The role of drug therapies in the treatment of anorexia and bulimia nervosa: a review of the literature

Il ruolo delle terapie farmacologiche nel trattamento dell'anoressia e della bulimia nervosa: una revisione della letteratura

A. Tortorella[1], M. Fabrazzo[1], A.M. Monteleone [1], L. Steardo [1], P. Monteleone[1 2]

[1] Department of Psychiatry, University of Naples - SUN, Naples, Italy; [2] Chair of Psychiatry, Department of Medicine and Surgery, University of Salerno, Italy

Summary

Background

The present review summarizes published papers reporting the results of both open-label and double-blind studies, which explored the potential efficacy of antidepressants, antipsychotics and mood stabilizers in the treatment of anorexia nervosa (AN) and bulimia nervosa (BN).

Methods

The literature was sourced from recent searches on Pubmed updated to January 2013 using the terms "eating disorders", "pharmacotherapy", "anorexia nervosa", "bulimia nervosa", "therapy" or "treatment". Studies were selected for inclusion if they met a level of evidence that minimized the risk of bias such as randomized controlled trials (RCTs) or systematic review of RCTs.

Results

This critical review seems to suggest that selective serotonin reuptake inhibitors (SSRI) have a proven efficacy in BN. Antipsychotics seem to be potentially promising options in the treatment of severe adult and adolescent AN patients, revealing positive psychopathological effects and good tolerability. Other treatments, such as the anticonvulsant topiramate in BN, may be promising.

Conclusion

Even if there have been useful researches on the efficacy of pharmacotherapy in the treatment of BN, there are still many unsolved issues regarding the optimal management of other EDs. Future directions for pharmacological treatment researches in EDs should include randomized controlled trials with different medications, inpatient versus outpatient trials and the assessment of medication effects for relapse prevention in recovered patients.

Key words

Pharmacologic treatment • Eating disorders • Anorexia nervosa • Bulimia nervosa • Binge eating disorder

Introduction

Eating disorders (EDs) are complex and multifactorial psychiatric diseases frequently occurring in female adolescents and young women that are characterized by severe disturbances in eating behaviour with acute, life threatening consequences [1]. According to the *Diagnostic and Statistical Manual of Mental Disorders - Text Revision* (DSM-IV-TR), EDs are divided into: anorexia nervosa (AN), bulimia nervosa (BN), and eating disorders not otherwise specified (ED-NOS), which include binge-eating disorder (BED).

AN is a severe disabling illness with one of the highest mortality rates among psychiatric disorders mainly due to undernutrition and suicide [2 3]. It is characterized by restricted eating, loss of weight, obsessive fears of weight gain, absence of menses and a disturbance in body image represented by the feeling of being fat even when underweight and a denial of the seriousness of emaciation [4-7]. The average prevalence of AN has been reported to be approximately 0.5% to 1% and is higher among adolescent girls and young women [8 9]. BN is characterized by binge-eating episodes, in which the individual consumes a large amount of food with a sense of loss of control, followed by compensatory behaviours to prevent weight gain such as purging, laxative abuse, excess physical exercise and fasting because of the pathological fear of weight gain [10-12]. The prevalence of BN is 1.5 % in young females and 0.5% in men [13]. BED is characterized by recurrent binge-eating episodes without compensatory behaviours that cause obesity [14-18]. The prevalence of BED ranges from 1% and 5% [9 13].

Correspondence
Alfonso Tortorella, Department of Psichiatry, Univesity of Naples - SUN, L.go Madonna delle Grazie, 80138 Naples, Italy • Tel. +39 081 5666516 • Fax +39 081 5666523 • E-mail: alfonsotortorella@gmail.com

The treatment of EDs is a complex process where nutritional counselling and psychotherapy are of primary importance, whereas psychotropic drugs play a secondary role. Recent data from animal and human research support the rationale for pharmacological treatment of EDs with drugs acting on serotonergic, dopaminergic and opioidergic systems [19 20]. New pharmacological approaches to EDs may arise from other biological markers involved in appetite modulation, such as ghrelin, leptin and cholecystokinin [21 22]. Nevertheless, at the moment, the main reason behind the use of drug therapy in patients with EDs remains the presence of a clear comorbid psychopathology and the similarity between some symptoms of EDs and the symptoms that usually respond to pharmacotherapy, such as affective, anxious and obsessive symptoms. Drug treatment is more effective on these "secondary" symptoms than on the basic features commonly considered typical of EDs such as fears of weight gain, disturbance in body image, binge-eating episodes with or without compensatory behaviours, etc. However, the approach of treating EDs with psychotropic drugs that are effective for phenomenologically similar conditions has proven to be simplistic, moreover, no drug or class of drugs has emerged as an effective agent to treat patients with these disorders [23-25].

Although developing effective treatments for these disorders is critical, the challenge for drug treatments in EDs patients should consider the restoration of body weight to a normal range, in order to resolve most of the physical and physiological complications, and the reduction of the distorted perception of body image and related consequences (mood and anxiety symptoms, obsessive-compulsive behaviours, aggressiveness). On the other hand, when using medications to treat comorbid conditions in people with EDs, particular attention should be given to dosage of drugs and physical monitoring. In particular, side effects of psychotropic medications should be carefully investigated, since these drugs may sometimes lead to development of adverse reactions or exacerbate the physical complications already present in EDs patients [26].

The present review summarizes published papers reporting the results of both open-label and double-blind studies that explored the potential efficacy of antidepressants, antipsychotics and mood stabilizers in the treatment of AN and BN. The literature was sourced from recent searches updated to January 2013 with a Pubmed search using the terms eating disorders, pharmacotherapy, anorexia nervosa, bulimia nervosa, therapy or treatment. Studies were selected for inclusion if they met a level of evidence that minimized risk of bias such as randomized controlled trials (RCTs) or systematic review of RCTs. We also included studies of case series or case reports or non-randomized trials where there were no RCTs of an agent or where they were of relevance in presaging RCTs.

Antidepressant drugs

Anorexia nervosa

Tricyclic antidepressants

The use of tricyclic antidepressants (TCAs) in the treatment of AN has been explored since the 1980s with varying results. A double-blind placebo controlled study [27] evaluated the efficacy of clomipramine in a group of 16 AN inpatients. Compared to placebo, clomipramine was significantly associated with increased hunger, appetite and energy intake, but there was a reduced rate of weight gain.

Biederman et al. [28] evaluated amitriptyline as a short-term treatment of AN patients. In a 5-week double-blind, placebo-controlled study, 11 patients received amitriptyline and 14 received placebo. Eighteen patients who refused to participate in the drug trial and received only psychosocial treatment were used as an additional comparison group. No statistically significant differences between placebo and amitriptyline were found in any outcome variables, and there was no evidence of improvement in either psychiatric symptomatology or body weight.

A placebo controlled double-blind study evaluated 72 AN patients randomly assigned to receive cyproheptadine (maximum daily dose 32 mg), amitriptyline (maximum daily dose 160 mg) or placebo. Cyproheptadine significantly increased treatment efficiency for the non-bulimic patients, and significantly impaired treatment efficiency for the bulimic patients compared with the amitriptyline- and placebo-treated groups [29].

Selective serotonin reuptake inhibitors

A small open trial with fluoxetine was conducted by Gwirtsman et al. [30] on 6 patients with chronic, refractory AN. Fluoxetine treatment was associated with weight gain and reduction of depressive symptoms. Kaye et al. [31] administered an open trial of fluoxetine to 31 AN patients. The authors judged response as good in 10, partial in 17 and poor in 4 anorexics as measured by improvements in eating behaviour, mood and obsessional symptoms. Restricting-type anorexics (AN-R) responded significantly better than bulimic and/or purging-type anorexics (AN-BP).

Brambilla et al. [32 33] published two papers on AN patients. In the first study, 22 female patients with AN-R, 14-35 years old, were treated with a 4-month course of combined cognitive-behavioural therapy, nutritional counselling and antidepressant drugs (nortriptyline, amineptine and fluoxetine). Body mass index (BMI), depression, anxiety and Eating Disorder Inventory (EDI) scores improved significantly and equally in both groups during the 4 months of therapy, while BITE scores did not change. In the second study, 13 women with AN-BP, 17-43 years

old, were treated and monitored in the same way with similar results.
A randomized, placebo-controlled, double-blind study was performed by Attia et al. [34]. Thirty-one AN women treated at an inpatient research unit with CBT were randomly assigned to fluoxetine (60 mg/day) or matching placebo for 7 weeks. No significant differences emerged in clinical outcome on any measure between the fluoxetine and placebo groups.
In a 24-month naturalistic, prospective longitudinal follow up study conducted in 33 AN patients treated with fluoxetine [35], there was no difference in probability at maintaining weight post discharge compared to a matched historic case-control sample. In a second study [36], the same research group investigated response to fluoxetine in adolescents hospitalized for treatment of AN. Patients received open label fluoxetine as add-on to their multidisciplinary treatment regimen for 6 weeks. Fluoxetine did not show any additive or synergistic therapeutic benefit compared with the effects of intensive, multidisciplinary inpatient therapy.
More recently, Yu et al. [37] published a randomized clinical trial with 122 participants treated with CBT, drug therapy (fluoxetine) or both (CBT + fluoxetine) for 12 months. The 52 participants who completed follow-up increased mean body weight. Using most stringent criteria for recovery, only 21% of the completers recovered.
Fluoxetine has been studied also as a maintenance treatment in AN patients after recovery from BW. A double-blind placebo-controlled trial with fluoxetine in 35 weight-recovered AN outpatients was carried out by Kaye et al. [38]. After 1 year, 10 out 16 (63%) subjects remained on fluoxetine, whereas only three out 19 (16%) remained on placebo. The subjects remaining on fluoxetine for one year had reduced relapse as shown by a significant increase in weight and reduction in symptoms.
Walsh et al. [39] performed a randomized, double-blind, placebo-controlled trial in 93 weight-recovered AN patients; 49 were assigned to fluoxetine (mean dose 63.5 mg/day) and 44 to placebo. The study failed to demonstrate any efficacy of fluoxetine in the treatment of AN patients following weight restoration.
The efficacy of the SSRI citalopram was evaluated in 32 AN-R patients, who were enrolled in a 6-month open trial with citalopram (20 mg/day) [40]. At the end of the trial, 46.9% of patients showed a satisfactory response, while 34.4% had an unsatisfactory response considering both clinically objective and subjective aspects.
Calandra et al. [41] investigated the efficacy and safety of 20 mg/day citalopram for 8 weeks in 18 ED patients (12 AN-R - 6 BN). The results showed that citalopram is effective and safe in the treatment of EDs, since patients showed a significant improvement in body dissatisfaction, but no effect on body weight.
An open trial was conducted by Fassino et al. [42] on 26 AN outpatients taking citalopram and 26 without medication. After 3 months of treatment, the citalopram group showed an improvement in depression, obsessive-compulsive symptoms, impulsiveness and trait-anger without any significant effect on BMI.
An open controlled trial with 22 AN-R patients compared 11 AN patients treated in an outpatient setting with sertraline to 11 AN patients evaluated as a control group. After 14-weeks, the sertraline group reported a significant effect on depressive symptoms, but not weight gain [43].

Other antidepressants

The efficacy of venlafaxine (75 mg/day) or fluoxetine (40 mg/day) plus CBT has been evaluated in 24 atypical AN patients. After 6 months of treatment, venlafaxine and fluoxetine were associated with an increase in BMI and a significant improvement in eating psychopathology, suggesting that venlafaxine is as effective as fluoxetine when combined with CBT in the treatment of atypical AN [44].
Case reports published in recent years also demonstrate the efficacy of new generation antidepressants such as duloxetine [45] and mirtazapine [46-50] in the treatment of acute AN patients. Double-blind controlled studies are needed to confirm the usefulness of these drugs in the acute phase of AN.

Bulimia nervosa

Tricyclic antidepressants

In 1986, Hughes et al. [51] published a double-blind, placebo-controlled trial of desipramine in 29 BN outpatients. Patients taking desipramine presented a significant benefit from treatment (91% decrease in binge frequency) in contrast with the results from the placebo group (19% increase in binge frequency). Subsequently, Barlow et al. [52] conducted a double-blind crossover trial with desipramine 150 mg/day. Forty-seven normal weight BN patients were randomly assigned to receive either desipramine for six weeks, no drug for three weeks, followed by placebo for six weeks, or the reverse sequence. The clinical effect was modest; desipramine was significantly more effective in reducing the frequency of weekly vomiting and binging.
Blouin conducted two different trials with desipramine. In the first study, desipramine and fenfluramine were administered to 22 normal weight BN patients in a 15-week, double-blind, placebo-controlled, crossover design trial. The results indicated that both drugs had beneficial effects on binge and vomit frequency, although a greater proportion of patients responded better to fenfluramine than to desipramine [53]. In the second study, 24 normal weight BN patients were assigned to a 15-week, rand-

omized double-blind crossover design in which they received either desipramine (150 mg/day) for six weeks, and no drug for three weeks, followed by placebo for six weeks or the reverse sequence. In terms of reduction in binge frequency, seven responders were identified; another seven were found to be borderline responders, while 10 were labelled as non-responders [54].

A group of 80 BN patients (aged 18-45 years) entered a 3-phase (8-week; 16-week; 4 month) treatment protocol to assess the efficacy of desipramine *vs*. placebo in the treatment of BN. In the 8-week initiation phase, desipramine was superior to placebo in reducing binge frequency and in other measures of behavioural and psychological disturbances characteristic of BN. There were not enough patients in the discontinuation phase to allow clear conclusions about the need to continue antidepressant medication after 6 months of treatment [55].

Agras et al. [56] performed a 16-24 week controlled trial in 71 BN outpatients randomly assigned to one of five groups: desipramine (withdrawn at 16 or 24 weeks), CBT (15 sessions), or combined treatment (18 sessions of CBT plus desipramine, withdrawn at 16 or 24 weeks). The results were analyzed as three groups (medication, cognitive-behavioural therapy and combined treatment). After 16 weeks and as five groups at subsequent assessment. At 16 weeks, both cognitive-behavioural therapy and combined treatment were superior to medication alone in reducing binge eating and purging. The combined treatment was superior to medication and more effective in reducing dietary preoccupation and hunger. Continuing CBT appeared to prevent relapse in patients withdrawn from medication after 16 weeks. The results demonstrated that CBT and combined therapy were superior to medication alone.

Recently, Walsh et al. [57] reviewed data from two previously published studies with desipramine in a total of 77 BN patients to evaluate whether an early response to medication predicted the efficacy of treatment at the end of a controlled trial. The authors concluded that BN patients who will not respond to antidepressant medication can be identified in the first 2 weeks of treatment.

Pope et al. [58] conducted a double-blind study of imipramine versus placebo in 22 bulimic women. Imipramine showed a significant reduction in the frequency of binge eating and the improvement on several other measures of eating behaviour. Agras et al. [59] performed a placebo-controlled double-blind trial with imipramine in 22 BN patients over a period of 16 weeks. Patients receiving the active drug demonstrated significantly greater reduction in purging at both the 6th and 16th weeks as well as a reduction in depressive symptomatology at week 6.

Mitchell et al. [60] in a 12 week comparison study of imipramine and structured group psychotherapy in BN outpatients showed that the addition of imipramine to group psychotherapy did not significantly improve outcome in terms of eating behaviour, but reduced symptoms of depression and anxiety.

Alger et al. [61] in an 8 week placebo-controlled study with imipramine (up to 150 mg/day), naltrexone (100-150 mg/day) and placebo in 33 obese bingers and 22 normoweight bulimics showed a significant reduction of binge duration with imipramine only in obese bingers.

Mitchell and Groat [62] conducted a placebo-controlled, double-blind study of amitriptyline (150 mg at bedtime) in a group of 32 BN outpatients showing a clear improvement in eating behaviour in both groups.

Selective serotonin reuptake inhibitors

Fichter et al. [63] randomly assigned 40 BN patients to either 60 mg fluoxetine or to a placebo control group in a double-blind trial lasting 35 days. Even in the presence of a significant reduction in body weight in the group treated with fluoxetine, especially during the first three weeks of treatment, there was no significant difference between the two groups in eating attitudes, eating behaviour and general psychopathology. The authors noted that these results were due to a "ceiling effect".

The Fluoxetine Bulimia Nervosa Collaborative Study Group in 1992 [64] published an 8-week, double-blind trial comparing fluoxetine (60 and 20 mg/day) with placebo in 387 BN outpatients. Fluoxetine 60 mg/day was superior to placebo in decreasing the frequency of weekly binge eating and vomiting episodes; depression, carbohydrate craving, and pathologic eating attitudes and behaviours also improved significantly. Fluoxetine at 20 mg/day produced an effect between that of the 60-mg/day dosage and that of placebo.

Goldbloom et al. [65] evaluated 382 BN patients in an 8 weeks multicentre, double-blind, randomized clinical trial of placebo and fluoxetine 20 and 60 mg/day. Patients receiving fluoxetine showed more clinically significant changes in the majority of psychological measures than those receiving placebo.

Beumont et al. [66] randomly assigned 67 BN patients treated with intensive nutritional counselling to either fluoxetine (60 mg/day) or placebo. Both groups of patients improved significantly during treatment, but the fluoxetine group did slightly better than placebo in eating-related psychopathology.

A large collaborative study published by Goldstein et al. [67] confirmed that fluoxetine is effective and safe in treating patients with BN. A total of 398 BN outpatients were randomly assigned to either a 60 mg fluoxetine group or to a placebo control group over 16 weeks, in a multicentre double-blind placebo-controlled study. Compared with placebo, fluoxetine treatment resulted in significantly greater reductions in vomiting and binge

TABLE I.
Summary of the main RCTs related to medications used in AN. *Sintesi dei principali RCT riferiti ai farmaci usati nell'AN.*

Medication	Daily doses	Effects	Authors
Antidepressant			
Amitriptyline	115 mg	= placebo	Biederman et al. (1985)
Clomipramine	50 mg	+ hunger, appetite	Lacey & Crisp (1980)
Fluoxetine	56 mg	= placebo	Attia et al. (1998)
Fluoxetine	20 mg	reduced relapse *vs*. placebo	Kaye et al. (2001)
Fluoxetine	60 mg	reduced relapse after weight gain *vs*. placebo	Yu et al. (2011)
Antipsychotic			
Pimozide	4-6 mg	= placebo	Vandereycken & Pierloot (1982)
Sulpiride	300-400 mg	= placebo	Vandereycken (1984)
Amisulpride	50 mg	+ weight gain *vs*. antidepressants	Ruggiero et al. (2001)
Olanzapine	5-20 mg	+ reduction in ruminations *vs*. 25-100 chlorpromazine	Mondraty et al. (2005)
Olanzapine	2.5-5 mg	+ weight gain and reduction psychological distress *vs*. placebo	Brambilla et al. (2007)
Olanzapine	2.5-10 mg	+ weight gain and reduction obsessive symptoms *vs*. placebo	Bissada et al. (2008)
Olanzapine	2.5-10 mg	+ weight gain *vs*. placebo	Attia et al. (2011)
Olanzapine	2.5-10 mg	= placebo	Kafantaris et al. (2011)
Quetiapine	177.7 mg	= placebo	Powers et al. (2012)
Risperidone	2.5 mg	= placebo	Hagman et al. (2011)

AN: anorexia nervosa; RCT: randomized controlled trial.

eating episodes per week as well as an improvement in other outcome measures. Goldstein et al. [68] made a retrospective analysis of two parallel, multicentre, double-blind, randomized, placebo-controlled fluoxetine clinical trials in order to determine whether the antibulimic effects of fluoxetine were related to its antidepressant effect. Treatment with fluoxetine (60 mg/day) significantly reduced the mean number of binge eating and vomiting episodes regardless of the presence or the absence of depression, and thus fluoxetine's efficacy in treating BN was not considered to be simply a secondary effect of its antidepressant properties.

The efficacy of fluoxetine in BN has also been evaluated in comparison to psychotherapies or in combination with psychotherapies. Walsh et al. [69] showed that patients receiving antidepressants (either fluoxetine or desipramine) in combination with psychological treatment experienced greater, although modest, improvement in binge eating and depression than patients receiving placebo and psychological treatment.

In a double-blind trial, Goldbloom et al. [70] randomly assigned 76 BN patients to either fluoxetine, CBT or fluoxetine + CBT combination. At the end of the trial, the combination of pharmacotherapy and psychotherapy was superior to pharmacotherapy alone, but there was no statistical evidence of an advantage of the combination over CBT alone. Similarly, Ricca et al. [71] assigned 51 BN outpatient either to CBT or combined Group Psychoeducation and fluoxetine treatment (GPF). The data obtained suggested that GPF is as effective as CBT in reducing bulimic symptomatology.

A double-blind, placebo-controlled trial evaluated 22 BN patients who had not responded to, or had relapsed following, a course of CBT or interpersonal psychotherapy. The authors randomly assigned BN patients to a placebo or fluoxetine group (60 mg/day) for 8 weeks. They found a decreased frequency of binge eating and purging in the group of patients treated with fluoxetine and concluded that fluoxetine may be a useful intervention for patients with BN who have not responded adequately to CBT treatment [72].

Two studies evaluated the efficacy of fluoxetine *vs*. self-help manual or guided self-help. Mitchell et al. in 2001 [73] found that fluoxetine and a self-help manual were equally effective in reducing the frequency of vomiting episodes and in improving response rates for vomiting and binging episodes. Walsh et al. [74], on the other hand, found that patients assigned to fluoxetine exhibited a greater reduction in binge eating and vomiting, and had a greater improvement in psychological symptoms than those assigned to placebo or guided self-help.

The long-term efficacy of fluoxetine in BN has been evaluated *vs*. placebo or CBT. Jacobi et al. [75] found that both CBT, fluoxetine and the combined treatments led to equally significant improvements in ED symptoms and in other psychological disturbances, which could be maintained at 1-year follow-up.
In the study of Romano et al. [76], 150 BN patients, responders to a single-blind 8-week treatment with fluoxetine or placebo, were followed for 52 weeks in order to compare the efficacy and safety of a treatment with fluoxetine (60 mg/day) versus placebo in preventing relapse. The fluoxetine group showed a time to relapse that was significantly longer compared to placebo, but at 1-year follow-up there were no significant differences between the two groups.
In the study of Fichter et al. [77], 72 BN patients treated successfully with psychotherapy were randomized in a double-blind, placebo-controlled study with fluvoxamine and placebo over a period of about 15 weeks. Fluvoxamine had a significant effect in delaying relapse of bulimic behaviour.
Schmidt et al. [78] conducted a randomized, double-blind, placebo-controlled trial with 267 BN patients divided into three groups: an 8 week short-term fluvoxamine therapy followed by 44 week placebo intake, a group receiving fluvoxamine over the entire 52 weeks and a placebo control group. There was no significant difference among the groups.
Milano et al. [79] performed a 12-week randomized placebo controlled trial with fluvoxamine (200 mg/day) in 12 female BN patients. Fluvoxamine determined a significant reduction in binge eating and purging episodes compared to placebo.
The efficacy of citalopram in BN has been evaluated in two studies. Sundblad et al. [80] randomized 46 BN patients to receive either the androgen receptor antagonist flutamide, the serotonin reuptake inhibitor citalopram, flutamide + citalopram, or placebo alone. Only the groups treated with flutamide showed a statistically significant reduction in binge eating. Leombruni et al. [81] compared fluoxetine with citalopram in the treatment of 37 BN patients. Patients treated with fluoxetine showed a greater reduction in interjected anger, whereas those in the citalopram group displayed a greater reduction in depressive feelings. The authors concluded that citalopram may be useful in depressed patients with BN, whereas fluoxetine is more specific for those with interjected anger and bulimia.
Two small trials [82 83] assessed the efficacy of sertraline in BN patients and found a significant reduction in the number of binges and purges per week.

Monoamine oxidase inhibitors

Walsh et al. [84-86] conducted 3 different double-blind placebo-controlled studies comparing the efficacy of the inhibitor of monoamino-oxidase A (IMAO-A) phenelzine and placebo. In all these studies, including a total of 100 BN patients, phenelzine was significantly superior to placebo in reducing binge frequency and several measures of psychopathological status. Patients did not experience severe side effects that could limit the use of phenelzine.
Rothschild et al. [87] examined the efficacy of phenelzine, imipramine and placebo in 24 BN patients with comorbid atypical depression. The improvement observed for both depressive and bulimic symptoms with phenelzine was greater than that with either imipramine or placebo.
Two double-blind, placebo-controlled studies showed that isocarboxazide [88] and brofaromine [89] significantly reduced binge eating and vomiting in BN patients.
A double-blind placebo-controlled trial was carried out to assess efficacy and tolerability of 600 mg/day of moclobemide in the treatment of 52 BN patients. Six weeks of treatment were not significantly superior to placebo in reducing the weekly number of binge eating episodes or in improving several measures of eating attitudes and behaviour [90].

Other antidepressants

Two open studies [91 92] have suggested the efficacy of reboxetine in reducing both binge eating frequency and eating-related psychopathology in BN.
The efficacy of bupropion was evaluated by Horne et al. [93] in 81 non-depressed BN patients randomly assigned to a double-blind study with bupropion (n = 55) and placebo (n = 26). Bupropion was significantly superior to placebo in reducing episodes of binge eating and purging behaviour, but four subjects experienced grand mal seizures during treatment with bupropion, a frequency far higher than that observed in previous studies with this drug.
Trazodone was shown to be significantly superior to placebo in reducing the frequency of episodes of binge eating and vomiting in a double-blind placebo-controlled study [94].
Sabine et al. [95] published an 8-week randomized, placebo–controlled, double-blind study with mianserin in 50 BN patients. Patients treated showed improvement over placebo for eating attitudes and behaviour as well as for anxiety and depression scores.

Antipsychotic drugs

Anorexia nervosa

First generation antipsychotics

Chlorpromazine (up to 1,000 mg/day) was the first typical antipsychotic drug assessed for the treatment of AN in a study by Dally and Sargant [96]. Subsequently, three controlled studies investigated the efficacy of pimozide (4 or 6 mg/day) [97 98] and sulpiride (300-400 mg/day) [99]. In general, no effects on weight or eating behaviour

were discernable. Ruggiero et al. [100] conducted a single-blind comparison to evaluate the efficacy of amisulpride, fluoxetine and clomipramine at the beginning of the re-feeding phase of the treatment of restricting AN patients. After three months of treatment, the amisulpride (mean dose 50 mg/day) and fluoxetine (mean dose 28 mg/day) groups showed a significant increase in weight from baseline to the end of trial, but no difference for weight phobia, body image and eating behaviour. Finally, Cassano et al. [101] reported an open trial with 13 outpatients affected by severe treatment-resistant ANR where haloperidol was effective when used as an adjunctive drug for more than six months.

Second generation antipsychotics

Olanzapine

Four randomized double-blind, placebo-controlled, studies of olanzapine in adult subjects affected by AN have been reported. Mondraty et al. [102], compared olanzapine with chlorpromazine in the treatment of intrusive cognitions in female AN patients. Olanzapine was started at 5 mg/day and then increased by 2.5-5 mg/day to a maximum dose of 20 mg/day (n = 8), while the dose of chlorpromazine was 25 mg at the beginning of the trial and increments of 25-50 mg/week up to a maximum dose of 2000 mg/day were allowed (n = 7). The Padua Inventory (PI) Scale was employed in order to quantify the distress and the level of rumination that subjects had about their anorexic cognition, and the authors concluded that the reduction in ruminative thinking, as shown by the PI subscale scores, was significantly greater in the olanzapine group than in the control group and that these changes were independent from weight gain or sedation, which did not differ significantly between the two groups.

Brambilla et al. [103] reported the effects of olanzapine therapy in patients affected by AN after three months of CBT. Thirty AN patients (18 restricted and 12 binge-purging) were randomly assigned to a double-blind, placebo-controlled trial with oral olanzapine (2.5 mg for 1 month, 5 mg for 2 months). BMI increased significantly in both treatment groups without any significant difference between the two treatments. When patients were divided according to the type of AN (AN-R and AN-BP), the increase in BMI was significantly greater in the CBT + olanzapine-treated AN-BP patients than in all the other participants. The results of the Eating Disorder Inventory-2 (EDI-2) revealed that there was no significant difference in the values of all items between CBT + olanzapine and CBT + placebo patients at each point of the treatments except for the ineffectiveness and maturity of fear items, which improved only in CBT + olanzapine-treated patients. No increase in bulimic symptomatology was observed in olanzapine + CBT treated AN-BP patients. The Yale Brown Cornell for Eating Disorders Rating Scale (YBC-EDS) for obsessiveness-compulsivity revealed significant improvement in total values and in the obsessiveness score (preoccupations) in both treatment groups, whereas only CBT + olanzapine-treated patients showed a significant improvement in compulsivity score (rituals). Significant improvement was found in total Buss-Durkee Hostility Inventory values in both treatment groups and in the subitem 'direct aggressiveness' only in CBT + olanzapine-treated patients. Depression improved significantly in both treatment groups, but the antidepressant effect was more significant in the CBT + olanzapine than in the CBT + placebo group. Taken together, these data show that the pharmacological treatment was significantly effective in improving specific aspects of AN suggesting that, in the future, pharmacotherapies must be targeted to well-known and carefully controlled brain biochemical impairments known to be responsible for specific psychopathological aspects.

A randomized, double-blind, placebo-controlled trial by Bissada et al. [104] investigated the use of olanzapine in the treatment of low-body weight and obsessive thinking of women with AN. The study was a 10-week flexible dose trial in which patients with AN (n = 34) were randomly assigned to either olanzapine plus day hospital treatment (n = 16) or placebo plus day hospital treatment (n = 18). Olanzapine was prescribed according to a flexible dose regimen, starting at the minimum dose of 2.5 mg/day and titrated slowly by increments of 2.5 mg/week to a maximum dose of 10 mg/day. Growth curves were used for the assessment of the differential rate or rapidity of increase in BMI across treatment conditions, and the results showed changes in the two trajectories indicating that all patients, both those receiving placebo and those receiving olanzapine, presented significant increases in BMI across the 13 weeks of the trial. However, patients receiving olanzapine showed a greater rate of increase in BMI across weeks compared to patients receiving placebo.

The efficacy of olanzapine was evaluated in AN outpatients by Attia et al. [105]. A total of 23 anorexic individuals were randomly assigned, according to a double-blind design, to receive olanzapine or placebo for 8 weeks together with medication management sessions that emphasized compliance. The end-of-treatment BMI, with initial BMI as a covariate, was significantly greater in the group receiving olanzapine. Psychological symptoms improved in both groups, but there were no statistically significant differences. Of the 23 participants, 17 (74%) completed the 8-week trial. Participants tolerated the medication well with sedation being the only frequent side effect, and adverse laboratory changes suggestive of metabolic abnormalities were not observed. This small study suggests that olanzapine is generally well tolerated by AN patients and may provide more benefits than placebo for outpatients with this type of ED.

The most recent studies conducted on adolescents include 3 different trials. Leggero et al. [106] performed a 6-month trial with 13 adolescent AN-R patients (age range 9.6-16.3 years). Patients were enrolled in multimodal treatment and evaluated at baseline and 1 and 6 months after starting low-dose olanzapine monotherapy (mean dose 4.13 mg/day). A significant improvement on weight, recovery and global functioning, hyperactivity, was evident at the end of the first month of treatment, and further increased in the following 5 months, with minimal side effects. The authors concluded that low-dose of olanzapine monotherapy may be useful as adjunctive treatment of young patients with AN-R. It is suggested that its efficacy may be mediated by a decrease of hyperactivity.

A placebo-controlled pilot study of adjunctive olanzapine for adolescents with AN has also been recently published by Kafantaris et al. [107]. In a 10-week, double-blind, placebo-controlled study the authors explored whether the addition of olanzapine versus placebo increased weight gain and improved psychological symptoms in 20 underweight female adolescents with AN-R type, who were participating in a comprehensive EDs treatment program. Fifteen out of 20 enrolled females (average age, 17.1 years; range, 12.3-21.8 years; mean BMI, 16.3) completed this 10-week pilot study. Change in average body weight did not differ between the treatment groups at midpoint or at the end of the study. Both groups gained weight at a similar rate and had similar improvements in eating attitudes and behaviours, psychological functioning and resting energy expenditure. A trend of increasing fasting glucose and insulin levels was found only in the olanzapine group at week 10. The conclusion of this study was that the findings do not support a role for adjunctive olanzapine in underweight adolescent females with AN-R types who were receiving standard care in ED treatment program.

Moreover, Norris et al. [108] recently completed a retrospective, matched-group comparison study in which they examined the assessment and treatment profiles of adolescents with AN who received olanzapine compared to untreated matched samples. Patients treated with olanzapine (the most common dose was 5 mg/day) displayed greater evidence of psychopathology and medical compromise at the time of first assessment compared to untreated patients. Moreover, the rate of weight gain was not statistically different between groups. Therefore, although this study provides some insight into the clinical parameters that might drive olanzapine prescription as an adjunctive treatment for adolescents with AN, the authors could not draw any firm conclusions about the potential efficacy of the antipsychotic because the patients treated with olanzapine presented a greater acuity and a more complex psychopathology than those not treated with olanzapine, which rendered comparisons on the efficacy of the drug difficult.

The effectiveness of olanzapine has been analyzed in several case reports. La Via et al. [109] treated with olanzapine in open trials 2 severe AN patients who had failed multiple other treatments. Olanzapine administration was associated with weight gain and maintenance as well as reduced agitation and resistance to treatment. Mehler et al. [110] published a case report of 5 children and adolescents with chronic AN treated with olanzapine, revealing that a variable dose of the drug (from 2.5 up to 10 mg/day) was efficacious in reducing weight phobia and body image disturbances without a significant weight increase induced by the drug. As a result, in the 5 cases reported, treatment with olanzapine demonstrated consistent improvement in severe chronic AN. A case report published by Boachie et al. [111] examined the therapeutic benefit and tolerability of olanzapine (2.5 mg/day) as adjunctive treatment in 4 children. Olanzapine use was associated with considerable weight gain and a clinically notable decrease in levels of agitation and premeal anxiety, and almost immediate improvement in sleep, general functioning and overall compliance with treatment.

Two small open-label trials with olanzapine have been published. The first by Powers et al. [112] is an open-label 10-week study of olanzapine 10 mg/day in 18 AN outpatients. All 14 patients who completed the study showed a clinically-significant increase in body weight. In the second trial, published by Barbarich et al. [113], 17 AN patients were enrolled in open-label treatment with olanzapine for 6 weeks. Olanzapine administration was associated with a significant reduction in depression, anxiety, eating symptoms and a significant increase in weight. An open-label retrospective study in 18 AN patients by Malina et al. [114] reported a significant reduction in frequency of obsessive thoughts about body image and fear of being fat, reduced anxiety before and during meals and an increased ability or desire to eat meals. In addition, subjects reported being less upset if they gained weight.

Taken together, the data from studies on olanzapine in adults, but not in adolescent anorexic patients, although with a number of different limitations, show that this pharmacological treatment can be significantly effective in improving specific aspects of AN, but not all symptoms. Olanzapine, with its side effect profile of weight gain and antiobsessive and antidepressant properties, is a promising drug to study for the treatment of severely emaciated and obsessional AN patients. Therefore, further studies are warranted to confirm these findings.

Quetiapine

An open, controlled 8-week trial with 8 AN patients conducted by Bosanac et al. [115] revealed a significant effectiveness of quetiapine (doses ranged from 50 mg to 800 mg per day, according to efficacy and tolerability).

TABLE II.
Summary of the main RCT related to medications used in BN. *Sintesi dei principali RCT riferiti ai farmaci usati nella BN.*

Medication	Daily doses	Effects	Authors
TCAs			
Imipramine	200 mg	Bulimic symptom reduction *vs*. Placebo	Pope et al. (1983)
Imipramine	300 mg	Outcome = placebo	Mitchell et al. (1990)
Desipramine	200 mg	Reduction on bingeing and vomiting *vs*. Placebo	Hughes et al. (1986)
Desipramine	desi 150 mg; fen 60 mg	Beneficial effects on bingeing and vomiting *vs*. Placebo	Blouin et al. (1988)
Desipramine	150 mg	Significant reduction on bingeing and vomiting *vs*. Placebo	Blouin et al. (1989)
Desipramine	300 mg	Beneficial effect in binge frequency *vs*. Placebo	Walsh et al. (1991)
Desipramine	300 mg	Cbt and combined therapy superior to medication alone	Agras et al. (1992)
MAOIs			
Phenelzine	60-90 mg	Bulimic symptom reduction *vs*. placebo	Walsh et al. (1984)
Phenelzine	90 mg	Bulimic symptom reduction *vs*. placebo	Walsh et al. (1985)
Phenelzine	90 mg	Bulimic symptom reduction *vs*. placebo	Walsh et al. (1988)
Isocarboxacid	60 mg	Bulimic symptom reduction *vs*. placebo	Kennedy et al. (1988)
Brofaromine	175-200 mg	Bulimic symptom reduction *vs*. placebo	Kennedy et al. (1993)
Moclobemide	600 mg	Bulimic symptom reduction *vs*. placebo	Carruba et al. (2001).
SSRI			
Fluoxetine	60 mg	= Placebo	Fichter et al. (1991)
Fluoxetine	20-60 mg	Bulimic symptom reduction *vs*. Placebo	(FBNCSG, 1992)
Fluoxetine	20-60 mg	Bulimic symptom reduction *vs*. Placebo	Goldbloom et al. (1993)
Fluoxetine	60 mg	Beneficial effects on bulimia symptom *vs*. Placebo	Beumont et al. (1997)
Fluoxetine	60 mg	Bulimic symptom reduction *vs*. Placebo	Goldstein et al. (1995)
Fluoxetine	flu 60 mg; desi 300 mg	Significant reduction on bingeing and depression *vs*. Placebo	Walsh et al. (1997)
Fluoxetine	60 mg	Beneficial effects on bulimic symptom *vs*. Placebo	Goldbloom et al. (1997)
Fluoxetine	60 mg	Beneficial effects on bulimic symptom in pz non responded psychotherapy	Walsh et al. (2000)
Fluoxetine	60 mg	Beneficial effects on bulimic symptom *vs*. Placebo	Mitchell et al. (2001)
Fluoxetine	60 mg	Beneficial effects on bulimic symptom *vs*. Placebo	Walsh et al. (2004)
Fluoxetine	flu 20 mg; cit 20 mg	No diferences in outcome *vs*. Citalopram	Leombruni et al. (2006)
Fluvoxamine	300 mg	Significant effect in reducing the return of bulimic behavior *vs*. Placebo	Fichter et al. (1996)
Fluvoxamine	300 mg	No significant difference between the groups	Schmidt et al. (2004)
Fluvoxamine	200 mg	Significant reduction on bingeing *vs*. Placebo	Milano et al. (2005)
Citalopram	cit 40 mg; flut 500 mg	No significant difference *vs*. Placebo	Sundblad et al. (2005)
Sertraline	100 mg	Significant reduction on bingeing *vs*. Placebo	Milano et al. (2004)
Other			
Mianserin	30-60 mg	Bulimic symptom reduction *vs*. Placebo	Sabine et al. (1983)
Trazodone	355-400 mg	Bulimic symptom reduction *vs*. Placebo	Pope et al., (1989)
Bupropion	450 mg	Reduced bulimic symptoms with high seizure rates	Horne et al. (1988)
Topiramate	25-400 mg	Reduced bulimic symptoms + weight loss *vs*. Placebo	Hoopes et al. (2003)

BN: bulimia nervosa; CBT: Cognitive Behavior Therapy; MAOIs: monoamine oxidase inhibitors; RCT: randomized controlled trial; SSRIs: selective serotonin re-uptake inhibitors; TCAs: tricyclic antidepressants.

All participants treated with quetiapine adjunct to specialist multidisciplinary treatment over the course of 4 and 8 weeks had a clinically significant improvement of anorexic symptoms, especially restrictive behaviour as shown by the Eating Disorder Examination-12th Edition, (EDE-12), whereas obsessive-compulsive and depressive symptoms as assessed by Yale-Brown Obsessive-Compulsive Scale (YBOCS) and Montgomery-Åsberg Depression Rating Scale (MADRS) as well as anorexic delusional beliefs about weight, eating and shape (as assessed by the delusion subscale of the Scale for the Assessment of Positive Symptoms (SAPS) after 4 weeks showed only a trend towards improvement. After 4 weeks of treatment, there was a significant difference in the restraint score of the EDE-12, but no change in BMI, while at the end of the 8-week study, significant differences both in BMI and in EDE-12 restraint score were reported. Quetiapine was safe and generally well tolerated in this group, except for initial mild sedation, and no subjects experienced any significant adverse events.

In an open, controlled 10 week trial quetiapine was administered to 19 AN subjects (5 patients dropped out and two discontinued the drug mainly in relation to lack of efficacy or fear of appetite increase) revealed that lower dosages of quetiapine (150-300 mg/day) might be sufficient in the treatment of AN, although individual cases needed higher doses up to 500 mg/day or even greater. Quetiapine was well tolerated and patients had significant improvements in several subscales of the Positive And Negative Syndrome Scale (PANSS) as well as decreases in measures of anxiety and depression [116].

Moreover, in three cases recently reviewed by Mehler-Wex et al. [117], quetiapine was used after insufficient response to conventional approaches and slowly titrated to 200 mg/day within 2 weeks. Psychopathological improvement was observed after 2-3 weeks, thus making the introduction of behavioural and cognitive therapeutic approaches possible. The normalization of BMI in these patients was not an indirect effect of quetiapine, and no side effects were observed. The authors concluded that quetiapine could be a potentially promising option in the treatment of severe AN even in children and adolescents, revealing positive psychopathological effects and good tolerability, although the authors recommended careful titration and intense drug monitoring.

In addition, Court et al. [118] conducted a randomized, controlled, open-label 12 week trial in which a group of 15 AN patients (14 females and 1 male, mean age of 23.8 ± 9.4) was treated with conventional therapy along with quetiapine (100-400 mg/day) and compared to another group of 18 AN patients (all females, mean age 21.0 ± 3.3) treated only with usual therapy. Both groups showed a modest weight gain over the 12-week trial period, with the mean weight gain in the quetiapine group being 5.0 kg (SD 3.5) and 4.5 kg (SD 4.0) in the control group. In addition, both groups showed an improvement in their EDI-2 outcome scores at the 12-week assessment, with the quetiapine group demonstrating a much greater improvement on most of the subscales. Importantly, these improvements were maintained at weeks 26 and 52 in the quetiapine group, but despite the numerical size of these improvements, they did not reach statistical significance, although this is not surprising in a small-scale pilot study.

Powers et al. [119] recently completed a double-blind placebo-controlled trial of quetiapine in AN. After 6 weeks there was no difference in outcome for any of the measures between the group of participants who received quetiapine and the group who received placebo.

Risperidone

Two case reports published respectively by Fisman et al. [120] and Newman-Toker et al. [121] raise the possibility that low-dose risperidone (0.5-1.5 mg daily dose) can be used in individual cases of AN. Higher doses were presumably avoided considering potential extrapyramidal motor side effects and unknown disposition of cachexic patients to long-term side effects such as tardive dyskinesia. Both case reports observed positive effects of risperidone on weight restoration and comorbid or eating-related psychopathology.

More recently, Hagman et al. [122], conducted a double-blind, placebo-controlled, 9 week trial in a group of 40 adolescent AN patients (12 to 21 years) randomly assigned to risperidone (max 4 mg/day) or placebo. Patients treated with risperidone showed a significant decrease in the EDI-2 drive for thinness and interpersonal distrust subscale; there were no significant differences between groups at baseline or at the end of the study for the other rating scales, change in weight, or laboratory measurements. The authors concluded that the study does not demonstrate a benefit for treatment with risperidone in adolescent AN patients.

Aripiprazole

A case report published by Aragona [123] reported the tolerability and efficacy of aripiprazole in a chronic psychotic AN patient in comorbidity with epilepsy and chronic renal failure, already treated with low-dose risperidone without efficacy. The patient had also refused to take olanzapine (fear of weight gain), but accepted a treatment with aripiprazole. This antipsychotic, at a dose of 30 mg/day, was associated with a considerable improvement of the scale for the assessment of negative and positive symptoms (SANS) and SAPS scores on hallucinations, delusions, aggressivity, abulia and asociality. Weight remained stable and no side effects were reported.

More recently, Trunko et al. [124] conducted an open trial with 8 patients (five with AN and three with BN). Patients were treated for periods ranging from 4 months to more than 3 years and the drug, used at doses ranging from 5 to 30 mg/day, was well tolerated by all patients. A notable reduction in eating-specific anxiety and obsessive thoughts about food, weight and body image was reported along with a degree of change in the underlying traits of rigidity and harm avoidance that may be significant, since such traits often remain after recovery. Three of the AN patients gained weight to normal range BMIs, and two others reached partially restored weight: all reported better tolerance to weight gain than they had experienced with other medications, thus revealing a better compliance. Moreover, the authors noted that since all patients were taking other medications, it was unclear whether the response was due to aripiprazole alone or to combined treatment. Similar results were observed in this study in 3 BN patients treated with the atypical antipsychotic in combination with different antidepressants (venlafaxine and trazodone in one, escitalopram in the other two BN patients).

Mood stabilizers

Anorexia nervosa

Lithium

The effect of lithium in AN was evaluated by Gross et al. [125] in a 4-week, double-blind, parallel group study, in 16 AN patients. The small sample size and the short duration of the study does not allow for reliable assessment except for weight gain. The results showed greater weight gain in the lithium group at weeks 3 and 4 of treatment.

Bulimia nervosa

Topiramate

Topiramate is an innovative anticonvulsant recently tested in different neurological (migraine, neuropathic pain, and essential tremor) and psychiatric conditions (bipolar disorder, post-traumatic stress disorder, schizoaffective disorder, BN and obesity).
Sixty-nine BN outpatients were randomly assigned to receive topiramate (median dose 100 mg/day) or placebo for 10 weeks in a randomized, double-blind, placebo-controlled trial published by Hoopes et al. [126]. Treatment with topiramate significantly decreased the mean weekly number of binge and/or purge days, the mean weekly number of binge days and the mean binge frequency. Three patients discontinued from the trial due to adverse events. In this study, topiramate was associated with significant improvements in both binge and purge symptoms and represents a potential treatment for BN.
Further analyses investigating the effect of topiramate on psychological symptoms associated with disordered eating were made by Hedges et al. [127] who analyzed the same cohort of BN patients evaluated in the previous trial. The authors reported that topiramate treatment improved multiple behavioural dimensions of BN characterized by the reduction of binge and purge behaviours, improvements in self-esteem, eating attitudes, anxiety and body image.
Nickel et al. [128] conducted a 10-week, double-blind placebo-controlled trial in BN patients randomly assigned to receive topiramate or placebo. Compared to placebo, the group treated with topiramate showed a significant reduction in frequency of binge/purging, weight and improvement in the quality of life. In some cases sedation, dizziness, headache and para-esthesia were reported, but there were no serious side effects.

Carbamazepine

The efficacy of carbamazepine was evaluated by Kaplan et al. [129] in a double-blind crossover trial with carbamazepine in 6 BN patients. One of these patients, showing a clear comorbidity with bipolar disorder, improved "dramatically" while the remaining five had no response.

Oxcarbamazepine

Two cases of BN patients with other psychiatric comorbidities and self-mutilating behaviour treated with oxcarbazepine were reported by Cordàs et al. [130]. Self-mutilating behaviour disappeared with the treatment, but not vomiting.

Lithium

Hsu et al. [131] conducted a double blind placebo controlled trial in 91 female BN outpatients randomly assigned to receive lithium carbonate or placebo. After 8 weeks, 68 patients completed the study. The treatment with lithium decreased bulimic episodes, but it was not more effective than placebo. However, depression and other psychopathologies decreased with improvement in bulimic behaviour.

Conclusions

The scientific literature is particularly lacking in the area of drug treatment of EDs because pharmacological trials for the treatment of these disorders are highly variable with large differences between results in AN and BN patients. The presence of a common neurobiological basis (serotonin dysfunction), psychopathological features (depressive and obsessional psychopathology) and high rates of lifetime comorbidity with depression and obsessive-compulsive symptomatology have suggested a role for antidepressant treatment in both AN and BN.

Antidepressant treatment does not seem to be helpful in increasing weight in AN patients, but may be useful in improving depressive and obsessive-compulsive symptomatology in long-term treatment. This topic is still debated in the literature as several authors have reported that antidepressants do not seem to significantly impact depressive symptomatology in this population.
For this reason, it is desirable that in AN patients antidepressants are used only with anxious, depressive or with obsessive compulsive comorbidity, and, in general, managing patients with AN using medications alone is not appropriate.
Typical antipsychotics have not proven helpful despite the weight gain side effects and the presence of ideas and beliefs that are often of almost delusional intensity and severity. A few randomized placebo-controlled studies appear to suggest that atypical agents such as quetiapine and olanzapine may be helpful in the treatment of psychopathological features of AN, such as depression, anxiety, obsessiveness and aggressiveness.
Despite the large number of publications in recent years, there are several points that still need to be clarified. For example: a) a clear pharmacological strategy is not defined yet; b) there is a lack of a substantial documentation in long-term efficacy of different drugs; c) almost all randomized controlled trials have a small number of patients because of the high drop-out rate.

References

1 Walsh BT. *The importance of eating behavior in eating disorders*. Physiol Behav 2011;104:525-9.

2 Birmingham CL, Su J, Hlynsky JA, et al. *The mortality rate from anorexia nervosa*. Int J Eat Disord 2005;38:143-6.

3 Millar HR, Wardell F, Vyvyan JP, et al. *Anorexia nervosa mortality in Northeast Scotland, 1965-1999*. Am J Psychiatry 2005;162:753-7.

4 Halmi KA, Tozzi F, Thornton LM, et al. *The relation among perfectionism, obsessive-compulsive personality disorder and obsessive-compulsive disorder in individuals with eating disorders*. Int J Eat Disord 2005;38:371-4.

5 Berkman ND, Lohr KN, Bulik CM. *Outcomes of eating disorders: a systematic review of the literature*. Int J Eat Disord 2007;40:293-309.

6 Halmi KA. *Anorexia nervosa: an increasing problem in children and adolescents*. Dialogues Clin Neurosci 2009;11:100-3.

7 Zanetti T, Santonastaso P, Sgaravatti E, et al. *Clinical and temperamental correlates of body image disturbance in eating disorders*. Eur Eat Disord Rev 2013;21:32-7.

8 Hoek HW, van Hoeken D. *Review of the prevalence and incidence of eating disorders*. Int J Eat Disord 2003;34:383-96.

9 Hoek HW. *Incidence, prevalence and mortality of anorexia nervosa and other eating disorders*. Curr Opin Psychiatry 2006;19:389-94.

10 Russell G. *Bulimia nervosa: an ominous variant of anorexia nervosa*. Psychol Med 1979;9:429-48.

11 Steinhausen HC, Weber S. *The outcome of bulimia nervosa: findings from one-quarter century of research*. Am J Psychiatry 2009;166:1331-41.

12 Mehler PS. *Medical complications of bulimia nervosa and their treatments*. Int J Eat Disord 2011;44:95-104.

13 Hudson JI, Hiripi E, Pope HG Jr, et al. *The prevalence and correlates of eating disorders in the National Comorbidity Survey Replication*. Biol Psychiatry 2007;61:348-58.

14 de Zwaan M. *Binge eating disorder and obesity*. Int J Obes Relat Metab Disord 2001;25(Suppl.1):S51-5.

15 Cooper Z, Fairburn CG. *Refining the definition of binge eating disorder and nonpurging bulimia nervosa*. Int J Eat Disord 2003;34(Suppl.):S89-95.

16 Mathes WF, Brownley KA, Mo X, et al. *The biology of binge eating*. Appetite 2009;52:545-53.

17 Wonderlich SA, Gordon KH, Mitchell JE, et al. *The validity and clinical utility of binge eating disorder*. Int J Eat Disord 2009;42:687-705.

18 Gearhardt AN, White MA, Potenza MN. *Binge eating disorder and food addiction*. Curr Drug Abuse Rev 2011;4:201-7.

19 Monteleone P, Castaldo E, Maj M. *Neuroendocrine dysregulation of food intake in eating disorders*. Regul Pept 2008;149:39-50.

20 Monteleone P. *New frontiers in endocrinology of eating disorders*. Curr Top Behav Neurosci 2011;6:189-208.

21 Monteleone P, Brambilla F. *Therapeutic approach to eating disorders: the biological background*. World Psychiatry 2009;8:163-4.

22 Treasure J, Claudino AM, Zucker N. *Eating disorders*. Lancet 2010;375:583-93.

23 Kaye WH, Strober M, Stein D, et al. *New directions in treatment research of anorexia and bulimia nervosa*. Biol Psychiatry 1999;45:1285-92.

24 Golden NH, Attia E. *Psychopharmacology of eating disorders in children and adolescents*. Pediatr Clin North Am 2011;58:121-38.

25 Aigner M, Treasure J, Kaye W, et al. *WFSBP Task Force On Eating Disorders. World Federation of Societies of Biological Psychiatry (WFSBP) guidelines for the pharmacological treatment of eating disorders*. World J Biol Psychiatry 2011;12:400-43.

26 Reinblatt SP, Redgrave GW, Guarda AS. *Medication management of pediatric eating disorders*. Int Rev Psychiatry 2008;20:183-8.

27 Lacey JH, Crisp AH. *Hunger, food intake and weight: the impact of clomipramine on a refeeding anorexia nervosa population*. Postgrad Med J 1980;56(Suppl.1):79-85.

28 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;5:10-6.

29 Halmi KA, Eckert E, LaDu TJ, et al. *Anorexia nervosa. Treat-*

ment efficacy of cyproheptadine and amitriptyline. Arch Gen Psychiatry 1986;43:177-81.

30 Gwirtsman HE, Guze BH, Yager J, et al. *Fluoxetine treatment of anorexia nervosa: an open clinical trial*. J Clin Psychiatry 1990;51:378-82.

31 Kaye WH, Weltzin TE, Hsu LK, et al. *An open trial of fluoxetine in patients with anorexia nervosa*. J Clin Psychiatry 1991;52:464-71.

32 Brambilla F, Draisci A, Peirone A, et al. *Combined cognitive-behavioral, psychopharmacological and nutritional therapy in eating disorders. 1. Anorexia nervosa-restricted type*. Neuropsychobiology 1995;32:59-63.

33 Brambilla F, Draisci A, Peirone A, et al. *Combined cognitive-behavioral, psychopharmacological and nutritional therapy in eating disorders. 2. Anorexia nervosa-binge-eating/purging type*. Neuropsychobiology 1995;32:64-7.

34 Attia E, Haiman C, Walsh BT, et al. *Does fluoxetine augment the inpatient treatment of anorexia nervosa?* Am J Psychiatry 1998;155:548-51.

35 Strober M, Freeman R, DeAntonio M, et al. *Does adjunctive fluoxetine influence the post-hospital course of restrictor-type anorexia nervosa? A 24-month prospective, longitudinal followup and comparison with historical controls*. Psychopharmacol Bull 1997;33:425-31.

36 Strober M, Pataki C, Freeman R, et al. *No effect of adjunctive fluoxetine on eating behavior or weight phobia during the inpatient treatment of anorexia nervosa: an historical case-control study*. J Child Adolesc Psychopharmacol 1999;9:195-201.

37 Yu J, Stewart Agras W, Halmi KA, et al. *A 1-year follow-up of a multi-center treatment trial of adults with anorexia nervosa*. Eat Weight Disord 2011;16:177-81.

38 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;49:644-52.

39 Walsh BT, Kaplan AS, Attia E, et al. *Fluoxetine after weight restoration in anorexia nervosa: a randomized controlled trial*. JAMA 2006;295:2605-12.

40 Pallanti S, Quercioli L, Ramacciotti A. *Citalopram in anorexia nervosa*. Eat Weight Disord 1997;2:216-21.

41 Calandra C, Gulino V, Inserra L, et al. *The use of citalopram in an integrated approach to the treatment of eating disorders: an open study*. Eat Weight Disord 1999;4:207-10.

42 Fassino S, Leombruni P, Abate Daga G, et al. *Efficacy of citalopram in anorexia nervosa: a pilot study*. Eur Neuropsychopharmacol 2002;12:453-9.

43 Santonastaso P, Friederici S, Favaro A. *Sertraline in the treatment of restricting anorexia nervosa: an open controlled trial*. J Child Adolesc Psychopharmacol 2001;11:143-50.

44 Ricca V, Mannucci E, Paionni A, et al. *Venlafaxine versus fluoxetine in the treatment of atypical anorectic outpatients: a preliminary study*. Eat Weight Disord 1999;4:10-4.

45 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;9:13-6.

46 Wang TS, Chou YH, Shiah IS. *Combined treatment of olanzapine and mirtazapine in anorexia nervosa associated with major depression*. Prog Neuropsychopharmacol Biol Psychiatry 2006;30:306-9.

47 Fountoulakis KN, Iacovides A, Siamouli M, et al. *Successful treatment of anorexia with a combination of high-dose olanzapine, fluoxetine and mirtazapine*. Int J Clin Pharmacol Ther 2006;44:452-3.

48 Jaafar NR, Daud TI, Rahman FN, et al. *Mirtazapine for anorexia nervosa with depression*. Aust N Z J Psychiatry 2007;41:768-9.

49 Hrdlicka M, Beranova I, Zamecnikova R, et al. *Mirtazapine in the treatment of adolescent anorexia nervosa. Case-control study*. Eur Child Adolesc Psychiatry 2008;17:187-9.

50 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 2011;44:178-81.

51 Hughes PL, Wells LA, Cunningham CJ, et al. *Treating bulimia with desipramine. A double-blind, placebo-controlled study*. Arch Gen Psychiatry 1986;43:182-6.

52 Barlow J, Blouin J, Blouin A, et al. *Treatment of bulimia with desipramine: a double-blind crossover study*. Can J Psychiatry 1988;33:129-33.

53 Blouin AG, Blouin JH, Perez EL, et al. *Treatment of bulimia with fenfluramine and desipramine*. J Clin Psychopharmacol 1988;8:261-9.

54 Blouin J, Blouin A, Perez E, et al. *Bulimia: independence of antibulimic and antidepressant properties of desipramine*. Can J Psychiatry 1989;34:24-9.

55 Walsh BT, Hadigan CM, Devlin MJ, et al. *Long-term outcome of antidepressant treatment for bulimia nervosa*. Am J Psychiatry 1991;148:1206-12.

56 Agras WS, Rossiter EM, Arnow B, et al. *Pharmacologic and cognitive-behavioral treatment for bulimia nervosa: a controlled comparison*. Am J Psychiatry 1992;149:82-7.

57 Walsh BT, Sysko R, Parides MK. *Early response to desipramine among women with bulimia nervosa*. Int J Eat Disord 2006;39:72-5.

58 Pope HG Jr, Hudson JI, Jonas JM, et al. *Bulimia treated with imipramine: a placebo-controlled, double-blind study*. Am J Psychiatry 1983;140:554-8.

59 Agras WS, Dorian B, Kirkley BG, et al. *Imipramine in the treatment of bulimia: a double-blind controlled study*. Int J Eat Dis 1987;6:29-38.

60 Mitchell JE, Pyle RL, Eckert ED, et al. *A comparison study of antidepressants and structured intensive group psychotherapy in the treatment of bulimia nervosa*. Arch Gen Psychiatry 1990;47:149-57.

61 Alger SA, Schwalberg MD, Bigaoueite JM, et al. *Effect of a tricyclic antidepressant and opiate antagonist on binge-eating behavior in normoweight bulimic and obese, binge-eating subjects*. Am J Clin Nutr 1991;53:865-71.

62 Mitchell JE, Groat R. *A placebo-controlled, double-blind trial of amitriptyline in bulimia*. J Clin Psychopharmacol 1984;4:186-93.

63 Fichter MM, Leibl K, Rief W, et al. *Fluoxetine versus placebo: a double-blind study with bulimic inpatients undergoing intensive psychotherapy*. Pharmacopsychiatry 1991;24:1-7.

64 Fluoxetine Bulimia Nervosa Collaborative Study Group. *Fluoxetine in the treatment of bulimia nervosa. A multicenter, placebo-controlled, double-blind trial*. Arch Gen Psychiatry 1992;49:139-47.

65 Goldbloom DS, Olmsted M, Davis R, et al. *A randomized controlled trial of fluoxetine and cognitive behavioral therapy for bulimia nervosa: short-term outcome*. Behav Res Ther 1997;35:803-11.

66 Beumont PJ, Russell JD, Touyz SW, et al. *Intensive nutritional counselling in bulimia nervosa: a role for supplementation with fluoxetine?* Aust N Z J Psychiatry 1997;31:514-24.

67 Goldstein DJ, Wilson MG, Thompson VL, et al. *Long-term fluoxetine treatment of bulimia nervosa. Fluoxetine Bulimia Nervosa Research Group*. Br J Psychiatry 1995;166:660-6.

68 Goldstein DJ, Wilson MG, Ascroft RC, et al. *Effectiveness of fluoxetine therapy in bulimia nervosa regardless of comorbid depression*. Int J Eat Disord 1999;25:19-27.

69 Walsh BT, Wilson GT, Loeb KL, et al. *Medication and psychotherapy in the treatment of bulimia nervosa*. Am J Psychiatry 1997;154:523-31.

70 Goldbloom DS, Olmsted MP. *Pharmacotherapy of bulimia nervosa with fluoxetine: assessment of clinically significant attitudinal change*. Am J Psychiatry 1993;150:770-4.

71 Ricca V, Mannucci E, Mezzani B, et al. Cognitive-behavioral therapy versus combined treatment with group psychoeducation and fluoxetine in bulimic outpatients. Eat Weight Disord 1997;2:94-9.

72 Walsh BT, Agras WS, Devlin MJ, et al. *Fluoxetine for bulimia nervosa following poor response to psychotherapy*. Am J Psychiatry 2000;157:1332-4.

73 Mitchell JE, Fletcher L, Hanson K, et al. *The relative efficacy of fluoxetine and manual-based self-help in the treatment of outpatients with bulimia nervosa*. J Clin Psychopharmacol 2001;21:298-304.

74 Walsh BT, Fairburn CG, Mickley D, et al. *Treatment of bulimia nervosa in a primary care setting*. Am J Psychiatry 2004;161:556-61.

75 Jacobi C, Dahme B, Dittmann R. *Cognitive-behavioural, fluoxetine and combined treatment for bulimia nervosa: short- and long-term results*. Eur Eat Disorders 2002;10:179-98.

76 Romano SJ, Halmi KA, Sarkar NP, et al. *A placebo-controlled study of fluoxetine in continued treatment of bulimia nervosa after successful acute fluoxetine treatment*. Am J Psychiatry 2002;159:96-102.

77 Fichter MM, Krüger R, Rief W, et al. *Fluvoxamine in prevention of relapse in bulimia nervosa: effects on eating-specific psychopathology*. J Clin Psychopharmacol 1996;16:9-18.

78 Schmidt U, Cooper PJ, Essers H, et al. *Fluvoxamine and graded psychotherapy in the treatment of bulimia nervosa: a randomized, double-blind, placebo-controlled, multicenter study of short-term and long-term pharmacotherapy combined with a stepped care approach to psychotherapy*. J Clin Psychopharmacol 2004;24:549-52.

79 Milano W, Siano C, Petrella C, et al. *Treatment of bulimia nervosa with fluvoxamine: a randomized controlled trial*. Adv Ther 2005;22:278-83.

80 Sundblad C, Landén M, Eriksson T, et al. *Effects of the androgen antagonist flutamide and the serotonin reuptake inhibitor citalopram in bulimia nervosa: a placebo-controlled pilot study*. J Clin Psychopharmacol 2005;25:85-8.

81 Leombruni P, Amianto F, Delsedime N, et al. *Citalopram versus fluoxetine for the treatment of patients with bulimia nervosa: a single-blind randomized controlled trial*. Adv Ther 2006;23:481-94.

82 Sloan DM, Mizes JS, Helbok C, et al. *Efficacy of sertraline for bulimia nervosa*. Int J Eat Disord 2004;36:48-54.

83 Milano W, Petrella C, Sabatino C, et al. *Treatment of bulimia nervosa with sertraline: a randomized controlled trial*. Adv Ther 2004;21:232-7.

84 Walsh BT, Stewart JW, Roose SP, et al. *Treatment of bulimia with phenelzine. A double-blind, placebo-controlled study*. Arch Gen Psychiatry 1984;41:1105-9.

85 Walsh BT, Stewart JW, Roose SP, et al. *A double-blind trial of phenelzine in bulimia*. J Psychiatr Res 1985;19:485-9.

86 Walsh BT, Gladis M, Roose SP, et al. *Phenelzine vs placebo in 50 patients with bulimia*. Arch Gen Psychiatry 1988;45:471-5.

87 Rothschild R, Quitkin HM, Quitkin FM, et al. *A double-blind placebo-controlled comparison of phenelzine and imipramine in the treatment of bulimia in atypical depressives*. Int J Eat Disord 1994;15:1-9.

88 Kennedy SH, Piran N, Warsh JJ, et al. *A trial of isocarboxazid in the treatment of bulimia nervosa*. J Clin Psychopharmacol 1988;8:391-6.

89 Kennedy SH, Goldbloom DS, Ralevski E, et al. *Is there a role for selective monoamine oxidase inhibitor therapy in bulimia nervosa? A placebo-controlled trial of brofaromine*. J Clin Psychopharmacol 1993;13:415-22.

90 Carruba MO, Cuzzolaro M, Riva L, et al. *Efficacy and tolerability of moclobemide in bulimia nervosa: a placebo-controlled trial*. Int Clin Psychopharmacol 2001;16:27-32.

91 El-Giamal N, de Zwaan M, Bailer U, et al. *Reboxetine in the treatment of bulimia nervosa: a report of seven cases*. Int Clin Psychopharmacol 2000;15:351-6.

92 Fassino S, Abbate-Daga GA, Boggio S, et al. *Use of reboxetine in bulimia nervosa: a pilot study*. J Psychopharmacol 2004;18:423-8.

93 Horne RL, Ferguson JM, Pope HG Jr, et al. *Treatment of bulimia with bupropion: a multicenter controlled trial*. J Clin Psychiatry 1988;49:262-6.

94 Pope HG Jr, Keck PE Jr, McElroy SL, et al. *A placebo-con-*

trolled study of trazodone in bulimia nervosa. J Clin Psychopharmacol 1989;9:254-9.

95 Sabine EJ, Yonace A, Farrington AJ, et al. *Bulimia nervosa: a placebo controlled double-blind therapeutic trial of mianserin*. Br J Clin Pharmacol 1983;15(Suppl.2):195S-202S.

96 Dally P, Sargant W. *Treatment and outcome of anorexia nervosa*. Br Med J 1966;2:793-5.

97 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;66:445-50.

98 Weizman A, Tyano S, Wijsenbeek H, et al. *Behavior therapy, pimozide treatment and prolactin secretion in anorexia nervosa*. Psychother Psychosom 1985;43:136-40.

99 Vandereycken W. *Neuroleptics in the short-term treatment of anorexia nervosa. A double-blind placebo-controlled study with sulpiride*. Br J Psychiatry 1984;144:288-92.

100 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;25:1049-59.

101 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;33:172-7.

102 Mondraty N, Birmingham CL, Touyz S, et al. *Randomized controlled trial of olanzapine in the treatment of cognitions in anorexia nervosa*. Australas Psychiatry 2005;13:72-5.

103 Brambilla F, Garcia CS, Fassino S, et al. *Olanzapine therapy in anorexia nervosa: psychobiological effects*. Int Clin Psychopharmacol 2007;22:197-204.

104 Bissada H, Tasca GA, Barber AM, et al. *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;165:1281-8.

105 Attia E, Kaplan AS, Walsh BT, et al. *Olanzapine versus placebo for out-patients with anorexia nervosa*. Psychol Med 2011;41:2177-82.

106 Leggero C, Masi G, Brunori E, et al. *Low-dose olanzapine monotherapy in girls with anorexia nervosa, restricting subtype: focus on hyperactivity*. J Child Adolesc Psychopharmacol 2010;20:127-33.

107 Kafantaris V, Leigh E, Hertz S, et al. *A placebo-controlled pilot study of adjunctive olanzapine for adolescents with anorexia nervosa*. J Child Adolesc Psychopharmacol 2011;21:207-12.

108 Norris ML, Spettigue W, Buchholz A, et al. *Olanzapine use for the adjunctive treatment of adolescents with anorexia nervosa*. J Child Adolesc Psychopharmacol 2011;21:213-20.

109 La Via MC, Gray N, Kaye WH. *Case reports of olanzapine treatment of anorexia nervosa*. Int J Eat Disord 2000;27:363-6.

110 Mehler C, Wewetzer C, Schulze U, et al. *Olanzapine in children and adolescents with chronic anorexia nervosa. A study of five cases*. Eur Child Adolesc Psychiatry 2001;10:151-7.

111 Boachie A, Goldfield GS, Spettigue W. *Olanzapine use as an adjunctive treatment for hospitalized children with anorexia nervosa: case reports*. Int J Eat Disord 2003;33:98-103.

112 Powers PS, Santana CA, Bannon YS. *Olanzapine in the treatment of anorexia nervosa: an open label trial*. Int J Eat Disord 2002;32:146-54.

113 Barbarich NC, McConaha CW, Gaskill J, et al. *An open trial of olanzapine in anorexia nervosa*. J Clin Psychiatry 2004;65:1480-2.

114 Malina A, Gaskill J, McConaha C, et al. *Olanzapine treatment of anorexia nervosa: a retrospective study*. Int J Eat Disord 2003;33:234-7.

115 Bosanac P, Kurlender S, Norman T, et al. *An open-label study of quetiapine in anorexia nervosa*. Hum Psychopharmacol 2007;22:223-30.

116 Powers PS, Bannon Y, Eubanks R, et al. *Quetiapine in anorexia nervosa patients: an open label outpatient pilot study*. Int J Eat Disord 2007;40:21-6.

117 Mehler-Wex C, Romanos M, Kirchheiner J, et al. *Atypical antipsychotics in severe anorexia nervosa in children and adolescents. Review and case reports*. Eur Eat Disord Rev 2008;16:100-8.

118 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;44:1027-34.

119 Powers PS, Klabunde M, Kaye W. *Double-blind placebo-controlled trial of quetiapine in anorexia nervosa*. Eur Eat Disord Rev 2012;20:331-4.

120 Fisman S, Steele M, Short J, et al. *Case study: anorexia nervosa and autistic disorder in an adolescent girl*. J Am Acad Child Adolesc Psychiatry 1996;35:937-40.

121 Newman-Toker J. *Risperidone in anorexia nervosa*. J Am Acad Child Adolesc Psychiatry 2000;39:941-2.

122 Hagman J, Gralla J, Sigel E, et al. *A double-blind, placebo-controlled study of risperidone for the treatment of adolescents and young adults with anorexia nervosa: a pilot study*. J Am Acad Child Adolesc Psychiatry 2011;50:915-24.

123 Aragona M. *Tolerability and efficacy of aripiprazole in a case of psychotic anorexia nervosa comorbid with epilepsy and chronic renal failure*. Eat Weight Disord 2007;12:54-7.

124 Trunko ME, Schwartz TA, Duvvuri V, et al. *Aripiprazole in anorexia nervosa and low-weight bulimia nervosa: case reports*. Int J Eat Disord 2011;44:269-75.

125 Gross HA, Ebert MH, Faden VB, et al. *A double-blind controlled trial of lithium carbonate primary anorexia nervosa*. J Clin Psychopharmacol 1981;1:376-81.

126 Hoopes SP, Reimherr FW, Hedges DW, et al. *Treatment of bulimia nervosa with topiramate in a randomized, double-blind, placebo-controlled trial, part 1: improvement in binge*

and purge measures. J Clin Psychiatry 2003;64:1335-41.

127 Hedges DW, Reimherr FW, Hoopes SP, et al. *Treatment of bulimia nervosa with topiramate in a randomized, double-blind, placebo-controlled trial, part 2: improvement in psychiatric measures*. J Clin Psychiatry 2003;64:1449-54.

128 Nickel C, Tritt K, Muehlbacher M, et al. *Topiramate treatment in bulimia nervosa patients: a randomized, double-blind, placebo-controlled trial*. Int J Eat Disord 2005;38:295-300.

129 Kaplan AS, Garfinkel PE, Darby PL, et al. *Carbamazepine in the treatment of bulimia*. Am J Psychiatry 1983;140:1225-6.

130 Cordás TA, Tavares H, Calderoni DM, et al. *Oxcarbazepine for self-mutilating bulimic patients*. Int J Neuropsychopharm 2006;9:789-91.

131 Hsu LK, Clement L, Santhouse R, et al. *Treatment of bulimia nervosa with lithium carbonate. A controlled study*. J Nerv Ment Dis 1991;179:351-5.