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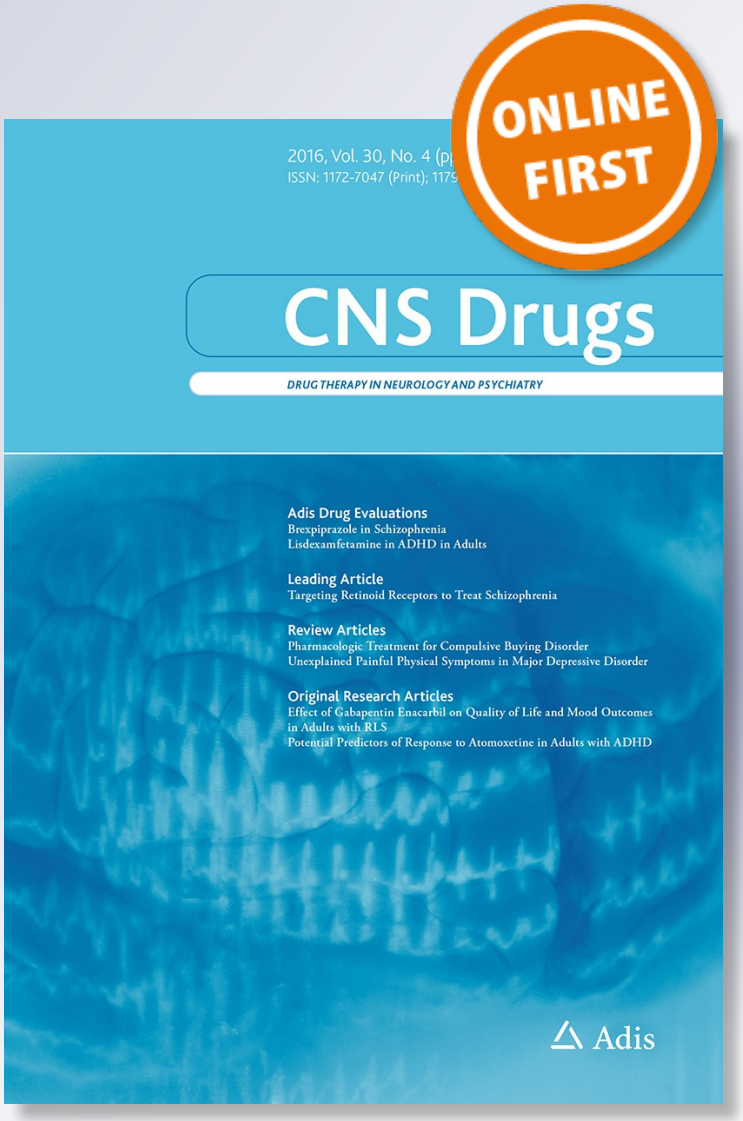
CNS Drugs

ISSN 1172-7047

CNS Drugs
DOI 10.1007/s40263-016-0335-6



Springer

CNS Drugs
DOI 10.1007/s40263-016-0335-6

REVIEW ARTICLE

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

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Abstract Anorexia nervosa (AN) 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 AN came to greater public recognition in the 1960s, including 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 AN is imperative as it continues to be a complex psychiatric disorder with high disease burden and mortality.

Key Points

Anorexia nervosa (AN) is a severe psychiatric illness with a complex interplay of bio-psycho-social factors.

A multitude of psychoactive drugs have been tried in AN but without robust effects.

Neuroscience-based models of behavior will help in the development of effective psychopharmacological treatments for AN.

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-fold higher than the expected death rate for 15- to 24-year-old females [4]. According to the *Diagnostic and Statistical Manual for Mental Disorders 5th edition* (DSM-5) [2], the diagnostic criteria for AN 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

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Published online: 22 April 2016

body weight to be below 85 % of that expected and the loss of regular 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. However, 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]. In general, treatment effectiveness for AN is limited [9] and, in particular, no medication has been approved for this disorder [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.

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 Anorexia Nervosa (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) guidelines [12]. However, there are too few trials in each medication category to discuss separately. 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* (1160 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 and 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], thereby making its use in AN appealing. The first double-blind, controlled study published in 1970 suggested weight gain in AN from the medication compared with 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 with 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 well tolerated. These medications are only rarely used now since selective serotonin reuptake inhibitors (SSRIs) have become available.

A rationale for the use of these medications was based on the hypothesis that AN is a form of depression as it is associated with dysphoric mood and anxiety. A 5-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 with placebo, perhaps due to more physical activity [19]. Clomipramine has direct hypothalamic effects and it has been 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

Table 1 Placebo-controlled and open-label studies in anorexia nervosa in historical chronological order

Study, year	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 and behavior therapy 2. Cyproheptadine and no behavior therapy 3. Placebo and behavior therapy 4. Placebo and no behavior therapy	Cyproheptadine start 12 mg; max. 32 mg	NA	81	NA	NA	Promoted weight gain in a subgroup that had a history of birth complications, had lost 41–52 % weight from normal, or who had a 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 a "marginal effect on decreasing the number of days necessary to achieve a normal weight" compared with placebo or amitriptyline; cyproheptadine showed some beneficial effect for restricting-type AN but worsened outcome for the binge/purge-type anorexia subgroup
Tricyclic antidepressants/monoamine oxidase inhibitors								
Lacey and Crisp, 1980 [19]	Double-blind, placebo-controlled	1. Clomipramine 2. Placebo	50 mg	76 days clomipramine 72 days placebo	8 8	21	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	NA	All three 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 during the study; however, AN 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. Amisulpride	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	Patients taking amisulpride gained significantly more weight than patients taking fluoxetine

Table 1 continued

Study, year	Study type	Treatment conditions	Daily medication dose	Length of treatment	*N*	Mean age ± SD (years)	Anorexia type	Results
Strobel et al., 2004 [22]	Retrospective	1. Paroxetine + intensive psychotherapy	Mean 18.4 ± 4.7 mg	39 ± 26 days paroxetine	39	No mean given, range 10.9–18.1	Restricting/ binge-purge	Paroxetine and clomipramine had the same BMI increase, but in significantly less time for paroxetine—72 days for paroxetine versus 97 days for clomipramine
		2. Clomipramine + intensive psychotherapy	Mean 75.3 ± 16.6 mg	58 ± 30 days clomipramine	57		All with an additional depressive episode	
Typical antipsychotic medications								
Vandereycken and Pierloot, 1982 [25]	Double-blind, placebo-controlled, crossover	1. Pimozide 2. Placebo	Range 4–6 mg	6 weeks	18	NA	NA	Pimozide did not significantly improve weight gain
Vandereycken, 1984 [64]	Double-blind, placebo-controlled, crossover	1. Sulpiride—placebo sequence	300 or 400 mg	2–3 weeks	9	23.2 ± 6.5	Restricting/ binge-purge	Sulpiride initially promoted weight gain over placebo but this was not sustained throughout the study
		2. Placebo—sulpiride sequence			9	23.7 ± 9.6		
Weizman et al., 1985 [26]	Open-label	1. Pimozide	3 mg	20 weeks	5	15.8 ± 0.8	NA	Pimozide did not aid in weight gain
		2. Behavior therapy program			5	16.2 ± 1.3		
Cassano et al., 2003 [27]	Open-label	1. Haloperidol	Months 1 to 3, mean 1.2 ± 0.4 mg; months 4 to 6, mean 1.1 ± 0.1 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, crossover	1. Lithium carbonate + behavior modification therapy	Start 300 mg, with 300 mg increases until mean plasma lithium level was 1.0 ± 0.1	4 weeks	8	20.6 ± 1.8	NA	Lithium was associated with greater weight gain at weeks 3 and 4 only
		2. Placebo + behavior modification therapy			8	18.8 ± 2.6		
Zinc								
Safai-Kutti, 1990 [33]	Open-label	1. Zinc	Range 45–90 mg	Range 8–56 months	20	Range 14–26	NA	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	NA	Zinc deficiency is common in AN, levels normalize after introducing normal diet without supplementation, and zinc levels are not related to weight gain

Table 1 continued

Study, year	Study type	Treatment conditions	Daily medication dose	Length of treatment	*N*	Mean age ± SD (years)	Anorexia type	Results
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	NA	The rate of increase in BMI of the zinc supplemented group was twice that of the placebo group; 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	NA	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	NA	No significant differences in weight or daily calorie intake were noted between 9-tetrahydrocannbinol 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	AN 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	5 mg	4 weeks dronabinol, 4 weeks washout, 4 weeks placebo	24	33.3	Restricting/ binge-purge	During dronabinol treatment, participants gained a small amount (0.73 kg) compared with placebo; no significant adverse events were reported
		2. Placebo – dronabinol		4 weeks placebo, 4 weeks washout, 4 weeks dronabinol				
Benzodiazepines and α2-adrenergic agonists								
Casper et al., 1987 [44]	Double-blind, placebo-controlled, crossover	1. Clonidine 2. Placebo	Range 500–700 μg	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

Table 1 continued

Study, year	Study type	Treatment conditions	Daily medication dose	Length of treatment	*N*	Mean age ± SD (years)	Anorexia type	Results
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	1. Fluoxetine + eating disorder treatment program	Mean 33.9 ± 18 mg	Follow-up at 6-month intervals after inpatient treatment for 24 months	33	17.6	NA	Fluoxetine showed no benefit for weight gain or prevention of relapse
		2. Controls + eating disorder treatment program			33			
Pallanti et al., 1997 [59]	Open-label	1. Citalopram	Start 20 mg	6 months	32		Restricting	Citalopram may have aided in weight improvement but this was uncertain without a control group
Attia et al., 1998 [49]	Double-blind, placebo-controlled	1. Fluoxetine	Mean 56 mg	7 weeks	15	Range 16–45	Restricting/ binge-purge	Fluoxetine showed no benefit over placebo
		2. Placebo	Mean 58.7 mg		16			
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
Ferguson et al., 1999 [62]	Retrospective	1. Clomipramine	Range 25–75 mg	Naturalistic follow-up	3	Mean 23 ± 10 (SSRI); mean 21 ± 8 (non-SSRI)	Restricting/ binge-purge	SSRI treatment did not improve treatment outcome
		2. Fluvoxamine	100 mg		1			
		3. Paroxetine	Range 10–40 mg		4			
		4. Fluoxetine	Range 10–40 mg		10			
		5. Sertraline	Range 25–150 mg		6			
Ricca et al., 1999 [55]	Open-label	1. Venlafaxine + cognitive behavior therapy	75 mg	6 months	12	18.9 ± 3.8	Atypical AN	Venlafaxine and fluoxetine showed no differences in weight change or behavior outcomes
		2. Fluoxetine + cognitive behavior therapy	40 mg		12	19.1 ± 3.6		
Kaye et al., 2001 [51]	Double-blind, placebo-controlled	1. Fluoxetine after weight restoration	Start range 20–60 mg	52 weeks	16	23 ± 9	Restricting/ binge-purge	Patients receiving fluoxetine had reduced relapse and higher weight gain
		2. Placebo after weight restoration			19	22 ± 6		

Table 1 continued

Study, year	Study type	Treatment conditions	Daily medication dose	Length of treatment	*N*	Mean age ± SD (years)	Anorexia type	Results
Santonastaso et al., 2001 [60]	Open-label	1. Sertraline	Range 50–100 mg	64 weeks	11	19 ± 3	Restricting	Sertraline was not superior to placebo in weight recovery; however it was associated with greater improvement of depressive symptoms, self-perceived ineffectiveness, lack of interoceptive awareness, and perfectionism
		2. Control group				20 ± 6		
Fassino et al., 2002 [58]	Open-label	1. Citalopram	20 mg	12 weeks	19	24.3 ± 5.4	Restricting	Citalopram did not improve weight gain over the control group but was associated with reduced depression scores
		2. Waitlist control group			20	25.2 ± 8.6		
Barbarich et al., 2004 [56]	Double-blind, placebo-controlled	1. Nutritional supplement + fluoxetine	Nutritional supplement (2.3 g of tryptophan; 600 mg docosahexaenoic acid; 180 mg arachadonic acid); 20–60 mg (fluoxetine)	6 months	15	23.0 ± 6.3	Restricting/ binge-purge	Fluoxetine plus supplement showed no benefit over placebo
		2. Fluoxetine	Range 20–60 mg (fluoxetine)		11			
Ruggiero et al., 2003 [52]	Single-blind, placebo-controlled	1. Nutritional management + fluoxetine	Mean 30 ± 9.4 mg	1 year	21	23.4 ± 4.0	Restricting/ binge-purge	Fluoxetine was not superior to support weight gain
		2. Nutritional management			74			
Holtkamp et al., 2004 [61]	Retrospective	1. Fluoxetine	35 mg	6-month follow-up	7	14.5 ± 1.4	Restricting/ binge-purge	SSRI treatment did not improve treatment outcome
		2. Fluvoxamine	20 mg		8			
		3. Sertraline	100 mg		4			
Walsh et al., 2006 [54]	Double-blind, placebo-controlled	1. Fluoxetine	Mean 63.5 ± 15.8 mg	52 weeks	49	22.4 ± 4.5	Restricting/ binge-purge	Fluoxetine showed no benefit over placebo
		2. Placebo	Mean 71.4 ± 15.2 mg		44	24.2 ± 4.5		
Yu et al., 2011 [48]	Naturalistic follow-up	1. Fluoxetine	Max 60 mg	1 year	14	25.6 ± 6.4	Restricting/ binge-purge	Fluoxetine was not superior to support weight gain
		2. Cognitive behavior therapy			17			
		3. Fluoxetine + cognitive behavior therapy			22			

Table 1 continued

Study, year	Study type	Treatment conditions	Daily medication dose	Length of treatment	*N*	Mean age ± SD (years)	Anorexia type	Results
Atypical antipsychotic medications								
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, 3 of whom 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	1. Olanzapine	Mean 4.7 ± 2.4 mg	Mean 17 ± 20 weeks	18	22 ± 7	NA	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	10 mg	Mean 46 ± 31 days	8	25.3 ± 7.4	NA	No significant difference in weight gain was noted between groups
		2. Chlorpromazine	50 mg	Mean 53 ± 26 days	7	25.3 ± 7.3		
Brambilla et al., 2007 [75]	Double-blind, placebo-controlled	1. Olanzapine + cognitive behavior therapy + nutritional rehabilitation	2.5 mg for 1 month; 5 mg for 2 months	3 months	10	23 ± 4.8	NA	Olanzapine was not superior to placebo to support weight gain
		2. Placebo + cognitive behavior therapy + nutritional rehabilitation			10			
Brambilla et al., 2007 [69]	Double-blind, placebo-controlled	1. Olanzapine + cognitive behavior therapy	2.5 mg for 1 month; 5 mg for 2 months	3 months	15	23.7 ± 4.8	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
		2. Placebo + cognitive behavior therapy			15	26.3 ± 8.5		
Bosanac 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	Start 2.5 mg; max. 10 mg—flexible dose regimen	10 weeks	16	23.6 ± 6.5	Restricting/ binge-purge	Olanzapine was associated with greater weight increase and faster achievement of weight goals
		2. Placebo			18	29.7 ± 11.6		
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

Table 1 continued

Study, year	Study type	Treatment conditions	Daily medication dose	Length of treatment	*N*	Mean age ± SD (years)	Anorexia type	Results
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 the quetiapine and control groups
Attia 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	NA	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	1. Olanzapine 2. Comparison group were patients matched for age, diagnosis and level of care	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
Hagman 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	NA	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 μg/kg body weight for 5 min 2×/day before lunch and dinner	26-day hospitalization	5	26 ± 8	Restricting	Daily energy intake during ghrelin infusion increased by 12–36 % compared with the pretreatment 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 min 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	NA	BMI increase in the DHEA group was significantly higher than the placebo group at 4 months
Levinson et al., 2015 [89]	Double-blind, placebo-controlled	1. D-cycloserine 2. Placebo	250 mg 1 h 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

Table 1 continued

Study, year	Study type	Treatment conditions	Daily medication dose	Length of treatment	*N*	Mean age ± SD (years)	Anorexia type	Results
Misra et al., 2013 [94]	Single-blind, placebo-controlled	1. Estrogen	100 μg twice weekly with 2.5 mg of medroxyprogesterone acetate administered daily for the first 10 days of every month	18 months	38	16.9 ± 0.2 (SE)	NA	At 18 months follow-up ($n = 20$, estrogen group; $n = 17$, placebo group), the estrogen group showed a significant decrease in STAIC-trait scores. No differences in BMI changes were noted between groups
		2. Placebo			34	16.2 ± 0.2 (SE)		
Kibanski et al., 1995 [95]	Randomized controlled	1. Estrogen plus progestin	0.625 mg Premarin (days 1–25) and 5 mg Provera (days 16–25) or 35 μg ethinylestradiol	1.57 ± 0.89 years	22	23.7 ± 7.2	NA	No differences in bone density between the estrogen-treated and control groups
		2. Unmedicated control group		1.41 ± 0.69 years	26	25.8 ± 6.6		
Miller et al., 2004 [96]	Single-blind, placebo-controlled	1. Testosterone	Range 150–300 μg	3 weeks	6	23.7 ± 3.5	NA	Brain glucose hypometabolism in AN changed toward normal in the posterior cingulate cortex with testosterone treatment
		2. Placebo			6			
Hill et al., 2000 [97]	Double-blind, placebo-controlled	1. rhGH	0.05 mg/kg	28 days	8	15	NA	Patients treated with rhGH reached medical/cardiovascular stability more rapidly than those treated with placebo
		2. Placebo			7	14.5		

AN anorexia nervosa, *SD* standard deviation, *SE* standard error, *max.* maximum, *NA* not available, *BMI* body mass index, *DHEA* dehydroepiandrosterone, *SE* standard error, *rhGH* recombinant human growth hormone, *STAIC* State-Trait Anxiety Inventory for Children

treatment, but 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 shortened 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 this 6-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. In general, they share strong dopamine D2 receptor antagonism. In 1976, Barry and Klawans 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]. In one study, haloperidol, a butyrophenone and the most commonly prescribed typical neuroleptic, administered as an adjunct to psychotherapy over 6 months, was associated with weight gain [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 conducted [28].

Neuroscience and, in particular, 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 that 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 regulation of food intake [37].

2.6 Opiates and Cannabinoids

Opiates and opiate antagonists are associated with hedonic aspects of food and drug use, and opiates are 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 the application of 9-tetrahydrocannabinol [40]. In fact, the medication caused dysphoria and sleep disturbance in AN. In contrast, a very recent 4-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 (approximately 1.5 pounds) [41]. New cannabis strains have recently been developed that may either stimulate (indica) or suppress appetite (sativa), but these 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 α2-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 α2-adrenergic agonist clonidine may increase feeding behavior, making a case to try this medication in AN [43]. However, administered in a placebo-controlled, crossover design, this medication had no beneficial effect in AN but was associated with hemodynamic side effects such as hypotension [44].

2.8 Selective Serotonin Reuptake Inhibitors

The introduction of the SSRI fluoxetine brought an effective and relatively well-tolerated 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, restricting-type AN improved or maintained weight better when receiving 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 1-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 2-year period [53]. Nonetheless, another study of a larger sample that prospectively used 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]. Compared with a waitlist control group, follow-up open-label citalopram studies found improvement in anxiety and depression but no benefit in weight gain [58, 59]. Paroxetine, another SSRI, 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-quarters of the time needed on clomipramine. A small, open-label study that compared sertraline with placebo over 14 weeks in an outpatient setting [60] found that sertraline improved depressive symptoms, perception of ineffectiveness, lack of interoceptive awareness, and perfectionism compared with 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 Medications

Compared with the first-generation ‘typical’ antipsychotics such as haloperidol, atypical neuroleptics have less extrapyramidal side effects. Some block dopamine D2 receptors as the first-generation drugs do, while 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], and 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 single-blind study that compared amisulpride with clomipramine and fluoxetine found this medication superior with respect to weight gain over a 3-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 both 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 a period of 10 weeks [70], and olanzapine was credited with faster and greater weight gain compared with 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]. In addition, in a study in which AN patients received more than 3 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, and 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 also has 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 with the other atypical antipsychotics as it is a dopamine D2 and 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 downregulate 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 glutaminergic NMDA agonist d-cycloserine, which has shown promising results in the treatment of anxiety disorders with respect to fear extinction [87]. In a laboratory design, one study tested this substance in AN in order to facilitate eating and found that d-cycloserine was associated with greater caloric intake compared with 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 the 1-month follow-up [89]. The opposite approach was taken in a study in which individuals with AN were administered the NMDA *antagonist* amantadine, and reported rapid improvement, including weight gain, over 3 months of treatment [90]. A study in which dehydroepiandrosterone (DHEA) was administered in a double-blind design to patients with AN in order to improve bone mineral density did not find the expected effect over placebo, but at the

4-month follow-up, BMI was higher in the DHEA group, as was improved reported mood [91]. Ghrelin is a gut hormone produced in the 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 type 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 common 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 the pathophysiology of AN. 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 for improving 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 2 decades we have started to better understand brain neurobiology that is involved in AN. Studies on brain volume have been inconsistent but with the general notion that brain volumes are reduced in AN [99]; however, 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 serotonin 1A receptor availability in AN was higher compared with controls, while the serotonin 2A receptor tended to be reduced across the cortex compared with controls [1]. The function of the serotonin system is multifold and is 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 anteroventral striatum [104], and the cannabinoid 1 receptor was higher in AN in the insular, infero-frontal, and inferotemporal pole [105] compared with healthy controls. Both dopamine and opioid circuits code neural reward processing. Dopamine neurons code motivation ('wanting') and 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. These studies do not usually 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 with 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 much further effort will be required [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 which 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 1-week treatment with olanzapine improved survival, but a 4-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 administered 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 in another [120, 121]. In contrast, the serotonin 1A receptor agonist 8-OH-DPAT reduced hyperactivity and associated weight loss [122]. Another group found that in the ABA model, 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 downregulate 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 the effects of agmatine, a metabolite of L-arginine, on ABA. That study indicated that 20 and 40 mg/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 α4-GABA receptors and worsens wheel-running behavior [130], supporting the notion that the increased hormone release during puberty is a vulnerability for developing 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 the neurobiology of AN [134, 135]. In fact, it has been suggested that this need for better integration of genetic, environmental, and developmental factors applies to animal models in relation to 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 when considering 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. For instance, it is 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. However, the past approach to medication treatment in AN 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 (i) we have limited knowledge about disorder-specific pathophysiology, and (ii) 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 and 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. In most cases, studies had a duration of 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 with other psychiatric disorders with respect to biological underpinnings. However, the complex interactions between intrinsic brain abnormalities and changes that occur during the illness and during 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 researchers 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, in particular, females in a low-estrogen state may 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 and extinction [148]. Taken together, the dopamine D1 and D2 receptors appear to be potential targets for the 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 the treatment of AN.

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 in AN the poor motivation to recover 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 with 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 downregulation might then 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 [84, 85].

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]. In particular, 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, in part, be 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, various compounds have been identified that are currently under investigation (see review by Papakostas and Ionescu [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 antidepressant 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. This drug has also been considered as 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, these agents could be investigated in animal

models of AN. From relevant research in the addiction literature, we learned that potential therapeutic target for the eating disorders field are gastrointestinal peptides, which are active in the brain [176]. These 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 is it 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 with 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 the use of 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 nonpharmacological interventions in psychiatry that effect brain activity, including 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 neurotransmitter 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 in improving outcome in psychiatric disorders, including eating disorders.

5.5 General Neural Protection

Nutritional supplements constitute a large segment in the personal health improvement market. In the US, these products are not regulated by the FDA 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], and docosahexaenoic acid [DHA]) are naturally occurring in foods such as fish or flax seeds and can be administered 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 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) to reach ideal body weight compared with the clomipramine group (97 days). Tricyclic medications have shown little benefit in the treatment of adolescent depression, while SSRIs have shown efficacy, although the specific effectiveness of paroxetine has recently been 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 uptitrate, depending on clinical response. Medication trials should then compare different dosages.

6 Conclusions

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.

Compliance with Ethical Standards

Conflict of interest Dr. Frank and Ms. Shott report no competing interests.

Funding None.

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