The World Journal of Biological Psychiatry, 2011; 12: 400–443

GUIDELINES

World Federation of Societies of Biological Psychiatry (WFSBP) Guidelines for the Pharmacological Treatment of Eating Disorders

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Abstract

Objectives. The treatment of eating disorders is a complex process that relies not only on the use of psychotropic drugs but should include also nutritional counselling, psychotherapy and the treatment of the medical complications, where they are present. In this review recommendations for the pharmacological treatment of eating disorders (anorexia nervosa (AN), bulimia nervosa (BN), binge eating disorder (BED)) are presented, based on the available literature. *Methods.* The guidelines for the pharmacological treatment of eating disorders are based on studies published between 1977 and 2010. A search of the literature included: anorexia nervosa bulimia nervosa, eating disorder and binge eating disorder. Many compounds have been studied in the therapy of eating disorders (AN: antidepressants (TCA, SSRIs), antipsychotics, antihistaminics, prokinetic agents, zinc, Lithium, naltrexone, human growth hormone, cannabis, clonidine and tube feeding; BN: antidepressants (TCA, SSRIs, RIMA, NRI, other AD), antiepileptics, odansetron, d-fenfluramine Lithium, naltrexone, methylphenidate and light therapy; BED: antidepressants (TCA, SSRIs, SNRIs, NRI), antiepileptics, baclofen, orlistat, d-fenfluramine, naltrexone). *Results.* In AN 20 randomized controlled trials (RCT) could be identified. For zinc supplementation there is a grade B evidence for AN. For olanzapine there is a category grade B evidence for weight gain. For the other atypical antipsychotics there is grade C evidence. In BN 36 RCT could be identified. For tricyclic antidepressants a grade A evidence exists with a moderate-risk-benefit ratio. For fluoxetine a category grade A evidence exists with a good risk-benefit ratio. For topiramate a grade 2 recommendation can be made. In BED 26 RCT could be identified. For the SSRI sertraline and the antiepileptic topiramate a grade A evidence exists, with different recommendation grades. *Conclusions.* Additional research is needed for the improvement of the treatment of eating disorders. Especially for anorexia nervosa there is a need for further pharmacological treatment strategies.

Key words: *eating disorder, drug treatment, guidelines, Anorexia nervosa, Binge Eating Disorder, Bulimia nervosa, pharmacotherapy, antidepressants, antipsychotics, antiepileptics, antihistaminics, tube feeding, light therapy*

Abbrevations: aAN, atypical Anorexia nervosa; AN, Anorexia nervosa; AN-BP, Anorexia nervosa binge-purging subtype; AN-R, Anorexia nervosa restricting subtype; BDI: Beck Depression Inventory; BED, Binge Eating Disorder; BES, Binge Eating Scale; BITE, Bulimic Investigation Test; BMI, Body Mass Index; BN, Bulimia nervosa; BN-NP, Bulimia nervosa – nonpurging type (BN-NP); BN-P, Bulimia nervosa - Purging type; BSQ, Body Shape Questionaire; CBT, cognitive behaviour therapy; CYP, Cyproheptadine; ED, Eating Disorder; EDI, Eating Disorder Inventory; GAAQ: Goldberg Anorectic Attitude Questionare; GABA, gamma-amino butyric acid; GAF: Global Assessment of Functioning; HAMA: Hamilton Anxiety Scale; HAMD, Hamilton Depression Scale; HSCL-90, Hopkins Symptom Checklist-90; IPT, Interpersonal Psychotherapy; PGI, Patient's global impression; PRS, Psychiatric rating scale; RIMA, Reversible Inhibitor of monoamine oxidase A; RCT, Randomised controlled trial; SIAB: Structured Interview for Anorexia and Bulimia; SNRI: Serotonin and noradrenaline reuptake inhibitor; SSRI, Selective Serotonin reuptake inhibitor; TCAs, Tricyclic Antidepressants; TFEQ, Three Factor Eating Questionnaire; THC, Tetrahydrocannabinol; WHOQoL-BREF, WHO-Quality of Life Questionnaire, brief Version; WFSBP: World Federation of Societies of Biological Psychiatry; Y-BOCS-BE, Y-BOCS-binge eating; ZSRDS: Zung self-rated depression scale

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(Received 30 June 2011; accepted 30 June 2011)

ISSN 1562-2975 print/ISSN 1814-1412 online
DOI: 10.3109/15622975.2011.602720

Introduction

The treatment of eating disorders is a complex process that relies not only on the use of psychotropic drugs but should include also nutritional counselling, psychotherapy and the treatment of the medical complications, where they are present. These guidelines make recommendations on the pharmacological treatment of the main 3 eating disorders (EDs): Anorexia nervosa (AN), Bulimia nervosa (BN) and Binge Eating Disorder (BED). Most of the drugs studied have not been approved for the treatment of eating disorders, so their clinical use is, at present, mostly off-label. Disordered eating behaviour is common in our society. However, the strict application of diagnostic criteria for eating disorders results in low-prevalence conditions with high clinical severity associated with physical and psychosocial disability.

Young women are especially affected by eating disorders. Eating disorders are a health concern because they are associated with additional psychiatric comorbidity, medical comorbidity and impairment of function. In a way they are orphan disorders, because of the combination of medical conditions and psychopathology. These guidelines have been assembled for the World Federation of Societies of Biological Psychiatry (WFSBP) with the intention of improving the treatment of eating disorders.

Goal and Target Audience of WFSBP Guidelines

The goal of the World Federation of Societies of Biological Psychiatry (WFSBP) Guidelines for the Pharmacological Treatment of Eating Disorders is to publish Treatment Guidelines for eating disorders (AN, BN, BED) in the World Journal of Biological Psychiatry. The Treatment Guidelines should apply world-wide. The treatment of the medical conditions associated with eating disorders such as osteoporosis, infertility etc. was not within the scope of this review.

Methods of Literature Research and Data Extraction

With the electronic database Medline the terms (anorexia nervosa, bulimia nervosa, binge eating disorder, eating disorder, antidepressants, antipsychotics, antiepileptics, light therapy, tube feeding, lithium, zinc, randomized controlled trial) were searched up to 2011. Additionally, other guidelines and systematic reviews were searched. For this guideline we decided to include small low quality studies to show the whole field of pharmacotherapy in eating disorders. Additional physical therapy procedures such as light therapy and nasogastric tube feeding were also included. The PRISMA checklist 2009 was used to structure the guidelines.

Evidence Based Classification of Recommendations

According to the WFSBP principles of evidence-based medicine, 5 categories of evidence are used and 5 recommendation grades are given (Bandelow et al., 2008; Table I). In addition to evidence of efficacy it is also important to consider tolerability with some evidence of the risk/benefit ratio. Also the cost effectiveness needs to be considered.

Other Eating Disorder Evidence Based Guidelines

In the NICE Guidelines (2004) pharmacotherapy is not seen as first choice for eating disorders, but is mentioned as an adjunct to psychological therapies for treating physical or comorbiod psychological problems. For anorexia nervosa, the NICE guidelines (2004) mention medication as disappointing in influencing the core symptoms of the disorder, promoting weight gain or reducing associated mood disturbance. For bulimia nervosa and binge eating disorder, the NICE guidelines (2004) see some evidence that antidepressants, particularly selective serotonin reuptake inhibitors (SSRIs) contribute to the cessation of binge eating and purging. Additionally, opiate antagonists are mentioned in this indication.

The Australia and New Zealand guidelines for AN (RANZCP, 2004) recommend a multidimensional approach (including family therapy, cognitive behaviour therapy, dietary advice) in the therapy of AN. They come to the conclusion that pharmacotherapy and antidepressants may help AN-patients with comorbid symptoms and that olanzapine may be useful for attenuating hyperactivity. Claudino et al. (2006) found not enough evidence in their Cochrane review to recommend antidepressants in the treatment of AN.

In their Cochrane review Bacaltchuk and Hay (2003) come to the conclusion that the use of a single antidepressant agent is clinically effective for the treatment of bulimia nervosa when compared to placebo, with an overall greater remission rate but a higher rate of dropouts compared with CBT. They found no differential effect regarding efficacy and tolerability among various classes of antidepressants.

Stefano et al. (2008) conducted a meta-analysis that showed binge-eating remission rates were higher in patients receiving antidepressants when compared with placebo. Most studies were short-term trials (median duration: 8 weeks) and the only 16-week study did not show superiority of antidepressants over placebo. They come to the conclusion that avail-

Table I. Categories of evidence (Bandelow et al. 2008).

Category of evidence	Description
↑↑ **A**	**Full Evidence From Controlled Studies**
	2 or more randomized controlled studies (RCTs) showing superiority to placebo (or in the case of psychotherapy studies, superiority to a 'psychological placebo') and 1 or more positive RCTs showing superiority to or equivalent efficacy compared with established comparator treatment in a three-arm study with placebo control or in a well-powered non-inferiority trial (only required if such a standard exists)
↑ **B**	**Limited Positive Evidence From Controlled Studies**
	is based on: 1 or more RCTs showing superiority to placebo (or in the case of psychotherapy studies, superiority to a 'psychological placebo') or a randomized controlled comparison with a standard treatment without placebo control with a sample size sufficient for a non-inferiority trial. and No negative studies exist
(↑) **C**	**Positive Evidence from Uncontrolled Studies or Case Reports/Expert Opinion**
C1	**Uncontrolled Studies** is based on: 1 or more positive naturalistic open studies or case series (with a minimum of 5 evaluable patients) or a comparison with a reference drug with a sample size insufficient for a non-inferiority trial and no negative controlled studies exist
C2	**Case Reports** is based on: 1 or more positive case reports and no negative controlled studies exist
C3	Based on the opinion of experts in the field, clinical experience or laboratory findings
↔ **D**	**Inconsistent Results** Positive RCTs are outweighed by an approximately equal number of negative studies
↓ **E**	**Negative Evidence** The majority of RCTs studies shows non-superiority to placebo (or in the case of psychotherapy studies, superiority to a 'psychological placebo') or inferiority to comparator treatment
? F	**Lack of Evidence** Adequate studies proving efficacy or non-efficacy are lacking

able data are not sufficient to formally recommend antidepressants as a single first line therapy for patients with BED.

Only small proportions of patients with a lifetime diagnosis of EDs requested medical treatment (Preti et al., 2009).

Indications and Goals of Treatment for Eating Disorders

Anorexia nervosa. Major goals in the treatment of AN include weight gain, prevention of weight loss after intensive care, a change in eating behaviour and reduction of associated psychopathology (e.g. preoccupations with body image), depression, OCD and treatment of associated medical conditions (e.g. disturbances of gonadal axis, infertility, osteoporosis.

Bulimia nervosa. Major goals in the treatment of BN include cessation of binge eating behaviour, cessation of compensatory behaviour (e.g. vomiting, misuse of laxatives and diuretics), and reduction of associated psychopathology and therapy of associated medical conditions.

Binge eating disorder. Major goals in the treatment of BED include cessation of binge eating behaviour, reduction of associated psychopathology and treatment of obesity.

Somatic and Biological Aspects of Eating Disorders

Research findings suggest substantial influence of genetic factors on the development of eating disorders and neurotransmitters such as serotonin and

Table I.1. Recommendation grade (Bandelow et al. 2008).

Recommendation grade	Based on:
1	Category A evidence and good risk–benefit ratio
2	Category A evidence and moderate risk–benefit ratio
3	Category B evidence
4	Category C evidence
5	Category D evidence

dopamine have been considered to be of aetiological importance (Kaye, 2008). AN is associated with secondary complications due to malnourishment and/or complications due to vomiting or laxatives misuse.

BN is also associated with secondary complications due to vomiting, misuse of laxatives. Type 1 diabetes is associated with a higher prevalence of bulimia nervosa in females (Mannucci et al., 2005).

BED with its elevated BMI is associated with secondary complications due to obesity.

Classification of Eating disorders

There are two broadly accepted definitions of eating disorders: Anorexia nervosa and Bulimia nervosa which are included in the International classification of diseases (ICD-10) and in the Diagnostic and Statistical Manual (DSM-IV). The third eating disorder: Binge Eating disorder is to be found in the chapter "eating disorders not otherwise specified (EDNOS)" or "atypical eating disorders", respectively. For diagnostic criteria see Table III.

Comorbidity in Eating Disorders

A broad spectrum of psychiatric comorbidity is seen in people with eating disorders. The rates of lifetime comorbid major depression, alcohol dependence, and a number of anxiety disorders are high (Sullivan et al., 1998). Fletcher et al. (2008) found high levels of interpersonal sensitivity, and depression. Berkman et al. (2007) reported individuals with AN were more likely to be depressed, have Asperger's syndrome and autism spectrum disorders, and suffer from anxiety disorders including obsessive-compulsive disorders.

Affective and anxiety disorders. Patients with AN have a high comorbidity with other psychiatric diagnoses especially affective and anxiety disorders (Halmi et al., 1991).

BED has a relatively high comorbidity with other psychiatric disorders. Obese patients with BED in particular have additional axis I psychiatric disorders mainly depressive disorders (Fontenelle et al., 2003). Full BED is significantly associated with bipolar disorder, major depressive disorder, bulimia nervosa but not with anorexia nervosa (Javaras et al., 2008).

Obsessive compulsive disorders, impulse control disorders. Jordan et al. (2008) found in AN an elevated prevalence of obsessive compulsive disorder and in the AN-binge-purging subtype (AN-BP) and the BN sample elevated prevalences of Cluster B personality disorders and elevated Cluster C prevalences across the samples. Full BED is significantly associated with body dysmorphic disorder and, kleptomania (Javaras et al., 2008).

Psychosis. Also psychotic symptoms were described as part of AN and BN comorbidity (Hudson et al., 1984).

Substance use disorders. Gadalla and Piran (2007) found in their meta-analysis (including the literature between 1985 and 2006) significant co-occurrence rates of alcohol use disorders ranging between small and medium effect size for all patterns of EDs except AN. The effect size for any eating disorder was 0.38, for AN 0.09, for BN 0.46, and for BED 0.39. A systematic review of substance abuse also found increased levels particularly in the binge eating. BED is significantly associated with substance use disorders (Javaras et al., 2008).

Pain. 36% of the patients with EDs report moderate to severe pain. Depression and pain are intimately related in EDs (Coughlin et al., 2008). Full BED is significantly associated with irritable bowel syndrome and fibromyalgia (Javaras et al., 2008).

Medication for Eating Disorders

Because of the broad spectrum of psychiatric disorders which have substantial comorbidity with eating disorders and their possible effect on eating behaviour many psychopharmacological agents including antidepressants, antipsychotics, antiepileptics, antihistaminics and other pharmacological compounds have been investigated in eating disorders.

Antidepressants

Their main action is thought to be in the serotonergic (SSRI) and/or the noradrenergic system (SNRI). According to Kaye (2008), who reviewed the neurobiology of AN and BN, it is possible that the central

Table II. Eating disorders, prevalence rates.

Eating disorder	Prevalence
Anorexia nervosa	overall prevalence of AN is 0.9–1.20% for women and 0.29–0.3% for men (Bulik et al. 2006; Makino et al. 2004)
	liftetime prevalence of AN 0.48% (over 18a) (Preti et al. 2009)
Bulimia nervosa	lifetime prevalence of DSM-IV bulimia nervosa was 2.3%, incidence rate of bulimia nervosa was 300/100,000 person-years (Keski-Rahkonen et al. 2008)
	lifetime prevalence of BN 0.51% (over 18a) (Preti et al. 2009)
Binge Eating disorder	lifetime prevalence of DSM-IV binge eating disorder was 3.5% among women, and 2.0% among men (Hudson et al. 2007)
	liftetime prevalence of BED 1.12% (over 18a) (Preti et al. 2009)

serotonin function contributes to the dysregulation of appetite, mood, and impulse control. Serotonin function and other monoamine function in AN and BN is disturbed, when people are ill and this persists even after their recovery.

Antipsychotics

Their main site of action is thought to be on the dopaminergic system with additional serotonergic involvement for the atypical antipsychotics. Altered striatal dopamine function may contribute to symptoms in AN (Kaye, 2008). The cortico-mesolimbic dopamine system may also be involved in addictive eating behaviour.

Antiepileptics

The neurostabilizing effect of antiepileptics may be of therapeutic benefit in eating disorders. For example, the antiepileptic drug topiramate has many sites of actions (e.g. on sodium, calcium, and potassium channels; on gamma-aminobutyric acid and glutamate receptors; and carbonic anhydrase inhibition) (McElroy et al., 2007a).

Antihistaminics

Histamine is a neurotransmitter that regulates appetite and energy metabolism. Neuronal histamine suppresses food intake via histamine-1-receptors within the paraventricular nucleus and the ventromedial hypothalamus (Gotoh et al., 2007).

Other compounds and sites of actions

Konturek et al. (2005) reviewed the neurohumoral control of food intake. They described two systems for the regulation of food intake, a short term regulation system (e.g. CCK, ghrelin,…) during each meal and a long term regulation (e.g. leptin, insulin,…) for the storage of energy in the form of fat. The nucleus tractus solitarius in the brain stem is the gateway for neural signals from the gastrointestinal tract via the vagal nerve to the hypothalamic feeding centers. The amygdala, the area postrema, the cortex prefrontalis, the nucleus arcuatus, the nucleus paraventricularis are also involved in eating behaviour. Neurohumoral factors inhibit (ghrelin, orexin-A, orexin-B) or stimulate (cholecystokinin, leptin, PYY, OXM, Cytokines) satiety (Konturek et al., 2005). The endocannabinoid system may have an influence on eating behaviour at different levels, in the central nervous system as well as in the periphery (Maccarrone et al., 2010). Prokinetic agents with their acceleration of peristalsis in the gastrointestinal system may as well have an effect on eating behaviour (Stacher et al., 1987).

Anorexia Nervosa (AN)

Diagnosis of Anorexia Nervosa

AN is defined by a refusal to maintain a minimal normal body weight. There are two subtypes: the binge-purging subtype (AN-BP) and the restricting subtype (AN-R). AN is a rare disorder, but has the highest mortality rate of any psychiatric disorder. For diagnostic criteria see Table III.

Epidemiology of Anorexia Nervosa

In the National Comorbidity Survey (USA) the lifetime prevalence of DSM-IV anorexia nervosa was 0.9% among women, and 0.3% among men (Hudson et al., 2007). The epidemiology of eating disorders in six European countries: (ESEMeD-WMH project) was presented by Preti et al. (2009): lifetime estimated prevalence of anorexia nervosa was 0.48%. Some groups, for example, professional fashion models have a high risk for eating disorders (Preti et al., 2008). The prevalence rate in non-Western countries (0.002% to 0.9%) is lower than in Western countries (0.1% to 5.7% in female subjects) according to Makino et al. (2004). High quality population-based prevalence studies from non-western countries are lacking and so there is uncertainty.

Table III. Definition of eating disorders as definded by ICD-10 (WHO 1991) and DSM-IV (APA 1994).

Anorexia nervosa

Diagnostic criteria for Anorexia nervosa (AN) (DSM-IV: 307.1) (APA 1994)

A. Refusal to maintain body weight at or above a minimally normal weight for age and height (e.g., weight loss leading to maintenance of body weight less than 85% of that expected; or failure to make expected weight gain during period of growth, leading to body weight less than 85% of that expected).
B. Intense fear of gaining weight or becoming fat, even though under weight.
C. Disturbance in the way in which one´s body weight or shape is experienced, undue influence of body weight or shape on self-evaluation, or denial of the seriousness of current low body weight.
D. In postmenarcheal females, amenorrhea, i.e. the absence of at least 3 consecutive menstrual cycles. (A woman is considered to have amenorrhea if her periods only following hormone, e.g., estrogen, administration.)

Specific type:

Anorexia nervosa – Restricting Type (AN-R): during the current episode of AN, the person has no regularly engaged in binge-eating or purging behaviour (i.e., self induced vomiting or the misuse of laxatives, diuretics, or enemas).

Anorexia nervosa – Binge-Eating/purging Type (AN-BP): during the current episode of AN, the person has regularly engaged in binge-eating or purging behaviour (i.e., self-induced vomiting or the misuse of laxatives, diuretics or enemas).

ICD-10 Criteria for Anorexia nervosa (AN) (ICD-10: F50.0) (WHO 1991)

A. There is weight loss or, in children, a lack of weight gain, leading to a body weight at least 15% below the normal or expected weight for age and height.
B. The weight loss is self-induced by avoidance of "fattening foods".
C. There is self-perception of being too fat, with an intrusive dread of fatness, which leads to a self-imposed low weight threshold.
D. A widespread endocrine disorder involving the hypothalamic-pituitary-gonadal axis is manifested in women as amenorrhoea and in men as a loss of sexual interest and potency. (An apparent exception is the persistence of vaginal bleeds in anorexic women who are on replacement hormonal therapy, most commonly taken as a contraceptive pill).
E. The disorder does not meet criteria A or B for bulimia nervosa.

ICD-10 Criteria for atypical Anorexia nervosa (aAN) (ICD-10: F50.1) (WHO 1991)

The disorder fulfils some of the features of anorexia nervosa, but in which the overall clinical picture does not justify that diagnosis. For instance, one of the key symptoms, such as amenorrhoea or marked dread of being fat, may be absent in the presence of marked weight loss or weight-reducing behaviour. This diagnosis should not be made in the presence of known physical disorders associated with weight loss.

Bulimia nervosa

Diagnostic criteria for Bulimia nervosa (BN) (DSM-IV 307.51) (APA 1994)

A. Recurrent episodes of binge eating. An episode of binge eating is characterized by both of the following:
   (1) eating, in a discrete period of time (e.g., within any 2-hour period), an amount of food that is definitively larger than most people would eat during a similar period of time and under similar circumstances
   (2) a sense of lack of control over eating during the episode (e.g., a feeling that one cannot stop eating or control what or how much one is eating)
B. Recurrent inappropriate compensatory behaviour in order to prevent weight gain as self-induced vomiting; misuse of laxatives, diuretics, enemas, or other medications; fasting; or excessive exercise.
C. The binge eating and compensatory behaviour both occur, on average, at least twice a week for 3 months.
D. Self-evaluation is unduly influenced by body shape and weight.
E. The disturbance does not occur exclusively during episodes of AN.

Specific type:

Bulimia nervosa – Purging type (BN-P): during the current episode of BN, the person has regularly engaged in self induced vomiting or the misuse of laxatives, diuretics, or enemas.

Bulimia nervosa – nonpurging type (BN-NP): during the current episode of BN, the person has used other inappropriate compensatory behaviours, such as fasting or excessive exercise, but has not regularly engaged in self-induced vomiting or the misuse of laxatives, diuretics, or enemas.

ICD-10 Criteria for Bulimia nervosa (BN) (ICD-10: F50.2) (WHO 1991)

A. There are recurrent episodes of overeating (at least 2 times a week over a period of 3 months) in which large amounts of food are consumed in short periods of time.
B. There is persistent preoccupation with eating, and a strong desire or sense of compulsion to eat (craving).
C. The patient attempts to counteract the "fattening" effects of food by one or more of the following:
   (a) self-induced vomiting
   (b) self-induced purging
   (c) alternating periods of starvation
   (d) use of drugs such as appetite suppressants, thyroid preparations, or diuretics; when bulimia occurs in diabetic patients they may choose to neglect their insulin treatment.
D. There is self-perception of being too fat, with an intrusive dread of fatness (usually leading to underweight).

(Continued)

Table III. *(Continued)*

Binge Eating Disorder
DSM IV Criteria for Binge Eating Disorder (DSM-IV: 307.50) (APA 1994) A. Recurrent episodes of binge eating. An episode of binge eating is characterized by both of the following: (a) Eating, in a discrete period of time (e.g., within any 2-hour period), an amount of food that is definitely larger than most people would eat in a similar period of time under similar circumstances. (b) The sense of lack of control over eating during the episode (e.g., a feeling that one cannot stop eating or control what or how much one is eating). B. Binge-eating episodes are associated with 3 (or more) of the following: (a) eating much more rapidly than normal. (b) eating until feeling uncomfortably full. (e) eating large amounts of food when not feeling physically hungry. (d) eating along because of being embarrassed by how much one is eating. (e) feeling disgusted with oneself, depressed, or very guilty after overeating. C. Marked distress regarding binge eating is present. D. The binge eating occurs, on average, at least 2 days a week for 6 months. E. The binge eating is not associated with the regular use of inappropriate compensatory. F. behaviour (e.g., purging, fasting, excessive exercise, etc.) and does not occur exclusively during the course of anorexia nervosa or bulimia nervosa.

Course of Anorexia Nervosa

Signorini et al. (2007) reported that the standardized mortality ratio is 9.7 which is in line with other studies from a review. They found in their 8-year follow-up, a mortality rate of 2.72% (1.82% after correcting for unrelated deaths) and confirm mortality rate to be dramatically high considering AN demographic characteristics, that is young female subjects in Westernized societies. There are especially high rates of suicidality. In a review of outcome (Bulik et al. 2006) a hospital discharge diagnosis of AN was associated with increased mortality (OR, 2.18; 95% CI, 1.33-3.58).

Treatment with Antidepressants

The rationale for treating AN with antidepressants is (1) the hypothetical dysfunction in the serotonergic and noradrenergic system in the pathophysiology of anorexia nervosa and (2) the comorbidity and psychopathological overlap with anxiety disorders, obsessive compulsive disorders and depression with anorexia nervosa.

Tricyclics. Lacey and Crisp (1980) conducted a double-blind controlled trial with clomipramine in 16 patients with anorexia nervosa. Clomipramine was associated with increased hunger, appetite and energy intake, but there was a reduced rate of weight gain.

Biederman et al. (1985) conducted a 5 week double blind placebo controlled trial with amitryptiline in 25 patients with anorexia nervosa. No significant differences in weight gain could be found.

Halmi et al. (1986) conducted a double blind placebo controlled trial with amitryptiline (maximal dosage 160 mg), cyproheptatine (maximal dosage 32 mg) in 72 female patients with anorexia nervosa. There was only a significant difference in weight gain for cyproheptadine: Increasing weight gain in the non-bulimic group and impaired treatment efficacy in the bulimic group. The depressive symptomatology (HAMD, BDI) responded to both treatment arms.

Crisp et al. (1987) conducted a randomized double blind placebo controlled trial in 16 patients with anorexia nervosa with 50 mg clomipramine treatment as adjunct to a strict weight restoration program. There was no significant difference in weight gain between pharmacological group and placebo group.

In conclusion, there is no clear evidence for the general use of tricyclics (amitryptiline and clomipramine) in patients with anorexia nervosa.

Selective Serotonin Reuptake Inhibitors (SSRIs). Concerning a potential effect of SSRIs treatment in psychopathology associated with anorexia nervosa the results of open studies are inconsistant (Brambilla et al., 1995a,b; Gwirtsman et al., 1990; Fassino et al., 2002; Holtkamp et al., 2005).

CITALOPRAM. The open randomized study of Fassino et al. (2002) in patients with restricting-type anorexia nervosa compared 26 patients treated with citalopram to a control group without a medication (waiting list) (n = 26). The authors observed no between-group differences regarding the BMI, but an improvement in depression, obsessive-compulsive symptoms, impulsiveness and trait-anger in the intervention group.

FLUOXETINE. Gwirtsman et al. (1990) conducted an open trial of fluoxetine in 6 patients with anorexia

Table IV. Studies on pharmacological treatment in anorexia nervosa.

Author	Year	No. of Patients	Dropouts	Agent	No. of studies	Psychotherapy	Randomized	Placebo-controlled	Double-blind	Treatment-duration	Parameters	Positive outcome
Antidepressants Tricyclics					**4**	**2**	**2**	**4**	**4**			
Lacy and Crisp	1980	16	3	clomipramine	1			1	1	variable	weight	no
Biederman et al.	1985	25		amitriptyline	1	1	1	1	1	5 weeks	weight	no
											psychiatric outcomes	no
Halmi et al.	1986	72		amitriptyline (max. 160 mg) + cyproheptadine (max. 32 mg)	1	0	?	1	1	4 weeks	weight	no, cyproheptadine increased treatmment efficacy in non-bulimic (restrictive) subgroup and impaire treatment efficacy in bulimic group
											depressive symptomatology (HAMD, BDI)	yes
Crisp et al.	1987	16	3	clomipramine	1	1	1	1	1		weight	no
SSRIs					**7**		**4**	**3**	**3**			
Holtkamp et al.	2005	32		SSRI	1	0	0	0	0	6 months follow-up	BMI	
											eating disorder psychopathology	no
											depressive psychopathology	no
											obsessive-compulsive psychopathology	no
Citalopram					1	0	1	0	0			
Fassino et al. (only AN-R)	2002	52	13	citalopram	1	0	1	0	0	3 months	EDI-2	subscales yes
											STAI	no
											BDI	yes
											SCL-90	subscales yes
											weight	no difference to control
Fluoxetine					4	3	3	3	3			
Gwirtsman et al.	1990	6		fluoxetine	1	0	0	0	0		weight	yes
											depressive symptoms	yes
Attia et al.	1998	31	2	fluoxetine 60 mg	1	1	1	1	1	7 weeks	body weigth	no
											CGI	no
											Body Shape Questionaire	no
											Eating Attitudes test	no
											SCL-90	no

(Continued)

Table IV. *(Continued)*

Author	Year	No. of Patients	Dropouts	Agent	No. of studies	Psychotherapy	Randomized	Placebo-controlled	double-blind	Treatment-duration	Parameters	Positive outcome
Kaye et al	2001	35	22	fluoxetine	1	1	1	1	1	12 months	weight	no
											Y-BOCS	yes
											HDRS	trend
											completers	yes
Walsh et al.	2006	93	53	fluoxetine	1	1	1	1	1	12 months	time-to-relapse	no
											completers after 1 year	no
Sertraline					**1**	**1**	**0**	**0**	**0**			
Santonastaso et al. (only AN-R)	2001	22		sertraline	1	1	0	0	0	14 weeks	BMI	no
											depressive symptomatology	yes
Other Antidepressants												
Mirtazapine					1							
Safer et al.	2010			mirtazapine	1	0	0	0	0	9 month	Weight gain	yes
Antipsychotics					**22**	**1**	**3**	**3**	**3**			
Typical Antipsychotics												
Haloperidol					1	0	0	0	0			
Cassano et al. (only tratment-resistent AN-R)	2003	13		haloperidol	1	0	0	0	0	6 months	EDI	yes
											EAT	yes
											CGI	yes
											BMI	yes
Sulpiride					1	1	1	1	1			
Vandereycken	1984	18		sulpiride 13 patients 300 mg 5 patients 400 mg	1	1	1	1	1		EAT	no
											BAT	no
											ABSIO	no
											weight	no
Pimozide					1	1	1	1	1			
Vandereycken and Pierloot	1982	18	2	pimozide	1	1	1	1	1		weight	no, but a trend for weight gain
atypical Antipsychotics					**19**							
olanzapine					**12**							
Hansen	1999	1		olanzapine	1	0	0	0	0	7 months	weight	yes

Jensen and Mejlhede	2000	3		olanzapine	1	0	0	0	0	2 / 9 Months	weight	yes
La Via et al.	2000	2		olanzapine	1	0	0	0	0	12 weeks	weight	yes
Powers et al.	2002	14	4	olanzapine	1	0	0	0	0	10 weeks	weight	yes
Malina et al.	2003	18		olanzapine	1	0	0	0	0	3-70 weeks	anxiety, difficulty eating, cire eating disorder symptoms	yes
Boachie et al.	2003	4		olanzapine	1	0	0	0	0		weight	yes
											psychopathology	yes
Barbarich et al.	2004	17		olanzapine 4,7 mg	1	0	0	0	0	6 weeks	body weight	yes
											STAI	yes
											BDI	yes
											Y-BOCS	no
											YBC-EDS	yes
Mondraty et al.	2005	15		olanzapine vs. Chlorpromazine	1	0	1	0	0		EDI-2/ anorexic rumination	yes
Brambilla et al.	2007	30	5	olanzapine 5 mg	1	1	1	1	1	3 months	BMI	only binge-purging
											EDI-2	no
											homovanillic	yes
											YBC-EDS	no
											HAMD	no
Bissada et al.	2008	34	6	olanzapine (mean dose: 6,61 md/day)	1	1	1	1	1	10 weeks	weight	yes
											BMI	yes
											obsessive symptoms	yes
											compulsions	no
Leggero et al. (only AN-R)	2010	13		olanzapine (mean dose: 4,13 mg/day)	1	1	0	0	0	6 months	BMI	yes
Spettigue et al.	2008	planned 67		olanzapine	1		1	1	1			ongoing study
Risperidone					2	0	0	0	0			
Fisman et al.	1996	1		risperidone 1 mg	1	0	0	0	0	12 months	weight gain	yes
Newman-Toker et al.	2000	2		risperidone 1,5 mg	1	0	0	0	0	10 months	weight gain	yes
											psychopathology	yes
Quetiapine					2	0	0	0	0			
Bosanac et al.	2007	8	2	quetiapine (50–800 mg)	1	0	0	0	0	8 weeks	EDE-12	yes/resraint subscales
											MADRS	no
											Y-BOCS	no
											SAPS-delusion	no
											CDR neuropsychological battery	no
											BMI	yes
											CGI	yes
											EPS-Score	no

(Continued)

Table IV. *(Continued)*

Author	Year	No. of Patients	Dropouts	Agent	No. of studies	Psychotherapy	Randomized	Placebo-controlled	double-blind	Treatment-duration	Parameters	Positive outcome
Quetiapine					2	0	0	0	0			
Powers et al.	2007	19		quetiapine (150–300 mg/day)	1	0	0	0	0	10 weeks	weight	modest (0.73 kg) (not statistically significant)
Mehler Wex et al.	2008	3		200–500 mg/day	1	0	0	0	0	10 weeks	weight	weight gain, might be favourable with regard to patients' compliance
Court et al.	2010	33		100–400 mg/day	1	0	1	0	0	12 weeks And 12 months follow up	Weight and body image	both psychological and physical improvements
Amisulpiride					1	0	1	0	0			
Ruggierio et al.	2001	35		amisulpiride/clomipramine/ fluoxetine	1	0	1	0	0	3 months	weight	yes (baseline vs. post) no (in between groups)
Aripiprazole					1	0	0	0	0			
Trunko et al.	2010	5		aripiprazole	1	0	0	0	0	>4 months	Weight and psychopathology	improved
Antihistaminics												
Cyproheptadine					1	1	1	1	1			
Goldberg et al.	1979	81	?	cyproheptadine	1	1	1	1	1	?	weight gain	no, posthoc: more severe subgroup responded
Periactine					1	0	0	0	0			
Silbert	1971			periactine	1	0	0	0	0			
Prokinetic agents												
Cisapride					3	2	1	2	2			
Stacher et al.	1987	12		cisapride 8 mg i.v.	1			1	1	acute effect	gastric emptying	yes
Stacher et al.	1993	12		cisapride 30 mg	1	1	?	1	1	12 weeks	weight gain gastric emptying	no yes
Szmukler et al.	1995	29		cisapride 30 mg	1	1	1	1	1	8 weeks	gastric emptying weight gain	no no
Metroclopramide					3	0	0	0	0			
Moldofsky et al.	1977				1							
Saleh and Lebwohl	1979				1							
McCallum et al.	1985				1							

Domperidone					1	0	0	0	0		
Russell et al.	1983	1		domperidone	1	0	0	0	0		gastric emptying	yes
Other compounds												
Zinc					3	0	2	2	2			
Katz et al.	1987			zinc (50 mg elemental zinc/ day)	1	0	1	1	1		level of depression	yes
											level of anxiety	yes
											Zung Depression scale	yes
											STAI	yes
Safei-Kutti	1990	20		zinc	1	0	0	0	0	8–56 months	weight gain	yes
Birmingham et al.	1994	35		zinc gluconate 100 mg	1	0	1	1	1		weight	yes (rate of BMI gain was twice)
Lithium					1	1	1	1	1			
Gross et al.	1981	16		lithium	1	1	1	1	1	4 weeks	weight	yes
											HSCL-90	significant differences in subscales
											GAAQ	significant differences in subscales
											PRS	significant differences in subscales
Naltrexone					1	1	1	1	1			
Marrazi et al.	1995	19	1	natrexone	1	1	1	1	1	6 weeks	weight	BN: fluctuate around normal; AN: some showed no weight restoration
											Binges	yes
											Purges	yes
human growth hormone					2	0	2	2	2			
Hill et al.	2000	15		recombinant human growth hormone	1	0	1	1	1	4 weeks	weight	numerical but not significant, weight gain per day: pharmacological group 0.235 ± 0.077 kg/d vs. placebo 0.166 ± 0.127 kg/d; $P = 0.221$
Fazeli et al.	2010	21	2	recombinant human growth hormone	1	0	1	1	1	12 weeks	weight	no
											% fat	yes
											total fat mass (kg)	yes
THC					1	1	1	1	1			
Gross et al.	1983	11		delta-9-tetrahydrocannabinol	1	1	1	1	1	4 weeks	weight	no
											caloric intake	no
											psychiatric assessment	no, in 3 patients dysphoric side effects

(Continued)

Table IV. *(Continued)*

Author	Year	No. of Patients	Dropouts	Agent	No. of studies	Psychotherapy	Randomized	Placebo-controlled	double-blind	Treatment-duration	Parameters	Positive outcome
Clonidine					1	0	0	1	0			
Casper et al.	1987	4		clonidine	1			1				
D-Cycloserin					1	1	1	1	1			
Steinglass et al.	2007	11		D-Cycloserin	1	1	1	1	1	session	Caloric intake	no
tube feeding					**1**	**1**	**1**	**0**	**0**			
Rigaud et al.	2007	81			1	1	1	0	0		weight relapse	yes yes

nervosa. The diminishing of depressive symptoms was associated with weight gain.

The 7 week placebo controlled double blind study of Attia et al. (1998) in 31 women with anorexia nervosa showed no significant differences in clinical outcomes. The authors conclude that fluoxetine does not appear to add significant benefit to the inpatient treatment of anorexia nervosa.

Kaye et al. (2001) performed a double blind placebo controlled trial on fluoxetine in 35 patients with anorexia nervosa. After one year 3 out of 19 in the placebo group and 10 out of 16 in the fluoxetine group took their medication. Only those patients who remained on fluoxetine had reduced relapse rate and significant increase in weight und reduction of symptoms.

The double blind placebo controlled one year trial of Walsh et al. (2006a) failed to demonstrate any benefit from fluoxetine in the treatment of patients with anorexia nervosa. This study included 93 patients with AN after an inpatient or day-treatment weight restoration program with a minimum BMI of 19 kg/m². Forty-nine patients were assigned to fluoxetine and 21 of those completed the full study. The mean dose of medication was 63.5 mg fluoxetine per day. All of the patients received a structured psychotherapy to prevent relapse, whereas there was no such standardized psychosocial treatment in the study of Kaye et al. (2001).

SERTRALINE. An open, controlled 14-week trial with 22 anrorexic patients (Type AN-R) revealed a significant effectiveness for sertraline regarding depressive symptoms, but not concerning weight gain (Santonastaso et al., 2001)

Other Antidepressants

MIRTAZAPINE. Safer et al. (2010) reported an efficacious treatment of an adult with long-standing anorexia nervosa (AN) with mirtazapine. A 9-month follow-up revealed a maintenance of weight gain and improvement of mood. Mirtazapine may be useful for older, chronically ill patients presenting with AN and comorbid depression.

In conclusion, there is no clear evidence for the general use of SSRIs (citalopram, fluoxetine, sertraline) in anorexia nervosa.

Treatment with Antipsychotics

Typical Antipsychotics

HALOPERIDOL. Cassano et al. (2003) report an open trial with haloperidol in 13 outpatients with treatment-resistant anorexia nervosa (restricting type) over 6 months. They suggest that haloperidol might be

effective as adjunct treatment for patients with severe AN-R.

Sulpiride. Vandereycken (1984) reports a double blind placebo controlled cross over trial on sulpiride (300-400mg) in 18 females with anorexia nervosa. Neither the behavioural and psychopathological measurements nor the weight gain reached statistical significance.

Pimozide. Vandereycken and Pierloot (1982) report a double blind placebo controlled cross over study on pimozide (4 or 6 mg) combined with behaviour therapy in 18 patients with anorexia nervosa. There was a trend for pimozide to induce weight gain.

There is a lack of evidence for the general use of typical antipsychotics (haloperidol, sulpiride, pimozide) in anorexia nervosa.

Atypical Antipsychotics

Olanzapine. There are some open or retrospective studies with olanzapine (Jensen and Mejlhede, 2000; La Via et al., 2000; Powers et al., 2002; Leggero et al., 2010; Malina et al., 2003; Boachie et al., 2003; Barbarich et al., 2004), with promising weight gain or psychopathological improvement in patients with anorexia nervosa.

Mondraty et al. (2005) compared in a randomized controlled trial olanzapine (5 – 15 mg) vs. chlorpromazine (25 – 100 mg). They found reduced anorexic ruminations in the olanzapine group, but no difference concerning BMI alterations between the two study groups.

Brambilla et al. (2007) conducted a double blind placebo controlled 3 month trial with olanzapine (1 month 2.5 mg olanzapine, 2 months 5 mg olanzapine) in 30 patients with anorexia nervosa. There was no significant difference in weight gain between olanzapine and placebo in the whole group, but there were significant differences in BMI changes and in some psychopathological parameters in the binge-purging subgroup.

In a double-blind, placebo-controlled trial Bissada et al. (2008) randomized 34 patients with anorexia nervosa either to the intervention group treated with olanzapine (mean dose for study completers (n = 14): 6,61 mg/day) over 10 weeks or the control-group treated with placebo. Additionally both groups received a day hospital program over the entire study-duration. The olanzapine group was significantly superior over the control-group concerning the rate of weight gain, earlier achievement of the target BMI and in the reduction of obsessive (but not compulsion) symptoms measured by the Y-BOCS.

Spettigue et al. (2008) conducted a study on olanzapine in adolescent patients with anorexia nervosa. At the present time, the results of the trial are not yet available. Norris et al. (2010) reported that only 7 patients with anorexia nervosa out of 92 could be enrolled in the study.

Olanzapine seems to be a promising agent in anorexia nervosa or at least in some subgroups (e.g. AN-BP).

Risperidone. Some case studies (Fishman et al., 1996; Newman-Toker, 2000) suggest that risperidone might be useful in anorexia nervosa. To evaluate the effectiveness of risperidone a larger number of clinical trails with a randomized study design is necessary.

Quetiapine. Bosanac et al. (2007) report an open label study of quetiapine in 8 severly ill patients with anorexia nervosa. Their study suggests benefit for patients with anorexia nervosa as far as weight gain is concerned and psychopathological improvement. Another open-label study by Powers et al. (2007) with 19 oupatient anorexic patients showed a trend, but no significant benefit from a medication with quetiapine concerning weight gain.

Court et al. (2010) conducted a naturalistic, open-label, 12-week randomized controlled trial of low-dose (100-400 mg/day) quetiapine treatment versus treatment as usual in 33 anorexia nervosa patients. Low-dose quetiapine treatment resulted in both psychological and physical improvements, with minimal associated side-effects.

Amisulpride. Ruggiero et al. (2001) compared in a single-blind randomized trial three different medications in anorexia nervosa: amisulpride (n = 12), clomipramine (n = 13) and fluoxetine (n = 10). After the 3-month study phase the authors revealed a significant increase of the mean weight for amisulride and fluoxetine. However it was not possible to detect any between-group differences regarding the body weight.

Aripiprazole. Trunke et al. (2010) report on the treatment of 5 patients with AN with aripiprazole for time periods longer than four months with promising results.

Treatment with Antihistaminics

Cyproheptadine (CYP) was studied by Goldberg et al. (1979) in a ranomized placebo (PLB) controlled trial with 4 arms in 81 female patients (CYP,

PLB, CYP + BT, PLB + BT) because of former studies and clinical experiences of weight restoration with CYP. But there was no clinically significant effect on weight gain with CYP 12 – 32 mg. Post hoc analysis showed only in a more severely ill subgroup of patients with anorexia nervosa a weight gain (patients with with a history of birth complications, a weight loss of 41-52% from norm and a history of failure of prior outpatient treatment).

Halmi et al. (1986) conducted a double blind placebo controlled trial with amitryptiline (maximal dosage 160 mg), cyproheptatine (maximal dosage 32 mg) in 72 female patients with anorexia nervosa. A significant difference in weight gain was only found for cyproheptadine, in fact there was increased weight gain in the non-bulimic group and impaired treatment efficacy in the bulimic group. The depressive symptomatology (HAMD, BDI) responded in both treatment arms. Antihistamines in association with H1-blocking antipsychotics may produce somnolence, metabolic syndrome and the prolongation of QT-interval (Kuchar et al., 2002; Sharif et al., 2003; Bartra et al., 2006).

Treatment with prokinetic agents

Cisapride. Stacher et al. (1987) report accelerated gastric emptying with intravenous cisapride in 12 patients with primary anorexia nervosa. In a following double blind placebo controlled trial in 12 patients with anorexia nervosa Stacher et al. (1993) found again accelerated gastric emptying, but no association with weight gain. Szmukler et al. (1995) found also no difference between cisapride group and placebo group concerning weight gain, not even a difference in gastric emptying.

Thus there seems to be no clear evidence to use cisapride generally in anorexia nervosa. Cisapride in association with tricyclic antidepressants or conventional or atypical antipsychotics generate a high risk for prolonged QT-interval (Glassman et al., 2001; Vieweg et al., 2004).

Metoclopramide. There seems to be an acute effect of metoclopramide on gastric emptying (Saleh and Lebwohl, 1979; McCallum et al., 1985; Stacher et al., 1993). Prokinetic agents are able to accelerate gastric emptying, but there is no clear association with weight restoration in anorexia nervosa.

Treatment with other Pharmacological Compounds

Zinc. The data of the double-blind, randomized, controlled trial of Katz et al. (1987) suggest that adolescent patients with anorexia nervosa may be at risk for zinc deficiency and may respond well after zinc supplementation (50 mg elemental zinc/day). Safai-Kutti (1990) presented an open study with favourable effects of zinc on weight gain in 20 females aged 14 – 26 with anorexia nervosa. They conducted a randomized placebo controlled trial with 100 mg zinc gluconate in 35 females with anorexia nervosa. The BMI gain/day was 0.079 ± 0.07 in the pharmacological group and 0.039 ± 0.06 ($p = 0.03$) in the placebo group.

Birmingham et al. (1994) conducted a randomized, double blind, placebo controlled trial with 100mg zinc gluconate in 35 female patients with AN. The rate of BMI increase in the zinc supplemented group ($n = 16$) was twice that of the placebo group ($n = 19$) and reached stastitical significance.

Birmingham and Gritzner (2006) come to the conclusion that oral administration of 14 mg of elemental zinc daily for 2 months in all patients with AN should be routine. Their hypothesis is that low zinc intake adversely affects neurotransmitters in various parts of the brain, including GABA and the amygdala, which are abnormal in AN. According to neurobiological aspects zinc-deficiency induced anorexia nervosa seems to cause increased levels of neuropeptided Y, for which significant stimulatory effects on food intake were found. A possible explanation for this paradox observation could be a resistance to neuropeptid Y during zinc-deficiency (Shay and Mangian, 2000).

Lithium. Gross et al. (1981) performed a placebo controlled trial with lithium in 16 patients with anorexia nervosa. There were significant differences in weight gain in week 3 and 4 (Difference: 3.9 kg) but the authors see their results preliminary, because of the small sample size and the short duration of the study. In some subscales of the HSCL-90, GAAQ and PRS there were also significant differences.

Naltrexone. The auto-addiction model of Marrazzi et al. (1995) proposes that both anorexia nervosa and bulimia nervosa are opioid-mediated addictions. They treated 19 patients with bulimia nervosa or anorexia nervosa in a double blind placebo controlled cross over design with 100 mg naltrexone twice a day with each period lasting 6 weeks with no wash out between treatment periods. The Binge and Purging Behaviour decreased in both, AN and BN. There was however no weight restoration in some of the patients with AN in week 6.

Growth Hormone. Hill et al. (2000) conducted a randomized, placebo controlled 4 week pilot study with recombinant human growth hormone (rhGH) in 15

patients with anorexia nervosa. The differences in weight gain between pharmacological group and placebo group were numerically but not statistically significant (weight gain per day: pharmacological group 0.235 ± 0.077 kg/d vs. placebo 0.166 ± 0.127 kg/d; $p = 0.221$). Additionally a second randomized, placebo-controlled sudy investigating a medication with recombinant human growth hormone (rhGH) in 21 anorexic women for 12 weeks was not able to uncover a significant weight decrease in the rhGH-treated individuals ($n = 10$) compared to the control subjects ($n = 11$). However between-group differences were found in favour of rhGH-medication regarding the total fat mass and the changes in percentage body fat and percentage lean mass. Another hormone under discussion is oxytocine.

Delta-9-Tetrahydrocannabinol. Gross et al. (1983) conducted a 4 week, double blind cross over study with delta-9-terahydrocannabiol (delta-9-THC) (7.5 – 30 mg) compared to diazepam (3 – 15 mg). 3 patients experienced severe dysphoric reactions during 9-Tetrahydrocannabinol administration. The authors conclude that delta-9-THC is not efficacious in short term administration of primary anorexia nervosa and it is associated with psychiatric disturbances. The weight gain in the delta-9-THC-group was not different to the diazepam-group. However, the dosage used in this study might have been too high and, thus, inhibitory for appetite (Berry and Mechoulam, 2002).

D-Cycloserine. Steinglass et al. (2007) conducted a study with D-Cycloserin to improve caloric intake with "exposure therapy intervention". But caloric intake did not increase significantly in the comparison group.

Nasogastric Tube Feeding

Rigaud et al. (2007) performed a randomized trial on the efficacy of tube feeding regimen in anorexia nervosa. Weight gain was 39% higher in the tube group than in the control group. After discharge the relapse free period was longer in the tube group. The authors conclude that tube feeding is helpful in malnourished patients with anorexia nervosa for weight gain without hindrance on eating behaviour.

Combining Pharmacotherapy with Psychotherapy

There is no clear evidence to recommend the addition of pharmacotherapy to psychotherapy in treating AN. Patients with with comorbidities (e.g. depression, obsessions, compulsions, anxiety) may benefit from pharmacological addition to psychotherapy.

Discussion of Guidelines for Anorexia Nervosa

There are 4 randomized controlled trials (RCT) with 32 patients for clomipramine and 97 patients for amitryptiline with no positive outcome over placebo concerning weight gain. In the study of Halmi et al. (1986) there was a positive outcome over placebo for depressive symptomatology (Category grade E evidence).

There is one RCT for citalopram with no efficacy over placebo concerning weight gain. Again depressive symptomatology was improved. There are 3 RCT for fluoxetine with no efficacy over placebo concerning weight gain. The study of Walsh et al. (2006a) showed no effect on relapse in AN after an weight restoration programm with psychotherapeutic relapse prevention. Obsessive-compulsive symptomatology was lowered in the study of Kaye et al. (2001) (Category grade E evidence).

Antidepressant treatment seems not to be helpful in increasing weight in anorexia, but can improve depressive symptomatology and obsessive-compulsive symptomatology. In conclusion, antidepressants may be used in AN with depressive symptomatology or with comorbid obsessive compulsive disorder, but not in general.

There is one RCT for sulpiride and one RCT for pimozide with no clearly significant effect over placebo concerning weight gain (Category of evidence grade E). There is one RCT for olanzapine with efficacy in EDI-2/anorex subscore and one with increase in BMI over placebo for the binge-purging subtype of anorexia nervosa. There is one RCT for olanzapine with olanzapine being useful in increasing the rate of weight gain and in reducing time to achievement of weight restoration among patients with AN. And there is one ongoing RCT for olanzapine. (Category B evidence). So far promising effects are only based on case studies and retrospective studies for risperidone, quetiapine and amisulpiride, evidence from RCTs is, however, still lacking (Category C1 to C2 evidence).

Cyproheptadine was only a little more effective than placebo in post-hoc analysis concerning weight gain. There may be an effect on weight gain of antihistaminics, but clear RCT evidence is still missing (Category grade F).

The effects of cisapride concerning gastric emptying are conflicting. Whereas one study found no efficacy over placebo, 1 study found a difference for gastric emptying. As far as weight gain is concerned both studies found no efficacy (Category grade E evidence).

There are 2 RCTs for zinc, with efficacy over placebo for weight gain, depression and anxiety (Category grade B evidence). One RCT found no efficacy for Lithium over placebo. One RCT found efficacy over placebo concerning binges or purges. One RCT found

no efficacy for Human growth hormone over placebo. One RCT found no efficacy for THC over placebo.

One RCT found efficacy for weight gain and relapse.

While there is no level A Evidence (see Table I) for the psychopharmacological treatment of anorexia nervosa, there is level B evidence for zinc supplementation in anorexia nervosa and there is a level C evidence for nasogastric tube feeding in malnourished patients with anorexia nervosa. There is evidence for prokinetics in acceleration of gastric emptying in anorexia nervosa, but not for general use in AN. There is no evidence to use antidepressants generally in anorexia, but concerning comorbidity in anorexia nervosa und some aspects of eating disorder psychopathology, there are possible benefits for antidepressants in anorexia nervosa.

Bulimia Nervosa (BN)

Diagnosis of Bulimia Nervosa

BN is defined by repeated episodes of binge eating followed by inappropriate compensatory behaviours such as self-induced vomiting; misuse of laxatives, diuretics, or other medications; fasting; or excessive exercise (DSM-IV). For diagnostic criteria see Table III.

Epidemiology of Bulimia Nervosa

In the National Comorbidity Survey (USA) the lifetime prevalence of DSM-IV bulimia nervosa was 1.5% among women, and 0.5% men (Hudson et al., 2007). The prevalence rate in non-Western countries (0.46% to 3.2% in female subjects) is lower than in western countries (0% to 2.1% in males and 0.3% to 7.3% in female subjects) according to Makino et al. (2004). But these results have to be seen with caution (see also Epidemiology of AN). The epidemiology of eating disorders in six European countries: results of the ESEMeD-WMH project was presented by Preti et al. (2009): Lifetime estimated prevalence of bulimia nervosa was 0.51%.

Course of Bulimia Nervosa

The lifetime prevalence of DSM-IV bulimia nervosa is 2.3%; (76% of females: purging subtype; 24%: non-purging subtype) (Hudson, Preti 2009). The incidence rate of bulimia nervosa is 300/100.000 person-years. Outcome: the 5-year clinical recovery rate is 55% (Keski-Rahkonen et al., 2008).

Treatment with Antidepressants

The rationale to treat BN with antidepressants is evidence of dysfunction in the serotonergic and noradrenergic systems and the comorbidity and psychopathological overlap with anxiety disorders, obsessive compulsive spectrum disorders and depression.

Tricyclics. Pope et al. (1983) conducted a placebo-controlled double blind study with imipramine in 22 patients with bulimia nervosa. Imipramine was associated with significant reduction in binge eating and other measures of eating behaviour.

Mitchell and Groat (1984) performed a placebo controlled double blind trial with amitryptiline in 32 female outpatients who received a minimal behavioural treatment program. Both groups demonstrated considerable improvement in eating behaviour. There was no significant difference between placebo and amitryptiline concerning weight gain or increased carbohydrate craving.

Huges et al. (1986) presented a placebo controlled double blind trial with desipramine in 29 outpatients with bulimia nervosa. Benefits could be shown in global clinical status, weekly binge eating frequency, bulimia symptoms scale and the depressive symptomatology (ZSRDS).

Agras et al. (1987) presented a placebo controlled double blind trial with imipramine in 22 women over a treatment period of 16 weeks. There was a significant reduction in the purging behaviour in week 6 and week 16 associated with imipramine as well as a reduction in depressive symptomatology in week 6.

Barlow et al. (1988) conducted a double blind cross over trial with desipramine 150 mg/day in 47 normal weight patients with bulimia nervosa. 23 patients dropped out. Desipramine was significantly more effective in reducing frequency of weekly vomiting and weekly binging. No significant effects were obtained from EDI and SCL-90.

Mitchell et al. (1990) performed a 12 week comparison study of imipramine and structured group psychotherapy in the treatment of bulimia nervosa with 4 arms (PLB, imipramine, group therapy + PLB, group therapy + imipramine). Imipramine did not significantly improve eating behaviour over placebo, but reduced symptoms of depression and anxiety.

Alger et al. (1991) conducted a 8 week 3 arm placebo controlled study: naltrexone 100-150 mg/day, imipramine up to 150 mg, placebo. In 41 obese bingers and 28 normoweight bulimics. There was a significant reduction of binge duration for naltrexone, only in obese bingers for imipramine. The binge frequency, however, could not be significantly reduced, due to a high placebo effect.

Table V. Studies on pharmacological treatment in bulimia nervosa.

Author	Year	No. of Patients	Dropouts	Agent	No. of studies	Psychotherapy	Randomized	Placebo-controlled	Double-blind	Treatment-duration	Parameters	Positive outcome/ Superiority
Antidepressants												
Trizyclics					11	4	11	9	9			
Pope et al.	1983	22		imipramine	1	0	1	1	1		frequency of binge eating	yes
											eating behaviour	yes
Mitchell and Groat	1984	32		amitryptiline 150 mg/day	1	1	1	1	1		Beatin behaviour	no
Hughes et al.	1986	29	7	desipramine	1	0	1	1	1		weekly binge frequency	yes
											global clinical status	yes
											Bulimia Symptom Scale	yes
											ZSRDS	yes
Agras et al.	1987	22	2	imipramine	1	0	1	1	1	16 weeks	reduction in purging (frequency of self-induced vomiting plus the use of laxatives)	yes
											depression	yes (week 6)
Barlow et al.	1988	47	23	desipramine 150 mg/day	1	0	1	1	1	6 weeks	EDI	no
											SCL-90	no
											POMS	yes (fatigue scale)
											weekly binding	yes
											weekly vomitting	yes
Blouin et al.	1988	22		desipramine and fenfluramine	1	0	1	1	1	15 weeks	EDI	yes
											profile of mood states	yes
											bulimia symptoms checklist	yes
Mitchell et al.	1990	171	16	imipramine	1	1	1	1	1	12 weeks	number of binge eating episodes	yes, but not with group therapy
											vomiting episodes	yes, but not with group therapy
											HAMD	yes
											HAMA	yes
Alger et al.	1991	69	14	imipramine, naltrexone	1	0	1	1	1	8 weeks	binge duration	yes, imipramine only in obese bingers
											binge frequency	no
Walsh et al.	1991	80		desipramine	1	0	1	1	1	8 weeks	binge frequency	yes
Agras et al.	1992	71		desipramin, and cognitive behaviour therapy	1	1	1			32 weeks	binge eating rates	yes (combination of medication and cognitive-behavioral therapy)
											purging rates	yes (combination of medication and cognitive-behavioral therapy)
Leitenberg et al.	1994	21	6	desipramine	1	1	1	0	0	20 weeks	EAT	no

(Continued)

Table V. *(Continued)*

Author	Year	No. of Patients	Dropouts	Agent	No. of studies	Psychotherapy	Randomized	Placebo-controlled	Double-blind	Treatment-duration	Parameters	Positive outcome/ Superiority
											BSI	no
											BSQ	no
											IDD	yes
											self-esteem	no
SSRIs												
Citalopram					2	0	2	1	1			
Sundblad et al.	2005	46		citalopram, flutamide	1	0	1	1	1	12 weeks	binge eating	no
											self rated symptom intensity	yes
Leombruni et al.	2006	37	9	Citalopram vs. fluoxetine	1	0	1	0	0	12 weeks	EDI-2	equal
											BSQ	equal
											BES	equal
											BDI	equal
											personality (Temerament and Character Inventory)	equal
fluoxetine					10	6	7	5	6			
Fichter et al.	1991	40		fluoxetine 60 mg	1	1	1	1	1	5 weeks	SCL-90-R	no
											HAMD	no
											EDI	no
											CGI	no
Goldstein et al.	1995	398	163	fluoxetine 60 mg	1	0	1	1	1	16 weeks	vomiting	yes
											bing-eating episodes	yes
											EDI	
											CGI	
											PGI	
Fluoxetine Bulimia Nervosa Collaborative Study Group	1992			fluoxetine	1				1	8 weeks		
Mitchell et al.	2001	91		fluoxetine 60 mg and manual based self-help	1	1	1	1	1	16 weeks	binge eating episode	yes
											vomiting	yes
Jacobi et al.	2002	53	18	fluoxetine and cognitive behaviour therapy	1	1	1	0	0	4 months	combined treatment	no

Kotler et al.	2003	10		fluoxetine 60 mg	1	1	0	0	0	8 weeks	average weekly binges	yes
											average weekly purges	yes
Goldbloom et al.	1997	76	33	fluoxetine	1	1	1	0	0	16 weeks	binges	yes
											vomit episodes	yes
											EDE	no
											BDI	no
Goldstein et al.	1999	383 + 390		fluoxetine max. 60 mg/day	1	0?	?0	?0	0?	8 16 weeks	depressve vs. non-depressive	both
Walsh et al.	2000	22 (treatment-resistant)		fluoxetine 60 mg/day	1	1?	1	1	1	8 weeks	frequency of binge eating	yes
											purging frequency	yes
Romano et al.	2002	232 150		fluoxetine 60 mg/day	1	0	1	1	1?	8 + 52 weeks	longer time to relapse	yes
											frequency of vomiting	yes
											frequency of binge eating	yes
Fluvoxamine					4	3	4	3	4			
Brambilla et al.	1995	15	0	combined cognitive-behavioural, psychopharmacological (5 amineptine, 10 fluvoxamine) and nutritional therapy	1	1	1	0	1	4 months	BMI	no change
											EDI	no
											BITE	yes
											HAMD	no
											HAMA	no
Fichter et al.	1996	72	27	fluvoxamine	1	1	1	1	1	15 weeks	EDI-bulimia	yes
											urges to binge in previous week	yes
											SIAB total score	yes
Schmidt et al.	2004	267	14?	fluvoxamine and graded psychotherapy	1	1	1	1	1	1 year	BSI	no
											binges over last week	no
Milano et al.	2005	12	0	fluvoxamine 200 mg/day	1	0	1	1	1	12 weeks	binge eating crisis	yes
											purging	yes
Sertraline					1	0	1	1	0			
Milano et al.	2004	20	0	sertraline 100 mg/day	1	0	1	1		12 weeks	binge eating crises	yes
											purging	yes
RIMA												
Moclobemide					1	0	1	1	1			
Carruba et al.	2001	78	25	moclobemide	1	0	1	1	1	6 week	weekly number of binge eating episodes	no

(Continued)

Table V. *(Continued)*

Author	Year	No. of Patients	Dropouts	Agent	No. of studies	Psychotherapy	Randomized	Placebo-controlled	Double-blind	Treatment-duration	Parameters	Positive outcome/ Superiority
											BITE, Edi, TFQE	no, improving several measures of eating attitudes and behaviour
Phenelzine					3	0	3	3	3			
Walsh et al.	1984	25	5	phenelzine	1	0	1	1	1	10 weeks	binges per week	yes
											EAT	yes
Walsh et al.	1988	62	12	phenelzine	1	0	1	1	1	10 week	binges/week	only trend
											SCL-90 (subscales)	yes
											EAT	yes
											HAMD	yes
											BDI	yes
Rothschild	1994	24	10	phenelzine/imipramine	1	0	1	1	1	6 week	SCL-90-"overeating"	yes
											HAMD	yes
Isocarboxazid					1	0	1	1	1			
Kennedy et al.	1988	18	7	Isocarboxazid	1	0	1	1	1	13 weeks	binge eating	yes
											vomiting	yes
											EAT-26	yes
											HAMD	yes
											HAMA	yes
Brofaromine					1	0	1	1	1			
Kennedy et al.	1993	36		brofaromine	1	0	1	1	1	8 weeks		no
											weight	yes
NRI					**2**	0	0	0	0			
El-Giamal et al.	2000	7	3	reboxetine 8 mg/day	1	0	0	0	0	12 weeks	binge eating frequency	yes
											frequency of vomiting episodes	yes
Fassino	2004	28		reboxetine 4 mg/day	1	0	0	0	0	3 months	GAF	yes
											HAMD	yes
											BSQ	yes
											EDI-2	some subscores
Other Antidepressants												
Duloxetine					1	0	0	0	0			

Hazen and Fava	2006	1	0	duloxetine	1	0	0	0	0	16 weeks	sucessful treatment	
Bupropion					1	0	1	1	1			
Horne et al.	1988	81		bupropion	1	0	1	1	1	8 weeks	reducing binge eating	yes
											reducing purging	yes
Trazodone					1	0	1	1	1			
Pope et al.	1989	46	4	trazodone	1	0	1	1	1		frequency of binge eating	yes
											frequency of vomiting	yes
Mianserin					1	0	1	1	1			
Sabine et al.	1983	50	14	mianserin	1	0	1	1	1	8 weeks	HAMD	no
											HAMA	no
											EAT	no
											BRS	no
											weight	no
Antipsychotics Aripiprazole												
Trunko et al.	2010	3		aripiprazole	1	0	0	0	0	>4 months	Eating disordered behaviour	significant lessening of eating-disordered behaviors
Antiepileptics Carbamazepine					1	0	0	1	0			
Kaplan et al.	1983	6		carbamazepine	1	0	0	1	0	6 weeks	1 patient with comorbid bipolar disorder improved, 5 did not	
Oxcarbamazepin					1	0	0	1	1			
Cordas et al.	2006	2		oxcarbazepine 1200 - 1500 mg/day for self-mutilating in patients with bulimia nervosa	1	0	0	1	1	after 2 weeks	self mutilatung behaviour	yes
											vomiting	no
Topiramate					3	0	3	3	3			
Hedges et al.	2003	69	5	topiramate	1	0	1	1	1	10 weeks	EDI	subscales yes
											EAT	yes

(Continued)

Table V. *(Continued)*

Author	Year	No. of Patients	Dropouts	Agent	No. of studies	Psychotherapy	Randomized	Placebo-controlled	Double-blind	Treatment-duration	Parameters	Positive outcome/ Superiority
											HAMA	yes
											HAMD	trend
											PGI	yes
Hoopes et al.	2003	69	5	topiramate	1	0	1	1	1	10 weeks	binges	yes
											purges	yes
Nickel et al.	2005	60		topiramate	1	0	1	1	1	10 weeks	binges/purges	yes
											weight	yes
											SF-36	yes
Other pharmacological compounds												
d-Fenfluramine					1	1	1	1	1			
Fahy et al.	1993	43		d-fenfluramine 45 mg/ day(5-HT agonist)	1	1	1	1	1	8 weeks	advantage over psychotherapy	no
Odansetron					1	0	1	1	1			
Faris et al.	2000	26	1	ondansetron	1	0	1	1	1	2 + 4 weeks	binge/vomit frequency	yes
											time spent engaging in bulimic behaviurs	yes
											number of eating episodes not followed by vomiting	yes
Lithium					1	1	1	1	1			
Hsu et al.	1991	91	23	lithium carbonate	1	1	1	1	1	8 week	bulimic episods	no
Naltrexone					5	0	1	2	2			
Jonas and Gold	1986	10		naltrexone 300 mg/day	1	0	0	0	0	6 weeks	bulimic symptoms	yes
Jonas and Gold	1988	16		naltrexone	1	0	0	0	0	6 weeks	frequency of binge eating/ purging	yes (but only for high dosages, 200-300 mg/d)
Mitchell et al.	1989	19	3	naltrexone	1	0	0	1	1	6 weeks	binge eating/vomiting	no
Huseman et al.	1990	10		naltrexone	1	0	1	1	1	10 weeks	frequency of binge eating	no
Alger et al.	1991	28		imipramine vs naltrexone	1	0	1	1	1	8 weeks	binge duration	yes

Methylphenidate					1	0	0	0	0					
Sokol et al.	1999	2		methylphenidate	1	0	0	0	0	4 days + 10 months	binging and purging			yes
baclofen					1	0	0	0	0					
Broft et al.	2007	7 (4 BED;1 3 BN)		baclofen	1	0	0	0	0	10 weeks	frequency of binge eating			yes
Light therapy					2	0	1	2	2					
Lam et al.	1994	17		light therapy	1	0	0	1	1	2 weeks BL 30 min/day, 2 weeks DRL 30 min/day	mood measures			yes
											eating outcome measures			yes
Braun et al.	1999	34		Light therapy	1		1	1	1	8 weeks	mean binge frequency			yes

Walsh et al. (1991) performed a 8 week placebo controlled trial with desipramine. Desipramine was superior to placebo after 8 weeks concerning binge frequency. But there are limitations in the long-term treatment.

Agras et al. (1992) performed a controlled trial with 5 groups: desipramine, combined treatment, and cognitive behaviour therapy. In week 16 both CBT and combined therapy were superior to medication. The authors conclude that the results favour the use of a combination of medication and CBT in the treatment of bulimia nervosa.

Leitenberg et al. (1994) compared CBT alone, desipramine alone and cognitive behaviour therapy combined with desipramine in the treatement of bulimia nervosa. The study was terminated after 7 subjects because of lack of positive response in the desipramine group alone compared to the two other groups and high drop out due to medication. In the desipramine group only the depressive symptomatology was significantly improved.

Walsh et al. (2006b) made an analysis over two studies with desipramine. Nonresponders to desipramine could be reliably indentified in the first 2 weeks of treatment.

SSRI.

Citalopram. Sundblud et al. (2005) performed a double blind placebo controlled pilot study with 4 arms: flutamide (androgen antagonist), citalopram, citalopram + flutamide, placebo. Binge eating was significantly reduced with flutamide, but not in the only citalopram study arm. Self-rated global assessments of symptom intensity were significantly reduced in all active medications over placebo.

Leombruni et al. (2006) performed a single blind randomized controlled trial with citalopram vs. fluoxetine in 37 patients with bulimia nervosa. No significant difference between treatments could be found.

Fluoxetine. Fichter et al. (1991) performed a placebo controlled double blind study with fluoxetine 60 mg in 40 patients with bulimia nervosa undergoing an intensive psychotherapy. There was no significant difference between the placebo and the fluoxetine group. The authors said that the results were due to a "ceiling effect".

Goldstein et al. (1995) reported a multicenter (15 outpatient clinics) double blind placebo controlled study with fluoxetine in 398 patients with bulimia nervosa. There was a significantly higher reduction of vomiting and binge eating for the fluoxetine-group compared to placebo.

Goldbloom et al. (1997) compared fluoxetine, individual cognitive behaviour therapy and as a third

study group a combination of both in 76 female patients with bulimia nervosa over 16 weeks. There was a superiority of the combined treatment over pharmacotherapy alone on specific parameters, but no statistical evidence that a combined treatment (psychotherapy + fluoxetine) is superior to psychotherapy alone.

Goldstein et al. (1999) made a stratified analysis (depressed vs. non-depressed) of two randomized placebo controlled trials. They found that fluoxetine 60 mg was effective in the treatment of bulimia nervosa (reduction of binge eating and vomiting episodes) regardless of presence or absence of depression.

Walsh et al. (2000) conducted a placebo controlled trial in 22 patients with psychotherapy (CBT or IPT) refractory bulimia nervosa. They found reduced frequencies of binge eating and purging in the fluoxetine group and concluded, that fluoxetine may be a useful intervention for patients with bulimia nervosa who have not responded to adequate psychotherapy.

Mitchell et al. (2001) conducted a 4 arm randomized 16 week placebo controlled study (PLB only, fluoxetine only, PLB and self-help manual, fluoexetine and self help manual) with 91 females with bulimia nervosa. Fluoxetine was superior to placebo. There were no significant differences in abstinence rates in the active treatment arms (16% fluoxetine; 24% manual + PLB, 26% manual + fluoxetine).

Jacobi et al. (2002) conducted a 3 arm study: CBT, fluoxetine and combination of CBT and fluoxetine. The results of the study did not favour the combined treatment over the CBT alone.

Romano et al. (2002) conducted a 52 week randomized placebo controlled study with a single blind run in phase (8 weeks) (n = 232). Responders were followed in the double blind phase (n = 150). The relapse time was significantly longer and binge eating and vomiting could be reduced in the fluoxetine group compared to placebo. They concluded that continued treatment with fluoxetine in acute treatment responders improve outcome and decrease likelihood of relapse.

Kotler et al. (2003) report that their open study with fluoxetine 60 mg over 8 weeks was well tolerated by the adolescent patients with bulimia nervosa und may be an effective treatment option in this population group.

Fluvoxamine. Brambilla et al. (1995c) conducted a study on combined cognitive-behavioural, psychopharmacological (5 amineptine, 10 fluvoxamine) and nutritional therapy in bulimia nervosa. After 4 months of therapy and BITE severity of illness improved significantly and equally in both groups. The global EDI scores and anxiety decreased, but not significantly. BMI was stable. No side effects were observed during fluvoxamine or amineptine therapy.

Fichter et al. (1996) conducted a double blind placebo controlled trial with 72 patients with bulimia nervosa. The patients received fluvoxamine or placebo over 15 weeks (2-3 weeks inpatient titration phase, 12 weeks outpatient relapse-prevention phase). Fluvoxamine had a significant effect in delating relapse of bulimic behaviour.

Schmidt et al. (2004) conducted a one year randomized double blind placebo controlled trial with 267 patients with bulimia nervosa containing three study groups: a 8 week short-time fluvoxamine therapy followed by a 44 week placebo intake, a group receiving fluvoxamine over the whole 52 weeks and a placebo control group. Neither the short- nor long-time fluvoxamine therapy brought any additional benefit to graded psychotherapy approach.

Milano et al. (2005) conducted a 12-week randomized placebo controlled trial with fluvoxamine 200 mg/day in 12 female patients with bulimia nervosa. There was a significant reduction in binge eating crises and purging episodes over placebo. In no case treatment was interrupted because of side effects.

Sertraline. Milano et al. (2004) conducted a 12-week randomized placebo controlled trial with sertraline 100 mg/day in 20 female patients with bulimia nervosa. There was a significant reduction in binge-eating crises and purging in the sertraline group compared to PLB.

RIMA.

Moclobemide. Carruba et al. (2001) conducted a 6-week double blind placebo controlled trial to examine the efficacy and tolerability of 600 mg moclobemide/day. 52 out of recruited 78/77 normal weight female patients with bulimia nervosa completed the study. There was no significant difference between moclobemide and placebo concerning eating attitudes and behaviour (BITE, EDI, TFEQ).

Phenelzine. Walsh et al. (1984) conducted a double blind placebo controlled trial with phenelzine in 25 normal weight females with bulimia nervosa. Phenelzine was associated with significant reduction of binges and lowering EAT score. Side effects were problematic. They conclude that phenelzine may be a treatment for normal weight females with bulimia

nervosa, who are capable of maintaining a tyramine-free diet. 5 patients dropped out.

Walsh et al. (1988) conducted a double blind placebo controlled trial with phenelzine in 62 females with bulimia nervosa. Phenelzine was superior to placebo in reducing SCL-90 (subscales), EAT, HAMD, BDI. There was a trend for reducing binges per week. Side effects were however problematic. 12 patients dropped out.

Rothschild et al. (1994) compared phenelzine and imipramine in a double blind placebo controlled trial. She included 24 patients from a prior study on atypical depression with additional bulimia nervosa. There was a significant difference for the phenelzine group over placebo and imipramine concerning HAMD and SCL-90-overeating.

Isocarboxazid. Kennedy et al. (1988) report a double-blind, placebo-controlled crossover trial of isocarboxazid for the treatment of bulimia nervosa in 18 females. Binge eating and vomiting were significantly reduced.

Brofaromine. Kennedy et al. (1993) reported an 8-week, double-blind, placebo-controlled trial of brofaromine with 36 female patients. There were no advantages of brofaromine over placebo.

NRI.

Reboxetine. Fassino et al. (2004) conducted an open study in 28 patients with bulimia nervosa to investigate the treatment effects of reboxetine 4mg/day over 3 months. There were significant reductions in BSQ total score, HAMD and GAF, as well as some subscores of EDI-2. El-Giamal et al. (2000) could provide evidence for a decreased binge eating frequency and a decreased frequency of vomiting episodes through a medication with reboxetine (8 mg) in seven cases of bulimia nervosa.

Other antidepressants.

Duloxetine. Hazen and Fava (2006) report a case with successful duloxetine treatment of bulimia nervosa with complete remission of the patient's bingeing and purging behaviours.

Bupropion. Horne et al. (1988) report a double blind placebo controlled trial with bupropion in 81 patients with bulimia nervosa. There was a significant reduction in binge eating und purging behaviour. However, 4 subjects experienced grand mal seizures during bupropion therapy and thus bupropion is not considered appropriate in this connection in many countries.

Trazodone. Pope et al. (1989) reported a double blind placebo controlled trial of trazodone in 46 females with bulimia nervosa. Trazodone was significantly superior to placebo in reducing frequency of binge eating and vomiting. Trazodone produced few adverse effects.

Mianserin. Sabine et al. (1983) reported a 8-week randomized placebo controlled double blind trial with mianserin with 50 females. There was no improvement over placebo for eating attitudes and behaviour as well as for anxiety and depression scores.

Treatment with Antiepileptics

Carbamazepine. Kaplan et al. (1983) performed a double blind crossover study with carbamazepine in 6 patients with bulimia nervosa. One patient with comorbid bipolar disorder improved "dramatically", the other five had no response.

Oxcarbamazepine. Cordas et al. (2006) report 2 cases of females with bulimic behaviour among other psychiatric comorbidity and self-mutilating behaviour. Self-mutilating behaviour disappeared, but not vomiting.

Topiramate. Hoopes et al. (2003) conducted a 10 week, randomized, double blind, placebo controlled trial in 69 patients with bulimia nervosa with topiramate. There was a significant reduction in binge and purge symptoms. Hedges et al. (2003) analysed the same sample and reported that there was also significant reduction in other behavioural und psychopathological dimensions.

Nickel et al. (2005) reported a 10 week, double blind placebo controlled trial with 60 BN patients receiving either topiramate ($n = 30$) or placebo ($n = 30$). There was a significant reduction in frequency of binging/purging, weight and health could be improved and thus the quality of life got better. In some cases sedation, dizziness, headache, and parasthesia were reported, but there were no psychotic symptoms, nor serious side effects.

Treatment with other Pharmacological Compounds

d-fenfluramine. Fahy et al. (1993) conducted an 8-week, placebo controlled trial of d-fenluramine in 43 patients with bulimia nervosa. The study failed to show additional effects over brief psychotherapy alone.

Odansetron. Faris et al. (2000) conducted a randomised double blind placebo controlled study with odandsetron, a 5-HT3-Antagonist, in 26 patients with bulimia nervosa. The treatment-phase with ondansetrone 4 mg/day was 4 weeks. Ondansetron treatment was associated with a significantly greater decrease in binge/vomit frequencies compared to placebo. There was also a significantly greater improvement in the normalization of eating behaviour in the ondansetron group (time spent in bulimic behaviour, number of eating episodes not followed by vomiting ("normal meals"). The use of this drug should be cautioned because of potential serious side effects.

Lithium. Hsu et al. (1991) conducted a randomised double blind placebo controlled study with lithium in 91 females with bulimia nervosa. There was no significant difference in the improvement of bulimic episodes to placebo after 8 weeks.

Naltrexone. Jonas and Gold (1986) conducted an open trial with naltrexone 300 mg in 10 patients with antidepressant-resistant bulimia nervosa. There was a 75% decrease in bulimic symptoms in 7 out of 10 patients. The authors conclude that naltrexone may be of use in unresponsive bulimia nervosa. In a second study Jonas and Gold (1988) compared the effectiveness of standard dosages (50-100 mg/day) with high dosages (200-300 mg/day) of naltrexone in 16 bulimic patients and could show that only a high-dose treatment is recommendable for a successful phamacological treatment.

The auto-addiction model of Marrazzi et al. (1995) proposes that both anorexia nervosa and bulimia nervosa are opioid-mediated addictions. They treated 19 patients with bulimia nervosa or anorexia nervosa in a double blind placebo controlled cross over design with 100 mg naltrexone twice a day with each period lasting 6 weeks with no wash out between treatment periods. The Binge and Purging Behaviour decreased in both, AN and BN. The weight of BN patients fluctuated around normal.

Methylphenidate. Sokol et al. (1999) reported two cases of treatment refractory bulimia nervosa with Cluster B personality disorder. Both patients had decreased binging and purging after 4 days of methylphenidate up to 20 mg a day. The effect lasted in the follow up after 10 or 12 months, respectively. The authors conclude that further studies on methylphenidate are worthwhile, but given the potential risks, treatment with methylphenidate is not recommended today.

Aripiprazole. Trunko et al. (2010) reported on the treatment of 3 patients with BN with aripiprazole for time periods longer than 4 months. The results were promising.

Light therapy

Lam et al. (1994) conducted a controlled crossover study with bright white light (BWL) (10.000 lux for 30 min/day) vs. dim red light (DRL) (500 lux 30 min/day) in 17 female patients with bulimia nervosa. The authors concluded that bright white light therapy is an effective-short-term treatment for both mood and eating disturbances associated with bulimia nervosa with greater efficacy, if there is a seasonal pattern.

Braun et al. (1999) conducted a 8-week, double blind placebo controlled study objective to determine the effect of winter bright light therapy on binge and purge frequencies and depressive symptoms in subjects with bulimia nervosa (n = 34). The mean binge frequency decreased significantly more from baseline to the end of treatment for the bright light group than for the placebo group.

Combining Pharmacotherapy with Psychotherapy

36% of the RCTs with tricyclic antidepressants involved psychotherapy in their study protocol. No clear evidence points to the superiority of the combined treatment of tricyclic antidepressants and psychotherapy (Category of evidence D). Fluoxetine seemed to have no additional benefit over psychotherapy in the combined treatment. The combination with psychotherapy and pharmacological group seems to have a ceiling effect, with no clear additional benefit not even for d-fenfluramine and lithium.

Discussion of Guidelines for Bulimia Nervosa

There are 4 RCTs for imipramine with efficacy in reducing bulimic behaviour (Category of evidence A, recommendation grade 2). There is one RCT for amitryptiline with no clear evidence of superiority

over placebo, only in the depressive subgroup there was a significant difference over placebo (Category of evidence D). There are 6 RCTs for desipramine with efficacy in reducing bulimic behaviour (Category of evidence A, recommendation grade 2).

For citalopram there is no clear efficacy in bulimia nervosa over placebo (Category of evidence E). For fluoxetine there are 7 RCTs with 6 showing an efficacy over placebo concerning bulimic behaviour (Category of evidence A, recommendation grade 1). For fluvoxamine there are 3 RCTs with 2 showing efficacy over placebo concerning bulimic behaviour (Category of evidence B, recommendation grade 2). For sertraline there is one RCT that shows efficacy over placebo concerning bulimic behaviour (Category of evidence B). SSRIs have to be used in daily doses higher than those required for the antidepressant effect to obtain an antibulimic action in BN. RIMA: Moclobemide shows no efficacy in bulimia nervosa in 1 RCT (Category of evidence E). Phenelzine shows an efficacy over placebo in 3 RCTs concerning bulimic behaviour The inability to maintain a tyrosine free diet under the therapy of phenelzine is associated with the serious side effects, therefore the drug cannot be recommended, even there is a evidence for the reduction of bulimic behaviour (Category of evidence A, no recommendation). Isocarboxazide shows efficacy over placebo in one RCT (Category of evidence B).

There is no general effect for brofaromine in BN, but it was associated with weight reduction.

For reboxetine there is only an openstudy which suggests efficacy in bulimia nervosa, but no RCT was found (Category of evidence C1).

The same is true for duloxetine. For bupropion as well trazodone one RCT shows efficacy over placebo in reducing bulimia nervosa associated psychopatholoy and behaviour.

No evidence was found for efficacy of mianserin in 1 RCT in bulimia nervosa.

There was no efficacy for carbamazepine and oxcarbamazepine in bulimia nervosa.

There were 2 RCTs for topiramate with efficacy in reducing bulimia nervosa associated psychopathology and behaviour. There is a grade A evidence for topiramate in BN, with a moderate risk-benefit ratio.

There is no effect over brief psychotherapy for d-fenfluaramine.

There is no efficacy for lithium in BN.

Odansetron has an efficacy over placebo in 1 RCT for BN associated behaviour. There is a grade B evidence, but the use of this drug should be cautioned because of potential serious side effects.

There are inconsistent results for naltrexone in BN (Category of evidence grade D).

There are no RCTs concerning methylphenidate and baclofen. There are 2 RCT for light therapy in reducing psychopathology in BN (Category of evidence grade A).

The available literature on pharmacological treatment of BN is based on trials of relatively short duration (most of the studies were less than 6 months length), so the is not enough information on the long-term efficacy of these treatments.

Binge Eating Disorder (BED)

Diagnosis of Binge Eating Disorder

Binge eating disorder (BED) is classified under eating disorders not otherwise specified (EDNOS) and is characterized by binge eating episodes without compensatory behaviour. Often binge eating disorder is associated with severe obesity (body-mass index ≥ 40) (Hudson et al., 2007). For diagnostic criteria see Table III.

Epidemiology of Binge Eating Disorder

In the National Comorbidity Survey (USA) the lifetime prevalence of DSM-IV binge eating disorder was 3.5% among women, and 2.0% among men (Hudson et al., 2007). In Europe the lifetime estimated prevalence of binge eating disorder, subthreshold binge eating disorder, and any binge eating was 1.12%, 0.72%, and 2.15%, respectively.

Course of Binge Eating Disorder

Full BED is significantly associated with bipolar disorder, major depressive disorder, bulimia nervosa, most anxiety disorders, substance use disorders, body dysmorphic disorder, kleptomania, irritable bowel syndrome, and fibromyalgia (Javaras et al., 2008). But the literature concerning outcomes was greaded weak for BED by Berkman et al. (2009), additional research in this field is warranted.

Treatment with Antidepressants

The rationale to treat BED with antidepressants is the evidence of dysfunctions in the serotonergic and noradrenergic system and the comorbidity and psychopathological overlap with anxiety disorders and depression.

Tricyclics. McCann and Agras (1990) conducted a 12-week double blind placebo controlled trial with desipramine (150 mg/day) in 23 female patients with non-purging bulimia. The number of days per week

engaged in binge eating decreased by 63% in the desipramine group and increased in 16% in the placebo group. The authors conclude that desipramine may be useful in the treatment of non purging bulimic patients.

Alger et al. (1991) conducted a 8-week double blind placebo controlled trial with naltrexone (100-150 mg/day) and imipramine (150 mg/day) in 88 obese binge eaters and 60 normal weight people with BN. Natrexone was associated with a significant decrease in binge duration in bulimics and imipramine was associated with reduced binge duration in obese bingers. The authors conclude that naltrexone and imipramine may be useful in the treatment of binge eating.

Agras et al. (1994) conducted a trial with a weight loss treatment, CBT and desipramine in 108 overweight patients with binge eating disorder. The additional desipramine or CBT together with weight loss therapy did not lead to greater reduction in frequency of binge eating.

Laerderach-Hofmann et al. (1999) conducted an 8-week randomised double blind placebo controlled trial with imipramine, followed by an open phase of 6 months. They found significant reductions in the imipramine group in binge frequency and weight loss. In the follow up, only the patients in the imipramine group continued to lose weight.

SSRI.

Citalopram/Escitalopram. McElroy et al. (2003) conducted a 6-week placebo controlled trial with citalopram in 38 outpatients with binge eating disorder. There was a significantly greater reduction in frequency of binge eating, weight and severity of illness.

Guerdjikova et al. (2008) conducted a 12-week placebo controlled trial with escitalopram in 44 patients with binge eating disorder. There were significant reductions in BMI, global severity of illness in the escitalopram group.

Fluvoxamine. De Zwaan et al. (1992) reported a placebo controlled study in 22 patients with binge eating disorder with 4 arms: fluvoxamine + G-CBT, CBT + PLB, dietary management + PLB, dietary management + fluoxetine. There was no additional weight loss in the fluoxetine group. Hudson et al. (1998) conducted a 9-week randomized double blind placebo controlled trial in 85 patients with binge eating disorder. Fluvoxamine reduced the frequency of binge eating.

Ricca et al. (2001) conducted a 24-week randomized placebo controlled trial 108 patients with binge eating disorder. Fluoxetine and fluvoxamine were given alone or in combination with CBT. Fluoxetine had no additional effect. In the CBT + fluvoxamine a greater reduction of EDE total score was observed. There was no additional effect of the pharmacological compounds on BMI.

Pearlstein et al. (2003) conducted a 12-week double blind, placebo controlled trial in 20 patients (5 dropouts) with binge eating disorder. Fluvoxamine was not associated with reduced binge eating frequency.

Fluoxetine. Marcus et al. (1990) conducted a double blind placebo controlled trial in 22 patients with BED. Fluoxetine and behaviour modification were associated over a treatment period of 52 weeks with weight reduction. There was no influence of the medication on eating disorder associated psychopathology (EDI). Ricca et al. (2001) reported a 1 year follow up of a placebo controlled trial with fluoxetine and fluvoxamine with individual CBT. CBT was more effective than fluoxetine and fluvoxamine in the treatment of BED. The addition of fluoxetine to CBT does not seem to provide any clear advantage. Arnold et al. (2002) conducted a 6-week placebo controlled trial with 60 patients. Fluoxetine reduced frequency of binge eating, weight / BMI, CGI, and for HAMD there was a trend. Devlin et al. (2005) conducted a 20-week randomized placebo controlled with 116 patients. Fluoxetine and cognitive behavour therapy did not reduce binge frequency, weight, and eating related psychopathology and depressive symptomatology over placebo.

Devlin et al. (2007) reported the 2 year follow up of 116 patients of the double blind trial. The patients received fluoxetine and cognitive behavour therapy. There was no association with fluoxetine in reduction of binge frequency, weight and eating related psychopathology at 2 year follow up. But there was an association with reduced depressive symptomatology.

Sertraline. McElroy et al. (2000) conducted a 6-week double blind placebo controlled trial in 34 patients (8 dropouts) with sertraline with significant reduction in frequency of binge eating, CGI, and BMI.

O`Reardon et al.(2006) performed a 8-week randomized controlled trial in 34 patients with night eating syndrome. Sertraline was associated with improvement of CGI, and night eating symptoms.

Leombruni et al. (2006) reported an open study with a waiting list control in 32 patients receiving sertraline over a treatment period of 24 weeks. There

Table VI. Studies on pharmacological treatment in binge eating disorder.

Author	Year	No. of Patients	Dropouts	Agent	No. of studies	Psychotherapy	Randomized	Placebo-controlled	Double-blind	Treatment-duration	Parameters	Positive outcome/ superiority to placebo
Antidepressants												
Triciyclics					**4**	**2**	**4**	**3**	**3**			
McCann and Agras	1990	23		desipramine	1	0	1	1	1	12 weeks	binge eating frequency	yes
Alger et al.	1991	41	8	imipramine (naltrexone)	1	0	1	1	1	8 weeks	binge duration in obese bingers	yes
Agras et al.	1994	108	24	desipramine and CBT additional to weight loss therapy	1	1	1	0	0	9 months	frequency of binge eating	No additional effect to CBT
Laerderach-Hofmann et al.	1999	31	2	imipramine and diet counseling	1	1	1	1	1	8 weeks	binge frequency	yes
											weight loss	yes
SSRIs												
Citalopram/Escitalopram					2	0	2	2	2			
McElroy et al.	2003	38	7	citalopram		0	1	1	1	6 weeks	frequency of binge eating	yes
											weight / BMI	yes
											severity of illness	yes
Guerdjikova et al.	2008	44		escitalopram 26.5 mg/day			1	1	1	12-week	BMI	yes
											global severity of illness	yes
											obsessive-compulsive symptoms of BED	no
Fluvoxamine					4	2	3	4	2			
de Zwaan et al.	1992	22	0	fluvoxamine + G-CBT, CBT + PLB, dietary management + PLB, dietary management + fluoxetine	1	1		1			weight loss	no
Hudson et al.	1998	85	18	fluvoxamine	1	0	1	1	1	9 weeks	frequency of binge eating	yes
											CGI	yes
											BMI	yes
											HAMD	no

(Continued)

Table VI. *(Continued)*

Author	Year	No. of Patients	Dropouts	Agent	No. of studies	Psychotherapy	Randomized	Placebo-controlled	Double-blind	Treatment-duration	Parameters	Positive outcome/ superiority to placebo
Ricca et al.	2001	108	12	fluvoxamine, fluoxetine + CBT	1	1	1	1		24 weeks	BMI	no
											EDE	no
Pearlstein et al.	2003	20	5	fluvoxamine	1	0	1	1	1	12 weeks	binge frequency	no
											ED	no
											BDI	no
Fluoxetine					5	4	3	3	3			
Marcus et al.	1990	45 (22 with BED)	1	fluoxetine + behaviour modificatiion	1	1	1	1	1	52 weeks	weight	yes
											EDI	no
											BDI	no
Ricca et al.	2001	108	12	fluoxetine and fluvoxamine with individual CBT	1	1	0	0	0	24 weeks 1 year follow up	BMI	no
											EDE	no
Arnold et al.	2002	60	24	fluoxetine	1	0	1	1	1	6 weeks	frequency of binge eating	yes
											weight/BMI	yes
											CGI	yes
											HAMD	trend
Devlin et al.	2005	116		fluoxetine and cognitive behavour therapy	1	1	1	1	1	20 weeks	binge frequency	no
											weight	no
											eating related psychopathology	no
											depressive symptomatology	yes
Devlin et al.	2007	116		fluoxetine and cognitive behavour therapy	1	1	0	0	0		binge frequency	no
											weight	no
											eating related psychopathology	no
											depressive symptomatology	yes
Sertraline					3	0	1	2	2			
McElroy et al.	2000	34	8	sertraline	1	0	0	1	1	6 weeks	frequency of binge eating	yes
											CGI	yes
											BMI	yes

O`Reardon et al.	2006	34 (night eating syndrome)	2	sertraline	1	0	1	1	1	8 weeks	CGI	yes
											night eating symptoms	yes
Leombruni et al.	2006	32	8	sertraline	1	0	0	0	0	24 weeks	BMI	yes
											EDI-2	subscores
											BES	yes
											BDI	yes
SNRIs												
Atomoxetine					1	0	1	1	1			
McElroy et al.	2007	40	4	atomoxetine 40–120 mg/day	1	0	1	1	1	10 weeks	binge-eating episode frequency	yes
											binge day frequency,	yes
											weight, body mass index, and scores on the	yes
											Clinical Global Impressions-Severity of Illness scale,	yes
											Yale-Brown Obsessive Compulsive Scale Modified for Binge Eating obsession sub-scale, and	yes
											Three Factor Eating Questionnaire hunger subscale	yes
Venlafaxine					1	0	0	0	0			
Malhort et al.	2002	35	0	venlafaxine	1	0	0	0	0	120 days	weekly binge frequency	yes
											severity of binge eating	yes
											weight/BMI	yes
Sibutramine					4	1	4	4	3			
Appoilnario et al.	2003	60	12	sibutramine	1	0	1	1	1	12 weeks	binge frequency	yes
											weight loss	yes
											BES	yes
											BDI	yes
Bauer et al.	2006	73 (29 with BED, other subclinical)	20	sibutramine	1	1	1	1	1	16 weeks	weight loss	yes
											binge eating	no
Milano et al.	2005	20		sibutramine	1	0	1	1	0	12 weeks	binge eating frequency	yes
											BES	yes
											weight loss	

(Continued)

Table VI. *(Continued)*

Author	Year	No. of Patients	Dropouts	Agent	No. of studies	Psychotherapy	Randomized	Placebo-controlled	Double-blind	Treatment-duration	Parameters	Positive outcome/ superiority to placebo
Wilfley et al.	2008	304	115	sibutramine	1	0	1	1	1	24 weeks	weekly binge frequency	yes
											weight loss	yes
											reduction in frequency of binge days;	yes
											reduction in body mass index;	yes
											global improvement;	yes
											level of response, including the percentage of abstinence from binge eating (sibutramine group: 58.7%; placebo group: 42.8%); and	yes
											reduction in eating pathology (cognitive restraint, disinhibition, and hunger).	yes
NRI					**1**	**0**	**0**	**0**	**0**			
Silveria et al.	2005	9	4	reboxetine	0	0	0	0	0	12 weeks	weight/BMI	yes
											BES	yes
											CGI	yes
											WHOQoL-BREF	yes
Antiepileptics												
Topiramate					7	1	3	3	3			
Appolinario et al.	2002	8	2	topiramate	1	0	0	0	0	16 weeks	binge episodes per week	yes
											BES	yes
											BDI	yes
											weight	yes
McElroy et al.	2003	61	9	topiramate	1	0	1	1	1	14 weeks	binge frequency	yes
											weight/BMI	yes
											CGI	yes
											Y-BOCS-BE	yes
De Bernardi et al.	2005	1	0	topiramate	1	0	0	0	0	28 weeks	weight/BMI	yes
											BED-symptomatology	yes
McElroy et al.	2004	43	21	topiramate	1	0	0	0	0	42 weeks	binge frequency	yes
											weight loss	yes
Guerdjikova et al.	2005	3	0	topiramate after bariatric surgery	1					10 months	binge eating symptoms	yes
											weight loss	yes
Claudino et al.	2007	73	17	topiramate + CBT	1	1	1	1	1	21 weeks	weight change, and secondary outcome measures were	yes

											binge frequencies,	no
											binge remission, .	yes
											Binge Eating Scale (BES) scores, and	no
											Beck Depression Inventory (BDI) scores	no
McElroy et al.	2007	394	118	topiramate	1	0	1	1	1	16 weeks	binge eating days/week	yes
											binge episodes/week	yes
											weight/BMI	yes
Zonisamide					3	1	1	1	1			
McElroy et al.	2004	15	7	zonisamide	1	0	0	0	0	12 weeks	binge eating frequency	yes
											weight/BMI	yes
											CGI	yes
											Y-BOCS-BE	yes
											TFEQ	yes
McElroy et al.	2006	60	12	Zonisamide	1	0	1	1	1	16 weeks	binge eating episode frequency (P = .021),	yes
											body weight (P < .001), BMI (P = .001), and scores on the	yes
											Clinical Global Impressions-Severity scale (P < .001),	yes
											Yale-Brown Obsessive Compulsive Scale Modified for Binge Eating (P < .001), and	yes
											Three Factor Eating Questionnaire disinhibition scales (P < .001)	yes
Ricca et al.	2009	28		zonisamide	1	1	0	0	0		reduction in binge eating frequency	yes
Other pharmacological compounds												
Baclofen					1	0	0	0	0			
Broft et al.	2007	7 (4 BED; 3 BN)	1	baclofen	1	0	0	0	0	10 weeks	frequency of binge eating	yes
Orlistat					8	2	5	4	3			
Norgren et al.	2003	11		orlistat	1	0	0	0	0	12 week	reduce fat intake, promoting weight loss	Yes (adolescents)
Chanoine et al.	2005	539		orlistat	1	0	1	1	1	54 weeks	weight loss	Yes (adolescents)
McDuffie et al.	2002	20		orlistat	1	1	0	0	0	3 month	weight loss	Yes (adolescents)
McDuffie et al.	2004	20		orlistat	1	1	0	0	0	6 month	weight loss	Yes (adolescents)
Golay et al.	2005	89	18	orlistat	1	0	1	1	1	24 weeks	weight loss	yes
											EDI-2	yes
Grilo et al.	2005	50	11	orlistat and CBT Self help	1	1	1	1	1	12 weeks	5% weight loss	yes

(Continued)

Table VI. *(Continued)*

Author	Year	No. of Patients	Dropouts	Agent	No. of studies	Psychotherapy	Randomized	Placebo-controlled	Double-blind	Treatment-duration	Parameters	Positive outcome/ superiority to placebo
Grilo and Masheb	2007	50	11	orlistat and CBT Self help	1	1	1	1	1	12 weeks	binge eating remission rapid response is more likely to achieve binge eating remission and 5% weight loss	yes
Yancy et al.	2010	146	24	orlistat and low fat diet	1	0	1	0	0	48 weeks	Weight loss vs a low-carbohydrate, ketogenic diet	similar
d-fenluramine					1	0	1	1	1			
Stunkard et al.	1996	28	1	d-fenfluramine	1	0	1	1	1	8 weeks	binges per week	yes
Naltrexon					2	0	1	1	1			
Alger et al.	1991	41		imipramine (naltrexone)	1		1	1	1	8 weeks	binge duration in obese bingers	no
Marrazzi et al.	1995				1							

was a reduction in BMI, EDI-2 subscores, BES, and BDI.

SNRI.

ATOMOXETINE. McElroy et al. (2007b) conducted a 10-week randomized placebo controlled double blind, single centre with 40 patients. Atomoxetine 40-120 mg/day was associated with reduced binge-eating episode frequency. 4 Patients dropped out (1 placebo, 3 atomoxetine). The cause of atomoxetine discontinuation was increased depressive symptoms, constipation, and nervousness.

VENLAFAXINE. Malhort et al. (2002) reported a series of 35 patients treated with venlafaxine over 120 days. There was a reduction in weekly binge frequency. The authors report, that venlafaxine was well tolerated. Dry mouth, sexual dysfunction, insomnia, and nausea were the most commonly reported side effects. No patient discontinued drug treatment.

SIBUTRAMINE. Appolinario et al. (2003) conducted a 12-week randomized double-blind placebo-controlled trial in 60 patients. Sibutramine was associated with reduced binge frequency, weight loss, reduction of BES, and BDI score. Dry mouth ($p = 0.01$) and constipation ($p < 0.001$) were associated with drug treatment. There were 7 dropouts in the pharmacological group and 5 dropouts in the PLB group. Dry mouth ($p < 0.01$), headache ($p < 0.01$), and constipation ($p < 0.001$) were associated with drug treatment. Blood pressure should be monitored.

Bauer et al. (2006) conducted a 16-week randomized double-blind placebo-controlled trial with 29 patients with BED and 44 obese patients without BED. Sibutramine and CBT weight loss treatment were associated with additional weight loss, but not with a reduction in binge eating. 20 patients dropped out with a random distribution concerning sibutramine and BED. No serious adverse reaction occurred due to the administration of sibutramine.

Milano et al. (2005) conducted a 12-week placebo controlled with 20 patients. Sibutramine was associated with reduction in binge eating frequency, BES score reduction, and weight loss. No serious adverse reaction occurred due to sibutramine. Patiens with adverse events had in 40% dry mouth, in 20% constipation, and in 10% tachycardia, insomnia, cephalgia or nausea.

Wilfley et al. (2008) conducted a 24-week randomized placebo controlled double blind trial with

304 patients. Sibutramine was associated with reduction in weekly binge frequency, weight loss, reduction in frequency of binge days, reduction in body mass index, global improvement, level of response, including the percentage of abstinence from binge eating (sibutramine group: 58.7%; placebo group: 42.8%); and reduction in eating pathology (cognitive restraint, disinhibition, and hunger). There were 115 dropouts, with 32.9% in the sibutramine group and 42.8% in the PLB group. 10 dropped out because of adverse events of sibutramine. Compared with placebo, sibutramine treatment was associated with significantly higher incidence of headache, dry mouth, constipation, insomnia, and dizziness

NRI. Silveria et al. (2005) report 9 cases (4 dropouts) treated with reboxetine in an open manner over 12 weeks. There was a significant weight /BMI change, BES, CGI and WHOQoL-BREF improvement with the noradrenergic antidepressant. No serious adverse event was observed.

Treatment with Antiepileptics

Topiramate. Appolinario et al. (2002a) report 8 cases (2 dropouts) treated with topiramate in an open trial over a treatment period of 16 weeks with significant reduction in binge episodes per week. The most common side effects were paresthesias, fatigue, and somnolence. De Bernardi et al. (2005) reported a case treated with topiramate over 28 weeks with significant weight/BMI reduction. Guerdjikova et al. (2005) report 3 cases treated with topiramate after bariatric surgery over 10 months. There was a reduction of binge eating symptoms (BES) and depressive symptoms (BDI).Topiramate was well tolerated. Side effects were mild fatigue (at 25 mg), insomnia, paresthesia (at 50 mg), cognitive dysfunction (at 150 or 625 mg, respectively), and evening anxiety (at 200 mg).

McElroy et al. (2003) conducted a 14-week randomized placebo controlled trial with 61 patients with BED. Topiramate reduced binge frequency, weight / BMI, CGI, and Y-BOCS-BE. 9 patients dropped out, 6 because of adverse events of topiramate. Headache and paresthesias were the most common side effects. McElroy et al. (2003c) reported a open 42-week follow up with completers after a double blind placebo controlled trial with 43 patients with BED. Topiramate was associated with reduced binge frequency, and weight loss. 68% of the patients entering the open label phase discontinued due to protocol nonadherence ($n = 17$) and due to adverse events ($n = 14$). The most common adverse events included paresthesias, dry mouth, headache, taste perversion and cognitive problems. Patients discontinuing because of adverse events were not taking a higher dose of topiramate than those discontinuing the drug for other reasons. Nevertheless, a gradual increase of topiramate is recommended to avoid occurrence of side effects.

Claudino et al. (2007) conducted a randomized placebo controlled double blind trial in 73 patients with BED. Topiramate + CBT were associated with weight change. Secondary outcome measures were also reduced (Beck Depression Inventory (BDI) scores), binge remission was increased but binge frequencies were not reduced. Altogether there were 17 dropouts. One patient withdrew for adverse events in the topiramate group. Paresthesia, taste perversion and insomnia were associated with topiramate.

McElroy et al. (2007a) conducted a 16-week placebo controlled trial in 195 patients receiving topiramate and 199 placebo patients. There was reduction of binge eating days/week, binge episodes/week, and weight/BMI. The discontinuation rate was 30%. In the topiramate group 16% discontinued due to adverse events. Paresthesia, upper respiratory tract infection, somnolence and nausea were the most common side effects.

Zonisamide. McElroy et al. (2004d) reported an open trial of 15 patients (7 dropouts) treated with zonisamide over 12 weeks. There was a reduction in binge eating frequency, weight/BMI, CGI, Y-BOCS-BE, and TFEQ. 7 patients discontinued zonisamide prematurely. Four of them due to adverse events. The most common adverse events were altered taste, fatigue, dry mouth, and cognitive impairment. One subject developed nephrolithiasis.

McElroy et al. (2006) conducted a 16-week randomized placebo controlled double blind trial with 60 patients with zonisamide. There was a significant reduction of binge eating episode frequency ($p = .021$), body weight ($p < .001$), BMI ($p = .001$), and scores on the CGI ($p < .001$), Y-BOCS-BE ($p < .001$), and TFEQ ($p < .001$). 12 patients dropped out because of adverse events. Reported causes for discontinuation in the zonisamide group were accidental injury with bone fracture, psychological complaints, and cognitive complaints.

Ricca et al. (2009) reported that zonisamide augmentation to individual cognitive behavior therapy can improve the treatment of binge eating disorder patients, reducing body weight and the number of binge eating episodes. These results are maintained 1 year after the end of treatment.

Treatment with other Pharmacological Compounds

Baclofen. Broft et al. (2007) report a case series of 7 patients (4 BED; 3 BN) receiving baclofen in an open manner over 10 weeks. There was a reduction in frequency of binge eating. Baclofen was well tolerated. The most frequently reported side effect was sedation. 1 Patient dropped out, another discontinued in week 10 and was not counted as dropout.

Orlistat. Golay et al. (2005) conducted a 24-week randomized double blind trial in 89 patients. Orlistat was associated with weight loss, and reduction in EDI-2 scores. 18 patients dropped out. 4 due to aderse events (all in the PLB group).

Grilo et al. (2005a) conducted a 12-week trial with 50 patients with orlistat and CBT Self help. Orlistat was associated with weight loss, and binge eating remission. Grilo and Masheb (2007) reported that in their 50 patients treated with orlistat and CBT Self help. There was a rapid respone in binge eating remission and 5% of the patients lose weight. Orlistat was generally well tolerated, 11 patients dropped out. Only 2 patients experienced side effects that were cause for their drop out.

The randomized trial of Yancy et al. (2010) compared orlistat with low fat diet versus a low-carbohydrate, ketogenic diet. The results concerning weight loss showed similar improvements.

Three open studies (Norgren et al., 2003 McDuffie et al., 2002, 2004) and 1 RCT (Chanoine et al., 2005) suggested that orlistat is benefical in pediatric over weight related to BED. One RCT (Maahs et al., 2006) showed negative results.

d-Fenfluramine

D-FENLURAMINE. Stunkard et al. (1996) conducted a 8-week double blind placebo controlled trial with 28 patients. D-fenfluramine was associated with reduction in binges per week. Headache (25% vs. 8%) and diarrhea (17% vs. 8%) were more common in the d-fenluramine group. One patient experienced a rash, that began 2 days after treatment start and 3 months later was no longer visible.

Naltrexone. Alger et al. (1991) conducted an 8-week double blind placebo controlled trial with naltrexone (100-150 mg/day) and imipramine (150 mg/day) in 88 obese bingers and 60 normoweight bulimics. Natrexone was associated with significant decrease in binge frequency in bulimics, imipramine was associated with reduced binge frequency in obese binge eaters. The authors conclude that naltrexone and imipramine may be useful in the treatment of binge eating.

Combining Pharmacotherapy with Psychotherapy

In many studies psychotherapy was given as a usual background treatment. 50% of the RCTs (2 out of 4) with TCAs were combined with psychotherapy. In one RCT no superiority to CBT was shown. Also for fluoxetine the combination brought no superiority to psychotherapy. For fluoxetine, the study without psychotherapy (Arnold et al., 2002) showed superiority to placebo. Sertraline was studied without psychotherapy and showed superiority to placebo. The same is true for atomoxetine. For sibutramine the study with psychotherapy (Bauer et al., 2006) only showed a benefit for weight loss. The other RCTs without psychotherapy showed superiority for sibutramine over placebo. A comparable situation exists for topiramate, the study with psychotherapy (Claudino et al., 2007) showed superiority in weight loss. Orlistat was combined in 2 RCTs with psychotherapy.

Discussion of Guidelines for Binge Eating Disorder

There are 3 RCTs (2 with imipramine, 1 with desipramine) which show a reduction in binge frequency more than placebo in BED. There is a category of evidence grade A for imipramine with a moderate risk-benefit ration, recommendation grade 2).

Citalopram/escitalopram: There are 2 RCTs showing efficacy in BED over placebo (Category of evidence grade A, recommendation grade 1).

There are 3 studies with no favourable results for fluvoxamine and 1 with favourable results in BED (Category of evidence grade D).

Concerning fluoxetine there are conflicting results concerning efficacy in BED. 2 studies found weight reduction, 2 studies no weight reduction. Two studies found reduction in depressive symptomatology, 2 no significant reduction of depressive symptomatology (Category of evidence grade D).

Sertraline could be proven to be effictive in 2 RCTs over placebo concerning psychopathology and BED associated behaviour in BED (Category of evidence grade A, recommendation grade 1).

There is 1 RCT that shows efficacy for atomoxetine in BED (Category of evidence grade B).

There is only 1 case series for venlafaxine, which suggests that there might be efficacy in BED (Category of evidence grade C).

There are 4 RCTs which show efficacy of sibutramine over placebo in BED (Category of evidence grade A, but there is a low risk-benefit ratio).

There is only 1 open study which suggests, that there might be an efficacy over placebo concerning reboxetine in BED (Category of evidence grade C).

There are 3 RCTs that suggest efficacy of topiramate over placebo in BED (Category of evidence grade A, with moderate risk-benefit ration, recommendation grade 2).

There is 1 RCT of zonisamide that showed efficacy in psychopathology, weight and BED behaviour over placebo (Category of evidence grade B).

There is only 1 open trial that suggests baclofen may be helpful in reducing frequency of binge eating (Category of evidence grade C).

Orlistat was shown to be effective in 3 RCTs over placebo in reducing weight in BED (Category of evidence grade A, with low to moderate risk-benefit ratio).

1 RCT showed efficacy over placebo for d-fenfluramin in reducing binges per week in BED (Category of evidence grade B). There is 1 RCT that shows efficacy over placebo for naltrexone in reducing binge duration in BED (Category of evidence grade B). The available literature on pharmacological treatment of BED is based on trials of relatively short duration (most of the studies were less than 6 months length), so that is not enough information on the long-term efficacy of these treatments.

Acknowledgements

We would like to thank Berenike Oppermann and Markus Dold for their general and editorial assistance.

Statement of Interest

Martin Aigner has recieved travel grants from CSC, Eli Lilly, Pfizer and speakers fees from CSC, Eli Lilly, Pfizer.

Janet Treasure has written self guided treatment books on eating disorders and has no statement of interest to declare.

Walter Kaye has received grant support from AstraZeneca.

Siegfried Kasper has received grant/research support from Bristol Myers-Squibb, Eli Lilly, GlaxoSmithKline, Lundbeck, Organon, Sepracor and Servier; has served as a consultant or on advisory boards for AstraZeneca, Bristol-Myers Squibb, Eli Lilly, GlaxoSmithKline, Janssen, Lundbeck, Merck Sharp and Dome (MSD), Novartis, Organon, Pfizer, Schwabe, Sepracor, and Servier; and has served on speakers' bureaus for Angelini, AstraZeneca, Bristol Myers-Squibb, Eli Lilly, Janssen, Lundbeck, Pfizer, Pierre Fabre, Schwabe, Sepracor, and Servier.

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