Published in final edited form as:

CNS Drugs. 2016 May ; 30(5): 419–442. doi:10.1007/s40263-016-0335-6.

Role of Psychotropic Medications in the Management of Anorexia Nervosa: Rationale, Evidence and Future Prospects

Guido K.W. Frank, M.D.^{a,b} and Megan E. Shott, B.S.^a

^a University of Colorado School of Medicine, Department of Psychiatry, University of Colorado Anschutz Medical Campus, Aurora, CO, USA

^b Neuroscience Program, University of Colorado Denver, Anschutz Medical Campus, Aurora, CO, USA

Abstract

Anorexia nervosa is a severe psychiatric disorder without approved medication intervention. Every class of psychoactive medication has been tried to improve treatment outcome; however, randomized controlled trials have been ambiguous at best and across studies have not shown robust improvements in weight gain and recovery. Here we review the available literature on pharmacological interventions since anorexia nervosa came to greater public recognition in the 1960s. This will include a critical review of why those trials may not have been successful. We further provide a neurobiological background for the disorder and discuss how cognition, learning and emotion-regulating circuits could become treatment targets in the future. Making every effort to develop effective pharmacological treatment options for anorexia nervosa is imperative, as it continues to be a complex psychiatric disorder with high disease burden and mortality.

1. Introduction

Anorexia nervosa (AN) is a severe mental illness with the highest mortality rate among the psychiatric disorders [1]. AN usually begins during adolescence and occurs most commonly in females [2]. It is the third most common chronic illness among adolescent females [3] with a mortality rate 12 times higher than the expected death rate for 15- to 24-year-old females [4]. The diagnostic criteria for AN according to the Diagnostic and Statistical Manual for Mental Disorders (5th ed.; *DSM-5* [2]) include restriction of energy intake relative to requirements leading to a significantly low body weight in the context of age, sex, developmental trajectory, and physical health; an intense fear of gaining weight or becoming fat, even though underweight; a disturbance in the way in which one's body weight or shape is experienced and undue influence of body weight or shape on self-evaluation; or denial of the seriousness of the current low body weight. Previous editions of the *DSM* indicated the requirement for body weight to be below 85% of that expected and the loss of regular

Corresponding Author Guido K.W. Frank, M.D., Associate Professor, Departments of Psychiatry and Neuroscience, Director, Developmental Brain Research Program, University of Colorado Anschutz Medical Campus, Children's Hospital Colorado, Gary Pavilion A036/B-130, 13123 East 16th Avenue, Aurora, CO 80045, Phone: 720-777-1909, ; Email: Guido.Frank@ucdenver.edu.

Compliance with Ethical Standards

Conflicts of Interest

Dr. Frank and Ms. Shott report no competing interests.

menses. In the latest edition, *DSM-5*, the weight criterion is now less strict, and the latter was dropped altogether. A restricting type (AN-R), marked by food restriction and commonly overexercising, has been distinguished from a binge-eating/purging type (AN-B/P), where afflicted individuals eat large amounts of food in a relatively short period of time (“binge eating”) yet remain underweight or engage in behaviors to counteract weight gain, such as self-induced vomiting or use of laxatives or diuretics (“purging”). AN is a chronic disorder characterized by frequent relapse, high treatment cost and disease burden. Yet we know little about its underlying neurobiology, and developing pharmacological treatments for AN has been difficult [5]. Depression and anxiety are common in AN [6] and are related to eating disorder severity and clinical outcome, which may have implications for the effectiveness of treatment interventions [7, 8]. Treatment effectiveness for AN in general is limited [9], and in particular, no medication has been approved for it [10]. On the other hand, a large proportion of individuals with AN are treated with psychotropic medications [11], which raises the question of what place medication interventions may have in its treatment.

Here we will review the medication trials that have been conducted in AN over the past 50 years. The purpose of this review is to determine whether there is a justified place for psychotropic medications in the management of AN. We will use a neuroscience-informed approach to discuss how we may be able to improve medication use in AN and will use basic and clinical brain research to support possible new psychopharmacological directions.

2. Medication Studies in AN

Our original goal was to review the use of psychotropic medications in AN using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [12]. However, there are too few trials in each medication category to discuss separately. Here we will discuss case series as well as open and controlled trials to provide an exhaustive summary of current literature relevant to medication use in the treatment of AN. We searched the National Center for Biotechnology Information database using the search terms *anorexia, nervosa, drug, treatments* (1,160 hits), as well as *anorexia, nervosa, medication* (237 hits). The relevant articles for this review consisted of 25 double-blind, placebo-controlled studies; seven double-blind, placebo-controlled crossover studies; five single-blind, placebo-controlled studies; 23 open-label studies; and six retrospective chart reviews. Single case reports were excluded due to their lack of generalizability. The studies are presented in historical chronological order. Placebo-controlled as well as open-label studies are described in Table 1.

2.1. Cyproheptadine

Cyproheptadine is a first-generation antihistamine with anticholinergic and antiserotonergic properties. In 1962, it was reported that cyproheptadine could stimulate appetite and weight gain in children [13]. This made its use in AN appealing. The first double-blind, controlled study published in 1970 suggested weight gain in AN from the medication compared to placebo [14]. In 1979, a study using this drug with and without behavior therapy found that it was helpful for weight gain in patients with AN who had a history of complications during

delivery, had lost between 40% and 50% weight from expected body weight, or had previous outpatient treatment failure [15]. A follow-up report from the same group indicated that the medication could reduce negative attitudes toward body weight and shape [16]. However, a later double-blind, controlled study found that cyproheptadine had a “marginal effect” on decreasing the number of days necessary to achieve normal weight compared to placebo [17]. Interestingly, cyproheptadine increased treatment efficiency for the restricting type of AN but not for the binge/purge subtype in that study.

2.2. Tricyclic Antidepressants and Monoamine Oxidase Inhibitors

Tricyclic antidepressants, first developed in the 1950s, were used for anxiety and obsessive-compulsive disorder aside from depressive disorders, but the side effect profile, including sedation and cardiac arrhythmia, makes these medications less safe. These medications are only rarely used since the availability of selective serotonin reuptake inhibitors (SSRIs),.

A rationale for the use of these medications was based upon the hypothesis that AN is a form of depression, as it is associated with dysphoric mood and anxiety. A five-week double-blind, controlled study using amitriptyline did not support benefits of this treatment for AN [18]. A double-blind, controlled study that administered clomipramine found that the drug stimulated hunger, appetite, and energy intake; however, the medication was paradoxically also associated with lower weight gain compared to placebo, perhaps due to more physical activity [19]. Clomipramine has direct hypothalamic effects, and it was suggested that this could be the mechanism of action of this medication in terms of its appetite-stimulating effects. In another report, the medication was associated with higher appetite and calorie consumption at the beginning of treatment, but it did not improve weight gain in the long run during inpatient hospitalization. However, that study seemed to only reanalyze data from the previous reference [20]. A single-blind study that compared the dopamine D2 antagonist amisulpride, the SSRI fluoxetine, and clomipramine in restricting AN found that clomipramine was not effective [21]. A study that directly compared clomipramine with the SSRI paroxetine while patients were in an eating-disorder program found no differences in weight gain between medications. Paroxetine did shorten the treatment duration for achieving a similar weight gain [22].

The antidepressants of the monoamine oxidase inhibitor type are also not widely used anymore due to their side effect profile. However, before the advent of SSRIs, these medications were commonly prescribed and also tried in AN. An open-label trial using isocarboxazid in AN indicated improved mood and anxiety but no significant weight gain during the six-week trial [23]. Collectively, tricyclics and monoamine oxidase inhibitors showed little consistent promise as effective treatments for AN. In addition, their unfavorable side effect profile and potential for use in committing suicide make this class of medications a less-used category in psychiatry in general.

2.3. Typical Antipsychotic Medications

The older, first-generation, so-called typical antipsychotics have been used in the past but are now only rarely used in new-onset psychosis. These medications can have severe side effects, such as drug-induced parkinsonism or tardive dyskinesia. They share, in general,

strong dopamine D2 receptor antagonism. Barry and Klawans in 1976 speculated that dopamine receptors could be hypersensitive in AN and contribute to body image distortion in the disorder [24]. This would make the prescription of dopamine antagonists a logical choice. A double-blind, controlled study of the diphenylbutylpiperidine pimozide or placebo combined with behavior therapy showed active drug-enhanced weight gain in the beginning phase of the treatment [25]. In a small study that compared pimozide with behavior therapy, both groups gained weight over a 20-week period [26]. Haloperidol, a butyrophenone and the most commonly prescribed typical neuroleptic, administered as an adjunct to psychotherapy over six months was associated with weight gain in one study [27]. In a more recent case series identified by chart review, it was found that low-dose haloperidol was well-tolerated in treatment-resistant AN inpatients and that it reduced body image distortion and drive for thinness [28]. Chlorpromazine, a phenothiazine, was suggested to be helpful in weight recovery in an open study, but no follow-up studies were done [28]. Neuroscience and especially reward-system research implicated dopamine circuits in AN, but the typical dopamine receptor blockers have shown little promise to consistently improve food reward in AN.

2.4. Mood Stabilizers

Lithium, probably the most effective mood stabilizer for both manic and depressed episodes, is prescribed as a salt, most frequently as lithium carbonate. Its specific mechanism of action is not well understood, but it reduces noradrenaline and increases serotonin activity in the brain. A small double-blind, controlled study of adults with AN, who were also enrolled in a behavior therapy program, showed at weeks 3 and 4 (end of study) a small benefit with respect to weight in the lithium-treated group [29]. However, the benefit did not seem to outweigh the risks, especially as lithium treatment is sensitive to fluid shifts, a problem in AN, where patients frequently restrict fluid intake, which could lead to lithium intoxication.

2.5. Zinc

Zinc is a mineral with key functions in human metabolism. It has long been hypothesized that zinc deficiency could contribute to the pathophysiology of AN [30, 31]. Reduced zinc levels in AN respond to supplementation [32], and an open-label study of youth and adults with AN suggested promotion of weight gain in AN [33]. One double-blind, controlled study of adult AN suggested more rapid weight gain when receiving zinc supplementation [34], but another study of youth with AN found that zinc deficiency normalized quickly with weight restoration and zinc levels were not related to rate of weight gain [35]. In summary, the role of zinc in the treatment of AN is still controversial. In support of zinc as a treatment agent is animal research that showed that zinc deficiency is associated with weight loss and zinc supplementation can stimulate food intake [36]. Research suggests that zinc may act mechanistically via neuropeptide Y and that zinc deficiency may inhibit neuropeptide Y release and interfere via that pathway with normal food-intake regulation [37].

2.6. Opiates and Cannabinoids

Opiates and opiate antagonists are associated with hedonic aspects of food and drug use, and opiates were used with the hope of stimulating eating in AN or interrupting the suspected auto-addictive properties of food restriction. Continuous infusion of the opiate antagonist

naloxone in one study was associated with weight gain in AN [38]. During that treatment, serum fatty acid levels were reduced, suggesting that the drug affected lipid metabolism. To interrupt the AN behavior spiral, naltrexone, an opioid antagonist was administered to patients with AN of the binge/purging type [39]. In that study, naltrexone was associated with reduced binge/purge frequency. Cannabinoids have long been indicated to stimulate appetite, but a double-blind, controlled study of adults with AN who were also in a behavior management program showed no benefit from application of 9-tetrahydrocannabinol [40]. In fact, the medication caused dysphoria and sleep disturbance in AN. In contrast, a very recent four-week randomized controlled trial in which the tetrahydrocannabinol dronabinol was administered to women with severe relapsing AN found that the medication was associated with weight gain, although weight increase was small, about 1.5 pounds [41]. There have been new cannabis strains developed recently that may either stimulate (indica) or suppress appetite (sativa), which have not been researched in AN. In summary, opiates and cannabinoids profoundly affect eating behavior, but how they relate to AN and how agonists or antagonists may be used to facilitate recovery requires further study.

2.7. Benzodiazepines and Alpha 2 Adrenergic Agonists

In the clinical environment, benzodiazepines are sometimes used in the treatment of AN with the hope of reducing eating-related anxiety. Studies that systematically investigated benzodiazepines in AN in animal models or humans are scarce. One recent study using a randomized and controlled design in humans investigated the benzodiazepine alprazolam in an inpatient setting and did not find this drug beneficial in the treatment of AN [42]. Basic research has shown that the alpha 2 adrenergic agonist clonidine may increase feeding behavior, making a case to try this medication in AN [43]. However, this medication administered in a placebo-controlled crossover design had no beneficial effect in AN but was associated with hemodynamic side effects such as hypotension [44].

2.8. Selective Serotonin Reuptake Inhibitors (SSRIs)

The introduction of the SSRI fluoxetine brought an effective and relatively safe antidepressant to the market. In an open trial of six women with chronic AN, fluoxetine was associated with reduced depression and weight gain [45]. In a mixed group of AN individuals at low weight or already weight recovered, especially restricting type AN had improved or maintained weight better on fluoxetine [46]. On the other hand, one report advised caution because fluoxetine could affect appetite to the degree of *inducing* AN [47]. A study that contrasted fluoxetine, cognitive behavior therapy, or a combination did not find a benefit from fluoxetine [48]. Furthermore, a double-blind, controlled study using fluoxetine in AN in an inpatient setting did not show beneficial effects [49], nor did an open-label study in inpatients with AN [50]. A later double-blind, controlled study tested whether fluoxetine was beneficial for relapse prevention in the treatment of AN and indeed suggested that AN patients, after short-term recovery and on active fluoxetine, had reduced relapse in the one-year follow-up period [51]. This was in line with an open-label study [52], but not with a naturalistic follow-up after specialized eating disorder treatment over a two-year period [53]. Yet, another study of a larger sample that used prospectively the randomized control design and tested time to relapse with fluoxetine versus placebo could not show that fluoxetine was superior to placebo [54]. A comparison between fluoxetine and the serotonin-

noradrenaline reuptake inhibitor venlafaxine could not distinguish the two drugs [55]. As AN is associated with poor nutritional intake and thus with a lack of dietary tryptophan, the precursor of the neurotransmitter serotonin, it seemed logical to test whether tryptophan supplementation would improve fluoxetine effectiveness. However, a double-blind, controlled study using fluoxetine with supplement or placebo did not show benefits from the added tryptophan [56].

A small open-label study using citalopram together with individual psychotherapy gave some indication of reduction in body dissatisfaction but no effect on weight gain [57]. Follow-up open-label citalopram studies found, compared to a wait-list control group, improvement in anxiety and depression but no benefit in weight gain [58, 59]. Another SSRI, paroxetine, was investigated in a retrospective chart review and compared with clomipramine [22]. Weight gain achieved was similar between medications, but the rate of weight gain with paroxetine took only three-fourths of the time needed on clomipramine. A small open-label study that compared sertraline over 14 weeks with placebo in an outpatient setting [60] found that sertraline improved depressive symptoms, perception of ineffectiveness, lack of interoceptive awareness, and perfectionism compared to placebo but not weight gain. Two retrospective studies in AN tested whether medication with any SSRI improved treatment outcome but did not show benefits [61, 62]. A retrospective case review on the serotonergic/noradrenergic medication mirtazapine did not support that mirtazapine was superior to other medications or no medication in AN [63].

2.9. Atypical Antipsychotic Medication

Compared to the first-generation “typical” antipsychotics such as haloperidol, atypical neuroleptics have less extrapyramidal side effects. Some of them block dopamine D2 receptors as the first-generation drugs do; others have more serotonergic and less or no significant dopamine receptor affinity. The benzamide and dopamine D2 antagonist amisulpride was studied in a double-blind design [64]. There the authors found that the active drug was superior to placebo with respect to weight gain but only in the beginning phase of therapy and not in the crossover phase. Another study, single-blind, that compared amisulpride with clomipramine and fluoxetine found this medication superior with respect to weight gain over a three-month period but no group differences with respect to fear of weight gain, body image distortion, or amenorrhea [21]. The atypical neuroleptic most frequently studied in AN is the thienobenzodiazepine olanzapine. It is a dopamine D2 antagonist and an inverse agonist at the serotonin 2A and histamine H1 receptor. The particular appeal of olanzapine is that it is associated with substantial weight gain in populations with psychosis or mania, presumably mediated by the histamine receptor. Open-label studies suggested improved weight gain in AN [65, 66] in inpatient and outpatient settings. A retrospective study of previously ill AN individuals suggested that olanzapine reduced fear of eating and weight gain [67]. The first randomized controlled study of olanzapine in AN that compared this medication with chlorpromazine in a small sample found that olanzapine—but not chlorpromazine—reduced eating disorder ruminations [68]. Another open-label study found that the effects of olanzapine on weight gain and mood were significant in the binge/purge subtype of AN, but not in the restricting subtype [69]. Eventually, a double-blind, controlled trial was conducted over 10 weeks’ duration [70], and

olanzapine was credited with faster and greater weight gain compared to placebo [70]. One small open-label study found that olanzapine reduced hyperactivity and improved weight gain in youth with AN [71]. A 2011 study randomized (double-blind) individuals with AN to medication management with olanzapine or placebo and found that the active drug was associated with significantly greater weight gain compared with placebo [72]. Several studies tested whether olanzapine was beneficial to enhance psychotherapy. One study of adolescents who received olanzapine or placebo in addition to a behavior modification program did not show benefits from the drug [73]. A retrospective chart review on olanzapine in addition to psychotherapy in adolescents was not able to draw firm conclusions in favor of olanzapine due to methodological problems of the study [74], and in a study in which AN patients received more than three months of cognitive-behavioral and specific weight gain support paired with olanzapine or placebo, olanzapine was not superior to placebo with respect to weight gain [75]. Of note here is that olanzapine in AN as in other conditions can lead to hyperglycemia [76].

The atypical antipsychotic quetiapine is a relatively weak antagonist at the dopamine D1 and D2 as well as serotonin 1A and 2A receptor sites; it also shows strong histamine H1 receptor antagonism. Aside from its antipsychotic effects, it is known to reduce anxiety and is often associated with weight gain. One open-label study in AN suggested improved weight gain related to the medication [77], and another suggested that quetiapine was helpful in reducing anxiety and depression, but the effects on weight gain were minimal [78]. A double-blind, controlled study in an outpatient setting from the same group did not find benefits from quetiapine on treatment outcome for AN core symptoms [79]. A more recent small open-label study using quetiapine in young adults suggested that the medication might improve anxiety and depression, but not weight [80].

The atypical antipsychotic risperidone has potent dopamine D2 antagonism, especially at higher doses, but has also serotonin 1A, 2A, and histamine H1 receptor antagonistic action. Case reports suggested that risperidone could benefit weight gain in AN [81, 82]. The only double-blind, controlled study of this medication in adolescent AN did not show benefits from the drug over placebo [83].

The atypical antipsychotic aripiprazole is different compared to the other atypical antipsychotics, as it is a dopamine D2, serotonin 1A and 2C receptor partial agonist, as well as a serotonin 2A receptor antagonist. No controlled studies exist, but case series on adults and youth similarly suggest that this medication may reduce fear of eating in AN and facilitate recovery and it was suggested that aripiprazole might down-regulate dopamine receptor sensitivity [84-86].

2.10. Other Agents

A variety of investigations have been undertaken to expand medication trials beyond the traditional psychoactive drugs. The most promise may come from the glutamatergic NMDA agonist d-cycloserine that has shown promising results in the treatment of anxiety disorders with respect to fear extinction [87]. One study tested this substance in AN in order to facilitate eating in a laboratory design and found that d-cycloserine was associated with greater caloric intake compared to no medication [88]. In a randomized controlled study that

used food exposure and d-cycloserine or placebo, the active treatment group showed greater weight gain after four exposure sessions and at one-month follow-up [89]. The opposite approach was taken by a study that gave the NMDA *antagonist* amantadine to individuals with AN and reported rapid improvement, including weight gain, over three months of treatment [90]. One study that administered dehydroepiandrosterone (DHEA) in a double-blind design to AN to improve bone mineral density did not find the expected effect over placebo, but at four-month follow-up, BMI was higher in the DHEA group as was improved reported mood [91]. Ghrelin is a gut hormone produced in stomach and pancreas that stimulates food intake, making it a potential treatment agent for AN. A study that provided infusion of ghrelin over 14 days in five individuals with AN reported quickly improved gastrointestinal discomfort and improved nutritional intake and weight gain [92]. In one case report, the serotonin 1A agonist tandospirone was tried in two female patients with AN, one of the restricting and the other of the binge/purge type [93]. There the authors suggested that the medication led to weight gain and relapse prevention. Onset of AN is commonly during adolescence and hormonal surge during puberty as well as the low gonadal hormone state in AN led to speculations that sex hormones might be involved in AN pathophysiology. In one report, the prescription of estrogen replacement in a randomized controlled trial reduced trait anxiety but had no eating disorder specific effects [94]. Another study that used estrogen replacement for bone restoration in AN did not find this treatment effective to improve bone mass or body weight [95]. One study used testosterone in order to improve bone loss, cognitive deficits, and mood in AN and this hormone was associated with improved spatial cognition and mood [96]. Another hormone, human growth hormone was hypothesized to be beneficial for weight recovery in AN but was not superior to placebo [97]. In summary, the majority of these pharmacological agents did not show significant benefits in AN treatment but it is also not certain whether their potential is fully explored. Also not well understood and not well studied in human AN are neuropeptides and whether they can improve recovery [98].

3. Neurobiology of AN

3.1. Human Studies

The role of neurobiological mechanisms including developmental and environmental factors that contribute to the beginning and perpetuation of AN, is not well understood, although over the past two decades, we have started to better understand brain neurobiology that is involved in AN. Studies on brain volume had been inconsistent but with the general notion that brain volumes are reduced in AN [99]. More recent studies contradict this perception. Acute food and fluid restriction reduces brain volume and this normalizes quickly with nutritional rehabilitation [100]. Moreover, AN individuals who were studied under short-term nutritionally controlled conditions showed *increased* orbitofrontal and insula cortical volumes across age groups and stages of illness [101, 102]. The insula contains the primary taste cortex and provides signals to the reward system, while the orbitofrontal cortex contributes to the mechanisms that determine when to stop eating [103]. Thus, altered brain volume in those structures could affect function and thus the normal biological food-reward circuitry. Neurotransmitter receptor studies using positron emission tomography (PET) to study receptor distribution showed that the serotonin 1A receptor availability in AN was

higher compared to controls, while the serotonin 2A receptor tended to be reduced across the cortex compared to controls [1]. The function of the serotonin system is multifold and frequently associated with high anxiety and low mood, behaviors that have long been associated with AN [1]. The dopamine D2 receptor was found to be higher in AN after recovery in the antero-ventral striatum [104], and the cannabinoid 1 receptor was higher in AN in insular, infero-frontal, and infero-temporal pole [105], compared to healthy controls. Both dopamine and opioid circuits code neural reward processing. Dopamine neurons code motivation (“wanting”), reward approach and learning, and the opioid system codes pleasurable experience from rewards (“liking”). Thus, altered receptor availability could interfere with this feedback circuitry in AN [106, 107]. Functional magnetic resonance brain imaging (fMRI) tests brain *activation* across brain regions and circuits, such as reward or anxiety pathways. Those studies usually do not test brain neurotransmitters directly, but the response during tasks that test specific behaviors might help in understanding neurotransmitters involved in the brain response [108]. In such studies during fMRI, individuals with AN showed greater brain activation compared to controls when viewing anxiety-provoking food pictures; during taste or monetary reward tasks, individuals with AN tended to show increased activation to unexpected stimulus presentation, while brain response tended to be lower when the specific stimulus was expected [109]. Importantly, a paradigm that specifically targets dopamine-related pathways (prediction error model [110]) suggested increased brain responsiveness in AN, implying high dopamine receptor sensitivity, which is consistent with basic science research. The field of genetic research also continues to investigate the neurobiological underpinnings of AN, including genes for neurotransmitters and neuropeptides [111], as well as genome-wide association studies [112, 113]. However, the aggregate of research has not yet led to breakthroughs in the field with respect to eating disorder etiology or psychopathology; this may be due in part to the large sample sizes needed and will take much further effort [114]. A potentially promising approach that might help in this effort is a new correlation analysis that uses data from different genome-wide studies and that could identify overlap between disorders such as AN, obesity, and schizophrenia [115].

3.2. Animal Models

The predominant animal model for AN is the rodent activity-based AN (ABA) model, where after food restriction and access to a running wheel, the animal increasingly uses the wheel, which seems to further reduce food intake, and if not stopped, the animal exerts itself to death [116]. That model replicates the vicious cycle of food restriction and excessive exercise, continuous weight loss, and death. One study applied olanzapine to rats, which reduced hyperactivity on the running wheel suggesting that this drug could reduce excessive exercise drive in AN [117]. A study that compared olanzapine and the SSRI fluoxetine found that one-week treatment with olanzapine improved survival, but a four-week course of fluoxetine did not [118]; interestingly, olanzapine did not affect feeding or wheel-running. The dopamine D1,2 and 3 receptor antagonist cis-flupenthixol was given to ABA rats and improved feeding behavior and reduced weight loss [119]. Application of the serotonin agonist fenfluramine resulted in faster weight loss in one study but not another [120, 121]; in contrast, the serotonin 1A receptor agonist 8-OH-DPAT reduced hyperactivity and associated weight loss [122]. Another group found in the ABA model that the application of

the cannabinoid receptor agonist delta(9)tetrahydrocannabinol in conjunction with a high-fat diet led to reduced use of the running wheel, as well as increased body weight [123]. One study investigated the cannabinoid system and applied either delta(9)tetrahydrocannabinol or the endocannabinoid uptake inhibitor, OMDM-2, to ABA mice that had lost weight and shown excessive wheel running [124]. In that study, both agents increased food intake but did not improve survival; in fact delta(9)tetrahydrocannabinol decreased survival rates. Leptin is a hormone produced by fat cells to down-regulate feeding drive, presumably via brain dopamine receptors and was found to reduce running wheel activity, suggesting that dopamine circuits in the context of food restriction drive hyperactivity [125, 126]. The ABA model also allows studying specific dietary manipulations and both high-fat and high-carbohydrate diets promoted fast weight recovery, but may also be associated with fatty liver development [127, 128]. Dietary supplementation is another strategy and recently a small study tested a metabolite of L-arginine, agmatine on its effects on ABA. That study indicated that 20 and 40mg/kg of agmatine ameliorated ABA weight loss and plasma corticosterone increase suggesting a protective effect, possibly mediated via blockade of dopamine D2 and activation of 5-HT1A receptors [129]. A recent ABA study suggested that progesterone interacts with α 4-GABA receptors and worsens wheel-running behavior [130], supporting the notion the increased hormone release during puberty is a vulnerability in some to develop AN [131]. Brain reward learning is altered in AN, behavior that has been associated with brain dopamine function suggesting that dopaminergic agents could ameliorate this dysfunction [132]. One study that tested serotonin 2A/2C, serotonin 3, dopamine D1-like, D2, D3 and D2/3 receptor antagonists indicated that the dopamine D2 and D3 receptor antagonists increased survival, while the other agents did not [133]. This is an interesting result, as the clinical studies using antipsychotics with dopamine D2/D3 antagonism have not shown benefits (see above).

In summary, a number of biological factors are involved in AN pathophysiology, including monoamine neurotransmitters, such as serotonin and dopamine, neuropeptides, and hormones, but environmental factors are also involved. This suggests that we have to start building more complex models that test interactions of those individual factors to better understand AN's neurobiology [134, 135]. In fact it has been suggested that this need for a better integration of genetic, environmental and developmental factors applies to animal models for psychiatric disorders in general [136]. What animal models do not represent well are the cognitive-emotional aspects of AN and its ego-syntonic nature of food restriction [137]. Another caveat to keep in mind from substance use disorder treatment research is that drug development can show much promise in animals, but not all of these results can be directly translated to humans [138].

4. Why Do No Medications Show Robust Benefits in the Treatment of AN?

The reasons why hypothesis driven drug development in psychiatry in general has been challenging is the complexity of the human brain [139]. The hope and expectation is that with increasing capability of novel research methods to study the human brain we will eventually understand mechanisms, which will then allow us to develop targeted pharmacological interventions. There are various aspects of the progression of AN that may have particular relevance when developing a medication. First, AN typically develops during

childhood and adolescence, and there is an interplay between normal brain development and AN start and progression. This interaction is associated with brain neurotransmitter receptor changes, and medication may only be effective for a discrete time. This is a problem in child psychiatry in general. Second, there may be premorbid conditions, such as anxiety or depression, that could respond to medication and impact AN development and course, but as soon as AN with all its associated behaviors has started, the changing biological conditions due to malnutrition may require ongoing adaptation of the most effective treatment regimen. It is, for instance well-known that weight loss is associated with a sensitization of dopamine neuronal function, while overweight and weight gain show decreased dopamine receptor activity [140-142], and any psychopharmacological approach has to take such changes into consideration. The past approach to medication treatment in AN, however, has not always been built on a systematic, neuroscience-based empirical approach. Historically in the field of psychiatry new medications have been typically found by serendipity [143]. The problem is that: 1. we have limited knowledge about disorder-specific pathophysiology, and 2. our medication arsenal is limited, and we try any medication we have with the hope that it will improve the condition. This approach is likely to lead to both type I as well as type II errors. Another potential source of errors and unsuccessful medication intervention trials is the dose of a medication. Typically, medications have been prescribed based on knowledge from mood disorder or schizophrenia literature. However, there is no reason to believe that those dose regimens apply to AN. Those “typical” doses may lead to side effects without benefit, while a different approach to dosage could be more effective. Ideally, research would pair animal models of starvation with the clinical trial and determine what medication dose is most adequate. As much as extremes of food restriction or intake alter neurotransmitters, so do medication doses need to be adjusted. Another potential confounder is comorbidity. Medication trials are often assessed for reductions in depression or anxiety scores. However, not every person with AN has a current anxiety or depressive disorder, and this variability could confound outcome. It is possible that only patients with a current comorbid major depressive disorder would truly benefit from an antidepressant medication, which, in turn, could improve AN treatment outcome and prognosis. Most medication trials are small, and a stratification that includes comorbidity is hard to accomplish, but if we do not do that, we cannot truly assess the effects from the medication. In support of this argument is that controlling for comorbid conditions in biological studies typically improves the signal to noise ratio. Another limitation of medication trials in eating disorders is that they typically focus on the acute phase of the illness and not whether a medication may prevent relapse long after weight recovery. Studies in most cases had a duration between 1 and 6 months and very rarely went to 12 months or beyond. In summary, it may be that AN is not that different compared to other psychiatric disorders with respect to biological underpinnings. However, the complex interactions between intrinsic brain abnormalities and changes that occur during the illness and food restriction will need extra effort to better understand and create biological models of the disorder.

5. New Approaches to Medication Intervention in AN

The first question we have to ask in this effort is, what aspect of AN do we want to treat, and what mechanisms do we target? Drug research in psychiatry in general has not always been

guided by systematically targeting a particular mechanism [143]. We still do not know well what mechanisms drive mental illness, or one may better say psychiatric brain disorders. Neuroscience and psychology have now provided us with a much better understanding of brain function, and we should take advantage of that. It is probably unlikely that we will identify a medication that will cure AN, but we may be able to identify medications that can improve outcome based on behavioral concepts and diagnostic subgroups. Importantly, new hypothesis driven drug research is necessary but often challenging, especially in psychiatry; however, clinicians can inform the researcher on new applications and dose regimens of existing agents to expand the available therapeutics [144]. Furthermore, specific AN associated behaviors that are encountered in clinical care need to become research and treatment targets.

5.1. Learning and Fear Extinction

AN is driven by fear of weight gain, and psychotherapy is designed to overcome this anxiety. The above-described studies used d-cycloserine-targeted fear extinction, but further studies are needed to determine whether this type of medication approach can be helpful. Animal studies have found that there is an interaction between hormonal state and fear extinction, and females in a lowestrogen state may especially benefit from dopamine receptor stimulation when trying to suppress previous fears after extinction training (“extinction retrieval”) [145]. Thus dopamine D1 receptor stimulation could support anxiety reduction specifically in females with AN, as the disorder is typically associated with low gonadal hormone levels. The dopamine D2 receptor could also be a target for reducing conditioned fear, as quinpirole reduced expression of conditioned fear response in rodents, and it was hypothesized that this was mediated by presynaptic dopamine release modulation via the dopamine D2 receptor [146]. In another study, the D2 receptor agonist quinpirole reduced amygdala dopamine levels and associated fear response [147]. An additional effect of the dopamine D2 agonist quinpirole was to block conditioned fear memories that affected both fear conditioning as well as extinction [148]. Taken together, the dopamine D1 and D2 receptors appear to be potential targets for treatment of anxiety and modulation of conditioned fear. Receptor stimulation could therefore be promising, although systemic application of dopamine D2 blockade facilitated fear extinction [149]. However, most studies generally used acute, short-term designs. Chronic dopamine D2 receptor antagonist application enhances this receptor system over time, while chronic agonists decrease dopamine receptor activity [150, 151]. Thus, the effects of dopamine D1 and D2 agonists and antagonists have to be studied over longer periods and in relation to weight state. The dopamine D2 receptor partial agonist aripiprazole showed anxiolytic effects during a fear conditioning paradigm in animals [152] and reduced distress around eating in individuals with AN [84]. Therefore, it is possible that dopamine receptor activation is beneficial in AN treatment.

5.2. Reward System Responsiveness

Dopamine circuits within the brain reward system drive food approach and the motivation to eat [153]. It is therefore conceivable that the poor motivation to recover in AN is in part related to dopamine system alterations [154, 155]. Animal studies have shown that extremes of food intake change brain dopamine chemistry, regardless of whether there was an

alteration before developing AN. Specifically, dopamine response becomes sensitized with food restriction and weight loss and does not quickly normalize with normalization of food intake [140, 142]. Using fMRI and a task that is specifically designed to test dopamine neuronal activation (“prediction error model” [156]), we found that AN was associated with greater brain response in insula and ventral striatum, suggesting abnormally heightened dopamine receptor sensitivity compared to controls [132]. If in fact there is a hypersensitivity of dopamine D1 and D2 receptors in AN, then long-term application of dopamine receptor antagonists could further increase receptor availability and system activity [150, 151, 157]. On the other hand, cautious application of dopamine receptor agonists could be beneficial, as it would result in a net decrease in dopamine binding sites and desensitization over time and possibly reduced response sensitivity [150, 158-161]. Such dopamine receptor down-regulation then might attenuate reward system responsiveness. One case report in a sample of six patients with AN showed that a low dose of the dopamine agonist levodopa was helpful for weight gain in four patients, while the two non-responders maintained their weight [162]. Other evidence for dopamine agonists comes from case reports that suggest that the dopamine receptor partial agonist aripiprazole at a relatively low dose can reduce fear of weight gain and support AN treatment outcome [85, 84].

5.3. Social Cognition

Social cognition has long been suspected of involvement in the psychopathology of AN, and the disorder has been compared with autism spectrum disorder [163, 164]. Whether such deficits exist is still under investigation, but various studies have applied pharmacological interventions in an attempt to improve social functioning in AN. Oxytocin is a neuromodulatory prosocial hormone that is released by the hypothalamus and stored in the pituitary gland. The literature is discrepant whether this hormone is increased, decreased, or normal in AN [165, 166], and one study found that plasma oxytocin levels predicted anxiety and depression ratings after a meal [167]. A series of double-blind studies from the same group indicated that oxytocin reduced attention bias to disgust in both AN and control groups, suggesting that in AN, oxytocin reduced attention bias to food and body-related stimuli but had no effect on emotion recognition or food intake [168-170]. Especially, the latter report does not support the usefulness of oxytocin as a therapeutic agent in AN; however, a long-term application might have produced different results.

5.4. Novel Therapeutics

The development of novel therapeutic agents in psychiatry has been very slow and may be in part due to the pharmaceutical industry's “withdrawal” from this area [171]. On the other hand neuroscience continues to make progress in identifying mechanisms that underlie disorder processes with the study of neuroplasticity, neurogenetics and neural circuitry [172]. This holds promise in identifying disease mechanisms and new molecules to treat psychiatric disorders. In depression treatment research there have been various compounds identified that are currently under investigation (see review in Papakostas and Ionescu, 2015) [173] including glutamatergic N-methyl-D-aspartate (NMDA) receptor antagonists, such as ketamine or lanicemine, which rapidly reduce depressive feelings with few side effects. Previously, a hypercholinergic state has been postulated as a mechanism that contributes to depression and the antimuscarinic agent scopolamine has shown fast anti-depressant

response. Vortioxetine, a novel medication that modulates serotonin receptors, has recently been approved for major depressive disorder and has not been tested in eating disorders. That drug has also been considered a potential treatment for generalized anxiety disorder [174]. Glutamatergic agents, corticotrophin releasing factor 1 antagonists, and angiotensin II receptor antagonists may also have anti-anxiety effects, but may not be available for clinical use for some time [175]. Nevertheless, those agents could be investigated in animal models of AN. A potential for the eating disorders field from relevant research in the addiction literature is on gastrointestinal peptides that are active in the brain [176]. Those peptides include substance P, neurotensin, ghrelin, neuropeptide Y and glucagon like peptide 1. They have been shown to increase or decrease alcohol consumption in animal models and could have implications for food intake in AN. Their activity is related to the body's immune system as well as monoaminergic neurotransmitters such as serotonin or dopamine [98]. Those peptides are often altered during the ill state of an eating disorder and normalize with recovery, but it is largely unknown whether they contribute mechanistically to AN [177]. A new area of research is the intestinal microbiome and one small study suggested that the bacterial composition in the intestine is altered in AN and that weight recovery is associated in changes in the microbiome [178]. Future research may identify pharmacological interventions that could be beneficial for the recovery from AN.

New techniques have been developed to manipulate and better understand brain neurocircuitry. One such technique is optogenetics, which allows using light to switch on or off certain brain circuits, but at this point is only applicable in the animal model [179]. There are several new non-pharmacological interventions in psychiatry that effect brain activity. They include repetitive transcranial magnetic stimulation (rTMS) [180], transcranial direct current stimulation (tDCS) [181] or deep brain stimulation [182]. Those approaches have been associated with modulation of dopamine, serotonin and other neuro-transmitter systems [183, 184]. While their effectiveness is still under investigation, it is possible that the combination of brain stimulation and pharmacological agents might be beneficial to improve outcome in psychiatric disorders including eating disorders.

5.5. General Neural Protection

Nutritional supplements constitute a large segment in the personal health improvement market. These products are not regulated in the United States by the Food and Drug Administration but other countries may have more stringent rules. The true effectiveness of many agents is still unclear, but omega-3 fatty acids, which are part of neuronal cell structures and support human metabolism, have been well studied. The omega-3 fatty acids (α -linolenic acid, ALA; eicosapentaenoic acid, EPA; docosahexaenoic acid, DHA) are naturally occurring in foods such as fish or flax seeds and can be given as a nutritional supplement. The available studies on the effects of omega-3 fatty acids in psychiatry are typically small and not well-controlled, but have shown beneficial effects in treating depression [185]. Basic research has suggested that these agents could increase survival in animal studies [186], and small case reports from one group indicated potentially beneficial effects in AN [187, 188]. Some have made a compelling theoretical argument that this class of nutritional supplements could support brain health in disordered eating [189], but rigorous studies supporting this hypothesis are still outstanding.

5.6. Comorbidity

Depression and anxiety are very common in AN [6], and one would expect that comorbidity affects treatment outcome. A recent meta-analysis indicated that depression and general psychopathology unfavorably affected treatment outcome; however, the studies typically assess depression or anxiety with continuous measures such as the Beck Depression Inventory or State Anxiety Questionnaire score and do not necessarily stratify by diagnosis [190]. This is a potential problem, as one would, for instance, in a clinical setting prescribe an anti-anxiety or antidepressant medication based on a diagnostic assessment. One retrospective chart review studied adolescent patients with AN, who all also had a depressive episode at the time of treatment, and compared the effectiveness of paroxetine with clomipramine [22]. In that study, BMI increase was similar between groups (2.6 and 2.8 BMI points), but the paroxetine group took significantly less time (72 days) compared to the clomipramine group (97 days) to reach ideal body weight. Tricyclic medications have shown little benefit in the treatment of adolescent depression, while SSRIs have shown efficacy, although paroxetine's specific effectiveness has been recently questioned [191]. At our treatment facility, we carefully assess comorbid conditions and if, for instance, a major depressive disorder or anxiety disorder is diagnosed that cannot be attributed to the eating disorder; then we typically treat those conditions. This is with the rationale that the eating disorder treatment work is already intense, and our impression is that treating anxiety and depressive disorder facilitates AN treatment and at the least, improves quality of life. One school of thought was that SSRIs could not be effective because of poor nutrition and low tryptophan intake, which contributes to low brain serotonin. This has never been proven and specific supplementation with tryptophan did not make the medication more effective [56]. It may be more likely that the SSRI is just not specific enough for AN treatment, and it might only be helpful in individuals who have a full major depressive episode. Thus, we suggest that specific research be undertaken that stratifies AN individuals by comorbid diagnoses and tests whether SSRIs are beneficial or not.

5.7. Dosage

Dosage in medication trials is guided by dose ranges established to treat disorders for which those medications were originally developed. However, there is no proof that this is the best approach. Individuals with AN are at a lower weight; therefore, caution should be used when prescribing any medication, and lower dosages should be considered first. In support of the low-dose approach is a study of AN that administered low-dose olanzapine to 13 patients and found that the medication showed indications supporting weight gain and reducing hyperactivity. Similarly, case reports of aripiprazole in AN suggest the use of low dosages [85]. Taking this small amount of information into consideration, it might be best to start medication below the typical dosage and slowly up-titrate, depending on clinical response. Medication trials should then compare different dosages.

6. Conclusion

AN continues to be one of the most difficult disorders in psychiatry to treat. Medication trials to date have not been very successful, although based on neurobiological models, there should be opportunities to disrupt the pathophysiology of AN and improve long-term

outcome. After reviewing the existing literature, we provide a look ahead to where medication treatment for AN may be developed in order to improve outcome and prognosis of this disorder. In the future, more effort will be required to integrate areas such as brain imaging, molecular biology, and neuroendocrinology in human and animal models. Combined with illness-related behaviors to build complex models for AN, we can improve our understanding of its pathophysiology and facilitate development of pharmacological interventions. The etiology of AN continues to be poorly understood, and it has to be expected that behavior-genetics research will require much more time to identify genetic underpinnings. In the meantime, basic science animal research has helped us understand the neuroscience of brain function during food restriction and weight loss and direct us toward neurotransmitter systems that are or become altered in AN. These systems could be targeted with pharmacological interventions and then be tested in humans to improve illness outcome. Specifically, we have to identify how to modulate serotonin, dopamine, opioid, or other receptors to improve the behavioral targets of cognitive flexibility, learning, reward circuit function, and anxiety in AN.

Acknowledgments

Funding

N/A

References

1. Kaye WH, Wierenga CE, Bailer UF, Simmons AN, Bischoff-Grethe A. Nothing tastes as good as skinny feels: the neurobiology of anorexia nervosa. *Trends Neurosci.* 2013; 36(2):110–20. doi: 10.1016/j.tins.2013.01.003. [PubMed: 23333342]
2. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5(TM))*. 5th ed.. American Psychiatric Publishing; Arlington, Va: May 27. 2013 5 edition 2013
3. Golden NH, Katzman DK, Kreipe RE, Stevens SL, Sawyer SM, Rees J, et al. Eating disorders in adolescents: position paper of the Society for Adolescent Medicine. *J Adolesc Health.* 2003; 33(6): 496–503. doi:S1054139X03003264 [pii]. [PubMed: 14642712]
4. Sullivan PF. Mortality in anorexia nervosa. *Am J Psychiatry.* 1995; 152(7):1073–4. [PubMed: 7793446]
5. Fitzpatrick KK, Lock J. Anorexia nervosa. *Clin Evid.* 2011:2011.
6. Hudson JI, Hiripi E, Pope HG Jr, Kessler RC. The prevalence and correlates of eating disorders in the National Comorbidity Survey Replication. *Biol Psychiatry.* 2007; 61(3):348–58. doi:10.1016/j.biopsych.2006.03.040. [PubMed: 16815322]
7. Brand-Gothelf A, Leor S, Apter A, Fennig S. The impact of comorbid depressive and anxiety disorders on severity of anorexia nervosa in adolescent girls. *J Nerv Ment Dis.* 2014; 202(10):759–62. doi:10.1097/NMD.000000000000194. [PubMed: 25265267]
8. Hughes EK, Goldschmidt AB, Labuschagne Z, Loeb KL, Sawyer SM, Le Grange D. Eating disorders with and without comorbid depression and anxiety: similarities and differences in a clinical sample of children and adolescents. *Eur Eat Disord Rev.* 2013; 21(5):386–94. doi:10.1002/erv.2234. [PubMed: 23681932]
9. Attia E. Anorexia nervosa: current status and future directions. *Annu Rev Med.* 2010; 61:425–35. doi:10.1146/annurev.med.050208.200745. [PubMed: 19719398]
10. Powers PS, Bruty H. Pharmacotherapy for eating disorders and obesity. *Child Adolesc Psychiatr Clin N Am.* 2009; 18(1):175–87. doi:S1056-4993(08)00059-X [pii] 10.1016/j.chc.2008.07.009. [PubMed: 19014865]

11. Monge MC, Forman SF, McKenzie NM, Rosen DS, Mammel KA, Callahan ST, et al. Use of Psychopharmacologic Medications in Adolescents With Restrictive Eating Disorders: Analysis of Data From the National Eating Disorder Quality Improvement Collaborative. *J Adolesc Health*. 2015; 57(1):66–72. doi:10.1016/j.jadohealth.2015.03.021. [PubMed: 26095410]
12. Moher D, Liberati A, Tetzlaff J, Altman DG, Group P. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *Int J Surg*. 2010; 8(5):336–41. doi:10.1016/j.ijsu.2010.02.007. [PubMed: 20171303]
13. Lavenstein AF, Dacanay EP, Lasagna L, Vanmetre TE. Effect of cyproheptadine on asthmatic children. Study of appetite, weight gain, and linear growth. *JAMA*. 1962; 180:912–6. [PubMed: 14462919]
14. Zubiarte TN. Tratamiento de la anorexia nervosa con una asociacion cyproheptadine-vitaminas. *Revista Medica de la Caja Nacional de Segura Social*. 1970; 19:147–53.
15. Goldberg SC, Halmi KA, Eckert ED, Casper RC, Davis JM. Cyproheptadine in anorexia nervosa. *Br J Psychiatry*. 1979; 134:67–70. [PubMed: 367480]
16. Goldberg SC, Eckert ED, Halmi KA, Casper RC, Davis JM, Roper M. Effects of cyproheptadine on symptoms and attitudes in anorexia nervosa. *Arch Gen Psychiatry*. 1980; 37(9):1083. [PubMed: 7416909]
17. Halmi KA, Eckert E, LaDu TJ, Cohen J. Anorexia nervosa. Treatment efficacy of cyproheptadine and amitriptyline. *Arch Gen Psychiatry*. 1986; 43(2):177–81. [PubMed: 3511877]
18. Biederman J, Herzog DB, Rivinus TM, Harper GP, Ferber RA, Rosenbaum JF, et al. Amitriptyline in the treatment of anorexia nervosa: a double-blind, placebo-controlled study. *J Clin Psychopharmacol*. 1985; 5(1):10–6. [PubMed: 3973067]
19. Lacey JH, Crisp AH. Hunger, food intake and weight: the impact of clomipramine on a refeeding anorexia nervosa population. *Postgrad Med J*. 1980; 56(Suppl 1):79–85. [PubMed: 6994086]
20. Crisp AH, Lacey JH, Crutchfield M. Clomipramine and 'drive' in people with anorexia nervosa: an in-patient study. *Br J Psychiatry*. 1987; 150:355–8. [PubMed: 3664105]
21. Ruggiero G, Laini V, Mauri M, Ferrari V, Clemente A, Lugo F, et al. A single blind comparison of amisulpride, fluoxetine and clomipramine in the treatment of restricting anorectics. *Prog Neuropsychopharmacol Biop Psychiatry*. 2001; 25(5):1049–59.
22. Strobel M, Warnke A, Roth M, Schulze U. Paroxetine versus clomipramine in female adolescents suffering from anorexia nervosa and depressive episode--a retrospective study on tolerability, reasons for discontinuing the antidepressive treatment and different outcome measurements. *Z Kinder Jugendpsychiatr*. 2004; 32(4):279–89.
23. Kennedy SH, Piran N, Garfinkel PE. Monoamine oxidase inhibitor therapy for anorexia nervosa and bulimia: a preliminary trial of isocarboxazid. *J Clin Psychopharmacol*. 1985; 5(5):279–85. [PubMed: 3862680]
24. Barry VC, Klawans HL. On the role of dopamine in the pathophysiology of anorexia nervosa. *J Neural Transm*. 1976; 38(2):107–22. [PubMed: 775021]
25. Vandereycken W, Pierloot R. Pimozide combined with behavior therapy in the short-term treatment of anorexia nervosa. A double-blind placebo-controlled cross-over study. *Acta Psychiatr Scand*. 1982; 66(6):445–50. [PubMed: 6758492]
26. Weizman A, Tyano S, Wijsenbeek H, Ben David M. Behavior therapy, pimozide treatment and prolactin secretion in anorexia nervosa. *Psychother Psychosom*. 1985; 43(3):136–40. [PubMed: 4001299]
27. Cassano G, Miniati M, Pini S, Rotondo A, Banti S, Borri C, et al. Six-month open trial of haloperidol as an adjunctive treatment for anorexia nervosa: a preliminary report. *Int J Eat Disord*. 2003; 33:172–7. [PubMed: 12616583]
28. Mauri M, Miniati M, Mariani MG, Ciberti A, Dell'Osso L. Haloperidol for severe anorexia nervosa restricting type with delusional body image disturbance: a nine-case chart review. *Eat Weight Disord*. 2013; 18(3):329–32. doi:10.1007/s40519-013-0052-9. [PubMed: 23907761]
29. Gross HA, Ebert MH, Faden VB, Goldberg SC, Nee LE, Kaye WH. A double-blind controlled trial of lithium carbonate primary anorexia nervosa. *J Clin Psychopharmacol*. 1981; 1(6):376–81. [PubMed: 6801096]

30. Bakan R. The role of zinc in anorexia nervosa: etiology and treatment. *Med Hypotheses*. 1979; 5(7):731–6. [PubMed: 514114]
31. Bryce-Smith D, Simpson RI. Case of anorexia nervosa responding to zinc sulphate. *Lancet*. 1984; 2(8398):350. [PubMed: 6146890]
32. Katz RL, Keen CL, Litt IF, Hurley LS, Kellams-Harrison KM, Glader LJ. Zinc deficiency in anorexia nervosa. *J Adolesc Health Care*. 1987; 8(5):400–6. [PubMed: 3312133]
33. Safai-Kutti S. Oral zinc supplementation in anorexia nervosa. *Acta Psychiatr Scand Suppl*. 1990; 361:14–7. [PubMed: 2291418]
34. Birmingham CL, Goldner EM, Bakan R. Controlled trial of zinc supplementation in anorexia nervosa. *Int J Eat Disord*. 1994; 15(3):251–5. [PubMed: 8199605]
35. Lask B, Fosson A, Rolfe U, Thomas S. Zinc deficiency and childhood-onset anorexia nervosa. *J Clin Psychiatry*. 1993; 54(2):63–6. [PubMed: 8444822]
36. Suzuki H, Asakawa A, Li JB, Tsai M, Amitani H, Ohinata K, et al. Zinc as an appetite stimulator - the possible role of zinc in the progression of diseases such as cachexia and sarcopenia. *Recent Pat Food Nutr Agric*. 2011; 3(3):226–31. [PubMed: 21846317]
37. Levenson CW. Zinc regulation of food intake: new insights on the role of neuropeptide Y. *Nutr Rev*. 2003; 61(7):247–9. [PubMed: 12918877]
38. Moore R, Mills IH, Forster A. Naloxone in the treatment of anorexia nervosa: effect on weight gain and lipolysis. *J R Soc Med*. 1981; 74(2):129–31. [PubMed: 7205847]
39. Marrazzi MA, Bacon JP, Kinzie J, Luby ED. Naltrexone use in the treatment of anorexia nervosa and bulimia nervosa. *Int Clin Psychopharmacol*. 1995; 10(3):163–72. [PubMed: 8675969]
40. Gross H, Ebert MH, Faden VB, Goldberg SC, Kaye WH, Caine ED, et al. A double-blind trial of delta 9-tetrahydrocannabinol in primary anorexia nervosa. *J Clin Psychopharmacol*. 1983; 3(3):165–71. [PubMed: 6308069]
41. Andries A, Frystyk J, Flyvbjerg A, Stoving RK. Dronabinol in severe, enduring anorexia nervosa: a randomized controlled trial. *Int J Eat Disord*. 2014; 47(1):18–23. doi:10.1002/eat.22173. [PubMed: 24105610]
42. Steinglass JE, Kaplan SC, Liu Y, Wang Y, Walsh BT. The (lack of) effect of alprazolam on eating behavior in anorexia nervosa: a preliminary report. *Int J Eat Disord*. 2014; 47(8):901–4. doi:10.1002/eat.22343. [PubMed: 25139178]
43. Rieg TS, Aravich PF. Systemic clonidine increases feeding and wheel running but does not affect rate of weight loss in rats subjected to activity-based anorexia. *Pharmacol Biochem Behav*. 1994; 47(2):215–8. [PubMed: 8146210]
44. Casper RC, Schlemmer RFJ, Javadi JI. A placebo-controlled crossover study of oral clonidine in acute anorexia nervosa. *Psychiatry Res*. 1987; 20(3):249–60. [PubMed: 3295935]
45. Gwirtsman HE, Guze BH, Yager J, Gainsley B. Fluoxetine treatment of anorexia nervosa: an open clinical trial. *J Clin Psychiatry*. 1990; 51(9):378–82. [PubMed: 2102671]
46. Kaye WH, Weltzin TE, Hsu LK, Bulik CM. An open trial of fluoxetine in patients with anorexia nervosa. *J Clin Psychiatry*. 1991; 52(11):464–71. [PubMed: 1744064]
47. Oliveros SC, Iruela LM, Caballero L, Baca E. Fluoxetine-induced anorexia in a bulimic patient. *Am J Psychiatry*. 1992; 149(8):1113–4. [PubMed: 1636812]
48. Yu J, Stewart Agras W, Halmi KA, Crow S, Mitchell J, Bryson SW. A 1-year follow-up of a multi-center treatment trial of adults with anorexia nervosa. *Eat Weight Disord*. 2011; 16(3):e177–81. [PubMed: 22290033]
49. Attia E, Haiman C, Walsh BT, Flater SR. Does fluoxetine augment the inpatient treatment of anorexia nervosa? *Am J Psychiatry*. 1998; 155(4):548–51. [PubMed: 9546003]
50. Strober M, Pataki C, Freeman R, DeAntonio M. No effect of adjunctive fluoxetine on eating behavior or weight phobia during the inpatient treatment of anorexia nervosa: an historical case-control study. *J Child Adolesc Psychopharmacol*. 1999; 9(3):195–201. [PubMed: 10521012]
51. Kaye WH, Nagata T, Weltzin TE, Hsu LK, Sokol MS, McConaha C, et al. Double-blind placebo-controlled administration of fluoxetine in restricting- and restricting-purging-type anorexia nervosa. *Biol Psychiatry*. 2001; 49(7):644–52. [PubMed: 11297722]

52. Ruggiero GM, Mauri MC, Omboni AC, Volonteri LS, Dipasquale S, Malvini L, et al. Nutritional management of anorexic patients with and without fluoxetine: 1-year follow-up. *Prog Neuropsychopharmacol Biol Psychiatry*. 2003; 27(3):425–30. doi:10.1016/S0278-5846(03)00029-0. [PubMed: 12691777]
53. Strober M, Freeman R, DeAntonio M, Lampert C, Diamond J. Does adjunctive fluoxetine influence the post-hospital course of restrictor-type anorexia nervosa? A 24-month prospective, longitudinal followup and comparison with historical controls. *Psychopharmacol Bull*. 1997; 33(3):425–31. [PubMed: 9550888]
54. Walsh BT, Kaplan AS, Attia E, Olmsted M, Parides M, Carter JC, et al. Fluoxetine after weight restoration in anorexia nervosa: a randomized controlled trial. *JAMA*. 2006; 295(22):2605–12. doi: 10.1001/jama.295.22.2605. [PubMed: 16772623]
55. Ricca V, Mannucci E, Paionni A, Di Bernardo M, Cellini M, Cabras PL, et al. Venlafaxine versus fluoxetine in the treatment of atypical anorectic outpatients: a preliminary study. *Eat Weight Disord*. 1999; 4(1):10–4. [PubMed: 10728173]
56. Barbarich NC, McConaha CW, Halmi KA, Gendall K, Sunday SR, Gaskill J, et al. Use of nutritional supplements to increase the efficacy of fluoxetine in the treatment of anorexia nervosa. *Int J Eat Disord*. 2004; 35(1):10–5. doi:10.1002/eat.10235. [PubMed: 14705152]
57. Calandra C, Gulino V, Inserra L, Giuffrida A. The use of citalopram in an integrated approach to the treatment of eating disorders: an open study. *Eat Weight Disord*. 1999; 4(4):207–10. [PubMed: 10728184]
58. Fassino S, Leombruni P, Abbate Daga G, Brustolin A, Migliaretti G, Cavallo F, et al. Efficacy of citalopram in anorexia nervosa: a pilot study. *Euro Neuropsychopharm*. 2002; 12:453–9.
59. Pallanti S, Quercioli L, Ramacciotti A. Citalopram in anorexia nervosa. *Eat Weight Disord*. 1997; 2(4):216–21. [PubMed: 14655831]
60. Santonastaso P, Friederici S, Favaro A. Sertraline in the treatment of restricting anorexia nervosa: an open controlled trial. *J Child Adolesc Psychopharmacol*. 2001; 11(2):143–50. doi: 10.1089/104454601750284045. [PubMed: 11436953]
61. Holtkamp K, Konrad K, Kaiser N, Ploenes Y, Heussen N, Grzella I, et al. A retrospective study of SSRI treatment in adolescent anorexia nervosa: insufficient evidence for efficacy. *J Psych Res*. 2004; 39:303–10.
62. Ferguson CP, La Via MC, Crossan PJ, Kaye WH. Are serotonin selective reuptake inhibitors effective in underweight anorexia nervosa? *Int J Eat Disord*. 1999; 25(1):11–7. [PubMed: 9924648]
63. Hrdlicka M, Beranova I, Zamecnikova R, Urbanek T. Mirtazapine in the treatment of adolescent anorexia nervosa. Case-control study. *Eur Child Adolesc Psychiatry*. 2008; 17(3):187–9. doi: 10.1007/s00787-007-0670-8. [PubMed: 18357426]
64. Vandereycken W. Neuroleptics in the short-term treatment of anorexia nervosa. A double-blind placebo-controlled study with sulpiride. *Br J Psychiatry*. 1984; 144:288–92. [PubMed: 6367876]
65. Powers PS, Santana CA, Bannon YS. Olanzapine in the treatment of anorexia nervosa: an open label trial. *Int J Eat Disord*. 2002; 32:146–54. [PubMed: 12210656]
66. Barbarich N, McConaha C, Gaskill J, LaVia M, Frank GK, Brooks S, et al. An open trial of olanzapine in anorexia nervosa. *J Clin Psychiatry*. 2004; 65:1480–2. [PubMed: 15554759]
67. Malina A, Gaskill J, McConaha C, Frank GK, LaVia M, Scholar L, et al. Olanzapine treatment of anorexia nervosa: a retrospective study. *Int J Eat Disord*. 2003; 33(2):234–7. [PubMed: 12616591]
68. Mondraty N, Birmingham CL, Touyz S, Sundakov V, Chapman L, Beumont P. Randomized controlled trial of olanzapine in the treatment of cognitions in anorexia nervosa. *Australas Psychiatry*. 2005; 13(1):72–5. doi:10.1111/j.1440-1665.2004.02154.x. [PubMed: 15777417]
69. Brambilla F, Garcia CS, Fassino S, Daga GA, Favaro A, Santonastaso P, et al. Olanzapine therapy in anorexia nervosa: psychobiological effects. *Int Clin Psychopharmacol*. 2007; 22(4):197–204. doi:10.1097/YIC.0b013e328080ca31. [PubMed: 17519642]
70. Bissada H, Tasca GA, Barber AM, Bradwejn J. Olanzapine in the treatment of low body weight and obsessive thinking in women with anorexia nervosa: a randomized, double-blind, placebo-

controlled trial. *The American journal of psychiatry*. 2008; 165(10):1281–8. doi:10.1176/appi.ajp.2008.07121900. [PubMed: 18558642]

71. Leggero C, Masi G, Brunori E, Calderoni S, Carissimo R, Maestro S, et al. Low-dose olanzapine monotherapy in girls with anorexia nervosa, restricting subtype: focus on hyperactivity. *J Child Adolesc Psychopharmacol*. 2010; 20(2):127–33. doi:10.1089/cap.2009.0072. [PubMed: 20415608]
72. Attia E, Kaplan AS, Walsh BT, Gershkovich M, Yilmaz Z, Musante D, et al. Olanzapine versus placebo for out-patients with anorexia nervosa. *Psychol Med*. 2011; 41(10):2177–82. doi:10.1017/S0033291711000390. [PubMed: 21426603]
73. Kafantaris V, Leigh E, Hertz S, Berest A, Schebendach J, Sterling WM, et al. A placebo-controlled pilot study of adjunctive olanzapine for adolescents with anorexia nervosa. *J Child Adolesc Psychopharmacol*. 2011; 21(3):207–12. doi:10.1089/cap.2010.0139. [PubMed: 21663423]
74. Norris ML, Spettigue W, Buchholz A, Henderson KA, Gomez R, Maras D, et al. Olanzapine use for the adjunctive treatment of adolescents with anorexia nervosa. *J Child Adolesc Psychopharmacol*. 2011; 21(3):213–20. doi:10.1089/cap.2010.0131. [PubMed: 21510781]
75. Brambilla F, Monteleone P, Maj M. Olanzapine-induced weight gain in anorexia nervosa: involvement of leptin and ghrelin secretion? *Psychoneuroendocrinology*. 2007; 32(4):402–6. doi:10.1016/j.psyneuen.2007.02.005. [PubMed: 17395395]
76. Yasuhara D, Nakahara T, Harada T, Inui A. Olanzapine-induced hyperglycemia in anorexia nervosa. *Am J Psychiatry*. 2007; 164(3):528–9. doi:10.1176/ajp.2007.164.3.528a. [PubMed: 17329484]
77. Bosanac P, Kurlender S, Norman T, Hallam K, Wesnes K, Manktelow T, et al. An open-label study of quetiapine in anorexia nervosa. *Human psychopharmacology*. 2007; 22(4):223–30. doi:10.1002/hup.845. [PubMed: 17487935]
78. Powers PS, Bannon Y, Eubanks R, McCormick T. Quetiapine in anorexia nervosa patients: an open label outpatient pilot study. *Int J Eat Disord*. 2007; 40(1):21–6. doi:10.1002/eat.20325. [PubMed: 16927383]
79. Powers PS, Klabunde M, Kaye W. Double-blind placebo-controlled trial of quetiapine in anorexia nervosa. *Eur Eat Disord Rev*. 2012; 20(4):331–4. doi:10.1002/erv.2169. [PubMed: 22535517]
80. Court A, Mulder C, Kerr M, Yuen HP, Boasman M, Goldstone S, et al. Investigating the effectiveness, safety and tolerability of quetiapine in the treatment of anorexia nervosa in young people: a pilot study. *J Psychiatr Res*. 2010; 44(15):1027–34. doi:10.1016/j.jpsychires.2010.03.011. [PubMed: 20447652]
81. Kracke EJ, Tosh AK. Treatment of anorexia nervosa with long-term risperidone in an outpatient setting: case study. *Springerplus*. 2014; 3:706. doi:10.1186/2193-1801-3-706. [PubMed: 25525567]
82. Newman-Toker J. Risperidone in anorexia nervosa. *J Am Acad Child Adolesc Psychiatry*. 2000; 39(8):941–2. doi:10.1097/00004583-200008000-00002. [PubMed: 10939220]
83. Hagman J, Gralla J, Sigel E, Ellert S, Dodge M, Gardner R, et al. A double-blind, placebo-controlled study of risperidone for the treatment of adolescents and young adults with anorexia nervosa: a pilot study. *J Am Acad Child Adolesc Psychiatry*. 2011; 50(9):915–24. doi:10.1016/j.jaac.2011.06.009. [PubMed: 21871373]
84. Trunko ME, Schwartz TA, Duvvuri V, Kaye WH. Aripiprazole in anorexia nervosa and low-weight bulimia nervosa: case reports. *The International journal of eating disorders*. 2011; 44(3):269–75. doi:10.1002/eat.20807. [PubMed: 20186719]
85. Frank GK. Aripiprazole, a partial dopamine agonist to improve adolescent anorexia nervosa-A case series. *Int J Eat Disord*. 2015 doi:10.1002/eat.22485.
86. Frank GK. Could dopamine agonists aid in drug development for anorexia nervosa? *Front Nutr*. 2014; 1:19. doi:10.3389/fnut.2014.00019. [PubMed: 25988121]
87. Otto MW, Kredlow MA, Smits JA, Hofmann SG, Tolin DF, de Kleine RA, et al. Enhancement of Psychosocial Treatment With d-Cycloserine: Models, Moderators, and Future Directions. *Biol Psychiatry*. 2015 doi:10.1016/j.biopsych.2015.09.007.
88. Steinglass J, Sysko R, Schebendach J, Broft A, Strober M, Walsh BT. The application of exposure therapy and D-cycloserine to the treatment of anorexia nervosa: a preliminary trial. *J Psychiatr Pract*. 2007; 13(4):238–45. doi:10.1097/01.pra.0000281484.89075.a8. [PubMed: 17667736]

89. Levinson CA, Rodebaugh TL, Fewell L, Kass AE, Riley EN, Stark L, et al. D-Cycloserine facilitation of exposure therapy improves weight regain in patients with anorexia nervosa: a pilot randomized controlled trial. *J Clin Psychiatry*. 2015; 76(6):e787–93. doi:10.4088/JCP.14m09299. [PubMed: 26132687]
90. Lechin F, van der Dijs B, Pardey-Maldonado B, Baez S, Lechin ME. Anorexia nervosa versus hyperinsulinism: therapeutic effects of neuropharmacological manipulation. *Ther Clin Risk Manag*. 2011; 7:53–8. doi:10.2147/TCRM.S16958. [PubMed: 21445279]
91. Bloch M, Ish-Shalom S, Greenman Y, Klein E, Latzer Y. Dehydroepiandrosterone treatment effects on weight, bone density, bone metabolism and mood in women suffering from anorexia nervosa-a pilot study. *Psychiatry Res*. 2012; 200(2-3):544–9. doi:10.1016/j.psychres.2012.07.012. [PubMed: 22858403]
92. Hotta M, Ohwada R, Akamizu T, Shibasaki T, Takano K, Kangawa K. Ghrelin increases hunger and food intake in patients with restricting-type anorexia nervosa: a pilot study. *Endocr J*. 2009; 56(9):1119–28. [PubMed: 19755753]
93. Okita K, Shiina A, Nakazato M, Iyo M. Tandospirone, a 5-HT_{1A} partial agonist is effective in treating anorexia nervosa: a case series. *Ann Gen Psychiatry*. 2013; 12(1):7. doi:10.1186/1744-859X-12-7. [PubMed: 23497393]
94. Misra M, Katzman DK, Estella NM, Eddy KT, Weigel T, Goldstein MA, et al. Impact of physiologic estrogen replacement on anxiety symptoms, body shape perception, and eating attitudes in adolescent girls with anorexia nervosa: data from a randomized controlled trial. *J Clin Psychiatry*. 2013; 74(8):e765–71. doi:10.4088/JCP.13m08365. [PubMed: 24021517]
95. Klibanski A, Biller BM, Schoenfeld DA, Herzog DB, Saxe VC. The effects of estrogen administration on trabecular bone loss in young women with anorexia nervosa. *J Clin Endocrinol Metab*. 1995; 80(3):898–904. [PubMed: 7883849]
96. Miller KK, Grieco KA, Klibanski A. Testosterone administration in women with anorexia nervosa. *J Clin Endocrinol Metab*. 2005; 90(3):1428–33. doi:10.1210/jc.2004-1181. [PubMed: 15613421]
97. Hill K, Bucuvalas J, McClain C, Kryscio R, Martini RT, Alfaro MP, et al. Pilot study of growth hormone administration during the refeeding of malnourished anorexia nervosa patients. *J Child Adolesc Psychopharmacol*. 2000; 10(1):3–8. doi:10.1089/cap.2000.10.3. [PubMed: 10755576]
98. Smitka K, Papezova H, Vondra K, Hill M, Hainer V, Nedvickova J. The role of “mixed” orexigenic and anorexigenic signals and autoantibodies reacting with appetite-regulating neuropeptides and peptides of the adipose tissue-gut-brain axis: relevance to food intake and nutritional status in patients with anorexia nervosa and bulimia nervosa. *Int J Endocrinol*. 2013; 2013:483145. doi:10.1155/2013/483145. [PubMed: 24106499]
99. Van den Eynde F, Suda M, Broadbent H, Guillaume S, Van den Eynde M, Steiger H, et al. Structural magnetic resonance imaging in eating disorders: a systematic review of voxel-based morphometry studies. *European eating disorders review : the journal of the Eating Disorders Association*. 2012; 20(2):94–105. doi:10.1002/erv.1163. [PubMed: 22052722]
100. King JA, Geisler D, Ritschel F, Boehm I, Seidel M, Roschinski B, et al. Global cortical thinning in acute anorexia nervosa normalizes following long-term weight restoration. *Biol Psychiatry*. 2015; 77(7):624–32. doi:10.1016/j.biopsych.2014.09.005. [PubMed: 25433902]
101. Frank GK, Shott ME, Hagman JO, Mittal VA. Alterations in brain structures related to taste reward circuitry in ill and recovered anorexia nervosa and in bulimia nervosa. *Am J Psychiatry*. 2013; 170(10):1152–60. doi:10.1176/appi.ajp.2013.12101294. [PubMed: 23680873]
102. Frank GK, Shott ME, Hagman JO, Yang TT. Localized brain volume and white matter integrity alterations in adolescent anorexia nervosa. *J Am Acad Child Adolesc Psychiatry*. 2013; 52(10):1066–75. e5. doi:10.1016/j.jaac.2013.07.007. [PubMed: 24074473]
103. Rolls ET. Information processing in the taste system of primates. *J Exp Biol*. 1989; 146:141–64. [PubMed: 2689559]
104. Frank GK, Bailer UF, Henry SE, Drevets W, Meltzer CC, Price JC, et al. Increased dopamine D₂/D₃ receptor binding after recovery from anorexia nervosa measured by positron emission tomography and [¹¹C]raclopride. *Biol Psychiatry*. 2005; 58(11):908–12. [PubMed: 15992780]

105. Gerard N, Pieters G, Goffin K, Bormans G, Van Laere K. Brain type 1 cannabinoid receptor availability in patients with anorexia and bulimia nervosa. *Biol Psychiatry*. 2011; 70(8):777–84. doi:10.1016/j.biopsych.2011.05.010. [PubMed: 21718968]
106. Berridge KC. 'Liking' and 'wanting' food rewards: brain substrates and roles in eating disorders. *Physiol Behav*. 2009; 97(5):537–50. doi:S0031-9384(09)00120-6 [pii] 10.1016/j.physbeh.2009.02.044. [PubMed: 19336238]
107. Kelley AE, Berridge KC. The neuroscience of natural rewards: relevance to addictive drugs. *J Neurosci*. 2002; 22(9):3306–11. doi:20026361. [PubMed: 11978804]
108. Frank GK. Reward and neurocomputational processes. *Curr Top Behav Neurosci*. 2011; 6:95–110. doi:10.1007/7854_2010_81. [PubMed: 21243472]
109. Frank GK. Advances from neuroimaging studies in eating disorders. *CNS Spectr*. 2015;1–10. doi:10.1017/S1092852915000012.
110. Schultz W. Predictive reward signal of dopamine neurons. *J Neurophysiol*. 1998; 80(1):1–27. [PubMed: 9658025]
111. Yilmaz Z, Kaplan AS, Tiwari AK, Levitan RD, Piran S, Bergen AW, et al. The role of leptin, melanocortin, and neurotrophin system genes on body weight in anorexia nervosa and bulimia nervosa. *J Psychiatr Res*. 2014; 55:77–86. doi:10.1016/j.jpsychires.2014.04.005. [PubMed: 24831852]
112. Boraska V, Franklin CS, Floyd JA, Thornton LM, Huckins LM, Southam L, et al. A genome-wide association study of anorexia nervosa. *Mol Psychiatry*. 2014; 19(10):1085–94. doi:10.1038/mp.2013.187. [PubMed: 24514567]
113. Wang K, Zhang H, Bloss CS, Duvvuri V, Kaye W, Schork NJ, et al. A genome-wide association study on common SNPs and rare CNVs in anorexia nervosa. *Mol Psychiatry*. 2011; 16(9):949–59. doi:10.1038/mp.2010.107. [PubMed: 21079607]
114. Brandys MK, de Kovel CG, Kas MJ, van Elburg AA, Adan RA. Overview of genetic research in anorexia nervosa: The past, the present and the future. *Int J Eat Disord*. 2015; 48(7):814–25. doi:10.1002/eat.22400. [PubMed: 26171770]
115. Bulik-Sullivan BK, Loh PR, Finucane HK, Ripke S, Yang J, Schizophrenia Working Group of the Psychiatric Genomics C, et al. LD Score regression distinguishes confounding from polygenicity in genome-wide association studies. *Nat Genet*. 2015; 47(3):291–5. doi:10.1038/ng.3211. [PubMed: 25642630]
116. Gutierrez E. A rat in the labyrinth of anorexia nervosa: contributions of the activity-based anorexia rodent model to the understanding of anorexia nervosa. *Int J Eat Disord*. 2013; 46(4):289–301. doi:10.1002/eat.22095. [PubMed: 23354987]
117. Hillebrand JJ, van Elburg AA, Kas MJ, van Engeland H, Adan RA. Olanzapine reduces physical activity in rats exposed to activity-based anorexia: possible implications for treatment of anorexia nervosa? *Biol Psychiatry*. 2005; 58(8):651–7. doi:10.1016/j.biopsych.2005.04.008. [PubMed: 16018979]
118. Klenotich SJ, Seiglie MP, McMurray MS, Roitman JD, Le Grange D, Dugad P, et al. Olanzapine, but not fluoxetine, treatment increases survival in activity-based anorexia in mice. *Neuropsychopharmacology*. 2012; 37(7):1620–31. doi:10.1038/npp.2012.7. [PubMed: 22395732]
119. Verhagen LA, Luijendijk MC, Hillebrand JJ, Adan RA. Dopamine antagonism inhibits anorectic behavior in an animal model for anorexia nervosa. *Eur Neuropsychopharmacol*. 2009; 19(3):153–60. doi:10.1016/j.euroneuro.2008.09.005. [PubMed: 18977121]
120. Atchley DP, Eckel LA. Fenfluramine treatment in female rats accelerates the weight loss associated with activity-based anorexia. *Pharmacol Biochem Behav*. 2005; 80(2):273–9. doi:10.1016/j.pbb.2004.11.006. [PubMed: 15680180]
121. Hillebrand JJ, Heinsbroek AC, Kas MJ, Adan RA. The appetite suppressant d-fenfluramine reduces water intake, but not food intake, in activity-based anorexia. *J Mol Endocrinol*. 2006; 36(1):153–62. doi:10.1677/jme.1.01887. [PubMed: 16461935]
122. Atchley DP, Eckel LA. Treatment with 8-OH-DPAT attenuates the weight loss associated with activity-based anorexia in female rats. *Pharmacol Biochem Behav*. 2006; 83(4):547–53. doi:10.1016/j.pbb.2006.03.016. [PubMed: 16643997]

123. Verty AN, Evetts MJ, Crouch GJ, McGregor IS, Stefanidis A, Oldfield BJ. The cannabinoid receptor agonist THC attenuates weight loss in a rodent model of activity-based anorexia. *Neuropsychopharmacology*. 2011; 36(7):1349–58. doi:10.1038/npp.2011.19. [PubMed: 21412227]
124. Lewis DY, Brett RR. Activity-based anorexia in C57/BL6 mice: effects of the phytocannabinoid, Delta9-tetrahydrocannabinol (THC) and the anandamide analogue, OMDM-2. *Eur Neuropsychopharmacol*. 2010; 20(9):622–31. doi:10.1016/j.euroneuro.2010.04.002. [PubMed: 20471226]
125. Verhagen LA, Luijendijk MC, Adan RA. Leptin reduces hyperactivity in an animal model for anorexia nervosa via the ventral tegmental area. *Eur Neuropsychopharmacol*. 2011; 21(3):274–81. doi:10.1016/j.euroneuro.2010.11.006. [PubMed: 21190812]
126. Exner C, Hebebrand J, Remschmidt H, Wewetzer C, Ziegler A, Herpertz S, et al. Leptin suppresses semi-starvation induced hyperactivity in rats: implications for anorexia nervosa. *Mol Psychiatry*. 2000; 5(5):476–81. [PubMed: 11032380]
127. Brown AJ, Avena NM, Hoebel BG. A high-fat diet prevents and reverses the development of activity-based anorexia in rats. *Int J Eat Disord*. 2008; 41(5):383–9. doi:10.1002/eat.20510. [PubMed: 18306342]
128. Gile E, Hagman J, Pan Z, MacLean P, Higgins J. Weight restoration on a high carbohydrate refeeding diet promotes rapid weight regain and hepatic lipid accumulation in female anorexic rats. *Nutr Metab*. 2016; 13(18):11. doi:DOI 10.1186/s12986-016-0077-y.
129. Taksande BG, Chopde CT, Umekar MJ, Kotagale NR. Agmatine attenuates hyperactivity and weight loss associated with activity-based anorexia in female rats. *Pharmacol Biochem Behav*. 2015; 132:136–41. doi:10.1016/j.pbb.2015.03.005. [PubMed: 25782747]
130. Wable GS, Chen YW, Rashid S, Aoki C. Exogenous progesterone exacerbates running response of adolescent female mice to repeated food restriction stress by changing alpha4-GABAA receptor activity of hippocampal pyramidal cells. *Neuroscience*. 2015; 310:322–41. doi:10.1016/j.neuroscience.2015.09.006. [PubMed: 26383252]
131. Baker JH, Girdler SS, Bulik CM. The role of reproductive hormones in the development and maintenance of eating disorders. *Expert Rev Obstet Gynecol*. 2012; 7(6):573–83. doi:10.1586/eog.12.54. [PubMed: 23585773]
132. Frank GK, Reynolds JR, Shott ME, Jappe L, Yang TT, Tregellas JR, et al. Anorexia nervosa and obesity are associated with opposite brain reward response. *Neuropsychopharmacology*. 2012; 37(9):2031–46. doi:10.1038/npp.2012.51. [PubMed: 22549118]
133. Klenotich SJ, Ho EV, McMurray MS, Server CH, Dulawa SC. Dopamine D2/3 receptor antagonism reduces activity-based anorexia. *Transl Psychiatry*. 2015; 5:e613. doi:10.1038/tp.2015.109. [PubMed: 26241351]
134. Mequinion M, Chauveau C, Viltart O. The use of animal models to decipher physiological and neurobiological alterations of anorexia nervosa patients. *Front Endocrinol (Lausanne)*. 2015; 6:68. doi:10.3389/fendo.2015.00068. [PubMed: 26042085]
135. Diane A, Vine DF, Russell JC, Heth CD, Pierce WD, Proctor SD. Interrelationship of CB1R and OBR pathways in regulation of metabolic, neuroendocrine, and behavioral responses to food restriction and voluntary wheel running. *J Appl Physiol* (1985). 2014; 117(2):97–104. doi: 10.1152/japplphysiol.01303.2013. [PubMed: 24903921]
136. McOmish CE, Burrows EL, Hannan AJ. Identifying novel interventional strategies for psychiatric disorders: integrating genomics, 'enviromics' and gene-environment interactions in valid preclinical models. *Br J Pharmacol*. 2014; 171(20):4719–28. doi:10.1111/bph.12783. [PubMed: 24846457]
137. Guarda AS, Schreyer CC, Boersma GJ, Tamashiro KL, Moran TH. Anorexia nervosa as a motivated behavior: Relevance of anxiety, stress, fear and learning. *Physiol Behav*. 2015; 152(Pt B):466–72. doi:10.1016/j.physbeh.2015.04.007. [PubMed: 25846837]
138. Yardley MM, Ray LA. Medications development for the treatment of alcohol use disorder: insights into the predictive value of animal and human laboratory models. *Addict Biol*. 2016 doi: 10.1111/adb.12349.

139. Poldrack RA, Farah MJ. Progress and challenges in probing the human brain. *Nature*. 2015; 526(7573):371–9. doi:10.1038/nature15692. [PubMed: 26469048]
140. Avena NM, Rada P, Hoebel BG. Underweight rats have enhanced dopamine release and blunted acetylcholine response in the nucleus accumbens while bingeing on sucrose. *Neuroscience*. 2008; 156(4):865–71. doi:S0306-4522(08)01179-2 [pii] 10.1016/j.neuroscience.2008.08.017. [PubMed: 18790017]
141. Carr KD. Chronic food restriction: enhancing effects on drug reward and striatal cell signaling. *Physiol Behav*. 2007; 91(5):459–72. doi:S0031-9384(06)00425-2 [pii] 10.1016/j.physbeh.2006.09.021. [PubMed: 17081571]
142. Johnson PM, Kenny PJ. Dopamine D2 receptors in addiction-like reward dysfunction and compulsive eating in obese rats. *Nat Neurosci*. 2010; 13(5):635–41. doi:nn.2519 [pii] 10.1038/nn.2519. [PubMed: 20348917]
143. Ban TA. The role of serendipity in drug discovery. *Dialogues Clin Neurosci*. 2006; 8(3):335–44. [PubMed: 17117615]
144. Stahl SM. Finding what you are not looking for: strategies for developing novel treatments in psychiatry. *NeuroRx*. 2006; 3(1):3–9. doi:10.1016/j.nurx.2005.12.002. [PubMed: 16490409]
145. Rey CD, Lipps J, Shansky RM. Dopamine D1 receptor activation rescues extinction impairments in low-estrogen female rats and induces cortical layer-specific activation changes in prefrontal-amygdala circuits. *Neuropsychopharmacology*. 2014; 39(5):1282–9. doi:10.1038/npp.2013.338. [PubMed: 24343528]
146. de Souza Caetano KA, de Oliveira AR, Brandao ML. Dopamine D2 receptors modulate the expression of contextual conditioned fear: role of the ventral tegmental area and the basolateral amygdala. *Behav Pharmacol*. 2013; 24(4):264–74. doi:10.1097/FBP.0b013e32836356c4. [PubMed: 23751519]
147. de Oliveira AR, Reimer AE, Brandao ML. Dopamine D2 receptor mechanisms in the expression of conditioned fear. *Pharmacol Biochem Behav*. 2006; 84(1):102–11. [PubMed: 16780936]
148. Nader K, LeDoux J. The dopaminergic modulation of fear: quinpirole impairs the recall of emotional memories in rats. *Behav Neurosci*. 1999; 113(1):152–65. [PubMed: 10197915]
149. Ponnusamy R, Nissim HA, Barad M. Systemic blockade of D2-like dopamine receptors facilitates extinction of conditioned fear in mice. *Learn Mem*. 2005; 12(4):399–406. [PubMed: 16077018]
150. Cooper, JR.; Bloom, FE.; Roth, RH. The biochemical basis of neuropharmacology. 8th ed.. Oxford University Press; Oxford UK: 2003.
151. Braun AR, Laruelle M, Mouradian MM. Interactions between D1 and D2 dopamine receptor family agonists and antagonists: the effects of chronic exposure on behavior and receptor binding in rats and their clinical implications. *J Neural Transm*. 1997; 104(4-5):341–62. [PubMed: 9295170]
152. Biojone C, Casarotto PC, Resstel LB, Zangrossi H Jr, Guimaraes FS, Moreira FA. Anti-aversive effects of the atypical antipsychotic, aripiprazole, in animal models of anxiety. *J Psychopharmacol*. 2011; 25(6):801–7. doi:10.1177/0269881110376690. [PubMed: 20699351]
153. Kelley AE, Schiltz CA, Landry CF. Neural systems recruited by drug- and food-related cues: studies of gene activation in corticolimbic regions. *Physiol Behav*. 2005; 86(1-2):11–4. [PubMed: 16139315]
154. Dignon A, Beardsmore A, Spain S, Kuan A. 'Why I won't eat': patient testimony from 15 anorexics concerning the causes of their disorder. *J Health Psychol*. 2006; 11(6):942–56. [PubMed: 17035265]
155. Thaler L, Israel M, Antunes JM, Sarin S, Zuroff DC, Steiger H. An examination of the role of autonomous versus controlled motivation in predicting inpatient treatment outcome for anorexia nervosa. *Int J Eat Disord*. 2016 doi:10.1002/eat.22510.
156. Schultz W. Getting formal with dopamine and reward. *Neuron*. 2002; 36(2):241–63. [PubMed: 12383780]
157. Callier S, Snapyan M, Le Crom S, Prou D, Vincent JD, Vernier P. Evolution and cell biology of dopamine receptors in vertebrates. *Biol Cell*. 2003; 95(7):489–502. [PubMed: 14597267]
158. Barton AC, Black LE, Sibley DR. Agonist-induced desensitization of D2 dopamine receptors in human Y-79 retinoblastoma cells. *Mol Pharmacol*. 1991; 39(5):650–8. [PubMed: 1674585]

159. Jiang D, Sibley DR. Regulation of D(1) dopamine receptors with mutations of protein kinase phosphorylation sites: attenuation of the rate of agonist-induced desensitization. *Mol Pharmacol*. 1999; 56(4):675–83. [PubMed: 10496949]
160. Kim KM, Valenzano KJ, Robinson SR, Yao WD, Barak LS, Caron MG. Differential regulation of the dopamine D2 and D3 receptors by G protein-coupled receptor kinases and beta-arrestins. *J Biol Chem*. 2001; 276(40):37409–14. doi:10.1074/jbc.M106728200. [PubMed: 11473130]
161. Lamey M, Thompson M, Varghese G, Chi H, Sawzdargo M, George SR, et al. Distinct residues in the carboxyl tail mediate agonist-induced desensitization and internalization of the human dopamine D1 receptor. *J Biol Chem*. 2002; 277(11):9415–21. doi:10.1074/jbc.M111811200. [PubMed: 11773080]
162. Johanson AJ, Knorr NJ. Letter: Treatment of anorexia nervosa by levodopa. *Lancet*. 1974; 2(7880):591. [PubMed: 4140299]
163. Zucker NL, Losh M, Bulik CM, LaBar KS, Piven J, Pelphrey KA. Anorexia nervosa and autism spectrum disorders: guided investigation of social cognitive endophenotypes. *Psychol Bull*. 2007; 133(6):976–1006. doi:10.1037/0033-2909.133.6.976. [PubMed: 17967091]
164. Treasure J, Corfield F, Cardi V. A three-phase model of the social emotional functioning in eating disorders. *Eur Eat Disord Rev*. 2012; 20(6):431–8. doi:10.1002/erv.2181. [PubMed: 22539368]
165. Monteleone AM, Scognamiglio P, Volpe U, Di Maso V, Monteleone P. Investigation of Oxytocin Secretion in Anorexia Nervosa and Bulimia Nervosa: Relationships to Temperament Personality Dimensions. *Eur Eat Disord Rev*. 2015 doi:10.1002/erv.2391.
166. Lawson EA, Holsen LM, Santin M, Meenaghan E, Eddy KT, Becker AE, et al. Oxytocin secretion is associated with severity of disordered eating psychopathology and insular cortex hypoactivation in anorexia nervosa. *J Clin Endocrinol Metab*. 2012; 97(10):E1898–908. doi: 10.1210/jc.2012-1702. [PubMed: 22872688]
167. Lawson EA, Holsen LM, Santin M, DeSanti R, Meenaghan E, Eddy KT, et al. Postprandial oxytocin secretion is associated with severity of anxiety and depressive symptoms in anorexia nervosa. *J Clin Psychiatry*. 2013; 74(5):e451–7. doi:10.4088/JCP.12m08154. [PubMed: 23759466]
168. Kim YR, Eom JS, Yang JW, Kang J, Treasure J. The Impact of Oxytocin on Food Intake and Emotion Recognition in Patients with Eating Disorders: A Double Blind Single Dose Within-Subject Cross-Over Design. *PLoS One*. 2015; 10(9):e0137514. doi:10.1371/journal.pone.0137514. [PubMed: 26402337]
169. Kim YR, Oh SM, Corfield F, Jeong DW, Jang EY, Treasure J. Intranasal Oxytocin Lessens the Attentional Bias to Adult Negative Faces: A Double Blind within-Subject Experiment. *Psychiatry Investig*. 2014; 11(2):160–6. doi:10.4306/pi.2014.11.2.160.
170. Kim YR, Kim CH, Cardi V, Eom JS, Seong Y, Treasure J. Intranasal oxytocin attenuates attentional bias for eating and fat shape stimuli in patients with anorexia nervosa. *Psychoneuroendocrinology*. 2014; 44:133–42. doi:10.1016/j.psyneuen.2014.02.019. [PubMed: 24703429]
171. Hyman SE. Psychiatric drug development: diagnosing a crisis. *Cerebrum*. 2013; 2013:5. [PubMed: 23720708]
172. Weinberger DR. New directions in psychiatric therapeutics. *NeuroRx*. 2006; 3(1):1–2. doi: 10.1016/j.nurx.2005.12.011. [PubMed: 16490408]
173. Papakostas GI, Ionescu DF. Towards new mechanisms: an update on therapeutics for treatment-resistant major depressive disorder. *Mol Psychiatry*. 2015; 20(10):1142–50. doi:10.1038/mp.2015.92. [PubMed: 26148812]
174. Reinhold JA, Rickels K. Pharmacological treatment for generalized anxiety disorder in adults: an update. *Expert Opin Pharmacother*. 2015; 16(11):1669–81. doi: 10.1517/14656566.2015.1059424. [PubMed: 26159446]
175. Perna G, Schruers K, Alciati A, Caldirola D. Novel investigational therapeutics for panic disorder. *Expert Opin Investig Drugs*. 2015; 24(4):491–505. doi:10.1517/13543784.2014.996286.
176. Vadnie CA, Park JH, Abdel Gawad N, Ho AM, Hinton DJ, Choi DS. Gut-brain peptides in corticostriatal-limbic circuitry and alcohol use disorders. *Front Neurosci*. 2014; 8:288. doi: 10.3389/fnins.2014.00288. [PubMed: 25278825]

177. Bailer UF, Kaye WH. A review of neuropeptide and neuroendocrine dysregulation in anorexia and bulimia nervosa. *Curr Drug Targets CNS Neurol Disord*. 2003; 2(1):53–9. [PubMed: 12769812]
178. Kleiman SC, Watson HJ, Bulik-Sullivan EC, Huh EY, Tarantino LM, Bulik CM, et al. The Intestinal Microbiota in Acute Anorexia Nervosa and During Renourishment: Relationship to Depression, Anxiety, and Eating Disorder Psychopathology. *Psychosom Med*. 2015; 77(9):969–81. doi:10.1097/PSY.0000000000000247. [PubMed: 26428446]
179. Jarvis S, Schultz SR. Prospects for Optogenetic Augmentation of Brain Function. *Front Syst Neurosci*. 2015; 9:157. doi:10.3389/fnsys.2015.00157. [PubMed: 26635547]
180. Aleman A. Use of repetitive transcranial magnetic stimulation for treatment in psychiatry. *Clin Psychopharmacol Neurosci*. 2013; 11(2):53–9. doi:10.9758/cpn.2013.11.2.53. [PubMed: 24023548]
181. Kuo MF, Paulus W, Nitsche MA. Therapeutic effects of non-invasive brain stimulation with direct currents (tDCS) in neuropsychiatric diseases. *Neuroimage*. 2014; 85(Pt 3):948–60. doi:10.1016/j.neuroimage.2013.05.117. [PubMed: 23747962]
182. Fitzgerald PB, Segrave RA. Deep brain stimulation in mental health: Review of evidence for clinical efficacy. *Aust N Z J Psychiatry*. 2015; 49(11):979–93. doi:10.1177/0004867415598011. [PubMed: 26246408]
183. Post A, Keck ME. Transcranial magnetic stimulation as a therapeutic tool in psychiatry: what do we know about the neurobiological mechanisms? *J Psychiatr Res*. 2001; 35(4):193–215. [PubMed: 11578638]
184. Nitsche MA, Kuo MF, Karrasch R, Wachter B, Liebetanz D, Paulus W. Serotonin affects transcranial direct current-induced neuroplasticity in humans. *Biol Psychiatry*. 2009; 66(5):503–8. doi:10.1016/j.biopsych.2009.03.022. [PubMed: 19427633]
185. Appleton KM, Sallis HM, Perry R, Ness AR, Churchill R. Omega-3 fatty acids for depression in adults. *Cochrane Database Syst Rev*. 2015; 11:CD004692. doi: 10.1002/14651858.CD004692.pub4. [PubMed: 26537796]
186. Avraham Y, Saidian M, Burston JJ, Mevorach R, Vorobiev L, Magen I, et al. Fish oil promotes survival and protects against cognitive decline in severely undernourished mice by normalizing satiety signals. *J Nutr Biochem*. 2011; 22(8):766–76. doi:10.1016/j.jnutbio.2010.07.001. [PubMed: 21109417]
187. Ayton AK, Azaz A, Horrobin DF. Rapid improvement of severe anorexia nervosa during treatment with ethyl-eicosapentaenoate and micronutrients. *Eur Psychiatry*. 2004; 19(5):317–9. doi:10.1016/j.eurpsy.2004.06.002. [PubMed: 15276668]
188. Ayton AK, Azaz A, Horrobin DF. A pilot open case series of ethyl-EPA supplementation in the treatment of anorexia nervosa. *Prostaglandins Leukot Essent Fatty Acids*. 2004; 71(4):205–9. doi: 10.1016/j.plefa.2004.03.007. [PubMed: 15301789]
189. Yehuda S, Rabinovitz S. The Role of Essential Fatty Acids in Anorexia Nervosa and in Obesity. *Crit Rev Food Sci Nutr*. 2015; 0. doi:10.1080/10408398.2013.809690. [PubMed: 26068122]
190. Vall E, Wade TD. Predictors of treatment outcome in individuals with eating disorders: A systematic review and meta-analysis. *Int J Eat Disord*. 2015; 48(7):946–71. doi:10.1002/eat.22411. [PubMed: 26171853]
191. Le Noury J, Nardo JM, Healy D, Jureidini J, Raven M, Tufanaru C, et al. Restoring Study 329: efficacy and harms of paroxetine and imipramine in treatment of major depression in adolescence. *BMJ*. 2015; 351:h4320. doi:10.1136/bmj.h4320. [PubMed: 26376805]

Key Points

1. Anorexia nervosa is a severe psychiatric illness with a complex interplay of bio-psycho-social factors.
2. A multitude of psychoactive drugs has been tried in anorexia nervosa but without robust effects.
3. Neuroscience-based models of behavior will help in the development of effective psychopharmacological treatments for anorexia nervosa.

	Study Type	Treatment Conditions	Daily Medication Dose	Length of Treatment	N	Mean Age ± SD (Years)	Anorexia Type	Results
Cyproheptadine								
Goldberg et al., 1979 [15]	Double-blind placebo controlled	1. Cyproheptadine & behavior therapy 2. Cyproheptadine & no behavior therapy 3. Placebo & behavior therapy 4. Placebo & no behavior therapy	Cyproheptadine Start = 12 mg; Max = 32 mg	n.av.	81	n.av.	n.av.	Promoted weight gain in a subgroup who had a history of birth complications, had lost 41-52 percent weight from norm or who had history of prior outpatient treatment failure
Halmi et al., 1986 [17]	Double-blind placebo controlled	1. Cyproheptadine 2. Amitriptyline 3. Placebo	Max = 32 mg Max = 160 mg	Until within 5% of target weight	72	21 ± 5	Restricting/binge-purge	Cyproheptadine had "marginal effect on decreasing the number of days necessary to achieve a normal weight" compared to placebo or amitriptyline; cyproheptadine showed some beneficial effect for restricting type anorexia nervosa but worsened outcome for the binge/purge type anorexia subgroup
Tricyclic Antidepressants Monoamine Oxidase Inhibitor								
Lacey & Crisp, 1980 [19]	Double-blind placebo controlled	1. Clomipramine 2. Placebo	50 mg	76 Days Clomipramine 72 days Placebo	8 8	21 years	Restricting/binge-purge	Clomipramine was associated with increased hunger, appetite and energy intake but reduced weight gain
Biederman et al., 1985 [18]	Double-blind placebo controlled	1. Amitriptyline 2. Placebo 3. No Intervention	Amitriptyline 2.8 ± 0.3 mg/kg	5 weeks	11 14 18	18 ± 5 17 ± 4 16 ± 2	n.av.	All 3 groups showed little improvement; no differences favoring amitriptyline were found in any outcome variables
Kennedy et al., 1985 [23]	Open label	1. Isocarboxazid	Mean = 34 mg	6 weeks	6	24.5	Restricting	No weight change for either group during the study, however, anorexia nervosa patients gained weight in the 6 months following the study; mood and anxiety ratings improved by week 4
Ruggiero et al., 2001 [21]	Open-label	1. Clomipramine 2. Fluoxetine 3. Amitulpride	Mean= 57.7 ± 25.8 mg Mean = 26.0 ± 10.3 mg Mean= 50.0 ± 0.0 mg	3 months	10 13 12	23.7 ± 4.6 4.5 ± 5.1 24.3 ± 5.8	Restricting	Amitulpride patients gained significantly more weight than Fluoxetine patients
Strobel et al., 2004 [22]	Retrospective study	1. Paroxetine + intensive psychotherapy 2. Clomipramine + intensive psychotherapy	Mean = 18.4 ± 4.7 mg Mean = 75.3 ± 16.6 mg	39 ± 26 days Paroxetine 58 ± 30 days Clomipramine	39 57	No mean given Range 10.9 - 18.1 years	Restricting/binge-purge All with additional depressive episode	Paroxetine and clomipramine had the same BMI increase but for paroxetine in significantly less time, 72 days for paroxetine versus 97 days for clomipramine
Typical Antipsychotic Medications								
Vandereycken and Pierloot, 1982 [25]	Double-blind placebo controlled crossover	1. Pimozide 2. Placebo	Range = 4 - 6 mg	6 weeks	18	n.av.	n.av.	Pimozide did not significantly improve weight gain
Vandereycken, 1984 [64]	Double-blind placebo controlled crossover	1. Sulpiride +placebo sequence 2. Placebo- sulpiride sequence	300 or 400 mg	2-3 weeks	9 9	23.2 ± 6.5 23.7 ± 9.6	Restricting/binge-purge	Sulpiride initially promoted weight gain over placebo, but this was not sustained throughout the study
Weizman et al., 1985 [26]	Open label	1. Pimozide 2. Behavior therapy program	3 mg	20 weeks	5 5	15.8 ± 0.8 16.2 ± 1.3	n.av.	Pimozide did not aid in weight gain
Cassano et al., 2003 [27]	Open label	1. Haloperidol	Months 1-3 Mean = 1.2 ±- 0.4 mg; Months 4-6 Mean = 1.1 ± - 0.2 mg	6 months	13	22.8 ± 4.2	Restricting	A significant increase in BMI was reported in a chronic and treatment refractory group
Mood Stabilizers								
Gross et al., 1981 [29]	Double-blind placebo controlled cross-over	1. Lithium Carbonate + behavior modification therapy 2. Placebo + behavior modification therapy	Start = 300 mg, 300-mg increases until mean plasma lithium level was 1.0 ± 0.1	4 weeks	8 8	20.6 ± 1.8 18.8 ± 2.6	n.av.	Lithium was associated with greater weight gain at weeks 3 and 4 only

	Study Type	Treatment Conditions	Daily Medication Dose	Length of Treatment	N	Mean Age ± SD (Years)	Anorexia Type	Results
Zinc								
Safai-Kutti, 1990 [33]	Open label	1. Zinc	Range = 45-90 mg	Range = 8 - 56 months	20	Range = 14 - 26	n.av.	17 patients increased their weight by over 15 % and no patient lost weight
Lask et al., 1993 [35]	Double-blind placebo controlled crossover	1. Zinc 2. Placebo	50 mg	6 weeks	26	Children	n.av.	Zinc deficiency is common in anorexia nervosa, levels normalize after introducing normal diet without supplementation, and zinc levels are not related to weight gain
Birmingham et al., 1994 [34]	Double-blind placebo controlled	1. Zinc 2. Placebo	100 mg	24.6 ± 10.0 days 31.5 ± 18.5 days	16 19	20.6 ± 3.8 23.8 ± 6.1	n.av.	The rate of increase in BMI of the zinc supplemented group was twice that of the placebo group and this difference was statistically significant (p<0.03)
Opiates and Cannabinoids								
Moore et al., 1981 [38]	Open label	1. Naloxone	Range = 3.2 - 6.4 mg	5 weeks (range 1-11 weeks)	12	22.5	n.av.	Naloxone infusion was associated with significantly greater weight gain compared with the periods before and after
Gross et al., 1983 [40]	Double-blind placebo controlled crossover	1. 9-tetrahydrocannabinol 2. Active Placebo, Diazepam	Range = 7.5 - 30 mg Range = 1 - 15 mg	4 weeks	11	24 ± 2	n.av.	There was no significant differences in weight or daily calorie intake between 9-tetrahydrocannabinol and placebo
Marrazzi et al., 1995 [39]	Double-blind placebo controlled crossover	1. Naltrexone 2. Placebo	100 mg	12 weeks	19	27.3 ± 6.7	Anorexia nervosa binge/purge type or bulimia nervosa	Reduction in binge-purge behaviors but no effect on weight reported
Andries et al., 2014 [41]	Double-blind placebo controlled crossover	1. Dronabinol - placebo 2. Placebo - dronabinol	5 mg	4 weeks dronabinol, 4 weeks washout, 4 weeks placebo 4 weeks placebo, 4 weeks washout, 4 weeks dronabinol	24	33.3	Restricting/binge-purge	During dronabinol treatment, participants gained a small amount 0.73 kg compared to placebo; there were no significant adverse events reported
Benzodiazepines and Alpha 2 Adrenergic Agonists								
Casper et al., 1987 [44]	Double-blind placebo controlled crossover	1. Clonidine 2. Placebo	Range = 500-700 micrograms	4 weeks on placebo alternating with 4 weeks on clonidine.	4	Range = 19 - 28	Restricting/binge-purge	Clonidine did not influence the rate of weight gain or hunger or satiety sensations
Steinglass et al., 2014 [42]	Double-blind placebo controlled crossover	1. Alprazolam 2. Placebo	0.75 mg	2 test meals, 1 week apart	20	25.6 ± 7.8	Restricting/binge-purge	Alprazolam was not superior to placebo
Selective Serotonin Reuptake Inhibitors (SSRIs)								
Gwirtsman et al., 1990 [45]	Open label	1. Fluoxetine	Mean = 43 ± 15 mg; Range = 20 - 60 mg	Range = 2 - 5 months	6	27 ± 9	Restricting	Fluoxetine was associated with reduced depressive symptoms and weight gain
Kaye et al., 1991 [46]	Open label	1. Fluoxetine after weight restoration	Mean = 38 ± 18 mg	Mean = 11 ± 6 months	31	20 ± 7	Restricting/binge-purge	29 patients had maintained weight at or above 85% average body weight
Strober et al., 1997 [53]	Retrospective study	1. Fluoxetine + eating disorder treatment program 2. Controls + eating disorder treatment program	Mean = 33.9 ± 18 mg	Follow-up at 6 month intervals after inpatient treatment for 24 months	33 33	17.6	n.av.	Fluoxetine showed no benefit for weight gain or prevention of relapse
Pallanti et al., 1997 [59]	Open label	1. Citalopram	Start = 20 mg	6 months	32		Restricting	Citalopram may have aided in weight improvement but uncertain without control group
Atia et al., 1998 [49]	Double-blind placebo controlled	1. Fluoxetine 2. Placebo	Mean = 56 mg Mean = 58.7 mg	7 weeks	15 16	Range = 16 to 45	Restricting/binge-purge	Fluoxetine showed no benefit over placebo
Calandra et al., 1999 [57]	Open label	1. Citalopram	20 mg	8 weeks	6	20.5 ± 4.7	Restricting/binge-purge	Citalopram was associated with reduced body dissatisfaction, but no weight change reported

	Study Type	Treatment Conditions	Daily Medication Dose	Length of Treatment	N	Mean Age ± SD (Years)	Anorexia Type	Results
Ferguson et al., 1999 [62]	Retrospective study	1. Anafranil 2. Luvox 3. Paxil 4. Prozac 5. Zoloft	Range = 25 - 75 mg 100 mg Range = 10 - 40 mg Range = 10 - 40 mg Range = 25 - 150 mg	Naturalistic follow up	3 1 4 10 6	Mean = 23 ± 10 (SSRI); Mean=21±8 (non-SSRI)	Restricting/binge-purge	SSRI treatment did not improve treatment outcome
Ricca et al., 1999 [55]	Open label	1. Venlafaxine + cognitive behavior therapy 2. Fluoxetine + cognitive behavior therapy	75 mg 40 mg	6 months	12 12	18.9 ± 3.8 19.1 ± 3.6	Atypical anorexia nervosa	Venlafaxine and Fluoxetine showed no differences in weight change or behavior outcomes
Kaye et al., 2001 [51]	Double-blind placebo controlled	1. Fluoxetine after weight restoration 2. Placebo after weight restoration	Start Range = 20 - 60 mg	52 weeks	16 19	23 ± 9 22 ± 6	Restricting/binge-purge	Patients on fluoxetine had reduced relapse and higher weight gain
Santonastaso et al., 2001 [60]	Open label	1. Serrraline 2. Control group	Range = 50 - 100 mg	64 weeks	11	19± 3 20± 6	Restricting	Serrraline was not superior to placebo in weight recovery, however was associated with greater improvement of depressive symptoms, self perceived ineffectiveness, lack of interoceptive awareness, and perfectionism
Fassino et al., 2002 [58]	Open label	1. Citalopram 2. Wait list control group	20 mg	12 weeks	19 20	24.3 ± 5.4 25.2 ± 8.6	Restricting	Citalopram did not improve weight gain over control group, but was associated with reduced depression scores
Barbarch et al., 2004 [56]	Double-blind placebo controlled	1. Nutritional supplement + fluoxetine 2. Fluoxetine	Nutritional supplement (2.3 g of tryptophan; 600 mg docosahexanoic acid; 180 mg arachadonic acid); 20 - 60 mg (fluoxetine) Range = 20 - 60 mg (fluoxetine)	6 months	15 11	23.0 ± 6.3	Restricting/binge-purge	Fluoxetine plus supplement showed no benefit over placebo
Ruggiero et al., 2003 [52]	Single-blind placebo controlled	1. Nutritional management + fluoxetine 2. Nutritional management	Mean = 30 ± 9.4 mg	1 year	21 74	23.4 ± 4.0	Restricting/binge-purge	Fluoxetine was not superior to support weight gain
Holtkamp et al., 2004 [61]	Retrospective study	1. Fluoxetine 2. Fluvoxamine 3. Serrraline	35 mg 20 mg 100 mg	6 month follow-up	7 8 4	14.5 ± 1.4	Restricting/binge-purge	SSRI treatment did not improve treatment outcome
Walsh et al., 2006 [54]	Double-blind placebo controlled	1. Fluoxetine 2. Placebo	Mean = 63.5 ± 15.8 mg Mean = 71.4 ± 15.2 mg	52 weeks	49 44	22.4 ± 4.5 24.2 ± 4.5	Restricting/binge-purge	Fluoxetine showed no benefit over placebo
Yu et al., 2011 [48]	Naturalistic follow-up	1. Fluoxetine 2. Cognitive behavior therapy 3. Fluoxetine + cognitive behavior therapy	Max = 60 mg	1 year	14 17 22	25.6 ± 6.4	Restricting/binge-purge	Fluoxetine was not superior to support weight gain
Atypical Antipsychotic Medication								
Powers et al., 2002 [65]	Open label	1. Olanzapine	10 mg	10 weeks	14	26.8 ± 12.3	Restricting/binge-purge	Of the 14 patients who completed the study, 10 gained an average of 8.75 lb and 3 of these patients attained their ideal body weight. The remaining 4 patients who completed the study lost a mean of 2.25 lb
Malina et al., 2003 [67]	Retrospective study	1. Olanzapine	Mean = 4.7 ± 2.4 mg	Mean = 17 ± 20 weeks	18	22 ± 7	n.av.	Subjects reported a significant reduction in anxiety and difficulty eating
Barbarich et al., 2004 [66]	Open label	1. Olanzapine	Mean = 4.7 ± 1.6 mg	6 weeks	17	20.5 ± 5.1	Restricting/binge-purge	Olanzapine was associated with weight increase and decrease in anxiety and depression
Mondraty et al., 2005 [68]	Double-blind placebo controlled	1. Olanzapine 2. Chlorpromazine	10 mg 50 mg	Mean = 46 ± 31 days Mean = 53 ± 26 days	8 7	25.3 ± 7.4 25.3 ± 7.3	n.av.	There was no significant difference in weight gain between groups

	Study Type	Treatment Conditions	Daily Medication Dose	Length of Treatment	N	Mean Age ± SD (Years)	Anorexia Type	Results
Brambilla et al., 2007a [75]	Double-blind placebo controlled	1. Olanzapine + cognitive behavior therapy + nutritional rehabilitation 2. Placebo + cognitive behavior therapy + nutritional rehabilitation	2.5 mg for 1 month; 5 mg for 2 months	3 months	10 10	23 ± 4.8	n.av.	Olanzapine was not superior to placebo to support weight gain
Brambilla et al., 2007b [69]	Double-blind placebo controlled	1. Olanzapine + cognitive behavior therapy 2. Placebo + cognitive behavior therapy	2.5 mg for 1 month; 5 mg for 2 months	3 months	15 15	23.7 ± 4.8 26.3 ± 8.5	Restricting/binge-purge	No difference for weight gain between groups, but olanzapine was associated with greater improvement of eating disorder inventory ineffectiveness and maturity fear scores
Bosnac et al., 2007 [77]	Open label	1. Quetiapine	Range = 50 - 800 mg	8 weeks	8	33.3 ± 7.7	Restricting/binge-purge	Quetiapine was not associated with significant weight gain
Powers et al., 2007 [78]	Open label	1. Quetiapine	Range = 150 - 300 mg	10 weeks	19	26.8 ± 11.2	Restricting/binge-purge	Patients gained 1.6 lbs over the study duration
Bissada et al., 2008 [70]	Double-blind placebo controlled	1. Olanzapine 2. Placebo	Start = 2.5 mg; Max = 10 mg - flexible dose regimen	10 weeks	16 18	23.6 ± 6.5 29.7 ± 11.6	Restricting/binge-purge	Olanzapine was associated with greater weight increase and faster achievement of weight goals
Leggero et al., 2010 [71]	Open label	1. Olanzapine + psychotherapy	4.1 ± 2.9 mg	6 months	13	13.7 ± 2.3	Restricting	Patients gained weight but the effect of olanzapine was not certain
Court et al., 2010 [80]	Open label	1. Quetiapine 2. Treatment as Usual	Start = 50 mg; max = 400 mg	12 weeks	10 11	23.8 ± 9.4 21.0 ± 3.3	Restricting/binge-purge	No significant difference in outcome measures between quetiapine and control group
Aftia et al., 2011 [72]	Double-blind placebo controlled	1. Olanzapine 2. Placebo	Start = 2.5 mg; Last 4 Weeks = 10 mg	8 weeks	11 12	27.7 ± 9.1	n.av.	Olanzapine was associated with a small but significant increase in BMI over placebo
Kafantaris et al., 2011 [73]	Double-blind placebo controlled	1. Olanzapine + psychotherapy 2. Placebo + psychotherapy	Start = 2.5 mg; week 4 target = 10 mg	10 weeks	10 10	16.4 ± 2.2 18.1 ± 2.0	Restricting	Olanzapine was not superior to placebo to support weight gain
Norris et al., 2011 [74]	Retrospective study	1. Olanzapine 2. Comparison	Median = 5 mg	1038 ± 585 days 540 ± 441 days	43 43	14.4 ± 1.9 14.8 ± 1.6	Restricting/binge-purge	No firm conclusions could be drawn due to methodological problems of the study
Hagnan et al., 2011 [83]	Double-blind placebo controlled	1. Risperidone 2. Placebo	Mean = 2.5 ± 1.2 mg Mean = 3.0 ± 1.0 mg	17 weeks	18 22	16.2 ± 2.5 15.8 ± 2.3	n.av.	No significant difference in weight gain between groups; the risperidone group showed greater reduction in drive for thinness over the first half of the study, but this was not sustained
Powers et al., 2012 [79]	Double-blind placebo controlled	1. Quetiapine 2. Placebo	Mean = 177.7 ± 90.8 mg	8 weeks	4 6	34 ± 14.5	Restricting/binge-purge	No difference in any outcome measure between quetiapine and placebo
Other								
Hotta et al., 2009 [92]	Open label	1. Ghrelin	3 microgram/kg body weight for 5 minutes 2x/day before lunch & dinner	26 day hospitalization	5	26 ± 8	Restricting	Daily energy intake during ghrelin infusion increased by 12-36 % compared with pre-treatment period
Lechin et al., 2011 [90]	Open label	1. Amantadine	100 mg	3 months	22	22 ± 6.4	Restricting/binge-purge	Amantadine reduced AN symptoms when given 45 minutes prior to meal; all subjects showed significant and sustained BMI increases
Bloch et al., 2012 [91]	Double-blind placebo controlled	1. DHEA 2. Placebo	100 mg	6 months	13 8	26.9 ± 8.2	n.av.	BMI increase in DHEA group was significantly higher than placebo group at 4 months
Levinson et al., 2015 [89]	Double-blind placebo controlled	1. D-cycloserine 2. Placebo	250 mg 1 hr before exposure therapy session	4 exposure therapy sessions	20 16	25.4	Restricting/binge-purge	D-cycloserine group showed a significantly greater increase in BMI than those in the placebo group
Misra et al., 2013 [94]	Single-blind placebo controlled	1. Estrogen 2. Placebo	100 micrograms twice weekly with 2.5 mg of medroxyprogesterone acetate given daily for the first 10 days of every month	18 months	38 34	16.9 ± 0.2 (SE) 16.2 ± 0.2 (SE)	n.av.	At 18 months follow-up (n=20, estrogen group; n=17, placebo group), the estrogen group showed a significant decrease in STAIC-trait scores. There were no differences in BMI changes between groups.

	Study Type	Treatment Conditions	Daily Medication Dose	Length of Treatment	N	Mean Age $\pm$ SD (Years)	Anorexia Type	Results
Kibanski et al., 1995 [95]	Randomized controlled	1. Estrogen plus progestin 2. Unmedicated control group	0.625 mg Premarin (days 1-25) and 5 mg Provera (days 16-25) or 35 micrograms ethinyl estradiol	1.57 $\pm$ 0.89 years 1.41 $\pm$ 0.69 years	22 26	23.7 $\pm$ 7.2 25.8 $\pm$ 6.6	n.av.	No differences in bone density between the estrogen-treated and control groups.
Miller et al., 2004 [96]	Single-blind placebo controlled	1. Testosterone 2. Placebo	Range = 150 - 300 microgram	3 weeks	6 6	23.7 $\pm$ 3.5	n.av.	Brain glucose hypometabolism in AN changed toward normal in the posterior cingulate cortex with testosterone treatment.
Hill et al., 2000 [90]	Double-blind placebo controlled	1. Recombinant human growth hormone (rhGH) 2. Placebo	0.05 mg/kg	28 days	8 7	15 14.5	n.av.	Patients treated with rhGH reached medical/cardiovascular stability more rapidly than those treated with placebo.