CNS Spectrums (2016), **21**, 134–142.
doi:10.1017/S1092852914000790

REVIEW ARTICLE

Psychopharmacological options for adult patients with anorexia nervosa

Mario Miniati, * *Mauro Mauri, Agnese Ciberti, Michela Giorgi Mariani, Donatella Marazziti, and Liliana Dell'Osso*

Dipartimento di Medicina Clinica e Sperimentale, Section of Psychiatry, University of Pisa, Pisa, Italy

The aim of this review was to summarize evidence from research on psychopharmacological options for adult patients with anorexia nervosa (AN). Database searches of MEDLINE and PsycINFO (from January 1966 to January 2014) were performed, and original articles published as full papers, brief reports, case reports, or case series were included. Forty-one papers were screened in detail, and salient characteristics of pharmacological options for AN were summarized for drug classes. The body of evidence for the efficacy of pharmacotherapy in AN was unsatisfactory, the quality of observations was questionable (eg, the majority were not blinded), and sample size was often small. More trials are needed, while considering that nonresponse and nonremission are typical of patients with AN.

Received 16 July 2014; Accepted 5 December 2014; First published online 6 July 2015

Key words: Anorexia nervosa, antidepressants, antipsychotics, eating disorders, pharmacological treatment.

Introduction

Eating disorders (EDs) represent a group of persistent and potentially fatal psychiatric conditions that rank among the top-10 leading causes of disability in young adults.[1,2] Typically, clinical onset is during infancy/adolescence, and less frequently in early adulthood. The estimated lifetime prevalence of EDs is now considered as ranging between 0.3% and 0.9% for anorexia nervosa (AN) and up to 10% for other conditions.[3–7] EDs are characterized by heterogeneous clinical presentations and include anorexia nervosa restricting type (AN-R), anorexia binge-eating/purging type (AN-BP), bulimia nervosa (BN), and binge-eating disorder (BED), and also encompass other atypical or subthreshold forms. Moreover, even if AN and BN are typically regarded as discrete diagnostic entities, they share several psychopathological elements, and patients frequently cross the diagnostic categories.[8–11] Not surprisingly, it has been reported that in 20–50% of cases, AN and BN might occur together across the lifespan.[12]

Anorexia nervosa (AN) is the most severe ED. It affects about 1:200 women and 1:2000 men in western countries.[13] The etiology of AN is complex, and several factors, such as genetics and personality traits, may contribute to its development and maintenance. In addition, environment, such as sociocultural pressure toward thinness, is likely to act as a trigger during the vulnerable period of pubertal development. The increase in satisfaction gained from bodily and dietary control is often reinforced in societies where a number of individuals are facing problems of overweight and obesity. As a consequence, AN patients have a tendency to conceal their problems, and to seek for professional help only when the long-lasting malnutrition produces severe physical complications, including osteoporosis, gastrointestinal and cardiac failures, liver damage, or electrolyte disturbances.

According to the National Institute for Clinical Excellence Guidelines (NICE),[14] and also according to the Italian Guidelines,[15] most patients with AN should be managed on an outpatient basis using psychological treatment methods. Hospitalization has to be considered when there is substantial medical or suicidal risk, or after failure to improve despite an adequate course of psychotherapy. Inpatient programs provide structured regimens focused on refeeding and weight gain in combination with broader psychosocial interventions. Whenever possible, hospitalization should occur within or near the patient's own community and followed by a minimum of 12 months of outpatient treatment. First-choice psychological treatments for AN include cognitive

* Address for correspondence: Mario Miniati, MD, Dipartimento di Medicina Clinica e Sperimentale, Section of Psychiatry, University of Pisa, 57 Via Roma, Pisa, Italy.
(Email: m.miniati@psico.med.unipi.it)

behavior therapy (CBT), interpersonal psychotherapy (IPT), psychodynamic therapy, family interventions, psychosocial interventions based on addiction models, support groups, Internet-based support, and nonverbal therapeutic methods. Psychopharmacological treatments represent only a second choice for those patients who are resistant to psychotherapy.[14–16]

In any case, a summary of 68 studies dealing with psychotherapeutic and pharmacological strategies in AN published before 1989 with a follow-up length ranging between 1 and 33 years reported that only 43% of patients recovered completely, 36% improved, 20% developed a chronic form, and 5% died from physical complications and/or suicide.[17] Subsequent long-term observations reported on a standardized mortality ratio (SMR), (defined as the ratio of observed deaths in the study population to expected deaths in population of origin) of 5.86 (95% CI: 4.17-8.26) with a mean follow-up period of 14 years.[18] Moreover, clinical experiences would indicate that a large number of patients show unsatisfactory response to all available treatments.

Clinical trials carried out regarding AN up until now have focused on a wide range of pharmacological compounds, but unfortunately, data on their effectiveness are still limited. As a consequence, currently there is no proven or unequivocal treatment for this disorder. However, it may be wrong to consider the modest results obtained as "absence of evidence." The present article aims at providing an exhaustive review of current knowledge on psychopharmacological options for adult patients with AN. Studies only on children or adolescents were not included, considering that the vast majority of drugs are not permitted for patients younger than 18 years. Conversely, studies including both patients younger and older than 18 years were included.

Methods

The following criteria were used to select studies assessing psychopharmacological options for AN patients: (a) inclusion in at least 1 of 2 databases, MEDLINE and PsycINFO, from January 1966 to January 2014; (b) original articles published as full papers, brief reports, case reports, or case series; (c) original articles not specifically focused on special populations (namely, children and adolescents); (d) original articles including patients identified as suffering from some form of AN based on international diagnostic standards, such as the *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition (DSM-IV), DSM Fourth Edition Text Revision (DSM-IV-TR), or International Classification of Diseases (ICD)-9 or −10; (e) studies published in the English language. The following keywords were used: [eating disorders], [anorexia], [treatment], [resistance], [refractory]. A specific form was designed for data extraction, including (a) authors; (b) therapeutic setting (inpatient or outpatient) and AN diagnosis; (c) number of subjects; (d) type of treatment; (e) type of study; and (g) outcomes. All of the studies reviewed are reported in Table 1.

Results

A total of 75 publications was found. Thirty-four references were excluded following the selection criteria (Figure 1). The full text of 41 papers retrieved from PubMed and PsycINFO searches was selected and analyzed. The main characteristics of the 41 studies are listed in Table 1. In view of the paucity of reports, we did not apply rigorous quality criteria to the experimental designs of studies, such as substantial subject number, random assignment, adequate control subjects, reliable methods of assessment, or long-term follow-up. The heterogeneity of sample compositions, treatment, settings of treatment, and analyzed predictors did not permit us to carry out a meta-analysis of all of the available studies.

Seventeen (41.5%) studies used a randomized controlled trial (RCT) methodology, while the others were open (n = 9, 22.0%), case series and case reports (n = 12, 29.3%), or retrospective observations (n = 2, 4.9%). One trial was conducted with a single-blind randomized design (2.4%).

The numbers of subjects included in the studies varied widely, between 1 and 93 (mean ± SD: 22.3 ± 22.4). Three studies also included men (7.3%) for a total of 4 patients, therefore making a comparison based on gender impossible. The size of the samples and the diagnosis/gender composition depended on the characteristics of the setting (inpatient/outpatient) and on the duration of observation, whereas the power of the study was not considered in the majority of published papers. Results were statistically nonsignificant not because the hypothesis being tested was untrue or clinically nonsignificant but because the sample size was too small.

After differentiating by setting, 25 studies were conducted on inpatients (61.0%), 15 on outpatients (36.6%), while one case did not specify the therapeutic setting of the patients. The total number of inpatients included was 594 (mean + SD: 23.7 ± 23.2, range: 1–93) that of outpatients 321 (mean + SD: 21.4 ± 21.7; range: 1–81).

The age (mean ± SD, years) of patients was mentioned in 35 out of a total of 41 studies (85.3%), and was 27.2 ± 8.1 years (range: 18.4–50.0). The age of inpatients was significantly lower than that of outpatients (24.8 ± 4.2 vs 29.1 ± 9.5, t-test: $p < .018$).

The illness duration (mean ± SD, years) for the overall settings (available data for 19 out of 41 observations, 46.3%) was 7.9 ± 7.1 (range: 2.9–35.0), that of inpatients was 6.8 ± 3.4 (range: 2.9–14.1), and that of outpatients was 5.5 ± 1.4 (range: 3–7).

https://doi.org/10.1017/S1092852914000790 Published online by Cambridge University Press

TABLE 1. Studies on psychopharmacological treatments available for anorexia

Authors	Year	Number of patients	Study design	AN subtype	Treatments	Rating scales/instruments
Dally *et al.*[39]	1966	57	Open label	Unspecified	Chlorpromazine and insuline	No rating scales
Barcai[57]	1977	2	Case report	Unspecified	Lithium	No rating scales
Goldberg *et al*[61]	1979	81	RCT	Unspecified	Cyproeptadine vs PBO vs CBT	No rating scales
Lacey & Crisp[21]	1980	16	RCT	Unspecified	Clomipramine vs PBO	No rating scales
Gross *et al*[58]	1981	16	RCT	Unspecified	Lithium vs PBO	HSCL-90, GAAQ, PRS
Vandereycken and Pierlot[41]	1982	18	RCT	Unspecified	Pimozide vs PBO	ABOS
Vandereycken[34]	1984	18	RCT	Unspecified	Sulpiride vs PBO	EAT, BAT
Biederman *et al*[19]	1985	43	RCT	Unspecified	Amytriptiline vs PBO	SADS-C, HSCL-90, EAT, CGI
Halmi *et al*[20]	1986	72	RCT	AN-R + AN-BP	Amytriptiline vs Cypr. vs PBO	HAM-D; HSCL-90; BDI; SEI; ABS; BDI
Casper *et al*[60]	1987	4	Case report	AN-R + AN-BP	Clonidine	No rating scales
Crisp *et al*[22]	1987	16	RCT	Unspecified	Clomipramine vs PBO	No rating scales
Gwirtsman *et al*[26]	1990					
Attia *et al*[27]	1998	31	RCT	Unspecified	Fluoxetine vs PBO	BSQ, EAT, BDI, CGI, SCL-90, YBC-ED, ABS
Hansen[50]	1999	1	Case report	Unspecified	Olanzapine	No rating scales
Jensen & Mejlhede[51]	2000	3	Case report	Unspecified	Olanzapine	No rating scales
La Via *et al*[52]	2000	1	Case report	AN-BP	Olanzapine	No rating scales
Kaye *et al*[29]	2001	39	RCT	AN-R + AN-BP	Fluoxetine vs PBO	Y-BOCS-ED, HDRS, HARS
Ruggiero *et al*[40]	2001	35	Single blind	AN R	Amisulpiride vs fluoxetine vs clomipramine	LIFE II BEI
Fassino *et al*[31]	2002	52	Open label	AN-R	Citalopram	EDI-2, STAXI, SCL-90, EDI-SC, BDI
Powers *et al*[42]	2002	20	Open label	AN-R + AN-BP	Olanzapine	SCID-IV, AIMS, HAM-D, CGI, EDI-2, PANSS
Cassano *et al*[37]	2003	13	Open label	AN R	Haloperidol	EDI, EAT, CGI
Malina *et al*[45]	2003	18	Retrospective	Unspecified	Olanzapine	10 items, 5-point scale of AN-related behaviors
Barbarich *et al*[28]	2004	26	RCT	AN-R + AN-BP	Fluoxetine vs placebo	STAI-Y, YBOCS, BDI, YBC-EDS
Barbarich *et al*[43]	2004	17	Open label	AN-R + AN-BP	Olanzapine	STAI-Y, YBOCS
Mondraty *et al*[44]	2005	15	RCT	Unspecified	Olanzapine vs chlorpromazine	EDI-2
Schule *et al*[63]	2006	5	Case report	AN-R	Mirtazapine	HAM-D
Walsh *et al*[30]	2006	93	RCT	AN-R + AN-BP	Fluoxetine vs PBO	BDI, BAI, RSE, Q-LES-Q, EDI, YBC-EDS
Wang *et al*[53]	2006	1	Case report	Unspecified	Olanzapine and mirtazapine	No rating scales
Bosanac *et al*[54]	2007	8	Open label	AN-R + AN-BP	Quetiapine	EDE-12, MADRS, SAPS, YBC-EDS, CGI-I, CGI-S, AIMS, SAS, CDR
Brambilla *et al*[48]	2007	30	RCT	AN-R + AN-BP	Olanzapine vs PBO	EDI-2, TCI, HRS-D, YBOCS-ED
Brambilla *et al*[49]	2007	20	RCT	Unspecified	Olanzapine vs PBO	No rating scales
Powers *et al*[55]	2007	20	Open label	AN-R + AN-BP	Quetiapine	PANSS, EDI-2, YBC-EDS, HDRS, CGI-I, CGI-S, STAI
Yasuhara *et al*[64]	2007	1	Case report	AN-R	Olanzapine	No rating scales
Bissada *et al*[46]	2008	34	RCT	AN-R + AN-BP	Olanzapine vs PBO	Personality Assessment Inventory (PAI) Y-BOCS
Court *et al*[65]	2010	33	Open label	Unspecified	Quetiapine	EDI-2, CESD, MASQ, PWI, MADS
Trunko *et al*[56]	2010	5	Case report	AN + BP	Aripiprazole	No rating scales

Attia *et al*[47]	2011	23	RCT	Unspecified	Olanzapine vs PBO	PANSS, EDI, YBOCS-ED, BAI, BDI, BSQ, EDE
Safer *et al*[32]	2011	1	Case report	AN-R	Mirtazapine	No rating scales
Safer *et al*[33]	2012	1	Case report	AN-BP	Duloxetine	No rating scales
Delsedime *et al*[66]	2013	1	Case report	AN-R	Olanzapine	SCL-90, SCID-I-, SCID-II, BPRS
Mauri *et al*[38]	2013	9	Retrospective	AN-R	Haloperidol	No rating scales

List of Abbreviations: HSCL: The Hopkins Symptom Checklist; HSCL-90: The Hopkins Symptom Checklist 90–Revised; GAAQ: Goldberg Anorectic Attitude Questionnaire; PRS: Psychiatric Rating Scale; ABOS: Anorectic Behaviors Scale for Inpatients Observation; EAT: Eating Attitudes Test; BAT: Body Attitudes Test; SADS-C: Schedule for Affective Disorders & Schizophrenia; CGI: Clinical Global Impression; CGI-I: Clinical Global Impression–Improvement; CGI-S: Clinical Global Impression–Symptoms; HAM-D: Hamilton Depression Scale; BDI: Beck Depression Inventory; BDS: Beck Depression Score; SEI: Self Esteem Inventory; ABS: Anorexic Behavior Scale; EDE: Eating Disorders Examination; EDI: Eating Disorder Inventory; BIT: Body Image Test; BDS: Beck Depression Score; BSQ: Body Shape Questionnaire; TCI: Temperament and Character Inventory; SCL-90: Symptom Checklist–90-R; Y-BOCS: Yale–Brown Obsessive Compulsive Scale; YBC-EDS: Yale–Brown–Cornell Eating Disorder Scale; YBOCS-ED: Yale–Brown Obsessive Compulsive Scale for Eating Disorder; STAI: State-Trait Anxiety Inventory; HDRS: Hamilton Depression Rating Scale; HARS: Hamilton Anxiety Rating Scale; STAXI: State-Trait Anger Expression Inventory; TESS: Traumatic Exposure Severity Scale; BAI: Beck Anxiety Inventory; RSE: Rosenberg Self-Esteem; Q-LES-Q: Quality of Life Enjoyment and Satisfaction Questionnaire; SAS: Sympson-Angus Scale; CDR: Cognitive Drug Research; PANSS: Positive and Negative Symptoms Score; CESD: Center for Epidemiologic Studies Depression Scale; MASQ: Mood and Anxiety Symptoms Questionnaire; PWI: Personal Wellbeing Index; MADS: Managing Affect and Differences Scale; SCID-I: Structured Clinical Interview for DSM-IV-TR (Axis I Disorders); SCID-II: Structured Clinical Interview for DSM-IV-TR (Axis II Disorders); BPRS: Brief Psychiatric Rating Scale; PAI: Personality Assessment Inventory; MADRS: Montgomery–Asberg Depression Rating Scale; SAPS: Scale for the Assessment of Positive Symptoms–Delusion Subscale; AIMS: Abnormal Involuntary Movement Scale; EDI-SC: Eating Disorder Inventory (2)–Symptom Checklist; LIFE II BEI: Eating Disorder Interview Based on Long Interval Follow up Evaluation; EDI-2: Eating Disorder Inventory-2; EDE-12: Eating Disorder Examination–12th Edition; STAI-Y: Spielberger State-Trait Anxiety Inventory; VAS: Visual Analog Scale; PBO: Placebo; RCT: Research Clinical Trial; CBT: Cognitive-Behavioral Therapy; AN-R: Anorexia Restricter; AN-BP: Anorexia Bingeing-Purging.

With regard to DSM-IV or DSM Third Edition Revised (DSM-III-R) diagnoses, 18 studies did not specify the AN subtype (43.9%), 9 (22.0%) included only patients with AN-R, 2 (4.9%) included those with AN-BP, and 11 (26.8%) included both AN-R and AN-BP patients. One study (2.4%) included patients with AN and BN.

Out of a total of 41 observations (70.7%), 29 investigated Axis I comorbidity, with 6 studies (14.6%) excluding patients with Axis I mood or psychotic disorders. OCD spectrum comorbidity was diagnosed in 9 studies (22.0%). No information was provided in 12 studies (29.3%). Only four studies (9.8%) investigated Axis II comorbidities.

Twenty-four studies (58.6%) used ED-related inventories, while 17 (41.4%) utilized no rating scales. Details on rating scales administered are summarized in Table 1. Body mass index (BMI) at intake was available in 21 studies (51.2%). Mean BMI at baseline was 14.9 ± 1.9 kg/m^2 (range: 9.8–17.9), and at the end 17.1 ± 1.5 kg/m^2 (range: 14.7–20).

Discussion

The results of the present review confirm the paucity of empirical evidence on the available pharmacological treatments of adult AN. Therefore, challenges to the identification of evidence-based treatments for AN are discouraging. Available studies are affected by several methodological limitations, so that the overall strength of the available evidence is poor, with a lack of consensus and inconclusive outcomes. Most studies were conducted at a single center. None of the pharmacological options tested, including antidepressants, antipsychotics, or mood stabilizers, achieved relevant treatment goals. Sample sizes were small, and dropout rates were often high. The few results that favored one form of treatment over another were not replicated. As a consequence, impressions about "positive" and "negative" findings for AN were shaped by single studies with a few participants, and were often extrapolated across patient groups of different age, illness duration, and severity. Here the available evidence is summarized by drug class.

Antidepressants

The biological and psychopathological similarities between AN and depression led to the early clinical trials with tricyclic antidepressants (TCAs), such as amitriptyline[19,20] and clomipramine.[21,22] However, TCAs are no longer studied or recommended for AN, mainly because they may induce fatal arrhythmias in patients with low body weight (especially in younger patients).

Selective serotonin reuptake inhibitors (SSRIs) replaced TCAs in the 1980s. Again, the rationale for the use of SSRIs was related to the similarities between

https://doi.org/10.1017/S1092852914000790 Published online by Cambridge University Press

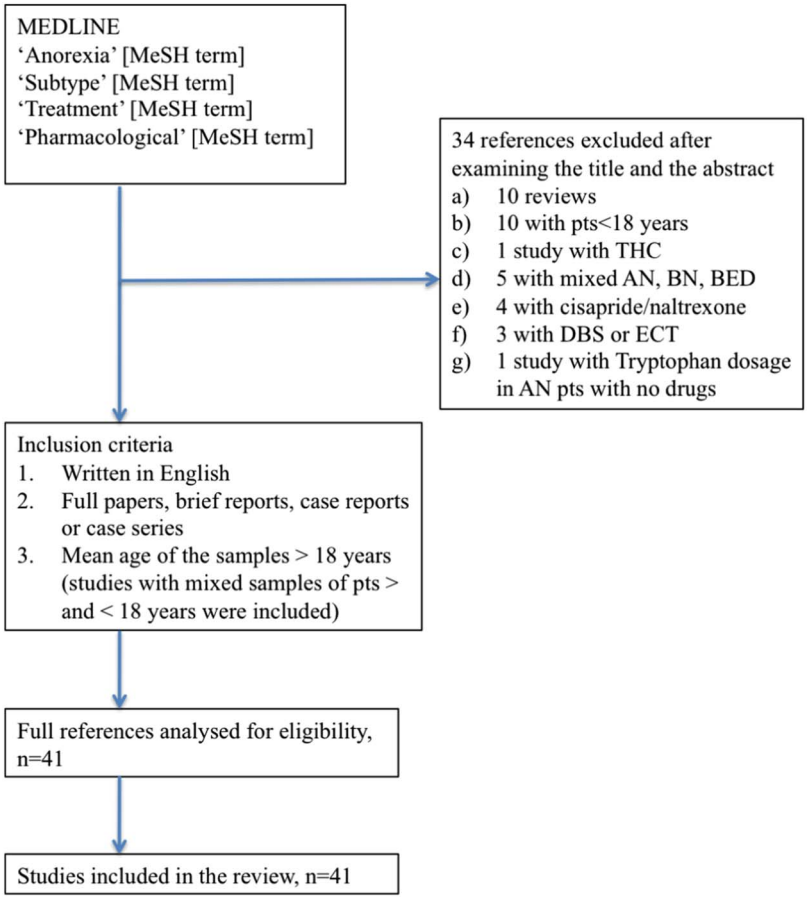

FIGURE 1. Flow chart summarizing the procedure for selecting studies for review.

AN, depression, and OCD. According to the spectrum model proposed by Hollander *et al*,[23] AN restricting subtype could be included in the obsessive-compulsive spectrum[24] and underpinned, perhaps, by a serotoninergic dysfunction.[25] However, to date, there is no clear evidence supporting the use of SSRIs in AN. Studies on fluoxetine provided controversial results. The first trial was a small, open study in 6 patients with chronic, refractory AN.[26] The authors observed an improvement of depressive symptoms and a significant weight gain. Patients seemed to tolerate fluoxetine even at the higher dosages. Conversely, no differences were found between fluoxetine and placebo in 2 studies conducted in AN-R inpatients.[27,28] In a third study, patients with AN-R were randomly assigned to fluoxetine or placebo after a period of hospitalization and weight restoration, and followed up for 1 year.[29] Patients receiving fluoxetine showed a significantly lower rate of relapse than those randomized to placebo. However, the limitations of this study included the small sample size (13 completers) and the lack of standardized psychological treatment during the trial. Negative results were found in a larger clinical trial, with 93 weight-restored outpatients already in treatment with CBT randomized to fluoxetine or to placebo.[30] No differences in relapse rate emerged during the 1-year follow-up.

Citalopram was compared to a waiting-list condition (WL) in patients affected by AN-R (participants in WL received no active treatment during the trial; it was anticipated that they could receive one after the end of the study).[31] Citalopram improved depression, obsessive-compulsive symptoms, impulsiveness, and trait anger. Weight gain was similar in both groups.

Mirtazapine showed its effectiveness in an adult patient, in which weight-gain maintenance and mood improvement were observed in a 9-month follow-up.[32] The same research group reported the efficacy of high doses (180 mg/day) of duloxetine in the management of treatment-refractory symptoms in a patient affected by severe depression, OCD, and comorbid AN-BP, with a significant improvement of affective, obsessive, and eating-refractory symptomatology.[33]

In conclusion, available data on antidepressants demonstrated their limited effectiveness in AN. However, they might improve the anxiety, irritability, mood lability, and depressive symptoms that often complicate the course of AN.

https://doi.org/10.1017/S1092852914000790 Published online by Cambridge University Press

Antipsychotics

In the past, the rationale for the use of antipsychotics in AN was mainly linked to the psychomotor hyperactivity control (with the induction of weight gain), or to the reward system regulation.[34] Several core symptoms of AN, including body image disturbance and fear of weight gain, have been closely related to an underlying dopaminergic dysregulation.[35] A recent study postulated the existence of an altered expression of dopaminergic genes among patients suffering from EDs.[36] This provided a more robust rationale for the use of antipsychotics, especially when fears of weight gain and body image disturbance might reach a delusional level.

Data on first-generation antipsychotics were controversial.[37–41] Results regarding the safety and efficacy of haloperidol on delusional body image alteration were promising, but were limited by the small samples size. To our knowledge, only 2 observations were available concerning haloperidol as adjunctive treatment for AN-R. The first was a mid-term naturalistic study on a sample of 13 outpatients (mean BMI of 15.6 kg/m^2)[37]; the second one was a chart-review of 9 inpatients (BMI < 13 kg/m^2).[38] Chlorpromazine is no longer utilized for AN because of its severe adverse effects, including seizures. These preliminary studies suggested that low doses of haloperidol might be effective as an adjunctive treatment for patients with severe, treatment resistant AN-R and delusional body image alteration.

There was inconsistent evidence from 2 trials on the efficacy of sulpiride[34] and pimozide.[41] In a third single-blind study, amisulpiride (50 mg/day) was compared with fluoxetine and clomipramine in a small sample (n = 35) of hospitalized patients with AN who attended a 12-week weight restoration program. Those taking amisulpiride showed a significantly greater weight gain, while the other clinical features did not significantly differ between groups.[40]

More evidence on second-generation antipsychotics is now available. Olanzapine is the most studied antipsychotic, with 8 trials in adult AN patients (4 compared to placebo, 1 to chlorpromazine, 2 open label, and 1 retrospective study)[42–49] and 4 case reports involving adult patients.[50–53] The first 10-week, open-label trial examined the efficacy and safety of olanzapine 10 mg daily in 18 patients (2 male) with AN, with 10 patients gaining weight.[42] Again, 17 AN women received olanzapine 2.5–7.5 mg daily (mean 4.7) in an open-label fashion, and were evaluated at baseline and every 2 weeks. Twelve patients completed the 6-week study period, and showed significant improvements in weight, and in depression and anxiety signs and symptoms.[43] Another open-label study comparing olanzapine and chlorpromazine in the treatment of 15 AN patients showed no significant differences in the average weight gain between the 2 groups, although there was a statistically significant reduction in ruminative thinking in the olanzapine group vs the chlorpromazine group ($p < .01$).[44] The effect of olanzapine on behaviors associated with AN was evaluated in a retrospective study on 18 inpatients (mean age 22 years).[45] The average duration of treatment was 17 weeks (range 3–70). Improvements were observed in the frequency of obsessive thoughts about body image and anxiety before and during meals ($p < 0.001$), and in the ability or desire to eat ($p < 0.001$). Moreover, patients reported being "less upset about weight gain" ($p = 0.002$), "less upset in stressful situations" ($p < 0.01$), and "better able to fall asleep at night" ($p < 0.01$). In any case, all these trials suffer from several limitations, such as the open-label design, the brief duration, the small sample sizes, the low completion rates, and the presence of confounding factors, such as concomitant treatments (benzodiazepines [BDZs], SSRIs, and psychotherapies).

In the first study vs placebo, a survival analysis was conducted comparing treatment conditions in time to achievement of target BMI (18.5 kg/m^2).[46] Of the total sample, 55.6% of patients receiving placebo and 87.5% of patients receiving olanzapine achieved weight restoration (Mantel-Cox test: $\chi^2 = 5.42$, df = 1, $p = 0.02$). Psychological outcomes according to treatment condition were also investigated and indicated that olanzapine resulted in greater positive change in obsession scores than placebo ($\beta 11 = 4.20$; $t = 2.37$, df = 55, $p = 0.02$). No differences in compulsion scores were demonstrated ($\beta 11 = 0.60$; $t = 0.45$, df = 55, $p = 0.70$).[46] The second double-blind study was conducted on AN patients ≥ 16 years. Participants were free of other psychiatric medications for at least 4 weeks prior to study enrollment, with the exception of SSRIs or SNRIs that were permitted if doses had not changed for 4 weeks prior to study enrollment. Participants did not receive individual psychotherapies. A total of 23 patients was randomized either to olanzapine or placebo for 8 weeks. End-of-treatment BMI was significantly higher in the olanzapine group ($p < .018$). Psychological symptoms improved in both groups, but there were no statistically significant differences.[47]

In addition, 2 double-blind randomized studies have been published on psychobiological effects of olanzapine in AN patients.[48,49] In the first one, one-half of the AN patients (including both the AN-R and the AN-BP subtypes) received a combined treatment of CBT and double-blinded olanzapine, whereas the other half received CBT + placebo. Homovanillic acid (HVA) blood concentrations for dopamine secretion were monitored at baseline and then monthly during the trial. BMI increased significantly in both treatment groups, with no difference between the two. There were also no significant differences between the groups regarding the

https://doi.org/10.1017/S1092852914000790 Published online by Cambridge University Press

Eating Disorder Inventory-2 (EDI-2) scores. HVA plasma concentrations did not change in the CBT + placebo patients, whereas they increased significantly in the CBT + olanzapine group.[48] In the second study, 20 AN patients received CBT for 3 months and a programmed nutritional rehabilitation, combined with olanzapine vs placebo (2.5 mg for 1 month and 5 mg for 2 months). BMI, leptin, and ghrelin plasma values were monitored at baseline and then monthly for 3 months. BMI increased significantly, but not differently in both treatment groups. Leptin and ghrelin secretions did not change during the course of the treatments, with no correlations with BMI values.[49]

Controversial results came from 2 small open studies with quetiapine. In the first one, quetiapine was effective on both BMI restoration and on the "restraint subscale" of the Eating Disorder Examination (EDE).[54] Conversely, in the second study, no significant changes in BMI were found, and the drug was effective in reducing anxiety symptoms and depressive symptoms comorbid with AN.[55]

In a long-term study (from 4 months to 3 years), the add-on of aripiprazole to antidepressants provoked a significant reduction in eating-specific anxiety and obsessive thoughts about food, weight, and body image.[56]

Taken as a whole, findings on antipsychotics demonstrate that, except perhaps haloperidol and olanzapine, they produce no significant effect on the core symptoms of AN, such as dysmorphophobia. Moreover, BMI does not seem to be significantly influenced by atypical antipsychotics, while suggesting that the simple increase of appetite is not enough to improve the clinical picture.

Lithium

The rationale for using lithium in patients with AN resistant to treatment was questionable since its first proposal, and mainly related to the observations of its induction of weight gain. In 1977, Barcai[57] carried out a pilot report on lithium in adult AN. Two patients suffering from AN for many years "who wished to gain weight" were treated successfully with lithium. One patient gained 12 kg and the other 9 kg within 6 weeks. The weight gain was maintained for 1 year of follow-up with lithium. Subsequently, a placebo-controlled trial with lithium was carried out in 16 patients.[58] There were significant differences in weight gain at weeks 3 and 4 (difference: 3.9 kg), but the sample size was small and the follow-up duration was short. In a review of clinical trials with lithium, positive results were described in a group of disorders with underlying affective dysregulation, including premenstrual tension and AN.[59] However, the use of lithium is no longer recommended in AN, even for patients with severe and resistant forms. Sodium and fluid depletion may lead to reduced lithium clearance, resulting in an increased potential toxicity.

Other pharmacological treatments

Reports on other pharmacological treatments of AN were anecdotal. Oral clonidine was administered to a small sample (n = 4) of treatment-resistant patients, with negative results.[60] Goldberg *et al*[61] used cyproheptadine (CYP), in a randomized placebo-controlled trial with 4 arms (n = 81). No clinically significant effect on weight gain with CYP was found, even at 32 mg/day. As already described for studies on TCAs, cyproheptadine (32 mg/day) was compared to amitriptyline (160 mg/day) and placebo in a sample of 72 AN patients aged 13–36 years.[20] Cyproheptadine decreased the length of time to achieve the goal of weight gain.

Conclusion

Several studies have addressed the problematic issue of the psychopharmacological management of adult AN, but only a few have offered valid options alternative to psychotherapy.

The findings of our review identified shortcomings in study design, including treatment-specific biases arising from small sample sizes, differences in study protocol, research conducted in single centers, and clinical rather than statistical interpretation of results. These limitations derive from the difficulties in conducting research studies with the AN population, including diagnostic heterogeneity, ethical issues in clinically relevant treatment, and challenges in the organization of a mid-term/long-term follow-up. Taken as a whole, treatment responses are unsatisfactory, raising the question of whether treatment resistance is a condition worthy of further clinical or biological exploration. Moreover, the merits of randomized controlled trials in this specific field are debatable, considering that, despite an extraordinary expenditure of efforts, the majority of trials produced equivocal findings.

Of the small amount of evidence that has emerged from the present review is that antipsychotics, such as olanzapine or haloperidol, might be useful in treatment-resistant AN, but only when severe or delusional dysmorphic features are present.

We believe that, above all, the disappointing findings of treatment research highlight the need for a better understanding of AN psychopathological features. Randomized controlled trials failed because several individuals with AN rejected treatment, dropped out prematurely, and sustained few behavioral changes in the absence of external concurrent factors. These outcomes seemed to be linked to patients' attitudes about their symptoms, which often included the conviction that thinness and restraint are more important than recovery. The influence of such over-valued ideas might help to explain why this longstanding eating disorder has

https://doi.org/10.1017/S1092852914000790 Published online by Cambridge University Press

remained "impressively resistant to a wide range of interventions."[62] According to our proposal, the search for more effective forms of pharmacotherapy should begin with a closer examination of the factors that make AN specifically difficult to study and to treat. We believe that it would be helpful to refine more accurate definitions of AN phenotypes and their treatment resistance. It is unclear if a distinction can be made between such resistance and the natural history of the disease, at least in its current clinical manifestations with available treatments. As a consequence, a fundamental recommendation concerning the profoundly important clinical challenge of improving both short- andlong-term treatments of AN patients is to employ designs of therapeutic trials with instruments that are able to detect the complete range of clinical manifestations of this polymorphic condition. Future studies should offer interventions that are better matched to the well-studied features of this disorder.

Disclosures

The authors do not have anything to disclose.

REFERENCES:

1. Simon J, Schmidt U, Pilling S. The health service use and cost of eating disorders. *Psychol Med*. 2005; **35**(11): 1543–1551.
2. Hudson JI, Pope HG Jr. Genetic epidemiology of eating disorders and co-occurring conditions: the role of endophenotypes. *Int J Eat Disord*. 2007; **40**(Suppl): 76–78.
3. Hoek HW, Van Hoeken D. Review of the prevalence and incidence of eating disorders. *Int J Eat Disord*. 2003; **34**(4): 383–396.
4. Hoek HW. Incidence, prevalence and mortality of anorexia nervosa and other eating disorders. *Curr Opin Psychiatry*. 2006; **19**(4): 389–394.
5. Grucza RA, Przybeck TR, Cloninger CR. Prevalence and correlates of binge eating disorder in a community sample. *Compr Psychiatry*. 2007; **48**(2): 124–131.
6. Mitchinson D, Hay PJ. The epidemiology of eating disorders: genetic, environmental, and social factors. *Clin Epidemiol*. 2014; **17** (6): 89–97.
7. Machado PP, Machado BC, Gonçalves S, Hoek HW. The prevalence of eating disorders not otherwise specified. *Int J Eat Disord*. 2007; **40**(3): 212–217.
8. Castellini G, Lo Sauro C, Mannucci E, *et al*. Diagnostic crossover and outcome predictors in eating disorders according to DSM-IV and DSM-V proposed criteria: a 6-year follow-up study. *Psychosom Med*. 2011; **73**(3): 270–279.
9. Bulik CM, Sullivan PF, Fear J, Pickering A. Predictors of the development of bulimia nervosa in women with anorexia nervosa. *J Nerv Ment Dis*. 1997; **185**(11): 704–707.
10. Eckert ED, Halmi KA, Marchi P, Grove W, Crosby R. Ten-year follow-up of anorexia nervosa: clinical course and outcome. *Psychol Med*. 1995; **25**(1): 143–156.
11. Strober M, Freeman R, Morrell W. The long-term course of severe anorexia nervosa in adolescents: survival analysis of recovery, relapse, and outcome predictors over 10–15 years in a prospective study. *Int J Eat Disord*. 1997; **22**(4): 339–360.
12. Eddy KT, Dorer DJ, Franko DL, Tahilani K, Thompson-Brenner H, Herzog DB. Diagnostic crossover in anorexia nervosa and bulimia nervosa: implications for DSM-V. *Am J Psychiatry*. 2008; **165**(2): 245–250.
13. Hoek HW, van Hoeken D. Review of the prevalence and incidence of eating disorders. *Int J Eat Disord*. 2003; **34**(4): 383–396.
14. Eating disorders. Core interventions in the treatment and management of anorexia nervosa, bulimia nervosa and related eating disorders. National Clinical Practice Guideline Number CG9 developed by National Collaborating Centre for Mental Health commissioned by the National Institute for Clinical Excellence. London: The British Psychological Society & The Royal College of Psychiatrists; 2004.
15. Brambilla F, Tortorella A. Disturbi del comportamento alimentare. In: Marazziti D, ed. *Psicofarmacoterapia Clinica*. 5th ed. Rome: Giovanni Fioriti Editore; 2013: 183–191.
16. American Psychiatric Association. *Practice Guideline for the Treatment of Patients with Eating Disorders*. 3rd ed. Washington, DC: American Psychiatric Association; 2006.
17. Steinhausen HC. Treatment and outcome of adolescent anorexia nervosa. *Horm Res*. 1995; **43**(4): 168–170.
18. Smink FR, van Hoeken D, Hoeck HW. Epidemiology of Eating Disorders: Incidence, Prevalence and Mortality Rates. *Curr Psychiatry Rep*. 2012; **14**: 406–414.
19. Biederman J, Herzog DB, Rivinus TM, *et al*. Amitriptyline in the treatment of anorexia nervosa: a double-blind, placebo-controlled study. *J Clin Psychopharmacol*. 1985; **5**(1): 10–16.
20. Halmi KA, Eckert E, LaDu TJ, Cohen J. Anorexia nervosa: treatment efficacy of cyproheptadine and amitriptyline. *Arch Gen Psychiatry*. 1986; **43**(2): 177–181.
21. Lacey JH, Crisp AH. Hunger, food intake and weight: the impact of clomipramine on a refeeding anorexia nervosa population. *Postgrad Med J*. 1980; **56**(1): 79–85.
22. Crisp AH, Lacey JH, Crutchfield M. Clomipramine and 'drive' in people with anorexia nervosa: an in-patient study. *Br J Psychiatry*. 1987; **150**(3): 355–358.
23. Hollander E, Kim S, Braun A, Simeon D, Zohar J. Cross-cutting issues and future directions for the OCD spectrum. *Psychiatry Res*. 2009; **170**(1): 3–6.
24. Phillips KA, Friedman MJ, Stein DJ, Craske M. Special DSM-V issues on anxiety, obsessive-compulsive spectrum, post-traumatic, and dissociative disorders. *Depress Anxiety*. 2010; **27**(2): 91–92.
25. Ramacciotti CE, Coli E, Paoli R, Marazziti D, Dell'Osso L. Serotonergic activity measured by platelet [3H] paroxetine binding in patients with eating disorders. *Psychiatry Res*. 2003; **118**(1): 33–38.
26. Gwirtsman HE, Guze BH, Yager J, Gainsley B. Fluoxetine treatment of anorexia nervosa: an open clinical trial. *J Clin Psychiatry*. 1990; **51**(9): 378–382.
27. Attia E, Haiman C, Walsh BT, Flater SR. Does fluoxetine augment the inpatient treatment of anorexia nervosa? *Am J Psychiatry*. 1998; **155**(4): 548–551.
28. Barbarich NC, McConaha CW, Halmi KA, *et al*. Use of nutritional elements to increase the efficacy of fluoxetine in the treatment of anorexia nervosa. *Int J Eat Disord*. 2004; **35**(1): 10–15.
29. Kaye WH, Nagata T, Weltzin TE, *et al*. Double-blind placebo-controlled administration of fluoxetine in restricting- and restricting-purging-type anorexia nervosa. *Biol Psychiatry*. 2001; **49**(7): 644–652.
30. Walsh BT, Kaplan AS, Attia E, *et al*. Fluoxetine after weight restoration in anorexia nervosa: a randomized controlled trial. *JAMA*. 2006; **295**(22): 2605–2612.

https://doi.org/10.1017/S1092852914000790 Published online by Cambridge University Press

31. Fassino S, Leombruni P, Daga G, *et al*. Efficacy of citalopram in anorexia nervosa: a pilot study. *Eur Neuropsychopharmacol*. 2002; **12**(5): 453–459.
32. Safer DL, Darcy AM, Lock J. Use of mirtazapine in an adult with refractory anorexia nervosa and comorbid depression: a case report. *Int J Eat Disord*. 2010; **44**(2): 178–181.
33. Safer DL, Arnow KD. Suprathreshold duloxetine for treatment-resistant depression, anorexia nervosa binge-purging type, and obsessive-compulsive disorder: a case report. *Innov Clin Neurosci*. 2012; **9**(3): 13–16.
34. Vandereycken W. Neuroleptics in the short-term treatment of anorexia nervosa: a double-blind placebo-controlled study with sulpiride. *Br J Psychiatry*. 1984; **144**(3): 288–292.
35. Ramacciotti CE, Dell'Osso L, Paoli RA, *et al*. Characteristics of eating disorder patients without a drive for thinness. *Int J Eat Disord*. 2002; **32**(2): 206–212.
36. Frieling H, Römer KD, Scholz S, *et al*. Epigenetic dysregulation of dopaminergic genes in eating disorders. *Int J Eat Disord*. 2010; **43**(7): 577–583.
37. Cassano GB, Miniati M, Pini S, *et al*. Six-month open trial of haloperidol as an adjunctive treatment for anorexia nervosa: a preliminary report. *Int J Eat Disord*. 2003; **33**(2): 172–177.
38. 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): 329–332.
39. Dally A, Sargant W. Treatment and outcome of anorexia nervosa. *Br Med J*. 1966; **2**(5517): 793–795.
40. Ruggiero GM, Laini V, Mauri MC, *et al*. A single blind comparison of amisulpride, fluoxetine and clomipramine in the treatment of restricting anorectics. *Prog Neuropsychopharmacol Biol Psychiatry*. 2001; **25**(5): 1049–1059.
41. 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): 445–450.
42. Powers PS, Santana CA, Bannon YS. Olanzapine in the treatment of anorexia nervosa: an open label trial. *Int J Eat Disord*. 2002; **32**(2): 146–154.
43. Barbarich NC, McConaha CW, Gaskill J, *et al*. An open trial of olanzapine in anorexia nervosa. *J Clin Psychiatry*. 2004; **65**(11): 1480–1482.
44. 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): 72–75.
45. Malina A, Gaskill J, McConaha C, *et al*. Olanzapine treatment of anorexia nervosa: a retrospective study. *Int J Eat Disord*. 2003; **33** (2): 234–237.
46. 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. *Am J Psychiatry*. 2008; **165**(10): 1281–1288.
47. Attia E, Kaplan AS, Walsh BT, *et al*. Olanzapine versus placebo for outpatients with anorexia nervosa. *Psychol Med*. 2011; **41**(10): 2177–2182.
48. Brambilla F, Monteleone P, Maj M. Olanzapine-induced weight gain in anorexia nervosa: involvement of leptin and ghrelin secretion? *Psychoneuroendocrinology*. 2007; **32**(4): 402–406.
49. Brambilla F, Garcia CS, Fassino S, *et al*. Olanzapine therapy in anorexia nervosa: psychobiological effects. *Int Clin Psychopharmacol*. 2007; **22**(4): 197–204.
50. Hansen L. Olanzapine in the treatment of anorexia nervosa. *Br J Psychiatry*. 1999; **175**(6): 592.
51. Jensen VS, Mejlhede A. Anorexia nervosa: treatment with olanzapine. *Br J Psychiatry*. 2000; **177**(1): 87.
52. La Via MC, Gray N, Kaye WH. Case reports of olanzapine treatment of anorexia nervosa. *Int J Eat Disord*. 2000; **27**(3): 363–366.
53. Wang TS, Chou YH, Shiah IS. Combined treatment of olanzapine and mirtazapine in anorexia nervosa associated with major depression. *Prog Neuropsychopharmacol Biol Psychiatry*. 2006; **30**(2): 306–309.
54. Bosanac P, Kurlender S, Norman T. An open-label study of quetiapine in anorexia nervosa. *Hum Psychopharmacol*. 2007; **22**(4): 223–230.
55. 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): 21–26.
56. Trunko ME, Schwartz TA, Duvvuri V, Kaye WH. Aripiprazole in anorexia nervosa and low-weight bulimia nervosa: case reports. *Int J Eat Disord*. 2010; **44**(3): 269–275.
57. Barcai A. Lithium in adult anorexia nervosa: a pilot report on two patients. *Acta Psychiatr Scand*. 1977; **55**(Suppl 2): 97–101.
58. 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): 376–381.
59. Yung CY. A review of clinical trials of lithium in medicine. *Pharmacol Biochem Behav*. 1984; **21**(Suppl 1): 51–55.
60. Casper RC, Schlemmer RF Jr, Javaid JI. A placebo-controlled crossover study of oral clonidine in acute anorexia nervosa. *Psychiatry Res*. 1987; **20**(Suppl 3): 249–260.
61. Goldberg SC, Halmi KA, Eckert ED, Casper RC, Davis JM. Cyproheptadine in anorexia nervosa. *Br J Psychiatry*. 1979; **134** (1): 67–70.
62. Walsh BT. The future of research on eating disorders. *Appetite*. 2004; **42**(1): 5–10.
63. Schüle C, Sighart C, Hennig J, Laakmann G. Mirtazapine inhibits salivary cortisol concentrations in anorexia nervosa. *Prog Neuropsychopharmacol Biol Psychiatry*. 2006; **30**(6): 1015–1019.
64. Yasuhara D, Nakahara T, Harada T, Inui A. Olanzapine-induced hyperglycemia in anorexia nervosa. *Am J Psychiatry*. 2007; **164**(3): 528–529.
65. Court A, Mulder C, Kerr M, *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): 1027–1034.
66. Delsedime N, Nicotra B, Giovannone MC, *et al*. Psychotic symptoms in a woman with severe Anorexia Nervosa: psychotic symptoms in Anorexia Nervosa. *Eat Weight Disord*. 2013; **18**(1): 95–98.