprazole to improve cognitive flexibility and the dopamine D1/D2 receptor antagonist olanzapine to reduce acute fear, dread, and avoidance. However, conducting controlled studies in this population has proven difficult since funding agencies lack interest in funding such studies, and set dosing regimens are often not possible in a population that is hesitant to take any medication. We are currently conducting large prospective and retrospective studies to further support using those medications.

Much of psychopharmacological research in AN has focused on weight gain as the primary or often only outcome measure. This is understandable since emaciation in AN can lead to death, while weight gain in treatment is predictive of short-term outcomes [126]. However, what may be most predictive of long-term outcomes are learned fear associations toward food, which may further enhance cognitive rigidity, interfering with behavior change. These aspects of the illness have been investigated only in the more recent past. Also, only recently has the importance of comorbid anxiety and depressive disorders been recognized as factors that may prolong the illness. Improving comorbid affective and anxiety symptoms and attenuating fear associations should, therefore, also be an important goal when researching new medications for AN to improve quality of life, which may have beneficial long-term effects on the recovery course.

The novel agents that are currently under investigation could have significant potential. While the NMDA receptor antagonist ketamine does not stand out as having much direct effect on AN-specific symptoms, it could be useful in treating depression that often persists or even emerges after successful treatment of AN. We, therefore, suggest referring patients who may be weight normalized but are depressed to consider ketamine treatment. Psilocybin, which stimulates serotonin 2A receptors and has received significant attention for its potential use in various psychiatric illnesses, could be useful to treat AN symptoms, but larger studies are still lacking. Similarly to ketamine, it could be that psilocybin is most potent in treating mood-related symptoms and may be particularly useful for individuals with this comorbidity. The results from the few metreleptin-treated patients are very promising, although the cost of this synthetic leptin analog drug is prohibitive to use at this point, and larger studies are needed. The neurosteroid brexanolone may have a high potential to relieve AN-associated anxiety that has not been targeted well by medications that typically alleviate anxiety. However, trials are lacking to date. Nutritional ketosis as a pharmacological intervention has so far shown may be the strongest indication of it being a highly effective treatment, but larger trials will need to test what weight or BMI range may be appropriate to use this intervention in AN since glucose reserves and altered metabolism in the very underweight group could make its use in low-weight individuals prohibitive until they have weight normalized. Trials are currently underway to replicate previous findings and expand the intervention to lower-weight groups. Lastly, CBD can have important effects on anxiety around food, shape, weight, and eating, and we are awaiting the results of an ongoing study.

Our ultimate goal when treating AN, like other disorders or diseases, must be symptom resolution and good quality of life. It is encouraging that the novel agents discussed here are targeting new mechanisms and go beyond previously studied types of medications. The key will be to carefully assess individuals for signs or symptoms beyond weight and test medication effects across many variables. We believe that this field will continue to test all available pharmacological interventions. However, we expect that specific interventions will have key roles in normalizing AN-associated behaviors, with aripiprazole enhancing cognitive flexibility, olanzapine decreasing acute distress, ketogenic nutrition improving energy and mood and decreasing body-related distress, and ketamine treating depressive symptoms. It will be critical to find out at what weight the interventions are most beneficial and what AN subgroups will benefit more or less compared to others.

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Declaration of interest

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